An economic evaluation of first-line cryoballoon ablation vs antiarrhythmic drug therapy for the treatment of paroxysmal atrial fibrillation from a U.S. Medicare perspective

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BACKGROUND Three recent randomized controlled trials have demonstrated that, as an initial rhythm control strategy, first-line cryoballoon ablation (cryoablation) reduces atrial arrhythmia recurrence compared with antiarrhythmic drugs (AADs) in patients with symptomatic paroxysmal atrial fibrillation (PAF).

OBJECTIVE The study sought to evaluate the cost-effectiveness of first-line cryoablation compared with first-line AADs for treating symptomatic PAF from a U.S. Medicare payer perspective.

METHODS Individual patient-level data from 703 participants with PAF enrolled into the Cryo-FIRST (NCT01803438), STOP AF First (NCT03118518), and EARLY-AF (NCT02825979) trials were used to derive parameters for the cost-effectiveness model. The cost-effectiveness model used a hybrid decision tree and Markov structure. The decision tree had a 1-year time horizon and was used to inform the initial health state allocation in the first cycle of the Markov model. The Markov model used a 40-year time horizon (3-month cycle length). Health benefits were expressed in quality-adjusted life years (QALYs). Costs and benefits were discounted at 3% per year.

RESULTS Cryoablation was estimated to yield higher QALYs (+0.17) and higher costs (+$4274) per patient over a 40-year time horizon than AADs. Ultimately, this produced an average incremental cost-effectiveness ratio of $24,637 per QALY gained. Independent of initial treatment, individuals were expected to receive ~1.2 ablations over a lifetime. There was a 45% relative reduction in time spent in atrial fibrillation health states for those initially treated with cryoablation compared with AADs.

CONCLUSION Initial rhythm control with first-line cryoballoon ablation is highly cost-effective compared with first-line AADs from a U.S. Medicare payer perspective.

KEYWORDS Cryoballoon; Ablation; Cryoablation; Cost-effectiveness; Paroxysmal atrial fibrillation; Antiarrhythmic drug; Initial rhythm control; Pulmonary vein isolation; Economic evaluation

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Introduction

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia, with a worldwide prevalence of 37.5 million cases.[1] The condition is associated with an increased risk of ischemic stroke, heart failure, myocardial infarction, and mortality and with symptoms that can impair health-related quality of life (HRQoL).[2,3] AF can progress and become more sustained over time.[4] Disease progression has been associated with an increased risk of adverse cardiovascular outcomes and escalating healthcare costs.[5]

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KEY FINDINGS

- Statistical analysis of pooled individual patient data (n = 703) from 3 randomized control trials—Cryo-FIRST (NCT01803438), STOP AF First (NCT03118518), and EARLY-AF (NCT02825979)—revealed a significant reduction in the rate of atrial fibrillation recurrence and repeat ablation for paroxysmal patients receiving cryoablation vs antiarrhythmic drugs (AADs).
- An economic evaluation, informed by parameters derived from the aforementioned statistical analysis, estimated first-line cryoablation to be a highly cost-effective alternative to AADs as an initial rhythm control intervention.
- Cryoablation was estimated to be more costly than AADs while yielding higher quality-adjusted life years over a patient's lifetime in all analyses and scenarios explored.
- Given the pertinence of early intervention regarding atrial fibrillation patients' health outcomes and quality of life, the current findings are supportive of cryoablation as an initial rhythm control strategy in a Medicare setting.

Between 1996 and 2016, expenditures for treating cardiovascular disease increased by approximately $108 billion in the United States, $16 billion of which was attributable to treating AF.[6]

In the United States, antiarrhythmic drugs (AADs) are recommended as a first-line rhythm control intervention.[7] Guidance published by the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society recommends pulmonary vein isolation with catheter ablation in younger, healthier patients who are refractory to 1 or more AADs.[7] Recently, 3 randomized control trials—Cryo-FIRST (Catheter Cryoablation Versus Antiarrhythmic Drug as First-Line Therapy of Paroxysmal Atrial Fibrillation) (NCT01803438),[8] STOP AF First (Cryoballoon Catheter Ablation in an Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation) (NCT03118518),[9] and EARLY-AF (Early Aggressive Invasive Intervention for Atrial Fibrillation) (NCT02825979)[10]—have demonstrated that, as an initial rhythm control strategy, cryoballoon ablation (cryoablation) is superior to AADs for reducing arrhythmia recurrence. Moreover, first-line cryoablation has been associated with a lower incidence of progression to persistent AF over 3 years compared with initial AAD therapy.[11]

Given the economic and HRQoL burden posed by AF and the supportive clinical evidence for cryoablation as an initial rhythm control strategy, this study aims to evaluate the cost-effectiveness of first-line cryoablation vs first-line AADs for treating symptomatic PAF from a U.S. Medicare payer perspective using data generated by the Cryo-FIRST, STOP AF First, and EARLY-AF trials.[8–10]

Methods

Statistical analysis of individual patient-level data

Individual patient-level data (IPD) from 703 patients with paroxysmal AF (PAF) who were enrolled into the Cryo-FIRST, STOP AF First, and EARLY-AF trials were used to derive prognostic equations to inform input parameters for the cost-effectiveness model. All sites across the 3 trials obtained approval from their respective institutional review board or Ethics Committee. Moreover, all patients provided written informed consent before participating, and study procedures were all performed adhering to the Principles of the Declaration of Helsinki. While similar economic analysis has been undertaken in a UK setting using outputs of the statistical models based on the IPD, this article focuses on the United States. To ensure transparency, all statistical methods and results used as part of the economic evaluation are outlined in the Supplemental Material (Section 1).

The following outcomes were incorporated into the model: AF recurrence and resolution, rate of repeat ablation (reablation), EQ-5D-3L utility values, rate of AF-related hospitalization, rate of emergency department visits, rate of pharmaceutical and electrical cardioversion, and rate of outpatient appointments.

A 12-week blanking period was also considered in accordance with an expert consensus statement, which recommends excluding AF recurrences within the initial 3 months in which reintervention should be avoided.[12] The blanking period was not included in the base case analysis; however, it was incorporated in a scenario analysis.

The economic model

The model used a hybrid decision tree and Markov structure. Costs and health benefits were captured in both model components for a hypothetical cohort of 1000 individuals that was reflective of the population from the trials. Health benefits were expressed as quality-adjusted life years (QALYs), and costs and benefits were reflective of a U.S. Medicare payer perspective. A 3% discount rate was applied to both outcomes.[13]

A 3-month cycle length was chosen to capture the recurring nature of arrhythmia associated with PAF throughout a year. A 40-year time horizon was used to capture the costs and health outcomes associated with the model cohort across a lifetime. Three willingness-to-pay (WTP) thresholds were examined, consistent with the ACC and AHA's recommended level of value categories ($50,000, $100,000, and $150,000).[14]

Decision tree

The decision tree included a 12-month time horizon and was used to estimate the patient pathway for 3 health states, including normal sinus rhythm state, defined as no recorded AF within 3 months, short-term (ST) episodic state, defined as at least 1 AF episode (paroxysmal or persistent) recorded within 3 months and death. The health state definitions were used in place of conventional definitions to align with the 3-monthly cycle length applied in the model and were based on

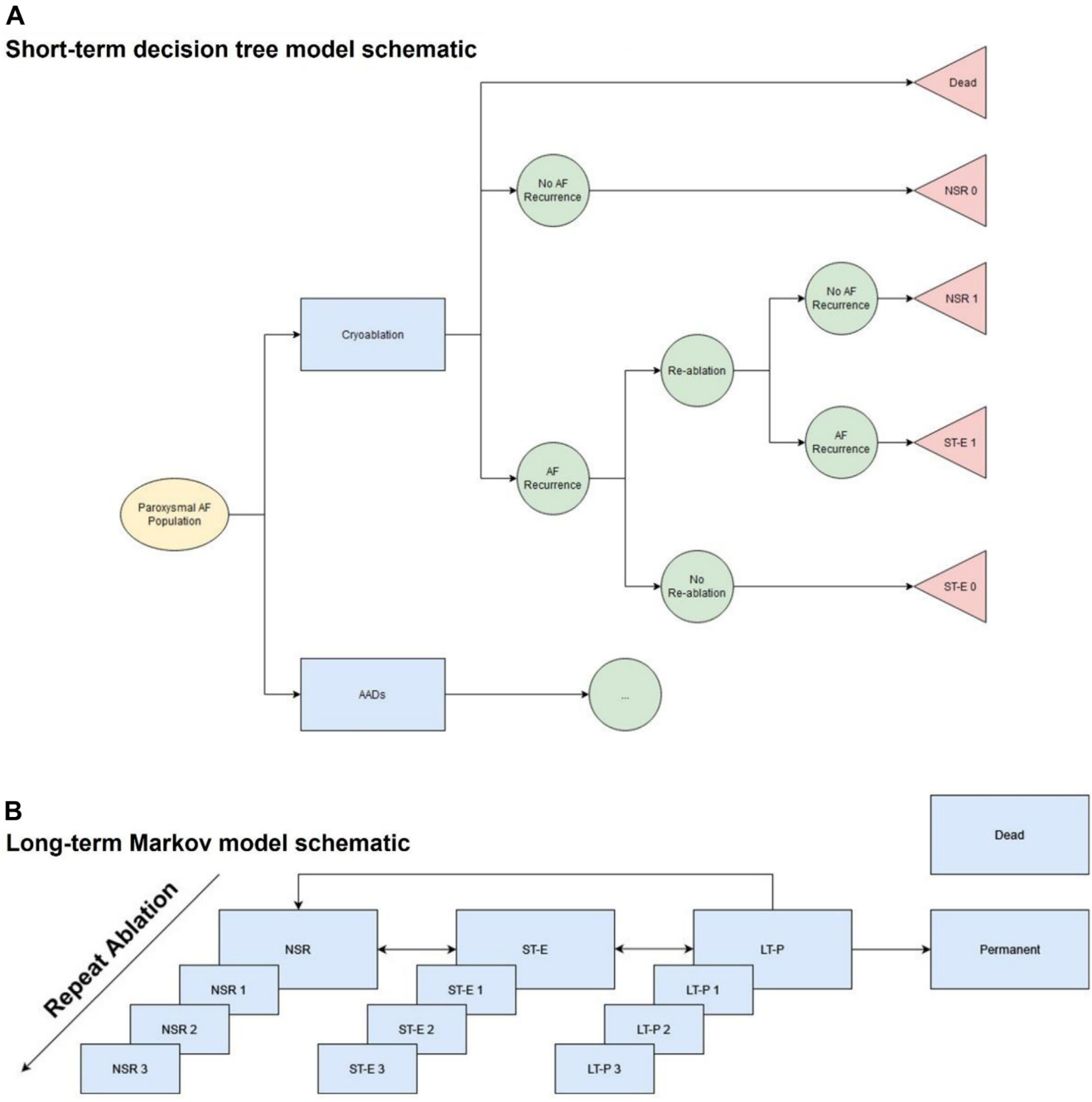

Figure 1 Economic model schematic. **A:** Decision tree; **B:** Markov model. The decision tree endpoints constitute the initial state allocation in the Markov model. AAD = antiarrhythmic drug; AF = atrial fibrillation; E = episodic; LT = long term; NSR = normal sinus rhythm; P = persistent; ST = short term.

clinical definitions defined by the European Society of Cardiology.[4] Said definitions were validated by the clinical authors to capture disease progression in the model while reflecting clinical definitions as closely as possible.

The number of ablations following the initial procedure (reablations) was captured by an ablation count within the 2 alive health states. Regardless of treatment arm, if patients received 1 reablation (excluding the initial procedure in the cryoablation arm), they were captured in the subhealth state 1 of the state that they occupied at the end of the decision tree (e.g. ST-episodic 1). The patients' outcome at the end of the decision tree determined their initial state allocation in the Markov model.

Markov model

The Markov model encompassed the remaining time horizon. In addition to the previously defined health states, the Markov model included the long-term persistent state, defined as AF symptoms that remain over at least a 12-month duration and do not remit without treatment, and the permanent state, defined as AF in which, accepted by the

Table 1 Key model input parameters

Parameter	Value	Source
Unit costs		
Procedure-related costs, $		
Ablation procedure	23,134	[22–24]*
Intraoperative AE costs (per event), $		
Esophageal injury	47,923	[25]†
Cardiac tamponade	6720	
Pulmonary vein stenosis	2944	
Vascular complications	7999	
Persistent phrenic nerve injury	1742	
Healthcare contact costs (excluding reablation procedures), $		
CV-related hospitalizations	25,661	[26] (derived using the proportion of AF patients receiving CV-related secondary healthcare and mean costs)
CV-related A&E department visits	5127	
CV-related outpatient appointments	7155	
Pharmaceutical cardioversion	263	[27]
Electrical cardioversion	254	
AF AE costs (per cycle), $		
Nondisabling stroke	12,641	[28]‡
Moderately disabling stroke	27,338	
Severely disabling stroke	63,707	
Stroke long-term cost	4999	[29]
Heart failure (NYHA functional class I)	2802	[30,31]
Heart failure (NYHA functional class II)	3712	
Heart failure (NYHA functional class III)	3604	
Heart failure (NYHA functional class IV)	3299	
Pharmaceutical costs (per cycle), $		
Cryoablation arm	108	Derived from per-cycle pharmaceutical costs weighted by resource use at 12 mo
AAD arm	143	
Utility decrements		
Health state decrements		
LT—persistent	0.08	Assumption
Permanent	0.11	[32]
AE decrements		
Nondisabling stroke ST	0.00	[28] (the AF population norm utility value was assumed equal to the utility value for mild stroke)
Moderately disabling stroke—ST	0.37	
Severely disabling stroke—ST	0.65	
Nondisabling stroke—LT	0.03	
Moderately disabling stroke—LT	0.18	
Severely disabling stroke—LT	0.36	
Heart failure (NYHA functional class I)—LT	0.00	[33]
Heart failure (NYHA functional class II)—LT	0.07	
Heart failure (NYHA functional class III)—LT	0.16	
Heart failure (NYHA functional class IV)—LT	0.30	

The parameters include those that were not derived from the IPD analysis.

A&E = adverse event; AAD = antiarrhythmic drug; AE = adverse event; AF = atrial fibrillation; CPT = Current Procedural Terminology; CV = cardiovascular; FFS = fee for service; LT = long term; MS-DRG = Medicare Severity Diagnosis Related Groups; NYHA = New York Heart Association; ST = short term.

*The procedure cost calculation is detailed in the Supplemental Material (Section 2).

†The calculations used to derive the AE costs are detailed in the Supplemental Material (Section 3).

‡The weighting used to derive the stroke costs is detailed in the Supplemental Material (Section 3).

patient and physician, no further attempts to restore or maintain normal sinus rhythm will be undertaken.

Numeric subhealth states were also assigned in the Markov model, corresponding to the number of ablation procedures patients received (excluding the initial procedure in the cryoablation arm). Individuals could have a maximum of 3 ablation procedures—including the initial procedure. The model structure is illustrated in Figure 1.

Model parameters

The parameters that were included in the model are displayed in Table 1. Where possible, parameter estimates were derived from the IPD analyses. The named clinical authors provided estimates for parameters where information was not collected in the randomized controlled trials (RCTs) or did not exist in the literature.

Costs

Unit costs were based on publicly available Medicare reimbursement rates, an analysis of the Medicare fee-for-service (FFS) claims data, the Medicare Part D Drug Dashboard, and literature-sourced values (Table 1). Where appropriate, costs were inflated to the 2021 U.S. dollar. The method used to calculate the procedure-related and pharmaceutical

Table 2 Probabilistic cost-effectiveness results (per patient)

Treatment	Cryoablation	AADs	Incremental
Cost, $	122,518 (101,214 to 147,903)	118,244 (96,834 to 144,019)	4274 (391 to 8126)
QALYs	12.37 (12.16 to 12.53)	12.19 (11.82 to 12.48)	0.17 (0.04 to 0.36)
Incremental cost-effectiveness ratio, $	—	—	24,637 (4910 to 132,703)
Net monetary benefit	—	—	4400 (−4124 to 15,292)
Probability of cost-effectiveness (WTP $50,000 per QALY), %	—	—	76.2
Probability of cost-effectiveness (WTP $100,000 per QALY), %	—	—	91.6
Probability of cost-effectiveness (WTP $150,000 per QALY), %	—	—	95.2

Values are mean (95% credible interval), unless otherwise indicated.
AADs = antiarrhythmic drug; QALY = quality-adjusted life year; WTP = willingness to pay.

unit costs is outlined in the Supplemental Material (Sections 2 and 3, respectively).

Utility values

The impact of symptom severity and adverse events (AEs) on HRQoL was captured by applying disutility to baseline utility norm values. The baseline utility norms were weighted by sex according to the distribution identified from the pooled trial data (Table 1).

Adverse events

The AE-related parameters are reported in the Supplemental Material (Section 4). The probability parameters for intraoperative events were sourced from the National Institute for Health and Care Excellence guideline NG196. As these events are short-lasting, it was assumed that they would not impact patients' HRQoL. The probability of stroke was health state and age-dependent and based on the cohorts' CHA_2DS_2-VASc (congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category) score. The probability of heart failure was health state and age dependent and based on the general population data.

Mortality

The mortality-related parameters, including the calculations used to derive said parameters, are reported in the Supplemental Material (Section 5). Mortality was captured via a combination of U.S. general population life tables (adjusted to exclude stroke and heart failure–related deaths) and published stroke and heart failure–related mortality rates. The annual probability of death for the general population was converted to an abridged probability of death across 5-year intervals using the method outlined in a Centers for Disease Control and Prevention report.[15]

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to generate the mean cost and QALY outcomes per patient across 5,000 model iterations. The 95% credible intervals (CrIs) around these mean values, the mean incremental cost-effectiveness ratio (ICER), and the probability of cryoablation being cost-effective at each WTP threshold were also reported. To generate the inputs for each iteration, distributions were fitted to uncertain parameters within the model. Beta distributions were used for probability and utility parameters and gamma distributions were used for cost parameters. The uncertainty around the regression equations was incorporated into the model by utilizing the Cholesky matrix derived from the regression variance-covariance matrix.

Scenario analyses

Scenario analyses, in which input parameters were changed to those obtained from alternative sources or varied according to clinical expert opinion or in which a 12-week blanking period was applied, were conducted to explore parameter uncertainty. The following parameters were explored in the scenario analyses: pharmaceutical agent costs, cardiovascular-related healthcare costs, AF recurrence and resolution risk, ablation success rate, stroke incidence rate, utility decrements, the health state–specific relative risk (RR) of stroke, and the RR of heart failure in the permanent state.

The alternate utility decrements were sourced from a validation paper examining the discriminative ability of the European Heart Rhythm Association (EHRA) symptom classification according to various HRQoL measures.[16] The decrements applied in the scenario analysis are presented in the Supplemental Material (Section 6). Additionally, due to uncertainty surrounding the proportion of patients treated by a physician vs an advanced practice provider at follow-up visits, in which, in the former, 85% of the physician fee schedule rate is covered by Medicare, a scenario applying a 15% discount to the cardiovascular-related healthcare costs was explored. Alternate pharmaceutical costs for the AAD arm were also employed in a scenario for parity with a recent publication examining the cost-effectiveness of radiofrequency ablation in a first-line U.S. setting, which included comparatively higher AAD costs than in the current study ($234 vs $143 per cycle).[17]

Results

The results of the statistical analysis can be found in the Supplemental Material (Section 1). The results of the PSA indicated that the cryoablation arm is estimated to yield

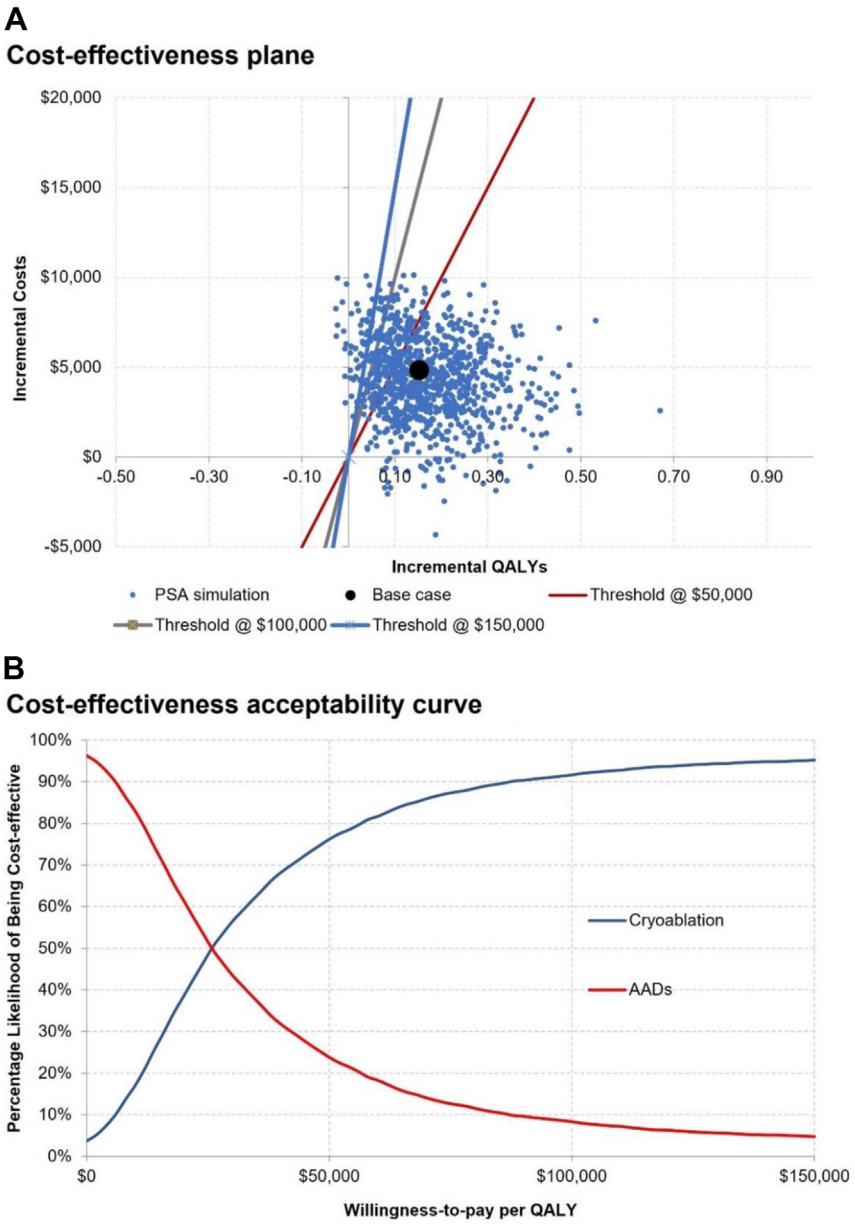

Figure 2 Graphical outputs from the probabilistic sensitivity analysis (PSA). **A:** Cost-effectiveness plane; **B:** cost-effectiveness acceptability curve. AAD = antiarrhythmic drug; QALY = quality-adjusted life-year.

higher QALYs (+0.17 [95% CrI 0.04 to 0.36]) and a higher cost (+$4274 [95% CrI $391 to $8126]) per person than the AAD arm. Ultimately, this produced a mean ICER of $24,637 (95% CrI $4910 to $132,703) per QALY gained (Table 2).

Most model iterations fell in the upper-right quadrant of the cost-effectiveness plane (Figure 2), indicating that cryoablation is more effective and more costly than AADs. Additionally, referring to the cost-effectiveness acceptability curve, cryoablation is the economically preferred intervention at a WTP threshold of $50,000 with an ICER of $26,000 (Figure 2).

The analysis indicated that cryoablation was cost-effective in 76.2%, 91.6%, and 95.2% of iterations with a WTP threshold of $50,000, $100,000, and $150,000, respectively.

The deterministic results (referring to the model outcomes whereby no PSA was conducted) and additional model outcomes are displayed in Tables 3 and 4, respectively. Consistent with the probabilistic analysis, cryoablation was predicted to yield higher costs (+$4834) and QALYs (+0.15) per person than AADs, generating an ICER of $31,802 per QALY gained. Patients in the cryoablation arm reported higher predicted life years gained and a lower lifetime stroke rate. They also spent less time in AF health states and received fewer reablations.

Cryoablation remained highly cost-effective vs AADs in all scenarios explored at a WTP threshold of $50,000 per QALY gained (except the alternate decrements scenario, in which decrements based on EHRA symptom classification were applied, which is cost-effective at a

Table 3 Deterministic cost-effectiveness results (per patient)

Outcome	Cryoablation	AADs	Incremental
Initial procedure, $	23,134	0	23,134
Reablations, $	4518	19,222	−14,705
Healthcare contact costs, $	47,153	47,493	−340
Pharmaceutical costs, $	6864	9094	−2229
AF-related adverse events, $	38,129	39,205	−1076
Intraoperative adverse events, $	172	123	50
Total cost per patient, $	119,971	115,137	4834
QALYs per patient	12.39	12.24	0.15
Incremental cost-effectiveness ratio, $	—	—	31,802

AAD = antiarrhythmic drug; AF = atrial fibrillation; QALY = quality-adjusted life year.

threshold of $100,000 per QALY gained). Cryoablation was estimated to yield higher QALYs and costs per patient in all scenarios.

Discussion

The current study explored the clinical and economic implications of implementing first-line cryoablation (Arctic Front Advance Cryoballoon; Medtronic, Minneapolis, MN) as an alternative therapy for symptomatic PAF vs first-line AADs in a U.S. Medicare setting. Cryoablation is estimated to be more costly than AADs while yielding higher QALYs over a patient's lifetime, resulting in an average ICER of $24,637 per QALY gained. These findings were consistent with the deterministic results (Table 3) and the scenario analyses (Table 5), with cryoablation predicted to be cost-effective in all scenarios explored, suggesting that the results are robust to parameter uncertainty. Employing comparatively higher pharmaceutical costs for the AAD arm for parity with a recent publication indicated a dominant ICER.[17] Moreover, applying the alternate EHRA classification-specific decrements produced an ICER of $64,989 per QALY gained. The comparatively higher ICER relative to the base case and other scenarios explored reflects the equivalent decrements applied to health states in both arms (as opposed to the lower decrements applied to the cryoablation arm when derived from the statistical analysis of the IPD), resulting in reduced incremental QALYs. However, this higher ICER is still considered cost-effective according to the intermediate value threshold suggested by the AHA and ACC.[14] Thus, cryoablation would be considered a highly cost-effective alternative to AADs as an initial rhythm control therapy in a first-line setting.

The statistical analyses indicated a significant reduction in AF recurrence and the reablation rate after initial treatment for the cryoablation arm. The cryoablation arm reported 0.85 fewer reablations per person and a 45% relative reduction in time spent in AF health states over a lifetime. Additionally, a predicted 4.26% higher 12-month utility was observed for those receiving cryoablation in the ST-episodic health state vs those who received AAD therapy. The higher estimated QALY yield in the cryoablation arm is likely attributable to the reduced time spent in health states associated with higher AF burden and reduced HRQoL. This finding is consistent with previous observations that the decline in patient-reported quality of life is due to symptoms and AEs associated with AF.[18]

In the current study, the primary driver of incremental costs was the index ablation procedure received by all patients in the cryoablation arm. The cost of this procedure is offset predominantly by ablation procedures received by those in the AAD arm who experience AF recurrence

Table 4 Additional model results (per patient)

Outcome	Cryoablation	AADs	Incremental	NNT
Time spent in each state, y				
Normal sinus rhythm	20.57	18.66	1.91	—
Short-term episodic	2.09	3.52	−1.43	—
Long-term persistent	0.31	0.57	−0.26	—
Permanent	0.24	0.44	−0.20	—
Life years				
Undiscounted life years	23.20	23.19	0.02	—
Discounted life years	15.94	15.93	0.01	—
Lifetime adverse event rates				
Stroke	0.24	0.25	0.01	83
Heart failure	0.09	0.09	0.00	−5,519
Number of ablations (excluding index ablation in the cryoablation arm)				
12 mo	0.07	0.25	−0.18	—
Time horizon (40 y)	0.26	1.11	−0.85	—

AAD = antiarrhythmic drug; NNT = number needed to treat; QALY = quality-adjusted life year.

Table 5 Scenario analyses results

Scenario*	Incremental costs ($)	Incremental QALYs	ICER ($)
Probabilistic base case	4274	0.17	24,637
Deterministic base case	4834	0.15	31,802
Blanking period implemented	2334	0.08	28,134
Alternative pharmaceutical costs	5690	0.15	37,435
Increased pharmaceutical costs in the AAD arm	−981	0.15	Dominant
15% discount applied to the CV-related healthcare contact costs	4833	0.15	31,794
Increased RR of AF recurrence relative to the number of previous ablations by 10%	3947	0.17	23,462
Increased RR of AF resolution relative to the number of previous ablations by 10%	5558	0.14	39,527
Decreased ablation success rate of 30% (proportionally)	4605	0.16	29,027
Decreased incidence rate of stroke by 30% (proportionally)	5088	0.15	34,236
Alternative literature-based utility decrements applied based on EHRA classification.	4834	0.07	64,959
Changed health state-specific stroke RR values to values sourced from published literature	271	0.21	1285
Increased RR of developing heart failure for those in the permanent health state by 10%	4833	0.15	31,773

CV = cardiovascular; EHRA = European Heart Rhythm Association; ICER = incremental cost-effectiveness ratio; RR = relative risk.
*All scenario analysis outputs are deterministic and incremental values are reported on a per-patient basis.

(Table 3). These findings are consistent with those observed in second-line indication comparisons. Chew and colleagues,[19] in a cost-effectiveness analysis of the Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) clinical trial comparing second-line cryoablation to AADs, found that despite cryoablation being more costly due to the initial procedure, the treatment provided a substantial enough QALY benefit to offset the higher incremental costs and generate a cost-effective result at a WTP threshold of $100,000 per QALY gained.

Minimizing the time from diagnosis to treatment is critical to ensure improved patient outcomes due to the progressive nature of AF. The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) trial showed that early rhythm control was associated with a lower risk of adverse cardiovascular outcomes than usual care.[5] In another study, first-line cryoablation was associated with a significantly reduced risk of progression from PAF to persistent AF, suggesting that ablation is disease modifying.[11] Additionally, approximately half as many AEs and a lower hospitalization rate have been observed for patients receiving first-line cryoablation vs AAD over 3 years.[11] Thus, cryoablation may facilitate slower disease progression and provide a cost-effective first-line alternative to AADs for initial rhythm control in paroxysmal patients.

Assumptions

The RR parameters for AF recurrence and resolution, stroke, heart failure, and reablation success according to the number of ablations received and the health state occupied were based on assumptions. These parameters, which were validated by the clinical authors, were included as conservative estimates. Similarly, the cited stroke rates are based on clinical opinion due to an inability to identify appropriate parameters in the literature. The decrements applied to the ST-episodic and long-term persistent states were assumed equivalent. Scenario analyses were conducted to investigate parameter uncertainty (Table 5). A cost-effective result was maintained across all the explored scenarios.

Strengths

Where possible, parameter estimates were derived from the IPD statistical analysis from the Arctic Front Advance cryoablation RCTs. Despite the necessity of adopting assumptions, the PSA and scenario analyses confirmed that the results were robust across all scenarios explored. The model structure, parameters, and assumptions were also validated by clinical experts to ensure clinical plausibility.

Limitations

The health state parameters were derived from electrocardiogram (ECG) monitoring data collected in the RCTs. As ECG monitoring detects symptomatic and asymptomatic PAF events, the rate of AF recurrence and, consequently, the retreatment costs may be an overestimation. Given that consistent monitoring procedures were applied to each arm within the trials, and the inclusion criteria specified the enrollment of symptomatic patients, both arms would be impacted equally by the likely minimal number of asymptomatic events. Therefore, it is unlikely that the proportion of events presenting as asymptomatic would be affected by treatment type. The ECG monitoring method was included as a confounding effect in the regression models to account for any impact that this may have on the results.

Similarly, a recent publication has indicated that identification of AF via electronic medical records is prone to misclassification, leading to uncertainty surrounding patients' symptom status at enrollment.[20] However, the cryoablation trial inclusion criteria were validated by, generally, a physician note indicating recurrent self-terminating AF, monitoring documentation (eg, ECG, Holter) within a maximum of 24 months of enrollment, and a minimum of 2 documented AF episodes within 12 months. Therefore, though the exact eligibility criteria differ between trials, the

cited validation methods mitigate uncertainty surrounding AF status at enrollment.

Another limitation concerns the application of publicly available costs based on Medicare Part D drugs. The data included represent the total spending for the prescription claim, including the amounts paid by the Medicare Part D plan and beneficiary payments. Medicare-only payments were, therefore, calculated based on 2020 Medicare Part D standard benefit parameters, applying an assumption regarding the distribution of patients in the Medicare Part D standard benefit parameter (Supplemental Material [Section 3]).[21] The associated parameter uncertainty was explored in the scenario analyses, and the results remained supportive of cryoablation (ICER = $37,435).

Conclusion

The findings suggest that first-line cryoablation is a highly cost-effective alternative to AADs from a U.S. Medicare payer perspective.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: All patients provided written informed consent before participating.

Ethics Statement: All sites across the 3 trials obtained approval from their respective institutional review board or Ethics Committee. Procedures were all performed adhering to the Principles of the Declaration of Helsinki.

Data Availability

The data underlying this article cannot be shared publicly due to privacy of the individuals that participated in the study.

References

1. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: an increasing epidemic and public health challenge. Int J Stroke 2021;16:217–221.
2. Adderley NJ, Nirantharakumar K, Marshall T. Risk of stroke and transient ischaemic attack in patients with a diagnosis of resolved atrial fibrillation: retrospective cohort studies. BMJ 2018;361:k1717.
3. Son Y-J, Baek K-H, Lee SJ, Seo EJ. Health-related quality of life and associated factors in patients with atrial fibrillation: an integrative literature review. Int J Environ Res Public Health 2019;16:3042.
4. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373–498.
5. Kirchhof P, Camm AJ, Goette A, et al. Early rhythm-control therapy in patients with atrial fibrillation. N Engl J Med 2020;383:1305–1316.
6. Birger M, Kaldjian AS, Roth GA, Moran AE, Dieleman JL, Bellows BK. Spending on cardiovascular disease and cardiovascular risk factors in the United States: 1996 to 2016. Circulation 2021;144:271–282.
7. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1–e76.
8. Kuniss M, Pavlovic N, Velagic V, et al. Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation. Europace 2021;23:1033–1041.
9. Wazni OM, Dandamudi G, Sood N, et al. Cryoballoon ablation as initial therapy for atrial fibrillation. N Engl J Med 2021;384:316–324.
10. Andrade JG, Wells GA, Deyell MW, et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. N Engl J Med 2021;384:305–315.
11. Andrade JG, Deyell MW, Macle L, et al. Progression of atrial fibrillation after cryoablation or drug therapy. N Engl J Med 2023;388:105–116.
12. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14:e275–e244.
13. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. JAMA 2016;316:1093–1103.
14. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. Circulation 2014;129:2329–2345.
15. Arias E, Xu J. United States Life Tables. 2020. 2022. Available at: Natl Vital Stat Rep 2022;71:1–63. https://www.cdc.gov/nchs/data/nvsr/nvsr71/nvsr71-01.pdf. Accessed October 17, 2022.
16. Wynn GJ, Todd DM, Webber M, et al. The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. Europace 2014;16:965–972.
17. Berman AE, Kabiri M, Wei T, Galvain T, Sha Q, Kuck K-H. Economic and health value of delaying atrial fibrillation progression using radiofrequency catheter ablation. Circ Arrhythm Electrophysiol 2023;16:e011237.
18. Dudink EA, Erküner Ö, Berg J, et al. The influence of progression of atrial fibrillation on quality of life: a report from the. Euro Heart Survey. Europace 2018;20:929–934.
19. Chew DS, Li Y, Cowper PA, et al. Cost-effectiveness of catheter ablation versus antiarrhythmic drug therapy in atrial fibrillation: the CABANA randomized clinical trial. Circulation 2022;146:535–547.
20. Chamberlain AM, Roger VL, Noseworthy PA, et al. Identification of incident atrial fibrillation from electronic medical records. J Am Heart Assoc 2022;11:e023237.
21. Cubanski J, Neuman J. How Will The Medicare Part D Benefit Change Under Current Law and Leading Proposals?. Available at: https://www.kff.org/medicare/issue-brief/how-will-the-medicare-part-d-benefit-change-under-current-law-and-leading-proposals/. Accessed October 28, 2022.
22. Centers for Medicare and Medicaid Services. CMS-1736-FC. Available at: https://www.cms.gov/medicaremedicare-fee-service-paymenthospitaloutpatientppshospital-outpatient-regulations-and-notices/cms-1736-fc. Accessed October 28, 2022.
23. Centers for Medicare and Medicaid Services. Medicare Physician Fee Schedule (MPFS) 2021 National payment rates. CMS-1734-F. 2020. Available from: https://www.cms.gov/medicaremedicare-fee-service-paymentphysicianfeeschedpfs-federal-regulation-notices/cms-1734-f. Accessed October 28, 2022.
24. Centers for Medicare and Medicaid Services. IPPS FY 2021 National payment rates. CMS-1735-F and CMS-1735-CN. 2021. Available from: https://www.cms.gov/medicare/acute-inpatient-pps/fy-2021-ipps-final-rule-home-page. Accessed October 28, 2022.
25. Centers for Medicare and Medicaid Services. Standard Analytical Files (Medicare Claims) - LDS. 2016. Available from: https://www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/LimitedDataSets/StandardAnalyticalFiles. Accessed October 28, 2022.
26. Deshmukh A, Iglesias M, Khanna R, Beaulieu T. Healthcare utilization and costs associated with a diagnosis of incident atrial fibrillation. Heart Rhythm O2 2022;3:577–586.

27. Chun KJ, Brugada J, Elvan A, et al. The impact of cryoballoon versus radiofrequency ablation for paroxysmal atrial fibrillation on healthcare utilization and costs: an economic analysis from the FIRE AND ICE trial. J Am Heart Assoc 2017;6:e006043.
28. Sawyer LM, Witte KK, Reynolds MR, et al. Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke. J Comp Eff Res 2021;10:127–141.
29. Shireman TI, Wang K, Saver JL, et al. Cost-effectiveness of solitaire stent retriever thrombectomy for acute ischemic stroke: results from the SWIFT-PRIME trial (solitaire with the intention for thrombectomy as primary endovascular treatment for acute ischemic stroke). Stroke 2017;48: 379–387.
30. Hussey LC, Hardin S, Blanchette C. Outpatient costs of medications for patients with chronic heart failure. Am J Crit Care 2002;11:474–478.
31. Bogner HR, Miller SD, de Vries HF, Chhatre S, Jayadevappa R. Assessment of cost and health resource utilization for elderly patients with heart failure and diabetes mellitus. J Card Fail 2010;16:454–460.
32. Witassek F, Springer A, Adam L, et al. Health-related quality of life in patients with atrial fibrillation: The role of symptoms, comorbidities, and the type of atrial fibrillation. PloS One 2019;14:e0226730.
33. Göhler A, Geisler BP, Manne JM, et al. Utility estimates for decision–analytic modeling in chronic heart failure—health states based on New York Heart Association classes and number of rehospitalizations. Value Health 2009; 12:185–187.