The Cost-Effectiveness of First-Line Cryoablation versus First-Line Antiarrhythmic Drugs in Canadian Patients with Paroxysmal Atrial Fibrillation

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Title: The Cost-Effectiveness of First-Line Cryoablation versus First-Line Antiarrhythmic Drugs in Canadian Patients with Paroxysmal Atrial Fibrillation

Short title: Assessing Cryoablation versus Antiarrhythmic Drugs

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Abstract

BACKGROUND: The EARLY-AF (NCT02825979), STOP AF First (NCT03118518), and Cryo-FIRST (NCT01803438), randomized controlled trials (RCTs) demonstrated that cryoballoon pulmonary vein isolation reduces atrial fibrillation (AF) recurrence compared with antiarrhythmic drugs (AADs) in patients with symptomatic paroxysmal AF (PAF). This study developed a cost-effectiveness model (CEM) of first-line cryoablation compared with first-line AADs for PAF, from a Canadian healthcare payer’s perspective.

METHODS: Data from the three RCTs were analysed to estimate key CEM parameters. The model structure used a decision tree for the first 12 months and a Markov model, with a three-month cycle length, for the remaining lifetime time horizon. Costs were set at 2023 Canadian dollars, health benefits were expressed as quality-adjusted life years (QALYs), and both were discounted 3% annually. Probabilistic sensitivity analysis (PSA) considered parameter uncertainty.

RESULTS: The statistical analysis estimated that first-line cryoablation generates a 47% reduction (p<0.001) in the rate of AF recurrence, a 73% reduction in the rate of subsequent ablation (p<0.001), and a 4.3% (p=0.025) increase in health-related quality of life (HRQoL), compared with first-line AADs.

The PSA indicates that an individual treated with first-line cryoablation accrues less costs ($-3,862) and more QALYs (0.19) compared with first-line AADs. Cryoablation is cost saving in 98.4% of PSA iterations and has a 99.9% probability of being cost-effective at a cost-effectiveness threshold of $50,000 per QALY gained. Cost-effectiveness results were robust to changes in key model parameters.
CONCLUSION: First-line cryoballoon ablation is cost-effective when compared with AADs for patients with symptomatic PAF.

KEYWORDS: Atrial fibrillation, catheter ablation, antiarrhythmic drugs, cost-effectiveness
INTRODUCTION

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia, with a worldwide prevalence of 37.6 million cases which is forecast to increase by a further 60% by 2050\(^1\). The prognosis of AF is highly heterogeneous, with a great variety of symptoms and range of severity\(^2\). However, AF is associated with poorer health-related quality of life (HRQoL) outcomes\(^3\) and an increased risk of stroke/systemic thromboembolism, heart failure, myocardial infarction, and mortality\(^4, 5\).

In Canada, the hospital sector costs of AF exceed $815 million annually (2010 Canadian dollars), of which 69% is attributable to hospitalizations\(^6\). Although integrated AF care management approaches have been shown to reduce healthcare resource utilisation\(^7\), the economic burden of AF will continue to increase due to population aging and evolving risk factors\(^1, 2, 8\).

The Canadian Cardiovascular Society (CCS) guidelines recommend rhythm control be the focus of management for patients with paroxysmal AF (PAF), which is defined as AF episodes lasting < 7 days. CCS recommends that antiarrhythmic drugs (AADs) be provided as first-line therapy, with catheter ablation (CA) recommended for patients in whom AADs have failed to maintain normal sinus rhythm (NSR)\(^9\). CA is used during pulmonary vein isolation (PVI) to scar or destroy tissue around pulmonary veins (PVs) responsible for irregular atrial contractions.

Three randomized controlled trials (RCTs) – EARLY-AF\(^10\) (NCT02825979), STOP AF First\(^11\) (NCT03118518), and Cryo-FIRST\(^12\) (NCT01803438) demonstrated that first-line cryoablation reduces AF recurrence compared with first-line AAD therapy in patients with symptomatic PAF. However, these procedures are invasive and incur a significant cost to the healthcare system. Through individual patient-level data (IPD)
we sought to estimate the cost-effectiveness of first-line cryoablation versus first-line AADs for treating symptomatic PAF from a Canadian healthcare payer’s perspective.
METHODS

Statistical analysis of individual patient-level data

The EARLY-AF (NCT02825979), STOP AF First (NCT03118518), and Cryo-FIRST (NCT01803438) RCTs provided IPD from a total of 703 enrolled individuals with treatment-naïve PAF. Baseline demographic characteristics from the clinical trials are presented in Table 1. The statistical methods used as part of this study are detailed in the Supplementary Material (Section S1).

Patient consent is not applicable to this article as it is post-hoc evaluation of anonymized data from the previously conducted RCTs. Patient consent was obtained for each of the three RCTs and reported in their respective publications.

The economic model

The cost-effectiveness model (CEM), as illustrated in Figure 1, used a hybrid decision tree Markov structure to estimate the costs and health outcomes generated for a hypothetical cohort of 1,000 individuals. To align with Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines, a 40-year time horizon was adopted as long-term divergence of clinical pathways and differential effects to mortality were anticipated in each model arm. The current study uses the same model structure as a published US cost-effectiveness of first line cryoablation versus first line AADs but has been adapted to the Canadian healthcare payers’ perspective.

In the initial 12 months, the decision tree simulated the allocation of patients across three health states. Health state definitions were broadly based on clinical definitions by the European Society of Cardiology, but adapted to incorporate a three-month timeframe to align with the subsequent Markov model cycle length. The clinical
authors validated the health state definitions to ensure they captured disease progression and reflect clinical definitions as accurately as possible. The health states included normal sinus rhythm (NSR), defined as no recorded AF within three months; short-term (ST) episodic, defined as at least one AF episode (paroxysmal or persistent) recorded within three months, and death.

The decision tree recorded the number of ablation procedures within the two ‘alive’ health states. In each treatment arm, if patients received an ablation procedure (excluding the initial procedure in the cryoablation arm), they transitioned to the sub-health state ‘1’ of the health state they occupied at the end of the decision tree (e.g., NSR 1). Following the conclusion of the decision tree, the allocation of patients across health states was used to inform the initial state allocation in the Markov model.

The Markov model simulated the remaining 40-year time horizon and used a three-month cycle length to reflect the possible recurrence of arrhythmia observed for patients with PAF annually. As well as the health states used in the decision tree, additional health states included long-term (LT) persistent, defined as AF symptoms that persist over at least a 12-month duration and fail to cease without treatment, and permanent, defined as AF where no further attempts to restore or maintain NSR are undertaken (following agreement between patient and physician).

The number of ablation procedures a patient received (excluding the initial procedure in the cryoablation arm) was recorded using sub-health states. In total, individuals could have a maximum of three ablation procedures (including the initial procedure in the cryoablation arm). Health state transition probabilities are presented in the Supplementary Material (Section S2).
Costs were set at 2023 Canadian dollars and health benefits were expressed as quality-adjusted life years (QALYs). The base case discounted both costs and health benefits at 3% annually, before scenario analysis considered the impact of alternative discount rates to align with CADTH guidelines\textsuperscript{15}. A cost-effectiveness threshold value of $50,000 per QALY gained was used to correspond with routine practice\textsuperscript{16}.

**Model population**

The model population was a hypothetical cohort of 1,000 individuals with baseline characteristics equal to the pooled trials population (Table 1), of which 43% of patients were derived from the Canadian multicentre, open-label, EARLY-AF\textsuperscript{10} (NCT02825979) RCT. The model cohort was, therefore, assumed to be representative of the symptomatic PAF population in Canada.

*Table 1 here.*

**Model parameters**

The statistical analysis of the IPD data estimated the rate of outpatient appointments, rate of emergency department visits, rate of pharmaceutical and electrical cardioversion, rate of AF-related hospitalisation, rate of subsequent ablation after index treatment with cryoablation or AADs, AF recurrence and resolution, and EQ-5D-3L utility values. The statistical methods and estimated parameter values are outlined in the Supplementary Material Section S1.
The remaining key model parameters are presented in Table 2. If parameter estimates could not be sourced from existing literature, the listed clinical authors provided estimated values. A consensus was achieved by all clinical experts for the assumption-based inputs based on what was deemed reasonable and conservative given their clinical experience.

**Costs**

Unit costs were sourced from either the Canadian Institute for Health Information (CIHI) patient cost estimator\(^{17}\), Alberta government Hospital Inpatient Care Case Costs\(^{18}\), the Ontario Schedule of Benefits and Fees\(^{19}\), the Ontario Drug Benefit Formulary\(^{20}\), or existing literature. Unit costs were inflated, when required, to 2023 Canadian dollars using the Bank of Canada’s inflation calculator\(^{21}\).

The Supplementary Material details the individual components of the procedure related cost (Section S3) and pharmaceutical cost calculations (Section S4).

**Health-related quality of life**

Baseline utility was calculated by using the baseline demographic characteristics of the model cohort to weight Canadian EQ-5D-3L population norm data\(^{22}\). To calculate the utility values associated with each health state, the statistical analysis generated EQ-5D-3L utility decrements associated with symptom severity and adverse events (AEs).

**Adverse events**

AE rate parameters are reported in Section S5 of the Supplementary Material. Intra-operative adverse events included: oesophageal injury, cardiac tamponade, pulmonary vein stenosis, vascular complications, and persistent phrenic nerve injury.
Stroke probabilities were calculated using model cohort age, health state membership, and the cohort’s CHA$_2$DS$_2$-VASc score, which is a measure of ischemic stroke risk among AF patients$^{23}$. Heart failure probabilities were calculated using model cohort age, health state membership, and general population heart failure incidence rates.

**Mortality**

The method for calculating the probability of mortality associated with each health state is presented in Section S6 of the Supplementary Material.

*Table 2 here*

**Sensitivity analysis**

Probabilistic sensitivity analysis (PSA) was used to quantify the impact of the uncertainty of all parameter estimates simultaneously. Statistical distributions were fitted to uncertain parameters. Gamma distributions were fitted to cost parameters, beta distributions were fitted to probability and utility parameters, and the parameters estimated from the statistical analysis of the IPD were varied using the Cholesky matrix derived from the regression variance-covariance matrix. In each of the 5,000 iterations, uncertain parameters were allocated a new value using the assigned statistical distribution.

The output of the PSA included mean and 95% credible interval estimates of costs per patient, QALYs per patient, and the incremental cost-effectiveness ratio (ICER) as well as an estimate of the number of iterations in which first-line cryoablation reduces costs per patient compared with first-line AADs.

**Scenario analysis**
Scenario analysis assigned certain parameters substitute values derived from alternative literature sources or expert clinical opinion, to quantify the impact of parameter uncertainty or alternative model assumptions on deterministic model outputs. The scenarios explored were:

1) A 12-week “blanking period”, which delayed the recording of AF recurrences within the initial three months of both model arms, to incorporate expert consensus on CA\textsuperscript{24}. This scenario intended to reflect the recommended design of the trials and prevent early recurrences of AF being attributed to index treatment and, therefore, being interpreted as treatment failure. In the base case, AF recurrences were recorded from index treatment.

2) Alternative discount rates as recommended by CADTH guidelines\textsuperscript{15}.

3) Alternative cryoablation procedure-related costs using values 20% above and below the base case estimate, respectively.

4) Stroke event and ongoing follow up costs collectively increased and decreased by 20%, respectively.

5) Replacement of the ongoing follow up costs of heart failure associated with each New York Heart Association (NYHA) class, which was originally calculated from a UK study\textsuperscript{25}, with estimates from a Canadian study which did not stratify ongoing costs by NYHA class\textsuperscript{26}.

6) Alternative EQ-5D-3L utility decrements based on European Heart Rhythm Association (EHRA) class membership\textsuperscript{27}, as reported in the Supplementary Material (Section S7).

7) The relative risk (RR) of AF symptom recurrence, adjusted for each quantity of previous ablation procedures, increased by 10%.
8) The RR of AF symptom resolution, adjusted for each quantity of previous ablation procedures, increased by 10%.

9) The probability of a successful re-ablation procedure decreased by 30%.

10) The incidence rate of stroke decreased by 30%.

11) The health state-specific stroke RR values increased by 10%
RESULTS

Statistical analysis of the IPD

The complete results of the statistical analysis are presented in the Supplementary Material (Section S1). Patients treated with first-line cryoablation experience a 47% reduction (p<0.001) in their three-monthly rate of AF recurrence compared with first-line AADs. However, there is no statistically significant treatment impact on AF resolution in patients who fail initial treatment (p>0.05).

Patients receiving first-line cryoablation have, on average, a 73% lower monthly rate of re-ablation (p<0.001), an 83% lower monthly rate of pharmaceutical cardioversion (p<0.001), and a 49% lower monthly rate of electrical cardioversion (p=0.021) than those receiving first-line AADs. First-line cryoablation patients also have a 4.3% (p=0.025) increase in HRQoL compared with first-line AADs.

Deterministic results

The deterministic results indicate that, over a 40-year time horizon, an individual treated with first-line cryoablation accrues less costs (-$3,201) and more QALYs (0.17) compared with first-line AADs. Cryoablation is therefore considered dominant even when no “blanking period” is applied and all costs and QALYs are captured from the start of the study (Table 3). Patients in the cryoablation arm experience 5.2% fewer lifetime stroke events which corresponds to a number needed to treat (NNT) of 67 patients to prevent one stroke event (Supplementary Material Table S8.1). Patients also spend longer in the NSR health state, have longer life expectancy, fewer re-ablations, and no difference in heart failure events.

Table 3 here

Table 4 here
**Probabilistic results**

The cost-effectiveness plane, illustrated in Supplementary Material Figure S8.1, presents the distribution of the 5,000 PSA iterations. The PSA results indicate that on average, over a 40-year time horizon, an individual treated with first-line cryoablation accrues less costs (-$3,862) and more QALYs (0.19) compared with first-line AADs. Cryoablation is therefore considered dominant (Table 4).

Convergence of the PSA results was achieved at approximately 2,000 iterations. First-line cryoablation is cost-saving in 98.4% of all PSA iterations and has a 99.9% probability of being cost-effective at a cost-effectiveness threshold of $50,000 per QALY gained.

**Scenario analysis**

The results of the scenario analyses are presented in the Supplementary Material Table S8.2. In each scenario, first-line cryoablation accrues less costs and more QALYs per patient, compared with first-line AADs, and is therefore considered dominant across all scenarios.
DISCUSSION

This study estimated the cost-effectiveness of implementing first-line cryoablation as an alternative therapy to first-line AADs for the treatment of symptomatic PAF, from the perspective of the Canadian healthcare payer. The results indicate that individuals treated with first-line cryoablation accrue less costs and more QALYs when compared with first-line AADs, over a 40-year time horizon. Cryoablation is therefore considered dominant. This conclusion is replicated in each of the scenario analysis performed, which suggests the results are robust to parameter uncertainty. Furthermore, in 98.4% of the PSA iterations, first-line cryoablation generated less costs per patient than first-line AADs.

The key factors which result in first-line cryoablation being cost saving can be identified by analysing the clinical outcomes (Supplementary Material Table S8.1). In the cryoablation arm, the number of ablations after index treatment (excluding index ablation in the cryoablation arm) is 72.5% and 76.5% lower over a 12-month and 40-year time horizon, respectively, which generates a total cost saving of $8,016 per patient. Furthermore, the increase of 2.19 years spent in the NRS health state contributes to the reduction in healthcare contact costs (-$3,725) and AF related adverse event costs (-$1,735) per person, as well as the incremental gain in QALYs (0.17).

Recently, a Canadian CEM estimated that second-line RFA in heart failure patients with AF generates more costs ($15,095 CAD) and more QALYs (0.45) per patient, and has a 90% probability of cost-effectiveness at a cost-effectiveness threshold of $50,000 CAD per QALY gained\textsuperscript{26}. The RFA procedure cost of $9,498 ($11,143 in 2023 CAD) was similar to the cryoablation procedure related cost of $11,893 used by our model. However, a key difference between the models, apart from patient
populations, is the use of CA in the comparator arm. In the RFA model, individuals in the comparator arm receive ongoing medical management and do not receive any form of CA. However, in our model, second-line CA is performed in the comparator arm. Therefore, the initial procedure costs in the first-line cryoablation arm are partially offset by the cost savings generated from fewer subsequent ablation procedures in the cryoablation arm compared to the comparator arm. This outlines a key reason why first-line cryoablation is estimated to be cost-saving as opposed to cost inducing.

Furthermore, the dominant result from this study, can be compared to the results generated from a US CEM of first-line cryoablation versus first-line AADs which used a US Medicare payer perspective. This model used an identical structure and the same outputs from the statistical analysis of the pooled IPD to populate the model, however, the model was adapted to a US Medicare payer perspective by using localised literature sources for the non-IPD generated model parameters. In the US, first-line cryoablation accrued more costs ($4,274 USD) and more QALYs (0.17) per patient. At cost-effectiveness threshold values of $50,000 USD and $100,000 USD per QALY gained, cryoablation had a 76.2% and 91.6% probability of being cost-effective, respectively. Although the US study reaffirms the cost-effective conclusions of this CEM, the Canadian setting is unique in estimating that cryoablation is cost saving as opposed to cost incurring.

A comparison of cryoablation procedure costs between Canada and the US explains why the Canadian model is alone in estimating cost savings. As outlined in the Supplementary Material (Section S9), after converting to 2023 Canadian dollars, the cryoablation procedure cost in Canada is $20,441 less expensive than in the US. Although a lower procedure cost reduces the cost savings associated with
preventing further ablation procedures, the total cryoablation procedure (initial and re-ablation) costs per patient are lowest in the Canadian model. Therefore, a lower initial procedure cost in the Canadian model reduces the amount of cost savings that are required for cryoablation to be cost-saving. Whilst cryoablation procedure costs are notably lower in Canada than in the US, the Canadian procedure cost of $11,893 is markedly similar to the RFA procedure cost estimates of $11,143 and $12,627 (inflated to 2023 Canadian dollars) used by two previous Canadian CA studies\textsuperscript{26, 28}.

The recommendation of this study, that first-line cryoablation is cost-effective, must also be placed into the current context of the Canadian healthcare system. As evidence supporting the efficacy of CA is currently increasing the demand for this therapy faster than the growth in procedure availability, wait-times for AF patients are increasing which is imposing significant morbidity\textsuperscript{29}. The CEM did not consider the impact of increased wait times on patient outcomes. The consequence, to the cost-effectiveness of first-line cryoablation, of delays in receiving CA may need to be researched further, especially as rhythm control for AF has been shown to more effective when delivered early\textsuperscript{30}.

**Limitations**

The method used by the RCTs to detect symptomatic and asymptomatic PAF events, the rate of AF recurrence and, consequently, the re-treatment costs may have resulted in an overestimation due to the intensity of rhythm monitoring. However, as consistent monitoring procedures were applied within the RCTs it is reasonable to consider that both treatment strategies would be equally impacted by asymptomatic arrhythmia events. Furthermore, the electrocardiogram (ECG) monitoring method varied between the RCTs. For example, patients in the EARLY-
AF trial were monitored using implantable loop recorders (ILRs), unlike in the STOP-AF or Cryo-FIRST trials. To account for any impact this may have on the results, the statistical analysis of the IPD data also included the ECG monitoring method as a control variable (Supplementary Material Section S1).

Where possible, statistical analysis of IPD data derived from RCTs has generated parameter estimates. However, due to a paucity of data in the existing literature, the RR parameters for AF recurrence and resolution, stroke, heart failure and re-ablation success according to the number of ablations received and the health state occupied were based on assumptions. Estimates of these parameters were deliberatively conservative and validated by the clinical experts. Moreover, the PSA and scenario analyses indicated that the results were robust across all scenarios explored.

Likewise, clinical experts were consulted to generate the cited stroke rates and the assumption that the utility decrements applied to the ST-episodic and LT-persistent states were equivalent. The scenario analyses undertaken explored the consequences to the deterministic model outcomes of adjusting these assumptions and using alternative model input parameters (Supplementary Material Table S8.2).

**CONCLUSION**

From a Canadian healthcare payer’s perspective, first-line rhythm control with cryoballoon ablation is cost-effective (dominant) when compared with first-line AADs.
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Disclosures:

Dr Andrade reports grants and personal fees from Medtronic, grants from Baylis, personal fees from Boston Scientific, Biosense-Webster. Dr Malte Kuniss reports honoraria for teaching, proctoring and lectures/presentations and participation in clinical trials from Medtronic. Dr Oussama Wazni has received grants from Medtronic; and has received personal fees from Biosense Webster and Boston Scientific. Dr Gian Battista Chierchia has received compensation for teaching purposes and proctoring from Medtronic, Abbott, Biotronik, Boston Scientific, and Acutus Medical. Dr Yaariv Khaykin has nothing to disclose.

Hamid Sadri, Alicia Sale, Eleni Ismyrloglou and Rachelle Kaplon are employees and stockholders of Medtronic. Oussama Wazni is consultant for Medtronic, Boston Scientific, Abbott and Biosense Webster.

Patient consent:

The authors confirm that patient consent is not applicable to this article, as this is a retrospective case report using de-identified data.
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TABLES

Table 1: Baseline characteristics from the clinical trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EARLY-AF</th>
<th>STOP AF First</th>
<th>Cryo-FIRST</th>
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<td>147</td>
<td>103</td>
<td>97</td>
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<td>Age in years (SD)</td>
<td>57.8 (11.5)</td>
<td>59.7 (10.5)</td>
<td>60.5 (11.2)</td>
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<td>69.4%</td>
<td>61.2%</td>
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<td>EQ-5D-3L derived utility (SD)</td>
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<td>0.87 (0.17)</td>
<td>0.89 (0.19)</td>
<td>0.90 (0.15)</td>
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<table>
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Abbreviations: AAD, antiarrhythmic drugs; Cryo, cryoablation; EQ-5D-3L, EuroQol 5-Dimensions 3-Levels; EHRA, European Heart Rhythm Association; SD, standard deviation.
Table 2: Key non-IPD based model parameters

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<td><strong>Procedure-related costs</strong></td>
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<td>Cryoablation procedure</td>
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<td>Pulmonary vein stenosis</td>
<td>$19,268</td>
<td>(^\text{26})</td>
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<td>Vascular complications</td>
<td>$13,709</td>
<td>(^\text{17})</td>
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<tr>
<td>Persistent phrenic nerve injury</td>
<td>$628</td>
<td>NHS reference costs 2020/21 currency code(s) RD20A/RD21A (weighted average of costs) and service code 320 (Cardiology outpatient visit - total [consultant and non-consultant led])(^\text{31}) Converted from GBP to CAN using the 2020 average exchange rate (1 GBP : 1.7202 CAD)(^\text{32})</td>
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<td>CV-related hospitalizations</td>
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<td>CV-related outpatient appointments</td>
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<td>Electrical cardioversion</td>
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<td>Parameter</td>
<td>Value</td>
<td>Source</td>
</tr>
<tr>
<td>-----------------------------------------------------------------</td>
<td>---------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Moderately disabling stroke</td>
<td>$31,904</td>
<td>A weighted average of ischemic and haemorrhagic stroke initial hospitalization costs[^{33}]†</td>
</tr>
<tr>
<td>Severely disabling stroke</td>
<td>$100,466</td>
<td></td>
</tr>
</tbody>
</table>

**Ongoing AF related stroke and heart failure and stroke ongoing costs (per cycle)**

<table>
<thead>
<tr>
<th>Stroke ongoing cost</th>
<th>$6,228</th>
<th>Supplementary Material Section S5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure (NYHA class I)</td>
<td>$235</td>
<td>3(^{\dagger}) (background medication cost per month + outpatient care cost per month)</td>
</tr>
<tr>
<td>Heart failure (NYHA class II)</td>
<td>$301</td>
<td>25</td>
</tr>
<tr>
<td>Heart failure (NYHA class III)</td>
<td>$346</td>
<td>Converted from GBP to CAD using the 2017 average exchange rate (1 GBP : 1.6719 CAD)[^{34}]</td>
</tr>
<tr>
<td>Heart failure (NYHA class IV)</td>
<td>$412</td>
<td></td>
</tr>
<tr>
<td>Alternative heart failure ongoing cost</td>
<td>$1,049</td>
<td>(Amiodarone + other drug costs + pharmacy fees + routine clinic follow-up costs)/4[^{26}]</td>
</tr>
</tbody>
</table>

**Pharmaceutical costs (per cycle)**

<table>
<thead>
<tr>
<th>Cryoablation arm</th>
<th>$33.58</th>
<th>Supplementary Material Section S4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAD Arm</td>
<td>$58.06</td>
<td></td>
</tr>
</tbody>
</table>

**Utility Decrement**

**Health state decrements**

<table>
<thead>
<tr>
<th>LT-persistent</th>
<th>0.08</th>
<th>Assumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent</td>
<td>0.11</td>
<td>35</td>
</tr>
</tbody>
</table>

**AE decrements**

<table>
<thead>
<tr>
<th>Non-disabling stroke short-term</th>
<th>0.00</th>
<th>The atrial fibrillation population norm utility value was assumed equal to the utility value for mild stroke [^{36}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderately disabling stroke – short-term</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Severely disabling stroke – short-term</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Non-disabling stroke – long-term</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Moderately disabling stroke – long-term</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Parameter</td>
<td>Value</td>
<td>Source</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>Severely disabling stroke – long-term</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Heart failure (NYHA class I) – long-term</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Heart failure (NYHA class II) – long-term</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Heart failure (NYHA class III) – long-term</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Heart failure (NYHA class IV) – long-term</td>
<td>0.30</td>
<td></td>
</tr>
</tbody>
</table>

† The weighting applied to stroke costs is detailed in the Supplemental Material (Section S5).

Table 3: Deterministic cost-effectiveness results (per patient)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cryoablation</th>
<th>AADs</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial procedure costs</td>
<td>$11,893</td>
<td>$0</td>
<td>$11,893</td>
</tr>
<tr>
<td>Subsequent ablation (following index treatment) costs</td>
<td>$2,464</td>
<td>$10,480</td>
<td>-$8,016</td>
</tr>
<tr>
<td>Healthcare contact costs</td>
<td>$7,073</td>
<td>$10,798</td>
<td>-$3,725</td>
</tr>
<tr>
<td>Pharmaceutical costs</td>
<td>$2,323</td>
<td>$4,016</td>
<td>-$1,693</td>
</tr>
<tr>
<td>AF-related adverse event costs</td>
<td>$51,945</td>
<td>$53,679</td>
<td>-$1,735</td>
</tr>
<tr>
<td>Intra-operative adverse event costs</td>
<td>$291</td>
<td>$218</td>
<td>$73</td>
</tr>
<tr>
<td>Total cost per patient</td>
<td>$75,990</td>
<td>$79,191</td>
<td>-$3,201</td>
</tr>
<tr>
<td>QALYs per patient</td>
<td>13.15</td>
<td>12.98</td>
<td>0.17</td>
</tr>
<tr>
<td>Incremental cost-effectiveness ratio (ICER)</td>
<td>Dominant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AADs, antiarrhythmic drugs; AF, atrial fibrillation; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
Table 4: Probabilistic cost-effectiveness results (per patient, mean 95% credible interval)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cryoablation</th>
<th>AADs</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost (95% CrI)</td>
<td>$76,628 ($69,082 to $84,653)</td>
<td>$80,490 ($72,297 to $89,386)</td>
<td>-$3,862 (-$7,042 to -$900)</td>
</tr>
<tr>
<td>QALYs (95% CrI)</td>
<td>13.13 (12.85 to 13.38)</td>
<td>12.93 (12.49 to 13.30)</td>
<td>0.19 (0.05 to 0.40)</td>
</tr>
</tbody>
</table>

Incremental cost-effectiveness ratio (ICER) Dominant
Probability of cost-effectiveness ($50,000 per QALY) 99.9%

Abbreviations: **AADs**, antiarrhythmic drugs; **CrI**, credible interval; **ICER**, Incremental cost-effectiveness ratio; **QALYs**, quality-adjusted life-years.
FIGURE LEGENDS

**Figure 1:** Cost effectiveness model structure. Abbreviations: **AAD**, antiarrhythmic drugs; **AF**, atrial fibrillation; **LT**, long-term; **NSR**, normal sinus rhythm; **ST**, short-term.
Section A - Short-term decision tree

Paroxysmal AF population

- Cryoablation
  - No AF recurrence
    - NSR 0
    - NSR 1
  - AF recurrence
    - Repeat ablation
      - No AF recurrence
        - ST episodic AF 1
      - AF recurrence
        - ST episodic AF 0
- AADs
  - No repeat ablation

Section B - Long-term Markov model

NSR 0  NSR 1  NSR 2  NSR 3  Death

- ST episodic AF 0  ST episodic AF 1  ST episodic AF 2  ST episodic AF 3

- LT persistent AF 0  LT persistent AF 1  LT persistent AF 2  LT persistent AF 3  Permanent AF