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ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Left Atrial Appendage Closure Device With Delivery System: A Health Technology Assessment

KEY MESSAGES

Atrial fibrillation is a common heart disease involving electrical disturbances in the atria (the top two chambers) of the heart, which can reduce the heart's ability to pump blood efficiently. Nonvalvular atrial fibrillation (atrial fibrillation that does not involve the heart valves) is the most common form of atrial fibrillation and can lead to stroke. To prevent stroke, people with nonvalvular atrial fibrillation often take oral anticoagulants (medications that prevent the blood from clotting) daily for life. However, on occasion, patients may be unable to take these medications owing to side effects. A new device, the left atrial appendage closure device with delivery system (LAAC device), may be able to prevent stroke in people with nonvalvular atrial fibrillation without the need for lifelong treatment with oral anticoagulants.

In this health technology assessment, we compared the effectiveness and cost-effectiveness of the LAAC device versus novel oral anticoagulants and oral antiplatelet medications in patients with nonvalvular atrial fibrillation.

We found moderate-quality evidence suggesting that the LAAC device and novel oral anticoagulants are similarly effective in preventing stroke. To date, no randomized controlled evidence is available regarding the effectiveness of the device in people with nonvalvular atrial fibrillation with contraindications to oral anticoagulants. However, some evidence suggests that the device may be effective in this patient population; if so, our results indicate that the device would be cost-effective in this patient population. People with nonvalvular atrial fibrillation with whom we spoke reported positive support for the LAAC device and reported valuing having access to the LAAC device if it were shown to be safe, effective, and recommended by their health care providers.

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ABSTRACT

Background

Atrial fibrillation is a common cardiac arrhythmia, and 15% to 20% of those who have experienced stroke have atrial fibrillation. Treatment options to prevent stroke in people with atrial fibrillation include pharmacological agents such as novel oral anticoagulants or nonpharmacological devices such as the left atrial appendage closure device with delivery system (LAAC device). The objectives of this health technology assessment were to assess the clinical effectiveness and cost-effectiveness of the LAAC device versus novel oral anticoagulants in patients without contraindications to oral anticoagulants and versus antiplatelet agents in patients with contraindications to oral anticoagulants.

Methods

We performed a systematic review and network meta-analysis. We also conducted an economic literature review, economic evaluation, and budget impact analysis to assess the cost-effectiveness and budget impact of the LAAC device compared with novel oral anticoagulants and oral antiplatelet agents (e.g., aspirin). We also spoke with patients to better understand their preferences, perspectives, and values.

Results

Seven randomized controlled studies met the inclusion criteria for indirect comparison. Five studies assessed the effectiveness of novel oral anticoagulants versus warfarin, and two studies compared the LAAC device with warfarin. No studies were identified that compared the LAAC device with aspirin in patients in whom oral anticoagulants were contraindicated. Using the random effects model, we found that the LAAC device was comparable to novel oral anticoagulants in reducing stroke (odds ratio [OR] 0.85; credible interval [Cr.I] 0.63–1.05). Similarly, the reduction in the risk of all-cause mortality was comparable between the LAAC device and novel oral anticoagulants (OR 0.71; Cr.I 0.49–1.22). The LAAC device was found to be superior to novel oral anticoagulants in preventing hemorrhagic stroke (OR 0.45; Cr.I 0.29–0.79), whereas novel oral anticoagulants were found to be superior to the LAAC device in preventing ischemic stroke (OR 0.67; Cr.I 0.24–1.64). The body of clinical evidence was found to be of moderate quality as assed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. Results from the economic evaluation indicate that the LAAC device is cost-effective compared with aspirin in patients with contraindications to oral anticoagulants. In patients without contraindications to oral anticoagulants, we found that the LAAC device is not cost-effective compared with novel oral anticoagulants. Publicly funding the LAAC device in patients with nonvalvular atrial fibrillation with contraindications to oral anticoagulants could result in additional funding of $1.1 million to $7.7 million over the first five years. Patients interviewed reported on the impact of living with nonvalvular atrial fibrillation and were supportive of the LAAC device as a treatment option.

Conclusions

Moderate-quality evidence suggests that the LAAC device is as effective as novel oral anticoagulants in preventing stroke in people with nonvalvular atrial fibrillation. However, our results indicate that the LAAC device is cost-effective only in patients with contraindications to oral anticoagulants. People with nonvalvular atrial fibrillation with whom we spoke reported positive support for the LAAC device.

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BACKGROUND

Health Condition

Heart disease and stroke are two of the most common medical conditions that lead to disability in Canada.[1] An estimated 1.3 million Canadians are living with heart disease, and more than 400,000 Canadians are living with long-term stroke disability.[1] In Ontario, stroke is the third-leading cause of death and the leading cause of disability in adults. Every year in Ontario, there are an estimated 25,500 new stroke events, with 15,500 hospital inpatient admissions. More than 5,500 (22%) of Ontarians die within one year of their stroke. Further, one in five residents in long-term care has had a stroke.[2]

The rate of stroke in people with atrial fibrillation is three to five times higher than in those without atrial fibrillation, and about 15% to 20% of those who have experienced stroke have nonvalvular atrial fibrillation.[3]

Nonvalvular atrial fibrillation (atrial fibrillation that does not involve the heart valves) is the most common cardiac arrhythmia (irregular heart rhythm), with about 350,000 Canadians living with the condition.[1,4] In nonvalvular atrial fibrillation, irregular electrical impulses sometimes prevent the left atrial appendage, a small sac in the muscle wall of the left atrium, from contracting effectively to push blood into the heart's ventricles.[4] In people with nonvalvular atrial fibrillation who experience stroke, the thrombi (blood clots) causing stroke arise from the left atrial appendage in 90% of cases.[3]

The incidence of nonvalvular atrial fibrillation increases with age and with other risk factors such as diabetes, hypertension, and other heart diseases.

Most people with nonvalvular atrial fibrillation are advised to take oral anticoagulants (medications that increase the time it takes for blood to clot) for life to prevent systemic embolization (obstruction in the blood vessels of the systemic circulatory system) and stroke.[5] The oral anticoagulant warfarin is a common medication for nonvalvular atrial fibrillation. However, novel oral anticoagulants, such as apixaban, dabigatran, edoxaban, and rivaroxaban, are increasingly being used, as regular blood testing to measure coagulation, typically required for warfarin, is not required with novel oral anticoagulants.[5] Nonetheless, many patients avoid treatment with oral anticoagulants altogether because of adverse effects and drug interactions.

One minimally invasive alternative to treatment with oral anticoagulants for patients with nonvalvular atrial fibrillation is the left atrial appendage closure (occlusion) device with delivery system (LAAC device). This device is increasingly being used in patients with nonvalvular atrial fibrillation to mitigate complications from oral anticoagulants.[6] The LAAC device closes the left atrial appendage, which reduces the risk of thrombus formation. This technology may reduce the risk of stroke while also decreasing the bleeding risk associated with oral anticoagulants, as well as the need for medication compliance. Current guidelines give the LAAC device a Class IIb recommendation for patients with nonvalvular atrial fibrillation.[7] A Class IIb recommendation means that (1) the benefit of the procedure or treatment is equal to or greater than its associated risk; (2) additional studies with broad objectives are needed; (3) additional registry data would be helpful; and, therefore, (4) the procedure or treatment may be considered.

Clinical Need and Target Population

Patients with nonvalvular atrial fibrillation are at high risk for stroke and are therefore often placed on long-term daily oral anticoagulant therapy to prevent stroke. Common oral anticoagulants include warfarin, as well as a class of newer medications called novel oral anticoagulants, which includes apixaban, dabigatran, edoxaban, and rivaroxaban. Studies have suggested that novel oral anticoagulants may be more effective at reducing the risk of stroke and systemic embolism than warfarin. However, many patients have contraindications to life-long oral anticoagulant treatment, and others, who are deemed suitable candidates for oral anticoagulants, may have an appropriate rationale to seek a nonpharmacologic alternative, such as the LAAC device. An appropriate rationale for treatment with the LAAC device may be physician assessment for eligibility and/or patient preference. However, no direct comparison of the effectiveness of the LAAC device versus novel oral anticoagulants yet exists, which limits decision-making on the optimal strategy for stroke prevention in patients with nonvalvular atrial fibrillation. The decision to implant the LAAC device is typically made on a case-by-case basis, after careful consideration of the safety and effectiveness of the device compared with oral anticoagulants for an individual patient.[8]

Technology

The LAAC device has been approved by Health Canada as an implant-based option for patients with nonvalvular atrial fibrillation. A transesophageal echocardiogram or intracardiac echocardiogram is performed before the implantation procedure to determine the appropriate size for the implanted device. The procedure is usually performed under general anesthesia in a catheterization laboratory in a hospital. The device is delivered through a catheter and permanently implanted at the opening of the left atrial appendage, which has been found to be the source of thrombus formation in 90% of patients with nonvalvular atrial fibrillation who have experienced stroke.[3] The procedure takes about one hour to complete, and patients typically remain in hospital for 24 hours following the procedure. By closing the left atrial appendage, the risk of thromboembolism is thought to be reduced. Following the procedure, patients continue to take oral anticoagulants for up to 12 weeks.

Regulatory Information

The LAAC device was approved by the Food and Drug Administration in the United States in March 2015[9] and by Health Canada in January 2016.[10] The device is licensed in Canada as a Class IV medical device. (In Canada, medical devices are categorized into four classes based on the level of risk associated with their use. Class I devices present the lowest potential risk [e.g., thermometers], and Class IV devices present the greatest potential risk [e.g., pacemakers].)[11]

Context

According to the health technology assessment application made to Health Quality Ontario, as well as clinical experts with whom we spoke, the LAAC device is currently being implanted in several hospitals in Ontario. However, clinical experts state that the LAAC device is not currently the standard of care for patients with nonvalvular atrial fibrillation, and there is currently no dedicated funding for the device.

Research Questions

- What is the clinical effectiveness of the LAAC device compared with novel oral anticoagulants in the management of patients with nonvalvular atrial fibrillation?
- What is the clinical effectiveness of the LAAC device compared with antiplatelet agents (e.g., aspirin) in the management of patients with nonvalvular atrial fibrillation contraindicated for oral anticoagulation?
- What is the cost-effectiveness of the LAAC device compared with novel oral anticoagulants in the management of patients with nonvalvular atrial fibrillation?
- What is the cost-effectiveness of the LAAC device compared with antiplatelet agents (e.g., aspirin) in the management of patients with nonvalvular atrial fibrillation contraindicated for oral anticoagulation?
- What is the five-year budget impact of the LAAC device from the perspective of the Ontario Ministry of Health and Long-Term Care?

CLINICAL EVIDENCE REVIEW

Objective

The objective of this study was to assess the effectiveness of the left atrial appendage closure device with delivery system (LAAC device) compared with novel oral anticoagulants in patients with nonvalvular atrial fibrillation within the context of the Ontario Ministry of Health and Long-Term Care.

Methods

Research questions are developed by Health Quality Ontario in consultation with experts, end users, and/or applicants in the topic area.

Literature Search

We performed a literature search on June 24, 2016, using Ovid MEDLINE; Embase; Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects (DARE); Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database; Health Technology Assessment; National Health Service (NHS) Economic Evaluation Database; Epub Ahead of Print, In-Process and Other Non-Indexed Citations; Ovid MEDLINE(R) Daily; and Ovid MEDLINE(R), for studies published until June 24, 2016.

Search strategies were developed by medical librarians using medical subject headings (MeSH). Methodological filters were used to limit retrieval to systematic reviews, meta-analyses, health technology assessments (HTAs), and randomized controlled trials. The final search strategy was peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) Checklist.[12] Database auto-alerts were created in MEDLINE and Embase and monitored for the duration of the HTA review. See Appendix 1 for full details, including all search terms.

Literature Screening

A single reviewer reviewed the abstracts and, for those studies meeting the eligibility criteria, we obtained full-text articles. We also examined reference lists for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- Studies published until June 24, 2016 (updated through to November 1, 2016)
- Randomized controlled trials
- Studies comparing novel oral anticoagulants and/or the LAAC device with warfarin
- Studies including participants with nonvalvular atrial fibrillation

Exclusion Criteria

- Animal and in vitro studies
- Editorials, case reports, or commentaries
- Studies with inadequate, incomplete, or duplicated data

Outcomes of Interest

- Primary outcome of interest: major stroke
- Secondary outcomes of interest: all-cause mortality, ischemic stroke, hemorrhagic stroke

Data Extraction

We extracted relevant data on study characteristics; risk-of-bias items; and population, intervention, comparator, outcome, and time (PICOT) criteria using Microsoft Excel. We collected information about the following:

- Source (i.e., citation information, contact details, study type)
- Methods (i.e., study design, study duration, years studies were published, participant allocation, allocation sequence concealment, blinding, reporting of missing data, reporting of outcomes, and whether or not the study compared two or more groups)
- Outcomes (i.e., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of measurement, upper and lower scale limits, and time points at which outcomes were assessed)

Statistical Analysis

Given that we identified no studies directly comparing the LAAC device with novel oral anticoagulants, we chose to perform an indirect assessment via a network meta-analysis, using warfarin as a common comparator. We report dichotomous variables as percentages and continuous variables as means (with standard deviation) or medians (with interquartile range). Our network meta-analysis is based on a mixed-treatment comparison model generation using the NetMetaXL software (a Microsoft Excel tool for WinBUGS, version 1.6.1). We also created a Bayesian hierarchical random-effects model using the Markov chain Monte Carlo method. We present our data as odds ratios with 95% credible intervals. In studies with zero events, NetMetaXL used the adjusted continuity factor, accounting for differences in sample size and centred on 0.5. We generated a network diagram to show the size of the different trials and the weight that size contributed to the estimate. We considered a *P* value less than .05 to be statistically significant.

Quality of Evidence

We examined the quality of the body of evidence for each outcome according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria for network meta-analysis.[13] We determined the overall quality to be high, moderate, low, or very low using a step-wise, structural methodology.

Expert Consultation

We sought expert consultation on stroke prevention treatments in patients with nonvalvular atrial fibrillation, including the LAAC device, between April and June 2016. Experts consulted included physicians in the specialty areas of cardiology and internal medicine. The role of the expert advisors was to contextualize the evidence, provide research guidelines, and provide advice on the use of the LAAC device in patients with nonvalvular atrial fibrillation. However, the

statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Literature Search

The database search yielded 2,914 citations published from inception to November 1, 2016. After removing duplicates, we reviewed 1,840 titles and abstracts to identify potentially relevant articles and obtained the full texts of relevant articles for further assessment. Seven randomized controlled trials met the inclusion criteria: two compared the LAAC device with warfarin, and five compared novel oral anticoagulants with warfarin. We hand-searched the reference lists of the included studies, along with health technology assessment websites and other sources, to identify additional relevant studies. Existing guidelines for use of the LAAC device are reported in Appendix 2 of this report.

Figure 1 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for the clinical evidence review. A summary of the baseline characteristics of the studies and their populations is presented in Table 1.

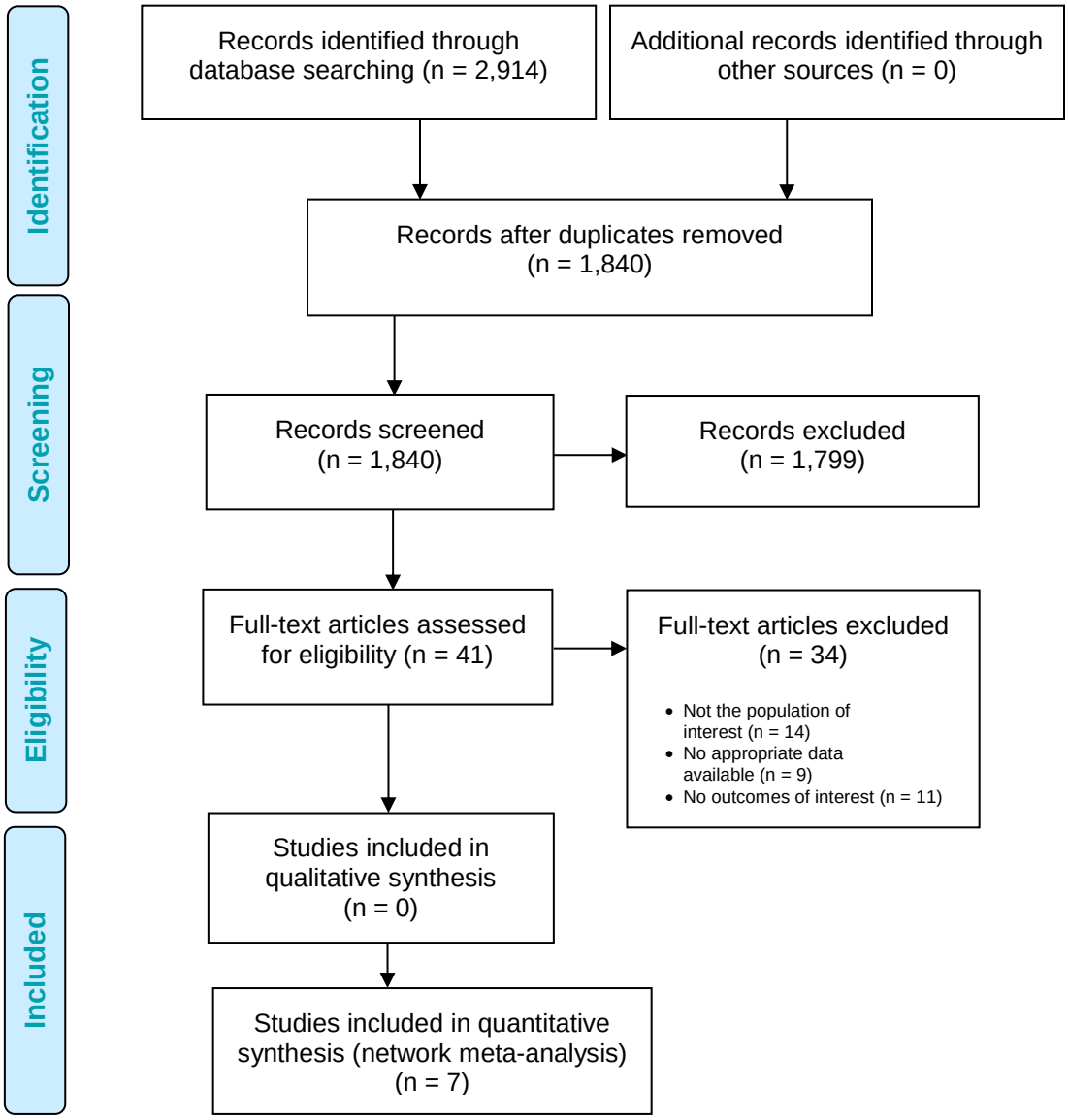

Figure 1: PRISMA Flow Diagram—Clinical Evidence Review

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al.[14]

Table 1: Study and Baseline Population Characteristics of Included Studies

Study, Year[a]	Intervention, Dosage (n)	Comparator, INR (n)	Follow-Up (years)	Patient Inclusion	Total no. of patients	Age (years)[b]	Male (%)	CHADS Score (mean)	Prior MI (%)
RE-LY, 2009[15]	Dabigatran, 110 mg bid (n = 6,015) Dabigatran, 150 mg bid (n = 6,076)	Warfarin, INR 2–3 (n = 6,022)	2	12/2005–3/2009	18,113	71.5 ± 8.5	63.5	2.1, 2.2	17
ARISTOTLE, 2011[16]	Apixaban, 2.5 mg bid (n = 9,120)	Warfarin, INR 2–3 (n = 9,081)	1.8	12/2006–4/2010	18,201	70	65	2.1 ± 1.1	14
ROCKET AF, 2011[17]	Apixaban, 5 mg bid (n = 9,120)	Warfarin, INR 2–3 (n = 7,090)	1.9	12/2006–5/2010	14,264	(63–76)	60	3.5 ± 1	17
J ROCKET AF, 2012[18]	Rivaroxaban, 20 mg (n = 7,081)	Warfarin, INR 2–3 in patients < 70 years, INR 1.6–2.6 in patients ≥ 70 years (n = 640)		6/2007–1/2010	1,278	73	80.6	3.25	8
ENGAGE AF, 2013[19]	Rivaroxaban, 15 mg (n = 640)	Warfarin, INR 2–3 (n = 7,036)	2.8	8/2008–11/2010	21,105	(65–78)	62	2.8 ± 1	–
PREVAIL, 2014[20]	Edoxaban, 30 mg (n = 7,034)	Warfarin, INR 2–3 (n = 138)	2.1	8/2010–1/2013	407	71.1	70	2.6 ± 1	–
PROTECT AF, 2014[21]	Edoxaban, 60 mg (n = 7,035)	Warfarin, INR 2–3 (n = 244)	4	2/2005–3/2009	707	72	70	2.2	–

Abbreviations: INR, international normalized ratio; FU, follow-up; CHADS, Congestive heart failure, Hypertension, Age, Diabetes, Stroke; MI, myocardial Infarction

[a]All studies were double-blinded randomized controlled trials except for PREVAIL and PROTECT AF, which were randomized but not double-blinded.

[b]Age is expressed as mean ± standard deviation or mean (interquartile range).

Methodological Quality of the Included Studies

Seven studies were deemed directly applicable to the primary research question. We assessed the methodological quality of these studies and found that two had an unclear risk of performance bias owing to not blinding participants. Our risk-of-bias assessment for the included studies is summarized in Table 2.

Methodological Quality of the Indirect Assessment

Seven studies were deemed applicable to the primary research question (regarding the clinical effectiveness of the LAAC device compared with novel oral anticoagulants in the management of patients with nonvalvular atrial fibrillation). Since there are currently no studies directly comparing the LAAC device with novel oral anticoagulants, we downgraded the quality of the evidence presented in the included studies based on indirectness. Table 3 presents the GRADE quality-of-evidence profile for the primary outcome of stroke.

Risk-of-Bias Assessment

Table 2: Risk-of-Bias Assessment for the Effectiveness of the LAAC Device Versus Novel Oral Anticoagulants With Warfarin as a Common Comparator

Study, Year[a]	Selection Bias[b]	Performance Bias[c]				Detection Bias[d]	Attrition Bias[e]	Reporting Bias[f]	Sum Bias
		Stroke	Mortality	Hem. Stroke	Isch. Stroke				
RELY, 2009[15]	Low	Low	Low	Low	Low	Low	Low	Low	Low
ARISTOTLE, 2011[16]	Low	Low	Low	Low	Low	Low	Unclear	Low	Low
ROCKET AF, 2011[17]	Low	Low	Low	Low	Low	Low	Low	Low	Low
J ROCKET AF, 2012[18]	Low	Low	Low	Low	Low	Low	Low	Low	Low
ENGAGE AF, 2013[19]	Low	Low	Low	Low	Low	Low	Low	Low	Low
PREVAIL, 2014[20]	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
PROTECT AF, 2014[21]	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear

[a]All studies were double-blinded randomized controlled trials except for PREVAIL and PROTECT AF, which were randomized but not double-blinded.
[b]Selection bias refers to bias with regard to random sequence generation and allocation concealment.
[c]Performance bias refers bias with regard to the blinding of participants and study personnel.
[d]Detection bias refers to bias with regard to the blinding of outcome assessment.
[e]Attrition bias refers to incomplete outcome data.
[f]Reporting bias refers to selective reporting.

Table 3: GRADE Quality-of-Evidence Profile for the Primary Outcome of Stroke

Comparison	Direct Evidence		Indirect Evidence		Network Meta-analysis	
LAAC Device vs. NOACs	OR (95% Cr.I)	Quality of Evidence	OR (95% Cr.I)	Quality of Evidence	OR (95% Cr.I)	Quality of Evidence
All stroke	Not available	Not applicable	0.85 (0.63–1.05)	⨁⨁⨁◯ Moderate[a]	Same as indirect evidence	Same as indirect evidence
All-cause mortality	Not available	Not applicable	0.71 (0.49–1.22)	⨁⨁⨁◯ Moderate	Same as indirect evidence	Same as indirect evidence
Hemorrhagic stroke	Not available	Not applicable	0.45 (0.29–0.79)	⨁⨁⨁◯ Moderate	Same as indirect evidence	Same as indirect evidence
Ischemic stroke	Not available	Not applicable	0.67 (0.24–1.64)	⨁⨁⨁◯ Moderate	Same as indirect evidence	Same as indirect evidence

Abbreviations: Cr.I, credible interval; LAAC device, left atrial appendage closure device with delivery system; NOAC, novel oral anticoagulant; OR, odds ratio.
[a]Downgraded for indirectness.

Study Results

We identified two studies that compared the LAAC device with warfarin and five studies that compared novel oral anticoagulants with warfarin (Figure 2). We conducted a network meta-analysis using a random effects model. We found that the probability of stroke reduction was comparable between patients with an LAAC device and patients taking novel oral anticoagulants (OR 0.85; Cr.I 0.63–1.05) (Figure 3). Similarly, the reduction in risk of all-cause mortality was similar between the two comparison groups (OR 0.71; Cr.I 0.49–1.22) (Figure 4). We found the LAAC device to be superior to novel oral anticoagulants in terms of hemorrhagic stroke prevention (OR 0.45; Cr.I 0.29–0.79) (Figure 5). For the outcome of ischemic stroke, we found novel oral anticoagulants to be superior to the LAAC device (OR 0.67; Cr.I 0.24–1.64) (Figure 6).

We were unable to identify any randomized controlled trials to answer our secondary research question (regarding the clinical effectiveness of the LAAC device compared with antiplatelet agents [e.g., aspirin] in the management of patients with nonvalvular atrial fibrillation contraindicated for oral anticoagulation). However, we did identify one observational study addressing this question: the ASAP registry study, the results of which were published in 2013.[22] ASAP was a multicentre prospective nonrandomized study of the LAAC device in 150 patients with nonvalvular atrial fibrillation who were ineligible for oral anticoagulation. All-cause stroke or systemic embolism occurred in four patients (2.3% per year, which represents 77% fewer events than expected), ischemic stroke occurred in three patients (1.7% per year), and hemorrhagic stroke occurred in one patient (0.6% per year). The authors of this study concluded that the LAAC device can be safely implanted without a warfarin transition and is a reasonable alternative to consider for patients at high risk for stroke but with contraindications to systemic oral anticoagulation.

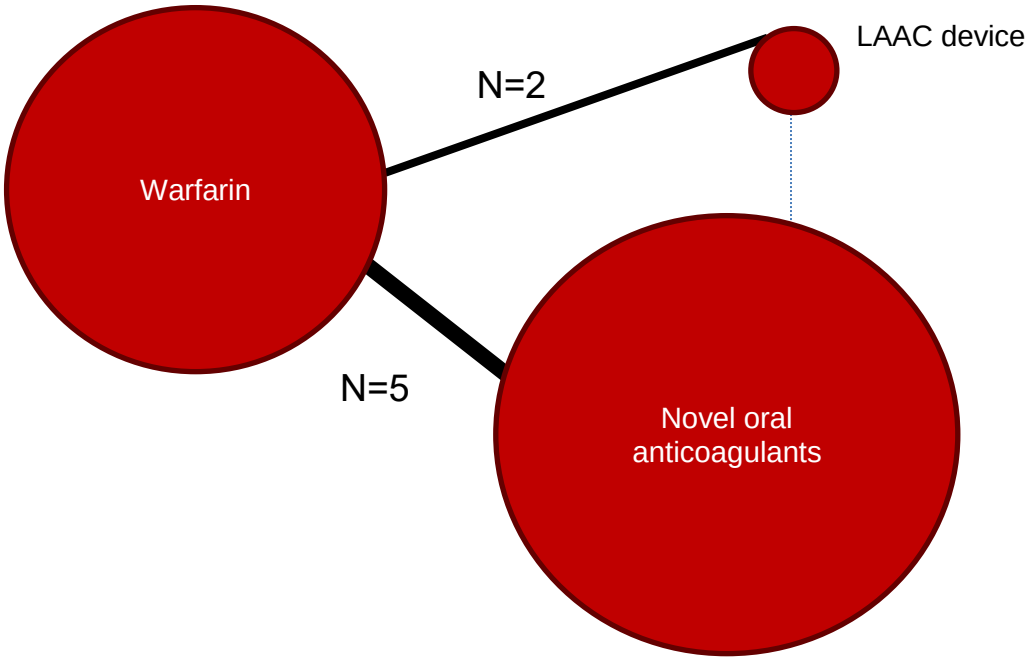

Figure 2: Network Graph—Number of Studies Involved in Indirect Comparisons

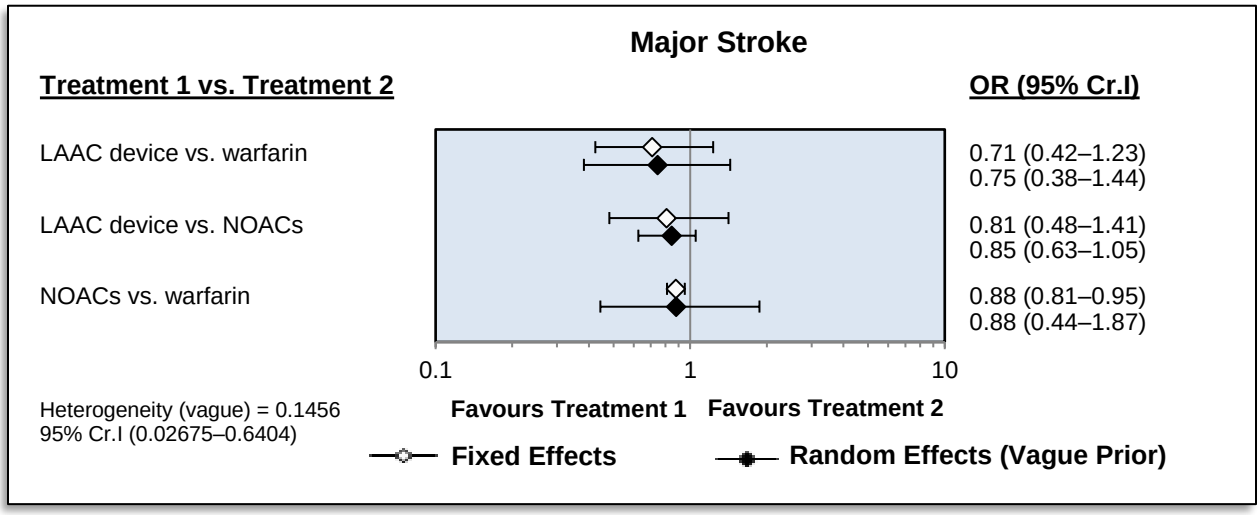

Figure 3: Forest Plot—Pooled Comparison of the LAAC Device, Novel Oral Anticoagulants, and Warfarin for the Primary Outcome of Stroke

Abbreviations: Cr.I, credible interval; LAAC device, left atrial appendage closure device with delivery system; NOAC, novel oral anticoagulant; OR, odds ratio.

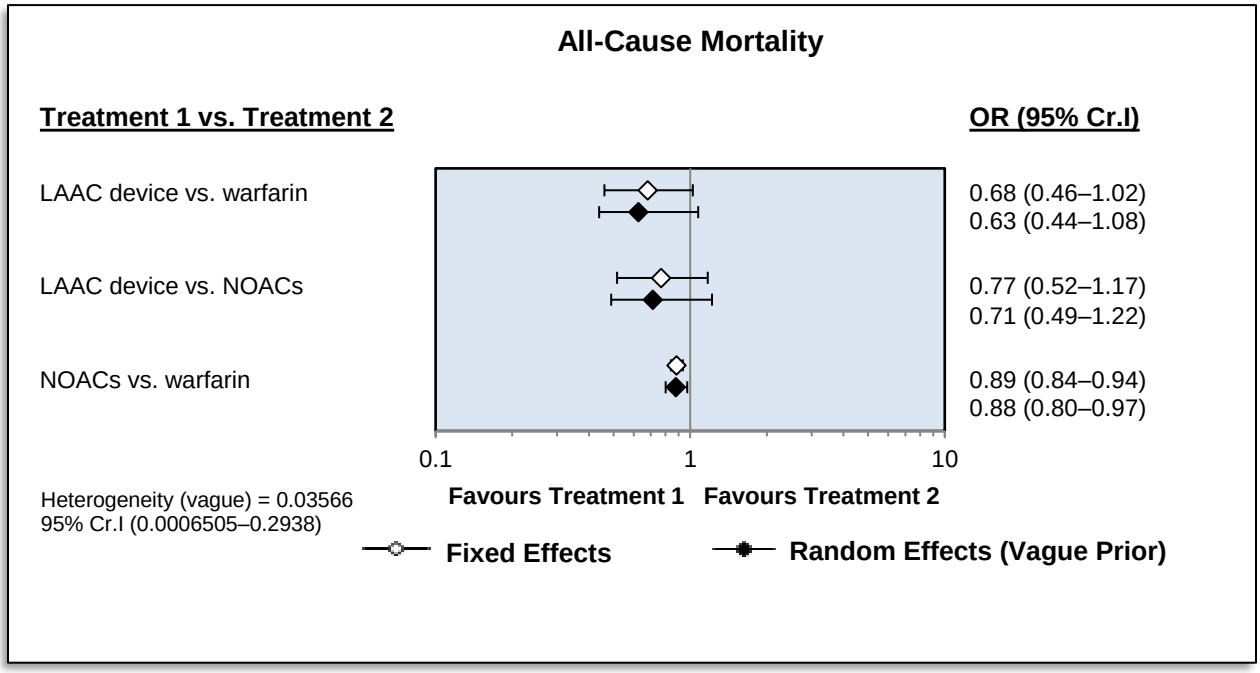

Figure 4: Forest Plot—Pooled Comparison of the LAAC Device, Novel Oral Anticoagulants, and Warfarin for the Outcome of All-Cause Mortality

Abbreviations: Cr.I, credible interval; LAAC device, left atrial appendage closure device with delivery system; NOAC, novel oral anticoagulant; OR, odds ratio.

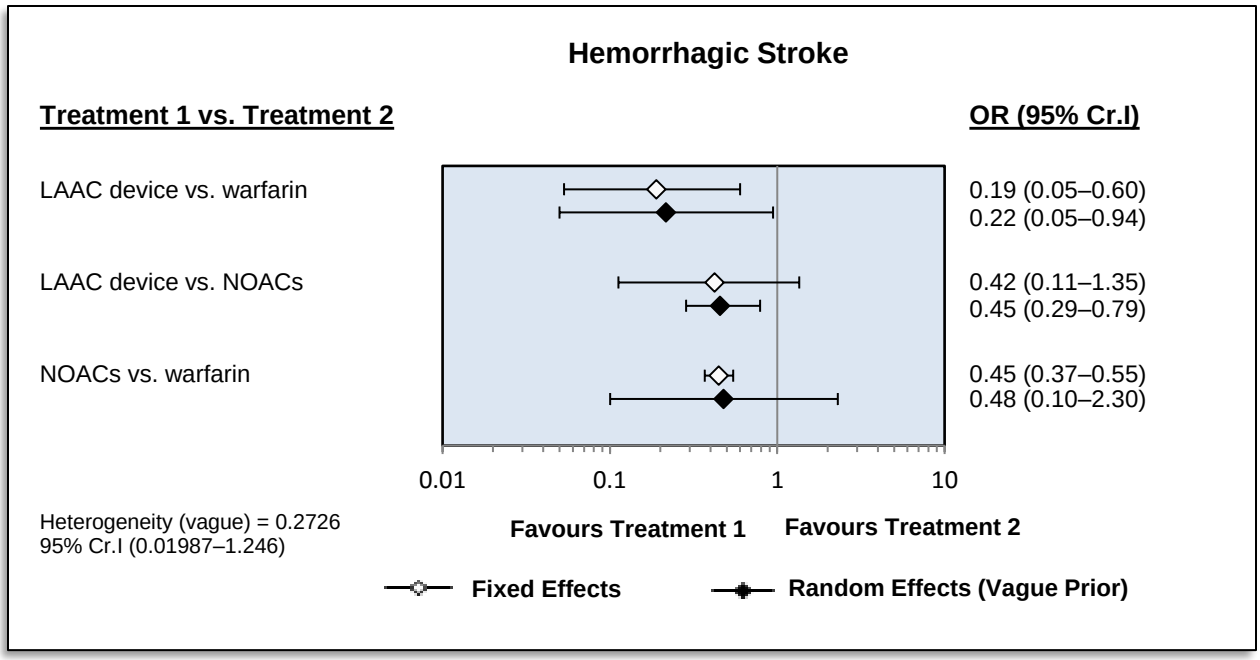

Figure 5: Forest Plot—Pooled Comparison of the LAAC Device, Novel Oral Anticoagulants, and Warfarin for the Outcome of Hemorrhagic Stroke

Abbreviations: Cr.I, credible interval; LAAC device, left atrial appendage closure device with delivery system; NOAC, novel oral anticoagulant; OR, odds ratio.

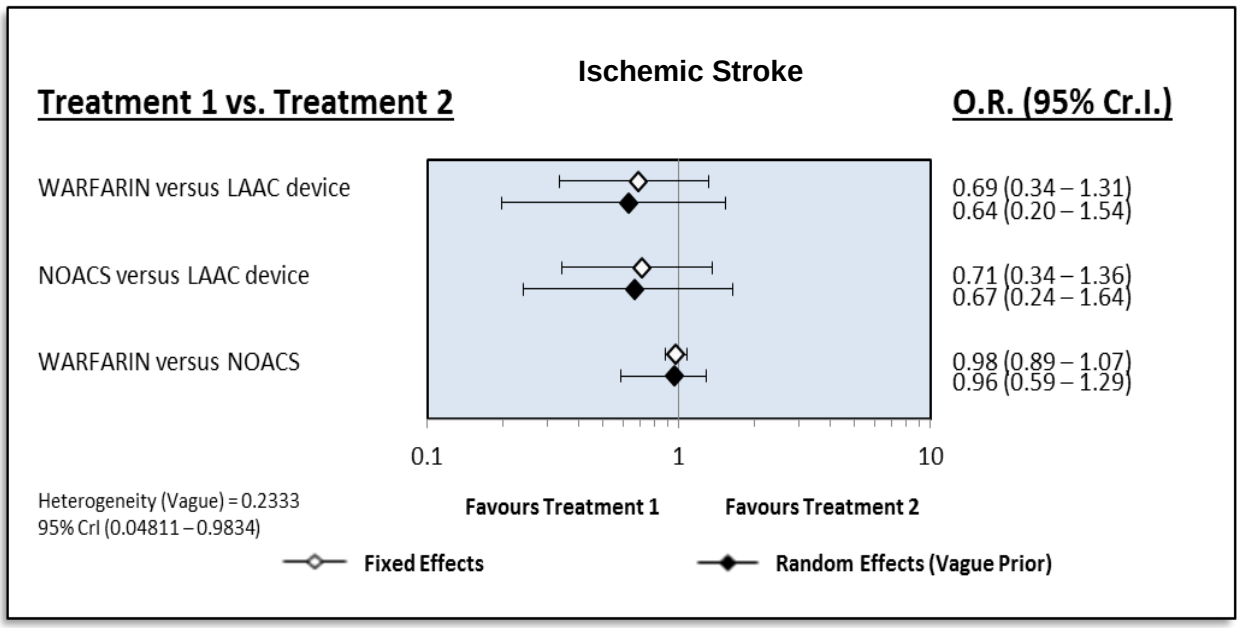

Figure 6: Forest Plot—Pooled Comparison of the LAAC Device, Novel Oral Anticoagulants, and Warfarin for the Outcome of Ischemic Stroke

Abbreviations: Cr.I, credible interval; LAAC device, left atrial appendage closure device with delivery system; NOAC, novel oral anticoagulant; OR, odds ratio.

Discussion

We found that the reduction in the risk of stroke was similar for the LAAC device and novel oral anticoagulants. These results are consistent with those of three recent network meta-analyses,[23-25] two of which did not have a robust search strategy for their studies in contrast to our approach for literature review.[23,24] Koifman et al found that novel oral anticoagulant therapy was superior to warfarin for multiple outcomes and that the LAAC device reduced the rate of hemorrhagic stroke.[23] Li et al conducted a systematic review of randomized controlled trials and observational studies comparing the post-one-year efficacy and safety of the LAAC device and novel oral anticoagulants with warfarin.[24] They conducted a network meta-analysis of six studies and concluded that the LAAC device was not superior to novel oral anticoagulants for stroke prevention. However, they found that patients with the LAAC device experienced a lower rate of hemorrhagic events during follow-up than those on novel oral anticoagulants. Another recent study by Tereshchenko et al, which was published after our review began, concluded that, compared with placebo, oral anticoagulants and the LAAC device reduced stroke significantly.[25]

Our review has the following limitations. First, we were unable to find any studies that directly compared the LAAC device with novel oral anticoagulants and thus had to conduct an indirect comparison. Second, we found only two randomized controlled trials comparing the LAAC device with warfarin. Last, real-world results may differ from study outcomes owing to factors such as different centres, the learning curve required to develop comfort with the LAAC device, operator experience with the LAAC device, and patient differences. Such differences may reduce the generalizability of our findings.

Conclusions

Moderate-quality evidence suggests that the LAAC device is as effective as novel oral anticoagulants in preventing stroke in people with nonvalvular atrial fibrillation. We were unable to identify any randomized controlled trials comparing the clinical effectiveness of the LAAC device versus antiplatelet agents (e.g., aspirin) in the management of patients with nonvalvular atrial fibrillation with contraindications to oral anticoagulation. However, one registry study (considered very low-quality evidence) found that the LAAC device may be a reasonable treatment alternative in patients with contraindications to oral anticoagulants.

ECONOMIC EVIDENCE REVIEW

Objectives

The primary objective of this study was to review the literature on the cost-effectiveness of the left atrial appendage closure device with delivery system (LAAC device) compared with novel oral anticoagulants in patients with nonvalvular atrial fibrillation and no contraindications to oral anticoagulants.

The secondary objective of this study was to review the literature on the cost-effectiveness of the left atrial appendage closure device with delivery system (LAAC device) compared with antiplatelet agents (e.g., aspirin) in patients with nonvalvular atrial fibrillation and contraindications to oral anticoagulants.

Methods

Sources

We performed an economic literature search on June 29, 2016, for studies published from inception to the search date. To retrieve relevant studies, the search was developed using the clinical search strategy with an economic filter applied.

Database auto-alerts were created in MEDLINE and Embase and monitored for the duration of the HTA review. We also searched the websites of Canadian HTA agencies, including the Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux, Alberta Heritage Foundation for Medical Research Health Technology Assessment Unit, Centre for Evaluation of Medicines of McMaster University, Centre for Health Economics and Policy Analysis of McMaster University, Centre for Health Services and Policy Research of the University of British Columbia, Institute of Health Economics, Institute for Clinical Evaluative Sciences Ontario, McMaster University, Programs for Assessment of Technology in Health, Technology Assessment Unit at the McGill University Health Centre, Therapeutics Initiative for Evidence-Based Drug Therapy of the University of British Columbia, Toronto Health Economics and Technology Assessment, and University of Calgary Institute for Public Health HTA unit, for reports related to atrial fibrillation. Finally, we reviewed the reference lists of included economic studies for any additional relevant studies not identified through the systematic search.

Literature Screening

We based our search terms on those used in the clinical evidence review of this report and applied economic filters to the search results. A single reviewer reviewed titles and abstracts, and, for those studies meeting the inclusion and exclusion criteria, we obtained full-text articles.

Inclusion Criteria

- English-language full-text publications
- Studies published from inception to June 29, 2016 (updated through to November 1, 2016)
- Studies in patients with nonvalvular atrial fibrillation
- Studies reporting on the cost-effectiveness of the LAAC device

- Studies performing full economic evaluations (i.e., cost–utility, cost-effectiveness, cost–benefit)

Exclusion Criteria

- Reviews
- Conference abstracts, posters, letters, editorials
- Foreign-language publications

Outcomes of Interest

- Cost per quality-adjusted life-year
- Cost per unit of clinical effect

Data Extraction

We extracted relevant data on the following:

- Source (i.e., name, location, year)
- Study design and perspective
- Population
- Intervention and all comparator(s)
- Outcomes (i.e., health outcomes, costs, and cost-effectiveness)
- Uncertainty (i.e., probability the LAAC device was cost-effective)

Methodological Appraisal

We determined the usefulness of each identified study for decision-making by applying a modified methodology checklist for economic evaluations developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom. The original checklist is used to inform development of clinical guidelines by NICE.[26] We modified the wording of the questions to remove references to guidelines and to make it Ontario specific. We separated the checklist into two sections. In the first section, the applicability of the study to the research questions was assessed. If the study was deemed directly applicable or partially applicable to the research questions, the quality of the study was assessed using the second section of the checklist. From the assessment of methodological quality, each study was assessed as having minor limitations, potentially serious limitations, or very serious limitations. The number of studies judged to be directly applicable, partially applicable, and not applicable to the research questions is presented, along with the number of studies with minor limitations, potentially serious limitations, and very serious limitations.

Results

Literature Search

The database search yielded 658 citations published from inception to November 1, 2016 (with duplicates removed). We excluded a total of 642 articles based on information in the title and abstract. We then obtained the full texts of 16 potentially relevant articles for further assessment. Eight studies met the inclusion criteria: six in patients with nonvalvular atrial

fibrillation without contraindications to oral anticoagulants and two in patients with nonvalvular atrial fibrillation patients with contraindications to oral anticoagulants. We hand-searched the reference lists of the included studies and health technology assessment websites to identify other relevant studies. No additional citations were included.

Figure 7 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for the economic evidence review.

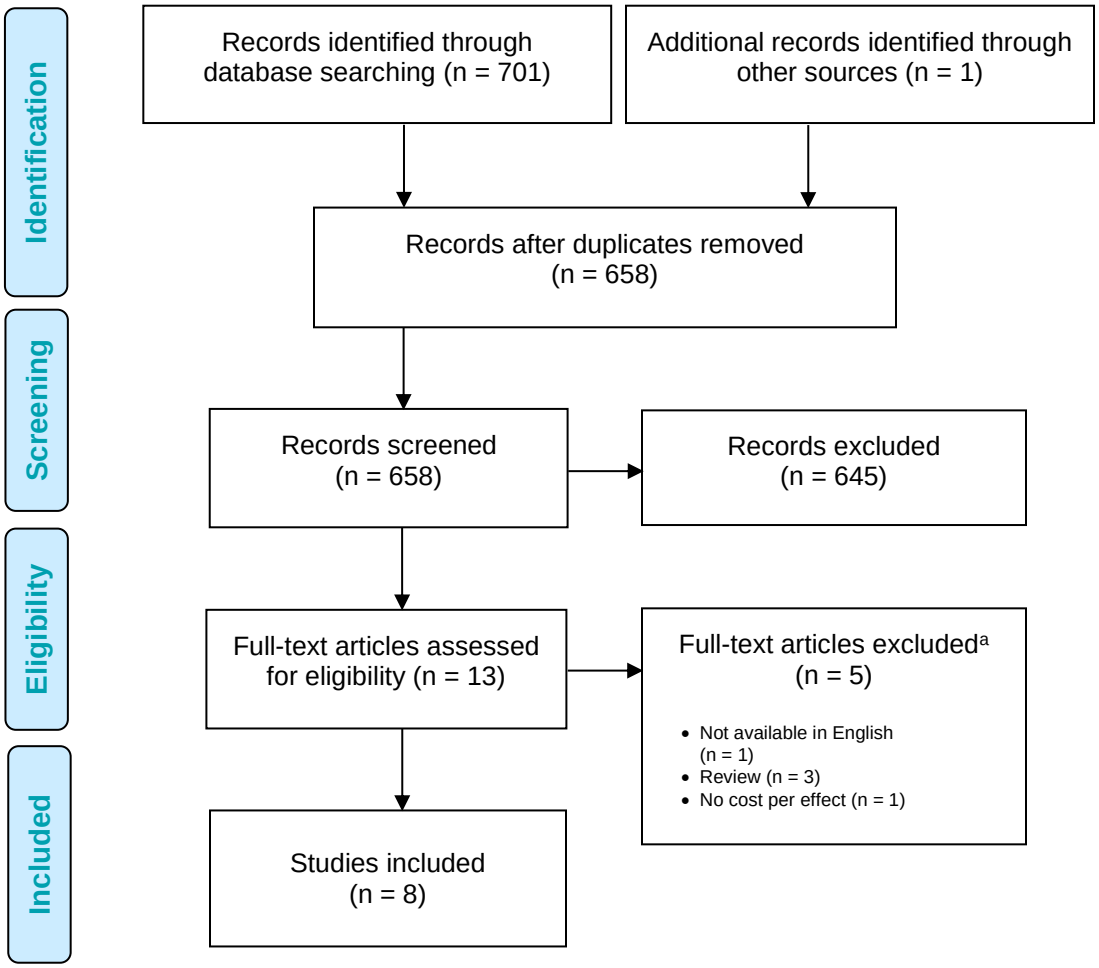

Figure 7: PRISMA Flow Diagram—Economic Evidence Review

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
[a]Not available in English: Jommi 2013[27]; review: Khaykin 2012,[28] Jones 2014,[29] Kreidieh 2016[30]; no cost per clinical effect: Panikker 2016.[31]
Source: Adapted from Moher et al.[14]

Review of the Included Studies

A summary of the included studies is provided in Tables 4 and 5. Studies used Markov cohort models (n = 4),[32-35] microsimulations (n = 3),[36-38] and a decision tree (n = 1)[39] to explore the cost-effectiveness of the LAAC device compared with alternatives. The majority of studies used a lifetime horizon,[33-35,37,38] and every study adopted the publicly funded health care payer perspective. All but one study,[39] which quantified cost-effectiveness as the incremental cost per life saved, calculated the incremental cost per quality-adjusted life-year.

Among the six studies in patients without contraindications to oral anticoagulants (Table 4), comparators included warfarin (n = 6), dabigatran (n = 5), apixaban (n = 2), rivaroxaban (n = 2), novel oral anticoagulants as a class (n = 1), aspirin (n = 1), and dual antiplatelet therapy (aspirin plus clopidogrel) (n = 1). At a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY), the cost-effectiveness of the LAAC device ranged from dominated (i.e., more costly, less effective) to dominant (i.e., less costly, more effective) compared with the assessed novel oral anticoagulants (apixaban, dabigatran, and rivaroxaban). Similarly, the cost-effectiveness of the LAAC device compared with warfarin ranged from dominated to dominant. One study found the LAAC device was cost-effective when compared with aspirin or dual antiplatelet therapy.[35]

Two studies adopted the perspective of the Ontario Ministry of Health and Long-Term Care. Micieli et al found that the LAAC device (i) was dominated by apixaban and rivaroxaban; (ii) was not cost-effective compared with warfarin (incremental cost-effectiveness ratio [ICER] = $75,162/QALY); and (iii) was cost-effective compared with dabigatran (ICER = $33,167/QALY).[37] Singh et al found that the LAAC device was cost-effective compared with dabigatran (ICER = $30,256/QALY) and warfarin (ICER = $41,565/QALY); however, substantial uncertainty was present.[38]

In patients in whom oral anticoagulants were contraindicated, two studies indicated that the LAAC device was the dominant strategy compared with aspirin or apixaban (Table 5).[32,36]

Table 4: Results of Economic Literature Review—Patients With Nonvalvular Atrial Fibrillation Without Contraindications to Oral Anticoagulants

Author, Year, Location	Study Design and Perspective	Population/Comparator	Interventions	Results			
				Health Outcomes	Costs	Cost-Effectiveness	Probability LAAC Device Is Cost-Effective (WTP Threshold)
Amorosi et al, 2015, Germany[39]	• Decision tree • German health payer perspective • 10-year model	• No description	• LAAC device • NOAC: dabigatran • Other: warfarin	**Risk of all-cause mortality** • LAAC device = 28.5% • Dabigatran = 30.3% • Warfarin = 38.6%	• LAAC device = €16,736/person • Dabigatran = < €20,000/person • Warfarin = €15,158/person	• No direct comparison provided vs. dabigatran • €15,544/life saved vs. warfarin	N/A
Freeman et al, 2016, United States[34]	• Markov cohort model • Ideal insurer perspective (U.S.), inpatient and outpatient medical care and prescription costs • Lifetime model	• Patients with AF at increased risk for stroke ($CHADS_2 \leq 1$) and no contradictions to OACs • Age = 70 years	• LAAC device • NOAC: dabigatran • Other: warfarin	**Based on PROTECT AF[40]** • LAAC device = 9.94 QALYs/person • Dabigatran = 8.28 QALYs/person • Warfarin = 7.96 QALYs/person **Based on PREVAIL[20]** • LAAC device = 8.44 QALYs/person • Dabigatran = 8.59 QALYs/person • Warfarin = 8.54 QALYs/person • 3% discount rate	**Based on PROTECT AF[40]** • LAAC device = $132,844/person • Dabigatran = $94,072/person • Warfarin = $92,120/person **Based on PREVAIL[20]** • LAAC device = $120,977/person • Dabigatran = $83,746/person • Warfarin = $73,077/person • 3% discount rate, USD	**Based on PROTECT AF[40]** • $23,422/QALY vs. dabigatran • $20,486/QALY vs. warfarin **Based on PREVAIL[20]** • Dominated vs. dabigatran • Dominated vs. warfarin	• vs. all comparators: 89% ($50,000/QALY)

Author, Year, Location	Study Design and Perspective	Population/Comparator	Interventions	Results			
				Health Outcomes	Costs	Cost-Effectiveness	Probability LAAC Is Cost-Effective (WTP Threshold)
Lee et al, 2016, United States[35]	• Markov cohort model • U.S. health care provider perspective • Lifetime model	• Patients with NVAF and no contraindications to antithrombotic therapies • Age = 65 years	• LAAC device • NOACs ○ Apixapan ○ Dabigatran 110 mg ○ Dabigatran 150 mg ○ Rivaroxaban • Other ○ Aspirin ○ Aspirin + clopidogrel ○ Warfarin	• LAAC device = 10.99 QALYs/person • Apixaban = 9.40 QALYs/person • Dabigatran 110 mg = 8.76 QALYs/person • Dabigatran 150 mg = 9.00 QALYs/person • Rivaroxaban = 9.86 QALYs/person • Aspirin = 6.12 QALYs/person • Aspirin + clopidogrel = 6.29 QALYs/person • Warfarin = 9.45 QALYs/person • 3% discount rate	• LAAC device = $37,789/person • Apixaban = $53,315/person • Dabigatran 110 mg = $42,712/person • Dabigatran 150 mg = $43,946/person • Rivaroxaban = $51,064/person • Aspirin = $12,877/person • Aspirin + clopidogrel = $26,287/person • Warfarin = $28,090/person • 3% discount rate, USD	• Dominant vs. apixaban • Dominant vs. dabigatran 110 mg • Dominant vs. dabigatran 150 mg • Dominant vs. rivaroxaban • $5,115/QALY vs. aspirin • $2,447/QALY vs. aspirin + clopidogrel • $6,298/QALY vs. warfarin	• vs. all comparators: 86.24% ($50,000/QALY)
Micieli et al, 2016, Canada[37]	• Markov microsimulation • Ontario Ministry of Health and Long-Term Care perspective • Lifetime model	• Patients with new onset NVAF, at risk for stroke and with no contraindications to OACs • Age (mean) = 68.9 • Male = 52.1%	• LAAC device • NOACs ○ Apixaban ○ Dabigatran ○ Rivaroxaban • Other ○ Warfarin	• LAAC device = 5.21 QALYs/person • Apixaban = 5.25 QALYs/person • Dabigatran = 5.18 QALYs/person • Rivaroxaban = 5.21 QALYs/person • Warfarin = 5.13 QALYs/person • 5% discount rate	• LAAC device = $21,789/person • Apixaban = $19,156/person • Dabigatran = $20,974/person • Rivaroxaban = $18,280/person • Warfarin = $15,776/person • 5% discount rate, CAD	• Dominated vs. apixaban • $33,167/QALY vs. dabigatran • Dominated vs. rivaroxaban • $75,162 vs. warfarin	• vs. all comparators: 31.9% ($50,000/QALY)

Author, Year, Location	Study Design and Perspective	Population/Comparator	Interventions	Results			
				Health Outcomes	Costs	Cost-Effectiveness	Probability LAAC Is Cost-Effective (WTP Threshold)
Reddy et al, 2015, United States[33]	• Markov cohort model • Centers for Medicare & Medicaid Services (U.S.) perspective • Lifetime model	• Patients with NVAF • CHA_2DS_2VASc (mean) = 3.2 • HAS-BLED (mean) = 2 • Age = 70 years	• LAAC device • NOACs (as a class) • Other ○ Warfarin	**At 5 Years** • LAAC device = 3.45 QALYs/person • NOACs = 3.45 QALYs/person • Warfarin = 3.39 QALYs/person **At 20 Years** • LAAC device = 8.03 QALYs/person • NOACs = 7.68 QALYs/person • Warfarin = 7.39 QALYs/person • 3% discount rate	**At 5 Years** • LAAC device = $20,892/person • NOACs = $20,924/person • Warfarin = $10,746/person **At 20 Years** • LAAC device = $31,198/person • NOACs = $61,701/person • Warfarin = $49,946/person • 3% discount rate, USD	**At 5 Years** • Dominant vs. NOACs • $149,468/QALY vs. warfarin **At 20 Years** • Dominant vs. NOACs • Dominant vs. warfarin	• vs. NOACs: 95% ($50,000/QALY) • vs. warfarin: 94% ($50,000/QALY)

Singh et al, 2013, Canada[38]	• Markov microsimulation
	• Ontario Ministry of Health and Long-Term Care perspective
	• Lifetime model
		• Patients with NVAF at risk for stroke with no contraindications to OACs
		• Age (mean) = 76 years
		• Male = 50%
			• LAAC device
			• NOAC
			  ○ Dabigatran
			• Other
			  ○ Warfarin
				• LAAC device = 4.68 QALYs/person
				• Dabigatran = 4.64 QALYs/person
				• Warfarin = 4.55 QALYs/person
				• 5% discount rate
					• LAAC device = $27,003/person
					• Dabigatran = $25,760/person
					• Warfarin = $21,429/person
					• 5% discount rate, CAD
						• $30,256 vs. dabigatran
						• $41,565/QALY vs. warfarin
							• vs. warfarin: 43% ($50,000/QALY)

Abbreviations: AF, atrial fibrillation; $CHADS_2$, Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke or transient ischemic attack symptoms previously (2 points); $CHADS_2DS_2VASc$, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, Stroke or transient ischemic attack symptoms previously (2 points), Vascular disease, Age 65–74 years, Sex category; HAS-BLED, Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratios (INRs), Elderly, Drugs or alcohol; LAAC device, left atrial appendage closure device with delivery system; N/A, not applicable; NOAC, novel oral anticoagulant; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant; PROTECT AF, Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation; QALY, quality-adjusted life-year; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; WTP, willingness to pay.

Table 5: Results of Economic Literature Review—Patients With Nonvalvular Atrial Fibrillation With Contraindications to Oral Anticoagulants

Author, Year, Location	Study Design and Perspective	Population/Comparator	Interventions	Results			
				Health Outcomes	Costs	Cost-Effectiveness	Probability LAAC Is Cost-Effective (WTP Threshold)
Reddy et al, 2016, Germany[32]	• Markov cohort model • German health care system perspective • 20-year model	• Patients with NVAF and contraindications to warfarin • CHA_2DS_2VASc (mean) = 3 • HAS-BLED (mean) = 3 • Age = 70 years	• LAAC device • Aspirin • Apixaban	• LAAC device = 4.82 QALYs/person • Aspirin = 4.21 QALYs/person • Apixaban = 4.59 QALYs/person • 3.5% discount rate	• LAAC device = €15837/person • Aspirin = €21077/person • Apixaban = €18869/person • 3.5% discount rate, EUR	• Dominant vs. aspirin • Dominant vs. apixaban	• vs. aspirin: 99% (€30,000/QALY) • vs. apixaban: 94% (€30,000/QALY)
Saw et al, 2016, Canada[36]	• Markov microsimulation • Ontario Ministry of Health and Long-Term Care perspective • Lifetime model	• Patients with NVAF and contraindications to OACs	• LAAC device • Aspirin	• LAAC device = 4.66 QALYs/person • Aspirin = 4.25 QALYs/person • 5% discount rate	• LAAC device = $30,748/person • Aspirin = $38,974/person • 5% discount rate	• Dominant vs. aspirin	• vs. aspirin: > 90% (€30,000/QALY)

Abbreviations: $CHADS_2DS_2VASc$, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, Stroke or transient ischemic attack symptoms previously (2 points), Vascular disease, Age 65–74 years, Sex category; HAS-BLED, Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratios (INRs), Elderly, Drugs or alcohol; LAAC device, left atrial appendage closure device with delivery system; NOAC, novel oral anticoagulant; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant; QALY, quality-adjusted life-year; WTP, willingness to pay.

Applicability of the Included Studies

The results of the applicability checklist applied to the included studies are presented in Appendix 3, Table A1. All studies were deemed either directly applicable (n = 2)[36,37] or partially applicable (n = 6)[32-35,38,39] to the research questions. Only two studies included all of the Health Canada–approved novel oral anticoagulants (i.e., apixaban, dabigatran, rivaroxaban) as comparators.[35,37] Three studies evaluated the LAAC device from the Ontario perspective[36-38]: two in patients without contraindications to oral anticoagulants[37,38] and one in patients with contraindications to oral anticoagulants.[36]

Methodological Quality of the Included Studies

The results of the methodological quality checklist applied to the included studies are presented in Appendix 3, Table A2. Among studies evaluating patients without contraindications to oral anticoagulants, three studies had very serious limitations,[34,35,39] and three studies had potentially serious limitations.[33,37,38] The majority of studies used lifetime horizons and captured most important health outcomes. The three studies[34,35,39] identified as having very serious limitations used absolute rather than relative treatment effects. In addition, the study by Amorosi et al[39] was framed as a budget impact analysis but presented cost-effectiveness results (cost per life saved). This study also did not discount future costs and outcomes or capture parameter uncertainty. The three studies[33,37,38] identified as having potentially serious limitations did not incorporate the most recent data comparing the LAAC device with warfarin. These data include those from the recently conducted PREVAIL trial[20] and publications capturing long-term outcomes from the PROTECT AF trial.[40]

Two studies[32,36] evaluated patients with contraindications to oral anticoagulants, and these studies did not have any serious limitations. Each study used a lifetime horizon, captured relevant health outcomes and costs, and evaluated parameter uncertainty. Relative treatment effects from the ASAP study[22] were used by Reddy et al,[32] whereas Saw et al[36] took a conservative approach using treatment effects from the PROTECT AF trial.[36]

Discussion

Studies Assessing the LAAC Device in Patients Without Contraindications to Oral Anticoagulants

In patients with nonvalvular atrial fibrillation without contraindications to oral anticoagulants, the cost-effectiveness of the LAAC device compared with novel oral anticoagulants or warfarin reported in the published literature varied considerably. This variation is likely owing to differences in treatment effects, costs, utilities, and resource utilization estimates. Sorensen et al found similar variation in models comparing dabigatran and warfarin,[41] which highlights the need to identify the best available parameter estimates and thoroughly examine the effects of uncertainty on results.

The reviewed models had several strengths, including the use of several comparators and a lifetime horizon and the inclusion of relevant health outcomes and costs. However, limitations were present with respect to treatment effects. Three of the models did not use relative effect estimates,[34,35,39] which can lead to a distortion of relative event rates, especially when pooling absolute rates from several clinical trials. Among studies using relative treatment effects,[33,37] a challenge has been assessing the cost-effectiveness of the LAAC device compared with novel oral anticoagulants, as there is no direct clinical evidence of this comparison. A commentary by Pokorney et al[42] highlighted that some models[33,34] have likely overestimated the benefits of the

LAAC device compared with novel oral anticoagulants. Until clinical evidence directly comparing the LAAC device with novel oral anticoagulants is available, we must be cautious in interpreting cost-effectiveness results for these interventions and thoroughly explore the effects of uncertainty.

One study was deemed directly applicable to our research question,[37] as it was conducted from the perspective of the Ontario Ministry of Health and Long-Term Care and included all pre-specified comparators. However, given substantial uncertainty across studies and new clinical data on the LAAC device's clinical effectiveness, an updated analysis for the Ontario population is warranted.

Studies Assessing the LAAC Device in Patients With Contraindications to Oral Anticoagulants

In patients with nonvalvular atrial fibrillation with contraindications to oral anticoagulants, the LAAC device was consistently found to be less expensive and more clinically effective than alternatives (i.e., aspirin, apixaban). This subgroup of patients, often including patients with hemorrhagic tendencies, is ineligible for oral anticoagulants, leaving few options for thromboembolic protection.[22] To date, no randomized clinical trials have been conducted in this population, but results from the ASAP study offer estimates of LAAC device effectiveness in this population.[22] Using these estimates, and more conservative estimates derived from the PROTECT AF trial,[20] we find that the current literature suggests that the LAAC device is less costly and more clinically effective than aspirin or apixaban.[32,36] Given that the evaluation by Saw et al[36] was conducted recently with the best available evidence from the perspective of the Ontario Ministry of Health and Long-Term Care, there is no need to conduct an additional primary economic evaluation in this subgroup.

Conclusions

Six studies were identified in patients with nonvalvular atrial fibrillation without contraindications to oral anticoagulants, but all had either very serious or potentially serious limitations. Two studies identified were conducted from the perspective of the Ontario Ministry of Health and Long-Term Care. In the populations of these studies, the cost-effectiveness of the LAAC device compared with apixaban, dabigatran, and rivaroxaban was found to be highly uncertain (ranging from dominated to dominant). In addition, two cost-effectiveness studies were identified in patients with nonvalvular atrial fibrillation with contraindications to oral anticoagulants, both of which we judged to have minor limitations. These two studies, one of which was conducted from the perspective of the Ontario Ministry of Health and Long-Term Care, indicate that the LAAC device is cost-effective compared with aspirin, resulting in lower costs and greater clinical effectiveness.

PRIMARY ECONOMIC EVALUATION

Several published economic evaluations identified in the economic literature review evaluated the LAAC device in patients with nonvalvular atrial fibrillation, including two studies conducted from the perspective of the Ontario Ministry of Health and Long-Term Care. In patients with nonvalvular atrial fibrillation with contraindications to oral anticoagulants, the literature indicates that the LAAC device is cost-effective compared with both aspirin[32,36] and apixaban.[32] Given these findings, as well as the inclusion of the most recent effectiveness evidence, we did not conduct an economic evaluation in this population. In patients with nonvalvular atrial fibrillation without contraindications to oral anticoagulants, conclusions about the cost-effectiveness of the LAAC device compared with novel oral anticoagulants remain uncertain. Additionally, Ontario evaluations were published prior to the PREVAIL trial,[20] which provides additional clinical evidence comparing the LAAC device with warfarin. Owing to the uncertainty in conclusions in the existing literature, as well as the availability of new evidence, we decided to conduct a primary economic evaluation in patients with nonvalvular atrial fibrillation without contraindications to oral anticoagulants.

Objective

The objective of this study was to assess the cost-effectiveness of the LAAC device compared with Health Canada–approved novel oral anticoagulants (i.e., apixaban, dabigatran, rivaroxaban) in patients with nonvalvular atrial fibrillation with no contraindications to oral anticoagulants, within the context of the Ontario Ministry of Health and Long-Term Care.

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards Statement.[43]

Type of Analysis

Given the availability of utilities for the treatments and health outcomes indicated in this economic evaluation, we performed a cost–utility analysis comparing the costs and quality-adjusted life-years (QALYs) of the LAAC device versus novel oral anticoagulants.

Target Population

The target population was Ontario men and women diagnosed with nonvalvular atrial fibrillation at risk for stroke and eligible for oral anticoagulants. Patients at risk for stroke included those with a CHA_2DS_2VASc score of equal to or greater than 2.[44] The age and risk factor profile of the population was obtained from the Canadian Institute for Health Information's National Ambulatory Care Reporting System; the population included all patients with new-onset atrial fibrillation presenting to emergency departments in Ontario between April 1, 2005, and March 31, 2010 (n = 35,143).[37] We assumed these patients to be representative of the newly diagnosed population of patients with nonvalvular atrial fibrillation in Ontario.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health and Long-Term Care.

Interventions

We conducted the evaluation for the LAAC device compared with each of the Health Canada–approved novel oral anticoagulants: apixaban, dabigatran, and rivaroxaban. To facilitate comparison with findings presented in the literature, we compared the LAAC device with warfarin. Table 6 summarizes the comparators evaluated in the primary economic model.

Table 6: Interventions and Comparators Evaluated in the Primary Economic Model

Intervention	Comparator	Comparator Dosing	Source
LAAC device	Apixaban	5 mg twice daily or 2.5 mg if patient has one or more of the following criteria: age ≥ 80 years, body weight < 60 kg, serum creatinine level ≥ 1.5 mg/dL	Granger et al, 2011[16]
LAAC device	Dabigatran	150 mg twice daily or 110 mg twice daily if patient age ≥ 80 years and/or ≥ 75 years with a creatinine clearance of 30–50 mL/min	Boehringer Ingelheim Canada[45]
LAAC device	Rivaroxaban	20 mg daily or 15 mg daily if patient has a creatinine clearance of 30–49 mL/min	Patel et al, 2011[17]
LAAC device	Warfarin	Adjusted-dose, target INR 2–3	Bristol-Myers Squibb Canada[46]; Connolly et al, 2013[15]; Granger et al, 2011[16]; Holmes et al, 2014[20]; Patel et al, 2011[17]; Reddy et al, 2013[40]

Abbreviations: INR, international normalized ratio; LAAC device, left atrial appendage closure device with delivery system.

Discounting and Time Horizon

We applied an annual discount rate of 5% to both costs and QALYs. We used a lifelong time horizon and a cycle length of one month in all analyses.

Main Assumptions

The major assumptions for this model were the following:

- Only patients with a CHA_2DS_2VASc score of equal to or greater than 2 were treated with the LAAC device or an oral anticoagulant
- Patients did not switch oral anticoagulant treatments, and there was no discontinuation of oral anticoagulant treatment after two years
- Treatment effects continued beyond the length of the clinical trials
- Ongoing utilities were based on most detrimental condition (e.g., major stroke was considered more detrimental than bleeding)
- Long-term stroke utilities were directly related to level of disability and did not differ between ischemic and hemorrhagic stroke
- Treatment-specific mortality was captured through clinical event occurrence and subsequent event-related mortality

Model Structure

We obtained and adapted a previously published microsimulation Markov model by Singh et al[38] to determine the incremental cost per QALY of the LAAC device compared with novel oral anticoagulants or warfarin. The model captures the treatment pathways, life history, and related costs and QALYs of Ontario patients newly diagnosed with nonvalvular atrial fibrillation. The model structure is depicted in Figure 8.

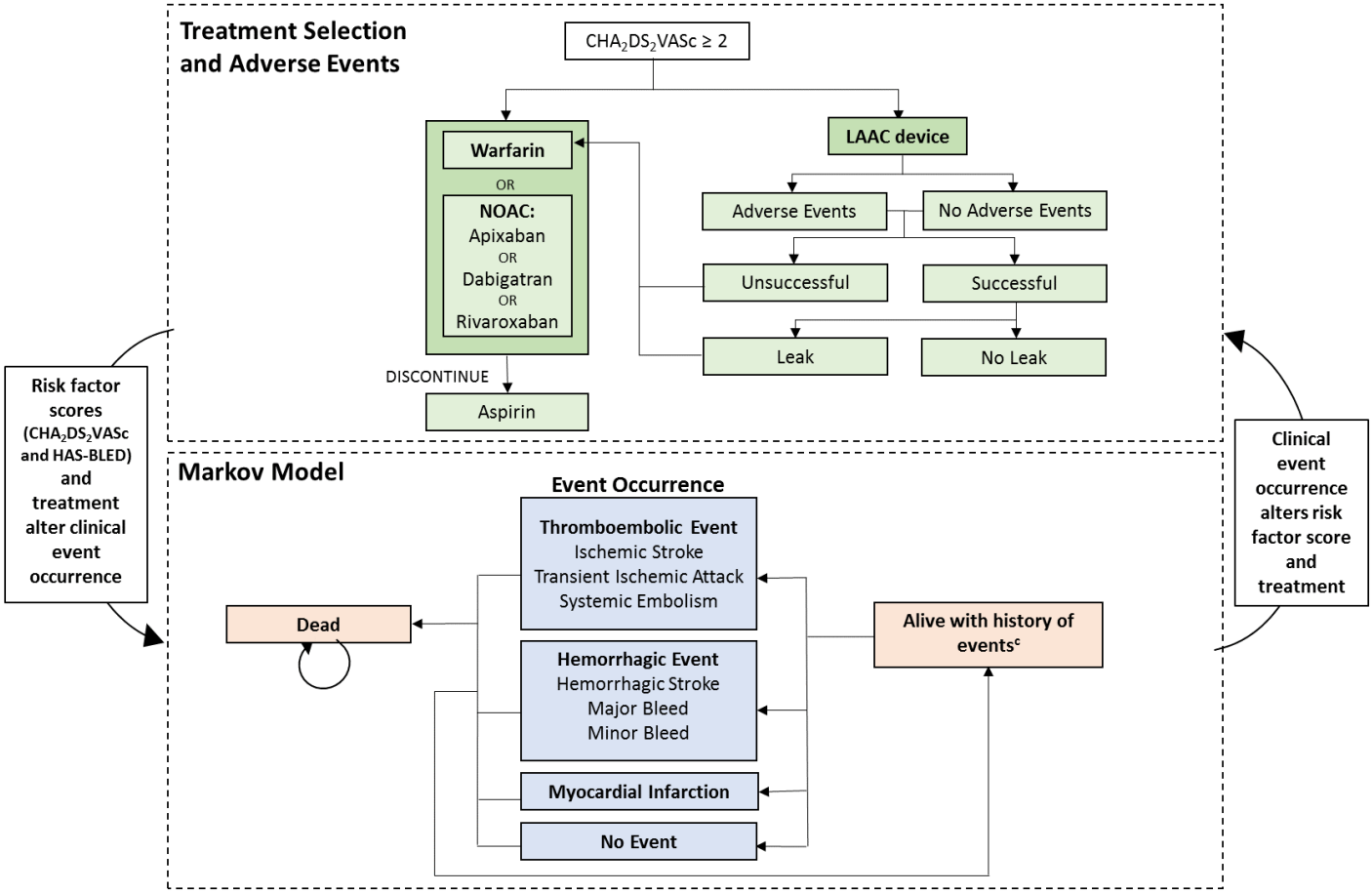

Figure 8: Model Structure

Abbreviations: $CHADS_2DS_2VASc$, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, Stroke or transient ischemic attack symptoms previously (2 points), Vascular disease, Age 65–74 years, Sex category; HAS-BLED, Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratios (INRs), Elderly, Drugs or alcohol; LAAC device, left atrial appendage closure device with delivery system; TIA, transient ischemic attack.

[a]CHA_2DS_2-VASc score predicts risk of thromboembolic events.

[b]HAS-BLED score predicts risk of hemorrhagic events.

[c]History of events alters risk, utilities, and costs.

We used a microsimulation, which follows patients throughout their lifetime, to best reflect the complex treatment pathways and clinical outcomes associated with nonvalvular atrial fibrillation. Patients receiving the LAAC device may have an adverse event, a successful or unsuccessful surgery, and/or a leak in the appendage closure. The clinical events modelled included ischemic stroke, transient ischemic attack, systemic embolism, myocardial infarction, hemorrhagic stroke, major bleeds, minor bleeds, and procedural adverse events associated with the implantation of

the LAAC device. Patients could experience multiple events throughout the model, and several events could lead to death or impact patients' lifetime costs or QALYs.

The CHA_2DS_2-VASc score (assessing congestive heart failure, hypertension, age equal to or greater than 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age between 65 and 74 years, and sex category) was used to predict the occurrence of thromboembolic events (i.e., stroke, transient ischemic attack, systemic embolism). The HAS-BLED score (assessing hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios (INRs), whether a patient is elderly, and use of drugs or alcohol) was used to predict the occurrence of hemorrhagic events (i.e., hemorrhagic stroke, major bleeding, minor bleeding). These scores have been well validated for prediction in patients with nonvalvular atrial fibrillation.[47-51] Patients with a CHA_2DS_2VASc score of equal to or greater than 2 are considered at high risk for thromboembolic events and should be treated with long-term oral anticoagulation therapy.[52] Patients with a HAS-BLED score of equal to or greater than 3 are considered at high risk for bleeding. Guidelines suggest that stroke prevention treatments and risk factors should be reviewed regularly for patients with a HAS-BLED score of equal to or greater than 3.[52]

Upon entry into the model, we calculated patients' initial CHA_2DS_2VASc and HAS-BLED scores from the baseline presence of risk factors (Table 7). The distribution of risk factors was obtained from the National Ambulatory Care Reporting System cohort described above (n = 35,143).[37] The mean baseline age, CHA_2DS_2VASc score, and HAS-BLED score in this population were 68.9 years,[37] 2.9, and 0.8, respectively. (The baseline HAS-BLED score for patients on warfarin was 1.1, owing to the inclusion of labile international normalized ratio [INR] as a risk factor.) The scores were updated throughout the model to reflect expected changes in risk over time. For example, when a patient reaches the age of 65 years, an additional point would be added to each of the CHA_2DS_2VASc and HAS-BLED scores to capture the increased risk of thromboembolic and hemorrhagic events with increased age.

Table 7: Baseline CHA_2DS_2VASc and HAS-BLED Scores in the Ontario Population[a]

Risk Factor		Score	Baseline Probability of Risk Factor
CHA_2DS_2VASc			
C	Congestive heart failure	1	0.127
H	Hypertension	1	0.652
A	Age ≥ 75 years	2	0.418
D	Diabetes mellitus	1	0.220
S	Prior stroke or transient ischemic attack	2	0.144
V	Vascular disease	1	0.087
A	Age 65–74 years	1	0.228
Sc	Sex category (female)	1	0.479
HAS-BLED			
H	Hypertension	1	0.652
A	Abnormal renal function	1	0.004
	Abnormal liver function	1	0.200
S	Prior stroke or TIA	1	0.144
B	Bleeding history or predisposition	1	0.047
L	Labile INR	1	0.268
E	Elderly (age > 65 years)	1	0.646
D	Medication use predisposing to bleeding	1	0.849
	History of drug or alcohol use	1	0.006

Abbreviation: INR, international normalized ratio.
[a]Obtained from 35,143 patients with new-onset atrial fibrillation.
Source: Micieli et al, 2016.[37]

Treatment Details

People with a CHA_2DS_2VASc score of less than 2 were considered low to moderate risk and received aspirin therapy until their score reached 2. After reaching a score of 2, patients received their intended treatments.

The LAAC device implantation procedure and associated complications correspond to the protocol and results of two clinical trials comparing the LAAC device with warfarin among patients with nonvalvular atrial fibrillation at risk for stroke: the PROTECT-AF trial (n = 707)[40] and the PREVAIL trial (n = 407).[20] All patients were assumed to be at risk for major surgical adverse events, which included device embolization (hemorrhage caused by the introduction of a foreign mass) and pericardial effusion (accumulation of fluid around the heart). Patients with successful implantation were treated with warfarin for 45 days, followed by dual antiplatelet therapy (aspirin plus clopidogrel) from day 45 through day 160, and aspirin alone thereafter. Patients with unsuccessful implantation required lifelong warfarin therapy. Residual leaks were assessed through transesophageal echocardiogram at 45 days and, if present, again at six months. Individuals with residual leaks were assumed to be placed on prolonged warfarin therapy.

The majority of anticoagulant dosing was based on the respective clinical trial protocols (see Table 4). A sequential dosing strategy was used for dabigatran, in line with Health Canada indications; patients in the model received 150 mg of the drug twice daily until they reached the age of 80 years, after which they were given 110 mg of the drug twice daily.[8]

Clinical Outcome and Utility Parameters

LAAC Device Adverse Events and Surgical Outcomes

Major surgical adverse events, implantation success, and device leaks present at six weeks and six months were modelled based on the weighted average of the PROTECT AF[40] and PREVAIL[20] trials (Table 8).

Table 8: LAAC Device Adverse Events and Surgical Outcomes

Treatment	Probability of Outcome	Standard Error	Source
Device embolization	0.007	0.003	PREVAIL, Holmes et al, 2014[20]; PROTECT AF, Reddy et al, 2014[40]
Pericardial effusion	0.037	0.007	PREVAIL, Holmes et al, 2014[20]; PROTECT AF, Reddy et al, 2014[40]
LAAC device implantation unsuccessful	0.075	0.010	PREVAIL, Holmes et al, 2014[20]; PROTECT AF, Reddy et al, 2014[40]
Device leak (6 weeks)	0.127	0.013	PREVAIL, Holmes et al, 2014[20]; PROTECT AF, Reddy et al, 2014[40]
Device leak (6 months)	0.054	0.009	PREVAIL, Holmes et al, 2014[20]; PROTECT AF, Reddy et al, 2014[40]

Abbreviation: LAAC device, left atrial appendage closure device with delivery system.

Treatment Discontinuation

Pharmacologic discontinuation rates were taken from the ARISTOTLE,[16] RE-LY,[15] and ROCKET AF[17] trials (Table 9). Further, we assumed that treatment was permanently discontinued after a hemorrhagic stroke, discontinued for one month for major bleeds, and discontinued for two days for minor bleeds. Discontinuation resulted in aspirin-only therapy. Dual antiplatelet therapy was given for two months post–myocardial infarction.

Table 9: Probabilities of Pharmacologic Treatment Discontinuation

Treatment	Two-Year Probability of Discontinuation	Standard Error	Duration	Source
Apixaban	0.22	0.043	2 years	ARISTOTLE, Granger et al, 2011[16]
Dabigatran 110 mg	0.21	0.052	2 years	RE-LY, Connolly et al, 2009[15]
Dabigatran 150 mg	0.21	0.052	2 years	RE-LY, Connolly et al, 2009[15]
Rivaroxaban	0.24	0.050	2 years	ROCKET AF, Patel et al, 2011[17]
Warfarin	0.21[a]	0.027	2 years	ARISTOTLE, Granger et al, 2011[16]; RE-LY, Connolly et al, 2009[15]; ROCKET AF, Patel et al, 2011[17]

[a]Weighted average.

Clinical Events

We based the monthly probabilities and severities of clinical events on several factors, including baseline risk (as determined by the CHA_2DS_2VASc and HAS-BLED scores), fatality rate, probability of disability, and treatment effects. The parameters and sources used to model clinical events are described below.

Thromboembolic Events

The baseline monthly probability of thromboembolic events (ischemic stroke, systemic embolism, or transient ischemic attack) for each possible CHA_2DS_2VASc score was derived from 90,490 patients from the Swedish Atrial Fibrillation cohort study taking either aspirin alone or no prophylaxis.[50] Annual probabilities for the model were calculated based on the reported events per 100 person-years at risk (Table 10).

To approximate treatment effects, we used the baseline probabilities multiplied by treatment-specific odds ratios. The probability of an event occurring in a patient taking warfarin was approximated using an odds ratio for warfarin relative to aspirin. This value was obtained from a Cochrane review comparing oral anticoagulants with antiplatelet therapy in patients with nonvalvular atrial fibrillation.[53] The probability of events occurring while on the remaining treatments (i.e., LAAC device, apixaban, dabigatran, or rivaroxaban) was determined by applying an odds ratio for the respective treatment relative to warfarin. These values were calculated based on data extracted in the clinical review portion of this report from the ARISTOTLE (apixaban),[16] RE-LY (dabigatran),[15] ROCKET AF (rivaroxaban),[17] PROTECT AF (LAAC device),[40] and PREVAIL (LAAC device)[20] clinical trials. Odds ratios from the PROTECT AF and PREVAIL trials were pooled using a Mantel–Haenszel adjustment, and estimates from the trials were assessed for homogeneity using the Breslow–Day test.

We divided thromboembolic events into systemic emboli, transient ischemic attacks, and ischemic strokes (see Table 10). We assumed that both systemic emboli and ischemic strokes could be fatal. We divided ischemic strokes based on severity and disability to capture variation

in health outcomes and costs. We obtained the distribution of strokes by disability at discharge from Goeree et al[54]; this distribution was based on the Modified Rankin Scale (MRS). Strokes were classified as fatal (MRS = 6), major (MRS = 5), moderate (MRS = 3–4), or minor (MRS = 0–2). The study compared ischemic and hemorrhagic strokes in an Ontario hospital setting, which allowed for the model to capture the relative severity of these events.

Table 10: Event Rates, Treatment Effects, and Severity: Ischemic Stroke, Systemic Embolism, and Transient Ischemic Attack

Baseline Risk of Ischemic Stroke, Systemic Embolism, or Transient Ischemic Attack			
CHA_2DS_2VASc Score	**Annual Probability of Event**	**Standard Error**	**Source**
0	0.003	0.0006	Friberg et al, 2012[50]
1	0.009	0.0009	Friberg et al, 2012[50]
2	0.029	0.0013	Friberg et al, 2012[50]
3	0.046	0.0013	Friberg et al, 2012[50]
4	0.067	0.0015	Friberg et al, 2012[50]
5	0.100	0.0021	Friberg et al, 2012[50]
6	0.136	0.0030	Friberg et al, 2012[50]
7	0.157	0.0048	Friberg et al, 2012[50]
8	0.152	0.0080	Friberg et al, 2012[50]
9	0.174	0.0208	Friberg et al, 2012[50]
Treatment Effects			
Intervention:Comparator	**Odds Ratio**	**Standard Error**	**Source**
Warfarin:aspirin	0.53	0.1291	Aguilar et al, 2007[53]
LAAC device:warfarin	1.56	0.3569	PREVAIL, Holmes et al, 2014[20]; PROTECT AF, Reddy et al, 2014[40]
Apixaban:warfarin	0.92	0.1053	ARISTOTLE, Granger et al, 2011[16]
Dabigatran 110 mg:warfarin	1.09	0.1126	RE-LY, Connolly et al, 2009[15]
Dabigatran 150 mg:warfarin	0.78	0.1220	RE-LY, Connolly et al, 2009[15]
Rivaroxaban:warfarin	0.84	0.1107	ROCKET AF, Patel et al, 2011[17]

Severity of Ischemic Stroke, Systemic Embolism, or Transient Ischemic Attack			
Event and Severity	**Proportion**	**Standard Error**	**Source**
Systemic embolism	0.149	0.0107	Connolly et al, 2009[15]; FDA, 2015[55]; Granger et al, 2011[16]; Patel et al, 2011[17]
Transient ischemic attack	0.188	0.0375	FDA, 2015[55]
Ischemic stroke	0.663	–	Calculation
Proportion of systemic embolisms that are:			
Fatal	0.247	0.0291	Bekwelem et al, 2015[56]
Proportion of ischemic strokes that are:			
Fatal	0.144	0.0287	Goeree et al, 2005[54]
Major	0.016	0.0032	Goeree et al, 2005[54]
Moderate	0.729	0.1457	Goeree et al, 2005[54]
Minor	0.111	0.0223	Goeree et al, 2005[54]

Abbreviations: $CHADS_2DS_2VASc$, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, Stroke or transient ischemic attack symptoms previously (2 points), Vascular disease, Age 65–74 years, Sex category; LAAC device, left atrial appendage closure device with delivery system.

Hemorrhagic Stroke

The baseline monthly probability of hemorrhagic stroke for each possible HAS-BLED score was derived from 61,396 patients on aspirin alone from the Swedish Atrial Fibrillation cohort study (Table 11).[50]

The same methodologies and sources used to modify thromboembolic baseline probabilities by treatment effect were used for hemorrhagic stroke. A summary of the odds ratios used is presented in Table 11. Additionally, hemorrhagic stroke was subdivided into fatal, major, moderate, and minor severity, as per Goeree et al.[54]

Table 11: Event Rates, Treatment Effects, and Severity: Hemorrhagic Stroke

Baseline Risk of Hemorrhagic Stroke			
HAS-BLED Score	**Annual Probability of Event**	**Standard Error**	**Source**
0	0.000	0.0007[a]	Friberg et al, 2012[50]
1	0.011	0.0007	Friberg et al, 2012[50]
2	0.021	0.0008	Friberg et al, 2012[50]
3	0.031	0.0011	Friberg et al, 2012[50]
4	0.047	0.0023	Friberg et al, 2012[50]
5	0.070	0.0077	Friberg et al, 2012[50]
6	0.145	0.0408	Friberg et al, 2012[50]
7	0.228	0.2576	Friberg et al, 2012[50]
Treatment Effects			
Intervention:Comparator	**Odds Ratio**	**Standard Error**	**Source**
Warfarin:aspirin	1.98	0.1289	Aguilar et al, 2007[53]
LAAC device:warfarin	0.21	0.5659	PREVAIL, Holmes et al, 2014[20]; PROTECT AF, Reddy et al, 2014[40]
Apixaban:warfarin	0.51	0.1950	ARISTOTLE, Granger et al, 2011[16]
Dabigatran 110 mg:warfarin	0.31	0.3066	RE-LY, Connolly et al, 2009[15]
Dabigatran 150 mg:warfarin	0.26	0.3254	RE-LY, Connolly et al, 2009[15]
Rivaroxaban:warfarin	0.58	0.2340	ROCKET AF, Patel et al, 2011[17]
Severity of Hemorrhagic Stroke			
Event and Severity	**Proportion**	**Standard Error**	**Source**
Proportion of hemorrhagic strokes that are:			
Fatal	0.429	0.0857	Goeree et al, 2005[54]
Major	0.119	0.0238	Goeree et al, 2005[54]
Moderate	0.429	0.0857	Goeree et al, 2005[54]
Minor	0.023	0.0048	Goeree et al, 2005[54]

Abbreviations: HAS-BLED, Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratios (INRs), Elderly, Drugs or alcohol; LAAC device, left atrial appendage closure device with delivery system.
[a]Standard error assumed to be the same as for a HAS-BLED score of 1.

Bleeding

The baseline monthly probability of major bleeds for each HAS-BLED score was derived from 61,396 patients on aspirin alone from the Swedish Atrial cohort study (Table 12).[50]

The same methodologies and sources used to modify thromboembolic event and hemorrhagic stroke baseline probabilities by treatment effect were used for major bleeds. A summary of the

odds ratios used is presented in Table 12. Major bleeds were divided into fatal and nonfatal events. Minor bleeds were assumed to occur at the same relative rates as major bleeds but at a greater frequency, according to De Caterina et al.[57]

Table 12: Event Rates, Treatment Effects, and Severity: Major Bleeds

Baseline Risk of Major Bleeds			
HAS-BLED Score	**Annual Probability of Event**	**Standard Error**	**Source**
0	0.000	0.0074[a]	Friberg et al, 2012[50]
1	0.011	0.0074	Friberg et al, 2012[50]
2	0.021	0.0077	Friberg et al, 2012[50]
3	0.031	0.0011	Friberg et al, 2012[50]
4	0.047	0.0023	Friberg et al, 2012[50]
5	0.070	0.0077	Friberg et al, 2012[50]
6	0.145	0.0408	Friberg et al, 2012[50]
7	0.228	0.2575	Friberg et al, 2012[50]
Treatment Effects			
Intervention:Comparator	**Odds Ratio**	**Standard Error**	**Source**
Warfarin:aspirin	1.90	0.2942	Aguilar et al, 2007[53]
LAAC device:warfarin	0.95	0.2011	FDA, 2015[55]
Apixaban:warfarin	0.69	0.0738	ARISTOTLE, Granger et al, 2011[16]
Dabigatran 110 mg:warfarin	0.80	0.0773	RE-LY, Connolly et al, 2009[15]
Dabigatran 150 mg:warfarin	0.93	0.0744	RE-LY, Connolly et al, 2009[15]
Rivaroxaban:warfarin	1.03	0.0736	ROCKET AF, Patel et al, 2011[17]
Severity of Major Bleeds			
Severity	**Proportion**	**Standard Error**	**Source**
Proportion of major bleeds that are:			
Fatal	0.080	0.0232	Walraven et al, 2002[58]
Occurrence of Minor Bleeds Relative to Major Bleeds			
	Relative Risk	**Standard Error**	**Source**
Minor bleed:major bleed	2.28	0.4552	De Caterina et al, 2010[57]

Abbreviations: HAS-BLED, Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratios (INRs), Elderly, Drugs or alcohol; LAAC device, left atrial appendage closure device with delivery system.
[a]Standard deviation assumed same as HAS-BLED score of one.

Myocardial Infarction

The annual probability of myocardial infarction occurring in patients on warfarin, apixaban, dabigatran, or rivaroxaban was derived from the RE-LY (warfarin, dabigatran),[15] ARISTOTLE (apixaban),[16] and ROCKET-AF (rivaroxaban)[17] trials (Table 13). We assumed the annual probability of myocardial infarction occurring in patients with the LAAC device to be equivalent to the warfarin probability. We derived the rates of myocardial infarction in patients on aspirin alone and on dual antiplatelet therapy by adjusting the warfarin rate by the odds ratio between the treatments and warfarin (Table 13). Myocardial infarctions were divided into fatal and nonfatal events.

Table 13: Event Rates, Treatment Effects, and Severity: Myocardial Infarction

Treatment Effects			
Treatment	**Annual Probability of Event**	**Standard Error**	**Source**
Warfarin	0.005	0.0009	Connolly et al, 2009[15]
LAAC device	0.005	0.0009	Connolly et al, 2009[15]
Apixaban	0.005	0.0007	Granger et al, 2011[16]
Dabigatran 110 mg	0.007	0.0011	Connolly et al, 2009[15]
Dabigatran 150 mg	0.007	0.0011	Connolly et al, 2009[15]
Rivaroxaban	0.009	0.0015	Patel et al, 2011[17]
Intervention:Comparator	**Odds Ratio**	**Standard Error**	**Source**
Aspirin:warfarin[a]	1.44	0.3562	Aguilar et al, 2007[53]
Dual antiplatelet:warfarin[b]	0.77	0.0724	Cupareti et al, 2001[59]
Severity of Myocardial Infarctions			
Severity	**Proportion**	**Standard Error**	**Source**
Proportion of myocardial infarctions that are:			
Fatal	0.080	0.0232	Walraven, 2002[58]

Abbreviation: LAAC device, left atrial appendage closure device with delivery system.
[a]Aspirin treatment effects were applied to patients who discontinued pharmacologic therapy and who had a CHA_2DS_2VASc score of less than 2.
[a]Dual antiplatelet treatment effects were applied to patients two months post–myocardial infarction.

Mortality

Baseline mortality was based on age- and sex-specific Ontario life tables[41] and modified based on event occurrence. Short-term hazard ratios of death (0–6 months) for events were obtained from an analysis of the ACTIVE W trial,[60] which assessed oral anticoagulants versus antiplatelet therapy in patients with nonvalvular atrial fibrillation (Table 14).[57] We also included long-term hazard ratios for ischemic and hemorrhagic strokes. We assumed that variation in treatment-specific mortality was directly related to event occurrence. This assumption was tested in sensitivity analyses.

Table 14: Mortality Impacts

Model Parameter	Mean	Standard Error	Source
Short-Term Death, Hazard Ratio 0–6 months			
Ischemic stroke			
Major/moderate	8.2	0.2141	De Caterina et al, 2010[57]
Minor	2.5	0.5068	De Caterina et al, 2010[57]
Systemic embolism	6.5	0.5825	De Caterina et al, 2010[57]
Hemorrhagic stroke			
Major/moderate	20.8	0.5117	De Caterina et al, 2010[57]
Minor	2.5	0.5068	De Caterina et al, 2010[57]
Major bleed	4.2	0.2109	De Caterina et al, 2010[57]
Minor bleed	1.6	0.5086	De Caterina et al, 2010[57]
Myocardial infarction	7.3	0.2983	De Caterina et al, 2010[57]
Ischemic stroke			
Major/moderate	2.9	0.1071	Fang et al, 2014[61]
Hemorrhagic stroke			
Major/moderate	2.2	0.1971	Fogelholm et al, 2003[62]

Utilities

We used several utilities and disutilities to determine the quality-of-life impact of treatment and clinical events (Table 15). As in the work of Micieli and colleagues,[37] the utilities of nonvalvular atrial fibrillation, CHA_2DS_2VASc risk factors, HAS-BLED risk factors, and myocardial infarction were obtained from the One Thousand Health-Related Quality-of-Life Estimates study.[37,63] The majority of these utilities used time-trade-off methodologies. Utilities for stroke (ischemic and hemorrhagic) were based on the disability level as indicated by the NIH Stroke Scale. These utilities, along with those for transient ischemic attack, were obtained from the Oxford Vascular Study, which followed 748 patients over five years using EQ-5D valuation to determine the long-term impacts of stroke and transient ischemic attack.[64] Averages of one-month and one-year utilities were used for the first month and ongoing utility values in the model, respectively. We chose one-year estimates for ongoing utilities as sample sizes decreased substantially after this time point, and mean utility estimates did not vary substantially. If a patient experienced multiple events in their lifetime, the model applied the ongoing utility score from the most severe event (i.e., major stroke).

Table 15: Utilities Used in the Economic Model

Health State	Duration	Utility	Standard Deviation	Source
Nonvalvular atrial fibrillation	Ongoing	0.998	0.3326	Tengs et al, 2000[63]
Abnormal liver function	Ongoing	0.920	0.3067	Tengs et al, 2000[63]
Abnormal renal function	Ongoing	0.580	0.1933	Tengs et al, 2000[63]
Diabetes mellitus	Ongoing	0.838	0.2793	Tengs et al, 2000[63]
Heart failure	Ongoing	0.630	0.0200	Tengs et al, 2000[63]
Hypertension	Ongoing	0.720	0.0051	Tengs et al, 2000[63]
Vascular disease	Ongoing	0.800	0.2667	Tengs et al, 2000[63]
Myocardial infarction	First year	0.870	0.2000	Tengs et al, 2000[63]
Myocardial infarction	Second year	0.937	0.3123	Tengs et al, 2000[63]
Myocardial infarction	Third year	0.950	0.3167	Tengs et al, 2000[63]
Ischemic and hemorrhagic stroke				
Major	1 month	0.13	0.3200	Luengo-Fernandez et al, 2013[64]
Major	Ongoing	0.41	0.3800	Luengo-Fernandez et al, 2013[64]
Moderate	1 month	0.5	0.3700	Luengo-Fernandez et al, 2013[64]
Moderate	Ongoing	0.65	0.2500	Luengo-Fernandez et al, 2013[64]
Minor	1 month	0.73	0.2500	Luengo-Fernandez et al, 2013[64]
Minor	Ongoing	0.74	0.2500	Luengo-Fernandez et al, 2013[64]
Transient ischemic attack	1 month	0.78	0.2500	Luengo-Fernandez et al, 2013[64]
Transient ischemic attack	Ongoing	0.78	0.2600	Luengo-Fernandez et al, 2013[64]

We applied disutilities to reflect treatment impacts on quality of life (Table 16). Disutilities for aspirin and warfarin were obtained from Gage et al.[65] We assumed all novel oral anticoagulants to have the same disutility as dabigatran.[66] As in the work of Micieli et al,[37] we used a one-time disutility for coronary angioplasty to represent the disutility associated with the LAAC device implantation surgery. Finally, we modelled several clinical events using disutilities at the time of event, including adverse events, bleeds, and systemic emboli. All one-time disutilities were modelled for a one-month cycle, with the exception of minor bleeds. As in the work of Micieli et al.,[37] we assumed the disutility of minor bleeds was the same as the disutility for major bleeds, but it was applied for only two days in the model.

Table 16: Disutilities Used in the Economic Model

Health State	Disutility	Standard Deviation	Duration	Source
Treatment-Related Disutilities				
LAAC device implantation	0.060	0.0012	One-time	Garg et al, 2008[67]
Aspirin	0.002	0.0004	Ongoing	Gage et al, 1996[65]
Apixaban	0.006	0.0012	Ongoing	O'Brien et al, 2005[66]
Dabigatran	0.006	0.0012	Ongoing	O'Brien et al, 2005[66]
Rivaroxaban	0.006	0.0012	Ongoing	O'Brien et al, 2005[66]
Warfarin	0.013	0.0026	Ongoing	Gage et al, 1996[65]
Event-Related Disutilities				
Device embolization	0.250	0.0558	One-time	Saw et al, 2016[36]
Pericardial effusion	0.159	0.0318	One-time	Saw et al, 2016[36]
Major bleed	0.159	0.172	One-time	Thomson et al, 2000[68]
Minor bleed	0.011	0.011	One-time	Thomson et al, 2000[68]
Systemic embolism	0.279	0.0558	One-time	Sullivan et al, 2005[69]

Abbreviation: LAAC device, left atrial appendage closure device with delivery system.

Cost Parameters

Costs used in the model included those associated with drug therapy, the LAAC device, surgery, and clinical events (one-time and ongoing). All costs are provided in 2016 Canadian dollars. We updated applicable costs to 2016 Canadian dollars using Statistics Canada's Consumer Price Index for all goods in Ontario.[70]

Drug Therapy Costs

We obtained unit drug costs from the Ontario Drug Benefit formulary[71] and converted these to monthly costs (Table 17) according to the dosing strategies presented in Table 6. Warfarin therapy included the cost of monthly international normalized ratio (INR) testing, which was obtained from the Ministry of Health and Long-Term Care's Schedule of Benefits for Physician Services Under the Health Insurance Act.[72]

Table 17: Costs Used in the Economic Model

Variable	Monthly Cost ($)	Source
Aspirin	0.85	Ontario Drug Benefit Formulary[71]
Aspirin + clopidogrel	15.25	Ontario Drug Benefit Formulary[71]
Apixaban	97.33	Ontario Drug Benefit Formulary[71]
Dabigatran 110 mg	100.25	Ontario Drug Benefit Formulary[71]
Dabigatran 150 mg	100.25	Ontario Drug Benefit Formulary[71]
Rivaroxaban	172.77	Ontario Drug Benefit Formulary[71]
Warfarin[a]	14.80	Ontario Drug Benefit Formulary[71]

[a] Includes the cost of monthly international normalized ratio (INR) monitoring (Schedule of Benefits, G271).[32]

LAAC Device–Specific Costs

Costs for the LAAC device included the cost of the LAAC device, physician, nurse and anesthesiologist fees, overnight hospitalization and catheterization lab costs, costs associated with treating adverse surgical events, and follow-up transesophageal electrocardiography costs (Table 18). Data sources for these costs included the Ministry of Health and Long-Term Care's Schedule of Benefits for Physician Services Under the Health Insurance Act,[72] the LAAC device manufacturer (Boston Scientific Corporation), and the Ontario Case Costing Initiative.[73] As there is currently no fee code for LAAC procedures in Ontario, we consulted with clinical experts to obtain current billing practices. We assumed that the surgery lasts 2.5 hours (but we realize that this time may decrease with physician experience).

Table 18: LAAC Device–Specific Costs Used in the Economic Model

Variable	Unit Cost ($)	Standard Deviation	Source
LAAC Surgery–Specific Costs			
Device	10,000	2,000	Manufacturer (Boston Scientific Corporation)
Physician fees[a]	1,194	–	Schedule of Benefits,[72] expert opinion
Anesthesiologist fees	255	–	Schedule of Benefits[72]
Overnight hospitalization	1,773	355	Saw et al, 2016[36]
Nursing fees	1,750	350	Saw et al, 2016[36]
Catheterization lab fees	3,000	600	Expert opinion
Follow-up TEE	271	–	Schedule of Benefits[72]
Surgical Adverse Event Costs			
Pericardial effusion (ICD 313)	6,422	7,531	Ontario Case Costing Initiative[73]
Device embolization (ICD T82.8)	10,217	12,412	Ontario Case Costing Initiative[73]

Abbreviations: ICD, International Classification of Diseases; LAAC, left atrial appendage closure; TEE transesophageal echocardiography.
[a]Includes fees for transseptal left heart catheterization (Z441), angiogram (G297), percutaneous transluminal catheter-assisted closure for arterial septal defects (Z466), surgical assistant time, and initial TEE (G574, G575, G585, G581, G580).

Clinical Event Costs

We divided clinical event costs into initial hospitalization costs and follow-up costs (Table 19).

We calculated the costs of ischemic stroke, transient ischemic attack, and hemorrhagic stroke based on a Canadian prospective costing study by Goeree et al.[54] The study captured the initial and one-year costs of 365 patients presenting to an Ontario emergency department with stroke or transient ischemic attack. Costs included those for hospitalization, rehabilitation, and home care. Although we included indirect costs, these represented less than 2% of costs and thus were considered negligible. For both ischemic and hemorrhagic stroke, we used Modified Rankin Scores (MRSs) to determine the total one-year costs (including those for initial hospitalization and follow-up) for fatal (MRS = 6), major (MRS = 5), moderate (MRS = 4–5), and minor (MRS = 0–3) strokes. Owing to a paucity of data, we assumed the cost of a minor hemorrhagic stroke was the same as for a minor ischemic stroke. We then divided total one-year costs into initial hospitalization and follow-up costs. We converted one-year follow-up costs

to monthly costs. We assumed costs after one year to be approximately one-fourth the first-year costs after comparing average first-year costs and annual three-to-five-year costs using longitudinal stroke costing data from Gloede et al.[74]

We obtained initial, one-year, and three-year myocardial infarction costs from an Ontario costing study by Cohen et al.[75] The study included the average costs from 16,450 patients with acute myocardial infarction. We assumed that costs after three years were negligible. Patients with fatal myocardial infarction were assumed to incur 40% of the costs of hospitalization for nonfatal initial myocardial infarction, as determined through the relative costs of fatal and nonfatal myocardial infarctions in Canadian studies.[76]

The remaining events were represented as one-time hospitalization costs. We obtained the cost of systemic embolism from the Ontario Case Costing Initiative.[73] We derived the cost of major bleeds from the Ontario GI Bleed Study.[77] Finally, we assumed that a minor bleed resulted in a primary care visit; thus, we costed minor bleeds using the Ministry of Health and Long-Term Care's Schedule of Benefits for Physician Services Under the Health Insurance Act.[72]

Table 19: Clinical Event Costs Used in the Economic Model

Variable	Unit Cost ($, 2016)	Standard Deviation	Source
Initial Hospitalization Costs			
Ischemic stroke			
Fatal	18,285	3,657	Goeree et al, 2005[54]
Major	89,013	17,802	Goeree et al, 2005[54]
Moderate	27,666	5,533	Goeree et al, 2005[54]
Minor	7,966	1,593	Goeree et al, 2005[54]
Systemic embolism	11,171	2,234	Ontario Case Costing Initiative[73]
Transient ischemic attack	1,852	370	Goeree et al, 2005[54]
Hemorrhagic stroke			
Fatal	9,333	1,867	Goeree et al, 2005[54]
Major	53,656	10,731	Goeree et al, 2005[54]
Moderate	19,778	3,956	Goeree et al, 2005[54]
Minor	7,966	1,593	Goeree et al, 2005[54]
Major bleed	6,424	1,284	Comay et al, 2002[77]
Minor bleed	77[a]	–	Schedule of Benefits[72]
Myocardial infarction			
Fatal	6,667[b]	7,766	Brennan et al, 2014[76]
Nonfatal	16,462	19,174	Cohen et al, 2014[75]
Monthly Ongoing Follow-Up Costs			
Ischemic stroke			
Major (year 1)	13,477	2,695	Goeree et al, 2005[54]
Major (post–year 1)	3,504	701	Goeree et al, 2005[54]
Moderate (year 1)	4,189	838	Goeree et al, 2005[54]
Moderate (post–year 1)	1,089	218	Goeree et al, 2005[54]
Minor (year 1)	1,206	241	Goeree et al, 2005[54]
Minor (post–year 1)	314	63	Goeree et al, 2005[54]
Transient ischemic attack (year 1)	1,488	298	Goeree et al, 2005[54]
Hemorrhagic stroke			
Major (year 1)	14,969	2,994	Goeree et al, 2005[54]
Major (post–year 1)	3,892	778	Goeree et al, 2005[54]
Moderate (year 1)	5,518	1,104	Goeree et al, 2005[54]
Moderate (post–year 1)	1,435	287	Goeree et al, 2005[54]
Minor (year 1)	1,206	241	Goeree et al, 2005[54]
Minor (post–year 1)	314	63	Goeree et al, 2005[54]
Myocardial infarction (year 1)	516	350	Cohen et al, 2014[75]
Myocardial infarction (years 2–3)	129	111	Cohen et al, 2014[75]

[a]Assume that a minor bleed results in one physician visit.
[b]Assume that the cost of a fatal myocardial infarction is 40% that of a nonfatal myocardial infarction (derived from relative costs from five Canadian studies).[76]

Analysis

For the base case analysis, we used a probabilistic sensitivity analysis to determine the mean incremental costs and mean incremental QALYs for each treatment. In addition, we calculated the incremental cost-effectiveness ratio (ICER) for the LAAC device compared with each of the assessed novel oral anticoagulants (i.e., apixaban, dabigatran, rivaroxaban) and with warfarin.

We performed the probabilistic sensitivity analysis using a Monte Carlo simulation with 1,000 outer loops, to capture parameter uncertainty, and 10,000 inner loops, to capture patient variability. We examined parameter uncertainty by specifying distributions around each estimate, using the mean and standard deviation. The distributions used include gamma distributions for cost inputs; log-normal distributions for relative risk, odds ratio, or hazard ratio inputs; and beta distributions for probability and utility inputs.

In addition to the base case results described, we present the impact of uncertainty and variability through a cost-effectiveness acceptability curve.

Deterministic Sensitivity Analyses

We conducted deterministic sensitivity analyses to assess how sensitive our base case results were to specific parameters. We performed sensitivity analyses on several parameters, including those related to adverse events associated with LAAC device implantation, clinical event rates, LAAC device treatment effects, utilities, and costs. Details of the analyses and the specific parameters are presented in Appendix 4, Table A3. To capture patient variability, we ran Monte Carlo simulations for 10,000 iterations per estimate analyzed.

Scenario Analyses

We conducted seven scenario analyses. For each scenario, we recalculated the mean incremental costs and QALYs for each treatment, along with the ICER for the LAAC device compared with each alternative. All scenarios were performed using a Monte Carlo simulation with 100 outer loops, to capture parameter uncertainty, and 1,000 inner loops, to capture patient variability.

Scenario 1: Cost-Effectiveness of the LAAC Device Among Patients with Nonvalvular Atrial Fibrillation at High Risk for Bleeding

A subgroup analysis was performed on individuals at high risk for bleeding. Health Canada indicates that the LAAC device is appropriate for individuals "suitable for warfarin" but who have "an appropriate rationale to seek a nonpharmacologic alternative."[10] Reasons for not taking oral anticoagulants include relative contraindications (e.g., the occurrence of previous bleeds or being at high risk for bleeding) or nonpreference for anticoagulants.[78-80] Thus, we examined the cost-effectiveness of the LAAC device compared with novel oral anticoagulants or warfarin in patients at high risk for bleeding, as determined by HAS-BLED score. We set all patients' HAS-BLED scores to 4, which is considered to indicate a high bleeding risk.[81] We assumed this risk to remain constant throughout a patient's lifetime.

Scenario 2: Distinguishing Between Procedural and Nonprocedural Ischemic Strokes and Major Bleeds

The treatment effects used in our base case analysis conservatively incorporated all ischemic strokes and major bleeding events in the LAAC device arm of the PREVAIL and PROTECT AF

clinical trials.[20,40] However, the authors of these clinical trials divided ischemic strokes and bleeds into procedural events (those occurring within seven days of device implantation) and nonprocedural events.[20,40] We assessed the impact of distinguishing between these two types of events on the cost-effectiveness of the LAAC device by adjusting base case treatment effects and including procedural strokes and bleeds in the model (Table 20). We assumed all procedural strokes were of moderate severity.

Table 20: Scenario Analysis 2—Parameter Inputs for Procedural and Nonprocedural Events

	Estimate	Standard Error	Source
Base Case			
Event	*OR, LAAC device:warfarin*		
Ischemic stroke	1.56	0.3569	Holmes et al, 2014[20]; Reddy et al, 2014[40]
Major bleed	0.95	0.2011	Holmes et al, 2014[20]; Reddy et al, 2014[40]
Scenario			
Event	*Probability of procedural event*		
Ischemic stroke	1.25	0.2239	Holmes et al, 2014[20]; Reddy et al, 2014[40]
Major bleed	0.55	0.1908	FDA, 2015[55]
	Nonprocedural OR, LAAC device:warfarin		
Ischemic stroke	0.008	0.0033	Holmes et al, 2014[20]; Reddy et al, 2014[40]
Major bleed	0.055	0.0084	FDA, 2015[55]

Abbreviations: LAAC device, left atrial appendage closure device with delivery system; OR, odds ratio.

Scenario 3: Including Treatment Effects on All-Cause Mortality

Conservatively, we assumed that treatment-related mortality was directly related to variation in clinical events. In this scenario, we loosened this assumption and directly included the treatment-related effects on all-cause mortality for the LAAC device and each of the novel oral anticoagulants relative to warfarin. We included mortality effects by adjusting warfarin death rates by the relative rate of death reported in the clinical trials (Table 21). We applied these effects for two years, the average follow-up period of the trials included.

Table 21: Scenario Analysis 3—Parameter Inputs for All-Cause Mortality Effects

Intervention:Comparator	Relative Mortality Estimate	Standard Error	Source
LAAC device:warfarin	0.71	0.1865	Holmes et al, 2014[20]; Reddy et al, 2014[40]
Apixaban:warfarin	0.91	0.0682	Granger et al, 2011[16]
Dabigatran 110 mg:warfarin	0.88	0.0685	Connolly et al, 2009[15]
Dabigatran 150 mg:warfarin	0.89	0.0582	Connolly et al, 2009[15]
Rivaroxaban:warfarin	0.83	0.0954	Patel et al, 2011[17]

Abbreviation: LAAC device, left atrial appendage closure device with delivery system.

Scenario 4: Adjusting Costs of Ischemic Stroke, Hemorrhagic Stroke, Major Bleeds, and Transient Ischemic Attack

We chose our costing sources based on the facts that they were Ontario specific and captured the monetary burden associated with the diverse follow-up care required for strokes of varying disability. As these sources were approximately 10 years old, we inflated the costs to 2016 dollars. To explore the impact of using alternative costing sources, we substituted the base case costs of stroke, transient ischemic attack, and bleeds with costs obtained from the Ontario Case Costing Initiative[73] (Table 22). We inflated the most recent data available (from 2011) to 2016 dollars. The Ontario Case Costing Initiative costs were based on International Statistical Classification of Diseases, 10th revision (ICD-10), codes, which do not allow for stratification by severity. Thus, fatal, major, moderate, and minor strokes were assumed to have the same costs. However, we were able to distinguish between ischemic and hemorrhagic events. We assumed the initial hospitalization costs derived from the Ontario Case Costing Initiative represented 55% of total first-year stroke costs, as in Mittmann et al.[82] Similar to our base case, we assumed that costs after one year would be 40% those of first-year costs.

Table 22: Scenario Analysis Using Ontario Case Costing Initiative Costs

Variable	Unit Cost ($)	Standard Error	Source
Initial Hospitalization Costs			
Ischemic stroke	13,207	11,105	Ontario Case Costing Initiative[73]
Transient ischemic attack	1,185	1,032	Ontario Case Costing Initiative[73]
Hemorrhagic stroke	17,145	12,746	Ontario Case Costing Initiative[73]
Major bleed	9,764	1,951	Ontario Case Costing Initiative[73]
Monthly Ongoing Follow-Up Costs			
Ischemic stroke			
Year 1	915	769	Based on Mittmann et al, 2012[82]
Post–year 1	229	57	Based on Gloede et al, 2014[74]
Transient ischemic attack			
Year 1	82	72	Based on Mittmann et al, 2012[82]
Hemorrhagic stroke			
Year 1	1,188	883	Based on Mittmann et al, 2012[82]
Post–year 1	297	74	Based on Gloede et al, 2014[74]

Scenario 5: Incorporating the Cost of Novel Oral Anticoagulant Reversal Agents

Currently, dabigatran is the only novel oral anticoagulant to have a reversal agent on the market (idarucizumab).[83] To capture the potential costs associated with this agent, and future reversal agents, we added an additional USD$3,500 (CAD$4,700), the wholesale cost of idarucizumab,[84] to major bleeds in each of the novel oral anticoagulant arms. We note that this agent may reduce the severity of bleeds in this arm, but we were unable to account for this in the model, which led to an optimistic scenario for the LAAC device.

Scenario 6: Treating All Patients Aged 65 Years or Older

A recent update to the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation suggests that all patients with atrial fibrillation aged 65 years or older should be

treated with oral anticoagulants.[85] We updated our model so that patients with a CHA_2DS_2VASc score of more than 1 and those aged 65 years or older were treated with the LAAC device or oral anticoagulants.

Scenario 7: Adverse Events and Surgical Outcomes from the PREVAIL Trial

Our base case analysis pooled events from the PROTECT AF and PREVAIL trials. The PREVAIL trial showed increased procedural success and reduced adverse events for patients treated with the LAAC device compared with those treated with the LAAC device in the PROTECT AF trial. To test the improved safety profile in this scenario, we used the estimates from the PREVAIL trial only (Table 23).

Table 23: LAAC Adverse Events and Surgical Outcomes from the PREVAIL Trial Only

Treatment	Probability of Outcome	Standard Error
Device embolization	0.007	0.005
Pericardial effusion	0.037	0.008
LAAC device implantation unsuccessful	0.075	0.013
Device leak (6 weeks)	0.127	0.019
Device leak (6 months)	0.054	0.008

Abbreviation: LAAC device, left atrial appendage closure device with delivery system.
Source: Holmes et al, 2014.[20]

Scenario 8: Proportion of Disabling and Nondisabling Stroke Modelled From the PROTECT AF Trial

Our base case analysis assumed that the severity of stroke was based on type (i.e., hemorrhagic or ischemic) and did not vary between treatments.[54] The PROTECT AF trial reported that patients in the LAAC device arm had fewer disabling strokes than patients in the warfarin arm.[40] In this scenario, as per the PROTECT AF trial, we assumed 31% and 55% of all strokes are disabling (MRS = 3–6) in patients treated with the LAAC device and warfarin, respectively. We assumed disabling strokes are evenly divided into fatal (MRS = 6), major (MRS = 5), and moderate (MRS = 3–4). In addition, we assumed that the proportion of disabling strokes in patients receiving a novel oral anticoagulant was the same as for those receiving warfarin.

Generalizability

The findings of this economic analysis cannot be generalized to patients with nonvalvular atrial fibrillation without contraindications to oral anticoagulation. They may, however, be used to guide decision-making about the specific patient populations addressed in the trials investigated by Health Quality Ontario.

Expert Consultation

In the fall of 2016, we solicited expert consultation on the LAAC device from physicians specializing in cardiology. The role of the expert advisors was to inform model parameters where literature was unavailable and to provide advice on the clinical pathways of patients with nonvalvular atrial fibrillation at risk for stroke. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Base Case Analysis

Results from the base case analysis are presented in Table 24. We found that the LAAC device has greater costs and lower QALYs compared with apixaban, dabigatran, and rivaroxaban. We found that, compared with warfarin, the LAAC device had higher QALYs and higher costs. We calculated the ICER of the LAAC device compared with warfarin to be $272,216.

Table 24: Base Case Analysis Results

Strategy	Average Total Costs, $	Incremental Cost of LAAC,[a] $	Average Total QALYs	Incremental QALYs of LAAC Device[b]	ICER of LAAC Device[c]
Intervention					
LAAC device	40,707	–	5.66	–	–
Comparator					
Apixaban	26,248	14,459	5.82	−0.16	Dominated[d]
Dabigatran	25,694	15,013	5.81	−0.15	Dominated[d]
Rivaroxaban	30,530	10,177	5.74	−0.08	Dominated[d]
Warfarin	24,374	16,333	5.60	0.06	$272,216/QALY

Abbreviations: ICER, incremental cost-effectiveness ratio; LAAC, left atrial appendage closure device with delivery system; QALY, quality-adjusted life-year.
[a]Incremental costs = average costs (LAAC device) − average costs (comparator).
[b]Incremental QALYs = average QALYs (LAAC device) − average QALYs (comparator).
[c]ICER = incremental costs ÷ incremental QALYs.
[d]Higher costs, lower QALYs.

Sensitivity Analysis

Figure 9 shows the cost-effectiveness acceptability curve, which captures parameter uncertainty and depicts the probability that the LAAC device is cost-effective relative to the novel oral anticoagulants assessed and warfarin across a range of willingness-to-pay values. At the maximum willingness-to-pay threshold of $100,000 per QALY, the probability that the LAAC device was cost-effective was 0.04 (4%). At the same willingness-to-pay threshold, the probability of apixaban, dabigatran, or rivaroxaban being cost-effective was 0.48 (48%), 0.47 (47%), and 0.01 (1%), respectively.

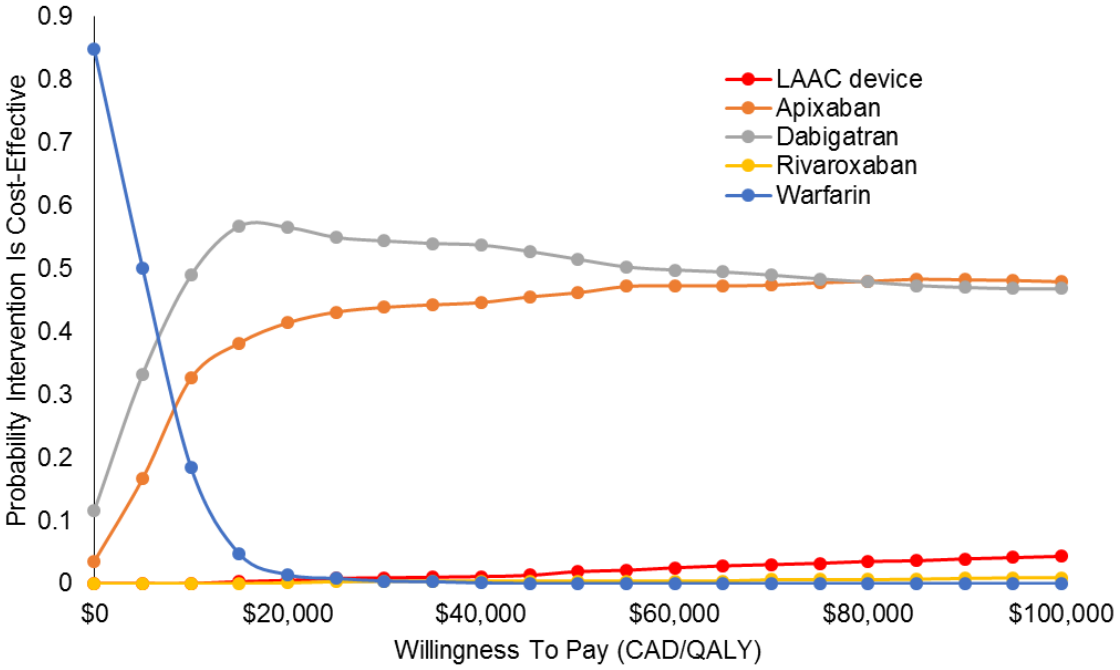

Figure 9: Cost-Effectiveness Acceptability Curve for the LAAC Device Compared With Novel Oral Anticoagulants

Abbreviation: LAAC device, left atrial appendage closure device with delivery system.

Results from our deterministic sensitivity analyses are presented in Appendix 4, Table A4. For the majority of parameters, the LAAC device remained dominated by apixaban, dabigatran, and rivaroxaban. Further, we found that the LAAC device was not cost-effective compared with warfarin (ICER ≥ $50,000/QALY). The results were sensitive to two parameters: the baseline rate of thromboembolic events, and the thromboembolic treatment effect between the LAAC device and warfarin. When we reduced baseline thromboembolic event rates (by CHA_2DS_2VASc score) by 50%, our results indicated that at a willingness-to-pay threshold of $50,000 per QALY, the LAAC device was cost-effective compared with rivaroxaban (ICER = $36,468/QALY) and warfarin (ICER = $45,423/QALY). In this scenario, the LAAC device had higher QALYs but was not cost-effective compared with apixaban (ICER = $426,041/QALY) or dabigatran (ICER = $812,338/QALY). Similarly, when the odds ratio comparing thromboembolic events in patients with the LAAC device versus patients on warfarin was at its lower bound estimate (OR = 0.77), the LAAC device was cost-effective relative to rivaroxaban (ICER = $14,331/QALY) and also warfarin (ICER = $28,414/QALY). At this lower bound estimate, the LAAC device remained not cost-effective compared with apixaban (ICER = $71,228/QALY) and dabigatran (ICER = $82,185/QALY).

Results from the various scenario analyses are presented in Table 25. Across the majority of scenarios, the LAAC device was dominated by each of the assessed novel oral anticoagulants. In scenario 1, which examined patients at high risk for bleeding, the LAAC device was dominated by the novel oral anticoagulants and had an ICER of $312,760 compared with warfarin. In scenario 2, in which LAAC device procedural and nonprocedural events were distinguished, at a willingness-to-pay value of $50,000 per QALY, we found the LAAC device to

be cost-effective, compared with rivaroxaban (ICER = $48,945/QALY) and warfarin (ICER = $49,608/QALY). In this scenario, the LAAC device remained dominated by apixaban and dabigatran. Further, at a willingness-to-pay value of $50,000 per QALY, the probability that the LAAC device was the most cost-effective intervention was 0.12 (12%). In scenarios 3 through 7, the LAAC device was dominated by apixaban, dabigatran, and rivaroxaban and was found not to be cost-effective compared with warfarin (scenario 3 ICER = $162,836/QALY; scenario 4 ICER = $379,350/QALY; scenario 5 ICER = $228,657/QALY; scenario 6 ICER = $333,880/QALY; scenario 7 ICER = $206,700).

Table 25: Scenario Analyses Results

Strategy	Average Total Costs, $	Incremental Cost of LAAC,[a] $	Average Total QALYs	Incremental QALYs of LAAC[b]	ICER of LAAC Device[c]	Probability Treatment Is Cost-Effective[d]
Scenario 1: High Risk of Bleeding (HAS-BLED = 4)						
Intervention						
LAAC device	42,904		5.48			0.04
Comparator						
Apixaban	28,751	14,153	5.63	−0.15	Dominated[e]	0.47
Dabigatran	28,124	14,780	5.62	−0.14	Dominated[e]	0.47
Rivaroxaban	33,125	9,779	5.55	−0.07	Dominated[e]	0.01
Warfarin	27,266	15,638	5.43	0.05	$312,760/QALY	0.00
Scenario 2: Procedural and Nonprocedural Stroke and Major Bleeds						
Intervention						
LAAC device	31,214		6.12			0.12
Comparator						
Apixaban	20,879	10,335	6.07	0.05	$206,700/QALY	0.41
Dabigatran	20,627	10,587	6.08	0.04	$264,675/QALY	0.47
Rivaroxaban	25,830	5,384	6.01	0.11	$48,945/QALY	0.00
Warfarin	19308	11,906	5.88	0.24	$49,608/QALY	0.00
Scenario 3: Treatment Effects on All-Cause Mortality Included						
Intervention						
LAAC device	42,638		5.71			0.03
Comparator						
Apixaban	26,953	15,685	5.84	−0.13	Dominated[e]	0.39
Dabigatran	26,301	16,337	5.84	−0.13	Dominated[e]	0.57
Rivaroxaban	31,250	11,388	5.79	−0.08	Dominated[e]	0.01
Warfarin	24,726	17,912	5.6	0.11	$162,836/QALY	0.00

Strategy	Average Total Costs, $	Incremental Cost of LAAC Device,[a] $	Average Total QALYs	Incremental QALYs of LAAC Device[b]	ICER of LAAC Device[c]	Probability Treatment Is Cost-Effective[d]
Scenario 4: Costs of Stroke, Bleed, and Transient Ischemic Attack Obtained From Ontario Case Costing Initiative[73]						
Intervention						
LAAC device	26,795		5.66			0.04
Comparator						
Apixaban	14,942	11,853	5.79	−0.13	Dominated[e]	0.53
Dabigatran	15,473	11,322	5.79	−0.13	Dominated[e]	0.42
Rivaroxaban	19,831	6,964	5.73	−0.07	Dominated[e]	0.01
Warfarin	12,035	14,790	5.58	0.08	$184,875/QALY	0.00
Scenario 5: Cost of Novel Oral Anticoagulant Reversal Agent Included						
Intervention						
LAAC device	41,162		5.67			0.02
Comparator						
Apixaban	27,457	13,705	5.82	−0.15	Dominated[e]	0.53
Dabigatran	27,003	14,159	5.81	−0.14	Dominated[e]	0.44
Rivaroxaban	31,616	9,546	5.77	−0.04	Dominated[e]	0.01
Warfarin	24,642	16,520	5.62	0.05	$330,400/QALY	0.00
Scenario 6: Treating All Patients Aged 65 Years or Older						
Intervention						
LAAC device	40,787		5.67			0.00
Comparator						
Apixaban	25,849	14,938	5.82	−0.15	Dominated[e]	0.47
Dabigatran	25,462	15,325	5.82	−0.15	Dominated[e]	0.52
Rivaroxaban	30,247	10,540	5.75	−0.08	Dominated[e]	0.01
Warfarin	24,093	16,694	5.62	0.05	$333,880/QALY	0.00
Scenario 7: LAAC Device Adverse Events and Surgical Outcomes From PREVAIL Trial Only						
Intervention						
LAAC device	40,662		5.68			0.00
Comparator						
Apixaban	26,096	14,566	5.84	−0.16	Dominated[e]	0.47
Dabigatran	25,493	15,169	5.83	−0.15	Dominated[e]	0.53
Rivaroxaban	30,210	10,452	5.76	−0.08	Dominated[e]	0.00
Warfarin	24,126	16,536	5.62	0.08	$206,700/QALY	0.00

Strategy	Average Total Costs, $	Incremental Cost of LAAC,[a] $	Average Total QALYs	Incremental QALYs of LAAC Device[b]	ICER of LAAC Device[c]	Probability Treatment Is Cost-Effective[d]
Scenario 8: Proportion of Disabling and Nondisabling Stroke Modelled From the PROTECT AF Trial						
Intervention						
LAAC device	38,165		5.81			0.20
Comparator						
Apixaban	28,725	9,440	5.83	−0.02	Dominated[e]	0.38
Dabigatran	27,929	10,236	5.82	−0.01	Dominated[e]	0.40
Rivaroxaban	33,021	5,144	5.76	0.05	102,880	0.01
Warfarin	27,253	10,912	5.65	0.16	68,200	0.00

Abbreviations: ICER, incremental cost-effectiveness ratio; LAAC device, left atrial appendage closure device with delivery system; QALY, quality-adjusted life-year.
[a]Incremental costs = average costs (LAAC) − average costs (comparator).
[b]Incremental QALYs = average QALYs (LAAC) − average QALYs (comparator).
[c]ICER = incremental costs ÷ incremental QALYs.
[d]At a willingness-to-pay threshold of $50,000/QALY.
[e]Higher costs, lower QALYs.

Discussion

Collectively, our results indicate that, in patients with nonvalvular atrial fibrillation and no contraindications to oral anticoagulants, the LAAC device is more costly and less clinically effective than each of the Health Canada–approved novel oral anticoagulants (i.e., apixaban, dabigatran, rivaroxaban). Sensitivity analyses indicate that this conclusion is robust to parameter uncertainty and several key assumptions. Individual parameters did not have a large influence on our results. Only two parameters influenced the cost-effectiveness of the LAAC device compared with the novel oral anticoagulants: baseline thromboembolic event rates and LAAC device thromboembolic treatment effects. When the LAAC device was favoured (as indicated by a lower baseline of thromboembolic events or a protective treatment effect of the LAAC device compared with warfarin), the LAAC device had higher QALYs than apixaban, dabigatran, and rivaroxaban and was cost-effective relative to rivaroxaban. These findings highlight thromboembolic events, including ischemic stroke, systemic embolism, and transient ischemic attack, as key drivers in the potential cost-effectiveness of the LAAC device. If future clinical evidence (i.e., trials comparing the LAAC device with novel oral anticoagulants) shows that the LAAC device improve relative thromboembolic event rates, then the device may be cost-effective in nonvalvular atrial fibrillation patients without contraindications to oral anticoagulants. However, when we captured the joint uncertainty in this parameter, and all other parameters through probabilistic sensitivity analysis, we found that the LAAC device was cost-effective only 4% of the time, at the upper willingness-to-pay threshold examined ($100,000/QALY).

Similar to our base case analysis, in the majority of our scenario analyses, all three novel oral anticoagulants assessed consistently dominated the LAAC device. We explored a population at high risk for bleeding as a proxy for patients with relative contraindications to oral anticoagulants, and in this scenario, the LAAC device remained more costly and less clinically effective than novel oral anticoagulants. While we found that the LAAC device outperforms novel oral anticoagulants in terms of hemorrhagic stroke (see Table 11), the major bleeding rates in patients with the device were closer to those found in patients on warfarin (see Table

12). Although some of the major bleeds may be related to procedural events, our conclusions conservatively indicate that the LAAC device is not cost-effective in the population of patients with nonvalvular atrial fibrillation population and a high HAS-BLED score (4). We note that the real-world, high-risk-bleed population may not have been fully captured by the PROTECT AF and PREVAIL trials and that the risk factor profile of this population may be more similar to that captured in the ASAP study. In addition, there are numerous other contraindications and reasons (including personal preference) for not taking oral anticoagulants.[78-80] Although we were unable to capture these fully in our analysis, previous economic evaluations have found the LAAC device to be cost-effective in contraindicated populations relative to aspirin and apixaban.[22,36]

In the scenario in which we distinguished between procedural and nonprocedural strokes and bleeds, we found the LAAC device to be cost-effective compared with rivaroxaban. This finding highlights the importance of surgical adverse events and operator experience. If training and experience with the LAAC device greatly reduce the number of procedural events, there is potential for the LAAC device to become cost-effective relative to rivaroxaban. However, in this scenario, the LAAC device remained dominated by alternative novel oral anticoagulants, suggesting that the LAAC device would still not be the most cost-effective therapy compared with oral anticoagulants.

Conclusions in the current economic literature vary widely. Our results are similar to those found with previous versions of the Ontario microsimulation model reported by Micieli et al.[37] In line with our evaluation, the authors reported that the LAAC device was not cost-effective relative to apixaban (dominated), rivaroxaban (dominated), and warfarin (ICER = $75,162/QALY). However, the authors found that the LAAC device was cost-effective relative to dabigatran (ICER = $33,167/QALY). This finding may be explained by a key modification we made in the model structure. We distinguished between the treatment effects of hemorrhagic stroke—a very costly event with poor outcomes—and major bleeds—which are less costly and less severe. Dabigatran is associated with very low hemorrhagic stroke rates relative to warfarin, and the corresponding improvements in quality of life and reduction in costs may have been more fully captured in our model. Our evaluation also incorporated clinical effectiveness evidence from the PREVAIL trial,[20] which previous Ontario analyses did not.

Two previous cost-effectiveness studies included the PREVAIL results.[34,35] Our results are consistent with Freeman et al,[34] who found that, when using treatment effects from the PREVAIL trial, the LAAC device was dominated by dabigatran and warfarin. We pooled the results of the PROECT AF and PREVAIL trials and found that dabigatran remains dominant when assessing the totality of the evidence available. Only one other study[35] used evidence from the PREVAIL trial, finding contradictory evidence that the LAAC device was cost-effective relative to all novel oral anticoagulants and warfarin. However, the authors did not use relative treatment effects but instead used crude event rates from several clinical trials. Baseline event rates may vary in each clinical trial and can lead to biased comparisons between interventions. In addition, the authors used an annual ischemic stroke rate of 0.84% for the LAAC device, which is the lowest rate used in their assessment. Even with the exclusion of procedural stroke (see Table 20), this value seems unusually low.

Our primary economic evaluation has several strengths. Our analysis used data from a large Ontario cohort identified in a previous analysis.[37] This allowed us to capture the real-world distribution of risk factors in Ontario, increasing the generalizability of our results to the provincial setting. In addition, through microsimulation methods and the use of validated thromboembolic and hemorrhagic risk scores, we were able to model the natural history of

nonvalvular atrial fibrillation and the impact interventions may have on economic and clinical outcomes. Our model captured the expected variation in costs, quality of life, and mortality based on the severity of ischemic and hemorrhagic events. The LAAC device may lead to a small increase in ischemic stroke rates and a decrease in hemorrhagic stroke rates relative to oral anticoagulants. Thus, capturing the differences in the severity of ischemic and hemorrhagic strokes and their impact on outcomes is crucial. Finally, we were able to compare the LAAC device to all Health Canada–approved novel oral anticoagulants and warfarin, using the most recent LAAC effectiveness data from the PREVAIL trial.

There were also limitations to our analysis. There is currently no direct clinical evidence comparing the LAAC device with novel oral anticoagulants. In the absence of such evidence, we used the relative treatment effects of the interventions and warfarin, a common comparator. In addition, we were unable to identify an Ontario source for utility estimates, and solicitation methods varied. Clinical event costs, while Ontario-specific and capturing the complexities associated with ischemic and hemorrhagic events, were outdated and inflated to 2016 dollars. These limitations were assessed using probabilistic and scenario-based analyses, and our results showed little variation. Finally, we were unable to thoroughly examine patients who are eligible for oral anticoagulants but have a “strong rationale” for alternatives as per the Heath Canada indications for the LAAC device.[10] This specific population remains difficult to define, as the decision to forego oral anticoagulants could be related to a variety of relative contraindications and physician or patient preferences. However, we suspect that many such patients were captured by the ASAP trial and previous economic evaluations in patients with nonvalvular atrial fibrillation with contraindications to oral anticoagulants, in which the LAAC device was found to be highly cost-effective.

Conclusions

Our economic analysis indicates that the LAAC device has higher costs and lower QALYs compared with the Health Canada–approved novel oral anticoagulants (i.e., apixaban, dabigatran and rivaroxaban) in patients with nonvalvular atrial fibrillation and without contraindications to oral anticoagulants. These results were robust to parameter uncertainties and several assumptions.

BUDGET IMPACT ANALYSIS

We conducted a budget impact analysis from the perspective of the Ontario Ministry of Health and Long-Term Care to determine the estimated cost burden for the LAAC device over the next five years. All costs are reported in 2016 dollars.

Objective

The objective of this study was to assess the budget impact of funding the LAAC device for the prevention of stroke in patients with nonvalvular atrial fibrillation, within the context of the Ontario Ministry of Health and Long-Term Care.

Methods

Target Populations

The primary economic evaluation indicated that the LAAC device is not cost-effective in the population of patients with nonvalvular atrial fibrillation without contraindications to oral anticoagulants. Further, expert consultation indicates that the LAAC device is primarily being used in patients with contraindications to oral anticoagulants, where the device has been found to be cost-effective relative to aspirin.[36] We therefore focused our budget impact analysis on the population of patients with nonvalvular atrial fibrillation with contraindications to oral anticoagulants.

In this assessment, we present the budget impact in patients with both absolute and relative contraindications. Table 26 presents the population estimates we used in our budget impact model.

Table 26: Population Estimates for Budget Impact Analysis of the LAAC Device, 2016–2020

Population	Year					Source
	2016	2017	2018	2019	2020	
NVAF at risk ($CHA_2DS_2VASc \geq 2$)	171,848	176,917	182,044	187,229	192,472	Calculation[a]
Absolute contraindications to OACs	3,712	3,821	3,932	4,044	4,157	Steinberg, 2015[78]
Relative contraindications to OACs	80,234	82,601	84,995	87,416	89,864	Steinberg, 2015[78]

Abbreviations: $CHADS_2DS_2VASc$, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, Stroke or transient ischemic attack symptoms previously (2 points), Vascular disease, Age 65–74 years, Sex category; LAAC device, left atrial appendage closure device with delivery system; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant.

[a]Calculated based on Ontario population estimates[86] and atrial fibrillation prevalence estimates[87] assuming that 90% of atrial fibrillation cases are nonvalvular[88] and 72% of patients are at risk of stroke.[37]

We estimated the population of patients with atrial fibrillation by multiplying the projected Ontario population from 2016 to 2020[86] by the prevalence of atrial fibrillation. We obtained Ontario atrial fibrillation prevalence estimates for 2000 through 2014 from Tu et al[87] and used linear projection to obtain prevalence estimates for 2015 through 2020. We assumed that 90% of atrial fibrillation is nonvalvular.[88] Further, based on the cohort of patients used in our primary economic

evaluation, we assumed that 72.3% of patients have a CHA_2DS_2VASc score higher than 2.[37] We estimated that the percentage of this population with absolute contraindications to oral anticoagulants is 2.2% and that the percentage of those with relative contraindications, or at risk of adverse events while on oral anticoagulants, is 46.6%.[78] It is important to note that, owing to variation in definitions and practice, these two subpopulations can be difficult to distinguish.[89] As a result, estimates of absolute and relative contraindications vary widely in the literature.[78-80,90]

Resources and Costs

Predicted LAAC Device Volumes

The estimated volume of LAAC device procedures over the next five years is presented in Table 27. In our base case, we assumed that uptake occurs in the population with absolute contraindications and increases by 3% each year. The 2016 value is based on information provided by the manufacturer (Boston Scientific Corporation) regarding the number of LAAC device implantations from January to July in Ontario. We projected this value until the end of 2016, with the assumption of approximately five procedures occurring each month. We then calculated the volumes of LAAC device procedures for 2017 through 2020 by multiplying the uptake rate of the LAAC device by the population estimate, accounting for those who had already received a device. Our 2020 volume is consistent with predicted implant volumes provided by the manufacturer (Boston Scientific Corporation), which take into account treatment capacity and global patterns of uptake.

In our scenario analyses, we examined a growth in uptake of the LAAC device of 1% and 5% per year in the population of patients with nonvalvular atrial fibrillation and absolute contraindications to oral anticoagulants. Further, we examined a growth in uptake of 3% per year in the population with nonvalvular atrial fibrillation and relative contraindications to oral anticoagulants.

Table 27: Uptake and Volume Estimates for the LAAC Device, 2016–2020

	Year				
Scenario	**2016**	**2017**	**2018**	**2019**	**2020**
Base Case					
3% growth per year					
Uptake	1.66%	4.66%	7.66%	10.66%	13.66%
Volume	63	180	291	386	458
Scenarios (Absolute Contraindications)					
1% growth per year					
Uptake	1.66%	2.66%	3.66%	4.66%	5.66%
Volume	63	103	142	179	214
5% growth per year					
Uptake	1.66%	6.66%	11.66%	16.66%	21.66%
Volume	63	258	434	567	639
Scenarios (Relative Contraindications)					
3% growth per year					
Uptake	0.08%	3.08%	6.08%	9.08%	12.08%
Volume	63	2,613	5,149	7,446	9,307

Technology Mix

In our base case, which focused on patients with absolute contraindications to oral anticoagulants, we assumed that the predicted volumes of the LAAC device would displace patients with nonvalvular atrial fibrillation currently on aspirin therapy.

In our scenario analyses, we examined the displacement of each aspirin user and oral anticoagulant user when we calculated the budget impact for patients with relative contraindications to oral anticoagulants. In the scenario in which we examined the displacement of oral anticoagulant users, we assumed that the displacement of each oral anticoagulant was proportional to its relative use in the nonvalvular atrial fibrillation population. Predicted current and future oral anticoagulant use by type is presented in Figure 10. We assumed that in 2016, warfarin was used by approximately 49% of oral anticoagulant users and novel oral anticoagulants by the remaining 51%. These values were based on 2014 oral anticoagulant prescriptions in patients with atrial fibrillation identified through the drug benefit database.[87] We based predicted changes in warfarin users relative to novel oral anticoagulant users over the five-year time horizon, in addition to the distribution of novel oral anticoagulants in 2016 and over time, on expert opinion.

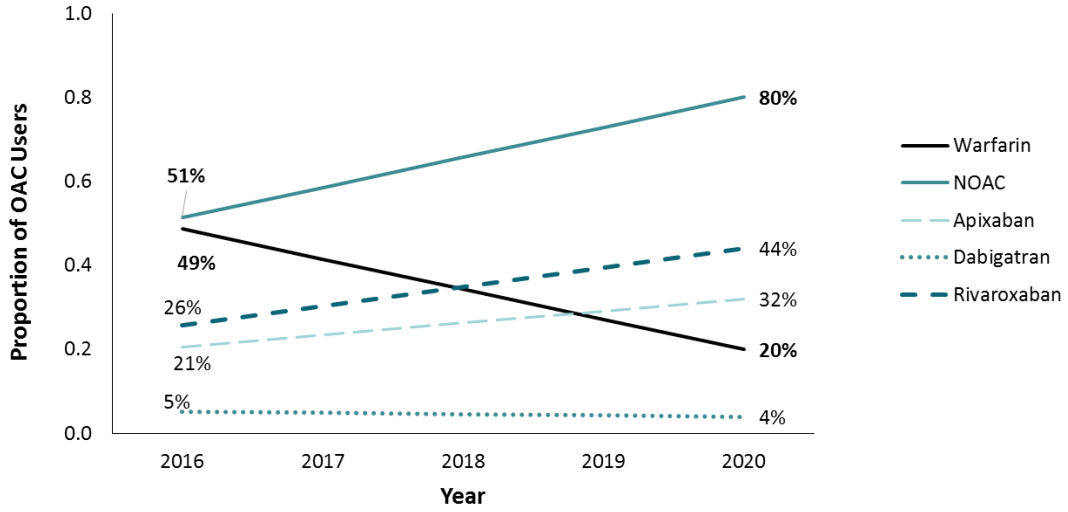

Figure 10: Predicted Oral Anticoagulant Use in Patients With Nonvalvular Atrial Fibrillation, 2016–2020

Abbreviations: NOAC, novel oral anticoagulant; OAC, oral anticoagulant.

Costs

For each treatment, we obtained the cost per patient from our primary economic evaluation. While these costs are based on patients without contraindications to oral anticoagulants, we also used them to represent the costs in contraindicated patients. We also included an aspirin arm in the primary economic model to determine the budget impact of the LAAC device when it displaces aspirin users.

We used annual undiscounted costs for five years from the base case analysis of the primary economic evaluation (Appendix 4, Table A5). To capture patient variability, we ran Monte Carlo simulations for 100,000 iterations. These included resource use and costs related to drug

therapy, LAAC device surgery, adverse events, and clinical events. A detailed description of these costs is provided in the methods section of the primary economic evaluation. All costs are reported in 2016 dollars.

Analysis

Base Case

We calculated our base case budget impact as the difference in annual total costs between patients expected to receive the LAAC device and patients receiving aspirin therapy. We calculated the costs for each treatment group as follows. We calculated the annual costs for 2016 by multiplying the volume of patients in 2016 (see Table 27) by first-year treatment costs (Appendix 5, Table A5; Equation 1). We calculated annual costs for subsequent years using the ongoing costs of 2016 patients and costs of volumes of patients expected in respective years (Equations 2, 3, 4, and 5). We based volumes in the base case on an annual uptake growth of 3%.

Equation (1) $Volumes_{2016} \times Cost_{Y1}$

Equation (2) $(Volumes_{2016} \times Cost_{Y2}) + (Volumes_{2017} \times Cost_{Y1})$

Equation (3) $(Volumes_{2016} \times Cost_{Y3}) + (Volumes_{2017} \times Cost_{Y2}) + (Volumes_{2018} \times Cost_{Y1})$

Equation (4) $(Volumes_{2016} \times Cost_{Y4}) + (Volumes_{2017} \times Cost_{Y3}) + (Volumes_{2018} \times Cost_{Y2}) + (Volumes_{2019} \times Cost_{Y1})$

Equation (5) $(Volumes_{2016} \times Cost_{Y5}) + (Volumes_{2017} \times Cost_{Y4}) + (Volumes_{2018} \times Cost_{Y3}) + (Volumes_{2019} \times Cost_{Y2} + Volumes_{2020} \times Cost_{Y1})$

Sensitivity Analyses

We calculated the budget impact for patients with absolute contraindications to oral anticoagulants under 1% and 5% annual uptake growth rates. In addition, we calculated the budget impact for patients with relative contraindications to oral anticoagulants assuming 3% annual uptake growth rates and either aspirin or oral anticoagulant displacement.

Expert Consultation

In the fall of 2016, we solicited expert consultation on the LAAC device from physicians specializing in cardiology. The role of the expert advisors was to inform model parameters where literature was unavailable and to provide advice on the clinical pathways of patients with nonvalvular atrial fibrillation at risk for stroke. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Base Case Analyses

The base case budget impact results are presented in Table 28. In the population of patients with nonvalvular atrial fibrillation and absolute contraindications to oral anticoagulants, the estimated net budget impact of the LAAC device compared with aspirin ranged from $1.1 million in the first year (2016) to $7.7 million in the fifth year (2020).

Table 28: Results of Base Case Budget Impact Analysis

	Year				
	2016	2017	2018	2019	2020
Cost (2016 $million)	1.1	3.2	5.0	6.6	7.7

Sensitivity Analyses

Results from the sensitivity analyses are presented in Table 29. When considering scenarios in patients with absolute contraindications to oral anticoagulants, the net budget impact of the LAAC device ranged from $1.1 million in the first year (2016) to $15.8 million in the fifth year (2020). When considering scenarios in patients with relative contraindications to oral anticoagulants, the net budget impact of the LAAC device ranged from $1.1 million in the first year to $168.8 million in the fifth year. In this population, the budget impact was higher when we assumed that the LAAC device would displace oral anticoagulants compared with aspirin.

Table 29: Results of Budget Impact Scenario Analyses

	Year				
	2016	2017	2018	2019	2020
Base Case					
3% growth in uptake per year, displacing aspirin (2016 $million)	1.1	3.2	5.0	6.6	7.7
Scenario: Absolute Contraindications					
1% growth in uptake per year, displacing aspirin (2016 $million)	1.1	1.8	2.5	3.3	3.8
5% growth in uptake per year, displacing aspirin (2016 $million)	1.1	4.6	8.2	11.9	15.8
Scenario: Relative Contraindications					
3% growth in uptake per year, displacing aspirin (2016 $million)	1.1	46.3	89.9	128.2	157.5
3% growth in uptake per year, displacing OACs (2016 $million)	1.1	45.3	87.8	124.7	168.8

Abbreviation: OAC, oral anticoagulant.

Discussion

The base case annual budget impact of the LAAC device relative to aspirin in patients with nonvalvular atrial fibrillation and absolute contraindications to oral anticoagulants ranged from $1.1 million in the first year (2016) to $7.7 million in the fifth year (2020). Although the downstream costs were slightly lower for the LAAC device, the high upfront costs of surgery and increasing volumes over time lead to a steadily increasing budget impact. Correspondingly, the higher uptake scenario leads to a larger budget impact. The largest uptake scenario (5% growth in uptake per year) in this population leads to an annual budget impact of up to $15.8 million.

Due to the population size, the budget impact of the LAAC device in patients with nonvalvular atrial fibrillation and relative contraindications to oral anticoagulants was much larger than in patients with absolute contraindications. It ranged from $1.1 million to $157.5 million when displacing aspirin and from $1.1 million to $168.8 million when displacing oral anticoagulants. Given the expected training capacities and the limited number of centres in Ontario that currently implant the LAAC device, these uptake values may be difficult to achieve and are possibly unrealistic over the next five years. However, this scenario illustrates that, with increased diffusion and training, the budget impact could vary quite drastically depending on the population of uptake.

Our analysis had several strengths. We were able to explore the budget impact in two important patient populations. Clinical experts have indicated that real-world uptake of the LAAC device could occur in several different populations, displacing various treatments, and our analysis highlights the variation in budget impact that could be seen as a result. In addition, we used multiple scenarios to explore the impacts of various uptake rates, showing the range of budget impacts that could be expected in the next five years. Finally, the cost per patient, derived from our primary economic model, captured costs associated with the LAAC device implantation, adverse events, clinical events, and disability caused by stroke.

Our analysis also had several limitations. While we captured a range of costs in our analysis, our primary economic model was based on patients without contraindications to oral anticoagulants. Conservatively, we assumed the costs in these two populations were equal. However, given that a recent Ontario-based cost-effectiveness analysis[36] showed that costs were lower in patients treated with the LAAC device compared with patients treated with aspirin, our costs are likely an overestimation of costs in the contraindicated population. This possibility means that the actual budget impact in the contraindicated population could be lower than that presented in our analyses.

An additional limitation of our analysis relates to data availability. We were unable to identify any literature on the current distribution of novel oral anticoagulant use in Ontario. A study by Weitz et al[91] reported the proportional use of these agents in 2013; however, because apixaban was approved just in 2012,[92] the numbers presented by Weitz et al do not reflect the rapid changes in oral anticoagulant use in the last two years. Given the lack of available data, we based our estimates on clinical expertise. Further, we did not incorporate forms of left atrial appendage closure devices on the market other than the “Watchman” device, such as the Amplatzer cardiac plug. The data on the Amplatzer device are limited to registry data, and no clinical trials have yet been performed comparing this device to the LAAC device or alternatives. Given the predicted volumes of the LAAC device relative to the large prevalence of nonvalvular atrial fibrillation, we assume that the five-year budget impact would not be affected by nonpharmacologic competitors. If additional data become available, our budget impact analysis should be updated.

Conclusions

Our budget impact analysis indicates that publicly funding the LAAC device may result in extra spending of $1.1 million to $7.7 million annually for the next five years.

PUBLIC AND PATIENT ENGAGEMENT

Background

Public and patient engagement explores the lived experience of a person with a health condition, including the impact that the condition and its treatment has on the patient as well as the patient's family or other caregivers, and on the patient's personal environment. Public and patient engagement increases awareness and builds appreciation for the needs, priorities, and preferences of the person at the centre of a treatment program. The insights gained through public and patient engagement provide an in-depth picture of lived experience, through an intimate look at the values that underpin the experience.

Lived experience is a unique source of evidence about the personal impact of a health condition and how that condition is managed, including what it is like to navigate the health care system with that condition and how technologies may or may not make a difference in people's lives. Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcome measures that do not reflect what is important to those with lived experience).[93-95] Additionally, lived experience can provide information or perspectives on the ethical and social values implications of technologies and treatments. Because the needs, priorities, preferences, and values of those with lived experience in Ontario are not often adequately explored by published literature, Health Quality Ontario reaches out to and directly speaks with people who live with the health condition, including those who may have experience with the intervention in question.

Nonvalvular atrial fibrillation is relatively common heart condition in Ontario and puts patients at an increased risk of stroke, a medical event that can have a significant impact on patients and their families and that has a significant bearing on quality of life. To understand this impact and the factors that influence treatment decision-making for these patients, we spoke directly with patients with nonvalvular atrial fibrillation who may or may not have had a previous stroke, as well as family members of patients. Understanding and appreciating the potential impact of stroke and preventive treatment decision-making helps to contextualize the potential value of the LAAC device from a lived experience perspective.

Methods

Engagement Plan

Engagement as a concept captures a range of efforts used to involve the public and patients in various domains and stages of health technology assessment decision-making.[96] Rowe and Frewer outline three types of engagement: communication, consultation, and participation.[97] Communication constitutes a one-way transfer of information from the sponsor to the patient, while participation involves the sponsor and patient collaborating through real-time dialogue. Consultation, on the other hand, refers to the sponsor's seeking out and soliciting information (e.g., experiential input) from the public, patients, and caregivers affected by the health technology or intervention in question.

The engagement plan for this health technology assessment focused on consultation. Within this typology, the engagement design focused on interviews to elicit the lived experience of patients with nonvalvular atrial fibrillation and their families, as well as their decision-making when it comes to potential stroke prevention treatments.[98]

The qualitative interview was selected as an appropriate method because it allowed Health Quality Ontario staff to deeply explore the meaning of central themes in the lived experience of the participants. The main task in interviewing is to understand the meaning of what participants say.[99] Interviews are particularly useful for getting the story and context behind a participant's experiences, which was the objective in this portion of the report. The sensitive nature of exploring quality-of-life issues is another reason for using interviews for this project.

Participant Recruitment

Our recruitment strategy for this project consisted of an approach called purposive sampling[100-103] to actively recruit individuals with direct lived experience. Patient, Caregiver, and Public Engagement staff contacted patients with nonvalvular atrial fibrillation through a variety of partner organizations, health clinics, provincial and national stroke support associations, and foundations. We also used word of mouth, as interview participants contacted other patients after they completed their interviews.

Inclusion Criteria

We sought patients diagnosed with nonvalvular atrial fibrillation. The time of diagnosis of nonvalvular atrial fibrillation varied, but all patients interviewed were taking oral anticoagulant medications. Several patients had previously suffered a stroke, but this was not a criterion for inclusion. We sought a broad geographic representation to elicit possible equity issues or different themes in treatment decision-making from across the province.

Exclusion Criteria

We set no exclusion criteria.

Participants

Patient, Caregiver, and Public Engagement staff spoke to nine patients with nonvalvular atrial fibrillation and family members from across Ontario. Four patients had previously suffered a stroke. No patients had undergone the LAAC device implantation procedure, but several were familiar with the device and its intended use.

Interview Approach

At the outset of the interview, Patient, Caregiver, and Public Engagement staff explained the purpose of the health technology assessment process (including the role and mandate of Health Quality Ontario and the Ontario Health Technology Advisory Committee), risks of participation, and protection of personal health information. Staff explained these attributes to participants orally and through a letter of information. We obtained consent from participants before commencing the interview. The letter of information and consent form can be found in Appendices 6 and 7, respectively. Interviews were recorded and transcribed.

The interviews were semistructured, consisted of a series of open-ended questions, and lasted for approximately 10 to 30 minutes. We based our interview questions on a list of questions developed by Health Technology Assessment International's Patient and Citizen Involvement Group to elicit lived experience specific to how a health technology or intervention affects lived experience and quality of life.[104]

Owing to the nature of the LAAC device implantation procedure as a stroke prevention treatment, we focused our interview questions on current stroke prevention therapies, their burden, and how patients and families would weigh various factors when choosing whether to have the LAAC device implanted. We explored patient and family member insights into the factors that shaped their decisions. The interview guide can be found in Appendix 8.

Data Extraction and Analysis

We selected a modified version of a grounded theory methodology to analyze transcripts of participant interviews because this methodology captures themes and allows elements of lived experience to be compared among participants. The inductive nature of grounded theory follows an iterative process of eliciting, documenting, and analyzing responses while simultaneously collecting and analyzing data using a constant comparative approach.[105,106] Through this approach, staff coded transcripts and compared themes using NVivo, a qualitative software program that enables the identification and interpretation of patterns in the interview data about the meaning and implications of the lived condition (QSR International, Doncaster, Victoria, Australia).

Results

Patients consistently reported being open to and supportive of the LAAC device, seeing it as potentially having medical value and a positive impact on quality of life. Patients who had previously suffered a stroke reported seeing the LAAC device as a way of preventing strokes in others and preventing future strokes in themselves. For patients who had not experienced stroke, the perceived benefit of the LAAC device was as an alternative to the mild burden of taking daily oral anticoagulant medications. All patients reported frustration and fatigue with their current oral anticoagulant medications, with several commenting on their cost, which was perceived as expensive, and the burden of use. When asked about potentially having the LAAC device implanted, all patients reported wanting to be certain that it was safe, effective, and recommended by their physicians.

Impact of Nonvalvular Atrial Fibrillation and Stroke

Patients who had not experienced stroke reported a mild impact of their diagnosis of nonvalvular atrial fibrillation. These patients were uncertain as to what had caused their nonvalvular atrial fibrillation, and its detection and diagnosis was often a byproduct of another medical incident:

> *"It was only because of the coincidence of me going in to have my pacemaker checked that they discovered I had AFib [nonvalvular atrial fibrillation]."*

Upon diagnosis, all patients who had not experienced stroke reported being informed by their health care provider that atrial fibrillation increased the risk of stroke and that anticoagulant medications would be required to help offset this risk. Patients reported high confidence in the medical information provided by their physicians and in the risk–benefit discussion of stroke prevention treatments. However, patients also reported seeking out other sources of information on atrial fibrillation, including online sources, other physicians, family members, colleagues, and acquaintances:

> *"This [new medication] was more effective, but the problem with the [medication] I was first put on was your blood won't clot. You have to wait until it gets out of your system—*

> *over 12 hours. So that was the risk factor. But they suggested the benefit outweighed the risk."*
>
> *"And then they explained how serious it was for maybe having a thrombus or a clot form, and that was common with that [nonvalvular atrial fibrillation]. So that's why they explained they had to put me on a strong blood thinner [anticoagulant]."*
>
> *"I don't mind reading about it on the Internet, and I did. And it sort of helped convince me that, wow, the risk is, you know, I don't want to have a clot. So that risk was…I felt more secure that that risk was being handled, the risk of a clot and causing a stroke. And I hoped that I wouldn't have a trauma incident."*

Patients reported that it was the necessity of taking oral anticoagulant medications daily that had the largest impact on their day-to-day life, although most reported that their quality of life was only mildly affected. The most common complaints mentioned were remembering to take their medication, the risk of bleeding, and cost:

> *"It does have some implications in day-to-day life. For example, if you have dental problems and you needed a dental extraction. So, therefore, in that time, I have had a dental extraction and had to go to an oral surgeon…so I had to go off the blood thinner [anticoagulant] for 24 hours before and then have the surgery and stay off another 24 hours. And that made me…I thought about it. Made me nervous because I thought, 'What if, during this time…?'"*
>
> *"And then the other thing in day-to-day life, if you have a bump or that, then you of course bruise, but you bruise very easily. So there's some caution, [but] I didn't mind using caution living [my] day-to-day life."*

For patients who had previously suffered a stroke, the medication regimen of daily oral anticoagulants was reported to be a mild burden, especially considering some of the physical and emotional challenges these patients and their families had faced as a result of the stroke. These patients and family members focused much less on the small burden of daily medications and more on the larger impact of stroke on quality of life:

> *"You know, our lives changed totally when this happened because he was very active and then, all of a sudden, he fell out of bed one night and that was it."*
>
> *"No, it is not the case, I can tell you right now. And I never forget [the pills] at night. It's before I go to bed… I have no problem with it. If I had to take a ton of pills, it might be a problem, but I don't have to. I can't say that this AFib is causing any big problems, otherwise."*
>
> *"I have care workers here all the time now [who] give me my pills when they're supposed to. If I had to do it myself, it probably would be an issue, because I was never on medication before."*

The burdens of the cost of stroke therapy and the required travel to medical appointments was mentioned by patients several times. Patients also mentioned the burden of living remotely and the challenges this posed in accessing health care follow-up for their stroke. This burden was not limited to patients but also affected family members:

> *"When you have a stroke, you've got to avoid stress. But if I want to access any program, I have to drive to Ottawa, which is roughly two hours there and back. And that stress of*

that driving that far and back is horrendous. Then you have the cost of it, which is another stress factor."

"Some of it's paid for. But once you've had a stroke, I know people who [have] had to sell their house just to be able to pay for everything."

Perceptions of the LAAC Device

We were unable to recruit patients who had had the LAAC device implanted, although several patients with whom we spoke were familiar with the device and its purpose in preventing clots from the left atrial appendage. We gave all patients interviewed basic information regarding the LAAC device and the implantation procedure, both in writing and verbally during the interview. We discussed the general purpose of the device, the location of its implantation, and the clinical nature of the implantation procedure. We then asked patients for their thoughts on the LAAC device and whether they believed this device would be valuable for their own condition, as well for others diagnosed with nonvalvular atrial fibrillation who may or may not have suffered a stroke.

Patients reported a fairly consistent positive response to the LAAC device. They saw the device as useful method to reduce the risk of stroke. Patients who had not experienced stroke tended to view it positively when compared with the alternative treatment of daily oral anticoagulant medications. Since taking daily medications was viewed as a mild burden, which the LAAC device could relieve, the device was viewed positively:

"And if the Watchman was available, if they give me a choice: 'Here's your medications a, b, and c, and you take this and that and the other, or you have Watchman, this little gadget thing that we stick in your heart, and away it goes.' Well, I say, 'What's there to discuss?' I'd have it."

"Well, it's an alternative. Would you rather take four pills per day, some twice a day? Now, that's without forgetting. Yeah, right. And do it [over and over]. The answer's no. No.…No, I would stop that."

"Yes, I can tell you exactly how I'd feel. I would want something that would be done and over with, like a device. I would far rather have that than having to do these pills regularly. I mean, yes. Far rather."

For patients who had experienced stroke, the positive response centred more on the capacity of the LAAC device to prevent stroke in the future, both in themselves and in those who had not yet suffered a stroke. This was reported as its main potential benefit, although several patients also mentioned its potential associated cost savings. For these patients, taking daily oral anticoagulant medications was seen as less of a burden than for those who had not yet experienced a stroke and was therefore less of a factor in their appraisal of the LAAC device:

"It's important we're trying to help those people that are going to have stroke in the future. We need to help them because, at the moment, we've got a problem for stroke survivors that takes them into a hospital, gives them an initial rehabilitation program, but once you come out of that hospital you're on your own. Therefore, if we had something like Watchman implanted, it would take care of many of the problems for them."

"But, in fact, it would seem to me, Watchman could well be a very good thing.…So you cut down the cost of the medications, remove the cost of medications, in fact, remove the cost of the clinical need for [a visit], so the cost savings to the province would be quite considerable and should be set against the cost of a Watchman."

> *"I think it is the future stroke survivors that we've got to look to; we may well be seen as the guinea pigs for it all. I think it's very important we try unselfishly to help others we don't know even."*

In each case, the LAAC device implantation procedure was not seen as a barrier, as long as it was safe and effective. All patients reported wanting assurance that the device was safe and stated they would trust the device if it were recommended by their physicians:

> *"So this would take away that risk, if I qualify for it. I don't think it would be that hard. I wouldn't be nervous about trusting the Watchman if it was recommended and approved."*

> *"Well, it depends on the risks of the surgery…I have many specialists, and I would ask them all."*

Several patients did mention a small level of anxiety at the idea of trusting the LAAC device to work; however, this anxiety was offset by confidence in the opinion and recommendation of physicians:

> *"If the implant was there, the Watchman, I would have the same feeling: How am I doing? How is it doing? Is it staying there? I would always be questioning."*

> *"So if I was offered it, and I'm going to now read up on it online so that when I see my cardiologist again, I can ask him about it, but I would almost be nervous about [it]; like, I don't mind the insertion, I don't mind all that, but I don't want it to disturb something that's been stable. Unless it was sort of guaranteed if I read about it, [and] it's being used everywhere, like the States and in Europe, and it was really well thought of and [had] little side effects, then, sure, I would consider it."*

Discussion

Some slightly different perspectives arose between patients with nonvalvular atrial fibrillation who had previously experienced a stroke and those who had not. The mild impact of nonvalvular atrial fibrillation reported by patients who had not experienced a stroke contrasted with the large emotional and physical impact of stroke reported by those who had experienced a stroke. All patients reported being well informed regarding their medical condition. They were able to clearly articulate the increased risk of stroke associated with nonvalvular atrial fibrillation, as well as the need for oral anticoagulant medication following diagnosis. Their high level of knowledge regarding the condition allowed patients to carefully consider the potential benefits and drawbacks of the LAAC device. Despite not having personal experience with the implantation or use of the LAAC device, patients reported their perceptions and values with regard to the device. These perceptions and values were the basis of their decisions regarding whether they would be interested in using the device.

The LAAC device, as it was explained to patients, was perceived positively as a potential alternative to treatment with oral anticoagulant medications. Patients reported a positive impression of the device in terms of its use in preventing stroke and in removing the burden of taking medications daily. However, without having first-hand experience with the device, patients remarked that their positive view of the device was contingent on its being proven to be a safe and effective treatment option recommended by trusted health care providers.

Conclusions

Patients with nonvalvular atrial fibrillation whom we interviewed, both those who had experienced stroke and those who had not, reported positive support for the LAAC device. While each group had a slightly different focus on the perceived benefits of the device, both reported that they would value having access to the LAAC device if it were shown to be safe, effective, and recommended by their health care providers.

ABBREVIATIONS

AMSTAR	A Measurement Tool to Assess Systematic Reviews
CI	Confidence interval
Cr.I	Credible interval
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICER	Incremental cost-effectiveness ratio
LAAC device	Left atrial appendage closure device with delivery system
MI	Myocardial infarction
NOAC	Novel oral anticoagulant
NVAF	Nonvalvular atrial fibrillation
OAC	Oral anticoagulant
OR	Odds ratio
QALY	Quality-adjusted life-year

GLOSSARY

Anticoagulants	Commonly referred to as blood thinners, they are any of a class of substances that thin the blood. They are used to prevent or treat blood clots.
Antiplatelet agents	Platelets are particles in the blood that collect around wounds to form a scab and prevent further bleeding. Antiplatelet agents prevent platelets from binding together and stopping blood flow. They are used to prevent clots from forming in blood vessels.
Atrial fibrillation	A common type of cardiac arrhythmia, which is a problem with the speed or rhythm of the heart. Atrial fibrillation can lead to an increased risk of stroke or heart attack.
Base case	The scenario, including any assumptions, that is considered most likely to be accurate.
Contraindication	Most drugs have side effects, unwanted results of taking a medication that range from minor to severe. Contraindications are factors that suggest a person is at increased risk of suffering a side effect.
Cost–utility analysis	A type of analysis that estimates the value for money of an intervention by weighing the cost of the intervention against the improvements in length of life and quality of life. The result is expressed as a dollar amount per "quality-adjusted life-year" or QALY.
Discount rate	Health economists assume that when a benefit is received affects its value (specifically, present benefits are more valuable than future benefits). In order to compare different benefits across different time frames, they calculate the present value of each benefit by reducing the future value by a specified percentage. For instance, a discount rate of 5% per year will reduce the value of benefit that won't be realized for a year by 5%. A benefit that won't be realized for two years would be reduced by 10% (2 years × 5% per year).

Embolism	A blockage in an artery caused by any of a number of different objects in the artery, including a blood clot, air bubble, fat globule, or other plaque buildup that has broken loose from a blood vessel.
Hemorrhagic stroke	A type of stroke that occurs when an artery in the brain breaks open, causing damage to the brain. People with high blood pressure are at higher risk of suffering hemorrhagic stroke.
Incremental cost	The extra cost associated with using one test or treatment instead of another.
Incremental cost-effectiveness ratio (ICER)	Determines the additional cost for an additional unit of benefit for an intervention by dividing the incremental cost by the effectiveness. The incremental cost is the difference between the cost of the treatment under study and an alternative treatment. The effectiveness is usually measured as additional years of life or as "quality-adjusted life years."
Ischemic stroke	A type of stroke that occurs when an artery in the brain is blocked by plaque buildup or a blood clot. This blockage reduces or stops blood flow, causing damage to the brain.
Nonvalvular atrial fibrillation	A type of atrial fibrillation that does not involve the heart valves; the most common form of atrial fibrillation.
Quality-adjusted life-year (QALY)	A measurement that takes into account both the number of years lived by a patient and the quality of those years (ability to function, freedom from pain, etc.). The QALY is commonly used as an outcome measure in cost–utility analyses.
Randomized controlled trial	A type of study in which subjects are assigned randomly into different groups, with one group receiving the treatment under study and the other group(s) receiving a different treatment or a placebo (no treatment) in order to determine the effectiveness of one approach compared with the other(s).
Sensitivity analysis	Every evaluation contains some degree of uncertainty. Study results can vary depending on the values taken by key parameters. Sensitivity analysis is a method that allows estimates for each parameter to be varied to show the impact on study results. There are various types of sensitivity analyses. Examples include deterministic, probabilistic, and scenario.
Thromboembolic event	A blood clot or other obstruction in the brain, which blocks the movement of blood through a vessel. A thromboembolic event is one of the most common causes of ischemic stroke (the other is blockage caused by a buildup of plaque in the blood vessel).
Utility	The perceived benefit (value) placed on a treatment by a person or society.

APPENDICES

Appendix 1: Literature Search Strategies

Clinical Literature Search

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2016>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 23, 2016>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Health Technology Assessment <2nd Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2016 Week 25>, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---
1 Atrial Fibrillation/ (57965)
2 (((atrial or atrium or auricular) adj3 fibrillation*) or a-fib or afib or ((non-valvular or nonvalvular) adj AF) or NVAF).tw. (138646)
3 Atrial Appendage/ (6397)
4 ((atrial or atrium or auricular) adj3 appendage*).tw. (11723)
5 or/1-4 (157345)
6 Septal Occluder Device/ (3439)
7 (((left atrial appendage or LA appendage or LAA) adj3 (occlu* or device* or system or systems or closure* or implant* or block* or percutaneous)) or LAAO or LAAC).tw. (2692)
8 watchman*.tw. (635)
9 Dabigatran/ (9072)
10 Rivaroxaban/ (9464)
11 (pradaxa or prazaxa or xarelto or eliquis or savaysa or lixiana or dabigatran or rivaroxaban or apixaban or edoxaban or BIBR 953 or BIBR953 or BAY 59-7939 or BAY59-7939 or BAY 597939 or BAY597939 or BMS 562247-01 or BMS562247-01 or BMS56224701 or DU-176 or DU176 or BIBR 1048 or BIBR1048).tw. (14356)
12 (211914-51-1 or 366789-02-8 or 503612-47-3 or 480449-70-5).rn,nm. (7003)
13 (NOAC or NOACs or NOA or NOAs or DOAC or DOACs or DOA or DOAs).tw. (6583)
14 ((novel or new or newer or non vitamin k or nonvitamin k or nonwarfarin or non warfarin or direct) adj3 (anticoag* or anti coag*)).tw. (12944)
15 or/6-14 (34687)
16 5 and 15 (12258)
17 Meta-Analysis/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (225424)
18 Meta Analysis.pt. (68286)
19 (((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).tw. (542502)
20 (meta analy* or metaanaly* or health technolog* assess*).mp. (353332)
21 Clinical Trials as Topic/ or Randomized Controlled Trials as Topic/ (390218)
22 (randomized controlled trial or controlled clinical trial).pt. (986594)
23 trial.ti. (521446)
24 (randomi#ed or randomly or RCT$1 or placebo* or sham).tw. (2385691)
25 or/17-24 (3550079)
26 exp Animals/ not (exp Animals/ and Humans/) (13569419)

27 25 not 26 (2776810)
28 16 and 27 (2264)
29 28 use ppez (1170)
30 16 use cctr,coch,dare,clhta,cleed (606)
31 29 or 30 (1776)
32 limit 31 to english language [Limit not valid in CDSR,DARE; records were retained] (1556)
33 16 not 32 (10702)
34 exp Animals/ not (exp Animals/ and Humans/) (13569419)
35 33 not 34 (4959)
36 (Comment or Editorial or Letter or Congresses).pt. (3018964)
37 35 not 36 (4432)
38 37 use ppez,cctr,coch,dare,clhta,cleed (2539)
39 limit 38 to english language [Limit not valid in CDSR,DARE; records were retained] (2041)
40 Atrial Fibrillation/ (57965)
41 (((atrial or atrium or auricular) adj3 fibrillation*) or a-fib or afib or ((non-valvular or nonvalvular) adj AF) or NVAF).tw. (138646)
42 heart atrium appendage/ (7065)
43 ((atrial or atrium or auricular) adj3 appendage*).tw. (11723)
44 or/40-43 (157421)
45 septal occluder/ (3435)
46 (((left atrial appendage or LA appendage or LAA) adj3 (occlu* or device* or system or systems or closure* or implant* or block* or percutaneous)) or LAAO or LAAC).tw. (2692)
47 watchman*.tw. (635)
48 dabigatran/ or dabigatran etexilate/ (10550)
49 Rivaroxaban/ (9464)
50 apixaban/ (5029)
51 edoxaban/ (1543)
52 (pradaxa or prazaxa or xarelto or eliquis or savaysa or lixiana or dabigatran or rivaroxaban or apixaban or edoxaban or BIBR 953 or BIBR953 or BAY 59-7939 or BAY59-7939 or BAY 597939 or BAY597939 or BMS 562247-01 or BMS562247-01 or BMS56224701 or DU-176 or DU176 or BIBR 1048 or BIBR1048).tw. (14356)
53 (211914-51-1 or 366789-02-8 or 503612-47-3 or 480449-70-5).tw. (0)
54 (NOAC or NOACs or NOA or NOAs or DOAC or DOACs or DOA or DOAs).tw. (6583)
55 ((novel or new or newer or non vitamin k or nonvitamin k or nonwarfarin or non warfarin or direct) adj3 (anticoag* or anti coag*)).tw. (12944)
56 or/45-55 (34790)
57 44 and 56 (12273)
58 Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/ (223067)
59 (((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).tw. (542502)
60 (meta analy* or metaanaly* or health technolog* assess*).mp. (353332)
61 exp "controlled clinical trial (topic)"/ (105107)
62 randomized controlled trial/ or controlled clinical trial/ (1056754)
63 trial.ti. (521446)
64 (randomi#ed or randomly or RCT$1 or placebo* or sham).tw. (2385691)
65 or/58-64 (3436153)
66 (exp animal/ or nonhuman/) not exp human/ (9796344)
67 65 not 66 (3126721)
68 57 and 67 (3587)

69 Comment/ or Editorial/ or Letter/ or conference abstract.pt. (5196886)
70 68 not 69 (2808)
71 70 use emez (1489)
72 limit 71 to english language [Limit not valid in CDSR,DARE; records were retained] (1358)
73 57 not 72 (10915)
74 (exp animal/ or nonhuman/) not exp human/ (9796344)
75 73 not 74 (10815)
76 Comment/ or Editorial/ or Letter/ or conference abstract.pt. (5196886)
77 75 not 76 (7244)
78 77 use emez (3200)
79 limit 78 to english language [Limit not valid in CDSR,DARE; records were retained] (2508)
80 32 or 72 (2914)
81 remove duplicates from 80 (1893)
82 80 use ppez (1065)
83 80 use emez (1358)
84 80 use cctr (355)
85 80 use coch (23)
86 80 use dare (39)
87 80 use clhta (20)
88 80 use cleed (54)
89 39 or 79 (4549)
90 remove duplicates from 89 (3135)
91 89 use ppez (2041)
92 89 use emez (2508)
93 89 use cctr (0)
94 89 use coch (0)
95 89 use dare (0)
96 89 use clhta (0)
97 89 use cleed (0)

Economic Literature Search

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2016>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 23, 2016>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Health Technology Assessment <2nd Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2016 Week 26>, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 Atrial Fibrillation/ (58207)
2 (((atrial or atrium or auricular) adj3 fibrillation*) or a-fib or afib or ((non-valvular or nonvalvular) adj AF) or NVAF).tw. (138909)
3 Atrial Appendage/ (6414)
4 ((atrial or atrium or auricular) adj3 appendage*).tw. (11740)
5 or/1-4 (157666)
6 Septal Occluder Device/ (3452)
7 (((left atrial appendage or LA appendage or LAA) adj3 (occlu* or device* or system or systems or closure* or implant* or block* or percutaneous)) or LAAO or LAAC).tw. (2703)
8 watchman*.tw. (638)
9 Dabigatran/ (9114)
10 Rivaroxaban/ (9515)
11 (pradaxa or prazaxa or xarelto or eliquis or savaysa or lixiana or dabigatran or rivaroxaban or apixaban or edoxaban or BIBR 953 or BIBR953 or BAY 59-7939 or BAY59-7939 or BAY 597939 or BAY597939 or BMS 562247-01 or BMS562247-01 or BMS56224701 or DU-176 or DU176 or BIBR 1048 or BIBR1048).tw. (14428)
12 (211914-51-1 or 366789-02-8 or 503612-47-3 or 480449-70-5).rn,nm. (7042)
13 (NOAC or NOACs or NOA or NOAs or DOAC or DOACs or DOA or DOAs).tw. (6628)
14 ((novel or new or newer or non vitamin k or nonvitamin k or nonwarfarin or non warfarin or direct) adj3 (anticoag* or anti coag*)).tw. (13010)
15 or/6-14 (34831)
16 5 and 15 (12336)
17 economics/ (250901)
18 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (733484)
19 economics.fs. (380968)
20 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw. (691034)
21 exp "costs and cost analysis"/ (509531)
22 cost*.ti. (235666)
23 cost effective*.tw. (250970)
24 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (157196)
25 models, economic/ (134062)
26 markov chains/ or monte carlo method/ (119487)
27 (decision adj1 (tree* or analy* or model*)).tw. (33933)
28 (markov or markow or monte carlo).tw. (101594)
29 quality-adjusted life years/ (26414)

30 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw. (51215)
31 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw. (98668)
32 or/17-31 (2286046)
33 16 and 32 (1537)
34 limit 33 to english language [Limit not valid in CDSR,DARE; records were retained] (1432)
35 (Comment or Editorial or Letter or Congresses).pt. (3022551)
36 34 not 35 (1365)
37 36 use ppez,cctr,coch,dare,clhta (323)
38 16 use cleed (55)
39 Atrial Fibrillation/ (58207)
40 (((atrial or atrium or auricular) adj3 fibrillation*) or a-fib or afib or ((non-valvular or nonvalvular) adj AF) or NVAF).tw. (138909)
41 heart atrium appendage/ (7082)
42 ((atrial or atrium or auricular) adj3 appendage*).tw. (11740)
43 or/39-42 (157742)
44 septal occluder/ (3448)
45 (((left atrial appendage or LA appendage or LAA) adj3 (occlu* or device* or system or systems or closure* or implant* or block* or percutaneous)) or LAAO or LAAC).tw. (2703)
46 watchman*.tw. (638)
47 dabigatran/ or dabigatran etexilate/ (10600)
48 Rivaroxaban/ (9515)
49 apixaban/ (5063)
50 edoxaban/ (1559)
51 (pradaxa or prazaxa or xarelto or eliquis or savaysa or lixiana or dabigatran or rivaroxaban or apixaban or edoxaban or BIBR 953 or BIBR953 or BAY 59-7939 or BAY59-7939 or BAY 597939 or BAY597939 or BMS 562247-01 or BMS562247-01 or BMS56224701 or DU-176 or DU176 or BIBR 1048 or BIBR1048).tw. (14428)
52 (211914-51-1 or 366789-02-8 or 503612-47-3 or 480449-70-5).tw. (0)
53 (NOAC or NOACs or NOA or NOAs or DOAC or DOACs or DOA or DOAs).tw. (6628)
54 ((novel or new or newer or non vitamin k or nonvitamin k or nonwarfarin or non warfarin or direct) adj3 (anticoag* or anti coag*)).tw. (13010)
55 or/44-54 (34934)
56 43 and 55 (12351)
57 Economics/ (250901)
58 Health Economics/ or Pharmacoeconomics/ (43870)
59 Economic Aspect/ or exp Economic Evaluation/ (393920)
60 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw. (691034)
61 exp "Cost"/ (509531)
62 cost*.ti. (235666)
63 cost effective*.tw. (250970)
64 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (157196)
65 Monte Carlo Method/ (50664)
66 (decision adj1 (tree* or analy* or model*)).tw. (33933)
67 (markov or markow or monte carlo).tw. (101594)
68 Quality-Adjusted Life Years/ (26414)
69 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw. (51215)
70 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw. (98668)

71 or/57-70 (1789149)
72 56 and 71 (1271)
73 Comment/ or Editorial/ or Letter/ or conference abstract.pt. (5206509)
74 72 not 73 (925)
75 limit 74 to english language [Limit not valid in CDSR,DARE; records were retained] (854)
76 75 use emez (487)
77 37 or 38 or 76 (865)
78 remove duplicates from 77 (630)
79 78 use ppez,emez (534)
80 78 use cctr,coch,dare,clhta,cleed (96)

Appendix 2: Existing Guidelines for the LAAC Device

Guideline	Year	Recommendation Synopsis
AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation[107]	2014	Surgical occlusion/excision of the left atrial appendage may be considered in patients undergoing cardiac surgery.
2012 Focused Update of the European Heart Journal Guidelines for the Management of Atrial Fibrillation[52]	2012	Interventional, percutaneous left atrial appendage closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation. (Level B; Class IIb)
2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation[108]	2014	Suggests nonapproved LAAC devices not be used, except in research protocols or in systematically documented use protocols in patients at high risk of stroke ($CHADS_2$ score ≥ 2) for whom antithrombotic therapy is precluded (conditional recommendation, low-quality evidence).
NICE Guidance, Atrial Fibrillation: Management (CG180)[29]	2014	Consider left atrial appendage occlusion (LAAO) if anticoagulation is contraindicated or not tolerated, and discuss the benefits and risks of LAAO with the person. Do not offer LAAO as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; HRS, Heart Rhythm Society; LAAC device, left atrial appendage closure device with delivery system; NICE, National Institute for Health and Care Excellence.

Appendix 3: Applicability and Quality of Studies Given Full-Text Review—Economic Evidence

Table A1: Applicability of Studies Given Full-Text Review

Objective: To Assess the Cost-Effectiveness of the LAAC Device					
Author, Year	**Is the study population similar to the question?**	**Are the interventions similar to the question?**	**Is the health care system in which the study was conducted sufficiently similar to the current Ontario context?**	**Was/were the perspective(s) clearly stated, and what were they?**	**Are estimates of relative treatment effect from the best available sources?**
Patients Without Contraindications to OACs					
Amorosi et al, 2015[39]	Yes (assumption)	Yes, but some absent (LAAC device vs. dabigatran vs. warfarin)	No (Germany)	Yes (public health care payer)	No, new evidence available (PREVAIL)
Freeman et al, 2016[34]	Yes	Yes, but some absent (LAAC device vs. dabigatran vs. warfarin)	No (U.S.)	Yes (public health care payer)	Yes
Lee et al, 2016[35]	Yes	Yes (LAAC device vs. aspirin vs. aspirin + clopidogrel vs. apixaban vs. dabigatran vs. rivaroxaban vs. warfarin)	No (U.S.)	Yes (public health care payer)	Yes
Micieli et al, 2016[37]	Yes	Yes (LAAC device vs. apixaban vs. dabigatran vs. rivaroxaban vs. warfarin)	Yes (Ontario)	Yes (public health care payer)	No, new evidence available (PREVAIL)
Reddy et al, 2015[33]	Yes	Yes, but some absent (LAAC device vs. dabigatran vs. warfarin)	No (U.S.)	Yes (public health care payer)	No, new evidence available (PREVAIL)
Singh et al, 2013[38]	Yes	Yes, but some absent (LAAC device vs. dabigatran vs. warfarin)	Yes (Ontario)	Yes (public health care payer)	No, new evidence available (PREVAIL)
Patients With Contraindications to OACs					
Reddy et al, 2016[32]	Yes	Yes (LAAC device vs. aspirin vs. apixaban)	No (Germany)	Yes (public health care payer)	Yes
Saw et al, 2016[36]	Yes	Yes (LAAC vs. aspirin)	Yes (Ontario)	Yes (public health care payer)	No, new evidence available (ASAP)

Objective: To Assess the Cost-Effectiveness of the LAAC Device				
Author, Year	Are all future costs and outcomes discounted? (If yes, at what rate?)	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgment (directly applicable/partially applicable/ not applicable)
Patients Without Contraindications to OACs				
Amorosi et al, 2015[39]	No	No	No	Partially applicable
Freeman et al, 2016[34]	Yes (3%)	Yes	No	Partially applicable
Lee et al, 2016[35]	Yes (3%)	Yes	No	Partially applicable
Micieli et al, 2016[37]	Yes (5%)	Yes	No	Directly applicable
Reddy et al, 2015[33]	Yes (3%)	Yes	No	Partially applicable
Singh et al, 2013[38]	Yes (5%)	Yes	No	Partially applicable
Patients With Contraindications to OACs				
Reddy et al, 2016[32]	Yes (3%)	Yes	No	Partially applicable
Saw et al, 2016[36]	No (5%)	Yes	No	Directly applicable

Abbreviations: LAAC device, left atrial appendage closure device with delivery system; OAC, oral anticoagulant.

Table A2: Quality of Studies Given Full-Text Review

Objective: To Assess the Cost-Effectiveness of the LAAC Device				
Author, Year	**Does the model structure adequately reflect the nature of the health condition under evaluation?**	**Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? (e.g., if the rate of mortality differs between interventions, does the model take a lifetime horizon?)**	**Are all important and relevant health outcomes included?**	**Are the estimates of relative treatment effects obtained from the best available sources (in terms of the LAAC device)?**
Patients Without Contraindications to OACs				
Amorosi et al, 2015[39]	Yes	No (10-year)	No (MI)	No (didn't use relative; rates of IS off)
Freeman et al, 2016[34]	Yes	Yes (lifetime)	Yes	No (didn't use relative; rates off for PREVAIL, major hemorrhage, bleed)
Lee et al, 2016[35]	Yes	Yes (lifetime)	Yes	No (didn't use relative; rates of IS off)
Micieli et al, 2016[37]	Yes	Yes (lifetime)	Most (SE, HS by severity)	No (no PREVAIL; underestimates IS; overestimates MB, HS)
Reddy et al, 2015[33]	Yes	Yes (lifetime)	Yes	No (no PREVAIL; underestimate IS; underestimates HS; overestimates MB)
Singh et al, 2013[38]	Yes	Yes (lifetime)	Most (SE, HS by severity)	No (no PREVAIL; underestimates IS; overestimates MB, HS)
Patients With Contraindications to OACs				
Reddy et al, 2016[32]	Yes	Yes (lifetime [20-year])	Yes	Yes
Saw et al, 2016[36]	Yes	Yes (lifetime)	Yes (HS by severity)	Yes

Objective: To Assess the Cost-Effectiveness of the LAAC Device					
Author, Year	Do the estimates of relative treatment effect match the estimates contained in the clinical report?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available resources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?
Patients Without Contraindications to OACs					
Amorosi et al, 2015[39]	N/A	No (cost of device unclear)	Unclear	Unclear	Yes
Freeman et al, 2016[34]	N/A	Yes	Yes	Yes	Yes
Lee et al, 2016[35]	N/A	Yes	Yes	Yes	Yes
Micieli et al, 2016[37]	N/A	No (only hospital costs for events)	Yes	Yes	Yes
Reddy et al, 2015[33]	N/A	Yes	Yes (U.S.)	Yes	Yes
Singh et al, 2013[38]	N/A	No (only hospital costs for events)	Yes	Yes	Yes
Patients With Contraindications to OACs					
Reddy et al, 2016[32]	Yes	Yes	Yes	Yes	Yes
Saw et al, 2016[36]	N/A	No (only hospital costs for events)	Yes	Yes	Yes

Objective: To Assess the Cost-Effectiveness of the LAAC Device			
Author, Year	**Are all important and uncertain parameters subjected to appropriate sensitivity analysis?**	**Is there a potential conflict of interest?**	**Overall assessment (minor limitations/ potentially serious limitations/ very serious limitations)**
Patients Without Contraindications to OACs			
Amorosi et al, 2015[39]	No	Yes	Very serious limitations
Freeman et al, 2016[34]	Yes	Yes	Very serious limitations
Lee et al, 2016[35]	Yes	Yes	Very serious limitations
Micieli et al, 2016[37]	Yes	No	Potentially serious limitations
Reddy et al, 2015[33]	Yes	Yes	Potentially serious limitations
Singh et al, 2013[38]	Yes	No	Potentially serious limitations
Patients With Contraindications to OACs			
Reddy et al, 2016[32]	Yes	Yes	Minor limitations
Saw et al, 2016[36]	Yes	No	Minor limitations

Abbreviations: HS, hemorrhagic stroke; IS, ischemic stroke; LAAC device, left atrial appendage closure device with delivery system; MB, major bleed; MI, myocardial infarction; N/A, not applicable; OAC, oral anticoagulant; SE, systemic embolism.

Appendix 4: Primary Economic Evaluation

Table A3: Inputs for Deterministic Sensitivity Analyses

Variable	Mean	Source	Lower Bound Estimate	Upper Bound Estimate	Calculation of Lower and Upper Bounds
Clinical Event Rates and Treatment Costs					
Device embolization	0.007	PREVAIL, Holmes et al, 2014[20]; PROTECT, AF, Reddy et al, 2014[40]	0	0.014	± 50% of original estimate
Pericardial effusion	0.037	PREVAIL, Holmes et al, 2014[20]; PROTECT, AF, Reddy et al, 2014[40]	0	0.074	± 50% of original estimate
LAAC device implant unsuccessful	0.075	PREVAIL, Holmes et al, 2014[20]; PROTECT, AF, Reddy et al, 2014[40]	0	0.150	± 50% of original estimate
Baseline thromboembolic event rate (by CHA_2DS_2VASc score)	See Table 17	Friberg et al, 2012[50]	Rate*0.5	Rate*1.5	± 50% of original estimate
Baseline hemorrhagic stroke rate (by HAS-BLED score)	See Table 18	Friberg et al, 2012[50]	Rate*0.5	Rate*1.5	± 50% of original estimate
Baseline major bleed rate (by HAS-BLED score)	See Table 19	Friberg et al, 2012[50]	Rate*0.5	Rate*1.5	± 50% of original estimate
OR of ischemic stroke, LAAC device: warfarin	1.56	PREVAIL, Holmes et al, 2014[20]; PROTECT, AF, Reddy et al, 2014[40]	0.77	3.13	Based on 95% CIs
OR of hemorrhagic stroke, LAAC device: warfarin	0.21	PREVAIL, Holmes et al, 2014[20]; PROTECT, AF, Reddy et al, 2014[40]	0.07	0.64	Based on 95% CIs
OR of major bleed, LAAC device: warfarin	0.95	PREVAIL, Holmes et al, 2014[20]; PROTECT, AF, Reddy et al, 2014[40]	0.64	1.42	Based on 95% CIs
Probability of fatal, major, moderate, and minor ischemic and hemorrhagic stroke	See Tables 17 and 18	Goeree et al, 2005[54]	N/A	N/A	Assume all equally probable (0.25)

Variable	Mean	Source	Lower Bound Estimate	Upper Bound Estimate	Calculation of Lower and Upper Bounds
Utilities					
Myocardial infarction, first year	0.87	Tengs and Wallace 2000[63]	0.5	1.00	Range of MI utilities in Tengs and Wallace 2000[63]
Myocardial infarction, second year	0.937	Tengs and Wallace 2000[63]	0.5	1.00	Range of MI utilities in Tengs and Wallace 2000[63]
Myocardial infarction, third year	0.95	Tengs and Wallace 2000[63]	0.5	1.00	Range of MI utilities in Tengs and Wallace 2000[63]
Stroke					
Major (1 month)	0.13	Luengo-Fernandez et al, 2013[64]	0.065	0.195	± 50% of original estimate
Major (post–1 month)	0.41	Luengo-Fernandez et al, 2013[64]	0.205	0.615	± 50% of original estimate
Moderate (1 month)	0.5	Luengo-Fernandez et al, 2013[64]	0.25	0.75	± 50% of original estimate
Moderate (post–1 month)	0.65	Luengo-Fernandez et al, 2013[64]	0.325	0.975	± 50% of original estimate
Minor (1 month)	0.73	Luengo-Fernandez et al, 2013[64]	0.365	1	± 50% of original estimate
Minor (post–1 month)	0.74	Luengo-Fernandez et al, 2013[64]	0.37	1	± 50% of original estimate
Costs					
Cost of device	$10,000	Manufacturer (Boston Scientific Corporation)	$5,000	$15,000	± 50% of original estimate
Physician fees	$1,194	Expert opinion	$597[a]	$2,031	Expert opinion

Abbreviations: $CHADS_2DS_2VASc$, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, Stroke or transient ischemic attack symptoms previously (2 points), Vascular disease, Age 65–74 years, Sex category; CI, confidence interval; HAS-BLED, Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratios (INRs), Elderly, Drugs or alcohol; LAAC device, left atrial appendage closure device with delivery system; OR, odds ratio.

[a]Based on 50% of base case cost.

Table A4: Results of Deterministic Sensitivity Analyses

Variable	Estimate (Upper or Lower Bound)	ICER LAAC Device:Apixaban ($/QALY)	ICER LAAC Device:Dabigatran ($/QALY)	ICER LAAC Device:Rivaroxaban ($/QALY)	ICER LAAC Device:Warfarin ($/QALY)
Clinical Event Rates and Treatment Costs					
Device embolization	Upper	Dominated	Dominated	Dominated	210,109
	Lower	Dominated	Dominated	Dominated	208,268
Pericardial effusion	Upper	Dominated	Dominated	Dominated	162,904
	Lower	Dominated	Dominated	Dominated	157,877
LAAC device implantation unsuccessful	Upper	Dominated	Dominated	Dominated	176,767
	Lower	Dominated	Dominated	Dominated	211,777
Baseline thromboembolic event rate (by CHA_2DS_2VASc score)	Upper	Dominated	Dominated	Dominated	218,622
	Lower	426,041	812,338	36,468	45,423
Baseline hemorrhagic stroke rate (by HAS-BLED score)	Upper	Dominated	Dominated	Dominated	240,387
	Lower	Dominated	Dominated	Dominated	Dominated
Baseline major bleed rate (by HAS-BLED score)	Upper	Dominated	Dominated	Dominated	234,201
	Lower	Dominated	Dominated	Dominated	209,948
OR of ischemic stroke, LAAC device: warfarin	Upper	Dominated	Dominated	Dominated	Dominated
	Lower	71,228	82,185	14,331	28,414
OR of hemorrhagic stroke, LAAC device: warfarin	Upper	Dominated	Dominated	Dominated	729,937
	Lower	Dominated	Dominated	Dominated	145,689
OR of major bleed, LAAC device: warfarin	Upper	Dominated	Dominated	Dominated	Dominated
	Lower	Dominated	Dominated	Dominated	143,707

Variable	Estimate (Upper or Lower Bound)	ICER LAAC:Apixaban ($/QALY)	ICER LAAC:Dabigatran ($/QALY)	ICER LAAC:Rivaroxaban ($/QALY)	ICER LAAC:Warfarin ($/QALY)
Clinical Event Rates and Treatment Costs					
Probability of fatal, major, moderate, and minor ischemic and hemorrhagic stroke	–	Dominated	Dominated	Dominated	290,357
Utilities					
Myocardial infarction, first year	Upper	Dominated	Dominated	Dominated	236,296
	Lower	Dominated	Dominated	Dominated	234,130
Myocardial infarction, second year	Upper	Dominated	Dominated	Dominated	158,183
	Lower	Dominated	Dominated	Dominated	158,183
Myocardial infarction, third year	Upper	Dominated	Dominated	Dominated	163,487
	Lower	Dominated	Dominated	Dominated	163,487
Stroke					
Major (1 month)	Upper	Dominated	Dominated	Dominated	218,413
	Lower	Dominated	Dominated	Dominated	218,718
Major (post–1 month)	Upper	Dominated	Dominated	Dominated	204,385
	Lower	Dominated	Dominated	Dominated	190,735
Moderate (1 month)	Upper	Dominated	Dominated	Dominated	151,644
	Lower	Dominated	Dominated	Dominated	318,747
Moderate (post–1 month)	Upper	Dominated	Dominated	Dominated	184,047
	Lower	Dominated	Dominated	Dominated	296,280
Minor (1 month)	Upper	Dominated	Dominated	Dominated	246,114
	Lower	Dominated	Dominated	Dominated	314,504
Minor (post–1 month)	Upper	Dominated	Dominated	Dominated	218,931
	Lower	Dominated	Dominated	Dominated	212,898

Variable	Estimate (Upper or Lower Bound)	ICER LAAC:Apixaban ($/QALY)	ICER LAAC:Dabigatran ($/QALY)	ICER LAAC:Rivaroxaban ($/QALY)	ICER LAAC:Warfarin ($/QALY)
Costs					
Cost of device	Upper	Dominated	Dominated	Dominated	270,663
	Lower	Dominated	Dominated	Dominated	154,148
Physician fees	Upper	Dominated	Dominated	Dominated	167,800
	Lower	Dominated	Dominated	Dominated	155,330

Abbreviations: $CHADS_2DS_2VASc$, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, Stroke or transient ischemic attack symptoms previously (2 points), Vascular disease, Age 65–74 years, Sex category; HAS-BLED, Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratios (INRs), Elderly, Drugs or alcohol; ICER, incremental cost-effectiveness ratio; LAAC device, left atrial appendage closure device with delivery system; OR, odds ratio; QALY, quality-adjusted life-year.

Appendix 5: Budget Impact Analysis

Table A5: Five-Year Treatment-Specific Costs per Patient, Undiscounted ($2016)

	Year				
	1	2	3	4	5
LAAC device	19,658	2,433	2,453	2,468	2,391
Apixaban	2,240	2,739	2,700	2,715	2,625
Dabigatran	2,310	2,760	2,713	2,695	2,588
Rivaroxaban	3,148	3,479	3,340	3,294	3,148
Aspirin	1,937	2,908	2,947	2,980	2,911
Warfarin	1,749	2,444	2,481	2,538	2,477

Abbreviation: LAAC device, left atrial appendage closure device with delivery system.

Appendix 6: Letter of Information Provided to Interview Participants

LETTER OF INFORMATION

SUMMARY

Health Quality Ontario (HQO) is conducting a formal assessment of an atrial appendage closure device known as "Watchman," to better understand whether this device should be funded by the health care system. Watchman is intended to help reduce the risk of stroke for patients with atrial fibrillation. An important part of this assessment involves speaking to patients at risk of stroke who may be deciding on treatment options, such as anticoagulants. Our goal is to illuminate the lived experience of these patients and families, their existing treatment options, and the context around the Watchman device—what families view as its possibilities, implications, and value.

WHAT DO YOU NEED FROM ME?

- ✓ Willingness to share your story
- ✓ 15–30 minutes of your time for a phone or in-person interview
- ✓ Permission to audio- (not video-) record the interview

WHY DO YOU NEED THIS INFORMATION?

Health Quality Ontario (HQO) is conducting a Health Technology Assessment of the left atrial appendage closure device with delivery system, used to lower the risk of stroke. As part of HQO's core function to promote health care supported by the best evidence available, established scientific methods are used to analyze the evidence for a wide range of health interventions, including diagnostic tests, medical devices, interventional and surgical procedures, health care programs, and models of care. These analyses may be informed and complemented by input from a range of individuals, including patients and clinical experts, and serve as the basis of recommendations about whether health care interventions should be publicly funded or not.

The perspective that you share will be useful to help provide context to the day-to-day realities of patients with atrial fibrillation at risk of stroke and the decisions they face in terms of therapies. The ultimate goal of the project is to provide recommendations to the Ontario Health Technology Advisory Committee, which advises the Ontario Ministry of Health and Long-Term Care on the appropriateness of funding.

WHAT YOUR PARTICIPATION INVOLVES

If you agree to enroll, you will be asked to participate in an interview or focus group conducted by HQO staff. The interview or focus group will likely last 15 to 30 minutes. The session will be conducted in a private location and will be audio-taped. The interviewer will ask you questions about your lived experience with atrial fibrillation, existing therapies, and values when it comes to risk, knowledge, decision-making.

Participation is voluntary. You may refuse to participate, refuse to answer any questions, or withdraw before your interview. Withdrawal will in no way affect care you receive.

CONFIDENTIALITY

All information collected for the review will be kept confidential and privacy will be protected except as required by law. The results of this review will be published; however, no identifying information will be released or published. Any records containing information from your interview will be stored securely.

RISKS TO PARTICIPATION

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their lived experience. If this is the case, please contact any staff.

HEALTH QUALITY ONTARIO STAFF

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Appendix 7: Consent and Release Form Provided to Interview Participants

Consent and Release Form

This form is to be read and completed in accordance with the following instructions before it can be signed.

1. I, _____, allow Health Quality Ontario (Ontario Health Quality Council) to use to inform the development of an evidence-based review:

Check off all appropriate boxes:

a) ___ a recording of my voice

b) ___ a quotation or summary of my opinion that I expressed during an interview

c) ___ name and contact information

2. Please read the following paragraphs before affixing your signature under section 3.

   a) Personal information collected pursuant to, and on this form, will be used for purposes described on this form and for no other purpose. Health Quality Ontario (Ontario Health Quality Council) acknowledges that you have provided this personal information freely and voluntarily. If you have any questions about this collection of this personal information, contact:

      Amy Lang

      Director, Patient, Caregiver, and Public Engagement

      Tel: (416) 323-6868, ext. 610; email: Amy.Lang@hqontario.ca

   b) By signing this form as indicated below, you agree to hereby release and forever discharge Health Quality Ontario (Ontario Health Quality Council), its officers, employees, agents and representatives from any and all claims, demands, expenses, actions, causes of action, and for any and all liability howsoever caused, arising out of, or in any way related to the collection, use and disclosure of information, recordings, and images authorized to be collected pursuant to or on this form.

   c) By signing this form as indicated below, you agree to forever waive any and all rights that you may have to the use of information and recordings that are authorized to be collected pursuant to or on this form, and you acknowledge that all information, recordings, and images shall hereafter remain the exclusive property of Health Quality Ontario (Ontario Health Quality Council).

3. Signature is to be affixed in the appropriate space provided below.

   I have read this form after it was completed, I understand and agree to be bound by its contents, and I am eighteen (18) years of age or over.

   Signature: _____

   Print name: _____

   Date: _____

Appendix 8: Interview Guide

Introduction

1. History of atrial fibrillation diagnosis and treatment (if applicable)
2. History of stroke (if applicable)

Lived Experience

1. Changes to day-to-day routine with diagnosis?
2. What is the impact on partner/spouse/family?
3. Impact of treatment options – medications? Does this affect quality of life? Risk of bleeding on anticoagulants: Does this affect quality of life?

Decision-Making

1. What treatment options were presented?
2. (Any equity issues in regard to treatment options? Cost/inconveniences?)
3. Role of family in decision-making? Physician? Other sources of information (Internet)?
4. Contrast emotion (anxiety, worry) vs. logic? As this applies to risks and side effects?
5. Value placed on having information in decision-making (vs. trusting physician, for example?)
6. Was it difficult to weigh up potential benefits and risks when deciding which therapies to go with?

Watchman

Explain Watchman to interviewee:

- Minimally invasive procedure but requires transesophageal echocardiography (TEE), anesthesia, and day in hospital
- Reduces need for anticoagulants
- Would this procedure be of value? Why/why not?

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About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are.

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do.

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters.

We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

About the Ontario Health Technology Advisory Committee (OHTAC)

About OHTAS

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