Journal of
Cardiology and Vascular Medicine

JScholar
Fostering Scholarly Communication

Research Article Open Access

A Preliminary Cost-Effectiveness Analysis of Low Dose Rivaroxaban Versus Placebo for the Prevention of Stroke and Cognitive Impairment in Non-Valvular Atrial Fibrillation Patients at Low Risk of Stroke

Gisèle Nakhlé[1,2*], Jean-Claude Tardif[2,3], Denis Roy[2,3], Léna Rivard[2,3], Michelle Samuel[2,3], Anick Dubois[3] and Jacques Le Lorier[1,2]

[1] CHUM Research Center, Pavilion S, St-Denis St., Montreal (Quebec) H2X 0A9, Canada
[2] University of Montreal, Edouard Montpetit Blvd, Montreal (Quebec) H3T 1J4, Canada
[3] Montreal Heart Institute, Belanger St., Montreal (Quebec) H1T 1C8, Canada

***Corresponding author:** Gisèle Nakhlé, CHUM Research Center - Pavillon S, 850, rue St-Denis, porte S03.300, Montreal (Québec) H2X 0A9, Canada, Tel: 514-677-9996, E-mail: gisele.nakhle@umontreal.ca

Received Date: July 31, 2021 **Accepted Date:** August 31, 2021 **Published Date:** September 02, 2021

Citation: Gisèle Nakhlé (2021) A Preliminary Cost-Effectiveness Analysis of Low Dose Rivaroxaban Versus Placebo for the Prevention of Stroke and Cognitive Impairment in Non-Valvular Atrial Fibrillation Patients at Low Risk of Stroke. J Cardio Vasc Med 7: 1-17.

Abstract

Objective: To estimate the cost-effectiveness of the novel oral anticoagulant rivaroxaban compared with placebo for the prevention of stroke and cognitive impairment in patients with nonvalvular atrial fibrillation (NVAF) at low stroke risk.

Methods: A Markov decision-analysis model was constructed using data from observational cohort studies to evaluate lifetime (60 years) costs and quality-adjusted life-years (QALY) of the novel oral anticoagulant rivaroxaban 15 mg daily compared with placebo. The modeled population was a hypothetical cohort of young patients (30 – 62 years) with NVAF, at low risk for stroke ($CHADS_2$ = 0), and no previous contraindications to anticoagulation. The willingness-to-pay threshold was $50,000/QALY gained.

Results: Rivaroxaban compared with placebo was projected to increase QALYs (11.26) at an increased cost ($128,543) over lifetime (60 years). The incremental cost-effectiveness ratio (ICER) of rivaroxaban was $11,411 per QALY gained. Deterministic sensitivity analyses indicated that results were insensitive to uncertainty in all model inputs. Probabilistic sensitivity analysis showed a probability of 100% for rivaroxaban being cost-effective at a willingness-to-pay of $50K. In a simulation of 1000 patients, treatment with rivaroxaban resulted in less stroke, systemic embolism, cognitive impairment, and death while causing more major bleeds compared with placebo.

Conclusions: In this hypothetical cohort of young patients with NVAF at low stroke risk, rivaroxaban 15 mg daily was a cost-effective alternative to placebo, over a lifetime horizon.

Keywords: Non-Valvular Atrial Fibrillation; Cognitive Impairment; Cost-Effectiveness; Rivaroxaban

Introduction

Atrial fibrillation (AF) affects 350,000 Canadians and its prevalence is rising due to the ageing population [1]. AF is a cause of considerable morbidity and mortality; among its most serious consequences is stroke [2-5]. Strokes caused by AF have poorer prognosis than those that are non-AF related [6-10]. Evidence-based guidelines recommend anticoagulant therapy for the prevention of stroke in AF patients with additional stroke risk factors [11]. Newer oral anticoagulants (NOACs), which have been shown to be as effective and safer than vitamin K antagonists (VKAs), have been approved for use in NVAF patients at moderate to high risk of stroke, as an alternative to VKAs [11].

In recent years, AF has also been linked to cognitive decline and dementia [12]. Several mechanisms have been proposed to explain this relationship including stroke [13-15], chronic cerebral hypoperfusion [14-17], silent cerebral ischemia due to micro-embolization [18,19], as well as underlying cardiovascular risk factors [12,14]. However, new evidence suggests that cognitive decline may be the result of AF independently of stroke and underscores the importance of an appropriate therapeutic management of AF to prevent related cognitive decline and dementia [12,20]. These studies showed treatment with anticoagulants to be effective in reducing the incidence of cerebral ischemic events and new-onset dementia [20,21].

For patients at low risk of stroke, current treatment guidelines [11], recommend NOAC or anti-platelet drugs depending on the presence of additional risk factors and no antithrombotic therapy for those at the lowest risk in this category. However, limited information exists on the benefits of treating this patient's group with anticoagulants to prevent cognitive decline. The ongoing "Brain-AF" trial, "Blinded Randomized trial of Anticoagulation to prevent Ischemic stroke and Neurocognitive impairment in Atrial Fibrillation" (NCT02387229), assesses the efficacy of rivaroxaban to lower the risk of stroke and cognitive decline in low stroke risk patients. Adding anticoagulation therapy to the treatment regimen of low stroke risk patients may nevertheless impact the healthcare costs. Here, we investigate the cost-effectiveness of rivaroxaban compared to placebo in a hypothetical cohort of patients with NVAF at low stroke risk. The results from the BRAIN-AF trial will inform future economic evaluations with observed event rates in this patient population.

Methods

This cost-utility study was conducted from a single-payer perspective, relating to the Quebec Ministry of Health, where only direct medical costs were considered.

Model Design

A multistate Markov model [22] was used to evaluate two treatment strategies for the prevention of stroke and cognitive decline in NVAF patients at low stroke risk: (1) rivaroxaban 15 mg QD, and (2) placebo. The model (Figure 1) simulated the progression of a hypothetical cohort of patients, aged 30 – 62 years with no other risk factors i.e., a $CHADS_2$ (congestive heart failure, hypertension, age, diabetes mellitus, and stroke/TIA) score of 0, and no contraindications to anti-coagulation, as they moved in 3-month cycles through a series of health states. The health states included: NVAF without complications (healthy), systemic embolism (SE), ischemic stroke (IS) (transient attack [< 24h], minor, major (moderate to severe), fatal), intra-cranial hemorrhage (ICH) (minor, major (moderate to severe), fatal), myocardial infarction (MI), major bleed, clinically relevant non-major bleed, cognitive decline (mild, mod-erate, severe, fatal), and all cause deaths. The patient cohort was assumed to start in the NVAF healthy state and allowed to move exclusively to one of the health states or die during each cycle. The health states were either permanent, indicating that patients remain in them until death, or transient, meaning that patients only spend some time in that health state before returning to the NVAF healthy state. Transition probabilities (risk of experiencing an event), based on the published literature [23-25], were built into the model and applied to the cohort during each cycle to calculate how the patients would be distributed between the health states at the end of the cycle (Table 1). The model assumed full compliance with the medication regimen and no change in the assigned medication for the whole follow-up period. Health benefits

(in terms of QALYs) and costs were assigned to each health state over a lifetime (60 years). Future costs and benefits were discounted at a rate of 1.5% annually [26].

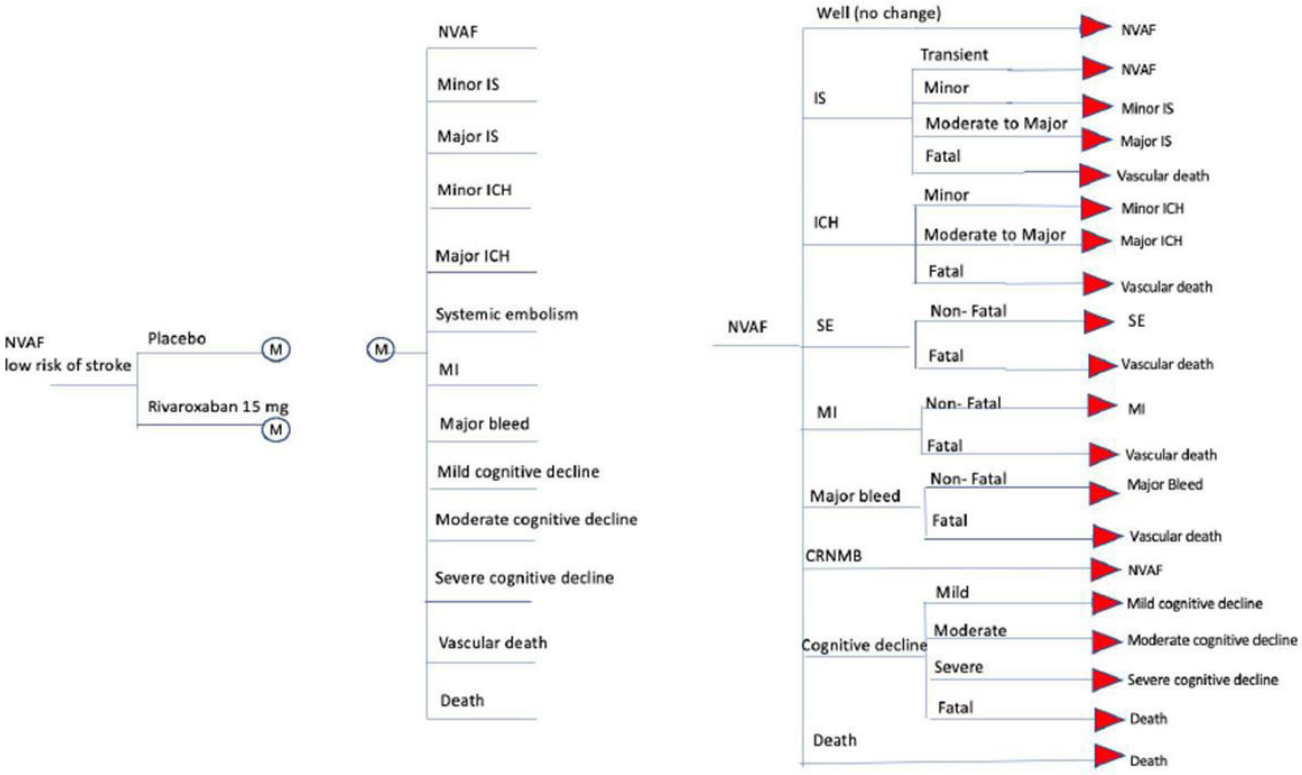
All analyses were performed using TreeAge Pro modeling software (TreeAge Pro 2021, R1. TreeAge Software, Williamstown, MA).

Table 1: Base-case model variables and distributions used in the sensitivity analysis

Clinical Events	Base case	Low value	High value	Distribution	References
Rate of SE on placebo (per 100 PY)	0.05	0.038	0.063	Beta	27
Rate of SE on Rivaroxaban (per 100 PY)	0.01	0.008	0.013	Beta	28,29
Severity (%)					
• Non-fatal	91	68	114	Beta	25
• Fatal	9	7	11	Beta	25
Rate of IS on placebo (per 100 PY)	0.43	0.323	0.538	Beta	27
Rate of IS on Rivaroxaban (per 100 PY)	0.01	0.008	0.013	Beta	28,29
Severity (%)					
• Transient (< 24h)	24	18	30	Beta	23
• Minor (mRS 0 - 2)	43	32.25	53.75	Beta	23
• Major (mRS 3 – 5)	29	21.75	36.25	Beta	23
• Fatal (mRS 6)	4	3	5	Beta	23
Rate of ICH on placebo (per 100 PY)	0.15	0.113	0.188	Beta	27
Rate of ICH on Rivaroxaban (per 100 PY)	0.4	0.3	0.5	Beta	28,29
Severity (%)					
• Minor (mRS 0 – 2)	17	13	21	Beta	25
• Major (mRS 3 – 5)	37	28	46	Beta	25
• Fatal (mRS 6)	46	35	58	Beta	25
Rate of MI on placebo (per 100 PY)	0.016	0.012	0.02	Beta	23
Rate of MI on Rivaroxaban (per 100 PY)	0.4	0.3	0.5	Beta	28,29
Severity (%)					
• Non-fatal	89	67	111	Beta	25
• Fatal	11	8	14	Beta	25

Rate of MB on placebo (per 100 PY)	0.0093	0.007	0.012	Beta	27
Rate of MB on Rivaroxaban (per 100 PY)	1.6	1.2	2	Beta	28-30
Severity (%)					
• Non-fatal	98	74	122	Beta	25
• Fatal	2	1	3	Beta	25
Rate of CRNMB on placebo (per 100 PY)	2.63	1.973	3.288	Beta	27
Rate of CRNMB on Rivaroxaban (per 100 PY)	12.8	9,6	16	Beta	28,29
Rate of CD on placebo (per 100 PY)	0.018	0.013	0.022	Beta	31
Rate of CD on Rivaroxaban (per 100 PY)	0.0114	0.0086	0.0143	Beta	31
Hazard ratio ($CHADS_2$-VASC = 0 - 1)	0.85	0.64	1.06	Beta	31
Severity (%) (all therapies):					
• Mild (CDR 0.5 - 1)	77	58	96	Beta	24
• Moderate (CDR 2)	16	12	20	Beta	24
• Severe (CDR 3)	1	0.75	1.25	Beta	24
• Fatal	6	4	8	Beta	24
Rate of death on placebo (per 100 PY)	0.039	0.029	0.048	Beta	27
Rate of death on Rivaroxaban (per 100 PY)	0.22	0.17	0.28	Beta	29

CD = cognitive decline; CDR = clinical dementia rating scale; CI = cognitive impairment; CRNMB = clinically relevant non-major bleed; ICH = intra-cranial hemorrhage; IS = ischemic stroke; MB = major bleed; MI = myocardial infarction; mRS = modified Rankin Scale adapted by the Oxfordshire Community Stroke Project to assess patient functional deficits at hospital discharge; PY = patient-years; SE = systemic embolism



"M" represents Markov process with 13 health states that are identical for each of the treatment options and a 3-month cycle length. Patients remain in the NVAF state until an event occurs. The branches from the state "NVAF" illustrate the possible events. The structure is similar for each treatment.

CRNMB = clinically relevant non major bleed; ICH = intracranial hemorrhages; IS= ischemic stroke; Ml= myocardial infarction; NVAF = non-valvular atrial fibrillation; SE = systemic embolism:

Figure 1: Schematic representation of the Markov model

Model Inputs

Event Rates

The clinical event rates (Table 1) for patients taking placebo were obtained from a retrospective cohort study [27] assessing the impact of antithrombotic therapy (aspirin, warfarin and no treatment) among 39,400 NVAF patients at low stroke risk. We used the rates per 100 person-years of stroke, SE, IS, bleeding, ICH, and death, from the "no treatment" and "no risk factors" arm (ITT analysis) in our model. The rates of MI and TIA were obtained from the placebo arm in the "Stroke Prevention in Atrial Prevention Study" (SPAF) [23]. This study compared ASA or warfarin to placebo for the prevention of ischemic stroke and systemic embolism in patients with NVAF. Although the population of "SPAF" was different from our hypothetical cohort of patients, in terms of age and comorbidities, no adjustments were made to the clinical event rates. The confidence around the rates was evaluated in sensitivity analyses.

The clinical event rates for patients on rivaroxaban (Table 1) were obtained from XANTUS [28,29], a prospective, international, observational, post-authorization, noninterventional study designed to collect safety and efficacy data on the use of rivaroxaban for stroke prevention in patients with NVAF, in routine clinical practice. The study enrolled 11,121 patients of whom 26% were below the age of 65, 73% received rivaroxaban 20 mg, and 40% had a $CHADS_2$ score equal 0 - 1. The rates of IS, SE, major bleed and all-cause death were obtained from a subgroup analysis in patients with $CHADS_2$ score equal 0 [29,30]. Other clinical event rates from XANTUS were applied to our model with no adjustment. The confidence around those rates was evaluated in sensitivity analyses.

The rates of dementia were obtained from Friberg [31], who assessed the incidence of new dementia in patients with AF taking NOACs compared to those not on NOACs. The probabili-

ties of new dementia observed in each group of patients were adjusted using the reported hazard ratio of dementia in the stroke low-risk group ($CHADS_2$-VASC = 0 – 1) [31]. Transition probabilities, based on Spackman, *et al.* [24], were applied to account for changes in the severity of dementia (Table 1).

An increased risk of recurrence after a first event was applied in the model to the event rate of ischemic stroke (2.20), myocardial infarction (2.04) and bleeding (2.66), based on long-term prognosis and survival data from epidemiological studies [32-34].

Utilities

Utility values were sourced from published studies in similar patients' population [35,36] and applied whenever a patient experienced an event in a cycle (Table 2). Given that patients had no history of stroke, a starting utility value of 0.81 was used, derived from the utility value for AF [35]. The analysis assumed no difference in utility values between the treatments. The utility values were assumed to apply from the cycle in which the event occurred until the end of the follow-up period or death. Upper and lower utility values (95% CI) (Table 2) were applied in the sensitivity analyses [35-41].

Table 2: Utility/ Disutility values

Health State	Utility/Decrement Base Case	Lower Value (2.5%)	Upper Value (97.5%)	Probability Distribution	References
NVAF	0.81000	0.67819	0.91373	Beta	35,64
SE	- 0.1199	-0.10224	-0.13880	Beta	35,64
IS					
• Minor	- 0.1385	- 0.1184	- 0.1600	Beta	35,64
• Major	- 0.2958	- 0.2372	- 0.3554	Beta	37,38
ICH					
• Minor	- 0.1385	- 0.1182	- 0.1602	Beta	35,64
• Major	- 0.2958	- 0.2372	- 0.3554	Beta	37,38
MI	- 0.1247	-0.10645	-0.14356	Beta	35,64
Major bleed (extracranial)	- 0.1814	-0.15476	-0.20899	Beta	35,64
CRNM bleed	- 0.0582	-0.02429	-0.09211	Beta	37,38
Cognitive decline		**(Base Case -25%)**	**(Base Case + 25%)**		
• Mild	- 0.13	- 0.01	- 0.29	Beta	40,41
• Moderate	- 0.27	- 0.11	- 0.51	Beta	40,41
• Severe	- 0.44	- 0.31	- 0.56	Beta	40,41

CRNM Bleed = clinically relevant non-major bleed; ICH = intracranial hemorrhages; IS = ischemic stroke; MI = myocardial infarction; NVAF = non valvular atrial fibrillation; SE = systemic embolism

Costs

One-time event and long-term costs of medical care and hospitalization were derived from the literature [42-45] and were based on the Ontario Case Costing Initiative, the Ontario Drug Benefit Formulary (ODBF), and the Canadian Institute for Health Information. The cost of rivaroxaban was obtained from the "Régie de l'Assurance Maladie du Québec" price list [46] with inclusion of an $8.50 dispensing fee and an 8% pharmacist's markup (Table 3). This cost assumed daily use and no discontinuation. All costs were updated to 2020 Canadian dollars by using the Bank of Canada inflation calculator which is based on the Consumer Price Index (CPI) [47].

Table 3: Cost of events and drugs

Cost of Event	Adjusted Cost*	Lower/Upper Values	Probability Distribution	References
SE	$9,610.42	7,208 – 12,013	Gamma	42
IS				
• Fatal stroke	$19,200	14,400 – 24,000	Gamma	43
• Minor stroke	$19,200	14,400 – 24,000	Gamma	43
• Major stroke	$65,055.46	48,791 – 81,319	Gamma	43
• Transient	$4,914.85	3,686 – 6,144	Gamma	43
ICH				
• Minor ICH	$18,944.38	14,208 – 23,680	Gamma	43
• Major ICH	$37,865	28,399 – 47,331	Gamma	Assumption
• Fatal ICH	$18,944.38	14,208 – 23,680	Gamma	43
Major bleed (extracranial)	$5,024.68	3,769 – 6,281	Gamma	43
CRNM bleed	$118.98	89 - 149	Gamma	43
MI fatal	$8,409.94	6,308 – 10,513	Gamma	43
MI non-fatal	$13,019.33	9,764 – 16,274	Gamma	43
Minor CD	$797 (3 months)	598 - 996	Gamma	44
Moderate CD	$1015 (3 months)	761 - 1268	Gamma	44
Severe CD	$16066 (3 months)	12,050 – 20,083	Gamma	44
Long Term Costs (per annum)				
MI	$3,743.34	2,807 – 4,679	Gamma	43
Major stroke	$21,809.09	16,357 – 27,261	Gamma	43
Minor stroke	$9,033.45	6,775 – 11,292	Gamma	43
ICH	$9,033.45	6,775 – 11,292	Gamma	43
SE	$2,256.94	1,693 – 2,821	Gamma	42
Drug Treatment (per 3 months)**				
Placebo	$0	-	-	
Rivaroxaban 15 mg	$284	241 - 327	Fixed	46

* Cost estimated using 2020 inflation rate

** Cost of rivaroxaban is based on the "Liste des Médicaments - Régie de l'assurance maladie du Québec", November 2020 with $8.50 dispensing fee and 8% mark-up.

CD = cognitive decline; CRNM Bleed = clinically relevant non-major bleed; ICH = intracranial hemorrhages; IS = ischemic stroke; MI = myocardial infarction; SE = systemic embolism

Analyses

The relative clinical and economic benefits of rivaroxaban compared to placebo were assessed using the incremental cost-effectiveness ratio (ICER), which was estimated based on the additional costs (Canadian dollars) per additional quality adjusted life-years (QALYs). The ICER was then compared with the commonly accepted Canadian payers' willingness-to-pay threshold of $50K for each QALY gained.

The robustness of the model's base case results was assessed in 1-way sensitivity analyses, which consisted of varying each model parameter, using its low and high values, while keeping all others constant. The base case value of clinical events and their costs were varied by ± 25%, the cost of rivaroxaban by ± 15% and utility decrements using either the literature reported 95% CI or a ± 25% variation in the base case value. Also, in these analyses, we used a discount rate of 0% or 3%, a cycle-length of 1 or 6-months and a time horizon of 10, 20 or 40 years.

Additionally, probabilistic sensitivity analyses (PSA), which allow all model parameters to be varied simultaneously, were performed using Monte Carlo simulations [48]. The analysis was run for 10,000 iterations where the value of each model parameter was randomly sampled from a probability distribution

uniquely determined for each type of model parameter. The results of the probabilistic analysis were used to generate a scatter-diagram representing the additional gains in QALYs with rivaroxaban compared to placebo (x-axis) against the additional costs of the drug (y-axis). The results of these analyses were also used to derive cost-effectiveness acceptability curves (CEACs) representing the proportion of simulations for which each treatment was the optimal strategy at a given willingness-to-pay threshold.

Results

Base Case Analysis

For a cohort of 1,000 patients followed over their lifetime, treatment with rivaroxaban rather than placebo was predicted to result in fewer cases of ischemic stroke (43 first and 39 recurrent), SE (30), MI (79 first and 7 recurrent), cognitive decline (36) and death (225). However, compared with placebo, rivaroxaban increased the number of ICH (93 first and 25 recurrent) and major bleed (326 first and 614 recurrent). The treatment with rivaroxaban 15 mg led to a net increment in total cost over a lifetime of $128,543 while generating a net increment in total QALY of 11.26. This resulted in an ICER of $11,411 per QALY gained (Table 4). This ratio is below the commonly accepted willingness-to-pay threshold [26] of $50K per QALY gained, indicating that rivaroxaban is cost-effective when compared to placebo in this hypothetical cohort of patients (Figure 2). There was no dominance in the model given that the less costly treatment also had less QALYs.

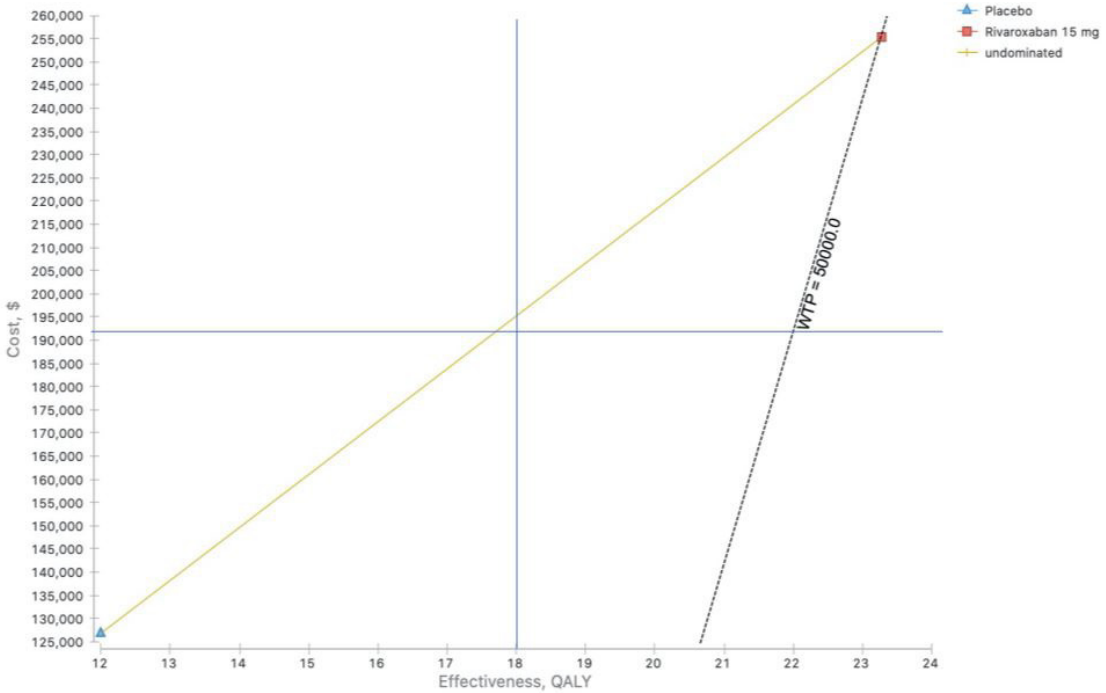
Table 4: Cost-Effectiveness Analysis – Base Case Results

Strategy	Cost♦	Δ Cost♦	QALYs	Δ QALY	Incremental cost per QALY (ICER)
Placebo	$126,836		12.00		
Rivaroxaban 15 mg	$255,379	$128,543	23.27	11.26	$11,411

♦ Canadian dollar

** rivaroxaban cost-effective (ICER below the willingness to pay value of $50K); Placebo undominated = less costly and less effective than rivaroxaban; Rivaroxaban undominated = more costly and more effective than placebo

QALY = Quality adjusted life years; ICER = Incremental cost-effectiveness ratio



The cost and effectiveness of each strategy are plotted on the x and y-axes. The placebo in the left lower quadrant is less effective and less costly; rivaroxaban in the upper right quadrant is more effective and more costly. The willingness-to-pay (WTP)line (in black) passes through the optimal strategy. The ICER line being to the left of the WTP line indicates that the optimal strategy is cost effective at a WTP of $50K.

Figure 2: Cost-Effectiveness Analysis -Base case results

Deterministic Sensitivity Analyses

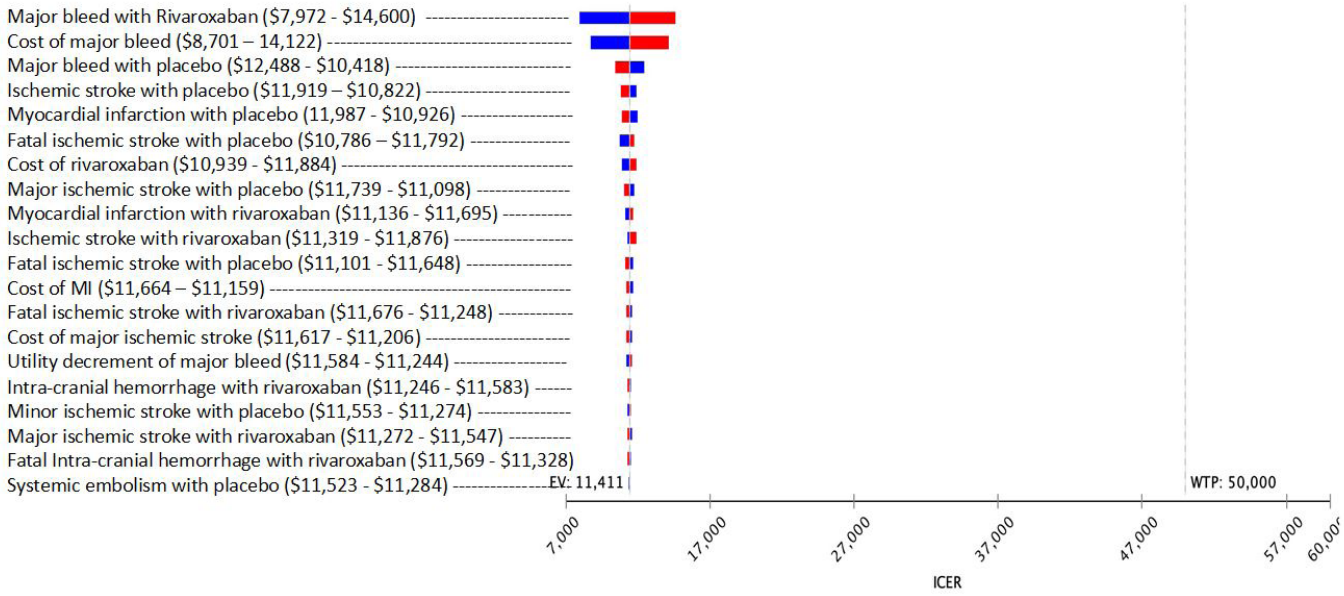
Figure 3 presents the results from the one-way sensitivity analyses for the top 20 parameters that had the largest effect on the ICER, in the order of their respective influence.

Regardless of the variation in costs, utility/disutility values or clinical event rates, the ICERs remained below the WTP threshold of $50K (Appendix 1). The lowest ($7,972) and highest ($14,600) ICER values were observed with a ± 25% variation in the base case value of major bleed with rivaroxaban. The next lowest and highest ICER values were obtained with a ± 25% variation in the cost of major bleed ($8,701 - $14,122).

Similarly, varying the discount rate, the cycle length and the time horizon resulted in ICERs below the WTP threshold of $50K. Nevertheless, greater variations were observed with: 1) a 6-month cycle ($22,769) and 2) a time horizon of 10 years. In this latter analysis, the ICER was negative ($-1,730) with absolute dominance of placebo (by rivaroxaban) due to a higher cost and less QALY.

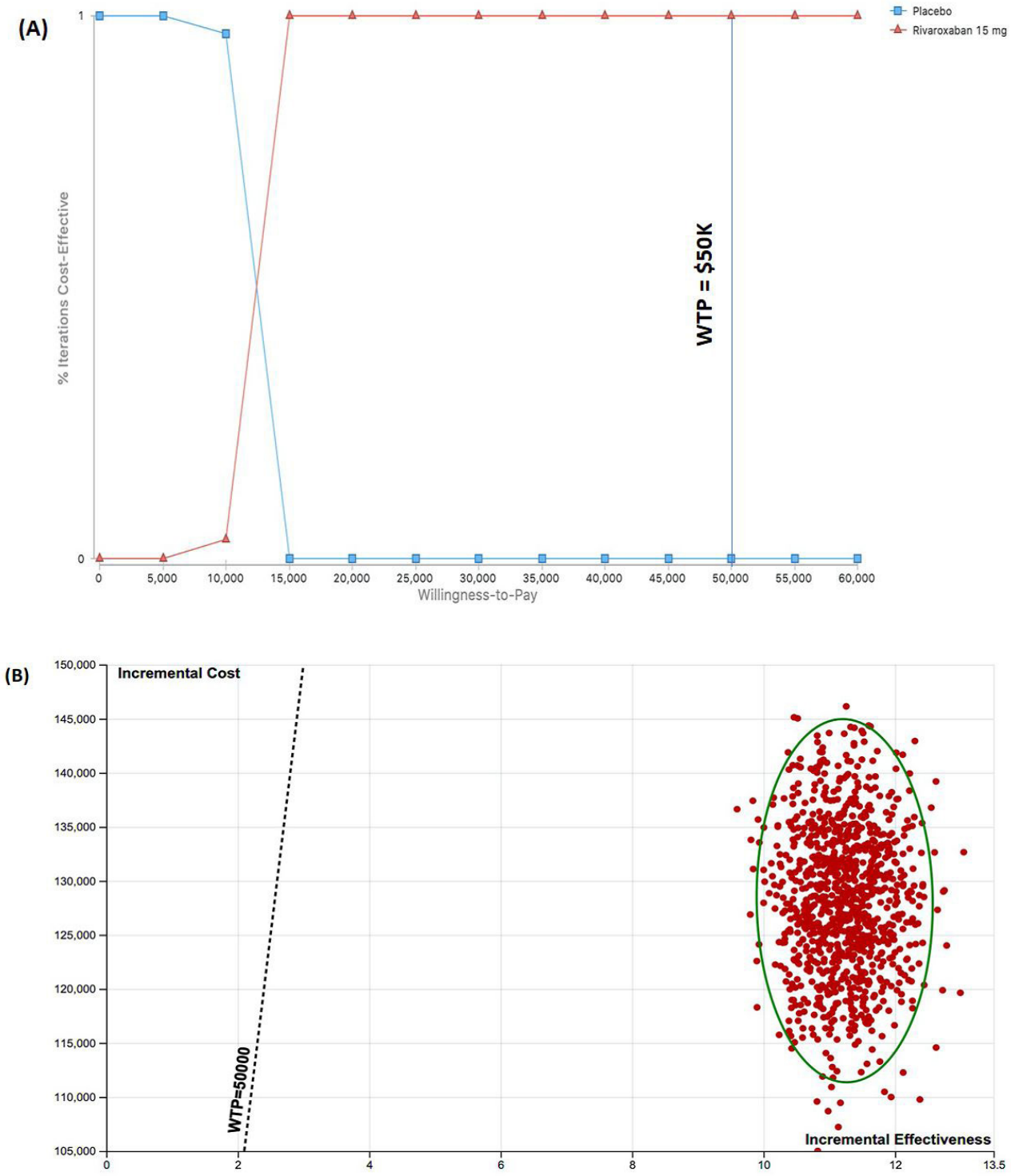
Probabilistic Sensitivity Analysis

The probabilistic sensitivity analyses demonstrated that rivaroxaban was more effective at a small additional cost versus placebo, over a lifetime horizon. The results of the probabilistic analyses are shown in Figure 4 (A) and in Figure 4 (B). The CEACs indicated that rivaroxaban was an optimal treatment choice representing a maximum net benefit over placebo, at a WTP of $50K per QALY gained. The scatter diagram showed ICERs below the WTP threshold of $50K per QALY gained in 100% of the simulations comparing the two agents. The results remained constant regardless of the time horizon.



A tornado of the top 20 parameters with most impact on the incremental cost effectiveness ratio (ICER): the solid vertical line on the left side of the graph represents the base case incremental costs per quality-adjusted life year (QALY) for rivaroxaban 15 mg compared with placebo. The solid vertical line on the right side represents the willingness-to-pay threshold set at $50K for the analysis. The horizontal bars indicate the range of incremental costs per QALY obtained (ICER) by setting each variable to its lowest and to its highest value while holding all other parameters constant. The ICER values are indicated on the left side of each horizontal line.

Figure 3: Results of the detenninistic sensitivity analyses



(A) Cost-effectiveness acceptability curves presenting the percentage of simulation iterations that favor each strategy for each willingness-to-pay (WTP) value. The percentage increases for more effective strategies as the WTP increases; (B) scatter diagram of rivaroxaban versus ASA, with the dotted black Iine presenting the willingness-to-pay (WTP) threshold set at $50K each colored dot presenting the incremental cost and incremental effectiveness value from a single calculation of the model and the ellipsis showing the 95% confidence interval. Rivaroxaban is a cost-effective alternative in cases that fall below to the right of the WTP line and is not cost-effective alternative in cases that fall to the left of the WTP line.

Figure 4: Results of the probabilistic sensitivity analyses

Discussion

The study assessed the cost-effectiveness of rivaroxaban in the prevention of stroke and cognitive decline in a hypothetical cohort of patients with NVAF at low stroke risk, compared with placebo. Patients on rivaroxaban were predicted to have fewer strokes, systemic embolisms, myocardial infarctions, cognitive impairment and death compared to those on placebo. Nevertheless, hemorrhagic events were predicted to be more likely with rivaroxaban, an expected result with anticoagulant medications, particularly, when compared to placebo or no drug.

In the base-case analysis, over a lifetime horizon (60 years), the net benefits in terms of reduction of clinical events with rivaroxaban yielded an incremental QALY at an incremental cost with a resulting ICER of $11,411, a value below the WTP of $50K, deeming rivaroxaban to be cost-effective compared to placebo. The results were insensitive to the variation in the model's inputs with ICERs constantly remaining below the WTP of $50K.

Our study is the first to compare the cost-effectiveness of rivaroxaban 15 mg daily versus placebo in preventing both stroke and cognitive decline among NVAF patients at low stroke risk. Existing cost-effectiveness studies of NOACs in NVAF patients at moderate to high stroke risk have consistently found these agents to be cost-effective. The higher up-front cost of NOACs compared to an alternative treatment such as a vitamin K antagonist (VKA) was offset by a reduction in clinical events and an increase in patients' quality of life [38,42,49-55]. In studies [53-55] assessing solely the cost-effectiveness of rivaroxaban in comparison to warfarin, the former was shown to be cost-effective with ICERs (US$27,498, €15,207, €8,809) below the country respective WTP threshold. All three studies used clinical event data observed in the pivotal randomized controlled trial "ROCKET-AF" (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) which assessed the efficacy and tolerability of rivaroxaban in moderate to high stroke risk patients. A recent real-world cost-effectiveness study of rivaroxaban and apixaban each in comparison to VKA [56], showed both agents to be cost-effective in moderate to high stroke risk patients, based on real-world evidence (RWE). The incremental cost-effectiveness ratio was £14,437 for rivaroxaban compared with VKA [56]. Comparisons between our results and those of previous rivaroxaban economic evaluation studies were not feasible given important differences in the model design, drug dosage and patient population characteristics.

Our analysis has some limitations. Given the lack of data in low stroke risk NVAF patients, certain clinical event rates as well as the probabilities of transitioning between events in our model were obtained from studies with moderate to high stroke risk patients. The SPAF (Stroke Prevention in Atrial Prevention Study) study [23], from which we obtained the MI and TIA rates for the placebo arm, included patients with co-morbidities such as hypertension (52%), diabetes (19%) and congestive heart failure (20%). Similarly, the XANTUS [28,29] main study, from which we obtained the ICH, MI and CRNMB rates for the rivaroxaban arm, included a majority of moderate to high stroke risk patients treated with rivaroxaban 20mg. Those rates are higher than what could have been expected in patients at low stroke risk treated with rivaroxaban 15 mg and likely could have impacted the ICER estimation. Nevertheless, the sensitivity analyses showed the ICER values to be insensitive to a variation of ± 25% in those rates and rivaroxaban to remain cost-effective in 100% of the simulations. Also, our model assumed patients' full persistence/compliance with the treatments which may have led to an over or under estimation of the ICER. Additionally, the patients' age, dosage regimen, risk score, and costs used in the model as well as the Canadian public health care perspective make the results not necessarily generalizable to other settings. Finally, given the lack of data, the model allowed patients to have one event per cycle and one type of event over lifetime. Data on the incidence of different combination of clinical events in patients with NVAF at low risk of stroke would have certainly contributed to more precise calculations of the overall cost and benefits of rivaroxaban treatment. The results from the BRAIN-AF trial, once available, will inform the analysis with observed event rates in this patient population.

Conclusion

This economic evaluation predicted that rivaroxaban would be a cost-effective alternative to placebo for the prevention of stroke and cognitive decline in NVAF patients at low stroke risk. The "no-treatment" therapeutic recommendation for this patients' group is based on the low stroke risk but does not take into consideration another potential risk as debilitating and life-threatening as cognitive impairment and dementia. Future economic evaluations of NOACs for the treatment of NVAF that account for the impact of the disease on patients' mental health would better estimate the patients' overall health benefits and the costs of these drugs. Our analysis of a hypothetical cohort of NVAF patients at low stroke risk has shown that rivaroxaban could offer health benefits for a marginal increase in healthcare costs.

References

1. O'Reilly DJ, Hopkins RB, Healey JS (2013) The burden of atrial fibrillation on the hospital sector in Canada. 29: 229-235.

2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, et al. (1998) Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 98: 946-52.

3. Benjamin EJ, Levy D, Vaziri SM, D'agostino RB, Belanger AJ,et al. (1994) Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. 271: 840-4.

4. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB (1998) Impact of atrial fibrillation on mortality, stroke, and medical costs. Archives of internal medicine 158: 229-34.

5. Wolf PA, Abbott RD, Kannel WB (1991) Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 22: 983-8.

6. Steger C, Pratter A, Martinek-Bregel M (2004) Stroke patients with atrial fibrillation have a worse prognosis than patients without: data from the Austrian Stroke registry. European heart J 25: 1734-40.

7. Lin H-J, Wolf PA, Kelly-Hayes M (1996) Stroke severity in atrial fibrillation: the Framingham Study. Stroke 27: 1760-4.

8. Carlsson J, Miketic S, Flicker E (2000) Neurological events in patients with atrial fibrillation: outcome and preventive practices. Zeitschrift fur Kardiologie 89: 1090-7.

9. Lamassa M, Di Carlo A, Pracucci G (2001) Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital–based registry (The European Community Stroke Project). Stroke 32: 392-8.

10. Dulli DA, Stanko H, Levine RL (2003) Atrial fibrillation is associated with severe acute ischemic stroke. Neuroepidemiology 22: 118-23.

11. Skanes AC, Healey JS, Cairns JA (2012) Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control 28: 125-36.

12. de Bruijn RF, Heeringa J, Wolters FJ (2015) Association between atrial fibrillation and dementia in the general population. JAMA neurology 72: 1288-94.

13. Kalaria RN (2003) Vascular factors in Alzheimer's disease. International Psychogeriatrics 15: 47-52.

14. de la Torre JC (2004) Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. The Lancet Neurology 3: 184-90.

15. De La Torre JC, Hachinski V (1997) Cerebrovascular pathology in Alzheimer's disease. New York Academy of Sciences.

16. Lavy S, Stern S, Melamed E, Cooper G, Keren A, et al. (1980) Effect of chronic atrial fibrillation on regional cerebral blood flow. Stroke 11: 35-8.

17. Petersen P, Kastrup J, Videbæk R, Boysen G (1989) Cerebral blood flow before and after cardioversion of atrial fibrillation. J Cerebral Blood Flow Metabol 9: 422-5.

18. Gaita F, Corsinovi L, Anselmino M (2013) Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. J Ame Coll Cardiol 62: 1990-7.

19. Kalantarian S, Stern TA, Mansour M, Ruskin JN (2013) Cognitive Impairment Associated With Atrial Fibrillation: A Meta-analysis. Annals of Internal Medicine 158: 338-46.

20. Marzona I, O'donnell M, Teo K (2012) Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies 184: E329-E336.

21. Jacobs V, May HT, Bair TL (2016) Long-term population-based cerebral ischemic event and cognitive outcomes of direct oral anticoagulants compared with warfarin among long-term anticoagulated patients for atrial fibrillation. Ame J cardiol 118: 210-4.

22. Sonnenberg FA, Beck JR (1993) Markov models in medical decision making: a practical guide. Medical decision making 13: 322-38.

23. Investigators SPiAF (1991) Stroke prevention in atrial fibrillation study: final results. Circulation 84: 527-39.

24. Spackman DE, Kadiyala S, Neumann PJ, Veenstra DL, Sullivan SD (2012) Measuring Alzheimer disease progression with transition probabilities: estimates from NACC-UDS. Current Alzheimer research 9: 1050.

25. Connolly SJ, Eikelboom J, Joyner C (2011) Apixaban in patients with atrial fibrillation. New England J Med 364: 806-817.

26. CADTH (2017) Guidelines for the economic evaluation of health technologies: Canada. 2017.

27. Lip GY, Skjøth F, Rasmussen LH, Larsen TBJJotACoC (2015) Oral anticoagulation, aspirin, or no therapy in patients with nonvalvular AF with 0 or 1 stroke risk factor based on the CHA2DS2-VASc score 65: 1385-94.

28. Kirchhof P, Radaideh G, Kim Y-H (2018) Global prospective safety analysis of rivaroxaban. Journal of the American College of Cardiology 72: 141-53.

29. Camm AJ, Amarenco P, Haas S (2016) XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. European heart J 37: 1145-53.

30. Tamayo S, Frank Peacock W, Patel M (2015) Characterizing major bleeding in patients with nonvalvular atrial fibrillation: a pharmacovigilance study of 27 467 patients taking rivaroxaban. Clinical cardiology 38: 63-8.

31. Friberg L, Rosenqvist M (2017) Less dementia with oral anticoagulation in atrial fibrillation. European heart J 39: 453-60.

32. Cupples LA, Gagnon DR, Wong ND, Ostfeld AM, Kannel WB (1993) Preexisting cardiovascular conditions and long-term prognosis after initial myocardial infarction: the Framingham Study. American heart J 125: 863-72.

33. Dennis MS, Burn J, Sandercock P, Bamford J, Wade D, et al. (1993) Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. Stroke 24: 796-800.

34. Pisters R, Lane DA, Nieuwlaat R, De Vos CB, Crijns HJ, Lip GY (2010) A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 138: 1093-100.

35. Sullivan PW, Lawrence WF, Ghushchyan V (2005) A national catalog of preference-based scores for chronic conditions in the United States. Medical care 2005: 736-49.

36. Sullivan PW, Arant TW, Ellis SL, Ulrich H (2006) The Cost Effectiveness of Anticoagulation Management Services for Patients with Atrial Fibrillation and at High Risk of Stroke in the US. Pharmaco Economics 24: 1021-33.

37. Lip GY, Lanitis T, Mardekian J, Kongnakorn T, Phatak H, et al. (2015) Clinical and economic implications of apixaban versus aspirin in the low-risk nonvalvular atrial fibrillation patients 46: 2830-37.

38. Dorian P, Kongnakorn T, Phatak H (2014) Cost-effectiveness of apixaban vs. current standard of care for stroke prevention in patients with atrial fibrillation 35: 1897-906.

39. Miller JD, Ye X, Lenhart GM (2016) Cost-effectiveness of edoxaban versus rivaroxaban for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) in the US. Clinico Economics and outcomes research: CEOR. 8: 215.

40. Neumann PJ, Hermann R, Kuntz K (1999) Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. Neurology 52: 1138.

41. Ruiz Vargas E, Sposato LA, Lee SA, Hachinski V, Cipriano LE (2018) Anticoagulation Therapy for Atrial Fibrillation in Patients With Alzheimer's Disease: A Cost-Effectiveness Analysis. Stroke 49: 2844-50.

42. Sorensen SV, Kansal AR, Connolly S (2011) Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. Thrombosis and haemostasis. 105: 908-19.

43. Coyle D, Coyle K, Cameron C (2013) Cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation. Value in health 16: 498-506.

44. Getsios D, Caro J, Caro Gf, Ishak K, Group AS (2001) Assessment of health economics in Alzheimer's disease (AHEAD): galantamine treatment in Canada. Neurology 57: 972-8.

45. Tanuseputro P, Wodchis WP, Fowler R (2015) The health care cost of dying: a population-based retrospective cohort study of the last year of life in Ontario, Canada. PloS one 10: e0121759-e0121759.

46. Liste des Médicaments 2020.

47. Calculator I. Bank of Canada. In.

48. Harrison RL (2010) Introduction to monte carlo simulation. Paper presented at: AIP conference proceedings.

49. Hicks T, Stewart F, Eisinga A (2016) NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis. Open heart 3: e000279.

50. Graham DJ, Baro E, Zhang R (2019) Comparative stroke, bleeding, and mortality risks in older Medicare patients treated with oral anticoagulants for nonvalvular atrial fibrillation. Ame J med 132: 596-604. e511.

51. Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN, Lip GY (2016) Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ 2016: 353.

52. Yao X, Abraham NS, Sangaralingham LR (2016) Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. Journal of the American Heart Association 5: e003725.

53. Ruff CT, Giugliano RP, Braunwald E (2014) Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. The Lancet. 383: 955-62.

54. Tereshchenko LG, Henrikson CA, Cigarroa J, Steinberg JS (2016) Comparative effectiveness of interventions for stroke prevention in atrial fibrillation: a network meta-analysis. J Ame Heart Association 5: e003206.

55. Bassand J-P, Virdone S, Badoz M (2021) Bleeding and related mortality with NOACs and VKAs in newly diagnosed atrial fibrillation: results from the GARFIELD-AF registry. Blood advances 5: 1081-91.

56. Freeman JV, Zhu RP, Owens DK (2011) Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Annals of internal med 154: 1-11.

57. Kansal AR, Sorensen SV, Gani R (2012) Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. Heart 98: 573-78.

58. Lip GY, Kongnakorn T, Phatak H (2014) Cost-effectiveness of apixaban versus other new oral anticoagulants for stroke prevention in atrial fibrillation. Clinical therapeutics 36: 192-210. e120.

59. Harrington AR, Armstrong EP, Nolan PE, Malone DC (2013) Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. Stroke 44: 1676-81.

60. Lee S, Anglade MW, Pisacane R, Kluger J, Coleman CIJTAjoc (2012) Cost–effectiveness of rivaroxaban compared to warfarin for stroke prevention in atrial fibrillation 110: 845-51.

61. Mensch A, Stock S, Stollenwerk B, Müller D (2015) Cost effectiveness of rivaroxaban for stroke prevention in German patients with atrial fibrillation. Pharmacoeconomics. 33: 271-83.

62. Kleintjens J, Li X, Simoens S (2013) Cost-effectiveness of rivaroxaban versus warfarin for stroke prevention in atrial fibrillation in the Belgian healthcare setting. Pharmacoeconomics 31: 909-18.

63. Bowrin K, Briere J-B, Levy P, Millier A, Tardu J, et al. (2020) Real-world cost-effectiveness of rivaroxaban and apixaban vs VKA in stroke prevention in non-valvular atrial fibrillation in the UK. J Market Access Health Policy 8: 1782164.

64. Sullivan PW, Ghushchyan V (2006) Preference-based EQ-5D index scores for chronic conditions in the United States. Medical Decision Making 26: 410-20.

Appendix 1

Table A1: Results of One-Way Sensitivity Analyses

Parameter	ICER (With Parameter Low Value)	ICER (With Parameter High Value)
Base Case ± 15%		
Cost of Rivaroxaban	$10,939	$11,884
Base Case ± 25%		
Cost of Rivaroxaban	$10,624	$12,198
Base Case ± 25%		
Cost of major IS	$11,617	$11,206
Cost of minor IS	$11,490	$11,333
Cost of fatal IS	$11,420	$11,403
Cost of major ICH	$11,373	$11,450
Cost of minor ICH	$11,403	$11,420
Cost of fatal ICH	$11,384	$11,439
Cost of SE	$11,477	$11,345
Cost of MI	$11,664	$11,159
Cost of fatal MI	$11,430	$11,393
Cost of major bleed	$8701	$14,122
Cost of minor bleed	$11,405	$11,418
Cost of minor CD	$11,424	$11,399
Cost of moderate CD	$11,418	$11,405
Cost of severe CD	$11,453	$11,370
Base Case ± (CI)		
Minor IS utility decrement	$11,410	$11,412
Major IS utility decrement	$11,409	$11,413
Minor ICH utility decrement	$11,412	$11,411
Major ICH utility decrement	$11,412	$11,411
SE utility decrement	$11,411	$11,414
MI utility decrement	$11,408	$11,416
Major bleed utility decrement	$11,584	$11,244
CRNMB utility decrement	$11,411	$11,411
Base Case ± 25%		
Minor CD utility decrement	$11,406	$11,417
Moderate CD utility decrement	$11,406	$11,417
Severe CD utility decrement	$11,408	$11,415
Base Case ± 25%		
Rate of IS with Rivaroxaban	$11,319	$11,876
Rate of IS with placebo	$11,919	$10,822
Rate of ICH with Rivaroxaban	$11,246	$11,583
Rate of ICH with placebo	$11,433	$11,376
Rate of SE with rivaroxaban	$11,388	$11,529

Rate of SE with placebo	$11,523	$11,284
Rate of MI with rivaroxaban	$11,136	$11,695
Rate of MI with placebo	$11,987	$10,926
Rate of MB with rivaroxaban	$7,972	$14,600
Rate of MB with placebo	$12,488	$10,418
Rate of CRNMB with rivaroxaban	$11,521	$11,303
Rate of CRNMB with placebo	$11,398	$11,426
Rate of CD with rivaroxaban	$11,360	$11,459
Rate of CD with placebo	$11,536	$11,303
Rate of death with rivaroxaban	$11,411	$11,412
Rate of death with placebo	$11,424	$11,400
Base case ± (low, high values)		
Discount rate (low = 0, High = 3%)	$12,790	$10,028
Cycle length (1 month, 6months)	$22,769	$9,158
Time horizon • 10 years • 20 years • 40 years	 $-1,730 $3,627 $8,629	

CI = Confidence interval; ICER = Incremental cost-effectiveness ratio

CD= Cognitive decline; CRNMB = Clinically relevant non major bleed; ICH = Intracranial hemorrhage; IS = Ischemic stroke; MI = Myocardial infarction; MB = Major bleed; SE = Systemic embolism