Common Drug Review
Clinical Review Report

April 2017

Drug	Edoxaban (Lixiana)
Indication	Prevention of stroke and systemic embolic events in patients with atrial fibrillation in whom anticoagulation is appropriate
Reimbursement Request	As per indication
Dosage Form (s)	Tablet 15 mg, 30 mg, and 60 mg
NOC Date	November 4, 2016
Manufacturer	Servier Canada, Inc.

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ABBREVIATIONS

AF	atrial fibrillation
$CHADS_2$	congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack or thromboembolism
CI	confidence interval
CrCL	creatinine clearance
CrI	credible interval
CSR	Clinical Study Report
CV	cardiovascular
DOAC	direct oral anticoagulant
HR	hazard ratio
IDC	indirect comparison
INR	international normalized ratio
ISTH	International Society on Thrombosis and Haemostasis
ITT	intention to treat
mITT	modified intention to treat
NI	noninferiority
NMA	network meta-analysis
NVAF	nonvalvular atrial fibrillation
OR	odds ratio
RCT	randomized controlled trial
RR	risk ratio
SAE	serious adverse event
SEE	systemic embolic event
TIA	transient ischemic attack
TTR	time in therapeutic range
VKA	vitamin K antagonist

EXECUTIVE SUMMARY

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia,[1,2] characterized by disorganized, rapid, and irregular activity of the atria (i.e., the upper chambers of the heart).[3] AF is recognized as a chronic, progressive disorder associated with increased morbidity and mortality.[4-6] The Heart and Stroke Foundation estimates that approximately 350,000 Canadians are affected by AF.[7] In all types of AF, embolization of atrial thrombi poses a significant risk of arterial thromboembolism, transient ischemic attack, and stroke, which are associated with high recurrence and substantial debilitating impact.[4,5]

Edoxaban is a direct factor Xa inhibitor. Inhibition of factor Xa in the coagulation cascade leads to an anticoagulant effect. Edoxaban is administered orally, at a dosage of 60 mg once daily, and its current proposed indication is for the prevention of stroke and systemic embolism in patients with AF. Edoxaban has a Health Canada indication for the prevention of stroke and systemic embolic events (SEEs) in patients with nonvalvular atrial fibrillation (NVAF).[8] We performed a systematic review of the beneficial and harmful effects of edoxaban 60 mg (30 mg dose reduced) once daily for the prevention of stroke and SEEs in patients with NVAF.

Results and Interpretation

Included Studies

The systematic search of the literature identified one study for inclusion. The ENGAGE AF-TIMI 48 study was a phase III, noninferiority (NI), double-blind, randomized, active-controlled, parallel-group trial. Investigators randomized 21,105 NVAF patients, who had a $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack or thromboembolism) score of at least 2, to edoxaban 60 mg, edoxaban 30 mg, or warfarin. This review will only focus on the approved edoxaban dose of 60 mg. The study primary efficacy outcome was the incident of stroke or SEE; major bleeding was a primary safety outcome. The study continued until 672 primary efficacy–related events were collected. At the end of the double-blind treatment period, all patients transitioned to an open-label anticoagulation therapy of their choice.

ENGAGE AF-TIMI 48 employed an NI design with a hierarchal approach to test for superiority if NI was achieved. To satisfy NI, the upper boundary of the one-sided 97.5% confidence interval (CI) of edoxaban compared with warfarin had to be lower than 1.38. This margin was based on six historical studies of warfarin versus placebo and should have maintained at least 50% of the efficacy of warfarin over placebo. NI testing was conducted using the modified intention-to-treat analysis set from the treatment period. All superiority testing was conducted using the intention-to-treat analysis set from the overall study period. Treatment effects were reported using the hazard ratio (HR). The analysis was performed by employing a Cox proportional hazard model that included treatment groups and randomization stratification factors.

To address the lack of comparative evidence of edoxaban and other direct oral anticoagulants (DOACs), the CADTH Common Drug Review reviewed one manufacturer-submitted indirect comparison (IDC), as well as seven published IDCs that assessed the efficacy and safety of different DOACs for the prevention of stroke and SEEs in patients with NVAF.

Efficacy

The results from the ENGAGE AF-TIMI 48 study met the pre-specified NI margin. Overall, patients treated with edoxaban had a lower event rate of stroke or systemic embolism than patients treated with warfarin (HR edoxaban versus warfarin = 0.79; 95% CI, 0.63 to 0.99), the median per-site warfarin international normalized ratio–time in therapeutic range was 68.4%. The pre-specified superiority analysis failed to show superiority. Failure to show superiority at this point should have constituted a stop sign in the predefined hierarchal pathway of outcomes testing. In other words, no further statistical comparisons regarding efficacy outcomes should have been carried out. Subgroup analyses were performed for the primary efficacy outcome of stroke or SEE on the basis of baseline characteristics (age, gender, race, body weight, creatinine clearance, $CHADS_2$ score, dose reduction, prior vitamin K antagonist status, and various comorbidities). The findings from subgroup analyses were reported as being consistent with the base-case results.

Although all the reviewed IDCs share the same limitations, specifically the use of a fixed-effects model in the presence of clinical heterogeneity and our inability to test and assess basic IDC assumptions because of the insufficient number of DOAC trials, the results are consistent with the notion that edoxaban may have a similar efficacy and safety profile to other DOACs.

Harms

Major bleeding represents the biggest safety concern associated with antithrombotic drugs. The incidence of major bleeding (modified International Society on Thrombosis and Haemostasis criteria) was lower with edoxaban 60 mg than with warfarin (418 patients, 2.75%, versus 524 patients, 3.43%; HR = 0.80; 95% CI, 0.71 to 0.91). The incidence of various key aspects of major bleeding — fatal bleeding and hemorrhagic stroke — were lower with edoxaban 60 mg than with warfarin, but there were more patients with gastrointestinal hemorrhage in the edoxaban 60 mg arm than in the warfarin arm. Although ENGAGE AF-TIMI 48 was able to detect a statistically significant difference in major bleeding, the interpretation of this relative value into the absolute number of patients who will experience this lower risk of bleeding can be challenging.

Overall, there were fewer deaths in the edoxaban 60 mg arm (769 patients, 11.0%) than in the warfarin arm (836 patients, 11.9%). In both arms, the bulk of the deaths were driven by cardiovascular causes (7.5% in the edoxaban 60 mg arm; 8.7% in the warfarin arm). Approximately one-third of the patients in the ENGAGE AF-TIMI 48 trial experienced a nonbleeding serious adverse event (SAE). In total, 2,315 patients (33.0%) experienced nonbleeding SAEs in the edoxaban 60 mg arm, and 2,516 patients (35.9%) experienced nonbleeding SAEs in the warfarin arm.

The reviewed IDCs suggest that edoxaban does result in fewer major bleeding events than does warfarin. However, the results of the IDC of edoxaban with other DOACs are mixed, with some showing statistically significance in favour of edoxaban and others not showing statistical significance. It is important to consider the results of the IDCs with considerable caution: There is no trial comparing DOACs head to head, only four trials are available to inform DOAC comparisons, there is clinical heterogeneity between these trials, and the fixed-effects model was used in all the reviewed IDCs. All these factors present a challenge in assessing the reliability and accuracy of the IDC results. As such, all results of the DOAC IDCs should be considered as exploratory in nature and in need of further hypothesis testing. However, given the currently available evidence, no better-quality IDC could have been produced.

Conclusions

The results of ENGAGE AF-TIMI 48 demonstrate that edoxaban 60 mg once daily is noninferior to well-managed warfarin in the prevention of stroke and SEEs in patients with NVAF. In addition, the trial results demonstrate statistically that edoxaban 60 mg once daily has led to significantly fewer major bleeding events than has warfarin. Overall, the trial was well conducted, and the primary results can be considered reliable.

The indirect evidence of edoxaban versus warfarin is in alignment with the results of efficacy and safety in the direct evidence. The IDC of edoxaban with other DOACs cannot reliably estimate the relative efficacy or safety from the currently available evidence network. A direct comparison between different DOACs is needed to establish the comparative efficacy and safety of these drugs.

TABLE 1: SUMMARY OF RESULTS

	ENGAGE AF-TIMI 48	
	Warfarin	**Edoxaban 60 mg**
First Stroke or SEE (Primary Efficacy Outcome, Testing for Noninferiority) mITT analysis, on-treatment period, set	**N = 7,012**	**N = 7,012**
No. of events (event rate per year)	232 (1.50)	182 (1.18)
HR edoxaban versus warfarin (97.5% CI)	0.79 (0.63 to 0.99)	
Breakdown of the Primary Outcome, Main Components and Select Subcomponents, n (%)		
Stroke	219 (1.41)	174 (1.13)
Ischemic stroke	144 (0.93)	135 (0.87)
Hemorrhagic stroke	76 (0.49)	40 (0.26)
Fatal stroke	43 (0.28)	45 (0.29)
Disabling stroke	41 (0.26)	35 (0.23)
SEE	13 (0.08)	8 (0.05)
SEE/ischemic stroke	157 (1.01)	143 (0.93)
First Stroke or SEE (Primary Efficacy Outcome, Testing for Superiority) ITT analysis, overall study period, set	**N = 7,036**	**N = 7,035**
No. of events (event rate per year)	337 (1.80)	296 (1.57)
HR edoxaban versus warfarin (99.0% CI)	0.87 (0.73 to 1.04)	
P value	0.0807	
Major Bleeding (Primary Safety Outcome) safety analysis set	**N = 7,012**	**N = 7,012**
No. of events (event rate per year)	524 (3.43)	418 (2.75)
HR (95% CI)	0.80 (0.71 to 0.91)	
P value	**< 0.001***	
Select Subcomponents of Major Bleeding, n (%)		
Fatal bleeding	59 (0.38)	32 (0.21)
Intracranial bleeding	132 (0.85)	61 (0.39)
Gastrointestinal bleeding	190 (1.23)	232 (1.51)
Other Safety Events, safety analysis set	**N = 7,012**	**N = 7,012**
Mortality, n (%)	836 (11.9)	769 (11.0)
Life-threatening bleeding, *No. of events (event rate per year)*	122 (0.78)	62 (0.40)
Clinically relevant non-major bleeding, *No. of events (event rate per year)*	1,396 (10.15)	1,214 (8.67)

	ENGAGE AF-TIMI 48	
	Warfarin	Edoxaban 60 mg
Minor bleeding, *No. of events (event rate per year)*	714 (4.89)	604 (4.12)
Myocardial infarction, *No. of events (event rate per year)*	105 (0.68)	88 (0.57)
Nonbleeding SAEs, n (%)	2,516 (35.9)	2,315 (33.0)

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; mITT = modified intention-to-treat; SAE = serious adverse event; SEE = systemic embolic event.
Source: CSR ENGAGE AF-TIMI 48[9] and Giugliano, 2013.[10]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Atrial fibrillation (AF) is a common cardiac arrhythmia[1,2] characterized by disorganized, rapid, and irregular activity of the atria (i.e., the upper chambers of the heart).[3] AF is recognized as a chronic, progressive disorder associated with increased morbidity and mortality.[4-6] The Heart and Stroke Foundation estimates that approximately 350,000 Canadians are affected by AF.[7] The prevalence of AF increases with age, and AF is more prevalent in patients with structural heart diseases, hypertension, obesity, diabetes, and other chronic conditions.[11,12] AF usually presents with recurrent episodes that are described as either paroxysmal, persistent, or permanent.[13-15] In all types of AF, the embolization of atrial thrombi poses a significant risk of arterial thromboembolism, transient ischemic attack (TIA), and stroke, which are associated with high recurrence and substantial debilitating impact.[4,5] The risk of stroke varies considerably among patients; therefore, selecting an appropriate stroke prevention strategy requires risk assessment.[4] Although various models have been proposed, major clinical guidelines[13-15] select the $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or TIA or thromboembolism) score to make recommendations based on the risk of stroke.

1.2 Standards of Therapy

Guidelines from the Canadian Cardiovascular Society[14] and the American College of Chest Physicians,[13] as well as the European Society of Cardiology[15] recommendations, include two classes of antithrombotic medication for stroke prevention in patients with AF: anticoagulant drugs and antiplatelet drugs.

TABLE 2: MAJOR CLINICAL RECOMMENDATIONS FOR ANTITHROMBOTIC MANAGEMENT IN AF

Risk of Stroke	Canadian Guidelines, CCS[14]	American Guidelines, ACCP[13]	European Guidelines, ESC[15]
Low ($CHADS_2$ = 0)	**Higher risk[a] = OAC** *A DOAC (dabigatran, rivaroxaban, apixaban, edoxaban) is recommended over warfarin.* **Lower risk[c] = ASA** Lowest risk[d] = no therapy	No therapy	**Higher risk[b] = OAC** *A DOAC (dabigatran, rivaroxaban, apixaban, edoxaban) is recommended over warfarin.* Lowest risk[b] = no therapy
Intermediate ($CHADS_2$ = 1)	**OAC** ***A DOAC (dabigatran, rivaroxaban, apixaban, edoxaban) is recommended over warfarin.***	**OAC** ***Dabigatran is recommended over warfarin.***[e]	**OAC** ***A DOAC (dabigatran, rivaroxaban, apixaban, edoxaban) is recommended over warfarin.***
High ($CHADS_2 \geq 2$)	**OAC** ***A DOAC (dabigatran, rivaroxaban, apixaban, edoxaban) is recommended over warfarin.***	**OAC** ***Dabigatran is recommended over warfarin.***[e]	**OAC** ***A DOAC (dabigatran, rivaroxaban, apixaban, edoxaban) is recommended over warfarin.***

ACCP = American College of Chest Physicians; AF = atrial fibrillation; CCS = Canadian Cardiovascular Society; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack or thromboembolism; DOAC = direct oral anticoagulant; ESC = European Society of Cardiology; OAC = oral anticoagulant; TIA = transient ischemic attack.

[a] Based on the following consideration: Patient is 65 years of age or older, and/or with one or more of hypertension, diabetes, stroke, or TIA.

[b] European guidelines are similar to Canadian guidelines, with the exception that OAC would be recommended for patients younger than 65 with vascular disease.

[c] Based on the following consideration: Patient is under 65 years of age, with no hypertension, diabetes, stroke, or TIA, but with a vascular disease.

[d] Based on the following consideration: Patient is under 65 years of age, with no hypertension, diabetes, stroke, or TIA and no vascular disease.

[e] At the time the American guidelines were published (2012), only dabigatran received regulatory approval for use in AF, and therefore, the American guidelines are currently being updated.

1.3 Drug

Edoxaban is a direct factor Xa inhibitor. The inhibition of factor Xa in the coagulation cascade leads to an anticoagulant effect. Edoxaban is administered orally, at a dosage of 60 mg once daily, and the drug's current proposed indication is for the prevention of stroke and systemic embolism in patients with AF.

Indication under review
Prevention of stroke and systemic embolic events in patients with nonvalvular atrial fibrillation
Reimbursement criteria requested by sponsor
As per indication

TABLE 3: KEY CHARACTERISTICS OF EDOXABAN, APIXABAN, RIVAROXABAN, DABIGATRAN, AND WARFARIN

	Edoxaban	Apixaban	Rivaroxaban	Dabigatran	Warfarin
Mechanism of action	Selective, direct, reversible inhibitor of factor Xa	Selective, direct, reversible inhibitor of factor Xa	Selective, direct, reversible inhibitor of factor Xa	Competitive, reversible direct thrombin inhibitor	Inhibitor of vitamin K–dependent factors II, VII, IX, and X
Indication[a]	Stroke prevention in NVAF patients	Stroke prevention in NVAF patients	Stroke prevention in NVAF patients	Stroke prevention in NVAF patients	Stroke prevention in NVAF patients
Route of administration	Oral	Oral	Oral	Oral	Oral
Recommended dosage	60 mg once daily	5 mg twice daily	20 mg once daily	150 mg twice daily	Titrated to INR of 2 to 3
Serious side effects / safety issues	Bleeding	Bleeding	Bleeding	Bleeding	Bleeding

INR = international normalized ratio; NVAF = nonvalvular atrial fibrillation.
[a] Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of edoxaban 60 mg (30 mg dose reduced) once daily for the prevention of stroke and systemic embolic events (SEEs) in patients with nonvalvular atrial fibrillation (NVAF).

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Other studies were selected for inclusion according to the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient population	Adult patients diagnosed with NVAF requiring anticoagulation
Intervention	Edoxaban 60 mg (30 mg dose reduced) once daily
Comparators	• Apixaban 2.5 mg or 5 mg b.i.d. • Rivaroxaban 15 mg or 20 mg q.d. • Dabigatran 110 mg or 150 mg b.i.d. • ASA • Clopidogrel 75 mg q.d. (with or without ASA) • Vitamin K antagonist (warfarin and acenocoumarol) • Placebo
Outcomes	**Key efficacy outcomes:** • Composite outcome of stroke and SEE • Ischemic stroke • Hemorrhagic stroke • Systemic thromboembolic event • Hospitalization • Quality of life **Harms outcomes:** • AEs • SAEs • WDAEs • All-cause mortality • Cardiovascular mortality Notable harms: Intracranial bleeding, extracranial bleeding, life-threatening bleeding, minor bleeding, GI bleeding, major bleeding, myocardial infarction
Study design	Published and unpublished phase III RCTs; studies considered pivotal by Health Canada

AE = adverse event; b.i.d. = twice daily; GI = gastrointestinal; NVAF = nonvalvular atrial fibrillation; q.d. = once daily; RCT = randomized controlled trial; SAE = serious adverse event; SEE = systemic embolic event; WDAE = withdrawal due to adverse event.

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's 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 on October 7, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee 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 Grey Matters checklist (http://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 CADTH Common Drug Review clinical reviewers independently selected studies for inclusion in the review on the basis of 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 5; excluded studies (with reasons) are presented in 0.

3. RESULTS

3.1 Findings from the Literature

A total of 874 reports were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5: Details of Included Studies and described in Section 3.2. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

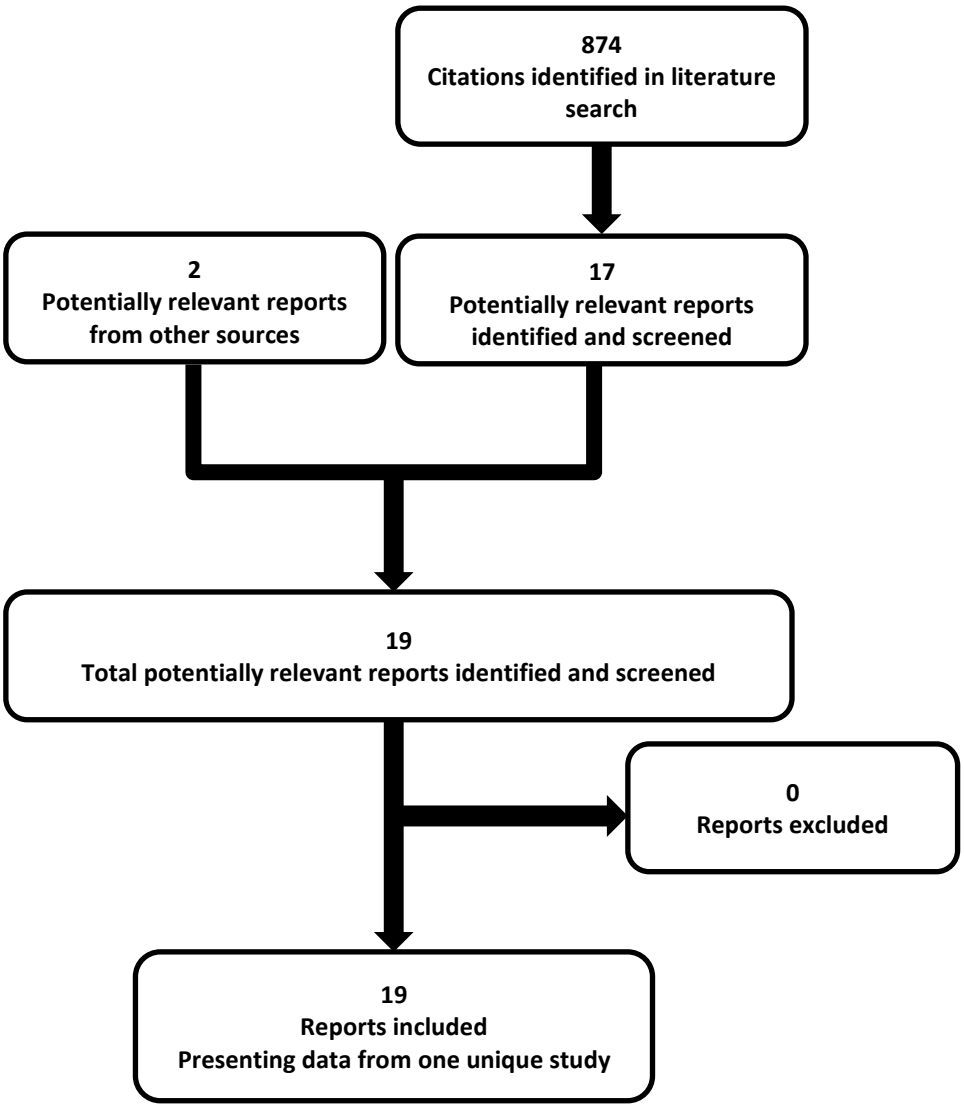

TABLE 5: DETAILS OF INCLUDED STUDIES

		ENGAGE AF-TIMI 48
DESIGNS & POPULATIONS	**Study design**	Double-blind, double-dummy, randomized controlled trial
	Locations	Conducted in 46 countries, including Canada, the US, and Western Europe
	Randomized (N)	21,105
	Inclusion criteria	• 21 years of age or older • Documented atrial fibrillation within the last 12 months through electrical tracing • Score of 2 or higher on the $CHADS_2$ risk assessment
	Exclusion criteria	• Atrial fibrillation secondary to reversible disorder • Patients with moderate or severe mitral stenosis, unresected atrial myxoma, a mechanical heart valve, left atrial appendage exclusion, intracardial mass or left ventricular thrombus, acute MI, stroke, acute coronary syndrome, percutaneous coronary intervention, hepatitis B or C positive, HIV positive, or active malignancy • Patients with high risk of bleeding (history of intracranial or spontaneous intraocular, spinal, retroperitoneal, or intra-articular bleeding; overt gastrointestinal bleeding or active ulcer; recent severe trauma, recent major surgery, or deep organ biopsy within the previous 10 days; active infective endocarditis, uncontrolled or hemorrhagic) • Patients receiving dual antiplatelet therapy • Patients receiving cyclosporine therapy • Patients receiving prohibited concomitant treatment • Creatinine clearance of less than 30 mL/min • Persistent elevation of liver enzymes
DRUGS	**Intervention**	High-dose edoxaban arm: 60 mg (reduced to 30 mg in renal insufficiency and low–body weight patients or specific concomitant medication), once daily, orally Low-dose edoxaban arm: 30 mg once daily; not reported in this review since it does not match the review protocol or Health Canada–approved dosage for this indication
	Comparator(s)	Warfarin, once daily, dose adjusted to maintain INR between 2.0 and 3.0
DURATION	**Phase**	
	Run-in	Up to 2 months
	Double-blind	No pre-specified duration; study continued until 672 targeted primary end point events were collected; median duration of treatment was 2.5 years
	Follow-up	No pre-specified duration; study continued until 672 targeted primary end point events were collected; median duration of follow-up was 2.8 years, which included the transition period
OUTCOMES	**Primary end point**	Composite of stroke and systemic embolic event (time to first adjudicated ischemic or hemorrhagic stroke or systemic embolic event)
	Other end points	• Composite of stroke, systemic embolic event, and cardiovascular mortality • Composite of myocardial infarction, stroke, systemic embolic event, and cardiovascular mortality • Composite of stroke, systemic embolic event, and all-cause mortality • Hospitalization due to cardiovascular conditions (exploratory outcome) • Venous thromboembolism (exploratory outcome)
NOTES	**Publications**	Giugliano 2013, Bohula 2016, Di Pasquale 2014, Eisen 2016, Giugliano 2014, Giugliano 2016, Kato 2016, Magnani 2016, Mega 2015, O'Donoghue 2015, Rost 2016, Ruff 2014, Shimada 2015, Steffel 2016, Skjoth 2014, Xu 2016, Yamashita 2016. [10,16-31]

$CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack or thromboembolism; INR = international normalized ratio; MI = myocardial infarction.
Source: CSR ENGAGE AF-TIMI 48;[9] Giugliano, 2013.[10]

3.2 Included Studies

3.2.1 Description of studies

The systematic search of the literature identified one study for inclusion. The ENGAGE AF-TIMI 48 study was a phase III, noninferiority (NI), double-blind, randomized, active-controlled, parallel-group study. Investigators randomized 21,105 NVAF patients to edoxaban 60 mg once daily, edoxaban 30 mg once daily, or warfarin. This review will only focus on the comparison between edoxaban 60 mg and warfarin on the basis of Health Canada–approved doses for this indication. The study's primary outcome was the incident of stroke or SEE. The study continued until 672 primary events were collected.

3.2.2 Populations

a) Inclusion and exclusion criteria

Patients in ENGAGE AF-TIMI 48 had been diagnosed with NVAF, with documented electrocardiogram tracing studies of AF, within the 12 months before enrolment. Patients in either study also had to have a $CHADS_2$ score of at least 2. ENGAGE AF-TIMI 48 patients could not have had AF due to a secondary cause. They also could not have had an increased risk of bleeding or suffered from liver dysfunction or severe renal impairment.

b) Baseline characteristics

Patients in the edoxaban 60 mg and warfarin arms of the ENGAGE AF-TIMI 48 study had balanced baseline characteristics, and most patients in each group were male. The mean $CHADS_2$ scores were also similar between arms, as was the proportion of patients at various $CHADS_2$ stages.

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS (MODIFIED INTENTION-TO-TREAT ANALYSIS SET)

Characteristics	ENGAGE AF-TIMI 48	
	Warfarin (N = 7,012)	Edoxaban 60 mg (N = 7,012)
Age (years)		
Mean (SD)	70.5 (9.44)	70.6 (9.51)
Median	72.0	72.0
Interquartile range	64 to 78	64 to 78
Female, No. (%)	2,641 (37.5)	2,669 (37.9)
Paroxysmal atrial fibrillation, No. (%)	1,778 (25.3)	1,753 (24.9)
Race, No. (%)		
Caucasian	5,679 (81.0)	5,679 (81.0)
Black	88 (1.3)	96 (1.4)
Asian	963 (13.7)	956 (13.6)
Other	282 (4.0)	281 (4.0)
Weight (kg), mean (SD)	83.7 (20.09)	84.2 (20.40)
Qualifying Risk Factor, No. (%)		
Age > 75 years	2,820 (40.1)	2,848 (40.5)
Prior stroke or transient ischemic attack	1,991 (28.3)	1,976 (28.1)
Congestive heart failure	4,048 (57.5)	4,097 (58.2)
Diabetes mellitus	2,521 (35.8)	2,559 (36.4)
Hypertension requiring	6,588 (93.6)	6,591 (93.7)

Characteristics	ENGAGE AF-TIMI 48	
	Warfarin (N = 7,012)	Edoxaban 60 mg (N = 7,012)
treatment		
$CHADS_2$ score, mean (SD)	2.8 ± 1.0	2.8 ± 1.0
< 3, No. (%)	5,445 (77.4)	5,422 (77.1)
4 to 6, No. (%)	1,591 (22.6)	1,613 (22.9)
Dose reduction at randomization, No. (%)	1,787 (25.4)	1,784 (25.4)
Creatinine clearance < 50 mL/min	1,361 (19.3)	1,379 (19.6)
Weight < 60 kg	701 (10.0)	684 (9.7)
Use of verapamil or quinidine	243 (3.5)	258 (3.7)
Previous VKA Use, No. (%)		
VKA experienced	4,124 (58.8)	4,133 (58.9)
VKA naive	2,888 (41.2)	2,879 (41.1)
Medication at Randomization, No. (%)		
Aspirin	2,083 (29.7)	2,060 (29.4)
Thienopyridine	163 (2.3)	172 (2.5)
Antiplatelet drug, excluding Aspirin and thienopyridines	59 (0.8)	54 (0.8)
NSAIDs	77 (1.1)	68 (1.0)
Lipid-lowering drugs (statins, others)	3,365 (48.0)	3,290 (46.9)
Verapamil	221 (3.2)	235 (3.4)
Quinidine	1 (< 0.1)	6 (< 0.1)
Amiodarone	826 (11.8)	862 (12.3)
Dronedarone	48 (0.7)	42 (0.6)
ACE inhibitors or ARBs	4,615 (65.8)	4,617 (65.8)
Beta blocker	4,693 (66.9)	4,592 (65.5)
Calcium channel blocker	2,153 (30.7)	2,181 (31.1)
Diuretics	4,184 (59.7)	4,245 (60.5)
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Characteristics	ENGAGE AF-TIMI 48	
	Warfarin (N = 7,012)	Edoxaban 60 mg (N = 7,012)
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation; VKA = vitamin K antagonist.
Source: CSR ENGAGE AF-TIMI 48;[9] Giugliano, 2013.[10]

3.2.3 Interventions

Patients in the ENGAGE AF-TIMI 48 study were randomized to warfarin, edoxaban 60 mg once daily, or edoxaban 30 mg once daily. Patients randomized to the warfarin arm received dose-adjusted warfarin to maintain a monthly measured international normalized ratio (INR) at 2.0 to 3.0. Patients randomized to the edoxaban 60 mg or 30 mg groups would have received the allocated dose unless one of the following criteria was present: creatinine clearance (CrCL) of 30 mL/min to 50 mL/min, body weight of 60 kg or less, or verapamil or quinidine use. In such cases, the edoxaban dose was halved.

All patients received two sets of drugs: the active allocated drug or a placebo. To maintain blinding, sham INR values were generated to patients who were randomized to edoxaban. The adjustment of the warfarin dose was carried out by the investigators according to the local or regional guidelines of warfarin therapy or to a predefined designated algorithm. INR doses were measured centrally.

At the end of the double-blind treatment period, all patients transitioned to an open-label anticoagulation therapy. The choice of which oral anticoagulation therapy to transition to was decided on by the patient and his or her treating physician. Patients who were randomized to edoxaban treatment and wished to transition to warfarin (regardless of the edoxaban arm) received a 14-day transition kit containing 30 mg edoxaban (15 mg in patients with reduced dose). Patients who were randomized to warfarin and wished to transition to warfarin received a matching placebo. Patients who were randomized to either warfarin or edoxaban and wished to transition to a direct oral anticoagulant (DOAC) did not receive a transition kit. The transition was a period of two weeks or until the patient's INR reached within the range of 2 to 3, whichever came first.

3.2.4 Outcomes

The primary outcome in the ENGAGE AF-TIMI 48 study was a composite of stroke and SEE. A stroke was defined as "an abrupt onset, over minutes to hours, of a focal neurological deficit in the distribution of a single brain artery that is not due to an identifiable nonvascular cause (i.e., brain tumour or trauma), and that either lasts at least 24 hours or results in death within 24 hours of onset." A retinal ischemic event (embolism, infarction) was considered as a stroke. A SEE was defined as "an arterial embolism resulting in clinical ischemia, excluding the central nervous system (CNS), coronary and pulmonary arterial circulation." [9] A TIA was defined as a non-traumatic abrupt onset of focal neurological symptoms lasting less than 24 hours.

The definition of major bleeding was adapted from the International Society on Thrombosis and Haemostasis (ISTH) definition. The study clarifies that minor modifications were made to the hemoglobin and transfusion criteria of the ISTH definition but provides no details. Specifically, a major bleeding event was defined as a clinically overt bleeding event that can be visualized by clinical examination or radiologic imaging that meets one or more of the following criteria: (1) causes fatal bleeding, (2) causes bleeding symptoms in critical areas or organs (e.g., retroperitoneal, intracranial,

intraspinal, or intraocular), or (3) causes a fall in hemoglobin level of ≥ 20 g/L. The third criterion can also be assessed through the use of a red blood cell transfusion (one unit of packed red blood cell or whole blood is counted as a 10 g/L decrease in hemoglobin) or through a drop in hematocrit of ≥ 6.0%. All blood values that were adjusted for transfusion are provided.

Any bleeding that required medical attention was adjudicated in a blind manner by the Clinical Events Committee. The Clinical Events Committee determined if a bleeding met the definition of major bleeding or, if it did not, if it would be classified as clinically relevant non-major bleeding. Any bleeding that did not require medical attention was not adjudicated.

3.2.5 Statistical analysis

ENGAGE AF-TIMI 48 employed an NI design. NI for the primary efficacy end point was assessed first; NI testing was intended just for the primary outcome. To satisfy NI, the upper boundary of the one-sided 97.5% confidence interval (CI) of edoxaban compared with warfarin had to be lower than 1.38. This margin was based on six historical studies of warfarin versus placebos and should maintain at least 50% of the efficacy of warfarin over a placebo. Sensitivity analysis for the primary outcome included the per-protocol on-treatment analysis set, the modified intention-to-treat (mITT) overall period analysis set, and the per-protocol overall period analysis set.

Originally, it was calculated that 448 on-treatment events were required for a two-group comparison to have > 90% power to reject a null hypothesis of inferiority. An initial annual rate of events assumption of 2.1% was later revised to 1.7%, leading to a decision of continuous enrolment until 20,500 patients were randomized. The study continued until 672 events were gathered.

The analysis followed a hierarchal testing pathway in which the primary outcome of stroke or SEE was first tested for NI. If NI was achieved, the primary outcome of stroke or SEE was tested at an alpha of 0.01 for superiority. If superiority was achieved, the secondary outcome of stroke, SEE, or cardiovascular (CV) mortality was tested for superiority at an alpha of 0.01. If superiority was achieved, the secondary outcome of major adverse CV events (including myocardial infarction, stroke, SEE, or CV mortality) was tested for superiority at an alpha of 0.01, and if superiority was achieved, the secondary outcome of stroke, SEE, or all-cause mortality was tested for superiority. No adjustment for multiple comparisons was applied for any other outcomes. Subgroup analyses were carried out on the basis of age, gender, $CHADS_2$ score, dose adjustment due to body weight, dose adjustment due to CrCL, dose adjustment due to concomitant use of verapamil or quinidine, vitamin K antagonist (VKA) previous use, geographic region, race, ethnicity, prior stroke, prior congestive heart failure, prior hypertension, prior diabetes, concomitant Aspirin use, concomitant use of lipid-lowering drugs, concomitant use of angiotensin converting enzyme or angiotensin II receptor blocker inhibitors, concomitant use of amiodarone or dronedarone, concomitant use of diuretics, and the international normalized ratio–time in therapeutic range (INR-TTR) values.

NI testing was conducted using the mITT analysis set during the treatment period. All superiority testing was conducted using the intention-to-treat (ITT) analysis set from the overall study period. Per-protocol analysis was also conducted on all comparisons.

The treatment effect was reported using the hazard ratio (HR) and the corresponding 95% CI. The analysis was performed by employing a Cox proportional hazard model that included treatment groups and the following two randomization stratification factors as covariates: (1) $CHADS_2$ score of 2 to 3 versus 4 to 6 and (2) full dose versus reduced dose in a given treatment group. Missing data were not

imputed, and the analysis was conducted on the observed data only. Censoring was applied: Patients who did not reach the primary end point were censored (i.e., the time to the first event was censored at the common study end date visit), as were intervals in the study period in which drug interruption lasted longer than three days.

a) Analysis populations

mITT Analysis Set: All patients who were randomized and received at least one dose of the allocated study drug. The reference date for end point consideration was the date of the first dose of the allocated drug.

ITT Analysis Set: All randomized patients. Patients were categorized according to the treatment group to which they were assigned, regardless of the treatment they actually received. The reference date for end point consideration was the date of randomization.

Per-Protocol Analysis Set: All patients who were randomized, received at least one dose of the allocated study drug, and had no major protocol violations. The reference date for end point consideration was the date of the first dose of the allocated drug.

Safety Analysis Set: All patients who were randomized and received at least one dose of the allocated study drug. The reference date for end point consideration was the date of the first dose of the allocated drug.

For each analysis set, on-treatment and overall study period populations exist. The on-treatment period is defined as the period in which a patient was taking the study drug and up to three days after his or her last dose. This period covers the double-blind study period and does not include the transition period. The overall study period was defined as the time from the reference date to the common study end date and included the open-label transition period.

3.3 Patient Disposition

The majority of patients completed the study. The most common reasons for study discontinuation were death (one of the outcomes to be collected) and withdrawal of consent. Only one patient was lost to follow-up in the warfarin arm. No major discrepancies in patients' dispositions were noted in any group.

TABLE 7: PATIENT DISPOSITION

	ENGAGE AF-TIMI 48		
	Warfarin	**High-Dose (60 mg) Edoxaban**	**Low-Dose (30 mg) Edoxaban[a] (excluded from this review)**
Screened, N	25,497		
Randomized overall, N (% of screened)	21,105 (83)		
Randomized (ITT analysis set), N	7,036	7,035	7,034
Received allocated treatment (mITT and safety analysis sets), N	7,012	7,012	7,002
No major protocol deviations (per-protocol analysis set), N	6,993	6,995	6,982
Did not complete study, N (%)	879 (12.5)	807 (11.5)	784 (11.1)
Due to death, N (%)	789 (11.2)	730 (10.4)	706 (10.0)
Withdrew consent, N (%)	90 (1.3)	77 (1.1)	77 (1.1)
Lost to follow-up, N	0	0	1

ITT = intention-to-treat; mITT = modified intention-to-treat.
[a]Excluded from this review
Source: CSR ENGAGE AF-TIMI 48;[9] Giugliano, 2013.[10]

3.4 Exposure to Study Treatments

Patients in all groups had a similar duration of drug exposure, with the warfarin group presenting a mean of 811 days (standard deviation: 383.14) and the edoxaban 60 mg group presenting a mean of 805.9 days (standard deviation: 390.82). No major discrepancies across the groups were noted.

TABLE 8: TOTAL DRUG EXPOSURE

	ENGAGE AF-TIMI 48		
	Warfarin (N = 7,012)	**High-Dose (60 mg) Edoxaban (N = 7,012)**	**Low-Dose (30 mg) Edoxaban (excluded from this review) (N = 7,002)**
On-Treatment Period Drug Exposure			
Mean, SD (days)	811.0 (383.14)	805.9 (390.82)	826.3 (374.24)
Median, days	904.0	904.0	916.0
Overall Study Period Drug Exposure			
Mean, SD (days)	[redacted]	[redacted]	[redacted]
Median, days	[redacted]	[redacted]	[redacted]
Percentage of exposed days, mean (SD)	[redacted]	[redacted]	[redacted]

SD = standard deviation.
Source: CSR ENGAGE AF-TIMI 48;[9] Giugliano, 2013.[10]

Compliance with warfarin in patients who were randomized to warfarin measured through a TTR in the INR range of 2.0 to 3.0, inclusive. Overall, all testing regions reported a good TTR control, with a median TTR in the INR range of 2.0 to 3.0 at 68.4% (mean 64.9%).

TABLE 9: PERCENTAGE TIME IN VARIOUS INR RANGES FOR PATIENTS IN THE WARFARIN GROUP, SAFETY ON-TREATMENT ANALYSIS SET

INR Range (Overall N = 6,897)	Mean, % (SD)	Median, %
< 1.5	6.10 (13.8)	1.90
1.5 to 2.0	22.70 (13.3)	21.00
< 2	22.80 (18.9)	17.70
2 to 3	64.90 (18.7)	68.40
> 3	12.40 (10.3)	10.80
≥ 4	1.80 (4.5)	0.40
> 5	0.30 (2.3)	0.00
≥ 8	0.00 (0.8)	0.00

INR = international normalized ratio; SD = standard deviation.

3.5 Critical Appraisal

3.5.1 Internal validity

ENGAGE AF-TIMI 48 was designed as an NI study to warfarin. This design appears to be reasonable considering that warfarin is the traditional standard of care in this population. The manufacturer mentions that the margin was calculated from six historical studies of warfarin versus placebo. The resulting margin was slightly more restrictive to those seen with rivaroxaban and dabigatran in the RE-LY and ROCKET-AF trials (NI margin of 1.46 in both); the margin in ENGAGE AF-TIMI 48 was equal to that in the ARISTOTLE trial that assessed apixaban (NI margin of 1.38). As such, the NI margin appears consistent with other DOAC trials.

Maintaining blinding in ENGAGE AF-TIMI 48 was complicated by the need for the constant monitoring of INR. The dosages of warfarin in ENGAGE AF-TIMI 48 were adjusted to achieve INR values within the range of 2 to 3. Sham INR values were generated for edoxaban groups to maintain blinding. Although it is likely that no other approach would be better at maintaining blinding with warfarin, some questions remain as to whether investigators might ascertain the difference between randomly generated INRs and actual INRs. Even with the possibility of a lack of complete concealment, outcomes were objective enough to not be substantially influenced by the knowledge of treatment allocation. Randomization was performed centrally, and allocation concealment appears to have been adequate.

The primary efficacy outcome of ENGAGE AF-TIMI 48 was stroke and systemic embolism, and the primary safety outcome was major bleeding. An intracranial hemorrhage could have been counted in either outcome: as a major bleeding and as a stroke (hemorrhagic stroke). This situation would represent a problem in the statistical assumption of the independency of events, as one event (hemorrhagic stroke) may also be registered as another event (intracranial bleeding), and could bias the results in favour of the intervention with the lower bleeding events — in this instance, edoxaban.

ENGAGE AF-TIMI 48 employed a hierarchal model to adjust for the multiple outcomes testing. However, as will be shown in the results section, the analysis failed to show superiority in the primary analysis. As such, the investigator should have stopped statistical testing for the remaining secondary outcomes. Exploratory outcomes were unadjusted for multiple comparisons.

Subgroup analyses were small and likely underpowered to find any differences and would therefore favour NI being declared. Also, subgroup analyses no longer represent a randomized population and

may exhibit unbalanced characteristics that may confound the results. These results would need to be interpreted with caution, as they did not account for the multiplicity of testing for subgroups.

3.5.2 External validity

ENGAGE AF-TIMI 48 was a large, multi-centre study that included sites in Canada and the US. The study had appropriate inclusion and exclusion criteria. The study established NI to warfarin, which is a widely used treatment for this group of patients.

Although having a large study such as ENGAGE AF-TIMI 48 is considered a strength, the drawback of ENGAGE AF-TIMI 48 is the difficulty in intuitively interpreting the study results with regard to how the treatment difference will affect the absolute risk in patients. Studies with large sample sizes are capable of producing findings that show a statistical difference between groups, but these findings may translate to a very low absolute benefit.

In addition, the choice of the primary outcome (a composite of stroke and SEE) in the ENGAGE AF-TIMI 48 study is difficult to translate into meaningful value in clinical practice; any differences that may be observed in secondary or exploratory outcomes would require further validation through new trials.

Edoxaban is the fourth of a new set of oral anticoagulants that are all positioned as alternatives for warfarin. All these drugs have been compared with warfarin, but none have been compared with one another. A direct comparison is needed between these drugs to determine which of the drugs, if any, might provide the most significant improvement over warfarin and in which patients these new drugs would be most appropriate. The manufacturer attempted to answer this question through an indirect comparison (IDC). However, the manufacturer's IDC, as well as other published IDCs, suffer from several limitations that make the value of such evidence much lower than that of a head-to-head trial.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (Section 2.2, Table 4) are reported below. See APPENDIX 4 for detailed efficacy data.

3.6.1 Composite of stroke and systemic embolic event (primary outcome)

Overall, patients treated with edoxaban had a lower event rate of stroke or systemic embolism compared with patients treated with warfarin (HR = 0.79; 97% CI, 0.63 to 0.99). In patients who received at least one dose of the medication (mITT analysis set) and only during the treatment period (edoxaban = 1.18%; warfarin = 1.50%), the per-protocol on-treatment analysis set gave an identical conclusion. This result satisfied the NI margin that was originally established (i.e., upper bound of 1.38). However, the pre-specified superiority analysis failed to show superiority (HR = 0.87; 99.0% CI, 0.73 to 1.04). This analysis used the ITT overall period analysis set (rate of events: edoxaban = 1.57%; warfarin = 1.80%). The failure to show superiority at this point should have constituted a stop sign in the predefined hierarchal pathway of outcome testing. In other words, no further statistical comparisons regarding efficacy outcomes should have been carried out.

When examining the individual components of the primary outcome, we notice that, in the mITT NI result, the main driver behind the lower events rate in edoxaban was the lower rate of hemorrhagic stroke. When moving to the ITT overall study period population, we notice that an almost equal number of ischemic stroke events took place in both groups, further adding to the difficulty of interpreting the study results because of the changing study populations.

a) Subgroup analyses

Subgroup analyses were performed for the primary efficacy outcome of stroke and SEE on baseline characteristics (age, gender, race, body weight, CrCL, $CHADS_2$ score, dose reduction, prior VKA status, and various comorbidities). Most findings from the subgroup analyses were reported as being consistent with base-case results.

One relevant subgroup analysis, although not statistically significant, showed a trend of decreased efficacy of edoxaban 60 mg compared with warfarin (HR = 1.36; 95% CI, 0.88 to 2.10) in patients with high CrCL (more than 95 mL/min). The subgroup results should be viewed cautiously since they are not sufficiently powered, adjusted for multiplicity, or ensured of preserved randomization to provide confidence in their findings.

3.6.2 Composite of stroke, systemic embolic event, and cardiovascular mortality

Fewer patients had this composite outcome in the edoxaban 60 mg arm (728 patients, 3.85%) than in the warfarin arm (831 patients, 4.43%). Statistical significance testing is not presented here since the hierarchal testing model failed to achieve statistical significance in the previous step.

3.6.3 Composite of myocardial infarction, stroke, systemic embolic event, and cardiovascular mortality

Fewer patients had this composite outcome in the edoxaban 60 mg arm (827 patients, 4.41%) than in the warfarin arm (926 patients, 4.98%). Statistical significance testing is not presented here since the hierarchal testing model failed to achieve statistical significance in a previous step.

3.6.4 Composite of stroke, systemic embolic event, and all-cause mortality

Fewer patients had this composite outcome in the edoxaban 60 mg arm (949 patients, 5.01%) than in the warfarin arm (1,046 patients, 5.57%). Statistical significance testing is not presented here since the hierarchal testing model failed to achieve statistical significance in a previous step.

3.6.5 Other efficacy outcomes

Fewer patients were hospitalized in the edoxaban 60 mg arm [redacted] than in the warfarin arm [redacted].

TABLE 10: KEY EFFICACY OUTCOMES

	ENGAGE AF-TIMI 48	
First Stroke or SEE	Warfarin	Edoxaban
Noninferiority mITT Analysis (On-Treatment Period)	(N = 7,012)	(N = 7,012)
No. of events (event rate per year)	232 (1.50)	182 (1.18)
HR edoxaban versus warfarin (97.5% CI)	0.79 (0.63 to 0.99)	
Noninferiority PP Analysis (On-Treatment Period)	(N = 6,993)	(N = 6,995)
No. of events (event rate per year)	[redacted]	[redacted]
HR edoxaban versus warfarin (97.5% CI)	[redacted]	

	ENGAGE AF-TIMI 48	
Superiority ITT Analysis (Overall Study Period)	(N = 7,036)	(N = 7,035)
No. of events (event rate per year)	337 (1.80)	296 (1.57)
HR edoxaban versus warfarin (99.0% CI)	0.87 (0.73 to 1.04)	
P value	0.0807	

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; mITT = modified intention-to-treat; PP = per-protocol; SEE = systemic embolic event.
Source: CSR ENGAGE AF-TIMI 48;[9] Giugliano, 2013.[10]

TABLE 11: BREAKDOWN OF THE MAIN COMPONENTS AND SELECT SUBCOMPONENTS OF THE PRIMARY OUTCOME

	ENGAGE AF-TIMI 48	
Component	Warfarin, n *(event rate per year)*	Edoxaban, n *(event rate per year)*
mITT Analysis Set (On-Treatment Period)	(N = 7,012)	(N = 7,012)
Stroke	219 (1.41)	174 (1.13)
Ischemic stroke	144 (0.93)	135 (0.87)
Hemorrhagic stroke	76 (0.49)	40 (0.26)
Fatal stroke	43 (0.28)	45 (0.29)
Disabling stroke	41 (0.26)	35 (0.23)
SEE	13 (0.08)	8 (0.05)
SEE/ischemic stroke	157 (1.01)	143 (0.93)
Superiority ITT Analysis (Overall Study Period)	(N = 7,036)	(N = 7,035)
Stroke	317 (1.69)	281 (1.49)
Ischemic stroke	235 (1.25)	236 (1.25)
Hemorrhagic stroke	90 (0.47)	49 (0.26)
Fatal stroke	86 (0.45)	80 (0.42)
Disabling stroke	57 (0.30)	54 (0.28)
SEE	23 (0.12)	15 (0.08)
SEE/ischemic stroke	255 (1.36)	251 (1.33)

ITT = intention-to-treat; mITT = modified intention-to-treat; SEE = systemic embolic event.
Source: Clinical Study Report: ENGAGE AF-TIMI 48;[9] Giugliano, 2013.[10]

TABLE 12: SUBGROUP ANALYSIS OF PRIMARY OUTCOME BASED ON INR-TTR

	ENGAGE AF-TIMI 48	
First Stroke or SEE	Warfarin	Edoxaban
Centres with TTR > 66.4% (median)	Number of patients with available information = 3,402	Number of patients with available information = 3,277
No. of events (event rate per year)	94 (1.19)	73 (1.00)
HR edoxaban versus warfarin (95% CI)	0.85 (0.623 to 1.148)	
Centres with TTR ≤ 66.4% (median)	Number of patients with available information = 3,602	Number of patients with available information = 3,517
No. of events (event rate per year)	138 (1.82)	107 (1.39)
HR edoxaban versus warfarin(95% CI)	0.77 (0.595 to 0.986)	
Centres with TTR ≥ 60%	Number of patients with available information = 5,195	Number of patients with available information = 4,960
No. of events (event rate per year)	155 (1.30)	120 (1.09)
HR edoxaban versus warfarin(95% CI)	0.84 (0.661 to 1.065)	
Centres with TTR < 60%	Number of patients with available information = 1,813	Number of patients with available information = 1,834
No. of events (event rate per year)	77 (2.14)	60 (1.51)
HR edoxaban versus warfarin(95% CI)	0.71 (0.503 to 0.989)	

CI = confidence interval; HR = hazard ratio; INR = international normalized ratio; SEE = systemic embolic event; TTR = time in therapeutic range.
Source: CSR ENGAGE AF-TIMI 48.[9]

TABLE 13: SUBGROUP ANALYSIS OF PRIMARY OUTCOME BASED ON RENAL FUNCTION

	ENGAGE AF-TIMI 48	
First Stroke or SEE	Warfarin	Edoxaban
Moderate Renal Dysfunction (CrCL 30mL/min to 50 mL/min)	n = 1,361	n = 1,379
No. of events (event rate per year)	91 (2.7)	82 (2.3)
HR edoxaban versus warfarin (95% CI)	0.87 (0.65 to 1.18)	
Mild Renal Dysfunction (CrCL > 50 mL/min to 95 mL/min)	n = 4,148	n = 4,060
No. of events (event rate per year)	211 (1.9)	165 (1.5)
HR edoxaban versus warfarin (95% CI)	0.78 (0.64 to 0.96)	
Normal Renal Function (CrCL > 95 mL/min)	n = 1,527	n = 1,596
No. of events (event rate per year)	35 (0.8)	49 (1.1)
HR edoxaban versus warfarin (95% CI)	1.36 (0.88 to 2.10)	

CI = confidence interval; CrCL = creatinine clearance; HR = hazard ratio; SEE = systemic embolic event.
Source: CSR Bohula 2016.[16]

TABLE 14: SECONDARY OUTCOMES

	ENGAGE AF-TIMI 48	
Superiority ITT Analysis (Overall Study Period)	(N = 7,036)	(N = 7,035)
Stroke, SEE, or CV Mortality	Warfarin	Edoxaban
No. of events (event rate per year)	831 (4.43)	728 (3.85)
MI, Stroke, SEE, or CV Mortality		
No. of events (event rate per year)	926 (4.98)	827 (4.41)
Stroke, SEE, or All-Cause Mortality		
No. of events (event rate per year)	1,046 (5.57)	949 (5.01)
Hospitalization — Exploratory Outcome (On-Treatment Period)		
Superiority mITT Analysis	(N = 7,012)	(N = 7,012)
No. (%)	[redacted]	[redacted]

CV = cardiovascular; ITT = intention-to-treat; MI = myocardial infarction; mITT = modified intention-to-treat; SEE = systemic embolic event.
Source: CSR ENGAGE AF-TIMI 48;[9] Giugliano, 2013.[10]

3.7 Harms

Only those harms identified in the review protocol are reported below (see Section 2.2). See APPENDIX 4 for detailed harms data.

3.7.1 Major bleeding

Major bleeding was presented in the ENGAGE AF-TIMI 48 study as a pre-specified primary safety outcome. Major bleeding is the biggest safety concern associated with antithrombotic drugs. The incidence of major bleeding (modified ISTH criteria) was lower with edoxaban 60 mg than with warfarin (418 patients, 2.75%, versus 524 patients, 3.43%; HR = 0.80; 95% CI, 0.71 to 0.91). The incidence of various key aspects of major bleeding — namely, fatal bleeding and hemorrhagic stroke — were lower with edoxaban 60 mg than with warfarin, although there were more patients with gastrointestinal hemorrhage in the edoxaban 60 mg arm than in the warfarin arm.

3.7.2 Adverse events

The incidence of nonbleeding adverse events was similar in the edoxaban 60 mg and warfarin groups.

3.7.3 Serious adverse events

Approximately one-third of the patients in the ENGAGE AF-TIMI 48 trial experienced a nonbleeding serious adverse event (SAE). Numerically, 2,315 patients (33.0%) experienced nonbleeding SAEs in the edoxaban 60 mg group, and 2,516 patients (35.9%) experienced nonbleeding SAEs in the warfarin group.

3.7.4 Withdrawals due to adverse events

The number of patients that discontinued the allocated treatment because of adverse events was similar in the edoxaban 60 mg group and in the warfarin group.

3.7.5 Mortality

Overall, there were fewer deaths in the edoxaban 60 mg group (769 patients, 11.0%) than in the warfarin group (836 patients, 11.9%). In both arms, the bulk of the deaths were driven by CV causes (7.5% in the edoxaban 60 mg arm; 8.7% in the warfarin arm).

3.7.6 Notable harms

Patients in the edoxaban 60 mg arm had fewer incidents of life-threatening bleeding, clinically relevant non-major bleeding, and minor bleeding. This numeric advantage was also present in various subgroups (age, gender, body weight, renal function, $CHADS_2$ score, or history of stroke or TIA).

TABLE 15: HARMS

	ENGAGE AF-TIMI 48	
	Warfarin N = 7,012	**Edoxaban N = 7,012**
Mortality, n (%) (Overall Study Period)	836 (11.9)	769 (11.0)
Most Common SAEs with Outcome of Death		
Cardiovascular	608 (8.7)	527 (7.5)
Malignancies	84 (1.2)	94 (1.3)
Infection	92 (1.3)	94 (1.3)
Nonbleeding SAEs, n (%) (on-treatment study period)	2,516 (35.9)	2,315 (33.0)
Most Common SAEs		
Infections and infestations	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Congestive cardiac failure	[redacted]	[redacted]
Nonbleeding AEs, n (%) (on-treatment study period)	5,867 (83.7)	5,866 (83.7)
Most Common AEs		
Infections and infestations	3,142 (44.8)	3,126 (44.6)
Anemia	242 (3.5)	368 (5.2)
Dizziness	592 (8.4)	514 (7.3)
Headache	336 (4.8)	334 (4.8)
Atrial fibrillation	491 (7.0)	474 (6.8)
Cardiac failure	448 (6.4)	425 (6.1)
Hypertension	438 (6.2)	481 (6.9)
Dyspnea	470 (6.7)	456 (6.5)
Cough	365 (5.2)	383 (5.5)
Diarrhea	499 (7.1)	482 (6.9)
Back pain	478 (6.8)	476 (6.8)
Arthralgia	386 (5.5)	385 (5.5)
Peripheral edema	675 (9.6)	577 (8.2)
Fall	565 (8.1)	453 (6.5)
Drug discontinuation due to nonbleeding AEs, n (%) (on-treatment study period)	[redacted]	[redacted]
Most Common Reasons		
Creatinine renal clearance decreased	[redacted]	[redacted]
International normalized ratio increased	[redacted]	[redacted]

	ENGAGE AF-TIMI 48	
	Warfarin N = 7,012	**Edoxaban N = 7,012**
Cardiac failure	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]
Chronic renal failure	[redacted]	[redacted]
Acute renal failure	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Major Bleeding		
No. of events (event rate per year)	524 (3.43)	418 (2.75)
HR (95% CI)	0.80 (0.71 to 0.91)	
P value	< 0.001	
Relevant Individual Event Type, n		
Fatal bleeding	59 (0.38)	32 (0.21)
Intracranial bleeding	132 (0.85)	61 (0.39)
Gastrointestinal bleeding	190 (1.23)	232 (1.51)
Life-Threatening Bleeding		
No. of events (event rate per year)	122 (0.78)	62 (0.40)
Clinically Relevant Non-Major Bleeding		
No. of events (event rate per year)	1,396 (10.15)	1,214 (8.67)
Minor Bleeding		
No. of events (event rate per year)	714 (4.89)	604 (4.12)
Myocardial Infarction		
No. of events (event rate per year)	105 (0.68)	88 (0.57)

AE = adverse event; CI = confidence interval; HR = hazard ratio; SAE = serious adverse event.
Source: CSR ENGAGE AF-TIMI 48;[9] Giugliano, 2013.[10]

4. DISCUSSION

4.1 Summary of Available Evidence

One published, phase III, NI, double-blind, randomized, active-controlled, parallel-group study was included in this review. ENGAGE AF-TIMI 48 (7,012 edoxaban 60 mg patients and 7,012 warfarin patients) evaluated the NI and superiority of edoxaban compared with warfarin in NVAF patients with at least one risk factor for stroke (mean $CHADS_2$ of 2.8). To conclude NI, the upper boundary of the one-sided 97.5% CI of edoxaban compared with warfarin in the composite outcome of stroke and SEE had to be lower than 1.38. This margin was based on six historical studies of warfarin versus placebo and was estimated to maintain at least 50% of the efficacy of warfarin over placebo.

Eight IDCs were reviewed; one was submitted by the manufacturer, and seven were published. All IDCs had similar research questions and included the same four trials that the producer of the manufacturer's IDC included in its analysis. The approach to conducting the IDC differed among the identified IDCs; some used a frequentist network meta-analysis approach, some used a Bayesian network meta-analysis approach, and one used the Bucher method. The reported outcomes were similar in definition. However, the treatment effect measure did differ among the IDCs.

4.2 Interpretation of Results

4.2.1 Efficacy

In ENGAGE AF-TIMI 48, edoxaban 60 mg was noninferior to well-controlled warfarin therapy. However, the trial failed to show superiority. When breaking down the NI primary outcome, we notice that edoxaban 60 mg has slightly fewer patients with ischemic stroke events than warfarin, but the largest driver behind the overall difference was the lower number of hemorrhagic stroke events in the edoxaban 60 mg group. The NI margin in ENGAGE AF-TIMI 48 was slightly more restrictive to those seen with dabigatran and rivaroxaban in the ROCKET-AF and RE-LY trials (NI margin of 1.46 in both); the margin in ENGAGE AF-TIMI 48 was equal to that in the ARISTOTLE trial that assessed apixaban (NI margin of 1.38). As such, the NI margin appears consistent with previous DOAC trials.

Although NI testing over the primary outcome of stroke and SEE produced an HR with a 97.5% CI that did not cross the 1, subsequent superiority testing did not produce a statistically significant finding. time frame for the additionally included from study drug to warfarin or another on-market new DOACs. Another difference is the population analysis used. In the NI primary outcome, a mITT population analysis set was used; in the primary superiority testing, an ITT population analysis set was used. The differences in these calculation sets are that ITT would include any patient randomized, regardless of whether the patient received any dose of the intervention therapy, and the overall study period would include the additional time during which patients were transitioned from the edoxaban 60 mg intervention to open-label anticoagulation therapy. When looking at the breakdown of the individual outcomes with superiority testing, we find that the rate of ischemic stroke is similar in the edoxaban 60 mg arm and in the warfarin arm, as opposed to being lower with NI testing. The increase was largely driven by ischemic stroke events disproportionally affecting the edoxaban 60 mg arm, leading to an almost equal number of ischemic strokes in both the edoxaban 60 mg and warfarin arms. Since around two-thirds of the patients in the ENGAGE AF-TIMI 48 moved to open-label warfarin, this would indicate a possible increased risk of ischemic stroke in patients transitioning from edoxaban to warfarin until such time that their INR became therapeutic.

Subgroup analyses were performed for the primary outcome, and the results were similar to the base case. Trends from the subgroup analyses suggest that edoxaban treatment may be less efficacious than warfarin in patients with high CrCL. However, since the trial was neither powered for nor meant to test these subgroups, the results from the subgroup analyses are to be considered exploratory in nature and should only be used for hypothesis generation that would require further hypothesis testing.

Secondary outcome analysis showed fewer events in the edoxaban 60 mg arm than in the warfarin arm. Specifically, edoxaban 60 mg was associated with fewer instances of myocardial infarction, CV mortality, and overall mortality. These outcomes, however, should not be statistically analyzed because of the failure of establishing superiority in the second step of hierarchal testing.

The eight IDCs reviewed (see 0) showed similar results, mostly supporting the notion that edoxaban 60 mg has similar efficacy to VKA (warfarin) and other DOACs. However, all comparisons between the different DOACs can only be informed indirectly through a comparison of single trials that independently compared a particular DOAC with a VKA. Such intertrial comparisons tend to be problematic, as adjustment of cross-trial differences can never be adequately achieved and only trials directly evaluating one DOAC against another can provide any confidence with regard to the respective merits of these drugs. Such an informative challenge precludes analysis using a random-effects model. Thus, a fixed-effects model was used with all the reviewed IDCs. The fixed-effects model makes unrealistic assumptions about the true treatment effect, specifically 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 the study methodology and patient characteristics between trials have no influence on the true treatment effect. Such assumptions are inappropriate given the clinical heterogeneity in the evidence network, consisting of the pooled populations of the four phase III studies of the DOACs presently on the market. However, considering the nature of the available evidence, no better IDC of DOACs could have been produced.

As with other DOAC trials, the composite outcome in ENGAGE AF-TIMI 48 is hard to translate into useful clinical insights. Breaking down the primary outcome into its individual components would lead to statistical uncertainty in the reliability of the results, as the trial is not powered to detect differences in the individual components, and adjusting for multiple outcomes and comparisons becomes impracticable. It is thus hard to say anything beyond that edoxaban 60 mg is noninferior in efficacy to warfarin and is similar in this regard to the other DOACs. Considering that warfarin treatment requires strict adherence, frequent testing and dose adjustments, and specific dietary restrictions, edoxaban can be viewed as a more convenient alternative to warfarin.

4.2.2 Harms

Major bleeding events were the primary safety outcome of ENGAGE AF-TIMI 48 and represent the biggest safety concern associated with antithrombotic drugs. In ENGAGE AF-TIMI 48, edoxaban 60 mg resulted in a statistically significantly lower rate of major bleeding events than did warfarin. The lower incidence of major bleeding was also mirrored in minor bleeding, clinically relevant non-major bleeding, and life-threatening bleeding. Only gastrointestinal bleeding showed a numerically higher incidence in the edoxaban 60 mg arm than in the warfarin arm. The rate of nonbleeding adverse events and nonbleeding SAEs were similar for edoxaban 60 mg and for warfarin.

Currently, there is no direct comparison relating to safety between edoxaban and any other DOACs. The available IDCs suggest that edoxaban does result in fewer major bleeding events than does warfarin. However, the results of the IDCs of edoxaban with other DOACs are mixed, with some showing

statistically significant results in favour of edoxaban, and others not showing statistical significance. It is important to consider the results of the IDCs with considerable caution. The reliability and accuracy of these analyses are limited given that there are no studies directly comparing DOACs head to head, that the four phase III trials comparing the individual DOACs to warfarin show substantive heterogeneity in their study methodology and clinical populations, and that the fixed-effects model was used in all IDCs reviewed. As such, all the results of the DOAC IDCs should be considered as exploratory in nature and in need of further hypothesis testing. However, given the data currently available, no IDC of better quality could have been produced.

4.3 Potential Place in Therapy[1]

Although warfarin has long been the standard-of-care antithrombotic drug for the prevention of stroke in AF, its use has always presented well-recognized challenges, such as the requirement for frequent monitoring of the therapeutic effect and consequent dosage adjustment, as well as food-drug and multiple drug-drug interactions. As a result, several new anticoagulant drugs (non-VKA oral anticoagulants, or DOACs) have been developed; specifically, these are direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban). Edoxaban, the subject of this report, is the fourth of these drugs (and the third factor Xa inhibitor) to market. Like the others, edoxaban has similar or greater incremental benefit than warfarin, especially with regard to bleeding. But even when the differences are statistically significant, they are so marginal in absolute terms that the primary differentiating feature of all these drugs in comparison to warfarin is most indisputably ease of use. This consideration has led Canadian and European guidelines to promote these drugs as the preferred oral anticoagulants to use for stroke prophylaxis in AF patients at elevated risk ($CHADS_2 \geq 1$).[8,32]

The ENGAGE AF-TIMI 48 trial established edoxaban's benefit for the purpose of regulatory approval by showing similar efficacy to warfarin in terms of ischemic stroke protection, yet with statistically fewer bleeds.[9] Given that the study's population was predominantly at moderate stroke risk (mean $CHADS_2$ of 2.8),[9] its results would be expected to translate well into real-world practice. However, even with the potential for edoxaban to confer similar stroke prevention to warfarin with statistically fewer bleeds, and the benefit of its convenient once daily dosage, it is unclear that these attributes are sufficient to distinguish it sufficiently from the other DOACs so as to confer it any hierarchical treatment advantage within the factor Xa inhibitor class. Its lower risk of bleeding than with warfarin is likely no better than that of apixaban, and rivaroxaban is also dosed on a once-daily basis. Edoxaban, as with other DOAC drugs, is not recommended for use in patients with severe renal diseases or patients with dialysis, a situation in which warfarin would be the best choice. None of the DOAC drugs has demonstrated clear benefit over the others. No AF guideline has distinguished any one DOAC over the others.

[1] This information is based on information provided in draft form by the clinical expert consulted by the CADTH Common Drug Review for the purpose of this review.

5. CONCLUSIONS

The results of ENGAGE AF-TIMI 48 demonstrate that edoxaban 60 mg once daily is noninferior to well-managed warfarin in the prevention of stroke and SEEs in patients with NVAF. In addition, the trial results demonstrate that edoxaban 60 mg once daily led to statistically significantly fewer major bleeding events than did warfarin. Overall, the trial was well conducted, and the primary results can be considered reliable.

Indirect evidence supports the results of the efficacy and safety of edoxaban compared with warfarin. The IDC of edoxaban with other DOACs cannot reliably estimate relative efficacy or safety from the currently available evidence network. A direct comparison between different DOACs is needed to establish the comparative efficacy and safety of these drugs.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff on the basis of input provided by patient groups.

No patient input was received for this submission.

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	(480448 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 16: RESULTS OF PRIMARY OUTCOME (STROKE OR SYSTEMIC EMBOLIC EVENT)

Primary End Point	Edoxaban 60 mg (N = 7,012)		Warfarin (N = 7,012)		Edoxaban 60 mg vs. Warfarin	
First Stroke or SEE	No. of Events	Event Rate (%/year)	No. of Events	Event Rate (%/year)	HR (97.5% CI)	*P*
mITT analysis set — on-treatment period	182	1.18	232	1.50	0.79 (0.632 to 0.985)	< 0.0001
mITT analysis set — overall study period	292	1.55	336	1.80	0.86 (0.719 to 1.029)	< 0.0001
	Edoxaban 60 mg (N = 6,995)		Warfarin (N = 6,993)		Edoxaban 60 mg vs. Warfarin	
PP analysis set — on-treatment period	[redacted]					
PP analysis set — overall study period	[redacted]					
	Edoxaban 60 mg (N = 7,035)		Warfarin (N = 7,036)		Edoxaban 60 mg vs. Warfarin	
ITT analysis set — overall study period	296	1.57	337	1.80	0.87 (0.709 to 1.068)	0.0807

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; mITT = modified intention-to-treat; PP = per-protocol; SEE = systemic embolic event.
Source: CSR ENGAGE AF-TIMI 48;[9] Giugliano, 2013.[10]

TABLE 17: RESULTS OF SECONDARY OUTCOMES THROUGH DIFFERENT ANALYSIS SETS

First Event	Edoxaban 60 mg (N = 7,035)		Warfarin (N = 7,036)		Edoxaban 60 mg vs. Warfarin
ITT Analysis Set — Overall Study Period	No. of Events	Event Rate (%/year)	No. of Events	Event Rate (%/year)	HR (95% CI)
Stroke, SEE, or CV mortality	728	3.85	831	4.43	0.87 (0.786 to 0.959)
MACE	827	4.41	926	4.98	0.89 (0.806 to 0.972)
Stroke, SEE, or all-cause mortality	949	5.01	1,046	5.57	0.90 (0.823 to 0.981)
First Event	Edoxaban 60 mg (N = 7,012)		Warfarin (N = 7,012)		Edoxaban 60 mg vs. Warfarin
mITT Analysis Set — On-Treatment Period	No. of Events	Event Rate (%/year)	No. of Events	Event Rate (%/year)	HR (95% CI)
Stroke, SEE, or CV mortality	[redacted]				

First Event	Edoxaban 60 mg (N = 7,035)		Warfarin (N = 7,036)		Edoxaban 60 mg vs. Warfarin
MACE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke, SEE, or all-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = intention-to-treat; MACE = major adverse cardiovascular event; mITT = modified intention-to-treat; SEE = systemic embolic event.
Source: CSR ENGAGE AF-TIMI 48;[9] Giugliano, 2013.[10]

TABLE 18: COMPONENTS OF THE PRIMARY OUTCOME

First Event	Edoxaban 60 mg (N = 7,012)		Warfarin (N = 7,012)	
ITT Analysis Set — Overall Study Period	**No. of Events**	**Event Rate (%/year)**	**No. of Events**	**Event Rate (%/year)**
Stroke	281	1.49	317	1.69
Ischemic stroke	236	1.25	235	1.25
Hemorrhagic stroke	49	0.26	90	0.47
Fatal stroke	80	0.42	86	0.45
Disabling stroke	54	0.28	57	0.30
SEE	15	0.08	23	0.12
SEE/ischemic stroke	251	1.33	255	1.36
mITT Analysis Set — On-Treatment Period				
Stroke	174	1.13	219	1.41
Ischemic stroke	135	0.87	144	0.93
Hemorrhagic stroke	40	0.26	76	0.49
Fatal stroke	45	0.29	43	0.28
Disabling stroke	35	0.23	41	0.26
SEE	8	0.05	13	0.08
SEE/ischemic stroke	143	0.93	157	1.01

ITT = intention-to-treat; mITT = modified intention-to-treat; SEE = systemic embolic event.
Source: CSR ENGAGE AF-TIMI 48;[9] Giugliano, 2013.[10]

TABLE 19: COMPONENTS OF SECONDARY OUTCOMES

First Event	Edoxaban 60 mg (N = 7,035)		Warfarin (N = 7,036)	
ITT Analysis Set — Overall Study Period	**No. of Events**	**Event Rate (%/year)**	**No. of Events**	**Event Rate (%/year)**
MI	133	0.70	141	0.75
Fatal	18	0.09	17	0.09
Non-fatal	117	0.62	125	0.66
CV mortality	530	2.74	611	3.17
All-cause mortality	773	3.99	839	4.35
mITT Analysis Set — On-Treatment Period				
MI	88	0.57	105	0.68
Fatal	10	0.06	11	0.07
Non-fatal	78	0.50	94	0.60
CV mortality	208	1.34	236	1.51
All-cause mortality	234	1.51	258	1.65

CV = cardiovascular; ITT = intention-to-treat; MI = myocardial infarction; mITT = modified intention-to-treat.
Source: CSR ENGAGE AF-TIMI 48;[9] Giugliano, 2013.[10]

TABLE 20: ADJUDICATED BLEEDING EVENTS

	Edoxaban 60 mg (N = 7,012)		Warfarin (N = 7,012)	
Bleeding Category — First Event	**No. of Events**	**Event Rate (%/year)**	**No. of Events**	**Event Rate (%/year)**
Major	418	2.75	524	3.43
ICH	61	0.39	132	0.85
N011-ICH	359	2.36	398	2.60
Fatal	32	0.21	59	0.38
ICH	24	0.15	42	0.27
N011-ICH	8	0.05	17	0.11
Non-fatal (major)	386	2.54	466	3.05
ICH	37	0.24	90	0.58
N011-ICH	351	2.31	381	2.49
Life-threatening	62	0.40	122	0.78
Clinically relevant non-major	1,214	8.67	1,396	10.15
Major or clinically relevant non-major	1,528	11.10	1,761	13.02
Minor	604	4.12	714	4.89
Any confirmed bleed	1,865	14.15	2,114	16.40

ICH = intracranial hemorrhage.
Source: CSR ENGAGE AF-TIMI 48;[9] Giugliano, 2013.[10]

APPENDIX 5: SUMMARY OF INDIRECT COMPARISONS

Introduction

Background

The aim of this section is to review and critically appraise any indirect comparisons (IDCs) that compare edoxaban 60 mg (30 mg reduced for reduced kidney function) once daily with any appropriate comparison in the prevention of stroke and systemic embolic event (SEE) in patients with nonvalvular atrial fibrillation (NVAF).

Edoxaban has been compared with warfarin in the ENGAGE AF-TIMI 48 trial.[9] However, no direct evidence exists that compares edoxaban with other new direct oral anticoagulants (DOACs). Therefore, IDCs that include edoxaban could provide information on the comparative effectiveness and safety of this drug and existing therapies and would be relevant to this CADTH Common Drug Review.

Methods

One IDC submitted by the manufacturer was reviewed and critically appraised. In addition, a comprehensive literature search was performed by an information specialist to identify published IDCs. Identified IDCs from the literature were summarized and contrasted with the manufacturer's IDC. The details of the literature search are available in 0.

Description of Indirect Comparisons Identified

In addition to the submitted manufacturer's IDC, the literature search identified seven published IDCs. A description of the research question from each study has been described in Table 21.

TABLE 21: PICO DESCRIPTION OF IDENTIFIED INDIRECT COMPARISONS

	Manuf. IDC	Bajaj 2016	Cameron 2014	Lip 2016	Morimoto 2015	Skjoth 2014	Tawfik 2016	Tereshchenko 2016
Population	Patients diagnosed with NVAF	Patients diagnosed with NVAF	Patients diagnosed with NVAF	Patients diagnosed with NVAF	Patients diagnosed with atrial fibrillation	Patients diagnosed with atrial fibrillation	Patients diagnosed with atrial fibrillation	Patients diagnosed with NVAF
Intervention	Vitamin K antagonists or DOACs	Vitamin K antagonist, DOAC, or Watchman device	Any anti-thrombotic treatment	Vitamin K antagonists or DOACs	Apixaban, betrixaban, dabigatran, edoxaban, and rivaroxaban	Vitamin K antagonists or DOACs	Any anti-thrombotic treatment	Vitamin K antagonist, DOACs, Aspirin, or Watchman device
Comparison	Vitamin K antagonists or DOACs	Vitamin K antagonist, DOACs, or Watchman device	Any anti-thrombotic treatment	Vitamin K antagonists or DOACs	Ximelagatran, warfarin, idraparinux, and Aspirin	Vitamin K antagonists or DOACs	Any anti-thrombotic treatment	Vitamin K antagonist, DOACs, Aspirin, or Watchman device
Outcomes	Stroke, SEE, and safety-related outcomes	Stroke, major bleed	SEE, major bleed	Stroke, SEE, safety-related outcomes	SEE, major bleed	SEE, safety-related outcomes	Stroke, safety-related outcomes	SEE, safety-related outcomes
Study Type	Phase III randomized controlled trial of 12 or more weeks	Phase III randomized controlled trials	Randomized controlled trials	Phase III randomized controlled trials	Phase III randomized controlled trials	Phase III randomized controlled trials	Phase III randomized controlled trials	Phase III randomized controlled trials
Reference	Manuf. IDC [8]	Bajaj 2016 [33]	Cameron 2014 [34]	Lip 2016 [35]	Morimoto 2015 [36]	Skjoth 2014 [29]	Tawfik 2016 [37]	Tereshchenko 2016 [38]

DOAC = direct oral anticoagulant; IDC = indirect comparison; Manuf. = manufacturer; NVAF = nonvalvular atrial fibrillation; SEE = systemic embolic event.

Review and appraisal of indirect comparisons

Review of manufacturer's indirect comparison

Objectives and rationale for indirect comparison A

The objective of the manufacturer's IDC was to analyze the comparative efficacy and safety of edoxaban 60 mg (30 mg reduced for reduced kidney function) once daily compared with other treatments for stroke and SEE prevention in NVAF patients. Specifically, the IDC aimed to answer the following research question: "What are the relative effectiveness and safety of edoxaban compared to other DOACs in patients diagnosed with nonvalvular atrial fibrillation in need of anticoagulation for stroke prevention?"[8]

The importance of understanding the relative efficacy and safety of DOACs for clinicians and policy-makers was used as a rationale for conducting this IDC. Although previous IDCs do exist and have been published, the manufacturer IDC claims that these IDCs reported in the literature do not adequately account for differences in trial methods — an issue that the manufacturer IDC attempted to address.

Methods for manufacturer's indirect comparison

Study eligibility and selection process

Inclusion criteria for the manufacturer's IDC were patients diagnosed with NVAF, receiving vitamin K antagonists (VKAs) or a DOAC, in a randomized controlled trial (RCT) setting of 12 or more weeks and reported on stroke, SEE, and safety-related outcomes. Studies were not limited by language or date of publication. Specific exclusion criteria included studies with heparin, ximelagatran, and betrixaban as interventions or comparators.

The manufacturer conducted a systematic literature search of more than three bibliographical databases (PubMed, Embase, and the Cochrane Library). The search was last updated on January 13, 2016.

Retrieved citations were screened by two independent reviewers according to predefined eligibility criteria. Discrepancy between the reviewers was handled by a third independent reviewer. Citations went through two stages of screenings: first, at the title or abstract level and, second, if the citation was relevant, a full-text screen.

Data extraction
Two independent reviewers conducted data extraction. Any discrepancy was managed through a third independent reviewer. Trial characteristics, patient demographics, disease condition, intervention, and outcomes-related information were extracted.

Comparators
All relevant comparators were included in the manufacturer IDC, including VKAs (warfarin, fluindione, phenprocoumon, and acenocoumarol) and DOACs (edoxaban, dabigatran, rivaroxaban, and apixaban). Aspirin was included as a comparator in an extended network presented in an appendix.

Outcomes
The following efficacy outcomes were included in the manufacturer's IDC:

- composite of stroke and SEE
- stroke (ischemic, hemorrhagic, undefined)
- SEE
- major bleed (International Society on Thrombosis and Haemostasis criteria)
- myocardial infarction
- cardiovascular mortality
- overall mortality.

Quality assessment of included studies
The producer of the manufacturer's IDC used criteria based on guidance from the Institute for Quality and Efficiency in Health Care. The manufacturer's IDC did not specify any specific action to be taken if an included study was of low quality (i.e., had a high risk of bias).

Evidence network
The manufacturer's IDC provided two graphical representations of the evidence network: Figure 2: depicts the full-study population; Figure 3: depicts an evidence network with a restricted ≥ 2 $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack [TIA] or thromboembolism) score.

FIGURE 2: EVIDENCE NETWORK OF FULL-STUDY POPULATIONS

FIGURE 3: EVIDENCE NETWORK OF CHADS$_2$ ≥ 2 SCORE POPULATION

Indirect comparison methods

The manufacturer's IDC reported using a Poisson regression model frequentist approach for the main analysis, with standard adjusted-dose VKA as a reference for analyses. In the Poisson model, treatments were considered as fixed effects and studies as random effects, and the total number of events and the number of person-years of exposure for each intervention group was modelled within each of the included studies. The overall approach has been conducted under the fixed-effects model assumptions, with a rationale that because of the limited number of included studies, a random-effects model would produce inaccurate and non-generalizable results. For efficacy analysis, the producers of the manufacturer's IDC attempted to use the intention-to-treat population whenever possible and the modified intention-to-treat or safety population for analyses related to safety outcomes. The producer of the manufacturer's IDC restricted the primary analysis to a patient population with a CHADS$_2$ score

≥ 2. Subsequent analysis with the whole population set was conducted. In addition, based on possible heterogeneity or uncertainty, several subgroup analyses were conducted, but the producer was not able to restrict the analysis to a patient population with a $CHADS_2$ score ≥ 2. These subgroups were for subpopulations of patients older than 75 years, renal function impairment and prior experience with VKA, time in therapeutic range (TTR) ≥ 60%, and a history of stroke or TIA at the baseline. A secondary network meta-analysis (NMA), which included Aspirin as a comparator, was reported in an appendix. The producer used a mixed log–binomial regression model for the secondary NMA as treatment follow-up was not available for the Aspirin trials. Relative risks with a corresponding 95% confidence interval (CI) were provided as an effect measure.

The producer of the manufacturer's IDC adjusted the result of the outcomes of the RE-LY dabigatran versus warfarin trial for its open-label design. The producer of the manufacturer's IDC utilized a published systematic review and meta-analysis that compared the pooled results of open-label and double-blind trials of DOACs versus VKA for the prevention of stroke and SEE in patients with atrial fibrillation.[39] It is not clear how the producers of the manufacturer's IDC employed the differences found in the results of the pooled double-blind versus open-label trials in their analysis.
The producer of the manufacturer's IDC could not perform any heterogeneity or inconsistency quantitative assessment as all comparisons (arms) were made of a single trial and no closed loop was available.

Results
Four phase III trials of DOACs were included in the primary NMA. Five unique interventions were included in the network: a once-daily edoxaban 60 mg (30 mg reduced-dose) regimen, a once daily edoxaban 30 mg (15 mg reduced-dose) regimen, a standard adjusted-dose VKA therapy, a once daily rivaroxaban 20 mg (15 mg dose reduced-dose) regimen, a twice daily dabigatran 150 mg regimen, a twice daily dabigatran 110 mg regimen, and a twice daily apixaban 5 mg (2.5 mg reduced-dose) regimen. Results from the 30 mg edoxaban (15 mg reduced-dose) regimen were not reported.

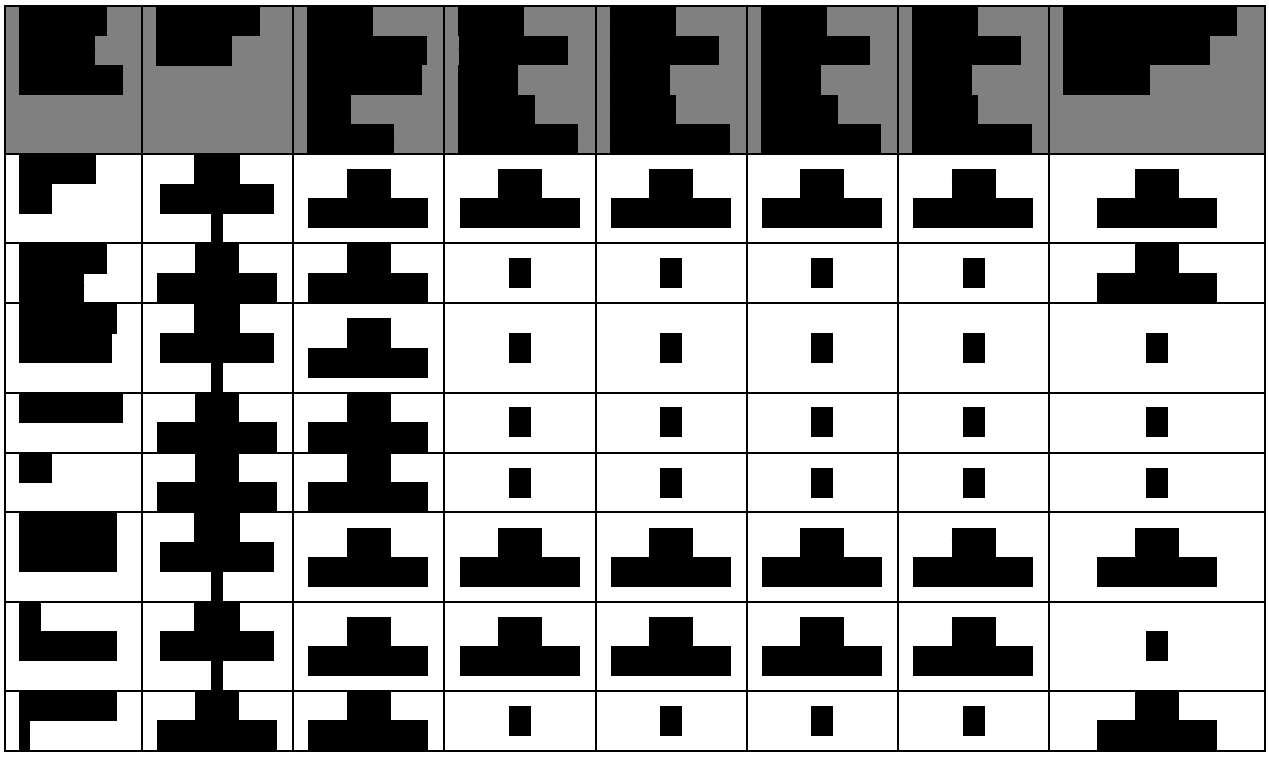
Of the included four trials in the primary NMA, three employed a double-blind design, and one (RE-LY) was of open-label design, in which the producer of the manufacturer's IDC used the Lega 2013 study to attempt an adjustment of the design issue.[39] Mean patient age and the proportion of female patients were similar across the studies. The mean $CHADS_2$ score was highest in the ROCKET-AF trial (3.5) and lowest in the RE-LY and ARISTOTLE trials (2.1 in both), reflecting that the inclusion criteria regarding $CHADS_2$ score was not consistent across the included trials. Patients in the ROCKET-AF trial had an increased prevalence of diabetes, prior stroke or TIA, and heart failure than in the other studies. The differences in the proportion of patients with prior VKA exposure slightly varied across the trials. The manufacturer IDC reported that the assessment of the risk of bias for each trial showed a low risk of bias.

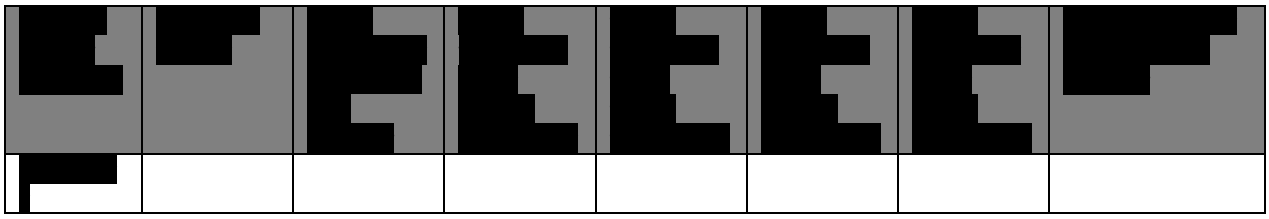
Clinical outcomes, Table 22, showed several statistically significant results when comparing edoxaban 60 mg (30 mg reduced dose) with standard adjusted-dose VKA therapy in favour of edoxaban. Specifically, the composite outcome stroke and SEE, all-cause mortality, and CV mortality were all in favour of edoxaban, but at the higher end if the 95% CIs in these outcomes were very close to 1. When comparing edoxaban with other DOACs, no statistically significant result was obtained. Subgroups analysis for the composite outcome stroke and SEE lost its statistical significance in the edoxaban-VKA comparison with the subpopulation of patients with TTR ≥ 60%, with the subpopulation of patients > 75 years of age, with the subpopulation of patients with renal insufficiency (creatinine clearance [CrCL] 30 mL/min to 50 mL/min), and with the subpopulation of patients with prior VKA exposure. However, the composite

outcome stroke and SEE gained statistical significance in favour of edoxaban when compared with rivaroxaban in the subpopulation of patients with renal insufficiency (CrCL 30 mL/min to 50 mL/min). The rest of the subgroup analysis showed similar results to the primary analysis.

Safety outcomes (Table 23) showed edoxaban to be statistically significantly better than VKA in terms of major bleed, intracranial bleed, fatal bleed, and clinically relevant non-major bleed. However, the safety outcomes also showed edoxaban to be statistically significantly more harmful than VKA therapy in terms of major gastrointestinal bleed. In addition, edoxaban was statistically significantly better than dabigatran 150 mg, but not 110 mg, in terms of major bleed. When compared with rivaroxaban, edoxaban showed a statistically significantly improvement in terms of major bleed, major gastrointestinal bleed, and clinically relevant non-major bleed. Subgroups analysis showed the outcome of major bleed losing its statistical significance in the edoxaban-VKA comparison in the subpopulation of patients with TTR ≥ 60%, the subpopulation of patients with renal insufficiency (CrCL 50 mL/min to 80 mL/min), and the subpopulation of patients with prior stroke. Comparison with rivaroxaban also lost its statistical significance status in major bleed in the subpopulation of patients with prior stroke and the subpopulation of patients with no previous VKA exposure. Along the same lines, the major bleed comparison with dabigatran 150 mg lost its statistical significance in the subpopulation of patients with TTR ≥ 60%, the subpopulation of patients with renal insufficiency (CrCL 50 mL/min to 80 mL/min), the subpopulation of patients with prior stroke, and the subpopulation of patients with no previous VKA exposure. In contrast, the comparison of edoxaban with dabigatran 110 mg in terms of major bleed gained significance when the population was restricted to $CHADS_2$ patients. Also, the major bleed comparison of edoxaban with apixaban gained statistical significance in favour of apixaban in the subpopulation of patients with TTR ≥ 60% and the subpopulation of patients with prior VKA exposure.

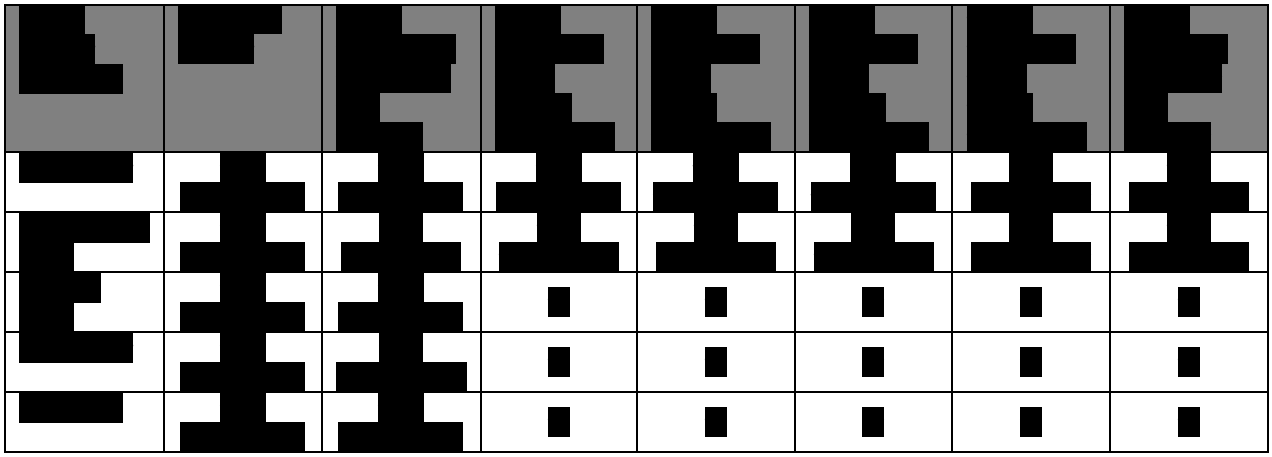
TABLE 22: CLINICAL OUTCOMES OF EDOXABAN VERSUS OTHER ANTICOAGULATION THERAPIES IN THE MANUFACTURER'S IDC





CI = confidence interval; CV = cardiovascular; IDC = indirect comparison; NA = not available; RR = risk ratio; SEE = systemic embolic event; VKA = vitamin K antagonist.
Source: Clinical Study Report: CONFIDENTIAL manufacturer's submission.[8]

TABLE 23: SAFETY OUTCOMES OF EDOXABAN VERSUS OTHER ANTICOAGULATION THERAPIES IN THE MANUFACTURER'S IDC



CI = confidence interval; CRNM = clinically relevant non-major bleeding; IDC = indirect comparison; NA = not available; VKA = vitamin K antagonist.
Source: CSR CONFIDENTIAL manufacturer's submission.[8]

Critical appraisal

The manufacturer's IDC provided research questions that incorporated clear population, intervention, comparisons, and outcomes. The population and the comparisons reported in the manufacturer's IDC are relevant to the Canadian setting. Also, the outcomes reported in the manufacturer's IDC were relevant to this review and to the assessment of the comparative clinical efficacy and safety of edoxaban. The literature search strategy employed in the manufacturer's IDC was comprehensive and covered several bibliographical databases. Screening and data extraction were carried out in duplicate, providing confidence in the accuracy of the extracted data. The included trials were thoroughly assessed for quality and have proven to be of sufficiently good quality. In addition, the manufacturer's IDC transparently reported the characteristics of the included trials. The assessment of the characteristics of the included studies shows similar values across the baseline characteristics. An exception was the ROCKET-AF trial having the highest mean $CHADS_2$ score and a higher proportion of patients with diabetes, prior stroke or TIA, and heart failure than in the other studies. A further exception was the variation in the proportion of patients with prior VKA exposure across trials and the open-label study design of the RE-LY trial, which the producer of the manufacturer's IDC attempted to adjust for.

The choice of the overall statistical method used in the analysis (frequentist Poisson regression model) is valid and would provide results that are similar to the Bayesian NMA approach. In the data analysis, the producer of the manufacturer's IDC chose to use the fixed-effects model to build the interpretations and

conclusion. The fixed-effects model offers less generalizability than the random-effects model and is based on an assumption that all trials share a common true treatment effect, regardless of any differences in the study or patient characteristics. The manufacturer's IDC argued that the choice to use the fixed-effects model was based on constraints imposed by the nature of the evidence network, which only provided one trial in the direct assessment of any two connected comparisons. The manufacturer's IDC argued that a random-effects model provides no viable results and that when a random-effects model was attempted, all the comparisons that were statistically significant under a fixed-effects model lost their statistical significance. Although the argument for the choice of the fixed-effects model is valid, the limitations imposed on the results will lead to a possible inflated type I error and uncertainty in the accuracy of the results.

The producer of the manufacturer's IDC attempted to adjust for the open-label study design in the RE-LY trial using a published systematic review and meta-analysis of double-blind trials compared with open-label trials of anticoagulants for stroke prophylaxis.[39] Although we agree with the overall assumption that an open-label design will bias the results in favour of the intervention, the source of the adjustment factor, Lega 2013, is not necessary reliable. In Lega 2013, the two meta-analyzed groups (open-label and double-blind trials) that were compared with one another had significant differences in the baseline characteristics beside the blinding design, thus precluding the possible conclusion that an observed difference is attributed solely to the open-label rather than the double-blind design.[39]

The structure of the network did not allow the producer of the manufacturer's IDC to provide statistical testing for possible heterogeneity and/or inconsistency. Thus, two essential assumptions for the validity of the IDC remain untested. The producer of the manufacturer's IDC attempted to conduct several subgroup analyses to try and gain insight into possible heterogeneity in the studies. These results indicated that heterogeneity existed in the included trials.

To summarize, although the conduct of the study was sound, the following major limitations add uncertainty to the results:

- Due to a lack of closed loops, there was no way to test if IDCs would be equal to direct comparisons; thus, we were unable to validate the consistency assumption.
- Because all direct comparisons were informed by the results of single trials, a statistical measure of heterogeneity was not provided. Possible evidence of heterogeneity is apparent in the results of a few subgroup analyses.
- The producer of the manufacturer's IDC opted to conduct the analysis under a fixed-effects model, thus adding another untestable assumption that all the studies in the network share a common (true) effect size. This assumption reduces the external validity of the results. The producer of the manufacturer's IDC reported that all statistically significant results found under a fixed-effects model were no longer statistically significant under a random-effects model. The exact values of these results were not reported.

Review of Literature Search–Identified Indirect Comparisons

Bajaj et al. 2016

Bajaj et al. aimed to compare the effectiveness and safety of FDA-approved stroke prophylaxis treatment strategies for patients diagnosed with NVAF. The authors conducted a systematic review and NMA. Their analysis approach used a frequentist multivariate meta-regression model. The authors do not specify how they handled between-study heterogeneity (fixed- or random-effects model). Although the authors mention that their regression model used random-effects multivariate regression, this

statement is not informative about the method of dealing with between-study heterogeneity. The authors did not report on the results of testing for statistical heterogeneity or inconsistency, even though they report in their methods that such tests were to be conducted. The authors reported, on an odds ratio (OR) scale, ischemic stroke outcome, major bleed outcome, and a "primary safety" outcome defined as major bleeding and clinically relevant non-major bleeding.

The Bajaj et al. IDC included six RCTs in the analysis; four were the same as those included in the manufacturer's IDC, and the two additional studies compared VKA to Watchman, a left atrial appendage closure device. Considering the outcome of ischemic stroke, edoxaban showed no statistically significant differences when compared with VKA, apixaban, dabigatran, rivaroxaban, or the Watchman device. In terms of the major bleed outcome, edoxaban showed a favourable statistically significant result when compared with VKA (OR edoxaban versus VKA = 0.78; 95% CI, 0.69 to 0.90) and when compared with rivaroxaban (OR rivaroxaban versus edoxaban = 1.31; 95% CI, 1.08 to 1.59). No statistically significant differences were observed when edoxaban was compared with apixaban, dabigatran, or the Watchman device. For the third outcome, a composite of major bleeding and clinically relevant non-major bleeding, edoxaban showed a favourable statistically significant result when compared with VKA (OR edoxaban versus VKA = 0.83; 95% CI, 0.77 to 0.90) and when compared with rivaroxaban (OR rivaroxaban versus edoxaban = 1.23; 95% CI, 1.10 to 1.38). However, it also showed a statistically significantly unfavourable result when compared with apixaban (OR edoxaban versus apixaban = 1.23; 95% CI, 1.08 to 1.41).

The Bajaj et al. IDC carries several limitations that are mainly related to a lack of reporting on the results of testing for inconsistency and statistical heterogeneity, especially considering that the authors recognize the existence of heterogeneity in study and patient characteristics. In addition, the authors do not specify many aspects of their methods approach and leave unclear whether they used a fixed-effects or random-effects model to account for between-study differences in treatment effects.

Compared with the manufacturer's IDC, Bajaj et al. included one more intervention in their analysis, used a slightly different approach in synthesizing the data, and did not report on the composite outcome of stroke and SEE. Bajaj et al. showed similar results in the outcome of major bleeding, except in the comparison of edoxaban and dabigatran, for which there is no longer any statistical significance.

Cameron et al. 2014

Cameron et al. aimed to compare the efficacy and safety of antithrombotic therapies (apixaban, dabigatran, edoxaban, rivaroxaban, and VKA) and ASA with or without clopidogrel in patients with NVAF. The authors conducted a systematic review and NMA. Their analysis approach used a noninformative prior Bayesian analysis with a binomial likelihood model fitted using Markov chain Monte Carlo simulations. The authors conducted the analysis under both random-effects and fixed-effects models but only reported the fixed-effects results because of data constraints. The consistency assumption was tested by comparing the deviance and the deviance information criterion of a fitted consistency and inconsistency model. No quantified statistical heterogeneity was provided; the authors conducted several subgroup analyses to test for possible heterogeneity. The authors reported the OR and the 95% credible intervals (CrIs) for the composite outcome of stroke and SEE and for the safety outcome of major bleeding.

Cameron et al. included 16 RCTs in their analysis: four were the same as those included in the manufacturer's IDC; the additional 12 RCTs compared VKA with ASA or with ASA and clopidogrel. Considering the outcome of ischemic stroke and SEE, edoxaban 60 mg showed no statistically significant differences when compared with VKA. In terms of the major bleeding outcome, edoxaban 60 mg

showed a favourable statistically significant result when compared with VKA (OR edoxaban 60 mg versus VKA = 0.79; 95% CrI, 0.69 to 0.90).

The Cameron et al. IDC carries several limitations that are reported by the authors: notable heterogeneity, insufficient data for subgroup analysis, and the use of the fixed-effects model for reporting values. These limitations are similar to the ones in the manufacturer's IDC.

Further, compared with the manufacturer's IDC, the main differences are in the wider inclusion of intervention and comparators in the Cameron et al. study, the use of OR in Cameron et al. instead of the risk ratio (RR) in the manufacturer's IDC, and the approach to the data synthesis, in which a Bayesian NMA was used in Cameron et al. as opposed to a Poisson frequentist regression model in the manufacturer's IDC. Despite these differences, both show very similar results when considering the stroke and SEE outcome and the major bleeding outcome of edoxaban versus VKA.

Lip et al. 2016

Lip et al. aimed to compare the effectiveness and safety of apixaban with dabigatran, rivaroxaban, and edoxaban for stroke prevention in NVAF patients with a $CHADS_2$ score ≥ 2 and in NVAF patients with a history of stroke or TIA. The authors conducted an update on a systematic review and NMA. Their analysis approach used a noninformative prior Bayesian analysis under a fixed-effects model fitted using Markov chain Monte Carlo simulations. Statistical testing for the consistency and heterogeneity was not presented. The authors reported the hazard ratio (HR) and the 95% CrI for the composite outcome of stroke and SEE and for the safety outcome of major bleeding.

The Lip et al. IDC included four RCTs in the analysis, the same as were included in the manufacturer's IDC. Considering the outcome of ischemic stroke and SEE in the subpopulation of patients with a $CHADS_2$ score ≥ 2 and in the subpopulation of patients with a previous stroke or TIA, edoxaban 60 mg showed no statistically significant differences when compared with VKA, apixaban, rivaroxaban, or dabigatran. In terms of the major bleeding outcome, edoxaban 60 mg showed a favourable statistically significant result when compared with VKA in the $CHADS_2$ subpopulation (HR edoxaban 60 mg versus VKA = 0.80; 95% CrI, 0.70 to 0.91), but not in the subpopulation of patients with a history of stroke or TIA. Edoxaban 60 mg also showed a favourable statistically significant result for the major bleeding outcome when compared with rivaroxaban in the $CHADS_2$ subpopulation (HR edoxaban 60 mg versus rivaroxaban = 0.76; 95% CrI, 0.63 to 0.91), but not in the subpopulation of patients with a history of stroke or TIA; it also showed a favourable statistically significant result when compared with dabigatran 150 mg in the $CHADS_2$ subpopulation (HR edoxaban 60 mg versus dabigatran 150 mg = 0.80; 95% CrI, 0.65 to 0.97), but not in the subpopulation of patients with a history of stroke or TIA. None of the rest of the comparisons for the major bleeding outcome in either patient population were statistically significant.

The Lip et al. IDC carries several limitations related to the use of the fixed-effects model, a lack of reporting on detailed methods, and a lack of testing for inconsistency and statistical heterogeneity, particularly given that the authors recognize the existence of heterogeneity in study and patient characteristics.

Compared with the manufacturer's IDC, the main differences lie in the choice of reporting on only subpopulations in the Lip et al. IDC; thus, the results of Lip et al. cannot be used as a contrast to the main results of the manufacturer's IDC. In addition, Lip et al. used HRs to report on the outcomes, as opposed to RRs used in the manufacturer's IDC. Also, for the approach to the data synthesis, a Bayesian

NMA was used in Lip et al. as opposed to a Poisson frequentist regression model in the manufacturer's IDC.

Morimoto et al. 2015

Morimoto et al. aimed to compare the efficacy and safety of apixaban, betrixaban, dabigatran, edoxaban, and rivaroxaban as DOAC with ximelagatran as an oral anticoagulant and warfarin, idraparinux, and Aspirin. The authors conducted a systematic review and NMA. Their analysis approach is unclear, as it has not been reported in the published article or appendices beyond a reference to a Bayesian NMA methods paper. The authors explain how they adjusted for the open-label study design but do not provide any details related to the conduct and validity of the NMA approach, nor do they mention if the results were based on a fixed- or random-effects model. The authors reported the OR and the 95% CrI for the composite outcome of stroke and SEE and for the safety outcome of major bleeding.

Morimoto et al. included nine RCTs in their analysis: four were the same as included in the manufacturer's IDC; four compared VKA with idraparinux, a Japan-specific dose of rivaroxaban, ximelagatran; and one compared Aspirin with apixaban. For the outcome of ischemic stroke and SEE, edoxaban 60 mg showed no statistically significant differences when compared with VKA or other DOACs. In terms of the major bleeding outcome, edoxaban 60 mg showed a favourable statistically significant result when compared with VKA (OR = 0.78; 95% CrI, not reported numerically), dabigatran 150 mg (OR = 0.72; 95% CrI, not reported numerically), and rivaroxaban (OR = 0.76; 95% CrI, not reported numerically).

The Morimoto et al. IDC has severely underreported the methods used in the NMA. Because of this underreporting, we cannot pass any informed judgment about the certainty of the results. As such, the most conservative approach is to assume a large degree of uncertainty and exert extreme caution when interpreting the results.

Compared with the manufacturer's IDC, the main differences lie in the choice of wider inclusion criteria for intervention or comparator, the use of the OR instead of the RR used in the manufacturer's IDC, and the approach to the data synthesis, in which a Bayesian NMA was used as opposed to a Poisson frequentist regression model in the manufacturer's IDC. In the results, the point estimates of Morimoto et al. (CrI was not reported numerically) were similar in the edoxaban versus VKA comparison and in all comparisons for the outcome of major bleeding, but differences in the point estimate were noticeable when edoxaban was compared with other DOACs for the outcome of stroke and SEE.

Skjoth et al. 2014

Skjoth et al. aimed to compare the efficacy and safety of edoxaban with apixaban, dabigatran, and rivaroxaban in patients with NVAF. The authors included four phase III RCTs that compared the aforementioned drugs with warfarin and performed an IDC meta-analysis. Their analysis approach used the Bucher method. The authors reported the HR and the 95% CrI for the composite outcome of stroke and SEE for the safety outcome of major bleeding and for several other efficacy and safety outcomes.

Skjoth et al. included the same four trials as the manufacturer's IDC. For the outcome of ischemic stroke and SEE, edoxaban 60 mg showed no statistically significant differences when compared with apixaban, dabigatran 110 mg, and rivaroxaban but showed an unfavourable statistically significance difference when compared with dabigatran 150 mg (HR dabigatran 150 mg versus edoxaban 60 mg = 0.75; 95% CI, 0.56 to 0.99). In terms of the major bleeding outcome, edoxaban 60 mg showed a favourable statistically significant result when compared with rivaroxaban (HR rivaroxaban versus edoxaban 60 mg HR = 1.30;

95% CI, 1.08 to 1.57). Most of the other comparisons with edoxaban 60 mg showed no statistically significant differences, with the following efficacy exceptions, which showed more favourable outcomes with dabigatran compared with edoxaban: HR of stroke in dabigatran 150 mg versus edoxaban 60 mg (0.73; 95% CI, 0.55 to 0.96), HR of hemorrhagic stroke in dabigatran 150 mg versus edoxaban 60 mg (0.48; 95% CI, 0.23 to 0.99).

The Skjoth et al. IDC carries several limitations, some of which are reported by the authors: notable heterogeneity, the use of the Bucher method restricting the comparisons to only two interventions with a common comparator, and the statement by the authors that the results are to be considered exploratory for hypothesis generation.

Compared with the manufacturer's IDC, the main difference lies in the choice of the approach to data synthesis: Skjoth et al. used the Bucher method as opposed to the Poisson frequentist regression model used in the manufacturer's IDC. Subsequently, the Bucher method restricts the number of trials that can inform on each IDC; this restriction does not apply in the Poisson frequentist regression model. Despite this difference, the results from Skjoth et al. were similar to the manufacturer's IDC.

Tawfik et al. 2016

Tawfik et al. aimed to compare the efficacy of all antithrombotic therapies for patients with AF. The authors conducted a systematic review and NMA. Their analysis approach used a noninformative prior Bayesian analysis with Poisson likelihood model fitted using the Markov chain Monte Carlo process. The authors conducted the analysis under both random-effects and fixed-effects models but only reported the fixed-effects results because of large variance in the results of the random-effects model. The consistency assumption was tested by inspecting heterogeneity plots. No quantified statistical heterogeneity was available; the authors conducted several sensitivity analyses to test for possible heterogeneity. The authors reported the rate ratio and the 95% CrI for the outcomes of stroke or major bleeding and for several other safety and efficacy outcomes.

Tawfik et al. included 16 RCTs in their analysis: four were the same as were included in the manufacturer's IDC; 12 compared VKA with ASA or with ASA and clopidogrel. For the outcome of stroke, edoxaban 60 mg showed no statistically significant differences when compared with VKA, apixaban, dabigatran 110 mg, and rivaroxaban. However, edoxaban 60 mg showed an unfavourable statistically significant difference in the stroke outcome when compared with dabigatran 150 mg (edoxaban 60 mg versus dabigatran 150 mg RR = 1.37; 95% CrI, 1.04 to 1.82). In terms of major bleeding, edoxaban 60 mg showed a favourable statistically significant result when compared with VKA (RR edoxaban 60 mg versus VKA = 0.80; 95% CrI, 0.71 to 0.91) and a favourable statistically significant outcome when compared with rivaroxaban (RR edoxaban 60 mg versus VKA = 0.78; 95% CrI, 0.64 to 0.94). All other outcomes showed no statistically significant differences between edoxaban 60 mg and VKA or other DOACs, except for the intracranial bleed outcome when edoxaban 60 mg was compared with VKA (RR = 0.46; 95% CrI, 0.34 to 0.62).

The Tawfik et al. IDC carries several limitations, some of which have been reported by the authors: notable heterogeneity, especially with the inclusion of patients with valvular atrial fibrillation and NVAF, and the use of fixed-effects model for reporting values.

Compared with the manufacturer's IDC, the main differences are the choice of wider inclusion criteria for intervention or comparator, Tawfik et al. not reporting on the composite outcome of stroke and SEE, and the approach to data synthesis (a Bayesian NMA was used as opposed to the use of a Poisson

frequentist regression model in the manufacturer's IDC). Tawfik et al. showed similar results for the outcome of major bleeding, except in the comparison between edoxaban and dabigatran, for which the Tawfik et al. result did not show the statistical significance exhibited in the manufacturer's IDC.

Tereshchenko et al. 2014

Tereshchenko et al. aimed to compare the efficacy and safety of DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban), VKA, Aspirin, and the Watchman device in patients with NVAF. The authors did not explain if this study followed a systematic review approach to capturing all relevant trials. The authors employed a frequentist NMA with an overall random-effects model assumption, which turned into a fixed-effects model in comparisons with fewer than two informing trials. The consistency assumption was tested by comparing direct and indirect results in closed loops. Statistical heterogeneity was assessed in closed loops using an empirical Bayes approach. The authors reported the OR and the 95% CIs for the composite outcome of stroke and SEE and for the safety outcome of major bleeding.

Tereshchenko et al. included 21 RCTs in their analysis: four were the same as those included in the manufacturer's IDC; the rest of the RCTs compared VKA with ASA, with ASA and clopidogrel, with control, or with the Watchman device or compared ASA with DOACs or control. For the outcome of ischemic stroke and SEE, edoxaban 60 mg showed no statistically significant differences when compared with VKA or other DOACs. In terms of the major bleeding outcome, edoxaban showed a favourable statistically significant result when compared with VKA (OR edoxaban versus VKA = 0.64; 95% CI, 0.46 to 0.90). No statistically significant differences were observed in the major bleeding outcome when edoxaban was compared with other DOACs.

The Tereshchenko et al. IDC carries several limitations, some of which were reported by the authors: notable heterogeneity, pooling of different doses of edoxaban, inconsistency and statistical heterogeneity testing not being feasible for any comparison that included a DOAC drug, and the use of a fixed-effects model for reporting values as most comparisons were informed by one or two trials. Compared with the manufacturer's IDC, the main differences lie in the wider inclusion of intervention or comparator in Tereshchenko et al., the slightly different approach to data synthesis, and the reporting of OR instead of RR. For the outcome of stroke and SEE, the Tereshchenko et al. results are similar to the manufacturer's IDC in the edoxaban comparison with dabigatran and apixaban but are different in the comparison with VKA (in which edoxaban is no longer statistically significant) and with rivaroxaban (in which the point estimate has switched sides around the 1 but remains statistically not significant). The Tereshchenko et al. results for the major bleeding outcome no longer show a statistically significant finding in the comparison with other DOACs, only in the comparison with VKA.

Discussion

Our search strategy identified seven IDCs in addition to the one submitted by the manufacturer. All IDCs had similar PICO research questions, and they all included the same four trials that the producer of the manufacturer's IDC included in its analysis. The approaches to conducting the IDC differed among the identified IDCs: some used a frequentist NMA approach, some used a Bayesian NMA approach, and one used the Bucher method. The reported outcomes were similar in definition. However, the treatment effect measure did differ among the IDCs, with some reporting HR, some OR, and some relative risk. Table 24 presents the stroke and SEE outcome and the major bleeding outcome from different IDCs that reported these two outcomes on the overall population.

TABLE 24: OUTCOME OF STROKE AND SEE OUTCOME AND MAJOR BLEEDING OUTCOME IN ALL IDCS REVIEWED

Outcome	IDC	Treatment Effect Measure	Versus VKA Therapy (95% Interval)	Versus Rivaroxaban (95% Interval)	Versus Dabigatran 150 mg (95% Interval)	Versus Dabigatran 110 mg (95% Interval)	Versus Apixaban (95% Interval)
Stroke and SEE	Manufacturer's IDC	RR	**0.84 (0.72 to 0.98)**	0.90 (0.70 to 1.16)	1.26 (0.97 to 1.64)	0.95 (0.74 to 1.22)	1.08 (0.86 to 1.37)
	Cameron 2014	OR	0.87 (0.74 to 1.02)	NA	NA	NA	NA
	Morimoto 2015	OR	0.87 (NA)	1.02 (NA)	1.14 (NA)	0.82 (NA)	1.10 (NA)
	Skjoth 2014	HR	NA	0.99 (0.78 to 1.25)	**1.33 (1.01 to 1.79)**	0.97 (0.74 to 1.27)	1.1 (0.85 to 1.43)
	Tereshchenko 2016	OR	1.00 (0.79 to 1.27)	1.39 (0.93 to 2.12)	1.28 (0.90 to 1.83)		1.21 (0.83 to 1.77)
Major Bleeding	Manufacturer's IDC	HR	**0.78 (0.70 to 0.88)**	**0.76 (0.66 to 0.89)**	**0.72 (0.61 to 0.84)**	**0.83 (0.71 to 0.98)**	1.08 (0.91 to 1.28)
	Bajaj 2016	OR	**0.78 (0.69 to 0.90)**	**0.76 (0.62 to 0.93)**	0.84 (0.69 to 1.03)		1.13 (0.93 to 1.38)
	Cameron 2014	OR	**0.79 (0.69 to 0.90)**	NA	NA	NA	NA
	Morimoto 2015	OR	**0.78 (NA)**	**0.76 (NA)**	**0.72 (NA)**	0.84 (NA)	1.13 (NA)
	Skjoth 2014	HR	NA	**0.77 (0.64 to 0.93)**	0.86 (0.71 to 1.04)	1.00 (0.83 to 1.20)	1.16 (0.96 to 1.41)
	Tawfik 2016	RR	**0.80 (0.71 to 0.91)**	**0.78 (0.64 to 0.94)**	0.85 (0.71 to 1.02)	0.98 (0.81 to 1.19)	1.10 (0.71 to 1.68)
	Tereshchenko 2016	OR	**0.64 (0.46 to 0.90)**	0.63 (0.36 to 1.06)	0.76 (0.50 to 1.16)		0.87 (0.55 to 1.37)

HR = hazard ratio; IDC = indirect comparison; NA = not available; OR = odds ratio; RR = risk ratio; SEE = systemic embolic event; VKA = vitamin K antagonist.
Source: CSRs CONFIDENTIAL manufacturer's submission,[8] Bajaj 2016 [33], Cameron 2014 [34], Lip 2016 [35], Morimoto 2015 [36], Skjoth 2014 [29], Tawfik 2016 [37], Tereshchenko 2016 [38].

Overall, the results from all the reviewed IDCs were similar to the manufacturer's IDC results. These results would mostly tend to indicate that edoxaban is superior to VKA in terms of safety and is similar in terms of efficacy to VKA and all other DOACs. However, since all the reported IDCs share the same evidence base, they also share the same limitations arising from the architecture of the evidence network. Specifically, all comparisons between different DOACs are informed indirectly through a single trial that compares a DOAC with VKA. This marginally informative connection precluded an analysis using a random-effects model; thus, a fixed-effects model was used in all the reviewed IDCs. The fixed-effects model makes unrealistic assumptions about the true treatment effect and 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 and differences in study design). In addition, the lack of any head-to-head DOAC comparative trial also means that we cannot assess the consistency assumption in the IDC.

The use of fixed-effects model analysis and the lack of assessment of inconsistency drastically reduce the external validity of the results. As such, the safest approach would be to consider all the results of the IDCs as exploratory in nature and requiring further hypothesis testing.

Conclusion

In addition to the manufacturer's submitted IDC, seven IDCs were identified in the literature. The eight IDCs were consistent in showing that edoxaban is statistically significantly superior to VKA in terms of major bleeding. The efficacy results from the IDCs tend to support the hypothesis that edoxaban is similar in efficacy to VKA and other DOACs. All the reviewed IDCs were limited by the small number of trials to support a robust analysis, the existence of clinical heterogeneity, and the use of fixed-effects models. These limitations considerably reduce the external validity of the results and can arguably limit their value to hypothesis generation. However, considering the current available evidence, no better-quality IDC could have been produced.

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