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

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Abstract

Objectives: To evaluate the potential cost-effectiveness of low dose rivaroxaban (15 mg od) compared with ASA (100 mg od) for the prevention of stroke and cognitive impairment in non-valvular atrial fibrillation patients with low risk of stroke.

Methods: Analysis used a Markov model that followed a hypothetical cohort of patients with $CHADS_2 = 0$ and vascular disease, not requiring anti-coagulation from initiation of pharmacotherapy over a lifetime period. Transition probabilities, utility values and costs were obtained from published data. The health states included: ischemic stroke, systemic embolism, hemorrhagic events, cognitive impairment, vascular and non-vascular death. Cost-effectiveness was assessed by the incremental cost per quality-adjusted life-year (QALY) gained over a lifetime and was assessed from the Quebec Ministry of Health perspective. Deterministic and probabilistic sensitivity analyses were conducted.

Results: Rivaroxaban compared to ASA was projected to increase QALYs (6.6) at an increased cost ($197,987) over lifetime. The incremental cost- effectiveness ratio (ICER) of rivaroxaban was $29,900 per QALY gained. Sensitivity analyses indicated that results were robust to a wide range of inputs. Probabilistic sensitivity analysis showed a probability of 100% for rivaroxaban being cost-effective at a willingness-to-pay of $50 K. 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 to ASA.

Conclusions: Our results showed that treatment with rivaroxaban reduced the risk of stroke and cognitive impairment and was cost-effective compared to aspirin for NVAF patients with low risk of stroke.

Keywords: Non-valvular atrial fibrillation, cognitive impairment, cost-effectiveness, rivaroxaban

Introduction

Atrial fibrillation (AF), the most common persistent cardiac arrhythmia, has been estimated to affect approximately 350,000 Canadians [1]. AF is associated with an increased risk of morbidities and mortality [2-4]. Amongst its devastating complications is stroke. In the Framingham's study [4], AF has been shown to increase the risk of stroke fivefold and mortality 1.5- to 1.9-fold after adjustment for related pre-existing cardiovascular conditions. This risk remains high even in AF patients at low stroke risk ($CHADS_2 = 0$). In this group, the annual risk of stroke has been estimated to be 0.49% and death to be 3.87% [5,6]. Symptoms of AF can also lead to temporary or permanent physical or mental disability which affects patients' well-being and quality of life [7] and often results in increased health care resource use and costs [2,8,9].

Cognitive decline (CD) may be a consequence to AF. Among the proposed mechanisms behind the development of CD in AF patients are stroke [10-12], chronic cerebral hypoperfusion [11-14], silent cerebral ischemia due to microembolization [15,16] as well as traditional cardiovascular risk factors [11,17]. However, few longitudinal studies have shown the association between AF and dementia to be independent of stroke. Marzona, *et al.* [18], in a group of 31,546 AF patients, have found a 14% increased risk of cognitive decline and a 30% increased risk of new dementia, in presence or absence of stroke. Similarly, De Brujin *et al.* [17] reported a 34% increased risk of dementia in persistent AF patients (N = 6,514), even when censoring for stroke. This association between AF and CD or dementia has clinical implications where the efficacy of the treatment for AF can have direct effects on the risk of CD and dementia. In a study by Jacobs and colleagues, greater proportion of time outside the therapeutic range with vitamin K antagonist was associated with an increased risk of dementia [19]. Further, patients prescribed direct oral anticoagulants (DOACs) had a lower risk of cerebral ischemic events and new-onset dementia compared to warfarin [20].

DOACs (epixaban, dabigatran, apixaban, rivaroxaban) are currently used for the treatment of patients with NVAF at moderate or high risk of stroke [21]. For patients at low risk of stroke, the therapeutic guidelines recommend DOACs or ASA depending on the presence of additional risk factors and no antithrombotic therapy for those at the lowest risk in this category [21]. For this last group of patients with a $CHADS_2$ score of 0, the benefits of expanding anticoagulation with DOACs versus ASA or no treatment is poorly understood. It is hypothesized that a therapy with DOACs, despite potentially increasing the risk of bleeding, will help to prevent stroke and reduce silent cerebral ischemia and hence, the incidence of cognitive impairment, which is a known precursor of dementia.

The efficacy of rivaroxaban in lowering stroke and cognitive decline in the low-risk patients (CHADS2 = 0) are being investigated in the "Brain-AF" trial, "Blinded Randomized trial of Anticoagulation to prevent Ischemic stroke and Neurocognitive impairment in Atrial Fibrillation" (NCT02387229). If the clinical outcomes of the "Brain-AF" trial are proven positives, then investigating the cost-effectiveness of adding anticoagulation to the treatment regimen of low stroke risk patients becomes important to inform decision-making. Therefore, the aim of the present study was to estimate the cost-effectiveness of rivaroxaban compared to ASA in a hypothetical cohort of non-valvular AF patients with low risk of stroke.

Methods

Type of Economic Analysis

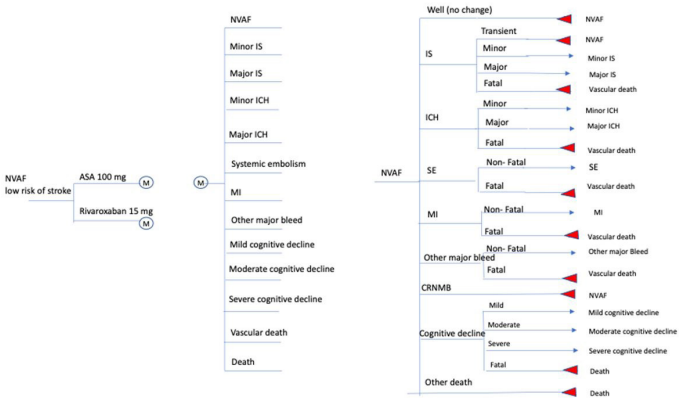
This was a cost-utility analysis with cost-effectiveness assessed by the incremental cost per quality-adjusted life year (QALY) gained. The analysis adopted a single payer perspective relating to the Quebec Ministry of Health, and only direct medical costs were considered.

Target Population

The target population was a hypothetical cohort of patients, aged 30 – 62 years, with NVAF and vascular disease at low risk of stroke ($CHADS_2 = 0$) not requiring anticoagulation. Vascular disease was defined as coronary artery disease or peripheral artery disease.

Decision Model

A Markov cohort model was developed to conduct the economic analysis (Figure 1). Two strategies were considered: a strategy where patients received rivaroxaban 15 mg and placebo daily, and a second where patients were treated with ASA 100 mg and placebo daily.



"M" represents Markhov process with 13 health states that are identical for each of the treatment options and a cycle length of three-month. Patients remain in the NVAF state until an event occurs. The transition probabilities of the events depend on the treatment. The branches from the state "NVAF" illustrate the possible events. The structure is similar for each treatment.
ASA = acetyl salicylic acid; CRNMB = clinically relevant non major bleed; ICH = intracranial hemorrhages; IS = ischemic stroke; MI = myocardial infarction; NVAF = non-valvular atrial fibrillation; Other M. Bleed = major bleed; SE = systemic embolism
Figure 1: Schematic representation of the Markhov model

The model simulated NVAF progression and the probabilities of patients experiencing health events depending on the treatment received. The outcomes were: systemic embolism, ischemic stroke (transient, minor, moderate, severe, fatal), intracranial hemorrhage (minor, major, fatal), myocardial infarction, other major bleed, clinically relevant minor bleed, cognitive decline (mild, moderate, severe, fatal), vascular death and non-vascular death. The Markov model allowed patients to move exclusively to one of the health states or die during each cycle. We assumed that patients could experience up to two events during the follow-up period. The health states were either permanent, indicating that patients remain in them until death, or transient, suggesting that patients only spend some time in that health state before returning to the NVAF well state.

At the end of each cycle, according to transition probabilities, the simulated patients could either stay healthy with NVAF, experience an event or die. Transition probabilities 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. An event rate adjustment was incorporated in the model to account for an increased risk of recurrence after a first event of ischemic stroke (2.20), myocardial infarction (2.04) and bleeding (2.66) based on long-term prognosis and survival data from epidemiological studies [22-24]. The model assumed total compliance with the medication regimen and no change in the assigned medication for the whole follow-up period.

Time Horizon

The base-case analysis adopted a lifetime horizon (60 years) with a cycle length of three months. Sensitivity analyses were conducted with horizons of 10, 20 and 40 years and cycle lengths of 1 and 6 months. Future events were discounted at a rate of 1.5% per annum with sensitivity analysis using discounting rates of 0% and 3%.

Clinical Events and Mortality

For ASA, the rates of clinical event were obtained from a sub-analysis [25] of the "AVERROES" clinical trial [26] (Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K treatment). In this sub-analysis, Lip *et al.* [25] evaluated the event rates in a group of patients at low risk of stroke (38.2% of patients with $CHADS_2$ = 0 -1 or $CHADS_2$-VASC = 1 or higher) who were on either ASA or apixaban. The probabilities of transitioning from "NVAF well" to an event were based on an economic analysis [27] which used data from the "AVERROES" trial (Table 1).

Table 1: Input Parameters

Annual Rates of Events (AR) per 100 patient-year / Severity	Base Case	Lower / Upper (± 25%)	Probability Distribution	References
AR Systemic Embolism (SE)				
▪ ASA	0.17	0.13 – 0.21	Beta	25
▪ Rivaroxaban	0.03	0.02 – 0.04	Beta	28
SE severity (%) (all therapies):				
▪ Non-fatal	91	68 – 114	Beta	27
▪ Fatal	9	7 - 11	Beta	27
AR Ischemic Stroke (IS)				
▪ ASA	1.38	1.04 – 1.73	Beta	25
▪ Rivaroxaban	0.87	0.65 – 1.09	Beta	28
IS severity with ASA (%):				
▪ Transient (< 24h)	36	27 – 45	Beta	27
▪ Minor (mRS 0 - 2)	38	29 – 48	Beta	27
▪ Major (mRS 3 – 5)	15	11 – 19	Beta	27
▪ Fatal (mRS 6)	11	8 – 14	Beta	27
IS severity with rivaroxaban (%):				
▪ Transient (< 24h)	50	38 – 63	Beta	29
▪ Minor (mRS 0 - 2)	13	10 – 16	Beta	29
▪ Major (mRS 3 – 5)	11	8 – 14	Beta	29
▪ Fatal (mRS 6)	26	20 - 33	Beta	29
AR Intracranial Haemorrhage (ICH)				
▪ ASA	0.08	0.06 – 0.1	Beta	25
▪ Rivaroxaban	0.33	0.25 – 0.41	Beta	28
ICH severity with ASA (%):				
▪ Minor (mRS 0 – 2)	17	13 – 21	Beta	27
▪ Major (mRS 3 – 5)	37	28 – 46	Beta	27
▪ Fatal (mRS 6)	46	35 – 58	Beta	27
ICH severity with rivaroxaban (%):				
▪ Minor (mRS 0 – 2)	24	18 – 32	Beta	29
▪ Major (mRS 3 – 5)	27	20 – 34	Beta	29
▪ Fatal (mRS 6)	49	37 – 61	Beta	29

AR Major Bleed (extracranial)				
▪ ASA	0.26	0.20 – 0.33	Beta	25
▪ Rivaroxaban	2.34	1.76 – 2.90	Beta	28
Major Bleed severity (%) (all therapies):				
▪ Non-fatal	98	74 – 122	Beta	27
▪ Fatal	2	1 - 3	Beta	27
AR Clinically Relevant Minor Bleed				
▪ ASA	2.63	1.97 – 3.29	Beta	25
▪ Rivaroxaban	7.67	5.75 – 9.59	Beta	28
AR Myocardial infarction (MI)				
▪ ASA	0.42	0.32 – 0.53	Beta	25
▪ Rivaroxaban	0.59	0.44 – 0.74	Beta	28
MI severity (%) (all therapies):				
▪ Non-fatal	89	67 – 111	Beta	27
▪ Fatal	11	8 - 14	Beta	27
AR Cognitive decline (CD)				
▪ ASA	1.78	1.34 – 2.23	Beta	30
▪ Rivaroxaban	1.14	0.86 – 1.43	Beta	30
Hazard ratio ($CHADS_2$-VASC = 0 - 1)	0.85	0.64 – 1.06	Beta	30
CD severity (%) (all therapies):				
▪ Mild (CDR 0.5 - 1)	77	58 – 96	Beta	31
▪ Moderate (CDR 2)	16	12 – 20	Beta	31
▪ Severe (CDR 3)	1	0.75 – 1.25	Beta	31
▪ Fatal	6	4 - 8	Beta	31
AR Death (non-vascular)				
▪ ASA	1.0	0.75 – 1.25	Beta	26,55
▪ Rivaroxaban	0.22	0.17 – 0.28	Beta	28

All rivaroxaban event rates from the ROCKET-AF trial reduced by 35%
ASA = acetyl salicylic acid; CDR = clinical dementia rating scale; mRS = modified Rankin scale adapted by the Oxfordshire Community Stroke Project to assess patient functional deficits at hospital discharge.

For rivaroxaban, our literature search did not identify publications in similar patient population and with similar daily dosage regimen. Therefore, the rates of clinical events were obtained from the ROCKET-AF trial [28] (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). Given major differences between the ROCKET-AF trial and our model, mainly in terms of higher dosage regimen (20 mg vs 15 mg), older patient population (median age 73 vs 46) and higher stroke risk (average $CHADS_2$ = 3.5 vs $CHADS_2$ = 0), the event rates were reduced by an arbitrary 35% as an adjustment for those differences, with sensitivity analyses using adjustment rates of ± 25%. The probabilities of transitioning from "NVAF well" to an event were based on rates reported in an economic analysis comparing rivaroxaban to warfarin [29] and using the ROCKET-AF data (Table 1).

The rates of dementia were obtained from Friberg [30] who assessed the incidence of new dementia in patients with AF taking OACs compared to those not on OACs. The probabilities 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) [30]. Transition probabilities, based on Spackman, *et al.* [31], were applied to account for changes in the severity of disease (Table 1).

Utility Values

Utility values were sourced from published studies in similar population [32,33] and applied whenever a patient experienced an event in a given 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 [32]. 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 also obtained from the literature and applied in the sensitivity analyses [25,27,32-36].

Table 2: Utility/ Disutility values

Health State	Utility/ Decrement Base Case	Lower Value (2.50%)	Upper Value (97.50%)	Probability Distribution	References
NVAF	0.81000	0.67819	0.91373	Beta	32,33
SE	- 0.1199	-0.10224	-0.13880	Beta	32,33
IS					
▪ Minor	- 0.1385	- 0.1184	- 0.1600	Beta	32,33
▪ Severe	- 0.2958	- 0.2372	- 0.3554	Beta	25,27
ICH					
▪ Minor	- 0.1385	- 0.1182	- 0.1602	Beta	32,33
▪ Major	- 0.2958	- 0.2372	- 0.3554	Beta	25,27
MI	- 0.1247	-0.10645	-0.14356	Beta	32,33
Major bleed (extracranial)	- 0.1814	-0.15476	-0.20899	Beta	32,33

CRNM bleed	- 0.0582	-0.02429	-0.09211	Beta	25,27,34
Cognitive decline ▪ Mild ▪ Moderate ▪ Severe	 - 0.13 - 0.27 - 0.44	(Base Case -25%) - 0.01 - 0.11 - 0.31	(Base Case + 25%) - 0.29 - 0.51 - 0.56	 Beta Beta Beta	 35,36 35,36 35,36

ASA = acetyl salicylic acid; 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 [37-40] and were based on the Ontario Case Costing Initiative, the Ontario Drug Benefit Formulary and the Canadian Institute for Health Information. The cost of medications was obtained from the "Régie de l'Assurance Maladie du Québec" price list [41] with inclusion of an $8.50 prescription fee and an 8% pharmacist's markup (Table 3). The cost of drugs 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) [42].

Table 3: Cost Inputs

Cost of Event	Adjusted Cost*	Lower/Upper Values	Probability Distribution	Source
SE	$9,610.42	7,208 – 12,013	Gamma	37
IS				
• Fatal	$19,200	14,400 – 24,000	Gamma	38
• Minor	$19,200	14,400 – 24,000	Gamma	38
• Major	$65,055.46	48,791 – 81,319	Gamma	38
• Transient	$4,914.85	3,686 – 6,144	Gamma	38
ICH				
• Minor	$18,944.38	4,736 – 23,680	Gamma	38
• Major	$37,865	28,399 – 47,331	Gamma	Assumption
• Fatal	$18,944.38	4,736 – 23,680	Gamma	38
Major bleed (extracranial)	$5,024.68	3,769 – 6,281	Gamma	38
CRNM bleed	$118.98	89 - 149	Gamma	38
MI fatal	$8,409.94	6,308 – 10,513	Gamma	38
MI non-fatal	$13,019.33	9,764 – 16,274	Gamma	38
Minor CD	$797 (3 months)	598 - 996	Gamma	39
Moderate CD	$1015 (3 months)	761 - 1268	Gamma	39
Severe CD	$16066 (3 months)	12,050 – 20,083	Gamma	39
Long Term Costs (per annum)				
MI	$3,743.34	2,807 – 4,679	Gamma	38
Major stroke	$21,809.09	16,357 – 27,261	Gamma	38
Minor stroke	$9,033.45	2,258 – 11,291	Gamma	38
ICH	$9,033.45	2,258 – 11,291	Gamma	38
SE	$2,256.94	1,693 – 2,821	Gamma	37
Drug Treatment (per 3 months)**				
ASA – 100 mg (generic)	$12.97	11 – 15	Fixed	41
Rivaroxaban 15 mg	$284	241 - 327	Fixed	41

* Cost estimated using 2020 inflation rate
ASA = acetyl salicylic acid; CD = cognitive decline; CRNM Bleed = clinically relevant non major bleed; ICH = intracranial hemorrhages; IS = ischemic stroke; MI = myocardial infarction; SE = systemic embolism.
** Cost of drugs is based on the "Liste des Médicaments - Régie d'Assurance Maladie du Québec", November 2020 with $8.50 prescription fee and 8% mark-up.

Analyses

The incremental cost-effectiveness ratio (ICER) was computed to determine the lifetime costs/QALYs of rivaroxaban 15 mg daily versus ASA 100 mg daily, at a Canadian willingness to pay of $50K (a commonly used threshold value) per added QALY.

Deterministic sensitivity analyses were conducted to examine the uncertainty in the model parameters. This was done by varying the base case value of one parameter at a time by a given amount and examining the impact that this change has on the model's results. The base case value of clinical events and their costs were varied by ± 25%, the cost of treatments by ± 15% and utilities using high and low values (95% CI) except for cognitive decline (base case ± 25%).

Probabilistic sensitivity analysis (PSA), which allows all model parameters to be varied simultaneously, was also conducted to test the robustness of model parameter values and their impact on the ICERs. PSA was conducted using a Monte Carlo simulation. 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. Cost-effectiveness acceptability curves were derived to present the probability that each treatment is optimal at different values of willingness to pay per additional QALY gained.

The analyses were carried out using the TreeAgePro 2020 software® (TreeAge Software, Inc., MA, USA).

Results

Base Case Analysis

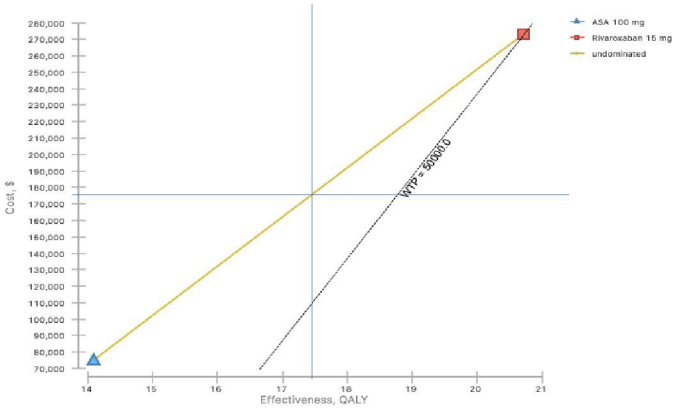
Among a hypothetical cohort of 1000 patients over a lifetime, use of rivaroxaban compared to ASA is predicted to result in 43 fewer first and 59 fewer second event ischemic strokes, 25 fewer systemic embolisms, 161 fewer cognitive declines, 29 fewer vascular deaths and 143 fewer non-vascular deaths. The model projected an additional 46 intracranial hemorrhages and 461 major bleeds with rivaroxaban.

Treatment with rivaroxaban 15 mg was more costly ($273,073) than treatment with ASA 100 mg ($75,086) while being more effective in terms of QALYs (20.7 with rivaroxaban versus 14.1 with ASA). The ICER per QALY gained over a lifetime was $29,900 (Table 4). This ratio is below the commonly accepted willingness-to-pay threshold [43] of $50K per QALY gained, indicating that rivaroxaban is cost-effective for this patient population (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) vs ASA	
ASA 100 mg	$75,086		14.1			Undominated
Rivaroxaban 15 mg	$273,073	$197,987	20.7	6.6	$29,900**	undominated

♦ Canadian dollar
** rivaroxaban cost-effective (ICER below the willingness to pay value of $50K); ASA undominated = less costly and less effective than rivaroxaban; Rivaroxaban undominated = more costly and more effective than ASA.
ASA = acetyl salicylic acid; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years.

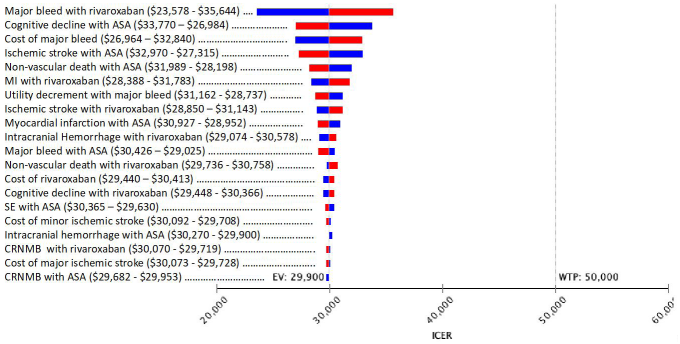


A plot of each strategy on the cost and effectiveness axes. ASA in the left lower quadrant is less effective and less costly; rivaroxaban in the upper right quadrant is more effective and more costly. The willingness-to-pay (WTP) line (in blue) passes through the optimal strategy. The ICER line being to the left of the WTP line indicates that the optimal strategy is cost-effective at a WTP of $50K.
ASA = acetyl salicylic acid; ICER = incremental cost-effectiveness ratio
Figure 2: Cost-Effectiveness Analysis - Base case results

Sensitivity Analyses

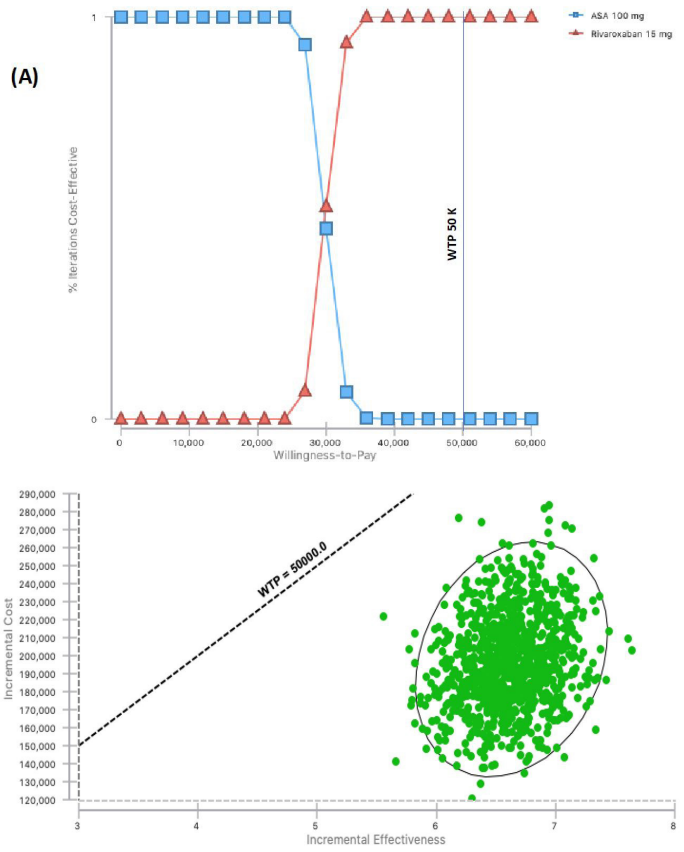
Table A1 in Data Supplement provides the results of the detailed deterministic sensitivity analysis. A tornado diagram (Figure 3) shows the top 20 parameters that had the most impact on the ICER value. Regardless of the variation in costs, utility/disutility values or event rates, the ICERs remained below the WTP threshold of $50K. The lowest ($23,578) and highest ($35,644) values observed were associated with a ± 25% variation in the base case value of major bleed with rivaroxaban.

The ICER also remained below the WTP threshold of $50 K with a time horizon of 10, 20 or 40 years ($29,298, $28,245 and $29,168, respectively) and with discount rates of 0% or 3% ($30,163 and $29,665, respectively). Similarly, varying the cycle length to 1-month or 6-month, despite having considerable impact on the ICER, resulted in values ($15,211 and $47,984, respectively) below the WTP threshold of $50 K.



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 ASA 100 mg. The solid vertical line on the right side represents the willingness-to-pay threshold set at 50 K for the analysis. The horizontal bars indicate the range of the ICER obtained by setting each variable to its lowest and high value while holding all other values constant.
ASA = acetyl salicylic acid; CRNMB = clinically relevant non major bleed; SE = systemic embolism
Figure 3: Results of the deterministic sensitivity analysis

Probabilistic Sensitivity Analysis



(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)** rivaroxaban versus ASA, with the dotted black line presenting the 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 of the WTP line i.e., 100% cost-effective.
ASA = acetyl salicylic acid
Figure 4: Results of the probabilistic sensitivity analyses

Figure 4 shows the results of the probabilistic sensitivity analysis. The cost-effectiveness acceptability curves (CEACs), shown in (A), present the probability that each treatment is optimal (cost-effective) over a range of WTP values. The scatter plot (Figure 4 (B)) illustrates the difference in the total aggregated costs between rivaroxaban and ASA on the y-axis versus the difference in QALYs accrued through a lifetime use of the drugs on the x-axis. The majority of the 10,000 Monte Carlo simulations showed rivaroxaban 15 mg to be more costly while being more effective than ASA 100 mg. At a WTP of $50K per QALY, when varying all the parameters (cost, utility/disutility and events) simultaneously by their defined ranges, rivaroxaban treatment was cost-effective (ICER < $50K per QALY gained) in 100% of the Monte Carlo simulations.

Discussion

The present cost-effectiveness evaluation of a hypothetical cohort of patients with NVAF, vascular disease and low risk of stroke, treated with either rivaroxaban or ASA, showed rivaroxaban to be associated with fewer strokes, systemic embolisms, cognitive declines and vascular and non-vascular deaths over a 60-year lifetime horizon. However, the drug caused additional intracranial hemorrhages and other major bleedings. Over a lifetime horizon, the net benefits in terms of reduction of clinical events with rivaroxaban yielded an incremental QALY of 6.6 at an incremental cost of $197,987 and an ICER below the WTP of $50K, deeming rivaroxaban to be cost-effective vs. ASA. The results were shown to be robust in deterministic and probabilistic sensitivity analyses.

Our study is the first to assess the cost-effectiveness of rivaroxaban 15 mg vs ASA 100 mg for patients with NVAF at low risk of stroke and to include cognitive decline as an adverse event in the model. Due to methodological differences, mainly relative to study design, patient population and drug dosage, it was impossible to place our results within the context of recent studies in this area. Nevertheless, several published economic evaluations have examined the value of DOACs in the treatment of AF patients with moderate to high stroke risk. Some of those studies found dabigatran [37,38,44-47] or apixaban [38,48-52] to be dominant vs. other DOACs or warfarin. A US study by Harrington, *et al.* found all DOACs to be cost-effective vs. warfarin [53], and a Canadian study, by Coyle, *et al.*, showed rivaroxaban and warfarin to be dominated by apixaban and dabigatran 150 mg [38]. Two studies focused on the cost-effectiveness of rivaroxaban vs. warfarin from a US payer/Medicare perspective, in patients with AF at moderate or high risk of stroke. Lee, *et al.* [54] found an ICER for rivaroxaban of $27,498 per QALY and the drug was deemed cost-effective in >80% of the Monte Carlo iterations using a WTP of $50K and $100K. Also, Mensch, *et al.*

[29] found an ICER of €15,207 per QALY and rivaroxaban to be a cost-effective alternative to warfarin from a German Statutory Health Insurance perspective.

There are a number of limitations to the underlying model structure and data. First, the rates of clinical events with rivaroxaban and ASA were drawn from RCTs [26,28] (ROCKET-AF and AVERROES) which used different drug dosages and involved patients with different characteristics, mainly older age and higher risk score. With ASA, this may have potentially led to an overestimation of the incidence of events and costs as well as an underestimation of the QALY. Nevertheless, looking at the impact a ± 25% variation in the rate of events with ASA had on the model, the results of the deterministic sensitivity analysis showed all the ICER values to remain below the WTP threshold. Similarly, with rivaroxaban, the 35% reduction of the ROCKET-AF data as an adjustment for differences in the populations was set arbitrarily and may have induced an underestimation or overestimation of the rates of events. Examining the uncertainty in these inputs, the deterministic sensitivity analyses results showed the model to be insensitive to a variation of ± 25% of the base case values. Second, these RCTs had limited follow-up period, an average of 1.1 years in the AVERROES [26] trial and a median of 1.9 years in ROCKET-AF [28] trial. By assuming a constant rate for most events through extrapolation over a lifetime follow-up period in the present study, the number of events and ICER may have been underestimated. Trials of DOACs in AF with longer follow-up periods would provide information on the long-term harms and benefits of these medication and would contribute to more precise economic evaluations. Third, the event rates inputted in the model may not reflect outcomes outside a RCT setting. Similarly, other data used in the model such as the patient's age, dosage regimen, risk score, costs and the Canadian health-care system perspective make the results not necessarily generalizable to other settings. Finally, 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. These data would be available once the Brain AF trial is completed.

Conclusion

Elevated costs associated with rivaroxaban compared to ASA were offset by an increased life expectancy for patients with NVAF and low risk of stroke. The present analysis demonstrates that treatment with rivaroxaban, when compared to the standard of care, was cost-effective for the prevention of stroke events and cognitive decline over a lifetime perspective. This finding suggests that rivaroxaban offers benefits to treating patients with a low-risk score from a clinical and economic perspective. The results from the BRAIN-AF trial will inform the analysis with observed event rates in this patient population.

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Conflict of Interest

Drs. G. Nakhlé and J. Le Lorier report grants from Montreal Heart Institute for this project. The Montreal Heart Institute received funding from the Health Collaboration Acceleration Fund (FACS) from the Government of Quebec.

Drs. D. Roy, M. Samuel, A. Dubois have nothing to disclose.

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Authorship Statement

All persons who meet authorship criteria are listed as authors and all authors certify that they have approved the version of the manuscript to be published and take responsibility for the content of the manuscript.

Authorship Contributions:

Gisèle Nakhlé: Ideas, formulation of research question, statement of hypothesis, development and design of methodology, creation of models, programming and statistical analysis, data collection, writing the initial draft, finalizing manuscript for publication.

Jean-Claude Tardif, Denis Roy, Léna Rivard, Anick Dubois: Funding acquisition, commentary and revisions.

Michelle Samuel: critical review, commentary and revisions.

Jacques Le Lorier: Ideas, supervising of research, funding acquisition, critical review, commentary and revisions.

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Data Supplement

Table A1 - Results of Deterministic Sensitivity Analyses

Parameter	Rivaroxaban ICER (With Parameter Low Value)	Rivaroxaban ICER (With Parameter High Value)
Base Case ± 15%		
Cost of Rivaroxaban	$29,440	$30,413
Cost of ASA	$29,914	$29,886
Base Case ± 25%		
Cost of major IS	$29,891	$29,909
Cost of minor IS	$30,092	$29,708
Cost of fatal IS	$29,919	$29,882
Cost of major ICH	$29,889	$29,912
Cost of minor ICH	$29,894	$29,907
Cost of fatal ICH	$29,888	$29,913
Cost of SE	$29,935	$29,865
Cost of MI	$29,844	$29,957
Cost of fatal MI	$29,896	$29,904
Cost of major bleed	$26,964	$32,840
Cost of minor bleed	$29,899	$29,902
Cost of minor CD	$29,929	$29,872
Cost of moderate CD	$29,917	$29,883
Cost of severe CD	$30,010	$29,790

Base Case ± (CI)		
Minor IS utility decrement	$29,885	$29,915
Major IS utility decrement	$29,891	$29,909
Minor ICH utility decrement	$29,901	$29,900
Major ICH utility decrement	$29,901	$29,899
SE utility decrement	$29,898	$29,908
MI utility decrement	$29,906	$29,894
Major bleed utility decrement	$31,162	$28,737
CRNMB utility decrement	$29,900	$29,900
Base Case ± 25%		
Minor CD utility decrement	$29,866	$29,935
Moderate CD utility decrement	$29,866	$29,936
Severe CD utility decrement	$29,877	$29,922
Base Case ± 25%		
Rate of IS with Rivaroxaban	$28,850	$31,143
Rate of IS with ASA	$32,970	$27,315
Rate of ICH with Rivaroxaban	$29,074	$30,578
Rate of ICH with ASA	$30,270	$29,900
Rate of SE with rivaroxaban	$29,842	$29,998
Rate of SE with ASA	$30,365	$29,630
Rate of MI with rivaroxaban	$28,388	$31,783
Rate of MI with ASA	$30,927	$28,952
Rate of MB with rivaroxaban	$23,578	$35,644
Rate of MB with ASA	$30,426	$29,025
Rate of CRNMB with rivaroxaban	$30,070	$29,719
Rate of CRNMB with ASA	$29,682	$29,953
Rate of CD with rivaroxaban	$29,448	$30,366
Rate of CD with ASA	$33,770	$26,984
Rate of non-vascular death with rivaroxaban	$29,736	$30,758
Rate of non-vascular death with ASA	$31,989	$28,198
Base case ± (low, high values)		
Discount rate (low = 0, High = 3%)	$30,163	$29,665
Cycle length (1 month, 6 months)	$47,984	$15,211
Time horizon • 10 years • 20 years • 40 years	 $29,298 $28,245 $29,168	

ICER = Incremental cost-effectiveness ratio;
CI = Confidence interval; IS = Ischemic stroke; ICH = Intracranial hemorrhage; SE = Systemic embolism; MI = Myocardial infarction; MB = Other major bleed; CD= Cognitive decline; CRNMB = Clinically relevant non major bleed