Common Drug Review
Clinical Review Report

June 2017

Drug	Edoxaban (Lixiana)
Indication	Treatment of venous thromboembolism (VTE) (deep vein thrombosis [DVT], pulmonary embolism [PE]) and the prevention of recurrent DVT and PE.
Reimbursement request	[redacted]
Dosage form(s)	15 mg, 30 mg and 60 mg oral tablets
NOC date	November 4, 2016
Manufacturer	SERVIER Canada Inc.

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

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ABBREVIATIONS

AE	adverse event
CDR	CADTH Common Drug Review
CEC	clinical events committee
CI	confidence interval
CrCl	creatinine clearance
CrI	credible interval
CRNM	clinically relevant non-major
DB	double-blind
DIC	deviance information criterion
DOAC	direct oral anticoagulants
DVT	deep vein thrombosis
EOT	end of treatment
EQ-5D	EuroQol 5-Dimensions questionnaire
GI	gastrointestinal
HRQoL	health-related quality of life
ITC	indirect treatment comparison
INR	international normalized ratio
ITT	intention-to-treat
LMWH	low-molecular-weight heparin
mITT	modified intention-to-treat
NI	noninferiority
NMA	network meta-analysis
NSAID	nonsteroidal antiiflammatory drug
PE	pulmonary embolism
P-gp	P-glycoprotein
PP	per-protocol
RCT	randomized controlled trial
RV	right ventricular
SAE	serious adverse event
TTR	time in therapeutic range
UFH	unfractionated heparin
VKA	vitamin K antagonist
VTE	venous thromboembolism

EXECUTIVE SUMMARY

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant health care concern leading to increased morbidity and mortality. In Canada, the annual incidence of VTE is approximately one to two cases per 1,000 in the general population. Signs and symptoms of DVT include unilateral leg pain, swelling, tenderness, increased temperature, pitting edema, and prominent superficial veins; the clinical presentation of PE is composed of non-specific signs and symptoms that may include breathlessness, chest pain, hemoptysis, collapse, tachycardia, hypotension, tachypnea, raised jugular venous pressure, focal signs in chest, and hypoxia or cyanosis.

Anticoagulant therapy aims to treat the current episode and avoid VTE recurrence. Initial anticoagulation is achieved with parenteral treatment options, such as low-molecular-weight heparins (LMWHs). 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. Despite being widely used, warfarin is the source of various concerns 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 experiencing recurrent or unprovoked idiopathic VTE.

In the 2016 CHEST Guidelines, the American College of Chest Physicians suggested using dabigatran, rivaroxaban, apixaban, or edoxaban (direct oral anticoagulants [DOACs]) over VKA therapy as long-term anticoagulant therapy for patients with VTE and no cancer. VKA therapy is recommended over LMWH for patients with VTE and no cancer who are not treated with DOACs. For patients with VTE and cancer, the guidelines suggest using an LMWH over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban. Initial bridging with an LMWH is required for patients managed with edoxaban and dabigatran, but not for those managed with rivaroxaban or apixaban.

Taken orally, Edoxaban is a highly selective, direct, and reversible inhibitor of factor Xa. It has a Health Canada indication for the treatment of VTE (DVT and PE) and the prevention of recurrent DVT and PE. The manufacturer has requested that edoxaban 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 edoxaban for the treatment of VTE (DVT and PE), and for the prevention of recurrent DVT and PE.

Results and Interpretation

Included Studies

One published manufacturer-sponsored, phase III, double-blind (DB), matching placebo, parallel-group, noninferiority (NI) study was included in the systematic review. Hokusai–VTE (n = 8,292) evaluated the benefits and risks of edoxaban compared with warfarin in reducing the risk of symptomatic recurrent VTE in patients with documented acute symptomatic DVT and/or PE. Eligible patients were randomized in a 1:1 ratio to receive edoxaban or warfarin using stratified randomization, where eligible patients were stratified by their presenting diagnoses: PE with or without DVT versus DVT only; baseline risk factors (temporary risk factors only [such as trauma, surgery, immobilization, estrogen therapy, etc.] versus all others); and need for edoxaban dose reduction to 30 mg (yes or no). All patients received initial therapy with open-label unfractionated heparin or enoxaparin for at least five days. Edoxaban or warfarin was administered in a DB, double-dummy fashion. Edoxaban (or placebo) was started after

discontinuation of initial heparin in the edoxaban treatment group. Edoxaban was administered at a dose of 60 mg orally once daily, or at a dose of 30 mg once daily in patients with a creatinine clearance (CrCl) between 30 mL and 50 mL per minute, a body weight of 60 kg or less, or who were receiving concomitant treatment with potent P-glycoprotein (P-gp) inhibitors. Warfarin (or placebo) was started at the same time as heparin. After discontinuing initial heparin in the warfarin treatment group, patients started placebo edoxaban (60 mg once daily) and continued warfarin (adjusted to maintain an international normalized ratio [INR] between 2.0 and 3.0). The intended treatment durations for edoxaban or warfarin of three, six, and 12 months were determined by the investigator. The primary efficacy end point was symptomatic recurrent VTE (i.e., the composite end point of DVT, non-fatal PE, and fatal PE during the 12-month study period).

Noninferiority (NI) was demonstrated if the upper bound of the two-sided 95% confidence interval (CI) of the hazard ratio was below the NI margin of 1.5. If NI was demonstrated, then superiority for the secondary efficacy end point (the composite clinical outcome of non-fatal symptomatic recurrent PE, symptomatic recurrent DVT, and all-cause mortality during the 12-month study period) was tested. The primary safety outcome was clinically relevant bleeding (i.e., major bleeding or clinically relevant non-major bleeding) that occurred during treatment or within three days of interrupting or stopping the study drug.

Hokusai–VTE was generally well conducted. The main limitation was that the NI analysis of the primary end point used the modified intention-to-treat (mITT) analysis set for the overall study period, while the per-protocol (PP) analysis that was undertaken for the overall study period was exploratory. There is a lack of direct evidence comparing edoxaban with other DOACs (apixaban, dabigatran, and rivaroxaban), as these drugs were not included as comparators in the Hokusai–VTE trial.

Efficacy

Results from Hokusai–VTE for the treatment of patients with acute symptomatic VTE and for the prevention of symptomatic recurrent VTE during the 12-month study period met the pre-specified NI margin (HR = 1.5) for the primary efficacy outcome of symptomatic recurrent VTE during the overall study period. The use of edoxaban was associated with a hazard ratio = 0.89 in the mITT population (95% CI, 0.703 to 1.128) and a hazard ratio = 0.87 in the PP population (95% CI, 0.688 to 1.107). However, when tested for superiority, the relative efficacy of edoxaban was not statistically significantly better than warfarin. A similar trend of treatment effect as the primary analysis was demonstrated in the subgroup analyses for the following subgroups of patients: patients with a presenting diagnosis of PE with or without DVT; patients with PE severity; patients with a presenting diagnosis of DVT only; either < 65 or ≥ 65 years of age; patients with baseline risk factors; patients with a body weight greater than 60 kg; patients with CrCl at randomization 30 mL/min to 50 mL/min or > 50 mL/min; patients with a history of cancer; patients with no active cancer; and centre-level INR percentage time in therapeutic range for warfarin patients (except for when time in therapeutic range is ≥ 75th percentile). However, these subgroup analyses were exploratory in nature; due to small sample sizes and few numbers of events, the analyses were not powered to detect any differences between groups. Superiority was not established for the secondary efficacy end point. The composite end point of recurrent VTE and all-cause mortality occurred in 228 patients (5.5%) in the edoxaban group and in 228 patients (5.5%) in the warfarin group (hazard ratio: 1.00; 95% CI, 0.832 to 1.200; *P* = 0.9933). Overall, the results of Hokusai–VTE trial suggest that edoxaban may be considered as effective as warfarin for the treatment of patients with acute symptomatic VTE and for the prevention of symptomatic recurrent VTE (up to 12 months).

Health-related quality of life (HRQoL) data were collected and reported in the Hokusai–VTE trial. However, analysis of the differential effects of edoxaban and warfarin on HRQoL was not carried out due to the small numbers of respondents [redacted]; therefore, the differential effects of edoxaban and warfarin on HRQoL are unknown. In addition, the small number of respondents severely limits the usefulness of the HRQoL data.

To address the issue of a lack of direct comparative evidence for edoxaban versus other DOACs, CADTH Common Drug Review (CDR) reviewed two indirect treatment comparisons (ITCs) submitted by the manufacturer, as well as five published ITCs that assessed the efficacy and safety of edoxaban compared with other anticoagulants, including DOACs, for the treatment of VTE and the prevention of recurrent VTE. The results of these ITCs were consistent in concluding that there were no major differences between edoxaban and other DOACs in treating and preventing recurrent VTE, as there were no statistically significant differences among treatments for the outcomes of VTE and mortality. However, the small number of studies available, the relative rarity of the events that were analyzed, and the high level of heterogeneity among studies (including blinding and variation in the duration of treatment across the studies) result in uncertainty in interpreting the comparative effectiveness of edoxaban versus other anticoagulants.

Harms

Results from the Hokusai–VTE trial demonstrated the superiority of edoxaban over warfarin for the primary safety outcome of clinically relevant bleeding (hazard ratio: 0.81; 95% CI, 0.705 to 0.936; $P = 0.004$ for superiority). The statistical significance of this composite outcome was mainly driven by the reduction of clinically relevant non-major (CRNM) bleeding (298 patients [7.2%] in the edoxaban treatment group versus 368 patients [8.9%] in the warfarin treatment group). The edoxaban group also had numerically fewer major bleeds than the warfarin group (56 [1.4%] versus 66 [1.6%]). Notable harms included fatal bleeding (three [0.1%] patients with edoxaban versus 10 [0.2%] patients with warfarin), intracranial bleeding (five [0.1%] patients versus 18 [0.4%] patients, respectively), and gastrointestinal (GI) bleeding (27 [0.7%] patients versus 18 [0.4%] patients, respectively).

Mortality as well as the overall incidence of serious adverse events (SAEs) in the Hokusai–VTE trial did not differ significantly between edoxaban and warfarin, and were not higher than would be expected in this patient population in clinical practice. The frequency for the most commonly reported SAEs was similar and low (< 2%) for both treatments, with the most common SAE in the edoxaban treatment group being pneumonia (0.7% and 0.4% for edoxaban versus warfarin, respectively). The most common SAE in the warfarin group was increased INR (< 0.1% and 1.9%, edoxaban versus warfarin, respectively). The proportion of patients experiencing adverse events (AEs) was slightly lower in the edoxaban treatment group compared with those in the warfarin group (68.5% versus 71%, respectively). Few patients discontinued treatment due to AEs in both treatment arms.

The results of two ITCs submitted by the manufacturer and five published ITCs on the safety of edoxaban compared with other anticoagulants, including other DOACs, yielded inconsistent results for bleeding-related outcomes, where all but one of the ITCs reported that apixaban was significantly less likely to cause major bleeding compared with edoxaban. Additionally, all but one of the ITCs indicated that apixaban was consistently superior to edoxaban for all bleeding outcomes. Edoxaban was associated with a significantly increased risk of major and CRNM bleeds compared with dabigatran. Given the small number of studies, the rarity of events, and different treatment durations, there is some degree of uncertainty related to interpreting the bleeding risks associated with apixaban compared with edoxaban.

Conclusions

Hokusai–VTE, a manufacturer-sponsored, phase III, DB matching placebo, parallel-group, NI study, was included in the systematic review that evaluated the benefits and risks of edoxaban compared with those of warfarin in reducing the risk of symptomatic recurrent VTE in patients with documented acute symptomatic DVT and/or PE. The intended treatment durations for edoxaban or warfarin were three, six, or 12 months, as determined by the study investigator. The results of the Hokusai–VTE study demonstrated that edoxaban was noninferior to, but not superior to, warfarin in the treatment of patients with acute symptomatic VTE for the prevention of symptomatic recurrent VTE during the 12-month study period, based on the frequency of recurrent symptomatic VTE. In the same study, edoxaban was associated with significantly fewer clinically relevant bleeding events than warfarin, an outcome that was driven mainly by the reduction in CRNM bleeding, not major bleeding. The results of two ITCs submitted by the manufacturer and five published ITCs of the efficacy and safety of edoxaban compared with other DOACs consistently have suggested that edoxaban is as efficacious as other DOACs in treating and preventing VTE, and that (except for the ITC by Wells et al.) edoxaban was associated with statistically significantly more major bleeding than apixaban and statistically significantly more major and CRNM bleeding than apixaban and dabigatran.

TABLE 1: SUMMARY OF RESULTS

	Hokusai–VTE	
	Edoxaban	**Warfarin**
Key Efficacy Outcomes	**N = 4,118**	**N = 4,122**
NI Analysis: All Patients With Recurrent VTE (mITT Analysis Set), Overall Study Period, n (%)[a]	130 (3.2)	146 (3.5)
HR edoxaban vs. warfarin (95% CI)[b]	0.89 (0.703, 1.128)	
Type of First Recurrent VTE, n (%)		
PE with/without DVT	73 (1.8)	83 (2.0)
PE-related deaths	24 (0.6)	24 (0.6)
Fatal PE	4 (< 0.1)	3 (< 0.1)
Unexplained death (and VTE cannot be ruled out)	20 (0.5)	21 (0.5)
Non-fatal PE	49 (1.2)	59 (1.4)
With DVT	2 (< 0.1)	2 (< 0.1)
Without DVT	47 (1.1)	57 (1.4)
DVT only	57 (1.4)	63 (1.5)
NI Analysis: Adjudicated Recurrent VTE in the PP Analysis Set, Overall Study Period, n (%)	[redacted]	[redacted]
HR edoxaban vs. warfarin (95% CI)[b]	[redacted]	
Superiority Analysis: All Patients with Recurrent VTE or All-Cause Mortality (mITT Analysis Set), Overall Study Period, n (%)[c]	228 (5.5)	228 (5.5)
HR edoxaban vs. warfarin (95% CI)[d]	1.00 (0.832 to 1.200)	
P value for superiority[d]	0.9933	
Key Harms Outcomes	**N = 4,118**	**N = 4,122**
Major/CRNM Bleeding		
n (%)	349 (8.5)	423 (10.3)
HR edoxaban vs. warfarin (95% CI)	0.81 (0.705 to 0.936)	
P value for superiority	0.0040	
Major Bleeding, n (%)	56 (1.4)	66 (1.6)
CRNM Bleeding, n (%)	298 (7.2)	368 (8.9)
Bleeding Events Required/Prolonged Hospitalization	[redacted]	[redacted]
Patients With ALT or AST ≥ 3 × ULN	106 (2.7)	100 (2.6)

	Hokusai–VTE	
	Edoxaban	Warfarin
Patients With TBL ≥ 2 × ULN	41 (1.1)	24 (0.6)
SAEs, n (%)	503 (12.2)	544 (13.2)
AEs, n (%)	2,821 (68.5)	2,928 (71.0)
WDAEs, n (%)	195 (4.7)	185 (4.5)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CRNM = clinically relevant non-major; DVT = deep vein thrombosis; HR = hazard ratio vs. warfarin; mITT = modified intention-to-treat; N = number of patients in mITT analysis set; n = number of patients with events; NI = noninferiority analysis; PE = pulmonary embolism; PP = per-protocol; SAE = serious adverse event; TBL = total bilirubin; ULN = upper limit of normal; vs. = versus; VTE = venous thromboembolism; WDAE = withdrawal due to adverse event.

[a] The primary efficacy end point is symptomatic recurrent VTE (i.e., the composite end point of DVT, non-fatal PE, and fatal PE).

[b] The HR, two-sided CIs are based on the Cox proportional hazards regression model including treatment and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT; DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban/edoxaban placebo dose at randomization (yes or no).

[c] The secondary efficacy end point is symptomatic recurrent VTE (i.e., the composite end point of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality).

[d] The HR and two-sided CI are based on the Cox proportional hazards regression model including treatment, and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT, DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban/edoxaban placebo at randomization (yes, no), *P* value alpha = 0.01 (two-sided).

Source: Clinical Study Report: Hokusai–VTE study.[1]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Venous thromboembolism (VTE) is 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.[2,3] The clinical manifestations of VTE include deep vein thrombosis (DVT) and pulmonary embolism (PE).[2,3] DVT is often seen in the lower extremities and may occur in a distal or proximal location; the latter is considered of greater clinical importance considering its association with higher PE and mortality rates.[2] VTE often is a result of an interaction between patient-related and setting-related risk factors.[4-6] Patient-related risk factors include age, obesity, chronic heart or respiratory failure, oral contraceptive therapy or hormone replacement therapy, previous VTE, and thrombophilia.[4,7,8] Other significant factors related to immobilization or setting include lower limb fractures, joint replacement surgery, and major general surgery or trauma.[4,8]

Signs and symptoms of DVT include unilateral leg pain, swelling, tenderness, increased temperature, pitting edema, and prominent superficial veins.[7] The clinical presentation of PE is composed of non-specific signs and symptoms that may include breathlessness, chest pain, hemoptysis, collapse, tachycardia, hypotension, tachypnea, raised jugular venous pressure, focal signs in chest, and hypoxia or cyanosis.[7] The manufacturer provided estimations of the incidence of VTE in Canada in 2015 that show a range of 35,852 to 71,704 cases per year.[9] The long-term burden of VTE includes a high risk of recurrence persisting for several years[3] as well as complications such as chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome, which is characterized by symptoms of venous insufficiency.[2,3]

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.[2] Resuscitation is the mainstream therapy in the acute phase of PE; however, anticoagulation should be started as soon as possible.[10] The objectives of anticoagulant therapy are to avoid the recurrence of VTE and to preclude the development of complications.[2] Initial anticoagulation is achieved with parenteral treatment options, including low-molecular-weight heparins (LMWH) and fondaparinux, both recommended over unfractionated heparin.[11] However, oral treatment options are usually preferred for extended treatment of VTE.[2,11] Despite being widely used, warfarin is the source of various concerns, especially considering the narrow therapeutic window of adequate coagulation without bleeding, as well as a highly variable dose–response relation among individuals and many interactions with food and other drugs.[11-13] As a result, patients on warfarin require frequent monitoring. In patients unable or unwilling to use warfarin, extended anticoagulation with an LMWH is expected to provide similar effectiveness without increasing the risk of bleeding.[2] Other treatment options include the direct oral anticoagulants (DOACs) edoxaban, apixaban, dabigatran, and rivaroxaban. All DOACs have a Health Canada indication for the treatment of VTE (DVT and PE) and the prevention of recurrent DVT and PE. Initial bridging with an LMWH is required for patients managed with edoxaban and dabigatran, but not for those managed with rivaroxaban or apixaban.

In 2016, the American College of Chest Physicians published the *CHEST Guideline and Expert Panel Report* for antithrombotic therapy for VTE disease. This guideline suggests using dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) as long-term anticoagulant therapy for patients with VTE and no cancer. VKA therapy is recommended over LMWH for patients with VTE and no cancer who are not treated with DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban). For

patients with VTE and cancer needing long-term anticoagulant therapy, LMWH was suggested over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban.[14] *The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines* (2012)[11] recommended the use of an oral VKA, such as warfarin, initiated when 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 internationalized normal ratio (INR) results reach the target value of 2.5 (range: 2.0 to 3.0).[11] Afterward, warfarin alone should be maintained for a minimum of three months; however, extending anticoagulant therapy beyond three months may prove beneficial for patients with persistent risk factors or who are experiencing recurrent or unprovoked idiopathic VTE.[11]

To date, CADTH Common Drug Review (CDR) has not received a drug submission for dabigatran. Previous reviews of apixaban and rivaroxaban resulted in the CADTH 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

Edoxaban is a highly selective, direct, reversible inhibitor of factor Xa.[15] Factor Xa is the serine protease located in the final common pathway of the coagulation cascade.[15] Edoxaban inhibits free and clot-bound factor Xa and prothrombinase activity. This inhibition of factor Xa in the coagulation cascade reduces thrombin generation, prolongs clotting time, and reduces the risk of thrombus formation or provoked thrombus formation.[15] Edoxaban has a Health Canada indication for the treatment of VTE (DVT and PE) and the prevention of recurrent DVT and PE.[15] Edoxaban is also indicated for the prevention of stroke and systemic embolic events in patients with atrial fibrillation, in whom anticoagulation is appropriate.[15] The recommended dose of edoxaban for the treatment of VTE and prevention of recurrent DVT and PE is 60 mg once daily following initial use of a parenteral anticoagulant for five to 10 days.[15] Edoxaban 30 mg once daily is recommended in patients with one or more of the following clinical factors: a) moderate renal impairment (creatinine clearance [CrCl] 30 mL/min to 50 mL/min); b) body weight ≤ 60 kg; c) concomitant use of P-glycoprotein inhibitors (except amiodarone and verapamil).[15] Duration of therapy should be individualized after carefully weighing the benefit of anticoagulant treatment against the individual risk of bleeding. Individuals with transient risk factors (e.g., surgery, trauma, immobilization) should receive treatment for at least three months, while extended duration therapy is recommended for patients with permanent risk factors or idiopathic DVT or PE.[15]

Indication under review
Treatment of VTE (DVT, PE) and the prevention of recurrent DVT and PE.
Reimbursement criteria requested by sponsor
Treatment of VTE, including DVT and PE, and the prevention of recurrent VTE.

A detailed table of comparators can be found in Appendix 5.

2. OBJECTIVES AND METHODS

2.1 Objective

To perform a systematic review of the beneficial and harmful effects of edoxaban for the treatment of VTE (DVT, PE) and the prevention of recurrent DVT and PE.

2.2 Methods

All manufacturer-provided trials considered pivotal in the manufacturer's submission were included in the systematic review. Phase III 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 Subgroups of potential interest: • treatment duration • cancer versus non-cancer patients • patient's age • renal function • body weight • patients with PE with or without DVT versus patients with DVT only • risk factors
Intervention	Edoxaban 60 mg once daily following initial use of a parenteral anticoagulant for 5 to 10 days Edoxaban 30 mg once daily in patients with one or more of the following clinical factors: • moderate renal impairment (CrCl 30 mL/min to 50 mL/min) • low body weight (≤ 60 kg) • concomitant use of P-gp inhibitors (except amiodarone and verapamil)
Comparators	VKA in combination with LMWH as initial treatment LMWH alone Rivaroxaban alone Apixaban 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, and AEs **Adverse events of interest:** • bleeding (major and minor) and hospitalization due to bleeding • heparin-induced thrombocytopenia • liver function
Study Design	Published and unpublished RCTs

AE = adverse event; CrCl = creatinine clearance; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; P-gp = P-glycoprotein; PE = pulmonary embolism; HRQoL = health-related quality of life; 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 through Ovid; Embase (1974–) through 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 concept was Lixiana (edoxaban).

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

The initial search was completed October 7, 2016. Regular alerts were established to update the search until the CDEC meeting on February 15, 2017. 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 CADTH Grey Matters checklist (www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search and Open Access Journals. 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.

3. RESULTS

3.1 Findings from the Literature

A total of one study was 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.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

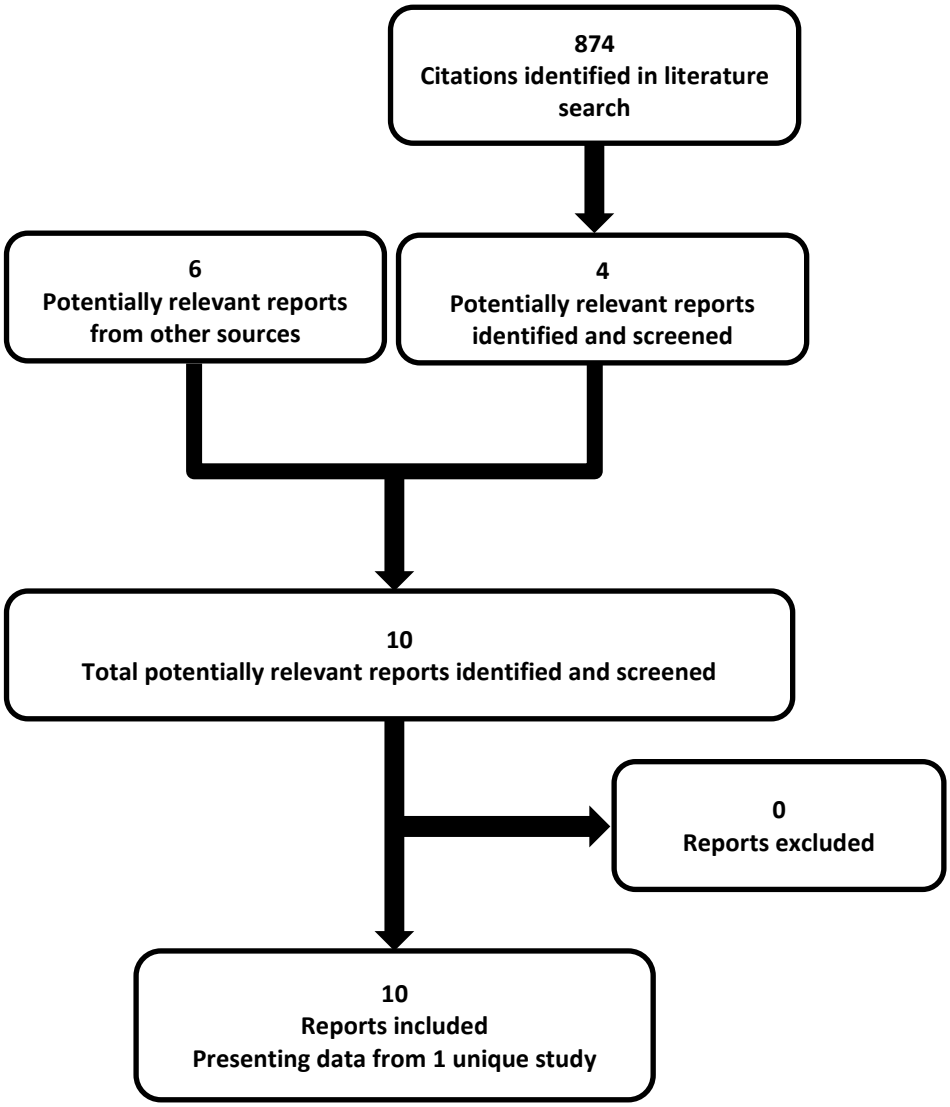


TABLE 3: DETAILS OF INCLUDED STUDY

		Hokusai–VTE
DESIGN & POPULATION	**Study Design**	Double-blind, double-dummy, NI RCT
	Locations	Conducted in 37 countries including, Canada, US, and Western Europe
	Randomized (N)	8,292
	Inclusion Criteria	Patients ≥ 18 years of age with acute symptomatic proximal DVT and/or symptomatic PE confirmed at the site by appropriate diagnostic imaging
	Exclusion Criteria	• Indication for warfarin other than DVT and/or PE • More than 48 hours' pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, UFH, and fondaparinux per local labelling) or more than a single dose of a VKA prior to randomization to treat the current episode • CrCl of less than 30 mL per minute • Significant liver disease • Patients with active cancer for whom long-term treatment with (LMW) heparin was anticipated • Active bleeding or high risk for bleeding contraindicating treatment with (LMW) heparin or warfarin • Life expectancy < 3 months • Uncontrolled hypertension as judged by the investigator
DRUGS	**Intervention**	Initial therapy heparin plus placebo warfarin for at least 5 days until the sham INR was ≥ 2.0 on two separate measurements at least 1 calendar day apart or a single supratherapeutic sham INR ≥ 3.0 had been achieved; then heparin was to be stopped, and patients started edoxaban 60 mg q.d. (reduced to 30 mg in patients with low body weight [≤ 60 kg] or moderate renal impairment [CrCl ≥ 30 mL/min and ≤ 50 mL/min], once daily, orally) and continued placebo warfarin (adjusted to maintain INR between 2.0 and 3.0) for 3, 6, and 12 months as determined by the investigator.
	Comparator(s)	Initial therapy with heparin plus warfarin for at least 5 days until the INR was ≥ 2.0 on two separate measurements at least 1 calendar day apart or a single supratherapeutic INR ≥ 3.0 had been achieved; then heparin was to be stopped, and patients started placebo edoxaban (60 mg q.d.) and continued warfarin (adjusted to maintain INR between 2.0 and 3.0) for 3, 6, and 12 months as determined by the investigator.
DURATION	**Phase**	
	Double-blind	3, 6, and 12 months
	Follow-up	12 months after randomization (i.e., patients who received 3 months of treatment had 9 months of follow-up; patients who received 6 months of treatment had 6 months of follow-up; and patients who received 12 months of treatment had no follow-up)
OUTCOMES	**Primary End Point**	Adjudicated symptomatic recurrent VTE (i.e., the composite of DVT, non-fatal PE, and fatal PE)
	Other End Points	The composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study period. Net clinical outcome, defined as the composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, major bleeding, and all-cause mortality Adjudicated clinically relevant bleeding (i.e., major or CRNM bleeding) occurring during treatment or within 3 days of interrupting or stopping the study drug

NOTES	**Publication**	The Hokusai–VTE Investigators, 2013[16]

CrCl = creatinine clearance; CRNM = clinically relevant non-major; DVT=deep vein thrombosis; INR = international normalized ratio; LMW = low-molecular-weight; LMWH = low-molecular-weight heparin; NI = noninferior; PE = pulmonary embolism; q.d. = once daily; RCT = randomized controlled trial; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.
Note: Five additional reports were included.[9,17-20]
Source: The Hokusai–VTE Investigators;[16] Verhamme et al.;[21] Raskob et al.;[22] Raskob et al.;[23] Clinical Study Reports: Hokusai–VTE study.[1]

3.2 Included Study

3.2.1 Description of Study

One published, manufacturer-sponsored, double-blind (DB) RCT was included in the systematic review.

Hokusai–VTE (n = 8,292) was a phase III, multinational, multi-centre, randomized, DB, matching placebo, parallel-group noninferiority (NI) study that evaluated the benefits and risks of edoxaban in reducing the risk of recurrent VTE in patients with documented acute symptomatic DVT and/or PE during the 12-month study period. Eligible patients were stratified by presenting diagnosis: PE with or without DVT versus DVT only; baseline risk factors (temporary risk factors only [such as trauma, surgery, immobilization, estrogen therapy, etc.] versus all others); and need for edoxaban dose reduction to 30 mg (yes or no). After stratification and confirmation of eligibility, patients were assigned randomly through an interactive voice/Web response system (IXRS) in a 1:1 ratio to one of two treatment groups: edoxaban or warfarin.

All patients received initial therapy with open-label unfractionated heparin (UFH) or enoxaparin plus placebo warfarin (in the edoxaban treatment group) or warfarin (in the warfarin treatment group) for at least five days. Edoxaban or warfarin was administered in a DB, double-dummy fashion. Edoxaban was started after discontinuing initial heparin in the edoxaban treatment group. Edoxaban was administered at a dose of 60 mg orally once daily, or at a dose of 30 mg once daily in patients with a CrCl between 30 mL per minute and 50 mL per minute, a body weight of 60 kg or less, or who were receiving concomitant treatment with potent P-glycoprotein (P-gp) inhibitors verapamil or quinidine. After discontinuing initial heparin in the warfarin treatment group, patients started placebo edoxaban (60 mg once daily) and continued warfarin (adjusted to maintain an INR between 2.0 and 3.0).

Hokusai–VTE was an event-driven study. The study continued until approximately 220 overall primary efficacy end point events (i.e., recurrent VTE) were projected to be achieved for the modified intention-to-treat (mITT) analysis set across both treatment groups. All patients were to receive a minimum of three months of treatment; the maximum possible treatment duration for any individual patient after randomization was 12 months.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Hokusai–VTE enrolled male and female adult patients with acute symptomatic DVT and/or PE documented by objective methods. Patients were excluded from the trial if they had active cancer (in which long-term treatment with LMWH treatment instead of VKA was anticipated), significant liver disease, severe renal impairment, or pregnancy, or if they were at high risk for bleeding or active bleeding, contraindicating treatment with heparin, warfarin, or potent P-gp inhibitors. Patients were also excluded if treatment of the current episode of DVT and/or PE required either thrombectomy,

insertion of a caval filter, or use of a fibrinolytic drug. They were also excluded if they had been treated within 30 days prior to randomization with any investigational drug, or had received more than a single dose of a VKA prior to randomization to treat the current episode, or had received more than 48 hours' pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, unfractionated heparin [UFH], or fondaparinux).

b) Baseline Characteristics

Details regarding the baseline characteristics of patients included in the Hokusai–VTE study are provided in Table 4. Baseline characteristics of patients included in the study were generally similar between the edoxaban and warfarin arms. Overall, the mean age of patients was 56 years ([redacted]) and the majority of patients were male (57%).

Approximately 59% of patients presented with a diagnosis of DVT only; 41% of patients presented with a diagnosis of PE (with or without DVT). The proportion of patients identified as having more severe PE within the edoxaban and warfarin treatment arms was 30.6% and 32.2% respectively, based on assessments of N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥ 500 pg/mL, and 34.5% and 35.5% respectively, based on assessments of right ventricular (RV) dysfunction present at baseline. Risk factors for VTE were temporary in approximately 28% of patients. Approximately half of the patients in both treatment arms had underlying risk factors at the time of entry. Risks factors such as trauma, recent surgery, prolonged sitting for more than four hours, embolization, or use of estrogen drug were similar between the two arms. The edoxaban dose was adjusted to 30 mg at randomization for 17.6% of patients. Approximately 5% of the patients in each treatment arm were to receive treatment for three months; 38% in each treatment arm were to receive the treatment for six months; and 57% were to receive the treatment for up to 12 months.

VKA and heparin use prior to randomization was similar between the edoxaban and warfarin treatment groups (Table 5).

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS

Characteristics	Hokusai–VTE					
	All Patients		Patients With Deep Vein Thrombosis Only		Patients With Pulmonary Embolism (With or Without DVT)	
	Edoxaban (N = 4,118)	Warfarin (N = 4,122)	Edoxaban (N = 2,468)	Warfarin (N = 2,453)	Edoxaban (N = 1,650)	Warfarin (N = 1,669)
Age (Years)						
Mean (SD)	55.7 (16.28)	55.9 (16.17)	54.7 (16.01)	54.9 (15.86)	57.1 (16.57)	57.4 (16.52)
Range, years	18 to 106	18 to 95	[redacted]	[redacted]	[redacted]	[redacted]
< 65 years, n (%)	2,784 (67.6)	2,752 (66.8)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65 years, n (%)	1,334 (32.4)	1,370 (33.2)	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	Hokusai–VTE					
	All Patients		Patients With Deep Vein Thrombosis Only		Patients With Pulmonary Embolism (With or Without DVT)	
	Edoxaban (N = 4,118)	Warfarin (N = 4,122)	Edoxaban (N = 2,468)	Warfarin (N = 2,453)	Edoxaban (N = 1,650)	Warfarin (N = 1,669)
Gender, n (%)						
Male	2,360 (57.3)	2,356 (57.2)	1,497 (60.7)	1,481 (60.4)	863 (52.3)	875 (52.4)
Female	1,758 (42.7)	1,766 (42.8)	971 (39.3)	972 (39.6)	787 (47.7)	794 (47.6)
Race, n (%)						
Caucasian	2,867 (69.6)	2,895 (70.2)	1,695 (68.7)	1,727 (70.4)	1,172 (71.0)	1,168 (70.0)
Black	156 (3.8)	144 (3.5)	99 (4.0)	84 (3.4)	57 (3.5)	60 (3.6)
Asian	866 (21.0)	861 (20.9)	561 (22.7)	544 (22.2)	305 (18.5)	317 (19.0)
Other	220 (5.3)	211 (5.1)	109 (4.4)	97 (4.0)	111 (6.7)	118 (7.1)
Weight at Randomization (kg), n (%)						
≤ 60	524 (12.7)	519 (12.6)	320 (13.0)	304 (12.4)	204 (12.4)	215 (12.9)
> 60	3,594 (87.3)	3,603 (87.4)	2,148 (87.0)	2,149 (87.6)	1,446 (87.6)	1,454 (87.1)
Creatinine Clearance at Randomization (mL/min), n (%)						
≥ 30 to ≤ 50	268 (6.5)	273 (6.6)	152 (6.2)	153 (6.2)	116 (7.0)	120 (7.2)
> 50	3,850 (93.5)	3,849 (93.4)	2,316 (93.8)	2,300 (93.8)	1,534 (93.0)	1,549 (92.8)
Presenting Diagnosis, n (%)						
PE	1,671 (40.6)	1,679 (40.7)	67 (2.7)	60 (2.4)	1,604 (97.2)	1,619 (97.0)
With DVT	611 (14.8)	560 (13.6)	[redacted]	[redacted]	[redacted]	[redacted]
Without DVT	1,060 (25.7)	1,119 (27.1)	[redacted]	[redacted]	[redacted]	[redacted]
DVT only	2,447 (59.4)	2,443 (59.3)	2,401 (97.3)	2,393 (97.6)	46 (2.8)	50 (3.0)
Intended Treatment Duration, n (%)						
3 months	221 (5.4)	245 (5.9)	NR	NR	NR	NR
6 months	1,555 (37.8)	1,502 (36.4)	NR	NR	NR	NR
12 months	2,339 (56.8)	2,371 (57.5)	NR	NR	NR	NR
Edoxaban 30 mg Dose at Randomization, n (%)						
Yes	733 (17.8)	719 (17.4)	425 (17.2)	411 (16.8)	308 (18.7)	308 (18.5)
No	3,385 (82.2)	3,403 (82.6)	2,043 (82.8)	2,042 (83.2)	1,342 (81.3)	1,361 (81.5)

Characteristics	Hokusai–VTE					
	All Patients		Patients With Deep Vein Thrombosis Only		Patients With Pulmonary Embolism (With or Without DVT)	
	Edoxaban (N = 4,118)	Warfarin (N = 4,122)	Edoxaban (N = 2,468)	Warfarin (N = 2,453)	Edoxaban (N = 1,650)	Warfarin (N = 1,669)
Cancer, n (%)						
Yes	378 (9.2)	393 (9.5)	NR	NR	NR	NR
Cancer active at baseline						
Yes	[redacted]	[redacted]	NR	NR	NR	NR
No	[redacted]	[redacted]	NR	NR	NR	NR
No	3,736 (90.8)	3,726 (90.5)	NR	NR	NR	NR
PE Severity at Baseline						
NT-ProBNP at baseline, N	NR	NR	NA	NA	1,484	1,505
< 500 pg/mL, n (%)	NR	NR	NA	NA	1,030 (62.4)	1,021 (61.2)
≥ 500 pg/mL, n (%)	NR	NR	NA	NA	454 (27.5)	484 (29.0)
RV dysfunction at baseline, N	NR	NR	NA	NA	498	504
No, n (%)	NR	NR	NA	NA	326 (65.5)	325 (64.5)
Yes, n (%)	NR	NR	NA	NA	172 (34.5)	179 (35.5)
Risk Factors, n (%)						
Temporary	1,132 (27.5)	1,140 (27.7)	655 (26.5)	655 (26.7)	477 (28.9)	485 (29.1)
Other	2,986 (72.5)	2,982 (72.3)	1,813 (73.5)	1,798 (73.3)	1,173 (71.1)	1,184 (70.9)
Risk Factors for VTE, n (%)						
No risk factors reported	1,963 (47.7)	1,983 (48.1)	[redacted]	[redacted]	[redacted]	[redacted]
Recent surgery, trauma, or immobilization	760 (18.5)	769 (18.7)	[redacted]	[redacted]	[redacted]	[redacted]
Use of estrogen-containing drugs	272 (6.6)	300 (7.3)	[redacted]	[redacted]	[redacted]	[redacted]
Puerperium	9 (0.2)	14 (0.3)	[redacted]	[redacted]	[redacted]	[redacted]
Active cancer	106 (2.6)	95 (2.3)	[redacted]	[redacted]	[redacted]	[redacted]
Previous episodes of PE/DVT	784 (19.0)	736 (17.9)	[redacted]	[redacted]	[redacted]	[redacted]
Prolonged sitting for more than 4 hours	288 (7.0)	284 (6.9)	[redacted]	[redacted]	[redacted]	[redacted]
Known thrombophilic condition	168 (4.1)	176 (4.3)	[redacted]	[redacted]	[redacted]	[redacted]
Other risk factors	199 (4.8)	171 (4.1)	[redacted]	[redacted]	[redacted]	[redacted]

DVT = deep vein thrombosis; NA = not applicable; NR = not reported; NT-proBNP = N-terminal pro-brain natriuretic peptide; PE = pulmonary embolism; RV = right ventricular; SD = standard deviation; VTE = venous thromboembolism.

[a] Not assessable in 188 (11.4%) of edoxaban index PE patients and 171 (10.3%) of index PE warfarin patients.

Source: The Hokusai–VTE Investigators;[16] Clinical Study Reports: Hokusai–VTE study.[1]

TABLE 5: EXPOSURE TO ANTICOAGULANT THERAPY PRIOR TO RANDOMIZATION

	Hokusai–VTE	
	Edoxaban (N = 4,118)	Warfarin (N = 4,122)
Warfarin Use Within 2 Days Prior to Randomization, n (%)		
No doses taken	3,794 (92.1)	3,745 (90.9)
1 dose taken	279 (6.8)	319 (7.7)
> 1 dose taken	45 (1.1)	58 (1.4)
(LMW) Heparin Use Within 2 Days Prior to Randomization, n (%)		
None	755 (18.3)	756 (18.3)
≤ 2 days' duration	3,260 (79.2)	3,262 (79.1)
> 2 days' duration	103 (2.5)	104 (2.5)

LMW = low-molecular-weight; N = number of patients in analysis set; n = number of patients meeting event criteria.
Source: Clinical Study Reports: Hokusai–VTE study.[1]

3.2.3 Interventions

A sham INR was used to maintain blinding in the edoxaban arm to ensure patients and clinicians were not unblinded throughout the trial. Patients in the edoxaban treatment group received initial heparin plus matching placebo warfarin for at least five days, until the sham INR was ≥ 2.0 on two separate measurements at least one calendar day apart, or until a single supratherapeutic sham INR measurement ≥ 3.0 was achieved. Then heparin was to be stopped, and the patient started edoxaban (60 mg once daily) and continued matching placebo warfarin (adjusted to maintain sham INR between 2.0 and 3.0). Patients whose body weight was ≤ 60 kg, whose CrCl was between 30 mL/min and 50 mL/min, or who had concomitant use of P-gp inhibitors verapamil or quinidine, had their edoxaban or edoxaban placebo dose adjusted to 30 mg once daily.

Patients in the warfarin treatment group received initial heparin plus warfarin for at least five days until the INR was ≥ 2.0 on two separate measurements at least one calendar day apart or after a single supratherapeutic INR measurement ≥ 3.0 was achieved (with the reasonable assumption that a therapeutic INR, i.e., ≥ 2.0, had been achieved for at least 24 hours). Once INR requirements were met, the heparin was to be stopped, and the patient received matching placebo edoxaban (60 mg once daily or adjusted to 30 mg once daily) and continued on warfarin (adjusted to maintain INR between 2.0 and 3.0).

Hokusai–VTE was an event-driven study. The study continued until approximately 220 overall primary efficacy end point events (i.e., recurrent VTE) were recorded for the mITT analysis set across both treatment groups. Throughout the study, the number of events was closely monitored. Further randomization to treatment was stopped when the required number of events was projected to be reached (end of randomization date [EOR]). Based on the EOR date, a global end-of-treatment (EOT) date was established that ensured a minimum of six months of treatment for the last patient(s) randomized to the study. All patients permanently discontinued study treatment on or before the EOT date.

All patients received a minimum of three months of treatment; the maximum treatment period for any individual patient after randomization was 12 months. The intended treatment durations of three, six, and 12 months were determined by the investigator based on the American College of Chest Physicians 2008 Clinical Practice Guidelines for the treatment of VTE.[24]

Restricting the dose of Aspirin to ≤ 100 mg daily was strongly encouraged, although higher doses were permitted for a strong clinical indication. The following drugs and devices were prohibited throughout the treatment period unless no alternative therapy was clinically suitable: oral anticoagulants other than the assigned study drugs; fibrinolytic drugs; dual antiplatelet therapy; chronic treatment with nonsteroidal antiiflammatory drugs (NSAIDs) including both COX-1 and COX-2 inhibitors other than Aspirin for four or more days per week; P-gp inhibitors ritonavir, nelfinavir, indinavir, saquinavir, cyclosporine, and dronedarone; certain macrolide antibiotics; and other investigational drugs or devices. Verapamil and quinidine were the only P-gp inhibitors allowed for concomitant use with the study drug at the time of randomization.

3.2.4 Outcomes

a) Efficacy

The primary efficacy end point was symptomatic recurrent VTE (i.e., the composite end point of DVT, non-fatal PE, and fatal PE during the 12-month study period). The events that were counted in this analysis were those that occurred from the date of randomization through the end of the 12-month study period, regardless of whether the patient was taking a study drug.

The secondary efficacy end point was defined as the composite clinical outcome of non-fatal symptomatic recurrent PE, symptomatic recurrent DVT, and all-cause mortality during the 12-month study period. The events that were counted in this analysis were those that occurred from the date of randomization through the end of the 12-month study period, regardless of whether the patient was taking the study drug.

Exploratory efficacy analyses were also conducted to assess the incidence and hazard ratio of net clinical outcome, defined as the composite of non-fatal symptomatic recurrent PE, symptomatic recurrent DVT, major bleeding, and all-cause mortality; and hazard ratio of net clinical benefit was defined as the composite of symptomatic recurrent DVT, symptomatic recurrent PE, and major bleeding.

Health-related quality of life (HRQoL) was assessed using the EuroQol 5-Dimensions questionnaire (EQ-5D); however, this outcome was not pre-specified in the study protocol and it is not clear which patients answered the questionnaire.

b) Safety

The primary safety outcome was clinically relevant bleeding (i.e., major bleeding or clinically relevant non-major [CRNM] bleeding) that occurred when a patient was receiving treatment or within three days of interrupting or stopping the study drug.

Major bleeding was defined as overt bleeding with one or more of the following:

- a fall in the hemoglobin level of 2 g/dL or more
- transfusion of two or more units of packed red blood cells or whole blood
- bleeding at a critical site, including intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal
- contributing to death.

Major bleeding events were also subclassified as life-threatening or non-life-threatening. A life-threatening major bleed was defined as a bleeding event that was either intracranial or associated with hemodynamic compromise requiring intervention.

CRNM was defined as overt bleeding not meeting the criteria for major bleeding but associated with (temporary) cessation of study treatment, medical intervention, unscheduled contact with a physician, or associated with any other discomfort, such as pain or impairment of daily life.

Hospitalization adverse events (AEs) were identified as any adverse event reported as requiring hospitalization or prolongation of hospitalization.

Other safety outcomes included AEs, serious adverse events (SAEs), all bleeding, clinical laboratory results, vital signs, physical examinations, deaths, and other cardiovascular events.

A clinical events committee (CEC) adjudicated and categorized the presenting index diagnosis, the protocol specified VTE end points, major adverse cardiovascular events, bleeding events, and death in a blinded manner.

3.2.5 Statistical Analysis

The study was designed to accumulate approximately 220 overall primary efficacy events in the mITT analysis set. Assuming equal efficacy, this design would have a power of 85% to demonstrate that edoxaban is noninferior to warfarin based on a relative NI margin for the hazard ratio of 1.5. The expected incidence of recurrent VTE was 3.0% during the 12-month study period. With these estimates, 7,500 patients were needed to be randomized to study treatment in order to accrue 220 overall primary efficacy events in the mITT analysis set. A total of 14 historical studies were identified by the manufacturer through a literature search to support estimation of the NI margin. The overall estimated difference between "more effective" treatment (UFH or LMWH followed by VKA for three to 12 months) compared with "less effective" treatments, such as placebo or no treatment, was calculated using the random-effects model on log odds ratio. The odds ratio calculated was 0.18 (95% confidence interval [CI], 0.14 to 0.25). The 0.25 upper limit of the 95% CI of the historical difference was considered, and the NI margin was calculated to be (1 ÷ 0.25)^(1 – 0.9) = 1.15 in order to retain at least 90% of available treatment benefit, and (1 ÷ 0.25)^(1 – 0.7) = 1.5 in order to retain at least 70% of available treatment benefit. A NI margin of 1.5 was chosen to retain at least 70% of available treatment benefit.

For the primary efficacy variable, the time to the first event was analyzed using the Cox proportional hazards model with model terms for treatment group and the following randomization stratification factors: presenting diagnosis (PE with or without DVT; DVT only) as recorded in the IXRS; baseline risk factors (temporary factors [e.g., trauma, surgery, immobilization, estrogen therapy, etc.]; all others); and need for dose reduction (yes or no). The NI analysis of the primary end point used the mITT analysis set for the overall study period (the time from randomization date or initial dose of study drug date to the last study follow-up visit). Sensitivity analyses included the per-protocol (PP) analysis set for the on-treatment period, treatment plus 30 days, and events occurring in the first 90 days. The on-treatment period was the period of time from when the patient was taking the study drug up to three days after their last dose for that time period. A patient may have had multiple periods of study-drug use if they temporarily interrupted and resumed the study drug during the study. The treatment-plus-30-days period was defined as the time period from randomization to up to 30 days after last dose of the study drug.

Exploratory subgroup analyses were performed for the primary efficacy end point using the overall study period approach for the mITT analysis set. Subgroup analyses included presenting diagnosis (PE with/without DVT, DVT only), age, risk factor, body weight, CrCl (30 mL/min to 50 mL/min versus > 50 mL/min), concomitant diseases (cancer: yes or no), and centre-level INR percentage time in therapeutic range (TTR) for warfarin patients.

The secondary efficacy analysis was based on the mITT analysis set and overall study period using the same model as that utilized for the primary efficacy analysis. Similar to the primary efficacy analysis, the events that were counted in this analysis were those that occurred from the date of randomization through the end of the 12-month study period (day 365) or to the day of global EOT, regardless of whether the patient was taking a study drug.

The exploratory efficacy end points were analyzed using the same approach as that used for the primary efficacy analysis.

Post-hoc analyses were conducted to provide a risk-benefit analysis of extended treatment with edoxaban compared with warfarin in patients who received therapy for more than three months, where outcomes among patients treated for different durations were compared.

Efficacy testing for NI and superiority utilized the followed test plan to control for study-wise type I error (all tests were two-sided):

- Step 1: Test the primary efficacy end point for NI (based on the mITT set at alpha = 0.05). If the upper limit of the two-sided 95% CI of the hazard ratio was below 1.5, then NI of edoxaban compared with warfarin was achieved.
- Step 2: NI of edoxaban compared with warfarin for the primary efficacy end point was achieved in step 1, the secondary efficacy end point was tested for superiority (based on the mITT set at alpha = 0.01).

Sensitivity analyses, subgroup analysis, exploratory analyses, and HRQoL were not adjusted for multiplicity.

Results from the EQ-5D were provided by the manufacturer; however, there were no details regarding which patients answered the questionnaire or what type of analyses were undertaken, and the results were not compared between treatment groups.

The time from date of initial study dose to the primary safety end point (first major or CRNM bleeding) was compared between treatment groups for superiority (alpha = 0.05 two-sided) for patients in the safety analysis set using a Cox's proportional hazard model with the same terms and covariates as in the primary efficacy analysis. However, for this analysis, patients were censored three days after the day of permanent study medication discontinuation.

In all analyses, including the primary analyses, patients who were lost to follow-up prior to the month-12 assessment were censored at their last assessment if they did not experience any primary end point events prior to being lost to follow-up. For patients who did not experience an event, the time to first event was censored at treatment day 365, or the last day on which the patient had a complete assessment (in-person visit or by telephone) for study outcomes, or the day of global EOT, whichever came first. In a sensitivity analysis, expected event data were inputted for missing data according to the expected number of events based on the missing duration of follow-up and the observed event rate in the trials. This resulted in two additional expected events being added to the edoxaban group and one to the warfarin group.

a) Analysis Populations

The mITT analysis set included all randomized patients who received at least one dose of study drug. Analyses were based on the randomized treatment even if a patient inadvertently received the incorrect study drug.

The PP analysis set included all randomized patients who received at least one dose of the study drug, who did not have treatment misallocation, and for whom the index DVT or PE event at baseline was confirmed by the CEC. Treatment misallocation was defined as a patient taking incorrect treatment during the entire study period.

The safety analysis set included all randomized patients who received at least one dose of the study drug. Analyses were based on the randomized treatment unless a patient inadvertently received the wrong medication during the entire study, in which case the patient was grouped according to the treatment received.

3.3 Patient Disposition

A total of 8,292 patients were randomized and assigned to the edoxaban (N = 4,143) or warfarin (N = 4,149) treatment groups. There was no screening period. The number of patients who did not complete the study was generally similar between treatment groups, where a total of 181 (4.4%) treated patients in the edoxaban arm and 167 (4.1%) treated patients in the warfarin arm did not complete study treatment. The most common reason for not completing study treatment was death in both treatment arms (3.3% in the edoxaban arm and 3.1% in the warfarin arm, respectively). Further details are provided in Table 6.

TABLE 6: PATIENT DISPOSITION

	Hokusai–VTE	
	Edoxaban	Warfarin
Randomized, N	4,143	4,149
Treated (mITT), N (%)	4,118 (99.4)	4,122 (99.3)
Completed Study, N (%)	3,937 (95.6)	3,955 (95.9)
Full 12-month follow-up	3,058 (74.3)	3,074 (74.6)
< 12-month follow-up due to study truncation[a]	879 (21.3)	881 (21.4)
Did not complete study follow-up	181 (4.4)	167 (4.1)
Death	136 (3.3)	127 (3.1)
Withdrew consent	32 (0.8)	33 (0.8)
Lost to follow-up	7 (0.2)	4 (<0.1)
Sponsor decision	0 (0.0)	0 (0.0)
Other	6 (0.1)	3 (<0.1)
mITT Analysis Set, N (%)	4,118 (99.4)	4,122 (99.3)
PP, N (%)	4,057 (97.9)	4,078 (98.3)
Safety Analysis Set, N (%)	4,118 (99.4)	4,122 (99.3)

mITT = modified intention-to-treat; PP = per-protocol.

[a] Patients were considered to have completed the study when they had a 12-month follow-up or a < 12-month follow-up due to truncation of the study. Patients completing less than 12 months of follow-up due to study truncation based on global study milestone dates were announced in a protocol amendment.

Source: Clinical Study Reports: Hokusai–VTE study.[1]

3.4 Exposure to Study Treatments

In the edoxaban and warfarin treatment groups, the median treatment duration was similar at 267 (range: one to 407) and 266 (range: one to 422) days, respectively. The median study drug exposure was also similar for patients in the edoxaban and warfarin treatment groups, at 265 and 261 days, respectively. In the edoxaban and warfarin treatment groups, 11.8% and 12.8% of patients received ≤ three months of treatment; 26.1% and 26.3% of patients received > three months to six months of treatment; 62.1% and 60.9% received more than six months of treatment; and 40.3% and 40.2% of patients, respectively, received a full 12 months of treatment. Further details are presented in Table 7.

TABLE 7: TREATMENT DURATION AND STUDY DRUG EXPOSURE

	Hokusai–VTE	
	Edoxaban N = 4,118	Warfarin N = 4,122
Duration of Actual Treatment (Days)[a,b]		
Mean (SD) duration (days ± SD)	251.9 (112.04)	250.3 (113.01)
Median duration (days) (range)	267.0 (1 to 407)	266 (1 to 422)
≤3 months, n (%)[b,c]	485 (11.8)	528 (12.8)
>3 to ≤6 months, n (%)	1,076 (26.1)	1,084 (26.3)
>6 months, n (%)	2,557 (62.1)	2,510 (60.9)
≥12 months, n (%)	1,661 (40.3)	1,659 (40.2)
Total Number of Days Exposed to Study Drug[d]		
Mean (days ± SD)	250.3 (111.75)	248.4 (112.61)
Median (days) (range)	265.0 (1 to 407)	261.0 (1 to 422)

N = number of patients in analysis set; n = number of patients meeting event criteria; SD = standard deviation.
Note: The median number of days for study drug interruption is derived by subtracting the median days exposed (days) from the median treatment duration (days).
[a] Duration of actual treatment period = date of last dose minus date of first dose plus 1 day.
[b] ≤ 3 months was ≤ 95 days; > 3 to ≤ 6 months was > 95 to ≤ 185 days; > 6 months was > 185 days; and ≥ 12 months was ≥ 353 days.
[c] < 3 months (< 85 days) was 353 (8.6%) in the edoxaban group and 360 (8.7%) in the warfarin group.
[d] Study-drug exposure is the total number of days the patient takes study drug during the overall study period, with interruptions not included in the interval of time. Number of days exposed = date of last dose minus date of first dose plus 1 day minus periods of interruptions.
Source: Clinical Study Reports: Hokusai–VTE study.[1]

The mean standard deviation TTR in the warfarin treatment group was 63.5% ([redacted]); the median was 65.6% [redacted]. The overall mean percentage of reported INR measurements that were > 3.0 was 17.6%; > [redacted], < 2.0 was 18.9%, and [redacted] respectively (Table 8).

TABLE 8: PERCENTAGE OF TIME IN VARIOUS INR RANGES FOR PATIENTS RANDOMIZED TO WARFARIN

Overall (N = 3,984)	Time in INR Range in Hokusai–VTE Trial[a]							
	< 1.5	< 2.0	2.0 to 3.0 (TTR)	> 3.0	> 4.0	≥ 5.0	≥ 8.0	1.8 to 3.2
Mean (SD)	[redacted]	18.9	63.5	17.6	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	65.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

INR = international normalized ratio; N = number of patients in analysis set; SD = standard deviation; TTR = time in therapeutic range.
Note: Only INRs taken on days where warfarin was received were included. INRs taken during the first seven days after an interruption of study drug or on days where warfarin was co-administered with heparin were excluded.
[a] Time in INR range is defined by the percentage of days in which patients have been within the specified range. TTR is calculated as the mean percentage in the range 2.0 to 3.0.
Source: Clinical Study Reports: Hokusai–VTE study.[1]

The mean and median initial heparin treatment duration in the warfarin treatment group was one day longer than in the edoxaban treatment group (Table 9).

TABLE 9: INITIAL HEPARIN TREATMENT DURATION

	Hokusai–VTE	
	Edoxaban N = 4,118	Warfarin N = 4,122
Initial Heparin Treatment Duration (Days)		
Mean (SD)	7.5 (2.85)	8.5 (3.99)
Median	7.0	8.0
Minimum	0	0
Maximum	54	64
Number of Days, n (%)		
0 to 5 days	870 (21.1)	583 (14.1)
6 days	922 (22.4)	717 (17.4)
7 days	726 (17.6)	749 (18.2)
8 days	532 (12.9)	638 (15.5)
9 days	353 (8.6)	373 (9.0)
≥ 10 days	715 (17.4)	1,062 (25.8)

N = number of patients in analysis set; n = number of patients meeting event criteria; SD = standard deviation.
Source: Clinical Study Reports: Hokusai–VTE study.[1]

In the edoxaban and warfarin treatment groups, a similar percentage of patients had 30 mg edoxaban (or edoxaban placebo) assignment at randomization (17.8% and 17.4%, respectively). Overall, the reasons for 30 mg edoxaban/edoxaban placebo at randomization were similar between the two treatment groups. The most frequent reason for 30 mg edoxaban or edoxaban placebo assignment at randomization was a body weight of 60 kg or less (10.7% for edoxaban and 10.3% for warfarin, respectively). The percentage of patients who had a 30 mg assignment at randomization due solely to having a CrCl of 30 mL/min to 50 mL/min was 4.5% for the edoxaban group and 4.3% for the warfarin group. The percentage of patients in the edoxaban and warfarin treatment groups who had a 30 mg dose allocation because of concomitant therapy with verapamil or quinidine was < 1% for both groups. A total of 123 (1.8%) patients in the edoxaban and warfarin treatment groups had their edoxaban or

edoxaban placebo dose adjusted from 60 mg to 30 mg after randomization (68 patients in the edoxaban treatment group and 55 patients in the edoxaban placebo [active warfarin] treatment group), mainly due to impaired renal function (Table 10).

TABLE 10: EDOXABAN DOSE SUMMARY, SAFETY ANALYSIS SET

	Hokusai–VTE	
	Edoxaban N = 4,118	Warfarin N = 4,122
Number of Patients With 60 Mg Dose at Randomization	3,385 (82.2)	3,403 (82.6)
Number of Patients With 30 mg Dose at Randomization	733 (17.8)	719 (17.4)
Reasons for 30 mg Dose:		
Weight only (≤ 60 kg)	442 (10.7)	425 (10.3)
CrCl only (≤ 50 mL/min and ≥ 30 mL/min)	184 (4.5)	179 (4.3)
Quinidine and/or verapamil use only	22 (0.5)	18 (0.4)
CrCl and quinidine/verapamil use	3 (< 0.1)	3 (< 0.1)
Weight and CrCl	81 (2.0)	90 (2.2)
Weight and quinidine verapamil use	1 (< 0 1)	3 (< 0.1)
Weight, CrCl and quinidine/verapamil use	0 (0.0)	1 (< 0.1)
Number of Patients With 30 mg Dose After Randomization	68 (2.0)	55 (1.6)

CrCl = creatinine clearance; N = number of patients in analysis set.
Source: Clinical Study Reports: Hokusai–VTE study.[1]

Table 11 details the use of selected concomitant medications during the study in the mITT analysis set on-treatment study period. The use of concomitant medications, including NSAIDs and antiplatelet drugs (including Aspirin), was generally similar between the treatment groups. The most frequently reported medications among the selected concomitant medications (other than heparin) were NSAIDs (excluding Aspirin), lipid lowering drugs (statins, others), and renin angiotensin aldosterone system inhibitors.

TABLE 11: CONCOMITANT MEDICATIONS OF INTEREST TAKEN AFTER THE INITIATION OF STUDY DRUG, ON-TREATMENT STUDY PERIOD

[redacted]	Hokusai–VTE	
[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]	Hokusai–VTE	
[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]

N = number of patients in analysis set; n = number of patients meeting event criteria; RAAS = Renin Angiotensin Aldosterone System.
[a] Non-study drug heparin use post-randomization (e.g., during study drug interruptions).
[b] Includes captopril, carvedilol, diltiazem, felodipine, ticagrelor, ranolazine, itraconazole, ketoconazole, and quercetin.
Source: Clinical Study Reports: Hokusai–VTE study.[1]

3.5 Critical Appraisal

3.5.1 Internal Validity

Hokusai–VTE was a DB NI trial that was generally well conducted. The comparator was an adequate treatment regimen consisting of heparin plus warfarin as initial treatment and then warfarin alone. The quality of INR control was adequately reported through TTR. Patients treated with warfarin spent on average 63.5% 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 arm, which may bias the results in favour of edoxaban.

The Hokusai–VTE trial used appropriate allocation strategies. Randomization was performed centrally through an IXRS. The trials used a double-dummy design with matching placebos and sham INR results for patients receiving edoxaban. Using a sham INR was appropriate for patients in the edoxaban group as it helped protect against the unblinding of clinicians and patients. Blinding appeared to be maintained throughout the follow-up period, given the similar follow-up time and patient disposition between groups. There may have been potential for unblinding if the sham INR had not changed, as expected by the clinicians; however, the end points were objective. Thus, it is unlikely that potential unblinding would have had a substantial impact on the results.

Baseline patient characteristics were similar between treatment groups. Patient discontinuation rates throughout the study and reasons for discontinuation were also similar between treatment groups.

The choice of outcome measures and definitions for efficacy and safety outcomes in the trial were appropriate, according to the clinical expert consulted for this review. The outcomes were also consistent with the outcomes that are used in assessing other DOACs. VTE recurrence and major

bleeding events are widely accepted outcome measures used to assess response to anticoagulant treatment. Events were evaluated by a central, blinded, independent adjudication committee.

For the Hokusai–VTE trial, 14 studies were identified by the manufacturer through a literature search to support estimation of the pre-specified NI margin (hazard ratio = 1.5). The manufacturer intended to maintain at least 70% of the proven efficacy of warfarin versus placebo or no treatment response. The FDA recommends a larger percentage (85% to 90%) retention of warfarin effect.[19] On the other hand, the NI margin of 1.5 was conservative when compared with recent studies of novel oral anticoagulants for the treatment of VTE, which used margins of 1.80 to 2.75.[20,25]

Analyses of NI trials using both the intention-to-treat (ITT) and PP populations are recommended, and the trial considered positive if both ITT and PP analyses support NI.[26] However, the NI analysis of the primary end point used the mITT analysis set for the overall study period; the sensitivity analyses included the PP analysis set for the on-treatment period, treatment plus 30 days, and events occurring in the first 90 days; and the PP analysis that was undertaken for the overall study period was exploratory. Thus, the outcomes were not assessed with the same rigour as is recommended for NI trials.

A large majority of events occurred after treatment had already been stopped in both groups. Thus, although the trial achieved its overall event rate, a large proportion of events occurred after treatment was stopped. The results of the PP analysis for the on-treatment period still support NI; however, the low number of events while on treatment limit the study's power to find any differences between treatment groups, thus favouring a conclusion of NI. In addition, only patients for whom the CEC could not confirm the index DVT or PE event at baseline were excluded from the PP analysis set, indicating that patients with major protocol deviations were not excluded from the PP analysis. Given that major protocol deviations were reported in 23% of patients, with 1,291 patients (15.7%) reporting the use of disallowed medications (NSAIDs), the interpretation of the primary efficacy or safety end points is affected. Results from the true PP analysis (which exclude all major protocol violations) were not reported in the manufacturer submission; however, the European Medicines Agency assessment report for edoxaban indicated that NI was demonstrated when the "true" PP analysis was conducted, which excluded all major protocol violations.[20]

To control type I error, the following test plan was followed in the efficacy analyses: step 1: Test the primary efficacy end point NI at alpha = 0.05; step 2: If NI was achieved in step 1, then the second efficacy end point was tested for superiority at alpha = 0.01. No other outcomes were included in the multiple comparisons or multiplicity adjustment. Hence, the hierarchical approach did not take into consideration all outcomes measured in the study, including the primary safety end point (first major or CRNM bleeding), sensitivity analyses for the primary end point, exploratory end points, and subgroup analyses for all outcomes. Given the large number of comparisons in the study, a statistically significant finding ($P < 0.05$) for the comparisons between the edoxaban treatment group and the warfarin treatment group may be attributable to an inflated type I error rate. In addition, subgroups and exploratory analyses were based on a small number of patients and not powered to find any differences; therefore, they would favour NI being declared; hence, results should be interpreted with caution.

Hokusai–VTE had sufficient power to demonstrate statistical significance for testing of the primary hypothesis. No imputation for missing data was planned for any analyses conducted, including the primary analysis. Missing data were imputed only for sensitivity analyses. The primary end point was to be assessed for the overall study period (12 months); however, approximately [redacted] were not followed for 12 months' duration (around 21% of patients were lost to follow-up due to study

truncation). The follow-up time was similar between treatment groups, as were the number of patients lost to follow-up between treatment groups, so it is unlikely that the losses to follow-up affected the results. However, patients were considered censored at time of loss-to-follow-up; consequently, it is uncertain how this could have affected the results. In addition, patients who were not followed for 12 months would also not have contributed to AEs; thus, AEs may be under-reported for both treatment arms. Although missing data were inputted into the sensitivity analyses, and results were robust, imputed data were based on hypothetical expected events; thus, the true impact of missing data on the results is uncertain.

A key exclusion criterion was treatment with more than a single dose of a VKA prior to randomization (to treat the current episode) or with therapeutic dosages of anticoagulant (LMWH, UFH, and fondaparinux) more than 48 hours pre-treatment. There were 1.1% and 1.4% of patients in the edoxaban treatment group and warfarin treatment group, respectively, who received more than one dose of warfarin within two days prior to randomization; 2.5% of patients in each treatment arm received LMWH for more than two days' duration within two days prior to randomization. It is uncertain why these patients were included in the study, given the stated exclusion criteria.

HRQoL was measured in a small subset of patients; therefore, it may not reflect the study's population as a whole (i.e., it may be biased because of the large amount of missing data). Further, no comparison between groups was provided.

3.5.2 External Validity

Inclusion and exclusion criteria appeared to generally reflect what would be seen in clinical practice. However, various groups of patients with comorbid conditions were excluded, including patients with active bleeding or at high risk for bleeding contraindicating treatment with heparin or warfarin, liver disease, and uncontrolled hypertension. Relatively few patients (208, 2.5%) had active cancer at the time of randomization. The definition of active cancer was not defined in the trial; however, the clinical expert consulted by CADTH indicated that active cancer would likely be defined as patients within one year of undergoing treatment for cancer. Due to the limited number of patients with active cancer, the generalizability of the results from Hokusai–VTE is limited for patients with active cancer. In addition, patients with active cancer for whom long-term treatment with LMWH was anticipated were excluded from the trial. All other baseline characteristics seem representative of patients likely to be seen in clinical practice, according to the clinical expert consulted by CADTH for this review.

The length of treatment duration was left to the discretion of the investigator. It was possible for the investigators to alter the dose (i.e., reduce to 30 mg if appropriate) during the conduct of the trial or to extend treatment until the trial ended (12 months). Although this approach may resemble what is likely to occur in clinical practice, the efficacy and safety results for a randomized set of patients who received edoxaban versus placebo in the setting of extended treatment of VTE were not available. However, the design and analysis (mITT overall versus on-treatment) of the study allowed for an assessment of extended therapy without the need for a formal extension study. Additionally, this "extension" study within Hokusai was performed with an active comparator — warfarin rather than placebo — allowing a sounder comparison regarding the real-world risk-benefit analysis of continued therapy for up to 12 months. Given that 26% of patients did not have a full 12 months of follow-up, the efficacy and safety of longer-term use of edoxaban is less certain. Additionally, the results according to length of treatment received were based on a post-hoc analysis, which was unplanned and performed after the data were collected; results from such analyses should be interpreted with caution.

Patients treated with warfarin spent, on average, 63.5% of the time within the target INR values of 2.0 to 3.0. As stated previously, non-optimal INR results affect the treatment efficacy and safety in the comparator arm, which may bias the results in favour of edoxaban. However, this also improves generalizability, since INR values are expected to vary naturally; the percentage of time patients spent within the target INR values (65.3%) appears generally reflective of clinical practice, and is consistent with a published meta-analysis of studies of VKAs in the treatment of DVT.[27]

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in Section 2.2, Table 2. See Appendix 4 for detailed efficacy data. No data were reported for the outcomes of chronic thromboembolic pulmonary hypertension or post-thrombotic syndrome.

3.6.1 Adjudicated Symptomatic Recurrent VTE

The primary efficacy analysis was based on 276 events of symptomatic recurrent VTE (i.e., the composite end point of DVT, non-fatal PE, and fatal PE). The primary efficacy analysis results are summarized in Table 12. Symptomatic recurrent VTE occurred in a total of 130 patients (3.2%) in the edoxaban group, compared with 146 (3.5%) patients in the warfarin group, during the overall study period. The estimated hazard ratio for the time to the first occurrence of adjudicated symptomatic recurrent VTE for the edoxaban group versus the warfarin group was 0.89 (95% CI, 0.703 to 1.128). The upper bound of the 95% CI was 1.128, which is below the pre-specified NI margin of 1.5; therefore, NI was demonstrated for the primary efficacy end point for patients treated with edoxaban compared with warfarin. It is worth noting that the upper 95% confidence limit of the hazard ratio was 1.128, indicating that edoxaban retained at least 91% of the treatment effect of warfarin. The *P* value for testing superiority for the primary efficacy end point was 0.34, indicating that treatment with edoxaban was not superior to treatment with warfarin for reducing the number of symptomatic recurrent VTE cases.

The percentage of patients in the edoxaban group and warfarin group who experienced recurrent PE (with or without DVT) was 1.8% versus 2.0%, respectively. Only 1.4% of patients in the edoxaban group and 1.5% of patients in the warfarin group experienced DVT. The number of patients with fatal PE was similar between the two arms (24 events in each arm) (Table 12).

The sensitivity efficacy analyses for NI for the time to the first occurrence of adjudicated symptomatic recurrent VTE was performed using the PP analysis set, the on-treatment and treatment-plus-30-days study periods, and the mITT analysis set, using treatment-plus-30-days study periods. The sensitivity analysis results were consistent with those from the primary analysis (i.e., edoxaban was noninferior to, but not superior to, warfarin) (Table 12). However, these sensitivity analyses were not included in the hierarchical statistical analysis approach and should be considered exploratory in nature because of the potential for inflated type I error.

An exploratory analysis was also undertaken for NI for the time to the first occurrence of adjudicated symptomatic recurrent VTE on the PP analysis set using the overall study period. This analysis was also consistent with that from the primary analysis (Table 12). Since this analysis was exploratory in nature, the results reported should be interpreted with caution.

TABLE 12: ADJUDICATED SYMPTOMATIC RECURRENT VENOUS THROMBOEMBOLISM

	Hokusai–VTE	
	Edoxaban N = 4,118	Warfarin N = 4,122
Primary Analysis: All Patients With Recurrent VTE (mITT Analysis Set), Overall Study Period, n (%)[a]	130 (3.2)	146 (3.5)
HR edoxaban vs. warfarin (95% CI)[b]	0.89 (0.703 to 1.128)	
Type of First Recurrent VTE. N (%)		
PE with/without DVT	73 (1.8)	83 (2.0)
PE-related deaths	24 (0.6)	24 (0.6)
Fatal PE	4 (< 0.1)	3 (< 0.1)
Unexplained death (and VTE cannot be ruled out)	20 (0.5)	21 (0.5)
Non-fatal PE	49 (1.2)	59 (1.4)
With DVT	2 (< 0.1)	2 (< 0.1)
Without DVT	47 (1.1)	57 (1.4)
DVT only	57 (1.4)	63 (1.5)
Exploratory Analysis: Adjudicated Recurrent VTE in the PP Analysis Set, Overall Study Period, n (%)	[redacted]	[redacted]
HR edoxaban vs. warfarin (95% CI)[b]	[redacted]	
Sensitivity Analysis: Adjudicated Recurrent VTE in the PP Analysis Set — On-Treatment Study Period[c]	64 (1.6)	80 (2.0)
HR edoxaban vs. warfarin (95% CI)[b]	0.80 (0.577 to 1.113)	
Sensitivity Analysis: Adjudicated Recurrent VTE in the PP Analysis Set — Treatment +30 Days Study Period[d]	87 (2.1)	102 (2.5)
HR edoxaban vs. warfarin (95% CI)[b]	0.85 (0.642 to 1.137)	
Sensitivity Analysis: Adjudicated Recurrent VTE in the mITT Analysis Set — Treatment +30 Days Study Period[d]	[redacted]	[redacted]
HR edoxaban vs. warfarin (95% CI)[b]	[redacted]	

DVT = deep vein thrombosis; HR = hazard ratio vs. warfarin; CI = confidence interval; mITT = modified intention to treat; N = number of patients in mITT analysis set; n = number of patients with events; PE = pulmonary embolism; PP = per-protocol; vs. = versus; VTE = venous thromboembolism.

Note: Events are included in the overall study period if they occurred on or after the randomization date up to day 365.

[a] The primary efficacy end point is symptomatic recurrent VTE (i.e., the composite end point of DVT, non-fatal PE, and fatal PE).

[b] The HR and two-sided CI are based on the Cox proportional hazards regression model, including treatment and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT; DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban/edoxaban placebo dose at randomization (yes or no).

[c] Events are included in the on-treatment study period if they occurred on or after the date of the first dose of any study drug up to day 365. Events that start after the third day following the date of any "last dose" and before the date of the next "first dose" are not considered for the on-treatment study period.

[d] Events are included in the treatment-plus-30-days study period if they occurred on or after the date of the first dose of any study drug. Events that start after 30 days following the last dose of study drug are not considered for the treatment-plus-30-days study period.

Source: Clinical Study Reports: Hokusai–VTE study.[1]

In general, the subgroup analyses demonstrated a similar trend in treatment effect as the primary analyses, where the upper bound of the 95% CI for the estimated hazard ratio for the time to the first occurrence of adjudicated symptomatic recurrent VTE for the edoxaban group versus the warfarin group was below the pre-specified NI margin of 1.5; therefore, NI was demonstrated for the primary efficacy end point for patients treated with edoxaban compared with warfarin for the following subgroups: patients with a presenting diagnosis of PE with or without DVT, patients with PE severity, patients with a presenting diagnosis of DVT only, patients aged < 65 years or ≥ 65 years, patients with baseline risk

factors, patients with body weight greater than 60 kg, patients with CrCl at randomization of 30 mL/min to 50 mL/min or > 50 mL/min, patients with a history of cancer, patients with no active cancer, and warfarin patients with centre-level INR percentage TTR (except for when TTR is ≥ 75th percentile). For the subgroup of patients with body weight ≤ 60 kg and the subgroup of patients with time in the therapeutic range ≥ 75th percentile, the upper bound of the 95% CI for the estimated hazard ratio for the primary efficacy end point was higher than 1.5; hence, NI was not demonstrated in these subgroups (Table 18). These subgroup analyses were exploratory in nature; subgroup analyses were small and likely unpowered to find any differences. They would, therefore, favour NI being declared; hence, results should be interpreted with caution.

In the mITT analysis set, overall period, a total of 1,452 (17.6%) patients met the pre-specified criteria requiring allocation to edoxaban 30 mg (or matching placebo), including 733 (17.8%) patients in the edoxaban treatment group and 719 (17.4%) patients in the warfarin treatment group. Recurrent VTE was reported in 22 patients (3.0%) in the edoxaban 30 mg group versus 30 patients (4.2%) in the edoxaban placebo (active warfarin) 30 mg group. The percentage of symptomatic recurrent VTE events in the edoxaban 30 mg and active edoxaban 60 mg dose cohorts were 3.0% and 3.2%, respectively (Table 18).

In the mITT analysis set, overall period, of the 4,921 patients with the presenting diagnosis of DVT alone, 2,468 were randomized to edoxaban and 2,453 to warfarin. For the overall study period, the hazard ratio for recurrent VTE was 1.02 (95% CI, 0.750 to 1.384). In patients with a presenting diagnosis of PE (with or without DVT), 1,650 were randomized to the edoxaban group and 1,669 were randomized to the warfarin group. For the overall study period, the relative reduction in risk for recurrent VTE was 27% (hazard ratio: 0.73; 95% CI, 0.502 to 1.062) (Table 18).

In the mITT analysis set, overall period, for patients with a PE index defined as more severe (baseline NT-proBNP ≥ 500 pg/mL), the primary end point (symptomatic recurrent VTE) occurred in 14 patients (3.1%) in the edoxaban group compared with 30 (6.2%) in the warfarin group, for a relative reduction in risk of 50% (hazard ratio: 0.50; 95% CI, 0.262 to 0.937). For patients with a PE index defined as more severe based on the presence of RV dysfunction, as measured by computed tomography at baseline, the primary end point (symptomatic recurrent VTE) occurred in five (2.9%) of the edoxaban patients compared with 12 (6.7%) in the warfarin patients, for a relative reduction in risk of 58% (hazard ratio: 0.42; 95% CI, 0.146 to 1.199) (Table 18).

In the mITT analysis set, overall period, the primary efficacy end point of recurrent VTE in patients ≥ 65 years of age occurred in 46 patients (3.4%) in the edoxaban group compared with 63 patients (4.6%) in the warfarin group (hazard ratio: 0.75; 95% CI, 0.513 to 1.099) (Table 18).

A post-hoc analysis of the Hokusai–VTE study evaluated the risk-benefit of extended treatment with edoxaban for up to 12 months among patients who continued therapy beyond three months (Raskob et al., 2016). The analysis found that patients with VTE who continued treatment with edoxaban beyond three months had a rate of recurrent VTE similar to that of patients treated with warfarin beyond three months. The cumulative incidence of recurrent VTE in the extended period (> 3 months to 12 months) for the overall treatment period was 1.8% in the edoxaban treatment group (66 of 3,633 patients) and 1.9% (67 of 3,594 patients) in the warfarin treatment group (hazard ratio 0.97; 95% CI, 0.7 to 1.4). Detailed results are presented in Table 20.

3.6.2 Recurrent Venous Thromboembolism and All-Cause Mortality

For the mITT analysis set, overall study period, the secondary end point of recurrent VTE and all-cause mortality occurred in 228 (5.5%) patients in the edoxaban treatment group and 228 (5.5%) patients in the warfarin treatment group (hazard ratio: 1.00; 95% CI, 0.832 to 1.200; *P* = 0.993). The results showed that treatment with edoxaban was not superior to warfarin in reducing the incidence of recurrent VTE or all-cause mortality. Detailed results are presented in Table 13.

All-cause mortality in the overall study period (death events both on and off treatment) was 122 (3.0%) in the edoxaban treatment group versus 106 (2.6%) in the warfarin treatment group. The number of VTE-related deaths was 24 (0.6%) in both the edoxaban and warfarin treatment groups. Non-VTE-related death (shown in Table 13 as "other death"), both on and off treatment in the overall study period, occurred in 98 (2.4%) edoxaban-treated patients versus 82 (2.0%) warfarin-treated patients. Detailed results are presented in Table 13.

TABLE 13: RECURRENT VENOUS THROMBOEMBOLISM AND ALL-CAUSE MORTALITY, MITT ANALYSIS SET — OVERALL STUDY PERIOD

	Hokusai–VTE	
	Edoxaban N = 4,118	Warfarin N = 4,122
All Patients with Recurrent VTE or All-Cause Mortality, n (%)[a]	228 (5.5)	228 (5.5)
HR edoxaban vs. warfarin (95% CI)[b]	1.00 (0.832 to 1.200)	
P value (for superiority)[b]	0.9933	
Type of Initial Recurrent VTE or All-Cause Mortality, n (%)		
All-cause mortality	122 (3.0)	106 (2.6)
VTE-related death	24 (0.6)	24 (0.6)
Fatal PE	4 (< 0.1)	3 (< 0.1)
Unexplained death (and VTE cannot be ruled out)	20 (0.5)	21 (0.5)
Other death[c]	98 (2.4)	82 (2.0)
Non-fatal PE	49 (1.2)	59 (1.4)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
DVT only	57 (1.4)	63 (1.5)

CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio vs. warfarin; N = number of patients in analysis set; n = number of patients meeting event criteria; PE = pulmonary embolism; vs. = versus; VTE = venous thromboembolism.
Note: Events are included in the overall study period if they occurred on or after the randomization date up to day 365.
[a] The secondary efficacy end point is symptomatic recurrent VTE (i.e., the composite end point of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality).
[b] The HR and two-sided CI are based on the Cox proportional hazards regression model, including treatment and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT, DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban or edoxaban placebo at randomization (yes, no); *P* value alpha = 0.01 (two-sided).
[c] Among "other deaths," infectious disease was the cause of death in 25 (0.6%) patients in the edoxaban group vs. 12 (0.2%) in the warfarin group.
Source: Clinical Study Reports: Hokusai–VTE study.[1]

3.6.3 Net Clinical Outcome and Net Clinical Benefit

The exploratory end point of the net clinical outcome (composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, major bleeding, and all-cause mortality) occurred in [redacted] in the edoxaban treatment group and [redacted] in the warfarin treatment group [redacted]. Detailed results are presented in Table 14.

TABLE 14: NET CLINICAL OUTCOME (SYMPTOMATIC RECURRENT DVT, NON-FATAL SYMPTOMATIC RECURRENT PE, MAJOR BLEEDING, AND ALL-CAUSE MORTALITY), PP ANALYSIS SET, ON-TREATMENT PERIOD

	Hokusai–VTE					
	[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]		

CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio vs. warfarin; N = number of patients in analysis set; n = number of patients meeting event criteria; PE = pulmonary embolism; PP = per-protocol; vs. = versus; VTE = venous thromboembolism.

Note: Events are included in the on-treatment study period if they occurred on or after the date of first dose of any study drug up to day 365. Events that start after the third day following the date of any "last dose" and before the date of the next dose are not considered for the on-treatment period.

[a] Net clinical outcome is defined as the composite end point of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, major bleeding, and all-cause mortality.

[b] The HR and two-sided CI are based on the Cox proportional hazards regression model, including treatment and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT, DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban or edoxaban placebo dose at randomization (yes, no); *P* value alpha = 0.01 (two-sided).

[c] Includes all non-fatal VTE events.

Source: Clinical Study Reports: Hokusai–VTE study.[1]

The exploratory end point of net clinical benefit (composite of symptomatic recurrent VTE [fatal and non-fatal] and major bleeding) occurred in [redacted] in the edoxaban treatment group [redacted] and [redacted] in the warfarin group [redacted] for a relative reduction in risk of [redacted]. Detailed results are presented in Table 15. The number needed to treat for net clinical benefit end point was [redacted] meaning that [redacted] need to be treated with edoxaban to prevent one additional case of the composite outcome of symptomatic recurrent VTE (fatal and non-fatal), and major bleeding.

TABLE 15: NET CLINICAL BENEFIT (SYMPTOMATIC RECURRENCE OF VTE AND MAJOR BLEEDING), PP ANALYSIS SET – ON-TREATMENT STUDY PERIOD

	Hokusai–VTE		
[redacted]			

CEC = clinical events committee; CI = confidence interval; HR = hazard ratio vs. warfarin; N = number of patients in analysis set; n = number of patients meeting event criteria; PP = per-protocol; vs. = versus; VTE = venous thromboembolism.
Note: Events are included in the on-treatment study period if they occurred on or after the date of first dose of any study drug up to day 365. Events that start after the third day following the date of any "last dose" and before the date of the next "first dose" are not considered for the on-treatment study period.
[a] Net clinical benefit is defined as symptomatic recurrent VTE (fatal and non-fatal) and major bleeding. CEC adjudication results only are considered for this summary.
[b] The HR and two-sided CI are based on the Cox proportional hazards regression model including treatment and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT, DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban or edoxaban placebo dose at randomization (yes, no); *P* value alpha = 0.01 (two-sided).
Source: Clinical Study Reports: Hokusai–VTE study.[1]

3.6.4 Hospitalizations

Hospitalization AEs were identified as any reported AE requiring hospitalization or prolongation of hospitalization. The proportion of patients requiring hospitalization due to AE during the on-treatment period was slightly lower in the edoxaban treatment group compared with warfarin treatment group [redacted]. The number of patients hospitalized due to recurrent VTE and bleeding was lower in the edoxaban treatment group than in the warfarin treatment group, while the number of patients hospitalized due to a cerebrovascular accident, myocardial infarction, or systemic embolic event was higher in the edoxaban treatment group than in the warfarin treatment group. The duration of hospital stay due to recurrent VTE and bleeding was approximately two days shorter, on average, for patients in the edoxaban treatment group than in the warfarin treatment group, while the duration of the hospital stay due to cerebrovascular accident, myocardial infarction, or systemic embolic event was approximately two days longer, on average, for patients in the edoxaban treatment group than those in the warfarin treatment group. Detailed results are presented in Table 16.

TABLE 16: HOSPITALIZATIONS ON-TREATMENT PERIOD

	Hokusai–VTE		
[redacted]			

	Hokusai–VTE			
[redacted]				
[redacted]				
[redacted]				

CVA = cerebrovascular accident; MI = myocardial infarction; SEE = systemic embolic event; VTE = venous thromboembolism.
Source: Clinical Study Reports: Hokusai–VTE study.[1]

3.6.5 Health-Related Quality of Life

Only [redacted] patients in Hokusai–VTE completed EQ-5D questionnaires. [redacted] at the various time points of the study. Utility scores were calculated using the UK time trade-off value set at baseline and at three-month intervals thereafter. Table 21 show the calculated scores for patients in the two study arms at various time points for all patients, for those with DVT only, and for those with PE, with or without DVT. [redacted]. However, analysis of the differential effects of edoxaban and warfarin on HRQoL was not carried out due to insufficient data. These data should, therefore, be interpreted cautiously. Also, the study protocol did not pre-specify that HRQoL data would be collected. Hence, it is not clear who filled in the questionnaire or how the analysis was done.

3.7 Harms

Only those harms identified in the review protocol are reported in Section 2.2.1, Protocol.
See Appendix 4 for detailed harms data.

3.7.1 Adverse Events

The percentage of patients experiencing AEs in the Hokusai–VTE trial was similar in the edoxaban and warfarin treatment groups (68.5% versus 71%, respectively) (Table 17). The most common AEs in the edoxaban treatment group were headache (5.8% and 4.9% for edoxaban versus warfarin, respectively) and nasopharyngitis (5.6% each). The most common AE in the warfarin group was an INR increase (0.5% and 8.2% for edoxaban versus warfarin, respectively) (Table 26).

3.7.2 Serious Adverse Events

The percentage of patients experiencing SAEs during the on-treatment period was similar in the edoxaban and warfarin treatment groups (12.2% versus 13.2%, respectively). The most common SAE in the edoxaban treatment group was pneumonia (0.7% and 0.4% for edoxaban versus warfarin, respectively). The most common SAE in the warfarin group was increased INR (< 0.1% and 1.9% for edoxaban versus warfarin, respectively) (Table 17).

3.7.3 Withdrawals Due to Adverse Events

The percentage of patients with AEs that caused permanent discontinuation of the study drug was similar between the edoxaban and warfarin treatment groups (4.7% and 4.5%, respectively). The AEs in the edoxaban treatment group that most commonly led to permanent discontinuation of the study drug were increased hepatic enzyme [redacted] and decreased creatinine renal clearance [redacted]. The most common AE in the warfarin group leading to permanent discontinuation of the study drug was increased INR [redacted] (Table 17).

3.7.4 Mortality

All-cause mortality during the on-treatment study period was similar between the two groups, with 35 deaths (0.8%) in the edoxaban group and 33 deaths (0.8%) in the warfarin group. VTE-related deaths in the edoxaban group compared with the warfarin group were 13 versus 10. Cardiovascular deaths in the edoxaban group compared with the warfarin group were six versus three, respectively, with the imbalance arising from ischemic stroke (two versus zero) and "other cardiac death" (three versus one). Cancer deaths were four (< 0.1%) in the edoxaban group versus seven (0.2%) in the warfarin group. Infectious disease was the cause of death in seven (0.2%) patients in the edoxaban group versus four (< 0.1%) in the warfarin group, and bleeding deaths were two (< 0.1%) in the edoxaban group and five (0.1%) in the warfarin group (Table 17). All-cause mortality for the overall study period was also similar between the two groups: 136 (3.3%) in the edoxaban group and 130 (3.2%) in the warfarin group (Table 27).

3.7.5 Notable Harms

In the Hokusai–VTE study, results for the primary safety outcome of clinically relevant bleeding show that edoxaban was associated with a relative risk reduction of 19% compared with warfarin in the safety population (8.5% versus 10.3%, respectively; hazard ratio: 0.81; 95% CI, 0.705 to 0.936; *P* = 0.004); therefore, the superiority of edoxaban over warfarin was demonstrated (Table 17). There were fewer critical-site major and CRNM bleeds in the edoxaban group than in the warfarin group [redacted] fewer intracranial bleeds in the edoxaban group than in the warfarin group (5 versus 1 and fewer fatal bleeds (2 versus 10). There was an increase in major and CRNM bleeds associated with a fall in hemoglobin > 2 g/dL (40 patients in the edoxaban group versus 33 patients in the warfarin group) and an increase in patients needing a transfusion of ≥ 2 units (28 patients in the edoxaban group versus 22 patients in the warfarin group), mainly due to an increase in "mucosal bleedings," including major and CRNM gastrointestinal bleedings (2.4% in edoxaban group versus 2.3% of warfarin group) and vaginal bleeds (4.6% in the edoxaban group versus 3.2% in the warfarin group) (Table 22).

The rate of major bleeding was similar between the treatment groups (1.4% in the edoxaban group and 1.6% in the warfarin group). There were fewer fatal bleeds (2 versus 10), including fewer fatal intracranial bleeds (0 versus 6) in the edoxaban group compared with the warfarin group. There were fewer critical-site bleeds (13 versus 32), including fewer intracranial bleeds (5 versus 18) in the edoxaban group compared with the warfarin group. In the edoxaban treatment group, all sites of bleeding had numerically fewer or the same number of bleed events compared with the warfarin treatment group, with the following exceptions: gastrointestinal (GI) tract, vaginal, and "other." There were 27 (0.7%) GI tract major bleeding events in the edoxaban group versus 18 (0.4%) in the warfarin group, with more upper-GI tract events versus lower-GI. There were 9 (0.5%) vaginal major bleeding events in the edoxaban group and 3 (0.2%) in the warfarin group (Table 23).

Numerical differences in major and CRNM bleeding for edoxaban compared with warfarin were consistently shown across all bleeding categories: the percentage of patients experiencing major bleeding was 1.4% versus 1.6%; CRNM bleeding was 7.2% versus 8.9%; nuisance bleeding was 16.1% versus 19.1%; and all bleeding was 21.7% versus 25.6%, in the edoxaban and warfarin treatment groups respectively (Table 17).

Bleeds that led to hospitalization were numerically lower in the edoxaban treatment group compared with the warfarin treatment group ([redacted] of patients in the edoxaban treatment group compared with [redacted] of patients in the warfarin treatment group) (Table 17).

The edoxaban treatment group had a numerical increase in abnormal changes in liver enzymes and bilirubin, including alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 times the upper limit of normal (ULN) and total bilirubin ≥ 2 times the ULN; however, these incidences were similar between the treatment groups (Table 17).

TABLE 17: HARMS ON-TREATMENT PERIOD

	Hokusai–VTE	
	Edoxaban N = 4,118	Warfarin N = 4,122
AEs, n (%)	2,821 (68.5)	2,928 (71.0)
SAEs, n (%)	503 (12.2)	544 (13.2)
Pneumonia	30 (0.7)	17 (0.4)
Bronchitis	8 (0.2)	1(<0.1)
Urinary tract infection	8 (0.2)	6 (0.1)
Sepsis	7 (0.2)	4 (< 0.1)
Cellulitis	5 (0.1)	11 (0.3)
Colon cancel	2 (< 0.1)	7 (0.2)
Anemia	3 (< 0.1)	10 (0.2)
Syncope	8 (0.2)	3 (< 0.1)
Cardiac failure	8 (0.2)	6 (0.1)
Cardiac failure (congestive)	4 (< 0.1)	8 (0.2)
Dyspnea	14 (0.3)	5 (0.1)
Chronic obstructive pulmonary disease	8 (0.2)	12 (0.3)
Chest pain	14 (0.3)	9 (0.2)
Non-cardiac chest pain	7 (0.2)	5 (0.1)
International normalized ratio increase	4 (< 0.1)	77 (1.9)
WDAEs, n (%)	195 (4.7)	185 (4.5)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Mortality, n (%), On-Treatment Study Period, n (%)		
All causes	35 (0.8)	33 (0.8)
VTE-related death	13 (0.3)	10 (0.2)
PE	2 (< 0.1)	0 (0.0)
Unexplained death (and VTE cannot be ruled out)	11 (0.3)	10 (0.2)
Cardiovascular death	6 (0.1)	3 (< 0.1)
MI	1 (< 0.1)	2 (< 0.1)
Ischemic stroke	2 (< 0.1)	0 (0.0)
SEE	0 (0.0)	0 (0.0)
Other cardiac death[a]	3 (< 0.1)	1 (< 0.1)
Other known cause	16 (0.4)	20 (0.5)
Cancer	4 (< 0.1)	7 (0.2)
Bleeding (including hemorrhagic stroke)	3 (< 0.1)	5 (0.1)
Infectious disease	7 (0.2)	4 (< 0.1)
Other[b]	3 (< 0.1)	4 (< 0.1)

	Hokusai–VTE	
	Edoxaban N = 4,118	Warfarin N = 4,122
Adjudicated Bleeding Events, On-Treatment Study Period		
Major and CRNM bleeding, n (%)	349 (8.5)	423 (10.3)
HR edoxaban vs. warfarin (95% CI)	0.81 (0.705 to 0.936)	
P value (for superiority)	0.0040	
Major bleeding, n (%)	56 (1.4)	66 (1.6)
Fatal, n (%)	3 (0.1)	10 (0.2)
CRNM bleeding, n (%)	298 (7.2)	368 (8.9)
Nuisance bleeding, n (%)	663 (16.1)	787 (19.1)
All bleeding, n (%)	895 (21.7)	1,056 (25.6)
Adjudicated Major or CRNM Bleeding Event Characteristics, On-Treatment Study Period, n (%)		
Fatal bleed	2 (< 0.1)	10 (0.2)
Clinically overt	349 (8.5)	423 (10.3)
Fall in hemoglobin ≥ 2 g/dL	40 (1.0)	33 (0.8)
Transfusions ≥ 2 units	28 (0.7)	22 (0.5)
Hemodynamic compromise	1 (< 0.1)	6 (0.1)
Requiring surgery	3 (< 0.1)	2 (< 0.1)
Bleeding Events Required/Prolonged Hospitalization, n (%)	[redacted]	[redacted]
Patients With ALT or AST ≥ 3 × ULN, n (%)	106 (2.7)	100 (2.6)
Patients With TBL ≥ 2 × ULN, n (%)	41 (1.1)	24 (0.6)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CRNM = clinically relevant non-major; HR = hazard ratio vs. warfarin; MI = myocardial infarction; N = number of patients in analysis set; n = number of patients meeting event criteria; PE = pulmonary embolism; SAE = serious adverse event; SEE = systemic embolic event; TBL = total bilirubin; vs. = versus; ULN = upper limit of normal; VTE = venous thromboembolism; WDAE = withdrawal due to adverse event.

Note: Deaths are included in the on-treatment study period if they occurred on or after the date of the first dose of any study drug. Deaths that occurred after the third day following the date of any "last dose" and before the date of the next "first dose" are not considered for the on-treatment study period.

[a] Other cardiac deaths were post-operative tamponade, heart failure, ruptured aortic aneurysm (edoxaban) and arrhythmia (warfarin).

[b] Three fatal edoxaban cases (perforated bowel, acute respiratory distress, and suicide) and four fatal warfarin cases (respiratory failure, MVA, suicide, and homicide).

Source: FDA Medical review(s);[18] Clinical Study Reports: Hokusai–VTE study.[1]

4. DISCUSSION

4.1 Summary of Available Evidence

One published manufacturer-sponsored, phase III, DB matching placebo, parallel-group, NI study was included in the systematic review. Hokusai–VTE (n = 8,292) evaluated the benefits and risks of edoxaban compared with warfarin in reducing the risk of symptomatic recurrent VTE in patients with documented acute symptomatic DVT and/or PE. All patients received initial therapy with open-label UFH or enoxaparin for at least five days. Edoxaban or warfarin was administered in a DB, double-dummy fashion. Edoxaban (or placebo) was started after discontinuation of initial heparin in the edoxaban treatment group. It was administered at a dose of 60 mg orally once daily, or 30 mg once daily in patients with a CrCl between 30 mL/min and 50 mL/min, or in patients who were receiving concomitant treatment with potent P-gp inhibitors or who had a body weight of 60 kg or less.

Warfarin (or placebo) was started at the same time as heparin, and after discontinuation of initial heparin in the warfarin treatment group, patients started placebo edoxaban (60 mg once daily) and continued warfarin (adjusted to maintain INR between 2.0 and 3.0). The intended treatment duration for edoxaban or warfarin was three, six, or 12 months, as determined by the study investigator. Hokusai–VTE was generally well conducted. The main methodological limitation of the study was that the NI analysis of the primary end point used the mITT analysis set for the overall study period, while the PP analysis that was undertaken for the overall study period was exploratory. The objective of this systematic review was to compare edoxaban to other anticoagulant drugs; therefore, additional evidence was assessed in the form of indirect treatment comparisons (ITCs). The trial population consisted of patients with acute symptomatic DVT and/or PE.

4.2 Interpretation of Results

4.2.1 Efficacy

Results from Hokusai–VTE met the pre-specified NI for the hazard ratio of 1.5 for the primary efficacy outcome of adjudicated symptomatic recurrent VTE (i.e., the composite end point of DVT, non-fatal PE, and fatal PE) during the 12-month study period in patients with documented acute symptomatic DVT and/or PE. The manufacturer used a literature search to support the estimation of the NI margin hazard ratio = 1.5, which was conservative when compared with recent studies of novel oral anticoagulants for the treatment of VTE which used margins of 1.80 to 2.75.[20] However, the margin was larger than recommended by the FDA, which recommends a more conservative margin.[19] The estimated hazard ratio for the time to the first occurrence of adjudicated symptomatic recurrent VTE for the edoxaban group versus the warfarin group was 0.89 (95% CI, 0.703 to 1.128); therefore, the upper 95% confidence limit of the hazard ratio was 1.128, indicating that edoxaban retained at least 91% of the treatment effect of warfarin, which is lower than the FDA recommended margin. NI of edoxaban compared with warfarin was also achieved in sensitivity and exploratory analyses in both the PP and mITT populations. However, these sensitivity analyses were not included in the hierarchical statistical analysis approach, and should be considered exploratory because of the potential for inflated type I error. Overall, treatment with edoxaban was associated with numerically fewer symptomatic recurrent VTE events compared with treatment with warfarin; however, the magnitude of the difference was small. Indeed, the superiority of edoxaban could not be demonstrated, as the results did not achieve statistical significance for such testing. Therefore, edoxaban may be considered noninferior to warfarin for acute VTE treatment and prevention of recurrent VTE.

There was a large difference in the number of recurrent VTE events that occurred during the mITT overall study period analysis (130 events in the edoxaban group versus 146 events in the warfarin group) and the PP on-treatment analysis (64 events in the edoxaban group versus 80 events in the warfarin group). This indicates that approximately half of the events that occurred during the overall study period (66 events in each group) took place after anticoagulant treatment had been stopped. On the one hand, it calls into question whether the duration of anticoagulant therapy was generally insufficient during the trial. On the other hand, it is reassuring that no differences in rebound thromboembolism were noticed between groups; as a result, the NI of edoxaban versus warfarin on-treatment was sustained at 12 months. The optimal treatment duration with edoxaban is unclear from the study.[16,20] Some patients with unprovoked events or non-reversible risk factors may require prolonged therapy. The product monograph indicates the duration of therapy should be individualized after carefully weighing the anticoagulant treatment benefit against the individual risk of bleeding, and does not include recommendations on the maximum duration of treatment.[15]

The subgroup analyses demonstrated a trend in treatment effect that was similar to that in the primary analyses. However, these subgroup analyses were exploratory, based on small sample sizes, and likely unpowered to find any differences. They would, therefore, favour NI being declared; hence, results should be interpreted with caution.

The subgroup analysis of the primary end point based on centres with different levels of TTR was reported to show no statistically significant differences. However, there is insufficient evidence to establish that TTR has no impact on the relative efficacy of edoxaban compared with warfarin because of the magnitude of uncertainty in the individual estimates (as illustrated by the wide 95% CIs); and the study was not powered to find any difference. In addition, the results were based on centre-level INR, not patient-level INR.

Superiority was not established for the secondary efficacy end point. The composite end point of recurrent VTE and all-cause mortality occurred in 228 of patients (5.5%) in the edoxaban group and in 228 patients (5.5%) in the warfarin group (hazard ratio: 1.00; 95% CI, 0.832 to 1.200, *P* = 0.9933). Although recurrent VTE (DVT or PE) favoured edoxaban versus warfarin numerically, all-cause mortality was higher numerically in the edoxaban arm compared with the warfarin arm in the overall study period (edoxaban 122 versus warfarin 106), leading to a hazard ratio of 1.00. There was no imbalance in on-treatment deaths (edoxaban 35 versus warfarin 33). The imbalance was attributed to an excess in deaths due to infectious disease (unrelated to VTE-related mortality) in the edoxaban arm after treatment stopped, although the number of events was small.

The Hokusai–VTE trial collected and reported HRQoL data. However, an analysis of the differential effects of edoxaban and warfarin on HRQoL was not carried out due to the small numbers of respondents [redacted]). In addition, the small numbers of respondents with data available over the course of the study period limits the usefulness of the HRQoL data [redacted]

Given that there are currently no direct head-to-head RCTs comparing edoxaban with other DOACs, the ability to draw conclusions about their relative efficacy is limited to evidence from ITCs. The CDR review team conducted a critical appraisal of two ITCs submitted by the manufacturer (one of which was manufacturer-sponsored) assessing the efficacy and safety of edoxaban compared with other DOACs for the acute treatment of VTE and the prevention of recurrent DVT and PE (further details in Appendix 6).

In the manufacturer-sponsored ITC, there were no significant differences for the outcomes of recurrent VTE and overall mortality. In the other submitted ITC by Wells et al., there were no significant differences for the outcomes in the recurrence of VTE, recurrence of DVT, recurrent PE, non-fatal recurrent PE, recurrent fatal PE, and all-cause mortality between treatments. CDR conducted a literature review to compare the results of the ITC performed by the manufacturer with other ITCs found in the literature. Five additional ITCs were retrieved; their results are consistent with the conclusion that there is no substantial difference among the efficacy of edoxaban when compared with DOACs or warfarin in treating and preventing recurrent VTE. However, the small number of studies available, the relative rarity of the events that were analyzed, and the high level of heterogeneity among studies (including blinding and variation in the duration of treatment across the studies) result in uncertainty in interpreting the comparative effectiveness of edoxaban versus other anticoagulants.

Of note, the use of edoxaban and dabigatran require parenteral anticoagulant to be administered for five to 10 days and then discontinued before treatment with edoxaban and dabigatran is started.[15,28] This is in contrast to rivaroxaban and apixaban, which do not require initial treatment with heparin.[29,30] Edoxaban, like rivaroxaban (after the first three weeks), offers once-daily dosing, while apixaban and dabigatran are administered twice daily.

4.2.2 Harms

In the Hokusai–VTE study, results for the primary safety outcome of clinically relevant bleeding show the superiority of edoxaban over warfarin. However, the statistical significance of this composite outcome was mainly driven by the reduction in CRNM bleeding (298 patients [7.2%] in the edoxaban treatment group versus 368 patients [8.9%] in warfarin treatment group). Edoxaban also had numerically fewer major bleeds than warfarin (56 [1.4%] versus 66 [1.6%]).

Neither mortality nor the overall incidence of SAEs during the Hokusai–VTE study differed significantly between edoxaban and warfarin, nor were they higher than would be expected in this patient population in clinical practice, according to the clinical expert consulted for this review. The most commonly reported SAEs with both drugs were infrequent (< 2%). The proportion of patients experiencing AEs was slightly lower with edoxaban compared with warfarin. The most common AEs in the edoxaban treatment group were headache and nasopharyngitis, while the most common AE in the warfarin group was INR increase. Limited proportions of patients discontinued due to AEs in both treatment groups, suggesting similar tolerability.

Overall, all harms results reported in the trial for both treatment groups did not identify any obvious unknown safety signal. A small proportion of patients with active cancer were included in the Hokusai–VTE trial; therefore, there is uncertainty regarding the safety of edoxaban in these patients.

There are currently no direct head-to-head RCTs comparing edoxaban with other DOACs. The results of the five ITCs[31-35] identified in the CDR review of the literature were similar to the manufacturer-submitted and -sponsored ITC analysis in that apixaban was significantly less likely to cause major bleeding compared with edoxaban. However, this difference was not found by Wells et al.,[36] likely because the Wells et al. review used random-effects models, which would yield a wider credible interval; therefore, it is more difficult to find differences between treatments. Except for the review by Wells et al., all summarized ITCs indicated that apixaban was consistently superior to edoxaban for all bleeding outcomes, and that edoxaban was associated with a significantly increased risk of major and CRNM bleeds compared with dabigatran.

4.3 Potential Place in Therapy[1]

The most recent version of the clinical practice guideline from the American College of Chest Physicians suggests using a DOAC (dabigatran, apixaban, rivaroxaban, or edoxaban) over a VKA to treat acute VTE.[14] According to the clinical expert consulted for this review, while DOACs seem to have a similar risk reduction for recurrent VTE when compared with VKA, the preference for DOACs is likely driven by the lower risk of bleeding (especially intracranial bleeding) compared with VKAs. Furthermore, in patients at high risk of recurrent VTE who require long-term oral anticoagulation to prevent a recurrent event, the American College of Chest Physicians suggests there is no need to change the choice of anticoagulant.[14] Therefore, DOACs will be used for a minimum of three months, but potentially longer in high-risk patients.

A number of factors may influence which oral anticoagulant is chosen for the treatment of acute VTE and its secondary prevention (for example, patient characteristics, cost, and frequency of administration). The underlying bleeding risk associated with anticoagulation is an important concern for clinicians. A number of risk factors have been shown to be associated with a higher risk of bleeding in patients on oral anticoagulation for VTE. For example, a recent study has reported that moderate renal impairment (CrCl 30 mL/min to 60 mL/min) was an important predictor of major bleeding events in this patient population. Although the risk reduction for bleeding events between the different DOACs has not been directly compared, ITCs suggest there may be some differences between apixaban and edoxaban.[31-35,37]

Given the nature and methods of the Hokusai trial (i.e., incorporating dose reductions for specific patient groups and including a large number of patients with RV dysfunction), which compared edoxaban to VKA for the acute treatment of VTE, clinicians may feel more comfortable using edoxaban in specific patient populations. The Hokusai trial is the only VTE trial for which a dose reduction was incorporated for patients with moderate renal impairment.[16] Dosing reduction was also performed in patients with lower body weight (< 60 kg) or on concomitant interacting medications. Similarly, clinicians might prefer to use edoxaban for patients with PE and associated RV dysfunction, given that there were a large number of these patients (28%) represented in the trial with supportive subgroup analysis results. Additionally, the efficacy of edoxaban was assessed following initial parenteral LMWH;[16] in Canada, these patients are frequently hospitalized and initially managed with parenteral anticoagulation.

Parenteral LMWH alone is the treatment of choice for the management of VTE for patients with active cancer.[14] The DOACs have not been compared with LMWH for the treatment of VTE in this patient population. An NI RCT comparing edoxaban to LMWH is currently underway in this population of patients.[38,39] According to the clinical expert consulted for this review, if the trial reports that edoxaban has a risk-benefit profile comparable to LMWH in cancer patients with VTE, clinicians might also want to use edoxaban in this high-risk subgroup; however, no results are available to date.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

5. CONCLUSIONS

Hokusai–VTE, a manufacturer-sponsored, phase III, DB matching placebo, parallel-group, NI study, was included in the systematic review that evaluated the benefits and risks of edoxaban compared with those of warfarin in reducing the risk of symptomatic recurrent VTE in patients with documented acute symptomatic DVT and/or PE. The intended treatment durations for edoxaban or warfarin were three, six, or 12 months, as determined by the study investigator. The results of the Hokusai–VTE study demonstrated that edoxaban was noninferior to, but not superior to, warfarin in the treatment of patients with acute symptomatic VTE for the prevention of symptomatic recurrent VTE during the 12-month study period, based on the frequency of recurrent symptomatic VTE. In the same study, edoxaban was associated with significantly fewer clinically relevant bleeding events than warfarin, an outcome that was driven mainly by the reduction in CRNM bleeding, not major bleeding. The results of two ITCs submitted by the manufacturer and five published ITCs of the efficacy and safety of edoxaban compared with other DOACs consistently have suggested that edoxaban is as efficacious as other DOACs in treating and preventing VTE, and that (except for the ITC by Wells et al.) edoxaban was associated with statistically significantly more major bleeding than apixaban and statistically significantly more major and CRNM bleeding than apixaban and dabigatran.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff. No patient input was received from any group for this submission; the patient input summary presented here was adapted from the patient input received in October 2014 for the CADTH Common Drug Review (CDR) review of apixaban (Eliquis) for the treatment of venous thromboembolism (deep vein thrombosis, pulmonary embolism) and prevention of recurrent deep vein thrombosis and pulmonary embolism. The patient input below was re-used with permission from the Heart and Stroke Foundation, which provided the original input.

1. Brief Description of Patient Group Supplying Input

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

HSF has received unrestricted financial support from Bristol–Myers Squibb Canada and/or Pfizer Canada over the last five years to develop educational and awareness activities and 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, HSF used a two-week online survey. Additional information was obtained through literature searches of publications, from HSF health information, and from the guidelines and policies of organizations such as the Canadian Cardiovascular Society. Of the 152 online survey participants, 45 indicated they had blood clots and 11 indicated they were caregivers; only responses from these participants were used to inform this submission.

Approximately 200,000 Canadians are affected by deep vein thrombosis (DVT) each year, with up to 60,000 requiring hospitalization. Responses from the 45 survey participants with blood clots indicate that their day-to-day lives have been affected, mostly due to the need to take medications at specific times or multiple times during the day. Some patients also mentioned having to manage their disease by using other forms of therapy, changing their diets, or taking time off work. More than half of patients indicated that their ability to do activities has not changed, but some reported that they are unable to do activities they have done in the past, such as exercising or lifting items. Symptoms experienced by patients included fatigue, general swelling of the legs and ankles, leg pain or 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 they faced no additional challenges, while others reported new challenges. Some caregivers reported feeling more overwhelmed and busier, anxious or stressed, and said they do not have as much freedom as they once did. Some even reported that their own health suffered. Daily routines were reported to be affected, since several caregivers are responsible for providing medications multiple times per day and at specific times, or are required to provide transportation to health care appointments. This resulted in some caregivers needing to take time off work.

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

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:	October 7, 2016
Alerts:	Weekly search updates until February 15, 2016
Study Types:	No search filters were applied
Limits:	No language or date limits Human only 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
fs	Floating subheading
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
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
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
.pt	Publication type
.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**
1	(Edoxaban* or Lixiana* or Savaysa* or DU 176* or DU176* or 32W99UE810 or UNII32W99UE810 or 606P02282F or UNII606P02282F or NDU3J18APO or UNIINDU3J18APO or 972203R4EW or UNII972203R4EW).ti,ab,kf,kw,ot,hw,rn,nm.
2	(480,448 29 1 or "480448291" or 48044829 1 or 48044829 1 or "0480448291" or 480449 70 5 or 48044970 5 or "480449705" or 480449 705 or 480449 71 6 or "480449716" or 48044971 6 or 480449 716 or 1229194 11 9 or "1229194119" or "122919411 9" or 1229194 119).rn,nm.
3	1 or 2
4	3 use ppez
5	exp *edoxaban/
6	(Edoxaban* or Lixiana* or Savaysa* or DU 176* or DU176*).ti,ab,kw.
7	5 or 6
8	7 use oemezd
9	4 or 8
10	exp animals/
11	exp animal experimentation/ or exp animal experiment/
12	exp models animal/
13	nonhuman/
14	exp vertebrate/ or exp vertebrates/
15	animal.po.
16	or/10-15
17	exp humans/
18	exp human experimentation/ or exp human experiment/
19	human.po.
20	or/17-19
21	16 not 20
22	9 not 21
23	22 not conference abstract.pt.
24	remove duplicates from 23

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:	October 10, 2016.
Keywords:	Drug name, Indication
Limits:	No language or date 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

TABLE 18: ADJUDICATED SYMPTOMATIC RECURRENT VENOUS THROMBOEMBOLISM, MITT ANALYSIS SET — OVERALL STUDY PERIOD SUBGROUP ANALYSIS

	Hokusai–VTE	
	Edoxaban N = 4,118	Warfarin N = 4,122
Presenting Diagnosis PE With/Without DVT	1,650	1,669
Patients with recurrent VTE, n (%)	47 (2.8)	65 (3.9)
HR edoxaban vs. warfarin (95% CI)[a]	0.73 (0.502 to 1.062)	
Type of initial recurrent VTE, n (%)		
[redacted]		
Recurrent VTE by PE Severity	1,650	1,669
NT-proBNP ≥ 500 pg/mL, n/N (%)	14/447 (3.1)	30/483 (6.2)
HR edoxaban vs. warfarin (95% CI)[a]	0.50 (0.262 to 0.937)	
RV dysfunction = yes, n/N (%)	5/172 (2.9)	12/179 (6.7)
HR edoxaban vs. warfarin (95% CI)[a]	0.42 (0.146 to 1.199)	
Presenting Diagnosis DVT Only	2,468	2,453
Patients with recurrent VTE, n (%)	83 (3.4)	81 (3.3)
HR edoxaban vs. warfarin (95% CI)[a]	1.02 (0.750 to 1.384)	
Type of initial recurrent VTE, n (%)		
[redacted]		
Age Group		
< 65 years	2784	2,752
Patients with recurrent VTE, n (%)	84 (3.0)	83 (3.0)
HR edoxaban vs. warfarin (95% CI)[a]	1.00 (0.739 to 1.357)	
≥ 65 years	1334	1,370
Patients with recurrent VTE, n (%)	46 (3.4)	63 (4.6)
HR edoxaban vs. warfarin (95% CI)[a]	0.75 (0.513 to 1.099)	
Baseline Risk Factors		
Temporary factors	1,132	1,140
Patients with recurrent VTE, n (%)	32 (2.8)	38 (3.3)
HR edoxaban vs. warfarin (95% CI)[a]	[redacted]	
All others	2,986	2,982
Patients with recurrent VTE, n (%)	98 (3.3)	108 (3.6)
HR edoxaban vs. warfarin (95% CI)[a]	[redacted]	

	Hokusai–VTE	
	Edoxaban N = 4,118	Warfarin N = 4,122
Need for Dose Adjustment at Randomization		
Yes	733	719
Patients with recurrent VTE, n (%)	22 (3.0)	30 (4.2)
HR edoxaban vs. warfarin (95% CI)[a]	0.73 (0.420 to 1.262)	
No	3,385	3,403
Patients with recurrent VTE, n (%)	108 (3.2)	116 (3.4)
HR edoxaban vs. warfarin (95% CI)[a]	0.93 (0.718 to 1.213)	
Body Weight at Randomization		
≤ 60 kg	524	519
Patients with recurrent VTE, n (%)	15 (2.9)	18 (3.5)
HR edoxaban vs. warfarin (95% CI)[a]	0.84 (0.43, 1.68)	
> 60 kg	3,594	3,603
Patients with recurrent VTE, n (%)	115 (3.2)	128 (3.6)
HR edoxaban vs. warfarin (95% CI)[a]	0.90 (0.697 to 1.153)	
Creatinine Clearance at Randomization		
30 mL/min to 50 mL/min	268	273
Patients with recurrent VTE, n (%)	8 (3.0)	16 (5.9)
HR edoxaban vs. warfarin (95% CI)[a]	0.50 (0.212 to 1.177)	
> 50 mL/min	3,850	3,849
Patients with recurrent VTE, n (%)	122 (3.2)	130 (3.4)
HR edoxaban vs. warfarin (95% CI)[a]	0.94 (0.734 to 1.202)	
Medical History: Cancer		
History of cancer	378	393
Patients with recurrent VTE, n (%)	14 (3.7)	28 (7.1)
HR edoxaban vs. warfarin (95% CI)[a]	0.53 (0.278 to 1.002)	
No history of cancer	3,740	3,729
Patients with recurrent VTE, n (%)	116 (3.1)	118 (3.2)
HR edoxaban vs. warfarin (95% CI)[a]	[redacted]	
Active Cancer at Randomization		
Active cancer	109	99
Patients with recurrent VTE, n (%)	4 (3.7)	7 (7.1)
HR edoxaban vs. warfarin (95% CI)[a]	NR	
No active cancer	4,009	4,023
Patients with recurrent VTE, n (%)	126 (3.1)	139 (3.5)
HR edoxaban vs. warfarin (95% CI)[a]	[redacted]	
Centre-Level INR Percentage Time in Therapeutic Range for Warfarin Patients		
< 60%	1,199	1,271
Patients with recurrent VTE, n (%)	38 (3.2)	45 (3.5)
HR edoxaban vs. warfarin (95% CI)[a]	0.89 (0.574 to 1.364)	
≥ 60%	2,876	2,845
Patients with recurrent VTE, n (%)	89 (3.1)	101 (3.6)
HR edoxaban vs. warfarin (95% CI)[a]	0.87 (0.653 to 1.153)	
< 25th percentile (55.82 %)	713	748
Patients with recurrent VTE, n (%)	28 (3.9)	27 (3.6)
HR edoxaban vs. warfarin (95% CI)[a]	1.09 (0.641 to 1.848)	
≥ 25th (55.82 %) to < 50th percentile (64.03 %)	1,329	1,291

	Hokusai–VTE	
	Edoxaban N = 4,118	Warfarin N = 4,122
Patients with recurrent VTE, n (%)	35 (2.6)	44 (3.4)
HR edoxaban vs. warfarin (95% CI)[a]	0.77 (0.496 to 1.205)	
≥ 75th percentile	1,115	1,180
Patients with recurrent VTE, n (%)	41 (3.7)	42 (3.6)
HR edoxaban vs. warfarin (95% CI)[a]	1.05 (0.681 to 1.610)	
≥ 50th to < 75th percentile (70.41 %)	918	897
Patients with recurrent VTE, n (%)	23 (2.5)	33 (3.7)
HR edoxaban vs. warfarin (95% CI)[a]	0.66 (0.384 to 1.129)	

CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio vs. warfarin; mITT = modified intention to treat; N = number of patients in mITT analysis set; n = number of patients with events; NT-proBNP = N-terminal pro-hormone of brain natriuretic peptide; PE = pulmonary embolism; RV = right ventricular; vs. = versus; VTE = venous thromboembolism.
[a] The HR, two-sided CI, and *P* value are based on the Cox proportional hazards regression model including treatment and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT; DVT only), baseline risk factors (temporary factors; all others), and the need for dose reduction (yes or no). For subgroups that are covariates in the primary safety analysis model, the regression model will contain only the other factors previously present as covariates.
Source: FDA Statistical review(s);[19] Clinical Study Reports: Hokusai–VTE study.[1]

TABLE 19: PATIENT CHARACTERISTICS BY TREATMENT DURATION

	Hokusai–VTE					
	> 3 Months to ≤ 6 Months		> 6 Months to < 12 Months		12 Months	
	Edoxaban Group (N = 1,076)	Warfarin Group (N = 1,084)	Edoxaban Group (N = 896)	Warfarin Group (N = 851)	Edoxaban Group (N = 1,661)	Warfarin Group (N = 1,659)
Age (Years)						
< 65	730 (68%)	735 (68%)	612 (68%)	602 (71%)	1,156 (70%)	1,126 (68%)
65 to < 75	198 (18%)	211 (19%)	183 (20%)	147 (17%)	304 (18%)	342 (21%)
≥ 75	148 (14%)	138 (13%)	101 (11%)	102 (12%)	201 (12%)	191 (12%)
Sex						
Male	588 (55%)	597 (55%)	534 (60%)	497 (58%)	1,012 (61%)	987 (59%)
Female	488 (45%)	487 (45%)	362 (40%)	354 (42%)	649 (39%)	672 (41%)
Creatinine Clearance (mL/min)						
> 50	1,012 (94%)	1,025 (95%)	848 (95%)	793 (93%)	1,563 (94%)	1,564 (94%)
≥ 30 to ≤ 50	64 (6%)	59 (5%)	48 (5%)	58 (7%)	98 (6%)	95 (6%)
Dose Reduction Criteria Met at Randomization	182 (17%)	178 (16%)	135 (15%)	142 (17%)	269 (16%)	274 (17%)
DVT Only	600 (56%)	602 (56%)	515 (57%)	497 (58%)	1,054 (63%)	1,048 (63%)
PE With and Without DVT	476 (44%)	482 (44%)	381 (43%)	354 (42%)	607 (37%)	611 (37%)
Causes of DVT or PE						
Unprovoked	628 (58%)	630 (58%)	592 (66%)	562 (66%)	1,224 (74%)	1,225 (74%)
Temporary risk factor	387 (36%)	378 (35%)	232 (26%)	229 (27%)	336 (20%)	332 (20%)
History of cancer	94 (9%)	109 (10%)	95 (11%)	79 (9%)	128 (8%)	132 (8%)
Previous VTE	137 (13%)	127 (12%)	165 (18%)	155 (18%)	409 (25%)	391 (24%)
Known thrombophilia	25 (2%)	43 (4%)	41 (5%)	37 (4%)	88 (5%)	85 (5%)

DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.
Source: Raskob et al.[23]

TABLE 20: INCIDENCE OF RECURRENT VENOUS THROMBOEMBOLISM AND BLEEDING OUTCOMES DURING THE INTERVALS OF TREATMENT

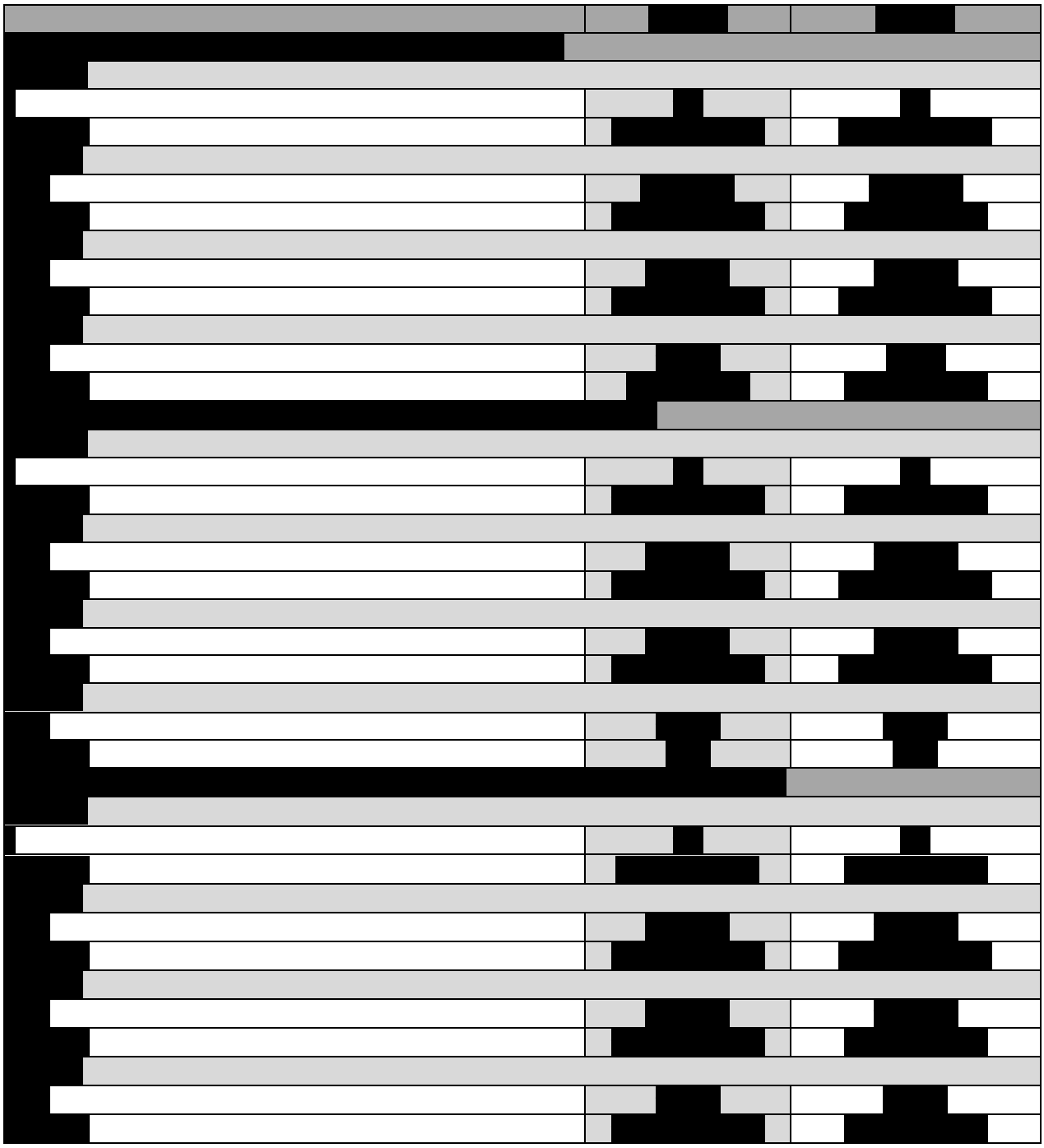
Hokusai–VTE														
	First 3 Months			> 3 to ≤ 6 Months			> 6 to < 12 Months			12 Months		Cumulative > 3 to 12 Months		
	Edoxaban Group (N = 4,118)	Warfarin Group (N = 4,122)	HR (95% CI)	Edoxaban Group (N = 1,076)	Warfarin Group (N = 1,084)	HR (95% CI)	Edoxaban Group (N = 896)	Warfarin Group (N = 851)	HR (95% CI)	Edoxaban Group (N = 1,661)	Warfarin Group (N = 1,659)	Edoxaban Group (N = 3,633)	Warfarin Group (N = 3,594)	HR (95% CI)
Incidence of Recurrent Venous Thromboembolism[a]														
Overall, n (%)	57 (1.4%)	72 (1.7%)	0.79 (0.56 to 1.12)	49 (4.6%)	48 (4.4%)	1.03 (0.69 to 1.53)	16 (1.8%)	17 (2.0%)	0.91 (0.46 to 1.77)	1 (< 0.1%)	2 (0.1%)	66 (1.8%)	67 (1.9%)	0.97 (0.7 to 1.4)
On-treatment, n (%)	44 (1.1%)	51 (1.2%)	0.87 (0.58 to 1.30)	8 (0.7%)	5 (0.5%)	1.64 (0.53 to 5.05)	2 (0.2%)	7 (0.8%)	0.29 (0.06 to 1.36)	1 (< 0.1%)	2 (0.1%)	11 (0.3%)	14 (0.4%)	0.78 (0.36 to 1.72)
Incidence of Bleeding Outcomes[a]														
Major or CRNM bleeding	213 (5.2%)	274 (6.6%)	0.77 (0.64 to 0.92)	31 (2.9%)	34 (3.1%)	0.92 (0.57 to 1.50)	38 (4.2%)	46 (5.4%)	0.80 (0.52 to 1.23)	74 (4.5%)	67 (4.0%)	143 (3.9%)	147 (401%)	0.97 (0.7 to 1.22)
Major bleeding	38 (0.9%)	29 (0.7%)	1.31 (0.81 to 2.13)	5 (0.5%)	11 (1.0%)	0.47 (0.16 to 1.34)	1 (0.1%)	7 (0.8%)	0.14 (0.02 to 1.11)	5 (0.3%)	6 (0.4%)	11 (0.3%)	24 (0.7%)	0.45 (0.22 to 0.92)

CRNM = clinically relevant non-major; HR = hazard ratio.

[a] Hazard ratio was analyzed using a Cox proportional hazards model with stratification factors used in the randomization as covariates (i.e., the index event at presentation [pulmonary embolism or deep vein thrombosis], temporary risk factors, and dose adjustment).

Source: Raskob et al.[23]

TABLE 21: [redacted]



Source: Servier Canada Inc.[40]

TABLE 22: ADJUDICATED MAJOR OR CLINICALLY RELEVANT NON-MAJOR BLEEDING EVENTS BY LOCATION, SAFETY ANALYSIS SET — ON-TREATMENT STUDY PERIOD

	Edoxaban N = 4,118 n (%)	Warfarin N = 4,122 n (%)
Adjudicated major and CRNM bleed[a]	349 (8.5)	423 (10.3)
Critical Site		
ICH	5 (0.1)	18 (0.4)
Subdural	[redacted]	[redacted]
Epidural	[redacted]	[redacted]
Subarachnoidal	[redacted]	[redacted]
Intra-cerebral (including intraventricular hemorrhage)	[redacted]	[redacted]
Hemorrhagic transformation of an ischemic stroke	[redacted]	[redacted]
Retroperitoneal	[redacted]	[redacted]
Pericardial	[redacted]	[redacted]
Intraocular	1 (< 0.1)	4 (< 0.1)
Intra-articular	4 (< 0.1)	4 (< 0.1)
Intramuscular with compartment syndrome	[redacted]	[redacted]
Intraspinal	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]
Non-Critical Site		
Cutaneous soft tissue	32 (0.8)	77 (1.9)
Gastrointestinal tract	98 (2.4)	94 (2.3)
Upper gastrointestinal tract	[redacted]	[redacted]
Lower gastrointestinal tract	[redacted]	[redacted]
Hemoptysis	[redacted]	[redacted]
Macroscopic hematuria/urethral	76 (1.8)	109 (2.6)
Puncture site	[redacted]	[redacted]
Vaginal[c]	81 (4.6)	56 (3.2)
Epistaxis	45 (1.1)	37 (0.9)
Intramuscular, no compartment syndrome	4 (< 0.1)	10 (0.2)
Oral/pharyngeal	11 (0.3)	20 (0.5)
Surgical	[redacted]	[redacted]
Conjunctiva/scleral	1 (< 0.1)	8 (0.2)
Other	[redacted]	[redacted]

CRNM = clinically relevant non-major; ICH = intracranial hemorrhage; N = number of patients in analysis set; n = number of patients meeting event criteria.
Note: Events are included in the on-treatment study period if they occurred on or after the date of the first dose of any study drug. Events that start after the third day following the date of any "last dose" and before the date of the next "first dose" are not considered for the on-treatment study period.
[a] Patients can have multiple events counted in more than one sub-category.
[redacted]
[c] For the gender-specific category "vaginal bleeding," the percentage is based on the number of female patients in each treatment group. (The number of female edoxaban patients = 1,758; number of female warfarin patients = 1,766.)
Source: Clinical Study Reports: Hokusai–VTE study.[1]

TABLE 23: ADJUDICATED MAJOR BLEEDING EVENTS BY LOCATION, SAFETY ANALYSIS SET — ON-TREATMENT STUDY PERIOD

	Edoxaban N = 4,118 n (%)	Warfarin N = 4,122 n (%)
Adjudicated major bleed[a]	56 (1.4)	66 (1.6)
Critical site		
ICH	5 (0.1)	18 (0.4)
Fatal ICH	0 (0.0)	6 (0.1)
Retroperitoneal	0 (0.0)	4 (< 0.1)
Fatal retroperitoneal	0 (0.0)	1 (< 0.1)
Pericardial	1 (< 0.1)	1 (< 0.1)
Intraocular	1 (< 0.1)	4 (< 0.1)
Intra-articular	4 (< 0.1)	4 (< 0.1)
Intramuscular with compartment syndrome	[redacted]	[redacted]
Intraspinal	[redacted]	[redacted]
Other[b]	2 (< 0.1)	0 (0.0)
Non-critical site		
Cutaneous soft tissue	[redacted]	[redacted]
Gastrointestinal tract	27 (0.7)	18 (0.4)
Fatal gastrointestinal tract	1 (< 0.1)	2 (< 0.1)
Upper gastrointestinal tract	[redacted]	[redacted]
Lower gastrointestinal tract	[redacted]	[redacted]
Hemoptysis	[redacted]	[redacted]
Macroscopic hematuria/urethral	[redacted]	[redacted]
Puncture site	[redacted]	[redacted]
Vaginal[c]	9 (0.5)	3 (0.2)
Epistaxis	[redacted]	[redacted]
Intramuscular, no compartment syndrome	[redacted]	[redacted]
Fatal intramuscular, no compartment syndrome	[redacted]	[redacted]
Oral/pharyngeal	[redacted]	[redacted]
Surgical	[redacted]	[redacted]
Conjunctiva/scleral	[redacted]	[redacted]
Other	[redacted]	[redacted]
Fatal other	[redacted]	[redacted]

ICH = intracranial hemorrhage; N = number of patients in analysis set; n = number of patients meeting event criteria.
Note: Events are included in the on-treatment study period if they occurred on or after the date of the first dose of any study drug. Events that start after the third day following the date of any "last dose" and before the date of the next "first dose" are not considered for the on-treatment study period.
[a] Patients can have multiple events counted in more than one sub-category.
[redacted]
[c] For the gender-specific category "vaginal bleeding," the percentage is based on the number of female patients in each treatment group. (The number of female edoxaban patients = 1,758; number of female warfarin patients = 1,766.)
[d] Extensive extremity hematoma.
Source: Clinical Study Reports: Hokusai–VTE study.[1]

TABLE 24: ADJUDICATED MAJOR/CRNM BLEEDING BY INDEX PE OR DVT, SAFETY ANALYSIS SET

Adjudicated Major or CRNM Bleeding	Edoxaban n/N (%)	Warfarin n/N (%)
On-Treatment Study Period		
Index PE with/without DVT	166/1,650 (10.1)	187/1,669 (11.2)
Index DVT only	183/2,468 (7.4)	236/2,453 (9.6)
Treatment-Plus-30-Days Study Period		
Index PE with/without DVT	[redacted]/1,650 [redacted]	[redacted]/1,669 [redacted]
Index DVT only	[redacted]/2,468 [redacted]	[redacted]/2,453 [redacted]

CRNM = clinically relevant non-major; DVT = deep vein thrombosis; N = number of patients in analysis set for each individual subgroup; n = number of patients in each individual subgroup with an event; PE = pulmonary embolism.
Note: Events are included in the on-treatment study period if they occurred on or after the date of the first dose of any study drug. Events that start after the third day following the date of any "last dose" and before the date of the next "first dose" are not considered for the on-treatment study period.
Note: Events are included in the treatment-plus-30-days study period if they occurred on or after the date of the first dose of any study drug. Events that start 30 days after the last dose of the study drug are not considered for the treatment-plus-30-days study period.
Source: Clinical Study Reports: Hokusai–VTE study.[1]

TABLE 25: ADJUDICATED MAJOR AND CRNM BLEEDING BY CENTRE-LEVEL PERCENTAGE TIME IN THERAPEUTIC RANGE, SAFETY ANALYSIS SET, ON-TREATMENT STUDY PERIOD

Adjudicated Major or CRNM Bleeding	Edoxaban n/N (%)	Warfarin n/N (%)
Centres with TTR < 60%	83/1,199 (6.9)	139/1,271 (10.9)
Centres with TTR ≥ 60%	265/2,876 (9.2)	284/2,845 (10.0)
Centres with TTR < 25th percentile (55.82%)	47/713 (6.6)	92/748 (12.3)
Centres with TTR ≥ 25th to < 50th percentile (64.03%)	117/1,329 (8.8)	140/1,291 (10.8)
Centres with TTR ≥ 50th to < 75th percentile (70.41%)	95/1,115 (8.5)	109/1,180 (9.2)
Centres with TTR ≥ 75th percentile	89/918 (9.7)	82/897 (9.1)

CRNM = clinically relevant non-major; N = number of patients analyzed within each individual subgroup; n = number of patients in each individual subgroup with an event; TTR = time in therapeutic range.
Note: Events are included in the on-treatment study period if they occurred on or after the date of the first dose of any study drug. Events that start after the third day following the date of any "last dose" and before the date of the next "first dose" are not considered for the on-treatment study period.
Source: Clinical Study Reports: Hokusai–VTE study.[1]

TABLE 26: TREATMENT-EMERGENT ADVERSE EVENTS REPORTED BY AT LEAST 2% OF PATIENTS, SAFETY ANALYSIS SET — ON-TREATMENT PERIOD

Adverse Events	Edoxaban N = 4,118 n (%)	Warfarin N = 4,122 n (%)
Nasopharyngitis	230 (5.6)	231 (5.6)
Urinary tract infection	165 (4.0)	149 (3.6)
Bronchitis	113 (2.7)	90 (2.2)
Influenza	101 (2.5)	91 (2.2)
Upper respiratory tract infection	85 (2.1)	93 (2.3)
Insomnia	83 (2.0)	66 (1.6)

Adverse Events	Edoxaban N = 4,118 n (%)	Warfarin N = 4,122 n (%)
Headache	240 (5.8)	201 (4.9)
Dizziness	113 (2.7)	124 (3.0)
Hypertension	110 (2.7)	121 (2.9)
Cough	127 (3.1)	109 (2.6)
Dyspnea	112 (2.7)	92 (2.2)
Diarrhea	159 (3.9)	170 (4.1)
Constipation	119 (2.9)	111 (2.7)
Nausea	112 (2.7)	103 (2.5)
Rash	85 (2.1)	89 (2.2)
Pain in extremity	203 (4.9)	190 (4.6)
Back pain	134 (3.3)	154 (3.7)
Arthralgia	114 (2.8)	104 (2.5)
Edema peripheral	141 (3.4)	170 (4.1)
Chest pain	92 (2.2)	108 (2.6)
Pyrexia	87 (2.1)	70 (1.7)
Hepatic enzyme increased	118 (2.9)	118 (2.9)
Blood creatine phosphokinase increased	66 (1.6)	86 (2.1)
International normalized ratio increased	21 (0.5)	336 (8.2)

Source: Clinical Study Reports: Hokusai–VTE study.[1]

TABLE 27: ADJUDICATED PRIMARY CAUSE OF DEATH — SAFETY ANALYSIS SET — OVERALL STUDY PERIOD

Cause of Death	Edoxaban N = 4,118 n (%)	Warfarin N = 4,122 n (%)
All causes	136 (3.3)	130 (3.2)
VTE-related death	27 (0.7)	28 (0.7)
PE	4 (< 0.1)	3 (< 0.1)
Unexplained death (and VTE cannot be ruled out)	23 (0.6)	25 (0.6)
Cardiovascular death	15 (0.4)	13 (0.3)
MI	2 (< 0.1)	2 (< 0.1)
Ischemic stroke	6 (0.1)	3 (< 0.1)
SEE	0 (0.0)	0 (0.0)
Other cardiac death	7 (0.2)	8 (0.2)
Other known cause	94 (2.3)	89 (2.2)
Cancer	51 (1.2)	59 (1.4)
Bleeding (including hemorrhagic stroke)	6 (0.1)	10 (0.2)
Infections disease	25 (0.6)	12 (0.3)
Other	12 (0.3)	8 (0.2)

MI = myocardial infarction; N = number of patients in analysis set; n = number of patients meeting event criteria; PE = pulmonary embolism; SEE = systemic embolic event; VTE = venous thromboembolism.
Note: Deaths are included in the overall study period if they occurred on or after the date of the first dose of any study drug. All deaths that occurred prior to last study follow-up contact are considered for d.
Source: Clinical Study Reports: Hokusai–VTE study.[1]

APPENDIX 5: SUMMARY OF COMPARATOR CHARACTERISTICS

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) and/or pulmonary embolism (PE) in Canada.

Findings

Table 28 shows a summary of the comparator pharmacological characteristics of the drugs and drug classes approved to treat DVT and PE in Canada.

TABLE 28: SUMMARY OF THE COMPARATOR PHARMACOLOGICAL CHARACTERISTICS OF THE DRUGS AND DRUG CLASSES APPROVED TO TREAT DVT AND PE IN CANADA

	Dabigatran	Edoxaban	Rivaroxaban	Apixaban	Dalteparin Sodium, Enoxaparin Sodium, Nadroparin Calcium, and Tinzaparin Sodium	Fondaparinux	Warfarin Sodium and Nicoumalone	Heparin Sodium
Therapeutic Class	Direct thrombin inhibitor	Direct factor Xa inhibitor			LMWH	Indirect factor Xa inhibitor	Vitamin K antagonist	Unfractionated heparin
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	VTE (DVT and PE) and prevention of DVT and PE	DVT	Acute DVT Acute PE	Venous thrombosis and PE for warfarin sodium; prevention and treatment of VTE for nicoumalone	Treatment of venous thrombosis and prevention of VTE
Mechanism of Action	Competitive, reversible, direct thrombin inhibitor	Highly selective, direct, reversible inhibitor of factor Xa	Highly selective, direct antithrombin independent factor Xa inhibitor	Reversible, direct, highly selective active site inhibitor of factor Xa	Blocks the formation of blood clots because by enhancing the action of antithrombin	Indirect inhibitor of factor Xa	Indirect inhibition of coagulation factors II, VII, IX, and X through vitamin K antagonism	Inhibits reactions that lead to blood clotting
Route of Administration	Oral	Oral	Oral	Oral	Subcutaneous	Subcutaneous	Oral	Intravenous or subcutaneous

	Dabigatran	Edoxaban	Rivaroxaban	Apixaban	Dalteparin Sodium, Enoxaparin Sodium, Nadroparin Calcium, and Tinzaparin Sodium	Fondaparinux	Warfarin Sodium and Nicoumalone	Heparin Sodium
Dosing	Recommended daily dose is 300 mg (or 220 mg for elderly ≥ 80 years) taken orally as one 150 mg capsule (or 110 mg capsule for elderly ≥ 80 years) twice daily following treatment with a parenteral anticoagulant for 5 to 10 days.[a]	The recommended dose is 60 mg once daily. For patients with one or more of the following clinical factors, it is 30 mg once daily: • Moderate renal impairment (CrCl 30 mL/min to 50 mL/min) • Low body weight (≤ 60 kg) • Concomitant use of P-gp inhibitors (except amiodarone and verapamil) following initial use of a parenteral anticoagulant for 5 to 10 days	The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first 3 weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE. The recommended maximum daily dose is 30 mg during the first 3 weeks of treatment and 20 mg thereafter.[b]	The recommended dose for treatment of acute DVT or PE is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily.[c]	**Enoxaparin** 1.5 mg/kg SC daily or 1 mg/kg SC every 12 hours. Single daily dose should not exceed 180 mg.[d] **Dalteparin** 200 anti-Xa IU/kg SC daily. Single daily dose should not exceed 18,000 IU. For patients at increased risk of bleeding: 100 anti-Xa IU/kg SC twice daily OR 100 anti-Xa IU/kg over 12 hours IV as a continuous infusion.[d] **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 twice daily.[d] **Tinzaparin** 175 anti-Xa IU/kg SC daily.[d] Single daily dose should not exceed 18,000 IU.	The recommended dose is 5 mg (body weight < 50 kg); 7.5 mg (body weight 50 kg to 100 kg); or 10 mg (body weight > 100 kg) SC once daily. 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). The average duration of administration is 7 days.	**Warfarin sodium** The administration and dosage of warfarin sodium must be individualized according to the patient's responsiveness to the drug. The dosage should be adjusted according to results of the patient's PT ratio/INR. Measurement of warfarin-induced effects on PT can vary substantially due to the sensitivity of different thromboplastin reagents.[e] **Nicoumalone (also known as acenocoumarol):** The recommended initial dose is 8 mg to 12 mg on the first day and 4 mg to 8 mg on the second day. Subsequent doses are determined by the INR.	**For treatment of VTE** Continuous IV: • bolus: 5,000 units, then 1,300 units/hour OR • bolus: 80 units/kg, then 18 units/kg/hour Subcutaneous: • monitored: 17,500 units or 250 units/kg every 12 hours OR • unmonitored: 333 units/kg first dose, then 250 units/kg every 12 hours Prophylaxis (fixed-dose therapy): • 5,000 units SC every 8 to 12 hours

	Dabigatran	Edoxaban	Rivaroxaban	Apixaban	Dalteparin Sodium, Enoxaparin Sodium, Nadroparin Calcium, and Tinzaparin Sodium	Fondaparinux	Warfarin Sodium and Nicoumalone	Heparin Sodium
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.	In healthy patents, edoxaban is absorbed with peak plasma concentrations attained within 1 to 2 hours of administration. Edoxaban is poorly soluble at a pH of 6.0 or higher. The absolute bioavailability is 62%. The elimination half-life ranges from 10 to 14 hours. The mean volume of distribution is 107 ± 19.9 L (SD). The renal clearance (11 L/hour) of unchanged drug contributes approximately 50% to the total clearance (22 L/hour), with the remaining 50% non-renal clearance occurring through metabolism and biliary secretion.	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 the 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 maximum concentrations (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 are well absorbed following SC injection, with bioavailability > 90%. Peak plasma activity would be expected 3 to 6 hours after a SC dose. The elimination half-lives vary between drugs: dalteparin 3 to 4 hours; enoxaparin 4 to 7 hours; nadroparin 3.5 to 11 hours; tinzaparin 1 to 2 hours. Longer half-lives are seen after repeat dosing. The half-life is extended in patients with renal failure.	Mostly excreted unchanged in urine. The peak steady-state plasma concentration is, on average, 1.20 mg/L to 1.26 mg/L. The minimum steady-state plasma concentration is 0.46 mg/L to 0.62 mg/L. The elimination half-life (T1/2) is 17 to 21 hours in healthy patients. Up to 77% of a single subcutaneous dose of fondaparinux is excreted in urine as unchanged compound within 72 hours in healthy individuals up to 75 years of age.	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 the cytochrome P450 system.	The onset of action is immediate after IV injection, but can be delayed 20 to 60 minutes following SC injection. Heparin is extensively bound to plasma proteins. Heparin does not cross the placental barrier and is not distributed into breast milk. Heparin is not removed by hemodialysis. The plasma half-life of heparin increases from approximately 60 minutes with a 100 unit/kg dose to about 150 minutes with a 400 unit/kg dose. Clinically, a half-life of approximately 90 minutes is used. At low doses, clearance is predominantly through a saturable mechanism by the reticuloendothelial system. At higher doses, renal clearance through a non-saturable mechanism also occurs.

	Dabigatran	Edoxaban	Rivaroxaban	Apixaban	Dalteparin Sodium, Enoxaparin Sodium, Nadroparin Calcium, and Tinzaparin Sodium	Fondaparinux	Warfarin Sodium and Nicoumalone	Heparin Sodium
Drug–drug Interactions	Potent P-gp inducers or inhibitors Not metabolized by the human cytochrome P450 system	Inhibitor of P450 enzymes. Does not induce cytochrome 1A2, cytochrome 3A4, or the P-gp transporter. Does not inhibit P-gp. Combined use with strong cytochrome 3A4 and P-gp (e.g., phenytoin, carbamazepine, and phenobarbital) should generally be avoided.	P-gp inhibitors, cytochrome 3A4 inhibitors	Inhibitors of both cytochrome 3A4 and P-gp Inducers of both cytochrome 3A4 and P-gp Drug products affecting hemostasis	Caution should be exercised when using LMWHs together with other medications that can increase the risk of bleeding; e.g., oral anticoagulants, platelet inhibitors, or NSAIDs. Avoid using steroidal anti-inflammatory drugs together with LMWHs if possible; monitor for signs of bruising or bleeding.	Not metabolized by liver, so cytochrome P450 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).	Oral anticoagulants (e.g., warfarin) can contribute to a small extent to an increase in APTT. Heparin can contribute to an increase in PT. While these two drugs are given together, the fact that each may contribute to an increase in PT and APTT should be taken into account. IV nitroglycerin may reduce heparin's anticoagulant effect and necessitate higher doses.

	Dabigatran	Edoxaban	Rivaroxaban	Apixaban	Dalteparin Sodium, Enoxaparin Sodium, Nadroparin Calcium, and Tinzaparin Sodium	Fondaparinux	Warfarin Sodium and Nicoumalone	Heparin Sodium
Monitoring	In certain infrequent situations (such as overdosage, acute bleeding, urgent surgery, suspected non-compliance, or other unusual circumstances), assessment of the anticoagulant effect of dabigatran may be appropriate.	Although there is no need to monitor the anticoagulation effect of edoxaban during routine clinical practice, in certain infrequent situations (such as overdosage, acute bleeding, urgent surgery, suspected non-compliance, or other unusual circumstances), assessment of the anticoagulant effect of edoxaban may be appropriate.	Although there is no need to monitor the anticoagulation effect of rivaroxaban during routine clinical practice, in certain infrequent situations (such as overdosage, acute bleeding, urgent surgery, suspected non-compliance, or other unusual circumstances), assessment of the anticoagulant effect of rivaroxaban may be appropriate.	Although there is no need to monitor the anticoagulation effect of apixaban during routine clinical practice, in certain infrequent situations (such as overdosage, acute bleeding, urgent surgery, suspected non-compliance, or other unusual circumstances), assessment of the anticoagulant effect of apixaban may be appropriate.	Factor Xa is sometimes measured; otherwise, no monitoring		Frequent monitoring is required due to narrow therapeutic index and numerous drug interactions.	When heparin sodium is administered in therapeutic amounts, its dosage should be regulated by frequent blood coagulation tests. If the coagulation test is unduly prolonged, or if hemorrhage occurs, discontinue heparin promptly. Periodic platelet counts, hematocrits, and tests for occult blood in the stool are recommended during the entire course of heparin therapy, regardless of the route of administration.

APTT = activated partial thromboplastin time; AUC = area under the curve; CrCl = creatinine clearance; DVT = deep vein thrombosis; INR = international normalized ratio; LMWH = low-molecular-weight heparins; IU = international unit; IV = intravenous; P-gp = P-glycoprotein; PE = pulmonary embolism; PT = prothrombin time; SC = subcutaneous; SD = standard deviation; VTE = venous thromboembolism.

[a] The duration of therapy should be individualized after carefully assessing 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); extended duration should be based on permanent risk factors or idiopathic DVT or PE.

[b] The duration of therapy should be individualized after carefully assessing 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); extended duration should be based on permanent risk factors or idiopathic DVT or PE.

[c] The duration of therapy should be individualized after carefully assessing 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); extended duration should be based on permanent risk factors or idiopathic DVT or PE. Further to the course of a minimum of 6 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.

[d] Treatment with warfarin is normally started immediately. LMWH therapy should continue concomitantly with warfarin therapy for at least 5 days, and should not be discontinued until the INR is in the therapeutic range for two consecutive days.

[e] For patients with a first episode of DVT or PE secondary to a transient (reversible) risk factor, treatment with warfarin for 3 months is generally recommended. For patients with a first episode of idiopathic DVT or PE, warfarin is generally recommended for at least 6 to 12 months. For patients with two or more episodes of documented DVT or PE, indefinite treatment with warfarin is suggested. The dose of warfarin should be adjusted to maintain a target INR of 2.5 (INR range: 2.0 to 3.0) for all treatment durations.

Source: Product monographs;[15,28-30,41-48] e-CPS.[49]

Summary

Edoxaban, apixaban, dabigatran, and rivaroxaban are all novel oral anticoagulants indicated in Canada for the treatment of venous thromboembolism (VTE) (DVT, PE) and the prevention of recurrent DVT and PE. Older approved drugs include vitamin K antagonists (VKAs), low-molecular-weight heparins (LMWHs), unfractionated heparin, and fondaparinux. The anticoagulant drug classes are differentiated by the elements they inhibit in the coagulation cascade, the nature of the inhibition (direct or indirect), and the pharmacokinetic characteristics, such as route of administration (oral or parenteral), propensity for drug interactions, and monitoring requirements. Compared with warfarin therapy, edoxaban, apixaban, dabigatran, and rivaroxaban may offer a more convenient therapeutic option for treating patients with VTE. Specifically, fewer monitoring requirements, easy dosing strategies, rapid onset of effect (obviating the need for initial bridging with an LMWH, except for edoxaban and dabigatran), and oral formulation (LMWH, fondaparinux, and unfractionated heparin are administered subcutaneously) may appeal to both patients and prescribers.

APPENDIX 6: SUMMARY OF INDIRECT TREATMENT COMPARISONS

Introduction

Background

No studies were identified in this review comparing edoxaban directly with other direct oral anticoagulants (DOACs) used in the treatment and prevention of venous thromboembolism (VTE). The objective of this section was to summarize and critically appraise published and unpublished indirect evidence available for the assessment of the comparative efficacy and harms of edoxaban versus appropriate comparators for the treatment of VTE and the prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE).

Methods

Two indirect treatment comparisons (ITCs) submitted by the manufacturer were reviewed,[36,37] of which one was manufacturer-sponsored.[37] CADTH Common Drug Review (CDR) conducted an independent literature search for published ITCs that compared edoxaban with other relevant comparators for the treatment of VTE and the prevention of recurrent DVT and PE; five additional publications were identified.[31-35]

Description of ITCs Identified

Table 29 presents the population, interventions, comparisons, outcomes, and study design (PICOS) criteria for each ITC identified.

TABLE 29: POPULATION, INTERVENTIONS, COMPARISONS, OUTCOMES, AND STUDY DESIGN CRITERIA FOR STUDY INCLUSION

	Manufacturer-Sponsored and -Submitted ITC 2016[37]	Manufacturer-Submitted ITC, Wells et al. 2016[36]	Cohen et al. 2015[31]	Mantha and Ansell 2015[32]	Hirschl and Kundi 2014[33]	Kang and Sobieraj 2014[34]	Castelucci et al. 2014[35]
Population	Patients diagnosed with VTE, including both DVT and PE, who were included in a study for a newly treated VTE episode (i.e., treated for less than one month)	Adults with acute or prior VTE (DVT, PE)	Adult patients with symptomatic VTE (DVT and/or PE), who were receiving initial or long-term treatment following an acute VTE event	Patients with DVT, PE or both	Patients with acute VTE		
Intervention and Comparators	• ***Primary interest***: apixaban, betrixaban, edoxaban, and rivaroxaban, and direct thrombin inhibitors (dabigatran) with or without initial treatment with parenteral anticoagulant (LMWH, UFH, or an indirect factor Xa inhibitor) • ***Secondary interest***: VKAs (warfarin, acenocoumarol, fluindione, phenindione, phenprocoumon) along with one of the above-noted parenteral anticoagulants; Aspirin with or without one of the above-noted parenteral anticoagulants • Placebo or other active therapies providing direct or indirect evidence for the treatments of interest	• Apixaban • Dabigatran • Rivaroxaban • Edoxaban • Standard treatment (LMWH followed by VKA) • ASA • Placebo	• Apixaban • Dabigatran • Rivaroxaban • Edoxaban • Warfarin/VKA	• Apixaban • Dabigatran • Rivaroxaban • Edoxaban • Initial parenteral drug followed by VKA	• Apixaban • Dabigatran • Rivaroxaban • Edoxaban • Vitamin K antagonist (VKA, warfarin, and acenocoumarol)	• Apixaban • Dabigatran • Rivaroxaban • Edoxaban • Parenteral drug followed by VKA	• Parenteral anticoagulants (UFH, LMWH, or fondaparinux) with transition to VKA • LMWH + dabigatran combination • LMWH + edoxaban combination • Rivaroxaban • Apixaban • LMWH alone

	Manufacturer-Sponsored and -Submitted ITC 2016[37]	Manufacturer-Submitted ITC, Wells et al. 2016[36]	Cohen et al. 2015[31]	Mantha and Ansell 2015[32]	Hirschl and Kundi 2014[33]	Kang and Sobieraj 2014[34]	Castelucci et Al. 2014[35]
Outcomes	• Recurrent VTE (DVT or PE) • Major bleeds • CRNM bleeds • VTE-related mortality • All-cause mortality • Total AEs • Post-thrombotic syndrome • Treatment discontinuation • Anticoagulant-induced clots • Chronic thromboembolic pulmonary hypertension • Cardiovascular events (e.g., heart attack)	• Recurrent VTE • Recurrent DVT • Recurrent PE (fatal and non-fatal) • Major bleeds • Acute coronary syndrome • Major adverse cardiovascular events • Stroke • Cardiovascular death • All-cause death • Intracranial bleeding	• Recurrent VTE and VTE-related death • Major bleeding • CRNM bleeding • Major or CRNM bleeding • All-cause mortality	• Recurrent VTE • Major bleeding • Major or CRNM bleeding • Mortality	• Recurrent VTE • Death • Major bleeding • Major and CRNM bleeding • Fatal bleeding • Intracranial bleeding	• Recurrent VTE • Recurrent PE • Recurrent DVT • Mortality • Major bleeding	• Recurrent VTE • PE • DVT • Major bleeding
Study Design	Phase II and III RCTs with a minimum follow-up duration of 3 months; both open-label and blinded studies were retained	Phase III RCTs	Phase III RCTs	Phase III RCTs	RCTs	Phase III RCTs	Phase III RCTs
Other			English language				

AE = adverse event; ASA = acetylsalicylic acid; CRNM = clinically relevant non-major; DVT = deep vein thrombosis; ITC = indirect treatment comparison; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; RCT = randomized controlled trial; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Review and Appraisal of Indirect Treatment Comparisons

Review of the Manufacturer-Sponsored Indirect Treatment Comparison

Objectives and Rationale for Indirect Treatment Comparison A

The objective of the network meta-analysis was to evaluate the relative effectiveness and safety of edoxaban relative to other DOACs for the treatment and secondary prevention of venous thromboembolism.

Methods for the Manufacturer-Sponsored Indirect Treatment Comparison

Study Eligibility and Selection Process

A systematic literature review was performed to identify randomized controlled trials (RCTs) that studied the efficacy and safety of edoxaban and other non-vitamin K antagonist (non-VKA) oral anticoagulants (namely rivaroxaban, apixaban, and dabigatran) for the treatment and secondary prevention of VTE. MEDLINE, the Cochrane Library, and Embase were searched; the search was last updated on January 13, 2016. Additional searches were performed by inspecting the reference lists of existing reviews, trial registers, and recent conference abstracts. Two reviewers independently screened all of the titles and abstracts identified by the electronic search using the selection criteria that were established a priori. Where needed, a third reviewer was consulted to settle disagreements through consensus discussion. Data extraction from the final set of included trials was performed by one reviewer using a structured data extraction sheet; a second reviewer verified the data.

Data Extraction

The network included nine trials that provided data specific to edoxaban and the three other DOACs (apixaban, dabigatran, and rivaroxaban) that are currently marketed in Canada. Across the nine trials, average patient age (range: 55.0 years to 61.4 years across study arms), body weight (range: 78.4 kg to 85.8 kg across study arms), and sex distribution (range: from 47.0% to 65.3% male) were similar across the studies. However, the type of VTE diagnosis varied across trials: four trials enrolled DVT patients only, one trial enrolled only PE patients, and the remaining four trials enrolled both PE and DVT patients. Among studies that provided data regarding the proportion of patients with idiopathic (unprovoked) VTE, values varied widely: proportions ranged from 35% to 36% in the RE-COVER studies to up to 90% in the AMPLIFY trial. However, the proportions of patients with unprovoked VTE were similar in the Hokusai–VTE (65% to 66%), EINSTEIN–DVT (61% to 63%), and EINSTEIN–PE (64% to 65%) studies. Among the seven studies that reported on the proportion of patients with cancer at baseline, values ranged between 2% and 12% of patients. Three studies reported the proportion of patients with a history of cancer, which ranged between 4% and 10%. The prevalence of renal insufficiency was reported by five trials, with values ranging between 4.9% and 8.6% across study arms (Table 30).

There was also variation between studies regarding the blinding of patients and clinicians. The AMPLIFY, RE-COVER, and RE-COVER II studies all employed double-blinding, while the Hokusai–VTE trial used double-blinding after open-label administration of heparin. The Boticelli, EINSTEIN–DVT Dose-Ranging, and ODIXa–DVT trials administered DOAC therapy in a double-blinded manner, while VKA therapy was administered open-label, and the EINSTEIN–DVT and EINSTEIN–PE studies were both open-label studies (with blinded outcome assessment).

Sample sizes ranged between 520 (Botticelli) and 8,292 patients (Hokusai–VTE) (Table 30). Treatment duration also varied widely: two studies (EINSTEIN–DVT Dose-Ranging Study; ODIXa–DVT) had a treatment duration of three months, while three studies (AMPLIFY, RE-COVER, and RE-COVER II) had a treatment duration of six months; one apixaban study (Botticelli) employed a variable length of therapy that ranged between 84 and 91 days; and three trials (Hokusai–VTE, EINSTEIN–PE, and EINSTEIN–DVT

trials) had variable treatment durations, ranging from three to 12 months. Treatment duration was considered an important treatment modifier in the current network meta-analysis (NMA), as patients with a higher risk of VTE recurrence are recommended to receive anticoagulation treatment for a longer duration. There were also variations in the initial therapy received by patients across the included studies (Table 31).

Comparators

Nine trials provided data specific to edoxaban and the three other DOACs (apixaban, dabigatran, and rivaroxaban) that are currently marketed in Canada. In these studies, the comparator arm was a VKA. Of these studies, one was for edoxaban, two were for apixaban, two were for dabigatran, and four were for rivaroxaban. A summary of the included studies is provided in Table 30 and Table 31.

Outcomes

Outcome definitions were similar across the included trials. All studies analyzed efficacy end points using an intention-to-treat (ITT) or modified intention-to-treat (mITT) approach except for the EINSTEIN–DVT Dose-Ranging Study, which used a per-protocol approach. Except for the Hokusai–VTE study, all studies monitored and counted efficacy and safety events that occurred until the end of the intended treatment duration. The Hokusai–VTE study included two efficacy outcomes assessments. Regardless of the length of the patient's study treatment, the primary efficacy analysis included all primary efficacy outcomes, from randomization through the end of 12 months or study closure (overall study period). Therefore, the Hokusai–VTE study was considered a potential outlier among the nine included trials. The Hokusai–VTE publication also reported an additional assessment of efficacy outcomes that included events that occurred during the on-treatment period, which also included three days after the study drug was stopped or interrupted. The latter approach (i.e., assessment of efficacy outcomes during the on-treatment period) is the method that is typically used in other studies.

Quality Assessment of Included Studies

The studies selected for inclusion in this systematic review for the primary analyses (i.e., the grouped initial therapies network) were assessed using the Cochrane Risk of Bias tool. Overall, the studies were found to be rigorous and were assigned a low risk of bias for sequence generation, allocation concealment, blinding of outcome assessors, completeness of outcome reporting, and selective reporting. All studies were double-blinded except for the EINSTEIN trials, which were open-label. However, given that the events were evaluated by a central, blinded, independent adjudication committee, the open-label design is unlikely to have influenced the outcome measurement.

TABLE 30: BASELINE CHARACTERISTICS OF INCLUDED STUDIES

Trial	Treatment, Number Randomized	Mean Age	PE Alone %	PE and PE/DVT %	DVT Alone %	Idiopathic/ Unprovoked %	Cancer History %	Active Cancer %	Renal Insuff %	Treatment Duration
Hokusai–VTE (2013), DB, NI, RCT	HEP + WAR INR 2.0 to 3.0 (n = 4,122)	55.9	NR	40.5	59.5	65.4	9.5	NR	6.6	3 to 12 months
	HEP + EDO 60 mg q.d., (n = 4,118)	55.7	NR	40.0	60.0	65.9	9.2	NR	6.5	
AMPLIFY (2013), DB, NI, RCT	ENO + WAR INR 2.0 to 3.0 (n = 2,704)	56.7	25.2	33.5	65.9	89.8	NR	2.8	5.5	6 months
	API 10 mg b.i.d. for the first 7 days followed by 5 mg b.i.d. (n = 2,691)	57.2	25.2	34.5	65.0	89.8	NR	2.5	6.0	
Botticelli (2008), DB (API); OL (LMWH, VKA), RCT	LMWH + VKA INR 2.0 to 3.0 (n = 128)	59	0	NR	NR	NR	NR	8.6	NR	84 to 91 days
	API 5 mg b.i.d. (n = 130)	56	0	NR	NR	NR	NR	8.5	NR	
	API 10 mg b.i.d. (n = 134)	59	0	NR	NR	NR	NR	4.5	NR	
	API 20 mg q.d. (n = 128)	60	0	NR	NR	NR	NR	7	NR	
RE-COVER (2009), DB, NI, RCT	INI + WAR INR 2.0 to 3.0 (n = 1,266)	55[a]	21.4	9.8	68.6	36.2[b]	4.5	5.3	4.9	6 months
	INI + DAB 150 mg b.i.d. (n = 1,273)	56[a]	21.2	9,5	69.1	35.0[b]	5.0	3.1	0	
RE-COVER II (2014), DB, NI, RCT	INI + WAR INR 2.0 to 3.0 (n = 1,288)	NR	23.1	9.1	67.8	36.2[b]	NR	3.9	NR	6 months
	INI + DAB 150 mg b.i.d. (n = 1,280)	NR	23.3	8.1	68.5	35.0[b]	NR	3.9	NR	
ODIXa–DVT (2007), DB (RIV); OL (ENO, VKA), RCT	ENO + VKA (n = 126)									12 weeks
	RIV 10 mg b.i.d. (n = 119)	58.5	0	0	100	NR	NR	3	NR	
	RIV 20 mg b.i.d. (n = 117)	57.5	0	0	100	NR	NR	3	NR	
	RIV 30 mg b.i.d. (n = 121)	61.4	0	0	100	NR	NR	2	NR	
	RIB 40 mg q.d. (n = 121)	59.5	0	0	100	NR	NR	1	NR	
EINSTEIN–DVT (2010), OL; blinded outcome adjudication, NI, RCT	ENO + VKA INR 2.0 to 3.0 (n = 1,718)	56.4	0	0.6	98.8	63.0	NR	5.2	7.0	3, 6, or 12 months
	RIV 15 mg b.i.d. for first 3 weeks; 20 mg q.d. thereafter (n = 1,731)	55.8	0	0.7	98.7	60.9	NR	6.8	6.6	
EINSTEIN–PE (2012), OL; blinded outcome adjudication, NI, RCT	ENO + VKA INR 2.0 to 3.0 (n = 2,413)	57.5	75.5	24.5	0	64.3	NR	4.5	7.9	3, 6, or 12 months
	RIV 15 mg b.i.d. for first 3 weeks; 20 mg q.d. thereafter (n = 2,419)	57.9	74.9	25.1	0	64.7	NR	4.7	8.6	
EINSTEIN–DVT Dose-Ranging (2008), DB (RIV doses) and OL	HEP + VKA INR 2.0 to 3.0 (n = 137)	57	0	0	100	NR	NR	7	NR	84 days (± 14 days)
	RIV 20 mg q.d. (n = 135)	58	0	0	100	NR	NR	8	NR	
	RIV 30 mg q.d. (n = 134)	57	0	0	100	NR	NR	10	NR	

Trial	Treatment, Number Randomized	Mean Age	PE Alone %	PE and PE/DVT %	DVT Alone %	Idiopathic/ Unprovoked %	Cancer History %	Active Cancer %	Renal Insuff %	Treatment Duration
(LMWH/VKA); blinded outcome assessment, RCT	RIV 40 mg q.d. (n = 136)	60	0	0	100	NR	NR	12	NR	

ACEN = acenocoumarol; API = apixaban; b.i.d. = twice daily; DAB = dabigatran; DB = double-blind; DVT = deep vein thrombosis; EDO = edoxaban; ENO = enoxaparin; HEP = heparin; INI = initial parenteral anticoagulation; INR = international normalized ratio; insuff = insufficiency; LMWH = low-molecular-weight heparin; NI = noninferior; NR = not reported; OL = open-label; PE = pulmonary embolism; q.d. = once daily; RCT = randomized controlled trial; RIV = rivaroxaban; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism; WAR = warfarin.
[a] Denotes median as opposed to mean.
[b] Pooled data of RE-COVER (2009) and RE-COVER II (2014).
Source: Manufacturer's submission.[37]

TABLE 31: DETAILS REGARDING INTERVENTIONS IN STUDIES INCLUDED IN THE NETWORK META-ANALYSIS

Study	Treatment Group	Long-term Treatment	Initial Treatment	Initial Treatment Duration	Dose/Adjustment/Admin of Long-Term Treatment	Frequency of Long-Term Treatment	Duration of Long-Term Treatment
Hokusai–VTE (2013)	HEP + WAR	WAR	ENO or UFH	> 5 days	Dose adjusted to maintain the INR between 2.0 and 3.0, oral	NR	Started concurrently w/heparin, continued for ≥ 3 months and max of 12 months (determined by treating physician on the basis of patient's clinical features and preference)
	HEP + EDO	EDO	ENO or UFH	> 5 days	60 mg q.d., or at 30 mg in patients with a CrCl of 30 mL/min to 50 mL/min or a body weight ≤ 60 kg or in patients receiving concomitant treatment with potent P-glycoprotein inhibitors	q.d.	Started after discontinuation of heparin, continued for ≥ 3 months and max of 12 months (duration determined by treating physician on the basis of the patient's clinical features and preference)
AMPLIFY (2013)	ENO + WAR	WAR	ENO	> 5 days, discontinued when a blinded INR of > 2.0 was achieved	Dose adjusted to maintain the INR between 2.0 and 3.0	NR	Started concomitantly with ENO and continued for 6 months
	API	API	NA	NA	10 mg b.i.d. for the first 7 days followed by 5 mg for 6 months b.i.d.	b.i.d.	6 months
Botticelli (2008)	LMWH + VKA	VKA	ENO or TIN	Minimum heparin treatment for 5 days, inclusive of up to 24 hours before randomization if a permitted LMWH was used	Dose adjusted to maintain the INR between 2.0 and 3.0 (target 2.5)	NR	84 days

Study	Treatment Group	Long-term Treatment	Initial Treatment	Initial Treatment Duration	Dose/Adjustment/Admin of Long-Term Treatment	Frequency of Long-Term Treatment	Duration of Long-Term Treatment
	API 5	API 5	NA	NA	5 mg	b.i.d.	84 days
	API 10	API 10	NA	NA	10 mg	b.i.d.	84 days
	API 20	API 20	NA	NA	20 mg	q.d.	84 days
RE-COVER (2009)	INI + WAR	WAR	Approved parenteral anticoagulant (generally UFH or LMWH)	Given for at least 5 days and the true or sham INR was recorded as 2.0 or higher on 2 consecutive days (median of 9 days)	Dose adjusted to achieve an INR of 2.0 to 3.0	NR	6 months
	INI + DAB	DAB			150 mg b.i.d.	b.i.d.	6 months
RE-COVER II (2014)	INI + WAR	WAR	UFH or LMWH	5 to 11 days	Dose adjusted to achieve an INR of 2.0 to 3.0	NR	6 months
	INI + DAB	DAB	UFH or LMWH	5 to 11 days	150 mg b.i.d.	b.i.d.	6 months
ODIXa–DVT (2007)	ENO + VKA	VKA	ENO	≥ 5 days and until INR had reached INR 2 to 3 on 2 consecutive days	NR	NR	12 weeks
	RIV 10	RIV 10	NR	NR	10 mg q.d.	b.i.d.	12 weeks
	RIV 20	RIV 20	NR	NR	20 mg q.d.	b.i.d.	12 weeks
	RIV 30	RIV 30	NR	NR	30 mg q.d.	b.i.d.	12 weeks
	RIB 40	RIV 40	NR	NR	40 mg q.d.	q.d.	12 weeks
EINSTEIN–DVT (2010)	ENO + VKA	VKA	ENO	≥ 5 days and until INR was 2.0 or more for 2 consecutive days	Dose adjusted to maintain an INR of 2.0 to 3.0	INR was determined at least once per month	Pre-specified 3, 6, or 12 months
	RIV	RIV	NA	NA	15 mg b.i.d. for first 3 weeks; 20 mg q.d. thereafter	b.i.d. for first 3 weeks, q.d. thereafter	Pre-specified 3, 6, or 12 months
EINSTEIN–PE (2012)	ENO + VKA	VKA	ENO	≥ 5 days and until INR > 2.0 for 2 consecutive days	Dose adjusted to maintain an INR of 2.0 to 3.0	INR was determined at least once a month	Pre-specified 3, 6, or 12 months (determined by treating physician before randomization)
	RIV	RIV	NA	NA	15 mg b.i.d.for first 3 weeks; 20 mg q.d. thereafter	b.i.d.for first 3 weeks, q.d. thereafter	Pre-specified 3, 6, or 12 months (determined by treating physician before randomization)

Study	Treatment Group	Long-term Treatment	Initial Treatment	Initial Treatment Duration	Dose/Adjustment/Admin of Long-Term Treatment	Frequency of Long-Term Treatment	Duration of Long-Term Treatment
EINSTEIN–DVT Dose-Ranging (2008)	HEP + VKA	VKA	HEP	≥ 5 days, including a period < 36 hours before randomization if a permitted heparin was used; continued until a stable INR > 2 was observed on 2 measurements at least 24 hours apart	Dose adjusted to maintain the INR within the therapeutic range; target 2.5, range 2.0 to 3.0	Initially, the INR had to be measured every 2 to 3 days, and thereafter at least once monthly	Started within 48 hours after randomization until day 84 (± 14 days)
	RIV 20	RIV 20	NA	NA	20 mg	q.d.	84 days
	RIV 30	RIV 30	NA	NA	30 mg	q.d.	84 days
	RIV 40	RIV 40	NA	NA	40 mg	q.d.	84 days

API = apixaban; b.i.d.= twice daily; CrCl = creatinine clearance; DAB = dabigatran; DVT = deep vein thrombosis; EDO = edoxaban; ENO = enoxaparin; HEP = heparin; INI = initial parenteral anticoagulation; INR = international normalized ratio; LMWH = low-molecular-weight heparin; NA = not available; NMA = network meta-analysis; NR = not reported; PE = pulmonary embolism; q.d. = once daily; RIV = rivaroxaban; TIN = tinzaparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism; WAR = warfarin.
Source: Manufacturer's submission.[37]

Evidence Network

There were several methodological differences between the included trials, such as treatment duration (overall duration of therapy ranged from three to 12 months across studies) and follow-up time for efficacy end points (most notably for the Hokusai–VTE trial). These cross-study differences posed a significant challenge to the assumption of exchangeability for the NMA. As a result, consideration was given to performing an exploratory NMA. To minimize biases across the studies, three sets of analyses were undertaken (referred to as scenarios A, B, and C).

Scenario A, an analysis of mixed-duration trials, was based on the three phase III pivotal trials that assigned patients to a diverse mixture of treatment durations (three, six, and 12 months). These trials included the Hokusai–VTE study, EINSTEIN–DVT, and EINSTEIN–PE (Figure 2). The phase II rivaroxaban studies (ODIXa–DVT and EINSTEIN–DVT Dose-Ranging) were excluded from scenario A because their treatment durations were three months.

FIGURE 2: NETWORK OF EVIDENCE FOR SCENARIO A

Scenario B was an analysis of trials where patients were assigned to six months of therapy. NMAs were also performed using data from the AMPLIFY, RE-COVER, and RE-COVER II studies, as well as from a subgroup of patients from the Hokusai–VTE study who were intended to receive six months of therapy (Figure 3). The phase II apixaban study (Botticelli) was excluded from scenario B because the duration of treatment was only three months.

FIGURE 3: NETWORK OF EVIDENCE FOR SCENARIO B

Scenario C was an analysis of all studies. NMAs of data from all nine studies were performed under the assumption that trial duration was not an important modifier of treatment effect (Figure 4).

FIGURE 4: NETWORK OF EVIDENCE FOR SCENARIO C

Indirect Treatment Comparison Methods

Base-case NMAs that grouped initial parenteral therapies using a Bayesian approach were used to compare the interventions of interest. Because of the presence of single-study connections, fixed-effects models were used to estimate the relative efficacy and safety of edoxaban versus other oral anticoagulants. The reference treatment for NMAs was VKA therapy. Vague prior distributions were used for all of the model parameters to enable the collected trial data to drive findings from analysis. Odds ratios with 95% credible intervals (CrIs) were estimated. All analyses used a burn-in duration of a

minimum of 30,000 iterations and a sampling period of 50,000 iterations. Model convergence was assessed by review of trace plots and inspection of Monte Carlo error. Model fit was assessed by comparing the posterior residual deviance of each model to the number of unconstrained data points (i.e., the number of entire treated groups across studies) in the analysis. All NMAs were performed using OpenBUGS software with an R interface.

Since the network structures used were small and based on few trials, they did not consist of any closed loops; thus, formal model-based inspections for the presence of inconsistency between direct and indirect evidence could not be performed.

A heterogeneity assessment of patient and study characteristics in the included studies was conducted to assess the feasibility and validity of conducting an NMA based on available evidence. This assessment indicated that a high degree of heterogeneity led to the decision to pursue three sets of NMAs. These analyses controlled for variations in the duration of treatment and length of patient follow-up for study outcomes as described in the previous evidence network section. Nevertheless, such an approach was still unable to control for other heterogeneity, such as VTE etiology (provoked versus unprovoked VTE), VTE severity, and the distribution of treatment duration noted across the included studies. Given the geometry of the network under study (i.e., mainly single-study connections), meta-regression analyses to control for these differences were not feasible.

Results

Scenario A: Network Meta-Analyses Based on Mixed Treatment Duration

Three phase III pivotal trials (Hokusai–VTE, EINSTEIN–DVT, and EINSTEIN–PE) that studied the efficacy and safety of DOACs among patients receiving intended treatment durations of three, six, and 12 months were included in this analysis. Table 32 presents the results from the overall population analysis. There was no statistically significance difference between edoxaban and both VKA and rivaroxaban in reducing the risk of VTE recurrence. Edoxaban was associated with a statistically significant reduced risk of the composite of major and clinically relevant non-major (CRNM) bleeds compared with VKA therapy. There was no statistically significance difference between edoxaban and rivaroxaban in the composite outcome of major and CRNM bleeds. There was no statistically significance difference between edoxaban and both VKA and rivaroxaban in reducing the risk of major bleeds. There was no statistically significance difference between edoxaban and both VKA and rivaroxaban in overall mortality (Table 32). There were no data for a comparison of edoxaban to apixaban or dabigatran.

TABLE 32: [redacted]

[redacted]	[redacted]
VTE recurrence	[redacted]
Major + CRNM bleeding	[redacted]
Major bleed	[redacted]
Overall mortality	[redacted]

CRNM = clinically relevant non-major; VTE = venous thromboembolism.
Source: Manufacturer's submission.[37]

Subgroup analyses by DVT, PE (with or without DVT), renal insufficiency, age ≥ 75 years, active cancer, fragility, extensive DVT, extensive PE, and unprovoked VTE recurrence, were undertaken. Except for fragile patients (defined as patients with body weight ≤ 50 kg, age ≥ 75 years, or creatinine clearance [CrCl] of 30 mL/min to 50 mL/min), there was no statistically significant difference between edoxaban and VKA across all subgroup analyses for reducing the risk of VTE recurrence. In the subgroup of fragile patients, results were statistically significant in favour of edoxaban relative to VKA [redacted]. There were no statistically significant differences between edoxaban and rivaroxaban in all subgroup analyses.

For the composite outcome of major and CRNM bleeds, subgroup analyses were undertaken by DVT, PE (with or without DVT), renal insufficiency, age ≥ 75 years, active cancer, and fragility. Among the subgroup of patients with DVT, edoxaban was associated with a reduced risk of major and CRNM bleeds compared with VKA therapy [redacted]. No other statistically significant differences were noted between edoxaban and VKA therapy for other subgroups. There were no statistically significant differences between edoxaban and rivaroxaban in all available subgroup analyses.

Data were only available to do subgroup analyses by DVT and PE (with or without DVT) for the outcome of major bleeding. There were no statistically significant differences between edoxaban and VKA therapy for major bleeding in both the DVT and PE subgroups. Compared with rivaroxaban, edoxaban was associated with a statistically significantly increased risk of major bleeding [redacted] for the PE subgroup, while no statistically significant difference was found in the DVT subgroup.

Data were only available to do subgroup analysis by DVT and PE (with or without DVT) for the outcome of overall mortality. Comparisons of edoxaban with VKA therapy and with rivaroxaban in both the DVT and PE subgroups were not statistically significant.

Scenario B: Network Meta-Analyses of Six Months' Treatment

The NMAs conducted in scenario B included data from the four studies that involved an intended treatment duration of six months (AMPLIFY, RE-COVER, RE-COVER II and Hokusai–VTE). Data from the Hokusai–VTE subgroup were reanalyzed by censoring outcomes at six months to mimic the analysis method employed in the AMPLIFY and RE-COVER studies. Table 33 presents results from the overall population analysis. There was no statistically significant difference between edoxaban and VKA therapy, apixaban, and dabigatran in reducing the risk of VTE recurrence. In the NMA of the composite end point of major and CRNM bleed, there was no statistically significance difference between edoxaban and VKA therapy; however, edoxaban was associated with a significantly increased risk of major and CRNM bleeds compared with both apixaban and dabigatran. There was no statistically significance difference between edoxaban and both VKA therapy and dabigatran in reducing the risk of major bleeding; however, the comparison with apixaban indicated a significantly increased risk of major bleeding with edoxaban. There was no statistically significance difference between edoxaban and VKA therapy, apixaban, and dabigatran in overall mortality.

TABLE 33: [redacted]

[redacted]				
	[redacted]			
VTE recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Major + CRNM bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Major bleed	[redacted]	[redacted]	[redacted]	[redacted]
Overall mortality	[redacted]	[redacted]	[redacted]	[redacted]

CRNM = clinically relevant non-major; VTE = venous thromboembolism.
Source: Manufacturer's submission[37]

Subgroup analyses by DVT, PE (with or without DVT), renal insufficiency, age ≥ 75 years, active cancer, extensive DVT, extensive PE, and unprovoked were undertaken for the outcome of VTE recurrence. There were no statistically significant differences between edoxaban and VKA therapy across all subgroups. No data were available for apixaban for the subgroup analysis by active cancer, and no comparisons of edoxaban with apixaban achieved statistical significance in any of the remaining subgroups. No data were available for dabigatran for the extensive DVT and extensive PE subgroups, and no statistically significant differences between edoxaban and dabigatran were found in all remaining subgroups, except for renal insufficiency, which was statistically significant in favour of dabigatran [redacted].

Data were only available to perform subgroup analyses by DVT and PE (with or without DVT), renal insufficiency, age ≥ 75 years, active cancer, and extensive PE for the outcome of major bleeding. No subgroup data were available for dabigatran. There were no statistically significant differences between edoxaban and VKA therapy in all available subgroup analyses. Compared with apixaban, edoxaban was associated with statistically significant increases in risk in both the PE [redacted] and extensive PE [redacted] subgroups.

NMAs of subgroup data for the composite end point of major and CRNM bleed and mortality were not feasible due to the lack of data.

Scenario C: Network Meta-Analysis of All Trials Included

NMAs conducted in scenario C included data from the nine studies included in this review. Table 34 presents results from the overall population analysis. No statistically significance differences were identified for edoxaban compared with VKA, dabigatran, apixaban, or rivaroxaban for VTE recurrence. Edoxaban was associated with a significantly reduced risk of the composite of major and CRNM bleeds compared with VKA therapy. Compared with both apixaban and dabigatran, the risk of these bleeds was significantly increased with edoxaban, while there was no statistically significance difference between edoxaban and rivaroxaban in the composite outcome of major and CRNM bleeds. No statistically significant differences were identified for edoxaban compared with VKA, dabigatran, or rivaroxaban in reducing the risk of major bleeds. Compared with apixaban, the risk of major bleeding was statistically significantly increased with edoxaban. No analysis was done for all-cause mortality (Table 34).

TABLE 34: [redacted]

	[redacted]			
VTE recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Major + CRNM bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Major bleed	[redacted]	[redacted]	[redacted]	[redacted]

CRNM = clinically relevant non-major; VTE = venous thromboembolism.
Source: Manufacturer's submission.[37]

Subgroup analyses by DVT, PE (with or without DVT), renal insufficiency, age ≥ 75 years, active cancer, fragile, extensive PE, and unprovoked, for VTE recurrence, were undertaken. Some subgroups were not feasible for apixaban (i.e., active cancer patients, fragile patients) or dabigatran (i.e., fragile patients and those with extensive PE). Except for fragile patients, there was no statistically significant difference between edoxaban and VKA across all subgroup analyses for reducing the risk of VTE recurrence. In the subgroup of fragile patients, results were statistically significant in favour of edoxaban relative to VKA [redacted] There were no statistically significant differences between apixaban, dabigatran, and rivaroxaban for all subgroup analyses.

Subgroup analyses were undertaken by DVT, PE (with or without DVT), renal insufficiency, age ≥ 75 years , active cancer, and fragility, for the composite outcome of major and CRNM bleeds. No data were available for the extensive PE or unprovoked DVT subgroups. No subgroup data were available for comparisons with dabigatran, and subgroup analysis involving apixaban was only feasible for the DVT subgroup. Among the subgroup of patients with DVT, edoxaban was associated with a reduced risk of major and CRNM bleeds compared with VKA therapy [redacted]. No other statistically significant differences were noted between edoxaban and VKA therapy for other subgroups. Comparison of edoxaban and apixaban in the DVT subgroup did not achieve statistical significance. All comparisons between edoxaban and rivaroxaban did not achieve statistical significance.

Data were only available to do subgroup analyses by DVT, PE (with or without DVT), renal insufficiency, age ≥ 75 years , and extensive PE for the outcome of major bleeding. No data were available for active cancer, fragility, and unprovoked DVT subgroups. No subgroup data were available for comparisons involving dabigatran, and subgroup data for rivaroxaban were only available for the DVT and PE subgroups. No statistically significant differences were observed in any of the subgroup comparisons between edoxaban and VKA therapy. In comparison with apixaban, edoxaban was associated with statistically significant reductions in the risk of bleeding in the PE [redacted] age ≥ 75 years [redacted], and extensive PE [redacted] subgroups. However, there were no statistically significant differences between edoxaban and apixaban in the DVT and renal insufficient subgroups. Compared with rivaroxaban, edoxaban was associated with a statistically significantly increased risk of bleeding in the PE subgroup [redacted], while there was no statistically significant difference in the DVT subgroup between both interventions.

Sensitivity analyses were undertaken where VKA regimens were distinguished from each other based upon the class of initial therapy that was provided to patients (i.e., unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], or indirect factor Xa inhibitor). This network included the nine trials that were included in the main analyses as well as additional studies comparing secondary interventions

of interest, such as fondaparinux + VKA, UFH + VKA, and LMWH + VKA. This distinct initial treatments network included data from 35 different trials. The level of heterogeneity observed across these trials was much greater than that seen in the initial treatment network. Inspection of the characteristics of the 35 included trials revealed several sources of heterogeneity related to study design, duration of treatment and follow-up, and comorbidities across studies.

Edoxaban was found to significantly reduce the risk of VTE recurrence relative to UFH + VKA therapy [redacted] there was no statistically significant difference between edoxaban and fondaparinux + VKA or LMWH + VKA therapies. Comparisons with all other treatments in the network (dabigatran, apixaban, rivaroxaban, fondaparinux + VKA, and LMWH + VKA) suggested no statistically significant differences, with 95% CrIs including 1.0. In the main analysis, there was no statistically significance difference between edoxaban and VKA, or between edoxaban and DOACs for VTE recurrence.

Edoxaban was associated with a significantly increased risk of major bleeding compared with apixaban [redacted]; comparisons with all other therapies (dabigatran, apixaban, rivaroxaban, fondaparinux + VKA, unfractionated heparin + VKA, and LMWH + VKA) suggested no statistically significant differences. Results from the sensitivity analysis for major bleeding were consistent with the main results.

Critical Appraisal

The ITC sponsored by the manufacturer satisfy the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) criteria. The rationale and objectives of the ITC were clearly stated. The inclusion criteria for individual RCTs were clearly stated, and 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 Cochrane Risk of Bias tool. The outcome measures assessed in the ITCs were appropriate and clearly stated. 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. The checklist from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) *Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses* was followed in preparing this report for the ITC. Also, the report adheres to the CADTH *Guidance Document on Reporting Indirect Treatment Comparisons*.

A heterogeneity assessment of patient and study characteristics in the included studies was performed to assess the feasibility and validity of conducting an NMA based on available evidence. These cross-study differences posed a significant challenge to the assumption of exchangeability for the NMA. As a result, a robust ITC between DOACs based on published data could not be conducted. Hence, an exploratory NMA was carried out as an attempt to provide results to inform health care decisions. Due to the high degree of heterogeneity, three sets of NMAs were conducted: scenario A, scenario B, and scenario C. None of the scenarios were able to adjust for differences in patient characteristics in the studies.

Scenario A, which analyzed mixed-duration trials, attempted to reduce differences between the three trials using a reanalysis of outcomes by planned treatment duration. It should also be noted that the EINSTEIN studies were open-label trials, while the Hokusai–VTE study was a double-blind (DB) trial. Thus, the two EINSTEIN trials may have been subject to performance bias due to the lack of blinding. Variation in the distribution of intended treatment duration among the three studies may suggest

differences in the baseline disease severity of the included patients. Therefore, the findings of scenario A should be considered with these limitations in mind.

Scenario B considered patients assigned to six months of therapy, where data from the Hokusai–VTE subgroup were reanalyzed by censoring outcomes at six months to mimic the analysis method employed in the AMPLIFY and RE-COVER studies. Considerable variation was noted across the trials regarding the proportion of patients with provoked/unprovoked VTE; this variation could not be accounted for.

Scenario C included data from all nine studies where there was a presumption that trial duration was not an important modifier of treatment effect. For these analyses, data from the on-treatment period of the Hokusai–VTE study were used to enhance comparability with the other included studies. This scenario also ignored differences in study blinding (i.e., open-label versus DB) and differences in patient characteristics. Further adjustment was not possible because individual patient-level data were unavailable from the other DOAC trials. Thus, the findings of this scenario should be viewed with these major limitations in mind.

While focusing on smaller homogeneous evidence networks may partially address issues with heterogeneity, it does not adequately adjust for other differences in study design (open-label versus DB; percentage of patients in each treatment duration cohort) and patient characteristics (e.g., disease severity and extensiveness). The use of an open-label design has the potential to exaggerate treatment effects relative to those estimated from a DB design. Similarly, variation in intended treatment durations in the mixed-duration network could potentially suggest the presence of differences in baseline disease severity, VTE risk, and bleeding risk, which could affect the study end points.

While it seems reasonable to focus on smaller homogenous evidence networks, which was the approach considered in the ITC sponsored by the manufacturer, this reduced the number of included studies in each scenario:

- scenario A was based on three phase III pivotal studies, two of which represented rivaroxaban and one represented edoxaban
- scenario B was based on four studies, with apixaban represented by one study, dabigatran by two, and edoxaban by one
- scenario C was based on nine studies, where apixaban was represented by two studies, dabigatran by two studies, rivaroxaban by four studies, and edoxaban by one study.

The sensitivity analyses that included 35 additional studies were not entirely consistent with the initial treatment grouping analysis, especially for recurrent VTE outcome when edoxaban was compared with UFH + VKA therapy.

The ITC conducted by the manufacturer used a fixed-effects model, which assumes that all trials share the same common effect and that any differences between trials are due to sampling error. In other words, the fixed-effects model assumes that all the differences in study and patient characteristics between studies have no effect on the true treatment effect. Given the observed clinical heterogeneity in the evidence network, such assumptions are likely not justifiable.

Review of the Manufacturer-Submitted Indirect Treatment Comparison by Wells et al.[36]

Objectives and Rationale for Indirect Treatment Comparison by Wells et al.

The objective of this systematic review and ITC was to evaluate the efficacy and harms of DOACs compared with standard therapy (heparin product followed by oral VKA) for the treatment of acute VTE.

Methods for Indirect Treatment Comparison by Wells et al.

Study Eligibility and Selection Process

A systematic review of the available RCT evidence in the published and grey literature was conducted. Studies were eligible for inclusion in the systematic review if they satisfied the population, intervention, comparator, and study design criteria identified in Table 29. Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and Embase Classic + Embase on November 5, 2014 were searched. CENTRAL in the Cochrane Library on Wiley was also searched. All database searches were limited to studies published between 2008 and November 5, 2014; hence, any trial published before 2008 would not have been captured in the literature search. Two independent review authors applied eligibility criteria to each title and abstract identified in the literature search. The full-text format of articles were retrieved for trials that were considered relevant by one reviewer. Relevant articles were assessed independently by two reviewers, and a final decision made for inclusion. Uncertainties were resolved by discussion and consensus with a third review author. One reviewer performed data extraction from selected trials, and a second reviewer checked the data. A standardized data abstraction form was used for data extraction.

Data Extraction

A total of six RCTs reported in 18 publications met the criteria for inclusion. These trials were RE-COVER, RE-COVER II, Hokusai–VTE, AMPLIFY, EINSTEIN–DVT, and EINSTEIN–PE. All these trials were also included in the manufacturer-sponsored ITC.[37] All trials had a target INR of 2.0 to 3.0. All trials except Hokusai–VTE included a 30-day observational period following the end of treatment. Detailed baseline characteristics of included studies are presented in Table 30.

Comparators

All trials involved the comparison of a DOAC with standard care, typically UFH or LMWH followed by warfarin. LMWH was the initial treatment for trials that involved edoxaban and dabigatran. Trials involving rivaroxaban and apixaban had no initial treatment with LMWH; however, patients started at a higher initial dose of the DOAC in these trials.

Outcomes

Outcomes assessed were: recurrent VTE, recurrent DVT, recurrent PE (fatal and non-fatal), major bleeds, all-cause death, and intracranial bleeding. The follow-up time ranged from four to 13 months from the time of randomization.

Quality Assessment

The Cochrane Collaboration's tool for assessing risk of bias for RCTs was used in assessing the risk of study bias. The risk of bias was low for all trials for all domains of Cochrane Collaboration's tool, with two exceptions: in Hokusai–VTE, the domain of allocation concealment was assessed as unclear; and in RE-COVER, the domain of incomplete outcome data addressed (safety outcomes) was assessed as unclear.

Evidence Network
Six studies were included in the evidence network for recurrent VTE, recurrent DVT, recurrent PE, non-fatal recurrent PE, major bleeds, intracranial bleeds, and all-cause death, with a total of 27,122 patients and five different treatments.

Five studies were included in the evidence network for fatal recurrent PE, with a total of 24,558 patients and five different treatments.

Indirect Treatment Comparison Methods for the Indirect Treatment Comparison by Wells et al.
An assessment of clinical diversity was undertaken for the included studies. This was done by examining whether the interventions, comparators, and participants were sufficiently similar to each other to make combining these studies appropriate. Methodological diversity was also assessed by checking that the studies were similar in design and risk of bias. Heterogeneity across trials with regard to patient characteristics, trial methodologies, and treatment protocols across trials was assessed.

Fixed- or random-effects models were used to conduct the meta-analyses if data were available, sufficiently similar, and of sufficient quality. The effect sizes for the outcomes were expressed in terms of hazard ratios (HRs) and 95% Crls.

Bayesian mixed treatment comparison meta-analyses were conducted for the following outcomes: recurrent VTE, recurrent DVT, recurrent PE (fatal and non-fatal), major bleeds, all-cause death, and intracranial bleeding. WinBUGS software was used to conduct Bayesian ITC meta-analysis using a binomial likelihood model that allows for the use of multi-arm trials. The reference group or index node in the model was standard therapy. Both fixed- effects and random-effects NMAs were conducted; the DIC and comparison of residual deviance to the number of unconstrained data points were used for the assessment of model fit and choice of model. Point estimates and 95% Crl for HRs were derived using Markov Chain Monte Carlo methods. Vague priors, such as N (0, 100^2), were assigned for basic parameters throughout, and informative priors were considered for the variance parameter. Trace plots and the Brooks–Gelman–Rubin statistic were assessed in order to ensure that model convergence was reached. Three chains were fit in WinBUGS for each analysis using at least 20,000 iterations and a burn-in of at least 20,000 iterations.

Subgroup analyses were undertaken by age, patient weight, and renal function.

Results of Indirect Treatment Comparison by Wells et al.

There were no significant differences in major bleeds, intracranial bleeds, all-cause death, or in the recurrence of VTE, DVT, PE, non-fatal and fatal PE in the head-to-head comparisons of the DOACs, nor were there significant differences between any of the DOACs and standard therapy.

TABLE 35: RESULTS FROM THE NMA — TREATMENT EFFECT OF EDOXABAN RELATIVE TO OTHER TREATMENTS

Outcome	Standard Therapy	Rivaroxaban	Apixaban	Dabigatran
	Hazard Ratios (95% Crl)			
VTE recurrence	0.89 (0.23 to 3.53)	0.90 (0.18 to 5.01)	1.05 (0.16 to 7.14)	0.81 (0.15 to 4.34)
Recurrent DVT	0.90 (0.15 to 5.61)	0.99 (0.11 to 8.80)	1.49 (0.12 to 20.0)	0.79 (0.09 to 7.14)
Recurrent PE	0.86 (0.14 to 5.03)	0.72 (0.08 to 6.32)	0.76 (0.06 to 11.11)	0.70 (0.07 to 6.38)
Non-fatal recurrent PE	0.82 (0.11 to 6.32)	0.75 (0.06 to 8.77)	0.70 (0.04 to 12.5)	0.76 (0.06 to 9.41)
Fatal recurrent PE	1.31 (0.24 to 7.19)	0.41 (0.06 to 2.76)	1.89 (0.16 to 25.0)	0.32 (0.01 to 4.68)

Outcome	Standard Therapy	Rivaroxaban	Apixaban	Dabigatran
	Hazard Ratios (95% CrI)			
Major bleeds	0.85 (0.23 to 3.07)	1.57 (0.31 to 7.82)	2.78 (0.43 to 20.0)	1.14 (0.23 to 5.59)
Intracranial bleeds	0.26 (0.02 to 4.03)	0.79 (0.02 to 24.84)	0.53 (0.01 to 33.33)	0.99 (0.03 to 62.57)
All-cause death	1.06 (0.27 to 4.24)	1.10 (0.20 to 6.25)	1.32 (0.19 to 10.0)	1.02 (0.18 to 5.48)

CrI = credible interval; DVT = deep vein thrombosis; NMA = network meta-analysis; PE = pulmonary embolism; VTE = venous thromboembolism.
Source: Wells et al.[36]

Edoxaban, rivaroxaban, apixaban, and standard therapy were included in the subgroup analysis by age and weight for recurrent VTE outcome. There were no statistically significant differences in recurrent VTE between patients older or younger than 75 years. Similarly, there were no statistically significant differences in recurrent VTE between patients whose weight was higher or lower than 60 kg.

Critical Appraisal of Indirect Treatment Comparisons by Wells et al.

The ITCs by Wells et al. for acute treatment of VTE satisfied the ISPOR criteria. The rationale and objectives for the both ITCs 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. Risk of study bias was assessed for the included RCTs using the Cochrane Collaboration's tool for assessing risk of bias. The outcome measures assessed in the ITCs were appropriate and clearly stated. Model fit was assessed using the DIC and by comparing the residual deviance with the number of unconstrained data points.

The main limitation of the ITC was the small number of included studies and the heterogeneity between studies. Apixaban was represented by one study; dabigatran and rivaroxaban by two studies each; and edoxaban by one study.

It was unclear if or how heterogeneity among studies was assessed. There was heterogeneity in the baseline characteristics of patients in the included studies. Specifically, there was variation in the baseline risk of VTE between studies: AMPLIFY reported 89.8% of patients as having unprovoked VTE, whereas this was reported for 61.9% and 64.5% of patients in EINSTEIN–DVT and EINSTEIN–PE respectively; this information was not reported for other studies. In addition, there were differences in study design (open-label versus DB; percentage of patients in each treatment duration cohort) and in patient characteristics (e.g., disease severity and extensiveness). There were also different treatment durations.

It was indicated in the methods section of this ITC that both fixed- and random-effects NMAs were conducted, and that the assessment of model fit and choice of model would be based on an assessment of the DIC and a comparison of the residual deviance versus the number of unconstrained data points. However, there was no mention of whether fixed- or random-effects results were reported, nor was the DIC reported. Hence, it is not clear whether the results reported are from the random-effects model or the fixed-effects model; nor is it reported which model was the better fit. It was not possible to assess the consistency of the model due to the absence of direct evidence.

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

A systematic literature review was conducted by CDR to compare the results of the ITCs performed by the manufacturer with other ITCs. The search yielded five publications presenting ITCs for the treatment of VTE.[31-35] A summary of the ITCs found in the literature is described in Table 36.

TABLE 36: SUMMARY OF OTHER INDIRECT TREATMENT COMPARISONS FOR VENOUS THROMBOEMBOLISM FOUND IN THE LITERATURE

Study	Population	Interventions[a]	Outcomes	Conclusions	Major Strengths	Major Limitations
Hirschl and Kundi 2014[33]	Patients with acute VTE	• Edoxaban 60 mg or 30 mg q.d. • Apixaban 10 mg or 5 mg b.i.d. • Dabigatran 150 mg b.i.d. • Rivaroxaban 15 mg b.i.d./20 mg b.i.d. • VKA control	• Recurrent VTE • Major bleeding • Major and CRNM bleeding • Mortality	• No difference in recurrent VTE and death between DOACs • Major bleeding was statistically significantly lower with apixaban compared with edoxaban and dabigatran • Major and CRNM bleeding was statistically significantly reduced with apixaban compared with edoxaban, 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 (number of patients with DVT, PE, or both) and treatment durations between studies
Cohen et al. 2015[31]			• Recurrent VTE and VTE-related death • Major bleeding • CRNM bleeding • Major or CRNM bleeding • All-cause mortality	• No difference in recurrent VTE and VTE-related death or in death between DOACs • Major bleeding was statistically significantly reduced with apixaban compared with edoxaban and dabigatran • Major or CRNM bleeding was statistically significantly reduced with apixaban compared with edoxaban, dabigatran, and rivaroxaban • Major or CRNM bleeding was statistically significantly reduced with dabigatran compared with edoxaban • CRNM bleeding was statistically significantly reduced with edoxaban compared with rivaroxaban • CRNM bleeding was statistically significantly reduced with apixaban and dabigatran compared with edoxaban and rivaroxaban		• Few included studies • Heterogeneity in patient baseline characteristics (number of patients with DVT, PE, or both) and treatment durations between studies
Mantha and Ansell 2015[32]			• Recurrent VTE • Death • Major bleeding • Major or CRNM bleeding	• No difference in recurrent VTE and death between DOACs • Major bleeding was statistically significantly reduced with apixaban compared with edoxaban • Major and CRNM bleeding was statistically significantly reduced with apixaban and dabigatran compared with edoxaban		• It is not stated if fixed-effects or random-effects models were used • Few included studies • Heterogeneity in patient baseline characteristics (number of patients with DVT, PE, or both) and treatment durations between studies

Study	Population	Interventions[a]	Outcomes	Conclusions	Major Strengths	Major Limitations
Kang and Sobieraj 2014[34]			• Recurrent VTE • PE • DVT • All-cause mortality • Major bleeding	• No differences for mortality, recurrent VTE, PE, or DVT between DOACs • Major bleeding significant greater with edoxaban and dabigatran compared with apixaban		• Few included studies • Heterogeneity in patient baseline characteristics (number of patients with DVT, PE, or both) and treatment durations between studies • Between-study heterogeneity was not assessed
Castelucci et al. 2014[35]			• Recurrent VTE • PE • DVT • Major bleeding	• No difference in recurrent VTE, PE or DVT between DOACs • Major bleeding was statistically significantly reduced with apixaban compared with edoxaban and dabigatran	• low risk of bias in most studies (except performance bias in open-label studies) • model fit and between-study heterogeneity was assessed • sensitivity analyses performed to address heterogeneity treatment durations between studies	• Few included studies

b.i.d.= twice daily; CRNM = clinically relevant non-major; DVT = deep vein thrombosis; DOAC = direct oral anticoagulants; PE = pulmonary embolism; q.d. = once daily; VKA = vitamin K antagonist; VTE = venous thromboembolism.
[a] Only interventions of interest that meet the a priori systematic review protocol for this review are listed in this table.

Hirschl and Kundi 2014[33]
The investigators carried out a systematic review to compare the efficacy and safety of apixaban, dabigatran, rivaroxaban, and edoxaban with VKA, and also to indirectly compare the DOACs with each other. Two reviewers independently assessed the trials for eligibility and risk of bias and extracted the data. Studies were included if they were RCTs that evaluated patients with acute VTE treated with a DOAC and reported at least one outcome of interest: mortality, recurrent VTE, major bleeding, or major and CRNM bleeding. The investigators performed an ITC using parameter estimates and covariance matrices (general linear model with binomial proportions) using a fixed-effects approach using IBM SPSS Statistics V22.0 software.

The risk of major bleeding was statistically significantly reduced with apixaban compared with dabigatran, with a relative risk of 0.42 (95% confidence interval [CI]; 0.21 to 0.86) and with edoxaban (relative risk: 0.36; 95% CI 0.18 to 0.71). The risk of major and CRNM bleeding was statistically significantly reduced with apixaban compared with dabigatran (relative risk: 0.71; 95% CI, 0.52 to 0.95); with rivaroxaban (relative risk: 0.47; 95% CI 0.37 to 0.61); and with edoxaban (relative risk: 0.54; 95% CI 0.42 to 0.70). There were no statistically significant differences between DOACs for recurrent VTE and death. There was heterogeneity in several baseline characteristics (e.g., number patients with DVT, PE, or both) and treatment durations between studies. The ITC 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 ITC results.

The analyses by Hirschl and Kundi 2014[33] consisted of the six studies included in the manufacturer-sponsored ITC[37] and the Wells et al.[36] ITC (RE-COVER, RE-COVER II, Hokusai–VTE, AMPLIFY, EINSTEIN–DVT, and EINSTEIN–PE). All results were nearly identical and support the manufacturer-sponsored ITC.

Cohen et al. 2014[31]
The investigators carried out a systematic review to compare the efficacy and safety of apixaban, LMWH/dabigatran, rivaroxaban, and LMWH/edoxaban for the initial and long-term treatment of VTE. Two reviewers independently assessed the trials for eligibility, extracted the data, and assessed the quality of the RCTs. Studies were included if they were phase III RCTs that evaluated adult patients with acute VTE (DVT and/or PE) who were receiving initial or long-term treatment, were treated with a DOAC, and reported at least one outcome of interest: recurrent VTE or VTE-related death, major bleeding, major and CRNM bleeding, CRNM bleeding, or all-cause mortality. The investigators performed an ITC using WinBUGS software to conduct a Bayesian NMA. The treatment effect was evaluated in terms of relative risk. Both fixed- and random-effects models were used. However, only data from the fixed-effects model were presented, as the fixed-effects model gave the lowest DIC compared with the random-effects model.

Edoxaban was associated with a significantly higher risk of major or CRNM bleeding compared with apixaban (relative risk: 1.87; 95% CrI, 1.45 to 2.42) or dabigatran (relative risk: 1.30; 95% CrI, 1.01 to 1.67). Edoxaban also had a significantly higher risk of major bleeding compared with apixaban, with a relative risk of 2.81 (1.45 to 5.70). Edoxaban was also associated with a significantly higher risk of CRNM bleeding compared with apixaban (relative risk: 1.68; 95% CrI, 1.28 to 2.23) or dabigatran (relative risk: 1.35; 95% CrI, 1.02 to 1.79). Edoxaban had a significantly lower risk of CRNM bleeding compared with rivaroxaban (relative risk: 0.79; 0.65 to 0.97). No other statistically significant differences were found between the DOACs for the outcomes reported. There was variation in the baseline risk of VTE and treatment durations between studies. The two rivaroxaban RCTs were 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 ITC results.

The analyses by Cohen et al. 2014[31] consisted of the six studies included in the manufacturer-sponsored ITC[37], Wells et al.[36] ITC, and Hirschl and Kundi 2014[33] (RE-COVER, RE-COVER II, Hokusai–VTE, AMPLIFY, EINSTEIN–DVT, and EINSTEIN–PE). Results were consistent and supported the findings from the manufacturer-sponsored ITC.

Mantha and Ansell[32]

The investigators carried out a systematic review to compare the efficacy of and safety of apixaban, dabigatran, rivaroxaban, edoxaban for the treatment of acute VTE. Two reviewers independently assessed the trials for eligibility. The quality of the RCTs was assessed using the Cochrane Collaboration's tool for assessing risk of bias. Studies were included if they were phase III RCTs that evaluated adult patients with acute VTE (DVT and/or PE), comparing dabigatran, rivaroxaban, apixaban, and edoxaban to standard therapy that included an initial parenteral drug followed by a VKA. Outcomes of interest were recurrent VTE, death, major bleeding, and major or CRNM bleeding. The relative risk of an event for patients receiving treatment x versus y was estimated by dividing the relative risk for treatment x versus z by the relative risk for treatment y versus z. The R 3.1.0 statistical platform was employed along with the ''meta'' package. The alpha level was set at 0.05.

Edoxaban was associated with a significantly higher risk of major or CRNM bleeding compared with apixaban (relative risk: 1.85; 95% CrI, 1.43 to 2.38) or dabigatran (relative risk: 1.31; 95% CrI, 1.02 to 1.68). Edoxaban also had a significantly higher risk of major bleeding compared with apixaban (relative risk: 2.7; 1.37 to 5.26). No other statistically significant differences were found between the DOACs for the outcomes reported. A major difference between the included studies is the initial use of a heparinoid for patients randomized to edoxaban or dabigatran, compared with no such treatment in patients receiving rivaroxaban or apixaban. The ITC 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 ITC results. Additionally, it is unclear if a random-effects model or fixed-effects model was used.

The analyses by Mantha and Ansell[32] consisted of the six studies included in the manufacturer-sponsored ITC[37], Wells et al.[36] ITC, and Hirschl and Kundi 2014[33] (RE-COVER, RE-COVER II, Hokusai–VTE, AMPLIFY, EINSTEIN–DVT, and EINSTEIN–PE). Results were consistent and support the findings of the manufacturer-sponsored ITC.

Kang and Sobieraj 2014[34]

The investigators carried out a systematic review to compare the efficacy and safety of apixaban, dabigatran, rivaroxaban, and edoxaban. Data were assessed by two independent reviewers to establish whether relevant outcomes were appropriately and sufficiently reported. Studies were included if they were RCTs that evaluated patients with acute VTE treated with a DOAC 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 III studies were included for the remaining DOACs. No specific exclusion criteria were provided. Study-quality assessment was performed using the Cochrane Collaboration's risk of bias tool. The investigators conducted an ITC using the Bucher method with a random-effects model using a publicly available tool for adjusted indirect meta-analysis by CADTH.

The risk of major bleeding increased with dabigatran compared with apixaban, with a relative risk of 2.69 (95% CI, 1.19 to 6.07) and with edoxaban compared with apixaban (relative risk: 2.74; 1.40 to 5.39). The risk of major bleeding was statistically significantly reduced with apixaban compared with VKA (relative risk: 0.31; 0.17 to 0.54). There was no other statistically significant difference between any of the DOACs and VKA. There were no statistically significant differences for mortality, recurrent VTE, PE, or DVT between DOACs. 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., 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 and Sobieraj 2014[34] consisted of the six studies included in the manufacturer-sponsored ITC[37], Wells et al.[36] ITC, and Hirschl and Kundi 2014[33] (RE-COVER, RE-COVER II, Hokusai–VTE, AMPLIFY, EINSTEIN–DVT, and EINSTEIN–PE). Results were consistent and supported the findings from the manufacturer-sponsored ITC.

Castellucci et al. 2014[35]

The investigators carried out a systematic review to compare the efficacy of apixaban, LMWH/dabigatran, rivaroxaban, LMWH/edoxaban and the combination of parenteral anticoagulants with VKA. Two independent reviewers assessed the data to establish whether the relevant outcomes were sufficiently and appropriately reported.

Studies were included if all of the following criteria were met:

- they were RCTs that evaluated patients with acute VTE who had qualifying recurrent VTE events that were symptomatic and objectively confirmed
- patients received treatment with a DOAC, LMWH alone, or a combination of a parenteral anticoagulant with VKA
- they reported at least one outcome of interest: recurrent VTE, recurrent DVT, recurrent PE, or major bleeding.

Studies were excluded if any of the following criteria were met:

- study design was phase I or II
- patients were randomized to idraparinux or ximelagatran
- patients were randomized to placebo or observation
- only patients with cancer-associated thrombosis were included
- studies evaluated extended VTE treatment for secondary prevention.

Study-quality assessment was performed using the Cochrane Collaboration's risk of bias tool. The investigators conducted an NMA using both random-effects and fixed-effects models with WinBUGS software. Model fit was assessed based on between-study standard deviation, assessment of the DIC, and a comparison of the residual deviance to the number of unconstrained data points. Additionally, NMA results were qualitatively compared with direct frequentist pairwise estimates.

A fixed-effects model was used in this ITC. The reason indicated by the authors for this is that the evidence network comprised connections consisting of either a few studies or single studies. The risk for major bleeding was statistically significantly reduced with apixaban compared with the combinations of UFH/VKA, with a hazard ratio of 0.26 (95% CI, 0.12 to 0.54); fondaparinux/VKA (hazard ratio 0.30; 95%

CI, 0.12 to 0.68); with dabigatran (hazard ratio 0.42; 95% CI, 0.17 to 0.99); and with edoxaban (hazard ratio 0.37; 95% CI, 0.15 to 0.89). The risk of major bleeding was also statistically significantly reduced with rivaroxaban compared with the combination of UFH and VKA (hazard ratio: 0.47; 95% CI, 0.27 to 0.80). There were no statistically significant differences for recurrent VTE, PE, or DVT when DOACs were compared with each other or with LMWH alone. To adjust for variation in study treatment duration between studies, sensitivity analyses for restricting studies to those that had a minimum treatment duration of six months were performed. Results aligned with those of the primary analysis. As with other ITCs found in the literature, it remains uncertain whether the inclusion of open-label studies affected the ITC results.

The analyses by Castelucci et al. 2014[35] comparing DOACs with LMWH/VKA consisted of the same six studies included in the manufacturer's indirect analyses (RE-COVER, RE-COVER II, Hokusai–VTE, AMPLIFY, EINSTEIN–DVT, and EINSTEIN–PE). Results were consistent and supported the findings from the manufacturer-sponsored ITC[37].

Discussion

The methodology of the manufacturer's sponsored ITC was appropriate and provided an up-to-date comparison of the treatment efficacy and safety of edoxaban versus apixaban, dabigatran, rivaroxaban, and VKAs. Overall, the results from the ITC suggest no significant difference in efficacy for edoxaban compared with apixaban, rivaroxaban, and dabigatran, as there were no significant differences in the outcomes of VTE and mortality. The results of another ITC submitted by the manufacturer (by Wells et al.[36]) and five additional ITCs[31-35] 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 ITCs. Therefore, it would appear there are no substantial differences in the efficacy of the DOACs in treating and preventing recurrent VTE. However, a major limitation associated with this conclusion is the fact that there are a small number of studies available to represent the treatment effects of each DOAC and there is no direct evidence available for edoxaban. This fact, in addition to the relative rarity of the events that are being analyzed, means the impact of the heterogeneity between studies on the comparative efficacy of treatment is highly uncertain. In addition, it is worth noting that the noninferiority (NI) design of RE-COVER, RE-COVER II, Hokusai–VTE, AMPLIFY, EINSTEIN–DVT, and EINSTEIN–PE studies has limited the opportunity for any DOAC to demonstrate a significant difference from any other DOAC in the network for prevention of VTE recurrence, should one exist.

The manufacturer-sponsored ITC and the ITCs identified in the literature used a fixed-effects model. The fixed-effects model makes unrealistic assumptions regarding the true treatment effect; it assumes that all trials share the same common effect and that any differences between trials are due to sampling error. In other words, the fixed-effects model assumes that all the differences in study and patient characteristics between studies have no effect on the true treatment effect. Such assumptions are not justifiable in the presence of the observed clinical heterogeneity in the evidence network (i.e., different inclusion and exclusion criteria, differences in study design). In addition, the lack of any head-to-head DOAC comparative trial meant we could not assess the consistency assumption in the ITC.

The evidence base was found to be similar between the manufacturer-sponsored review and the review performed by Wells and colleagues. Studies included in the latter review's network were the same as those informing scenarios A and B of the grouped initial therapies network in the manufacturer-sponsored review. The review performed by Wells and colleagues concluded that there were no differences between any of the DOACs (edoxaban, apixaban, dabigatran, and rivaroxaban) or between DOACs and standard VKA therapy with regard to recurrent VTE, recurrent PE, recurrent DVT, major

bleeding, intracranial hemorrhage, all-cause mortality, cardiovascular mortality, stroke, or acute coronary syndrome. Furthermore, the review also noted that there were no differences in the occurrence of recurrent VTE when assessed according to patient age, weight, or renal function. An important difference between the Wells et al. review and the manufacturer-sponsored review is the choice of model used for the ITCs. Despite the presence of primarily single-study connections in the evidence network, it seems (although it is not explicitly stated) that Wells and colleagues used random-effects models, while the manufacturer-sponsored review employed fixed-effects models.

The distinct initial therapies network in the manufacturer-sponsored review (sensitivity analysis) was found to be similar to the 2014 review reported by Castellucci and colleagues[35] regarding objectives, methods, and evidence base. Overall, the results of the key end points of recurrent VTE and major bleeding were similar.

Evidence bases were found to be similar between the manufacturer-sponsored review and the review performed by Hirschl and Kundi,[33] Cohen et al.,[31] Mantha and Ansell,[32]and Kang and Sobieraj.[34] The six studies (RE-COVER, RE-COVER II, Hokusai–VTE, AMPLIFY, EINSTEIN–DVT, and EINSTEIN–PE) included in each of these reviews were the same as those informing scenarios A and B of the grouped initial therapies network in the manufacturer-sponsored review. Even though each of these reviews used a different method to conduct the ITC, results were similar to the findings from the manufacturer-sponsored ITC.

The results of the comparisons of the DOACs on bleeding-related outcomes are more variable and somewhat harder to interpret. Apixaban was significantly less likely to cause major bleeding compared with edoxaban and dabigatran, but not compared with rivaroxaban. The results of the five ITCs[31-35] identified in the literature were similar to the manufacturer's analysis in that there were differences between apixaban and edoxaban with respect to major bleeding; however, such differences were not reported by Wells et al.,[36] most likely because the Wells et al. review used random-effects models, which would yield a wider CrI. Except for the Wells et al. review, all summarized ITCs indicated that apixaban was consistently superior to edoxaban for all bleeding outcomes. Given the small number of studies, the rarity of events, and different treatment durations, it seems that there is some degree of uncertainty related to interpreting the comparative bleeding risks associated with apixaban versus edoxaban.

Conclusion

The evidence available from ITCs of edoxaban with VKA and other DOACs suggests that edoxaban is as efficacious as apixaban, dabigatran, and rivaroxaban in treating and preventing recurrent VTE. Edoxaban was associated with statistically significant more major bleeding than apixaban, and statistically significant more major and CRNM bleeding than apixaban and dabigatran. Key limitations of the ITCs were the differences in study design and patient characteristics between studies, and the limited number of studies included in each network. Consequently, conclusions regarding the relative effects of edoxaban with VKAs and other DOACs for all outcomes are uncertain.

REFERENCES

1. Clinical Study Report: DU176b-D-U305 A phase 3, randomized, double-blind, double-dummy, parallel-group, multi-center, multi-national study for the evaluation of efficacy and safety of (LMW) heparin/edoxaban versus (LMW) heparin/warfarin in subjects with symptomatic deep-vein thrombosis and/or pulmonary embolism [**CONFIDENTIAL** internal manufacturer's report]. Edison (NJ): Daiichi Sankyo Pharma Development; 2013 Oct 17.
2. Lip GYH, Hull R. Overview of the treatment of lower extremity deep vein thrombosis (DVT). 2016 Jul 22 [cited 2017 Jan 30]. In: UpToDate [Internet]. Waltham (MA): UpToDate; c2005 -. Available from: www.uptodate.com Subscription required.
3. Cohen AT, Dobromirski M. The use of rivaroxaban for short- and long-term treatment of venous thromboembolism. Thromb Haemost. 2012 Feb 28;107(6):1035-43.
4. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galie N, Pruszczyk P, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008 Sep;29(18):2276-315.
5. Alikhan R, Peters F, Wilmott R, Cohen AT. Fatal pulmonary embolism in hospitalised patients: a necropsy review. J Clin Pathol [Internet]. 2004 Dec [cited 2014 Dec 15];57(12):1254-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1770519
6. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Arch Intern Med. 2002 Jun 10;162(11):1245-8.
7. Scottish Intercollegiate Guidelines Network. Prevention and management of venous thromboembolism: a national clinical guideline [Internet]. Edinburgh (GB): SIGN; 2010 Dec; updated 2014 Oct. [cited 2017 Jan 30]. (SIGN publication no. 122). Available from: http://sign.ac.uk/pdf/sign122.pdf
8. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003 Jun 17;107(23 Suppl 1):I9-16.
9. CDR submission: Lixiana (edoxaban): 15 mg, 30 mg and 60 mg film-coated tablets. Company: Daiichi Sankyo [**CONFIDENTIAL** manufacturer's submission]. Laval (QC): Servier Canada Inc.; 2016.
10. Tapson VF. Overview of the treatment, prognosis, and follow-up of acute pulmonary embolism in adults. 2016 Sep 1 [cited 2017 Jan 30]. In: UpToDate [Internet]. Waltham (MA): UpToDate. Available from: www.uptodate.com Subscription required.
11. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest [Internet]. 2012 Feb [cited 2014 Dec 9];141(2 Suppl):e419S-e494S. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278049
12. Hull RD, Garcia DA. Warfarin and other VKAs: Dosing and adverse effects. 2016 Nov 22 [cited 2017 Jan 30]. In: UpToDate [Internet]. Waltham (MA): UpToDate; c2005 -. Available from: www.uptodate.com Subscription required.
13. Merli G, Spyropoulos AC, Caprini JA. Use of emerging oral anticoagulants in clinical practice: translating results from clinical trials to orthopedic and general surgical patient populations. Ann Surg. 2009 Aug;250(2):219-28.

14. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016 Feb;149(2):315-52.
15. Pr Lixiana® (edoxaban): 15 mg, 30 mg and 60 mg film-coated tablets [product monograph]. Parsippany (NJ): Daiichi Sankyo, Inc.; 2016 Aug 31.
16. The Hokusai-VTE Investigators, Buller H, Decousus H, Mercuri M, Middeldorp S, Prins M, et al. Edoxaban versus Warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013 Oct 10;369(15):1406-15.
17. Edwards S, Crawford F, Wakefield V, Bacelar M, Marceniuk G. Edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [Internet]. London: BMJ Technology Assessment Group (BMJ-TAG); 2015 Apr 28. [cited 2016 Nov 15]. (NIHR HTA program; no.14/60). Available from: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0010/159985/ERGReport-14-60-01.pdf
18. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s). In: Savaysa (edoxaban tosylate) tablets. Company: Daiichi-Sankyo Inc. Application No.: 206316. Approval Date: 1/08/2015 [Internet]. Rockville (MD): FDA; 2015 Jan 13 [cited 2016 Nov 15]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206316Orig1Orig2s000MedRedt.pdf
19. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: Savaysa (edoxaban tosylate) tablets. Company: Daiichi-Sankyo Inc. Application No.: 206316. Approval Date: 1/08/2015 [Internet]. Rockville (MD): FDA; 2015 Jan 8 [cited 2016 Nov 15]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206316Orig1Orig2s000StatR.pdf
20. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Lixiana (edoxaban) [Internet]. London (GB): European Medicines Agency; 2015 Apr 23. [cited 2016 Nov 15]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002629/WC500189047.pdf
21. Verhamme P, Wells PS, Segers A, Ageno W, Brekelmans MP, Cohen AT, et al. Dose reduction of edoxaban preserves efficacy and safety for the treatment of venous thromboembolism. An analysis of the randomised, double-blind HOKUSAI VTE trial. Thromb Haemost. 2016 Sep 27;116(4):747-53.
22. Raskob GE, van Es N, Segers A, Angchaisuksiri P, Oh D, Boda Z, et al. Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomised, double-blind, double-dummy trial. Lancet Haematol. 2016 Aug;3(8):e379-e387.
23. Raskob G, Ageno W, Cohen AT, Brekelmans MP, Grosso MA, Segers A, et al. Extended duration of anticoagulation with edoxaban in patients with venous thromboembolism: a post-hoc analysis of the Hokusai-VTE study. Lancet Haematol. 2016 May;3(5):e228-e236.
24. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun;133(6 Suppl):454S-545S.
25. Bertoletti L, Ollier E, Duvillard C, Delavenne X, Beyens MN, De Magalhaes E, et al. Direct oral anticoagulants: Current indications and unmet needs in the treatment of venous thromboembolism. Pharmacol Res. 2016 Jun 24.
26. Snapinn SM. Noninferiority trials. Curr Control Trials Cardiovasc Med [Internet]. 2000 [cited 2016 Nov 30];1(1):19-21. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC59590

27. Erkens PM, ten CH, Buller HR, Prins MH. Benchmark for time in therapeutic range in venous thromboembolism: a systematic review and meta-analysis. PLoS ONE [Internet]. 2012 [cited 2016 Nov 30];7(9):e42269. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3458058

28. [Pr]Pradaxa® (dabigatran etexilate capsules): 75 mg, 110 mg and 150 mg dabigatran etexilate, (as dabigatran etexilate mesilate) [product monograph]. Burlington (ON): Boehringer Ingelheim Canada Ltd.; 2016 Aug 11.

29. [Pr]Xarelto® (rivaroxaban tablet): 10 mg, 15 mg and 20 mg [product monograph]. Mississauga (ON): Bayer Inc.; 2015 Jul 20.

30. [Pr]Eliquis® (apixaban talbets): 2.5 mg and 5mg [product monograph]. Kirkland (QC): Pfizer Canada Inc.; 2016 Jun 16. Co-published by Bristol-Myers Squibb Canada, Montreal.

31. Cohen AT, Hamilton M, Mitchell SA, Phatak H, Liu X, Bird A, et al. Comparison of the novel oral anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban in the initial and long-term treatment and prevention of venous thromboembolism: systematic review and network meta-analysis. PLoS ONE [Internet]. 2015 [cited 2016 Oct 25];10(12):e0144856. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4696796

32. Mantha S, Ansell J. Indirect comparison of dabigatran, rivaroxaban, apixaban and edoxaban for the treatment of acute venous thromboembolism. J Thromb Thrombolysis. 2015 Feb;39(2):155-65.

33. Hirschl M, Kundi M. New oral anticoagulants in the treatment of acute venous thromboembolism - a systematic review with indirect comparisons. VASA. 2014 Sep;43(5):353-64.

34. Kang N, Sobieraj DM. Indirect treatment comparison of new oral anticoagulants for the treatment of acute venous thromboembolism. Thromb Res. 2014 Jun;133(6):1145-51.

35. Castellucci LA, Cameron C, Le Gal G, Rodger MA, Coyle D, Wells PS, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. JAMA. 2014 Sep 17;312(11):1122-35.

36. Wells G, Kelly S, Elliott J, Carrier M, Hsieh S, Chen L, et al. Direct oral anticoagulants for the treatment of venous thromboembolic events: a systematic review and network meta-analysis [Internet]. Ottawa (ON): University of Ottawa Heart Institute; 2016 Jan. [cited 2016 Nov 15]. Available from: https://www.ottawaheart.ca/sites/default/files/uploads/documents/Researchers/gwells-doac-vte-scientific-report-2015-2016.pdf

37. Lixiana® (edoxaban) for treatment and prevention of venous thromboembolism: systematic review with network meta-analyses. Summary report. Burlington (ON): Cornerstone Research Group Inc.; 2016 Jun 27.

38. Daiichi Sankyo Inc. Cancer venous thromboembolism (VTE). 2014 Feb 25 [cited 2016 Nov 25; Last updated: 2016 Oct 14]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 -. Available from: https://clinicaltrials.gov/ct2/show/NCT02073682 Identifier: NCT02073682.

39. van Es N, Di Nisio M, Bleker SM, Segers A, Mercuri MF, Schwocho L, et al. Edoxaban for treatment of venous thromboembolism in patients with cancer. Rationale and design of the Hokusai VTE-cancer study. Thromb Haemost. 2015 Nov 25;114(6):1268-76.

40. Servier Canada Inc. response to November 16, 2016 CDR request for additional information regarding the Lixiana VTE CDR review: quality of life data request [**CONFIDENTIAL** additional manufacturer's information]. Laval (QC): Servier Canada Inc.; 2016.

41. [Pr]Innohep® (tinzaparin sodium): multi-dose vial: 10,000 anti-Xa IU/mL; 20,000 anti-Xa IU/mL, pre-filled syringe with safety needle device: 2,500 anti-Xa Iu/0.25 mL, 3,500 anti-Xa IU/0.35 mL, 4,500 anti-Xa Iu/0.45 mL, 8,000 anti-Xa IU/0.4 mL, 10,000 anti-Xa IU/0.5 mL, 12,000 anti-Xa IU/0.6 mL, 14,000 anti-Xa IU/0.7 mL, 16,000 anti-Xa IU/0.8 mL, 18,000 anti-Xa IU/0.9 mL [product monograph]. Thornhill (ON): LEO Pharma Inc.; 2016 Mar 23.
42. [Pr]Arixtra® (fondaparinux sodium injection): 2.5 mg/0.5 mL, 5.0 mg/0.4 mL, 7.5 mg/0.6 mL, 10.0 mg/0.8 mL [product monograph]. Dublin (GB): Aspen Pharma Trading Limited; 2015 Mar 12.
43. Heparin sodium injection USP: 1000 USP units per mL, 10 000 USP units per mL [product monograph]. Kirkland (QC): Pfizer Canada Inc.; 2016 Aug 10.
44. [Pr]Fragmin® (dalteparin sodium injection): solution: 10 000 IU (anti-factor Xa)/1 mL, ampoule, 25 000 IU (anti-factor Xa)/mL 3.8 mL, multi-dose vial, 2500 IU (anti-factor Xa)/mL 4 mL, single-dose vial; prefilled syringe with safety needle device: 2 500 IU (anti-factor Xa)/0.2 mL, 3 500 IU (anti-factor Xa)/0.28 mL, 5000 IU (anti-factor Xa)/0.2 mL, 7 500 IU (anti-factor Xa)/0.3 mL, 10 000 IU (anti-factor Xa)/0.4 mL, 12 500 IU (anti-factor Xa) /0.5 mL, 15 000 IU (anti-factor Xa)/0.6 mL, 18 000 IU (anti-factor Xa)/0.72 mL [product monograph]. Kirkland (QC): Pfizer Canada Inc.; 2016 Mar 21.
45. Sintrom: 1 mg and 4 mg tablets. Prescribing information. Montreal (QC): Paladin Labs Inc.; 2009 May 22.
46. [Pr]Lovenox® (enoxaparin sodium solution for injection, manufacturer's standard): 100 mg/mL, 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1.0 mL, 300 mg/3 mL; [Pr]Lovenox® HP (enoxaparin sodium solution for injection, manufacturer's standard): 150 mg/mL (high potency), 90 mg/0.6 mL, 120 mg/0.8 mL, 150 mg/1.0 mL [product monograph]. Laval (QC): Sanofi-Aventis Canada Inc.; 2014 Jul 7.
47. [Pr]Coumadin® (warfarin sodium tablets, Bristol-Myers Squibb Std., (crystalline)): 1, 2, 2.5, 3, 4, 5, 6 and 10 mg [product monograph]. Montreal (QC): Bristol-Myers Squibb Canada; 2016 May 20.
48. [Pr]Fraxiparine® (nadroparin calcium injection (9,500 anti-Xa IU/mL)): 0.2 mL, 0.3 mL, 0.4 mL, 0.6 mL and 1.0 mL prefilled syringes; [Pr]Fraxiparine Forte® (nadroparin calcium injection (19,000 anti-Xa IU/mL)): 0.6 mL, 0.8 mL and 1.0 mL prefilled syringes [product monograph]. Dublin (GB): Aspen Pharma Trading Limited; 2015 Feb 19.
49. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association; c2007 - [cited 2016 Nov 15]. Available from: https://www.e-therapeutics.ca/ Subscription required.