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A Decision Analysis of Percutaneous Left Atrial Appendage Occlusion Relative to Novel and Traditional Oral Anticoagulation for Stroke Prevention in Patients with New-Onset Atrial Fibrillation

Andrew Micieli, MMI, Harindra C. Wijeysundera, MD, PhD, Feng Qiu, MSc, Clare L. Atzema, MD, MSc, Sheldon M. Singh, MD

Background. *Percutaneous left atrial appendage occlusion (LAAO) is a nonpharmacologic approach for stroke prevention in nonvalvular atrial fibrillation (NVAF). No direct comparisons to novel oral anticoagulants (OACs) exists, limiting decision making on the optimal strategy for stroke prevention in NVAF patients. Addressing this gap in knowledge is timely given the recent debate by the US Food and Drug Administration regarding the effectiveness of LAAO.* ***Objective.*** *To assess the cost-effectiveness of LAAO and novel OACs relative to warfarin in patients with new-onset NVAF without contraindications to OAC.* ***Design.*** *A cost-utility analysis using a patient-level Markov micro-simulation decision analytic model was undertaken to determine the lifetime costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ICER) of LAAO and all novel OACs relative to warfarin. Effectiveness and utility data were obtained from the published literature and cost from the Ontario Drug Benefits Formulary and Case Costing Initiative.* ***Results.*** *Warfarin had the lowest discounted QALY (5.13 QALYs), followed by dabigatran (5.18 QALYs), rivaroxaban and LAAO (5.21 QALYs), and apixaban (5.25 QALYs). The average discounted lifetime costs were $15 776 for warfarin, $18 280 for rivaroxaban, $19 156 for apixaban, $20 794 for dabigatran, and $21 789 for LAAO. Apixaban dominated dabigatran and LAAO and demonstrated extended dominance over rivaroxaban. The ICER for apixaban relative to warfarin was $28 167/QALY. Apixaban was preferred in 40.2% of simulations at a willingness-to-pay threshold of $50 000/QALY.* ***Limitations.*** *Assumptions regarding clinical and methodological differences between published studies of each therapy were minimized.* ***Conclusions.*** *Apixaban is the most cost-effective therapy for stroke prevention in patients with new-onset NVAF without contraindications to OAC. Uncertainty around this conclusion exists, highlighting the need for further research.* ***Key words:*** *anticoagulants; atrial appendage; atrial fibrillation; bleeding; stroke; prevention.* ***(Med Decis Making XXXX;XX:xx–xx)***

INTRODUCTION

The current clinician's armamentarium for stroke prevention in nonvalvular atrial fibrillation (NVAF) has increased dramatically over the past 4 y with the availability of novel oral anticoagulants (OACs) that have been shown to be equivalent or superior to warfarin for atrial fibrillation (AF) stroke prevention.[1–3] Recently, percutaneous left atrial appendage occlusion (LAAO) has become available, and it has also been shown to be noninferior to warfarin.[4] This procedure is similar to other commonly performed percutaneous cardiovascular catheter-based procedures such as coronary angioplasty and provides a nonpharmacologic approach to AF stroke prevention. This approach is unique as stroke prevention may be achieved without the need for OAC, thus potentially reducing bleeding and also removing the need for drug compliance. Comparisons of all available novel OACs have been performed[5–7]; however, to date, similar studies evaluating these agents and LAAO have not been reported. The absence of this limits informed decision making

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by clinicians, health policy makers, and patients as to the most appropriate stroke prevention strategy in NVAF.

Decision-analytic models may offer insight by providing a framework to balance the benefits and disadvantages of each strategy. Given the acquisition costs of these therapies and potential for rapid uptake in clinical practice,[8] examining whether they improve efficiency is important particularly in the current environment of fiscal restraint. Addressing this gap in knowledge is timely in light of the recent debate by the US Food and Drug Administration Circulatory Systems Devices Panel regarding the effectiveness of LAAO with the Watchman device (Boston Scientific, Natick, MA).[9] Moreover, the 2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of AF suggests that outside of clinical studies, LAAO should be considered only in patients ineligible for OAC.[10] Accordingly, we have developed a decision-analytic decision model evaluating LAAO, all available novel OACs (dabigatran, apixaban, rivaroxaban), and warfarin. As stroke prevention therapies are initiated at the time of AF diagnosis, we evaluated these strategies in a real-world population of patients with new-onset AF in order to provide patients, payers, and practitioners a better appreciation of the merits of each strategy for the entire duration of this chronic disease.

Received 9 November 2014 from the Faculty of Medicine, University of Ottawa, Ontario, Canada (AM); Schulich Heart Centre, Sunnybrook Health Sciences Centre, Faculty of Medicine, University of Toronto, Ontario, Canada (HCW, SMS); Institute of Health Policy, Management and Evaluation, University of Toronto, Ontario, Canada (HCW); Institute for Clinical Evaluative Sciences (ICES), Toronto, Ontario, Canada (HCW, FQ, CLA); and Division of Emergency Medicine, Faculty of Medicine, University of Toronto, Ontario, Canada (CLA). The authors have no relevant conflicts. Financial support for this study was provided in part by a grant from the Heart and Stroke Foundation of Canada (HSF)/University of Toronto Polo Chair in Cardiology Young Investigator Award and the Institute for Clinical Evaluative Sciences, which is funded by an annual grant from the Ontario Ministry of Health and Long-term Care. Dr. Wijeysundera is supported by a Heart & Stroke Foundation (H&SF) of Canada Distinguished Clinical Scientist Award. Dr. Atzema is supported by an H&SF New Investigator Award. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report. Drs. Wijeysundera and Singh had cosupervisory/lead roles. Revision accepted for publication 30 May 2015.

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METHODS

Study Design and Outcomes

Similar to our prior work,[11] a probabilistic cost-utility analysis was performed using a Markov micro-simulation model with 10 000 patient iterations to evaluate: 1) warfarin (international normalized ratio [INR] = 2.0–3.0), 2) dabigatran, 3) rivaroxaban, 4) apixaban, and 5) LAAO. The population of interest was patients living in Ontario, Canada, with new-onset NVAF at risk for stroke without contraindications to OAC. The model was analyzed from the perspective of the Ontario Ministry of Health and Long-term Care, the single payer of health care services in Ontario, Canada. The cycle length was 1 mo with a lifetime horizon. Health outcomes and costs were discounted at 5%/y.[12] As LAAO is currently not funded in Ontario, Canada, the aim of our study was to inform policy makers of the merits of LAAO relative to all available OACs to help with decision making regarding funding for this procedure.

Dabigatran dosing was based on Health Canada's recommendations[13] and rivaroxaban and apixaban based on the ROCKET-AF[2] and ARISTOTLE[3] trials, respectively. LAAO was modeled on the PROTECT-AF study.[4] All model variables and their accompanying references[1-4,14-35] are documented in the supplemental appendix.

Outcomes included quality-adjusted life-years (QALYs), costs (2012 $CDN), and the incremental cost-effectiveness ratio (ICER) calculated as the incremental cost per QALY gained. A strategy that was more expensive and less effective than its comparator was dominated and ruled out. A less expensive strategy with a higher ICER than a more expensive alternative would be less efficient per unit cost and thus designated as being extendedly dominated.

Base Case

The Canadian Institutes for Health Information's National Ambulatory Care Reporting Service database was used to identify all patients with new-onset AF (*International Classification of Disease* [ICD], 10th revision, diagnosis code I48) presenting to emergency departments (and not admitted to hospital) in Ontario between 1 April 2005 and 31 March 2010. This population (n = 35 143; Table 1) was selected

Table 1 Base-Case Characteristics

Characteristic	Value, %
Age	68.9 ± 15.1 y
Female	47.9
Diabetes	22.0
Heart failure	12.7
Hypertension	65.2
Prior stroke	14.4
Prior myocardial infarction	0.17
Bleed history	4.7
Abnormal liver function	0.4
Abnormal renal function	20
Excessive alcohol consumption	0.6
Labile international normalized ratio	26.8
Vascular disease	8.7

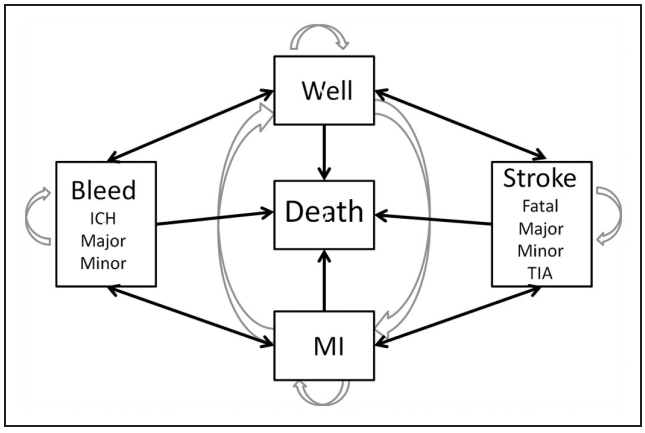

Figure 1 Model structure. For each treatment, patients may be in 1 of 5 states: well, sustain a myocardial infarction (MI), stroke, bleed, or die. Patients may transition between each of these health states with every cycle (1 mo). TIA = transient ischemic attack; ICH = intracranial hemorrhage.

as our base case since prior work has confirmed that the characteristics of patients presenting to the emergency department with new-onset AF are similar to those of patients with new-onset NVAF diagnosed in various outpatient settings.[36] The likelihood of developing comorbidities during the model's time horizon was obtained from the published literature.

Model Structure

A simplified model schematic is presented in Figure 1. With each cycle, patients may remain in their current health state, die, or suffer a clinical event. The stroke and bleed risk was updated with each cycle to reflect new events and changes in the prevalence of risk factors.

Transition Probabilities

Ischemic Stroke Risk and Severity

The monthly probability of an ischemic stroke in untreated patients was determined using the CHA_2DS_2VASc score, and the reduction in stroke risk with each strategy was then applied. As stroke prophylaxis is indicated for a CHA_2DS_2VASc score ≥ 2,[37,38] individuals with a score <2 were treated with aspirin until their score increased to ≥ 2. Stroke severity was based on the Modified Rankin Scale (see the appendix; legend to Supplemental Table S1). We estimated that 8.2% of ischemic strokes were fatal, 40.2% were severe with neurological deficits preventing independent living, 42.5% were minor with no impact on independent living, and 9.1% were transient ischemic attacks.

Bleeding Risk and Severity

Bleeding probabilities on warfarin were calculated using the HAS-BLED score. The odds ratio of bleeding with each strategy relative to warfarin was obtained from their respective clinical trial. Clopidogrel was used in conjunction with aspirin in only 2 situations: 1) between days 45 and 180 after LAAO and 2) for 2 mo post–myocardial infarction (MI). Bleeding with aspirin and clopidogrel in patients sustaining a MI while on warfarin or a novel OAC was modeled on the RE-LY study. The proportion of bleeds classified as intracranial, major, and minor and the risk of death with a bleed was obtained from the published literature.

Probability of MI

The 1-y probability of an MI on anticoagulation was modeled on the RE-LY, ROCKET, and ARISTOTLE trials. LAAO assumed the same MI risk as warfarin[39]; however, a reduction in risk from days 45 to 180 after LAAO was assumed due to the use of aspirin and clopidogrel.

Probability of Death

The probability of death was based on age and gender-specific Ontario life tables and modified in patients suffering an intracranial hemorrhage, bleed, major or minor stroke, or MI. The reduced mortality

associated with novel OACs[1–3] and LAAO[40] was not explicitly modeled as it was presumed to be a manifestation of the improved survival associated with the reduction in clinical events, which was already accounted for in the model.

Medication Discontinuation

Noncompliance was based on the RE-LY, ROCKET, and ARISTOTLE studies. Patients who discontinued anticoagulation would do so within the first 2 y and use aspirin alone.[41] Intracranial hemorrhage resulted in permanent discontinuation of anticoagulation and replacement with aspirin.[42] A major and minor bleed resulted in discontinuation of anticoagulation for 1 mo and 2 d, respectively. For patients receiving warfarin, no adjustment was made for compliance, affecting the time in the therapeutic range, as real-world warfarin control in Ontario, Canada, is similar to the average time in the therapeutic range reported in the pivotal clinical trials used to inform the model.[43–45]

LAAO Procedural Details and Complications

Successful implantation (91%) and complications (pericardial effusion requiring drainage [4.8%], procedure-related stroke [1.1%], device embolization [0.6%]) with LAAO were modeled on the PROTECT-AF trial. Unsuccessful LAAO resulted in lifelong warfarin. Patients with an acutely successful LAAO implantation may develop device-related leaks to an imperfect match between the LAAO device the native LAA. The presence of leaks would mandate longer periods of warfarin.

Quality-of-Life Estimates

Health state utilities were obtained from the literature. When possible, utilities were selected that were derived using a time tradeoff methodology in the general population. However, utilities for an intracranial hemorrhage and a major bleed were acquired using the standard gamble approach in an elderly cohort with AF, because of the paucity of another adequate source (appendix; Supplemental Table S4). The utility decrement for dabigatran was assumed to be the same as ximeligatran. The utility decrements for rivaroxaban and apixaban were assumed to be the same as dabigatran. As no quality-of-life estimates for LAAO exists, we assumed the utility decrement to be similar to coronary angioplasty, a procedure quite similar to LAAO occlusion. Additional utility decrements were applied if procedure-related complications occurred. The impact of time from the incident event was modeled for each health state.

Costs

Costs included direct costs associated with medication, device implantation, hospitalization, and physician reimbursement. Medications costs were obtained from the Ontario Drug Benefit (ODB) Formulary for patients $\geq$65 y. Non-ODB prices without markup or dispensing fees were used for patients <65 y. The monthly cost for physician-monitored warfarin therapy was $36 regardless of age. The monthly cost for aspirin and aspirin plus clopidogrel was $0.93 and $31, respectively, regardless of age. The monthly cost of dabigatran and rivaroxaban was $99.20 and $85.20, respectively, for patients $\geq$65 y and $101.30 and $89.90, respectively, for patients <65 y. Apixaban was $96/mo regardless of age.

The cost of LAAO was estimated based on the cost of an occlusion device ($8500), overnight hospitalization, cardiac catheterization costs, and physician fees including anesthesia administration, performance of a transesophageal echocardiogram at implantation, and during follow-up and for device implantation itself. Given the absence of specific physician fees for LAAO procedures in Ontario, physician fees were estimated by combining the billing codes for transseptal puncture, angiogram, and percutaneous transluminal catheter-assisted closure of an atrial septal defect, a procedure similar to LAAO. Our estimated costs associated with LAAO are consistent with those reported in other jurisdictions.[46,47]

ICD-10 codes were used to identify case costs for each clinical event from the Ontario Case Costing Initiative, a province-wide initiative of cost data for acute inpatient events, complex continuing care, and rehabilitation. This allowed one-time and ongoing monthly costs to be modeled for.

Sensitivity Analysis

A fully probabilistic sensitivity analysis was performed with 10 000 patient simulations (i.e., inner loop trials) and 1000 second-order simulations, thereby incorporating between-individual and parameter uncertainty in our estimates. The final outputs represent the mean values across 10 million simulations. A cost-effectiveness acceptability curve, which reported the proportion of the second-order simulations in which a particular strategy was the most favorable at different willingness-to-pay thresholds, was constructed.

Table 2 Cost and QALY

	Cost, $CDN (*s*)	Incremental Cost, $CDN	QALY (*s*)	Incremental QALY	ICER ($/QALY)
Discounted					
Warfarin	$15 776 (5353)	$0	5.13 (0.17)	Reference	Reference
Rivaroxaban	$18 280 (4721)	$2504	5.21 (0.16)	0.08[a]	$31 300[a]
Apixaban	$19 156 (5016)	$876	5.25 (0.16)	0.04[a]	$21 900[a]
Dabigatran	$20 794 (5789)	$1638	5.18 (0.17)	–0.07[a]	Dominated[a]
LAA occlusion	$21 789 (7408)	$995	5.21 (0.21)	–0.03[a]	Dominated[a]
Warfarin	$15 776 (5353)	$0	5.13 (0.17)	Reference	Reference
Apixaban	$19 156 (5016)	$3380	5.25 (0.16)	0.12[b]	$28 167[b]

Note: $CDN, 2012 Canadian dollars; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.
a. Incremental QALY and ICER compared with the next less expensive therapy.
b. Incremental QALY and ICER for apixaban compared with warfarin.

Beta distributions were used for all probabilities and utilities, normal distributions for the natural logarithms of all odds and hazard ratios, and gamma distributions for all costs. Distributions were estimated using the mean and standard deviations from source documentation. If standard deviations were not available, one-third of the mean was input.

Analyses were performed using TreeAge Pro Suite 2013 (TreeAge Software Inc., Williamstown, MA).

RESULTS

Clinical Events

The average age of the base-case cohort was 68.9 y, and 47.9% were female (Table 1). Based on the baseline distribution of CHA_2DS_2VASc scores, 26.3% of patients had a score <2, 16.3% of patients a score of 2, 19.5% a score of 3, and 38% a score ≥4. Of the patients, 32.2% had a HASBLED score ≥3, indicating a high bleeding risk.

Over a lifetime horizon, major strokes occurred in 12.2% (*s* = 5.7%) of patients on rivaroxaban, 12.8% (*s* = 5.7%) on apixaban, 13.7% (*s* = 6.4%) on warfarin, 15.0% (*s* = 7.1%) on dabigatran, and 15.1% (*s* = 9.4%) with LAAO (Supplemental Appendix Table S5). Major bleeding occurred in 4.4% (*s* = 0.9%) of patients on apixaban, 4.9% (*s* = 1.7%) with LAAO, 5.0% (*s* = 1.1%) on dabigatran, 6.4% (*s* = 1.3%) on rivaroxaban, and 7.6% (*s* = 1.7%) on warfarin.

Treatment Strategies and Discontinuation

Noncompliance resulted in the discontinuation of warfarin in 15.2% (*s* = 0.6%) of patients, dabigatran in 19.7% (*s* = 0.5%), rivaroxaban in 16.3% (*s* = 0.7%), and apixaban in 14.0% (*s* = 0.5%). In patients with LAAO, 11.1% (*s* = 1.5%) and 6.2% (*s* = 0.9) had a residual leak at 6 wk and 6 mo, respectively, with the latter requiring lifelong warfarin therapy.

Life Expectancy, QALY, and Cost

Table 2 summarizes the results of the discounted cost-effectiveness analysis. Warfarin had the lowest discounted quality-adjusted life expectancy of 5.13 QALYs, whereas apixaban the highest at 5.25 QALYs. The average discounted lifetime costs were $15 776 for warfarin, $18 280 for rivaroxaban, $19 156 for apixaban, $20 794 for dabigatran, and $21 789 for LAAO. Dabigatran and LAAO were dominated by apixaban, as both strategies cost more and were less effective. Apixaban demonstrated extended dominance over rivaroxaban as it was less expensive per additional unit of effectiveness. Compared with warfarin, the ICER for apixaban was $27 955.

Sensitivity Analyses

Probabilistic sensitivity analyses demonstrated substantial uncertainty. Apixaban was cost-effective in 40.2% of simulations using a willingness-to-pay threshold of $50 000/QALY and 48.1% of simulations at $100 000/QALY. LAAO was preferred in 31.9% and 36.6% of simulations at these thresholds (Figure 2).

DISCUSSION

We evaluated the cost-effectiveness of all currently available therapies for stroke prevention in patients with new-onset NVAF without contraindications to OAC. Our model suggests that novel pharmacologic and nonpharmacologic therapies are associated

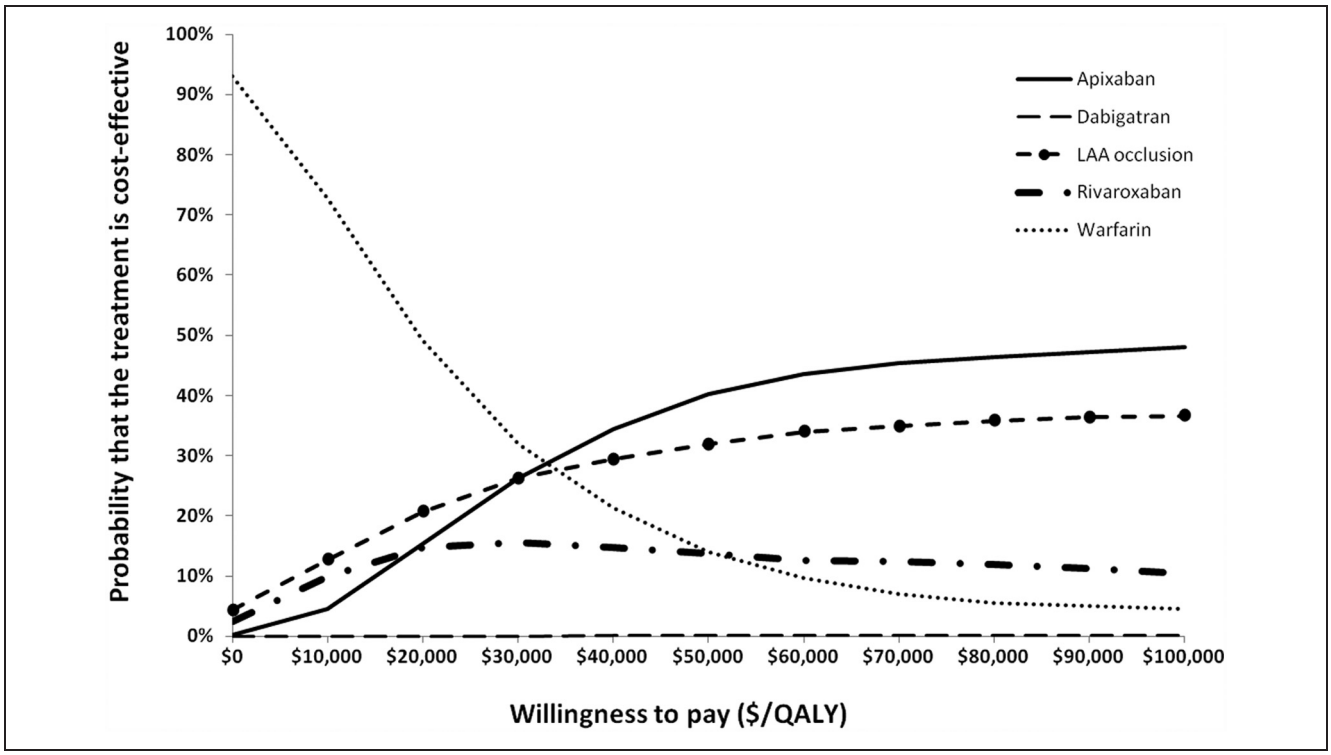

Figure 2 Cost-effectiveness acceptability curve. Probabilistic sensitivity analysis performed with 10 000 Monte Carlo simulations. Willingness to pay in $CDN 2012 per quality-adjusted life-year (QALY). The probability that dabigatran was cost-effective was zero at all willingness-to-pay thresholds.

with improved quality-adjusted survival compared with warfarin but come at an increased cost. The novel OAC apixaban was most cost-effective in our primary analysis.

Apixaban was associated with a lower rate of major bleeding when compared with LAAO. This is not surprising as prior work has demonstrated similar rates of major bleeding with apixaban and aspirin,[48] an agent required lifelong with LAAO after successful short-term use of warfarin (45 d) and combination aspirin and clopidogrel (5.5 mo). Furthermore, LAAO appears to be the least effective therapy for stroke reduction in our model. Thus, the promise of less bleeding and stroke reduction touted with LAAO may not hold when compared with apixaban. We believe our study is important as, in the absence of direct comparisons, it provides an objective assessment of the merits of novel OACs and LAAO in NVAF patients without contraindications to OAC. This is important given the rapid uptake of invasive cardiac therapies in clinical practice frequently prior to publication of robust clinical data.[49]

While previous decision models have evaluated all 3 novel OACs in relation to warfarin,[5–7] our model is unique as no published model evaluating LAAO in addition to all novel OACs exists. Our current analysis used a similar structure to prior decision models[5–7] with the additional enhancement of employing patient characteristics derived from a population with new-onset AF. This enhancement is important and unique. It should be no surprise that larger QALYs and lower long-term costs were noted in the current analysis when compared with prior work,[5–7,11] which is likely related to the younger age and lower prevalence of comorbidities in the base-case population with new-onset AF. Regardless, this population is important to study as it provides insight into the costs and outcomes for the entire duration of this chronic disease, thereby allowing for confident clinical decision making and policy development. Another unique and important strength of our model is the incorporation of the probability of developing stroke risk factors during the model's time horizon. This approach provides a more realistic simulation of real life in which stroke risk increases with time, compared with prior models in which these risk factors are held fixed. The dynamic nature of stroke risk in our model allows

for a better appreciation of the long-term benefits of OACs and LAAO on AF-related stroke.

What is observed consistently in all prior decision models evaluating stroke prevention therapies in NVAF,[5–7] and also demonstrated in our current model, is the uncertainty associated with the primary conclusion. This uncertainty is best demonstrated in the results of probabilistic sensitivity analyses. By varying each model's input parameters within their 95% confidence intervals, it was apparent that the primary conclusions for each study holds less than 50% of the time; that is, in approximately 50% of simulations in our model, apixaban may indeed not be preferred. Although the ICER is a single important value that is often used to drive health policy and reimbursement decisions, clinicians and policy makers must be made aware of the uncertainty surrounding this value as the clinical and financial consequences of incorrect decision making simply based on this single value may not be trivial, especially when magnified on a population level.[50] Real-world clinical experience with clinical events and complications is necessary to help refine input parameters for future models to reduce this uncertainty. However, given the worldwide increase in NVAF[51] and opportunity cost of decision making in the absence of perfect information,[50] we advise direct, preferably randomized, study of LAAO and novel OACs to better define the merits of LAAO relative to novel OACs in patients with NAVF without contraindications to OAC.

Limitations of our work merit discussion. First, our model relied on direct comparisons of pivotal studies comparing novel therapies to warfarin. This approach requires assumptions minimizing clinical and methodological differences between these trials. While indirect comparisons using a network meta-analysis may provide an alternate approach, prior work has suggested the absence of qualitative differences when direct and indirect methods were used to compare novel OACs for AF stroke prevention.[52] Second, our approach assumes that the results observed during the limited trial follow-up period remains constant for the duration of the lifetime horizon of the model. Third, no adjustment for time in therapeutic range, a factor demonstrated to impact clinical outcomes[53] and cost-effectiveness,[54] was made in our model. While this may not affect our results in Ontario, Canada, where real-world time in the therapeutic range is similar to the average time in the therapeutic range from the pivotal trials used to inform our model,[43–45] it may affect the applicability of our findings to regions with extremes of time in therapeutic range. Fourth, using the available real-world cost data did not allow us to allocate varying costs to the varying severity of stroke syndromes (that is minor versus major stroke). The impact of this is mitigated by the fact that the proportion of strokes and their attributed costs were applied equally across all treatment groups. Fifth, both improvements in LAAO device implantation and the fact that our model was extrapolated from clinical trials in which medication compliance is traditionally superior to real life may contribute to an underestimation of the real-world cost-effectiveness of LAAO. Finally, additional uncertainty may be present in our model owing to the fact that utility values were obtained from studies in the 1990s.

CONCLUSION

Our work suggests that apixaban is the preferred long-term strategy for NVAF stroke prevention in patients with new-onset NVAF without contraindications to OAC and is more economically attractive that LAAO. The observed uncertainty in our findings coupled with the global increase in NVAF mandate direct head-to-head comparisons to appreciate advantages associated with each strategy for stroke prevention in NVAF.

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