Common Drug Review
Pharmacoeconomic 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
CDR	CADTH Common Drug Review
$CHADS_2$	congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack or thromboembolism
HS	hemorrhagic stroke
ICH	intracranial hemorrhage
IS	ischemic stroke
MI	myocardial infarction
NOAC	new oral anticoagulant
QALY	quality-adjusted life-year
SEE	systemic embolic event
TIA	transient ischemic attack

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug product	**Edoxaban (Lixiana)**
Study question	What is the cost-effectiveness of edoxaban 60 mg (30 mg dose reduced) compared with warfarin and other NOACs for the prevention of stroke and SEEs in patients with NVAF?
Type of economic evaluation	Cost-utility analysis
Target population	NVAF patients requiring chronic anticoagulation (i.e., $CHADS_2 \geq 2$)
Treatment	Edoxaban 60 mg (30 mg dose reduced) daily
Outcome	QALYs
Comparator(s)	**Primary analysis** Warfarin Rivaroxaban 20 mg daily **Secondary analysis** Apixaban 5 mg b.i.d. Dabigatran 110 mg b.i.d. Dabigatran 150 mg b.i.d.
Perspective	Publicly funded health care system
Time horizon	Lifetime (36 years)
Results for base case	• Incremental cost per QALY gained for edoxaban versus warfarin is $12,672. • Edoxaban dominates rivaroxaban (less costly and more effective).
Key limitations	• Analysis limited to AF patients with $CHADS_2 \geq 2$ (i.e., $CHADS_2 = 1$ excluded). • Results highlighted only for comparison with warfarin and rivaroxaban. As apixaban and dabigatran are also relevant comparators, a single sequential analysis should have been performed of all currently available alternatives for NVAF.
CDR estimate(s)	The model structure and data inputs were considered appropriate; however, apixaban and dabigatran were not considered as comparators. Therefore, CDR performed a sequential comparison of all alternatives (warfarin, edoxaban, and other NOACs) on the basis of the submitted model design, using relative effects from the manufacturer-submitted NMA. • Apixaban was dominant (less costly, more effective) compared with all NOACs, including edoxaban, in this analysis. • The incremental cost per QALY gained for edoxaban versus warfarin was $8,184. • Other than apixaban, only dabigatran 150 mg was more effective in terms of total QALYs than edoxaban; the incremental cost per QALY gained for dabigatran 150 mg versus edoxaban was $4,182. Probabilistic analysis showed that apixaban had the highest probability (55%) of being the optimal strategy at a threshold of $50,000 per QALY; edoxaban had a probability of 6.4%.

AF = atrial fibrillation; b.i.d. = twice daily; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or TIA or thromboembolism; CDR = CADTH Common Drug Review; NMA = network meta-analysis; NOAC = new oral anticoagulant; NVAF = nonvalvular atrial fibrillation; QALY = quality adjusted life-year; SEE = systemic embolic event; TIA = transient ischemic attack.

EXECUTIVE SUMMARY

Background

Edoxaban (Lixiana) is indicated for the treatment of patients with nonvalvular atrial fibrillation requiring chronic anticoagulation. The recommended dosage is 60 mg once daily, with the potential for dosage reduction to 30 mg once daily if required. The cost per day of treatment with edoxaban is $2.84 for all dosages.

The manufacturer submitted a cost-utility analysis conducted using a Markov model with 18 health states: stable atrial fibrillation, mild ischemic stroke (IS), moderate IS, severe IS, post–mild IS, post–moderate IS, post–severe IS, mild hemorrhagic stroke (HS), moderate HS, severe HS, post–mild HS, post–moderate HS, post–severe HS, systemic embolic event (SEE), post-SEE, acute myocardial infarction (MI), post-MI, and death. Four additional events were incorporated as transient events: other intracranial hemorrhage (ICH), transient ischemic attack (TIA), non-ICH major bleed, and clinically relevant non-major bleed. The model adopts a lifetime horizon with a cycle length of one month.

Edoxaban is compared primarily to warfarin (5 mg once daily) and rivaroxaban (60 mg once daily) in the submitted analysis. For the comparison with warfarin, data from the ENGAGE AF-TIMI 48 trial are used to model the risks for the four health states (IS, HS, SEE, and MI) and the four events (other ICH, TIA, non-ICH major bleed, and clinically relevant non-major bleed). For the comparison with rivaroxaban, data from a manufacturer-submitted network meta-analysis were used.[1] Analyses comparing edoxaban with dabigatran (110 mg twice daily and 150 mg twice daily) and apixaban (5 mg twice daily) were included as sensitivity analyses, with the necessary clinical data obtained from the manufacturer-submitted network meta-analysis. The rationale for excluding these comparators from the primary analysis was twofold: (1) limited comparability of the ENGAGE AF-TIMI 48 trial of edoxaban with the pivotal trials for dabigatran and apixaban, and (2) rivaroxaban is the most commonly used new oral anticoagulant (NOAC) in Canada.

Costs are sourced from appropriate published articles or relevant databases containing Ontario data.[2-7] Utility data for the baseline health state and further health states and events were obtained from the ENGAGE AF-TIMI 48 trial and the published literature.[8-12] The choice of values appears appropriate and consistent with previous studies.

Summary of Identified Limitations and Key Results

According to the manufacturer's base-case analysis, treatment with edoxaban was more effective (quality-adjusted life-year gain of 0.1517) and more costly ($1,922) than warfarin, leading to an incremental cost per quality-adjusted life-year gained of $12,672. Edoxaban was dominant compared with rivaroxaban (i.e., it was less costly and more effective). The results were consistent across all deterministic sensitivity analyses.

No major limitations with respect to the model, assumptions, and data inputs were found. The limitations relate to the context of the decision problem:

- Given the patient population from the ENGAGE AF-TIMI 48 trial, analysis is relevant only to atrial fibrillation patients with a $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or TIA or thromboembolism) score ≥ 2; edoxaban may be used in patients with $CHADS_2$ = 1.

- The submitted report only highlights the comparisons of edoxaban with warfarin and rivaroxaban. Given the current funding of NOACs, comparisons with apixaban and dabigatran are as relevant and should have been given equal prominence.
- Current effective prices for rivaroxaban, apixaban, and dabigatran are unknown, which may limit the ability to accurately interpret the results of this submission.

Conclusions

The CADTH Common Drug Review (CDR) reanalysis, which incorporated all relevant comparators (warfarin and other NOACs), found edoxaban not to be cost-effective for patients with nonvalvular atrial fibrillation ($CHADS_2 \geq 2$) requiring anticoagulation; apixaban was the most cost-effective NOAC, and all other NOACs (including edoxaban) were dominated (i.e., they were less effective and more costly). Apixaban remained cost-effective compared with edoxaban unless the price of the latter was reduced by 33% or more. It was noted that the relative cost-effectiveness of edoxaban versus apixaban and dabigatran is somewhat uncertain because of the limitations of the clinical data. CDR considered that there was no justification for a price premium for edoxaban should drug plan costs for apixaban, dabigatran, or rivaroxaban be lower than their list prices.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis conducted from the perspective of a Canadian health care payer with a lifetime horizon.

Although the purported objective was to assess the cost-effectiveness of edoxaban compared with other approved therapies in Canada for stroke prevention in patients with atrial fibrillation (AF), only the analyses comparing edoxaban 60 mg once daily with rivaroxaban 20 mg once daily and warfarin 5 mg once daily were presented in detail. Comparisons with dabigatran 110 mg twice daily and 150 mg twice daily and with apixaban 5 mg twice daily were presented only as secondary analyses. According to the submission's authors, the focus on the comparison with rivaroxaban was justified for two reasons: rivaroxaban is the most commonly prescribed new oral anticoagulant (NOAC) in Canada, and the ROCKET-AF trial had a similar design to ENGAGE AF-TIMI 48.[8,13]

The model adopted was a Markov model constructed in Microsoft Excel. The model had a cycle length of one month and incorporated 18 health states — stable AF, mild ischemic stroke (IS), moderate IS, severe IS, post–mild IS, post–moderate IS, post–severe IS, mild hemorrhagic stroke (HS), moderate HS, severe HS, post–mild HS, post–moderate HS, post–severe HS, systemic embolic event (SEE), post-SEE, acute myocardial infarction (MI), post-MI, and death — and four transient events (other intracranial hemorrhage, transient ischemic attack, non–intracranial hemorrhage major bleed, and clinically relevant non-major bleed). Health states relating to events (IS, HS, SEE, and MI) were associated with increased costs, utility decrements, and mortality. In post-event health states, patients experienced increased health care costs, reduced utility, and increased risk of subsequent events. For transient events, patients experienced one-off costs and utility loss.

All patients are assumed to be in the stable AF state at model onset. The cohort then moves within the states in accordance with the underlying probability of events on edoxaban and the relative effects for both warfarin and the NOACs. Edoxaban monthly transition probabilities were derived from the ENGAGE AF-TIMI 48 trial.[8] For warfarin, the hazard ratios from the ENGAGE AF-TIMI 48 trial were applied to the edoxaban transition probabilities.[8] For other NOACs, a network meta-analysis was conducted to derive relative risks compared with edoxaban, which were then used to derive transition probabilities for patients treated with the other NOACs.[1]

Costs are presented in 2015 Canadian dollars and include treatment costs, event costs, and post-event costs. Drug costs were obtained from the Ontario Drug Benefit formulary, with warfarin management costs derived from a recent Canadian study.[2,14] Acute event costs and post-event costs were derived from administrative data (Canadian Institute of Health Information) or published Canadian literature.[3-7] The utility value for the stable AF state was derived from the ENGAGE AF-TIMI 48 trial.[1-9] Utility values for events, utility decrements for transient events, and utility values for post-event states were derived from the published literature.[10-12]

All data sources and data values were similar to the recent CADTH Therapeutic Review of NOACs.[15] Appropriate probabilistic sensitivity analysis and a vast array of deterministic sensitivity analyses were conducted.

2. MANUFACTURER'S BASE CASE

In comparison with warfarin, edoxaban was associated with more quality-adjusted life-years (QALYs) (7.12 versus 6.97) and higher costs ($28,734 versus $26,812), leading to an incremental cost per QALY gained of $12,672.

In comparison with rivaroxaban, edoxaban was associated with more QALYs (7.12 versus 7.04) and lower costs ($28,734 versus $29,866), leading to edoxaban being dominant compared with rivaroxaban.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Total Costs ($)	Incremental Cost of Edoxaban ($)	Total QALYs	Incremental QALYs with Edoxaban	Incremental Cost ($) per QALY Gained for Edoxaban
Edoxaban	28,734		7.12		
Warfarin	26,812	1,922	6.97	0.15	12,672
Rivaroxaban	29,866	−1,132	7.04	0.08	Dominant

QALY = quality-adjusted life-year.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

A thorough range of univariate sensitivity analyses for each variable in the model was conducted. In the comparison with warfarin, the results were moderately sensitive to patient age and the cost of edoxaban. However, the interpretation of the results did not change in any scenario, since the highest reported incremental cost-utility ratio across the analyses was $30,658 per QALY. In the comparison with rivaroxaban, the results were moderately sensitive to the costs of edoxaban and rivaroxaban, but again the interpretation of the results did not change in any scenario; edoxaban remained dominant in most scenarios, and the highest reported incremental cost-utility ratio across the analyses was $7,256 per QALY.

A further range of scenarios was considered relating to the time horizon, the discount rate, and the patient population. In these analyses, for the comparison with warfarin, the results were moderately sensitive to the time horizon of the model (10 years) and the time in therapeutic range for warfarin (> 60%). However, the interpretation of the results did not change in any scenario. In the comparison with rivaroxaban, the results were not sensitive to any changes.

Within the probabilistic sensitivity analysis, at a threshold of $50,000 per QALY, there was a 96% probability that edoxaban was cost-effective compared with warfarin and a 92% probability that edoxaban was cost-effective compared with rivaroxaban.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

The structure of the model is appropriate, and all data sources are valid and reasonable. Thus, limitations with the submission relate mainly to whether the decision problem at hand was adequately addressed:

- According to clinical experts, anticoagulation is appropriate in all patients with AF and a $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack or thromboembolism) score ≥ 1. However, the patient population in ENGAGE AF-TIMI 48 was restricted to AF patients with $CHADS_2$ ≥ 2. Thus, the submission does not address the cost-effectiveness of edoxaban in AF patients with $CHADS_2$ = 1.
- The submitted report highlights the separate comparisons of edoxaban with warfarin and rivaroxaban. According to the manufacturer's economic submission, rivaroxaban was selected as the main NOAC comparator because the trials of edoxaban and rivaroxaban were most comparable to one another. This permitted a more robust indirect comparison of these two agents than of edoxaban versus apixaban or dabigatran. Nevertheless, the latter two agents are relevant comparators for edoxaban given their current funding status. Thus, a single, sequential analysis should have been performed of all six alternatives for nonvalvular AF: edoxaban, warfarin, rivaroxaban, apixaban, and dabigatran (110 mg and 150 mg).
- The current effective prices for rivaroxaban, apixaban, and dabigatran are unknown, which may limit the ability to accurately interpret the results of this submission.

The first and last of these issues cannot be addressed but should be considered in making funding recommendations and decisions for edoxaban. The second issue is addressed below.

5. CADTH COMMON DRUG REVIEW REANALYSES

The model structure and data inputs are appropriate; therefore, no reanalyses were required in this regard. Rather, unlike the manufacturer's submission, the CADTH Common Drug Review (CDR) performed a full sequential comparison of all alternatives (warfarin, edoxaban, and other NOACs) on the basis of the submitted model but using relative effects from the manufacturer-submitted network meta-analysis (Table 4).

TABLE 3: RISK RATIO OF EVENT COMPARED WITH EDOXABAN — MANUFACTURER-SPONSORED NMA

	Warfarin	Rivaroxaban	Apixaban	Dabigatran 110mg	Dabigatran 150mg
IS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other ICH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TIA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-ICH major bleed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CRNMB = clinically relevant non-major bleed; HS = hemorrhagic stroke; ICH = intracranial hemorrhage; IS = ischemic stroke; MI = myocardial infarction; NMA = network meta-analysis; SEE = systemic embolic event; TIA = transient ischemic attack.

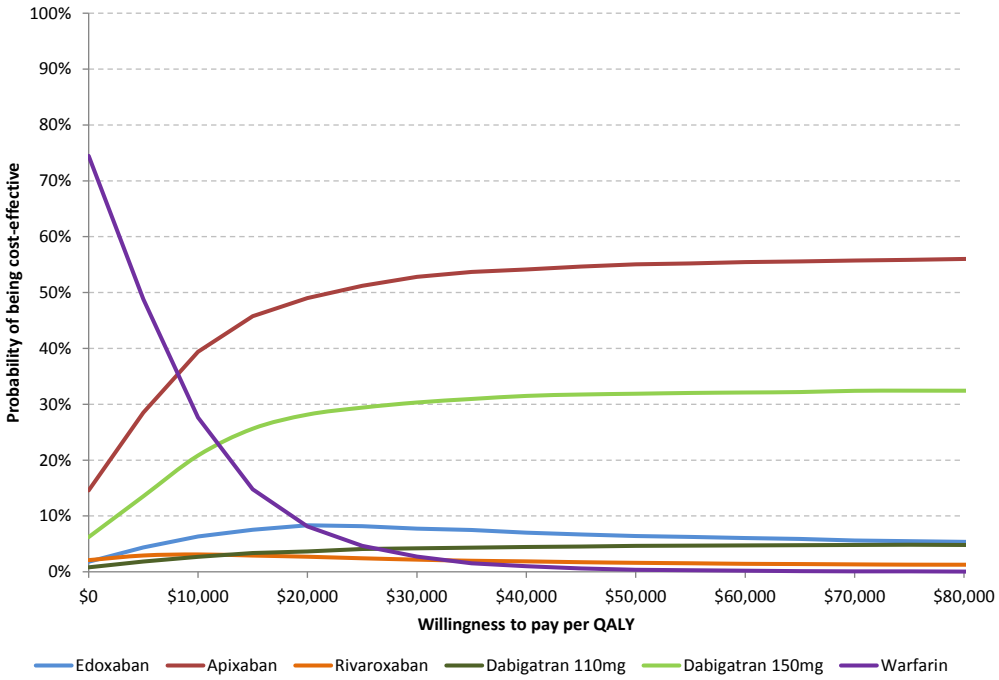
The results of the sequential analysis illustrate that apixaban is cost-effective versus warfarin assuming a willingness to pay of greater than $8,184 per QALY; edoxaban and the other NOACs are dominated by apixaban (i.e., they are less effective and more costly). Other than apixaban, only dabigatran 150 mg was more effective in terms of total QALYs than edoxaban; the incremental cost per QALY gained for dabigatran 150 mg versus edoxaban is $4,182. Similar to the manufacturer's base-case analysis comparing edoxaban with rivaroxaban, rivaroxaban was dominated by edoxaban in CDR's full sequential analysis.

TABLE 4: SEQUENTIAL COST-EFFECTIVENESS — CADTH REANALYSIS

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Warfarin	Sequential Incremental Cost per QALY Gained
Warfarin	26,862	6.97		
Apixaban	28,532	7.17	$8,184	$8,184
Rivaroxaban	29,866	7.04	$39,736	Dominated by apixaban, dabigatran 150 mg, and edoxaban
Dabigatran 110 mg	30,410	7.09	$27,331	Dominated by apixaban, dabigatran 150 mg, and edoxaban
Edoxaban	28,734	7.12	$12,281	Dominated by apixaban
Dabigatran 150 mg	28,872	7.15	$10,837	Dominated by apixaban

QALY = quality-adjusted life-year.

FIGURE 1: COST-EFFECTIVENESS ACCEPTABILITY CURVE — CADTH REANALYSIS



The cost-effectiveness acceptability curve illustrates that at a threshold of $50,000 per QALY, apixaban has the highest probability of being optimal (55.0%). The probability that edoxaban is optimal is 6.4% at a threshold of $50,000 and is between 8.9% and 4.3% for thresholds between $20,000 and $100,000.

Given the findings of the CDR reanalysis, a further analysis was conducted assessing the effect of various price reductions for edoxaban on the cost-effectiveness of edoxaban versus apixaban and dabigatran 150 mg (Table 5). Since the clinical benefits of apixaban and dabigatran 150 mg are greater than that of edoxaban, price reductions were considered for edoxaban to determine their effect on the incremental cost-effectiveness ratio for apixaban and dabigatran 150 mg versus edoxaban.

TABLE 5: PRICE REDUCTION SCENARIOS

Incremental Cost per QALY ($)		
Price	**Apixaban Versus Edoxaban**	**Dabigatran 150 mg Versus Edoxaban**
Submitted	Dominant	4,182
10% reduction	12,441	29,719
15% reduction	20,612	42,487
20% reduction	28,781	55,256
25% reduction	36,952	68,025
30% reduction	45,122	80,794
35% reduction	53,292	93,562

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Note: Apixaban continues to be cost-effective versus edoxaban at a threshold of $50,000 per QALY with edoxaban price reductions of 33% or less. Dabigatran 150 mg continues to be cost-effective versus edoxaban at a threshold of $50,000 per QALY with edoxaban price reductions of 18% or less.

6. PATIENT INPUT

No patient group input was received by CDR for this submission.

7. CONCLUSIONS

The manufacturer found that edoxaban was effective and cost-effective compared with rivaroxaban (dominant) and warfarin (incremental cost per QALY gained of $12,672) for patients with a $CHADS_2$ score of 2. The analysis was well conducted, and the results described appear valid. However, CDR considered that the most appropriate primary analysis was one in which dabigatran 150 mg and apixaban were included. CDR's reanalysis incorporating these comparators found apixaban was the most cost-effective NOAC, and all other NOACs (including edoxaban) were dominated (i.e., they were less effective and costlier). Apixaban remained cost-effective compared with edoxaban unless the price of edoxaban was reduced by 33% or more. It was noted that the relative cost-effectiveness of edoxaban versus apixaban and dabigatran is somewhat uncertain because of the limitations of the clinical data. CDR considered that there was no justification for a price premium for edoxaban should drug plan costs for apixaban, dabigatran, or rivaroxaban be lower than their list prices.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 6 have been deemed appropriate by the clinical expert consulted by the CADTH Common Drug Review. Costs are manufacturer list prices, unless otherwise specified. Existing product reimbursement agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 6: TREATMENTS FOR THE PREVENTION OF STROKE AND SEES IN PATIENTS WITH NVAF

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)	Total Cost of a 6-Month Course
New Oral Anticoagulants						
Edoxaban (Lixiana)	15 mg 30 mg 60 mg	Tablet	2.8400[a]	60 mg once daily	2.84	1,037
Apixaban (Eliquis)	2.5 mg 5.0 mg	Tablet	1.6000	2.5 mg or 5 mg twice daily	3.20	1,168
Dabigatran (Pradaxa)	110 mg 150 mg	Capsule	1.6000 1.6000	110 mg or 150 mg twice daily	3.20	1,168
Rivaroxaban (Xarelto)	10 mg 15 mg 20 mg	Tablet	2.8400	15 mg or 20 mg daily	2.84	1,037
Other Comparators						
ASA (generic)	80 or 81 mg 325 mg 650 mg	Enteric coated tablet	0.0560[b] 0.0280 0.0521	80 mg to 325 mg daily	0.03 to 0.06	10 to 20
Clopidogrel (generic)	75 mg	Tablet	0.4735	75 mg daily	0.47	173
Warfarin (generic)	1 mg 2 mg 2.5 mg 3 mg 4 mg 5 mg 10 mg	Tablet	0.0796 0.0841 0.0674 0.1043 0.1043 0.0675 0.1211	Usual maintenance: 2 mg to 10 mg daily	0.07 to 0.12	292 to 301

NVAF = nonvalvular atrial fibrillation; SEE = systemic embolic event.
[a] Manufacturer's submitted price.
[b] Quebec formulary list price (November 2016).
Source: Ontario Drug Benefit list prices (November 2016), unless otherwise indicated.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS EDOXABAN RELATIVE TO RIVAROXABAN (MANUFACTURER'S BASE CASE)?

	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)	X					
Drug treatment costs alone			X			
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	Dominant					

CE = cost-effectiveness; NA = not available.

TABLE 8: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS EDOXABAN RELATIVE TO WARFARIN (MANUFACTURER'S BASE CASE)?

	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	Incremental cost per QALY gained = $12,281 (edoxaban versus warfarin)					

CE = cost-effectiveness; NA = not available; QALY = quality-adjusted life-year.

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS EDOXABAN RELATIVE TO DABIGATRAN 150 MG (CDR ANALYSIS INCORPORATING ALL NOACS)?

	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone		X				
Clinical outcomes					X	
Quality of life					X	
Incremental CE ratio or net benefit calculation	Incremental cost per QALY gained = $4,182 (dabigatran versus edoxaban)					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; NA = not available; NOAC = new oral anticoagulant; QALY = quality-adjusted life-year.

TABLE 10: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS EDOXABAN RELATIVE TO APIXABAN (CDR ANALYSIS INCORPORATING ALL NOACS)?

	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone		X				
Clinical outcomes					X	
Quality of life					X	
Incremental CE ratio or net benefit calculation	Edoxaban is dominated (less effective, costlier) by apixaban					

CDR = CADTH Common Drug Review; CE= cost-effectiveness; NA = not available; NOAC = new oral anticoagulant.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 11: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments *Reviewer to provide comments if checking "no"*	None		
Was the material included (content) sufficient?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		

TABLE 12: AUTHOR INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to CDR
☐ Adaptation of global model/Canadian model done by the manufacturer
☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

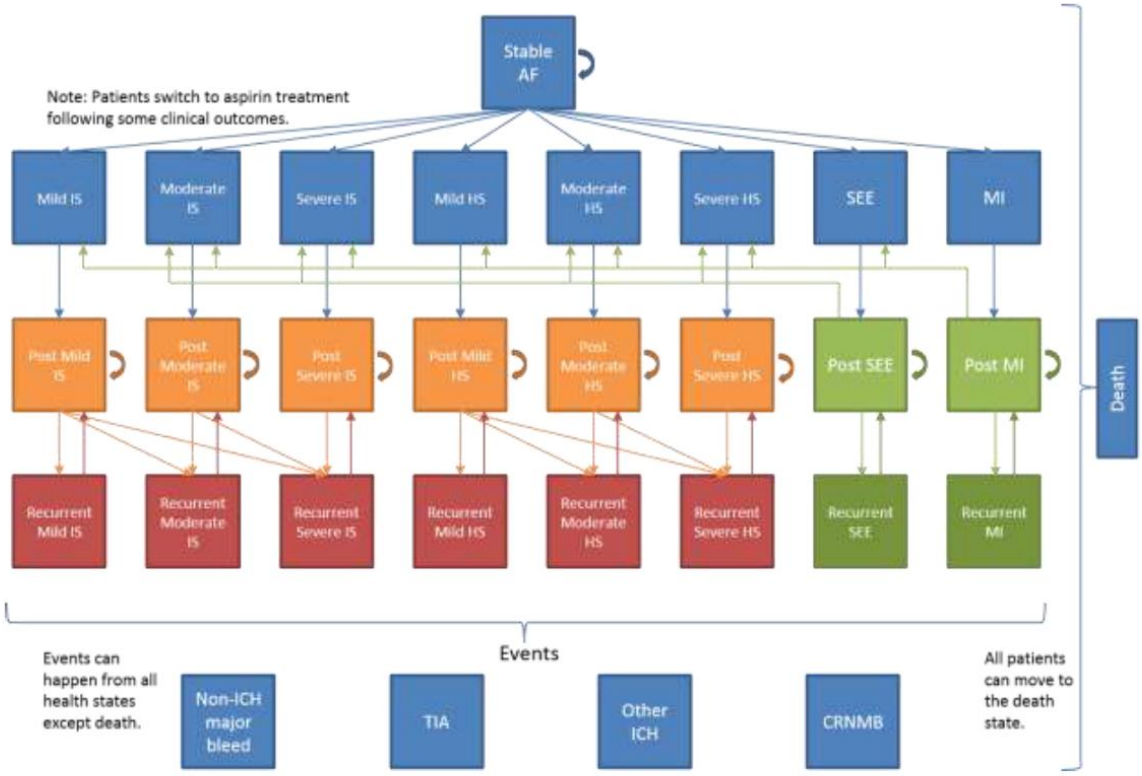
	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

CDR = CADTH Common Drug Review.

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

FIGURE 2: MANUFACTURER'S MODEL SCHEMATIC — FIGURE 3.1



Note: The recurrent event states are shown separately from the initial acute states for clarity; however, in the model the initial and recurrent events of the same nature were assigned the same acute costs and utility values. Patients were able to switch to aspirin treatment, with the associated event transition probabilities, following clinical events; see **Section 4.1.6** for details.
KEY: AF = atrial fibrillation; CRNMB = clinically relevant non-major bleed; CV = cardiovascular; HS = hemorrhagic stroke; ICH = intracranial hemorrhage; IS = ischemic stroke; MI = myocardial infarction; SEE = systemic embolic event; TIA = transient ischemic attack.

Source: Manufacturer's submission.[16]

The model was validated by a panel of "Canadian Clinical Advisors,"[16] and was consistent with previous models in this area, including CADTH Therapeutic Review.[15]

TABLE 13: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	ENGAGE AF-TIMI 48 trial[8] Manufacturer-submitted NMA	Appropriate Appropriate — results consistent with CADTH NMA[15]
Natural history	Probability of event on edoxaban, probability of stroke recurrence, case fatality rates: ENGAGE AF-TIMI 48 trial[8] Stroke severity distribution, case fatality rates: HETA Group (2014),[17] Miller et al. (2016)[18] Stroke risk after MI: Mohan et al. (2009)[19] Increase in events by age: AFI (1994),[20] Ariesen et al. (2003),[21] Flegel and Hanley (1989),[22] Freeman et al. (2011),[23] Hylek et al. (2014),[24] Bos et al. (2007)[25]	Appropriate Appropriate Appropriate Appropriate
Utilities	ENGAGE AF-TIMI 48,[8] Luengo-Fernandez et al. (2013),[11] Sullivan et al. (2006)[10]	Appropriate — similar values to CADTH Therapeutic Review
Mortality	Background mortality: Statistics Canada (2011),[26,27] Wyse et al. (2001)[28] Mortality post-event: Fang et al. (2014),[29] Berkwelem et al. (2015),[30] Harrington et al. (2013)[31]	Appropriate — consistent with CADTH Therapeutic Review Appropriate
Costs		
Drug	Rivaroxaban, warfarin, apixaban, and dabigatran: ODB (2016)[2] Edoxaban: manufacturer	Appropriate
Administration	Warfarin administration: Schulman et al. (2010)[14]	Appropriate
Event	Sorensen et al. (2011),[3] CIHI,[4] Cohen et al. (2014),[5] Regier et al. (2006)[7]	Appropriate — similar values to CADTH Therapeutic Review
Post-event health state	Sorensen et al. (2011),[3] Cohen et al. (2014),[5] Goeree et al. (2005)[6]	Appropriate — similar values to CADTH Therapeutic Review

AFI = Atrial Fibrillation Investigators; CIHI = Canadian Institute of Health Information; HETA = Health Economic and Technology Assessment; MI = myocardial infarction; NMA = network meta-analysis; ODB = Ontario Drug Benefit.

TABLE 14: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Can compare NOACs through NMA	Consistent with CADTH Therapeutic Review
Analysis restricted to comparison with warfarin and rivaroxaban	Inappropriate, as all NOACs are potential comparators for edoxaban
Population enrolled in ENGAGE AF-TIMI 48 trial is reflective of Canadian patients with NVAF requiring anticoagulation	Likely appropriate, except that patients with $CHADS_2$ = 1 are not reflected in the model
Patients could only move to a health state that was as or more severe than their current health state. This restricted the types and severity of subsequent events (e.g., a subsequent stroke could only be as or more severe than the previous stroke).	Likely appropriate, and consistent with previous analyses
Transient events (other ICH, non-ICH major bleed, TIA, and CRNMB) assumed to not be associated with long-term costs or resource use Risk of TIA assumed equivalent for edoxaban and other NOACs in the absence of data	Likely appropriate for most, but not all, patients Appropriate in the absence of data; unlikely to have a major impact on model results
Costs and utilities of clinical events assumed to be the same regardless of treatment (higher costs and disutilities for bleeding events assumed for NOACs in sensitivity analysis)	Likely appropriate given lack of specific cost data

$CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or TIA or thromboembolism; CRNMB = clinically relevant non-major bleed; ICH = intracranial hemorrhage; NMA = network meta-analysis; NOAC = new oral anticoagulant; NVAF = nonvalvular atrial fibrillation; TIA = transient ischemic attack.

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