Open Heart

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An economic evaluation of first-line cryoballoon ablation versus antiarrhythmic drug therapy for the treatment of paroxysmal atrial fibrillation from an English National Health Service perspective

Journal:	*Open Heart*
Manuscript ID	Draft
Article Type:	Original research
Date Submitted by the Author:	n/a
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Keywords:	Ablation Techniques < Electrophysiology, Atrial Fibrillation < Arrhythmias, Cardiac, Health Care Economics and Organizations < Health Services
Abstract:	Introduction Three recent randomised controlled trials have demonstrated that pulmonary vein isolation as an initial rhythm control strategy with cryoablation reduces atrial arrhythmia recurrence in patients with symptomatic paroxysmal atrial fibrillation (PAF) compared with antiarrhythmic drug (AAD) therapy. The aim of this study was to evaluate the cost-effectiveness of first-line cryoablation compared with first-line AADs for treating symptomatic PAF in an English National Health Service (NHS) setting. Methods Individual patient-level data from 703 participants with PAF enrolled into Cryo-FIRST, STOP AF First, and EARLY-AF were used to derive the parameters applied in the cost-effectiveness model (CEM). The CEM comprised a hybrid decision tree and Markov structure. The decision tree had a one-year time horizon and was used to inform the initial health state allocation in the first cycle of the Markov model (40-

	year time horizon; three-month cycle length). Health benefits were expressed in quality-adjusted life years (QALYs). Costs and benefits were discounted at 3.5% per year. Model outcomes were generated using probabilistic sensitivity analysis. Results The results estimated that cryoablation would yield more QALYs (+0.17) and higher costs (+£641) per patient over a lifetime than AADs. This produced an incremental cost-effectiveness ratio of £3,783 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 AF health states for those initially treated with cryoablation. Discussion AF rhythm control with first-line cryoablation is cost-effective compared with first-line AADs in an English NHS setting.

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1. TITLE PAGE

Title: *An economic evaluation of first-line cryoballoon ablation versus antiarrhythmic drug therapy for the treatment of paroxysmal atrial fibrillation from an English National Health Service perspective*

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2. STRUCTURED ABSTRACT

Introduction

Three recent randomised controlled trials have demonstrated that pulmonary vein isolation as an initial rhythm control strategy with cryoablation reduces atrial arrhythmia recurrence in patients with symptomatic paroxysmal atrial fibrillation (PAF) compared with antiarrhythmic drug (AAD) therapy. The aim of this study was to evaluate the cost-effectiveness of first-line cryoablation compared with first-line AADs for treating symptomatic PAF in an English National Health Service (NHS) setting.

Methods

Individual patient-level data from 703 participants with PAF enrolled into Cryo-FIRST, STOP AF First, and EARLY-AF were used to derive the parameters applied in the cost-effectiveness model (CEM).

The CEM comprised a hybrid decision tree and Markov structure. The decision tree had a one-year time horizon and was used to inform the initial health state allocation in the first cycle of the Markov model (40-year time horizon; three-month cycle length). Health benefits were expressed in quality-adjusted life years (QALYs). Costs and benefits were discounted at 3.5% per year. Model outcomes were generated using probabilistic sensitivity analysis.

Results

The results estimated that cryoablation would yield more QALYs (+0.17) and higher costs (+£641) per patient over a lifetime than AADs. This produced an incremental cost-effectiveness ratio of £3,783 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 AF health states for those initially treated with cryoablation.

Discussion

AF rhythm control with first-line cryoablation is cost-effective compared with first-line AADs in an English NHS setting.

3. KEYWORDS

Ablation techniques, cost-effectiveness analysis, paroxysmal atrial fibrillation, antiarrhythmic drug.

4. INTRODUCTION

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia [1]. Symptoms include light-headedness, shortness of breath, tiredness, and heart palpitations; however, pathology may differ drastically between individuals [1]. AF is associated with an increased risk of mortality [2], stroke, heart failure, myocardial infarction [3] and cognitive decline [4], and psychosocial factors such as job strain and depressive symptoms [5]. Both the symptoms and potential complications of PAF contribute to a significant loss in health-related quality of life (HRQoL) [6]. The treatment and management of AF are also associated with substantial healthcare costs. In 2020, AF was predicted to directly cost the National Health Service (NHS) between £1.4 billion and £2.5 billion [7].

For people who need long-term rhythm control, antiarrhythmic drugs (AADs) are the first-line treatment [8]. Guidance published by the National Institute for Health and Care Excellence (NICE) recommends pulmonary vein isolation (PVI) for people who are intolerant or refractory to AADs [8]. There are currently two leading techniques to achieve PVI: radiofrequency ablation (RFA), which uses electrical currents to heat tissue but requires multiple applications and targeted point-to-point delivery, and cryoablation, which is a single-delivery approach where cryogenic energy is applied in a balloon catheter to freeze tissue. Cryoablation has been an approved PVI technique in England since 2012 and was used in 39% of PVI procedures in the last reporting period [9, 10].

Randomised controlled trial (RCT) evidence suggests cryoablation may be non-inferior to RFA in terms of effectiveness and safety in PAF patients [11]. Additionally, three recent RCTs have evaluated PVI with cryoablation versus AADs as an initial rhythm control strategy in patients who are not intolerant or refractory to AADs: Cryo-FIRST (NCT01803438) [12], STOP AF First (NCT03118518) [13] and EARLY-AF (NCT02825979) [14]. All three trials demonstrated that, as an initial rhythm control strategy, cryoablation is superior to AAD therapy for reducing atrial arrhythmia recurrence [12-14].

While cryoablation has been demonstrated to be a cost-effective therapy for PAF in a second line setting based on data from the STOP-AF trial [15], the aim of this study was to evaluate the cost-effectiveness of first-line cryoablation versus first-line AADs for treating symptomatic PAF in an English NHS setting using data from all three randomised Arctic Front Advance cryoablation trials.

5. METHODS

Statistical Analysis of Individual Patient-level Data

Individual patient-level data (IPD) from 703 patients with PAF who were enrolled into Cryo-FIRST, STOP AF First and EARLY-AF were used to derive prognostic equations to inform input parameters for the cost-effectiveness model (CEM). Statistical analyses were performed in R v4.1.1 or later [16].

The baseline characteristics for all populations included in the IPD analyses are presented in Table 1. Patients who left the study less than 30 days after the initial ablation procedure or less than 30 days following their final ablation procedure in either treatment arm were excluded from the analyses as the impact of ablation could not be linked to any future costs or benefits to inform the economic evaluation. Each clinical trial was assigned a unique Study ID to allow for nesting effects to be controlled for in all statistical analyses. We assumed that the pooled characteristics are broadly representative of the general first-line population in the United Kingdom (UK). Any missing data were assumed missing completely at random.

Table 1: Baseline characteristics from the clinical trials

Characteristic	Cryo-FIRST		STOP AF First		EARLY-AF		Pooled	
	Cryo	AAD	Cryo	AAD	Cryo	AAD	Cryo	AAD
Patient counts	97	105	103	97	154	147	354	349
Age (Years)	49.9 (12.6)	54.4 (13.5)	60.5 (11.2)	61.3 (11.2)	57.8 (11.5)	59.7 (10.5)	56.5 (12.4)	58.5 (12.0)
Sex (% Male)	70.10%	64.76%	61.17%	58.76%	72.72%	69.39%	68.60%	65.00%
EQ-5D-3L-derived utility			0.89 (0.19)	0.90 (0.15)	0.87 (0.16)	0.87 (0.17)	0.88 (0.17)	0.88 (0.16)
EHRA Class								
I	0%	0%						
II	69.1%	75.2%						
III	28.9%	23.8%						
IV	2.06%	0.6%						

Abbreviations: AAD, antiarrhythmic drugs; Cryo, cryoablation; EQ-5D-3L, EuroQol 5-Dimensions 3-Levels; EHRA, European Heart Rhythm Association.
* Cells shaded grey indicate that this information was not collected in these studies.

The following outcomes were incorporated in the CEM:

- AF recurrence and resolution.
- Rate of ablation after index treatment (re-ablation; re-ablation may represent an index ablation for patients randomised to AAD).
- EQ-5D-3L utility values.
- Rate of AF-related hospitalisation.
- Rate of accident and emergency visits.
- Rate of pharmaceutical and electrical cardioversion.
- Rate of outpatient appointments.

All outcomes listed were defined as functions of the treatment arm. Selected additional covariates of potential clinical relevance were used to produce adjusted mean estimates. Statistical models (generalised linear models [GLMs] and generalised linear mixed models [GLMMs]), with either a Poisson (log link), Binomial (logit link) or a Beta (logit link) distribution, were used to model all outcomes. The most appropriate distribution for the statistical models was chosen based on the dependent variable type (e.g., count or continuous) and diagnostic criteria (e.g., Akaike's Information Criteria).

An offset variable was included within the long-term follow-up count-based statistical models to derive a rate per month rather than an absolute count for each patient to account for exposure time for the relevant models. Because no NICE-approved utility value sets for the EQ-5D-5L exist, EQ-5D-5L data were mapped to EQ-5D-3L utility values using the van Hout algorithm [17] before the statistical analysis.

A secondary statistical analysis was performed whereby outcomes that occurred within 12 weeks of the initial procedure were not considered. This "blanking period" is in accordance with the Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, which recommends that counting AF recurrences should be avoided within the first three months [18]. These analyses were conducted to test the sensitivity of the CEM to resource usage in the first 12 weeks of the clinical trial to ensure no excessive resource use unduly influenced the results. The blanking period was not applied in the base case analysis. Only covariates deemed to significantly contribute to the predictive ability of the statistical model are shown.

Description of the Economic Model

The CEM was a hybrid of a decision tree and Markov structure. Cost and benefits were captured in both parts of the model for a hypothetical cohort of 1,000 individuals, reflecting the population from the three clinical trials. The model was built in Microsoft Excel and developed from the perspective of the UK NHS and personal social services (PSS). As PAF is expected to occur at any point in time, a three-month cycle was chosen to capture the multiple changes in AF status throughout a year. In order to capture all costs and health outcomes associated with the model cohort, a lifetime time horizon (40 years) was considered. Health benefits were expressed in terms of quality-adjusted life years (QALYs), and all benefits and costs were discounted at 3.5% per year in line with methodological guidance from NICE [9].

Decision Tree

A one-year time horizon was used in the decision tree component of the CEM to reflect the length of the RCTs, shown in Figure 1a. The decision tree was used to estimate the patient pathway using three health states: NSR ("Normal Sinus Rhythm"), defined as no AF episodes (persistent or paroxysmal) recorded within three months; short-term (ST)-episodic AF ("ST-Episodic"), defined as at least one AF episode (either paroxysmal or persistent) documented within three months, and death. The definitions of all the health states used in both parts of the CEM were agreed upon with the clinical experts (the listed clinical authors) to best capture the progression of the disease in an economic model while reflecting clinical definitions as closely as possible. The cited health states were used in place of conventional clinical definitions to align with the three-month cycle length applied in the model, and are based on those defined by the European Society of Cardiology [19]. The outcome of the decision tree determined the initial state allocation in the Markov model.

Markov Model

A Markov model was used for the remaining time horizon of the CEM, shown in Figure 1b. This portion of the CEM included two additional health states: long-term persistent AF ("LT-Persistent"), defined as the same symptoms as in the ST Episodic AF health state but over at least a 12-month duration which does not resolve on its own, and permanent AF, defined as AF where, accepted by the patient and physician, no further attempts to restore or maintain NSR will be undertaken.

Numerical health states were assigned corresponding to the number of ablation procedures patients underwent during the 12-month follow-up period (excluding the initial procedure in the cryoablation arm). Individuals could have a maximum of three ablation procedures (including the initial procedure in the cryoablation arm). Thus, the Markov model has 14 distinct health states, including death.

Figure 1: Model schematic

Model Parameters

The parameters included in the model are shown in Table 2. 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 RCTs or did not exist in the literature.

Costs

Unit costs were based on NICE clinical guidelines (NG196) and NHS reference costs 2018/19. Where appropriate, costs were inflated using the PSSRU 2020/21 inflation indices (Table 2) [8]. The ablation procedure costs are available in Section 1 of the Supplementary Material. Additionally, a breakdown of the method used to derive the per cycle pharmaceutical costs is provided in Section 2 of the Supplementary Material.

Utilities

The impact of symptom severity and adverse events 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 2).

Adverse Events

The adverse event-related parameters are reported in Section 3 of the Supplementary Material. The probability of intra-operative events, including oesophageal injury, cardiac tamponade, pulmonary vein stenosis, vascular complications and persistent phrenic nerve injury, were sourced from the NICE guideline NG196. As these intra-operative events are typically short-lasting, it was assumed they would only result in additional treatment costs and there would be no impact on a patient's HRQoL. The probability of stroke was health state and age-dependent and based on the cohorts' CHA_2DS_2-VASc score. The probability of heart failure was health state and age-dependent and based on the general population data.

Mortality

The mortality-related parameters are reported in Section 4 of the Supplementary Material. Mortality was captured via a combination of UK general population life tables (adjusted to exclude stroke and heart failure-related deaths) and published stroke and heart failure-related mortality rates. The mortality rates were weighted by sex using the proportion identified in the pooled clinical trial data. These final annual rates where then converted to three-monthly rates for use in the CEM.

203 **Table 2: Key model input parameters**

Parameter	Value	Source
Unit Costs		
Procedure-related costs		
Ablation procedure	£9,779	Derived from ablation HRG procedure cost and average list prices provided by Medtronic [8].**
Intra-operative adverse event costs (per event)		
Oesophageal injury	£26,733	[8]
Cardiac tamponade	£2,083	
Pulmonary vein stenosis	£2,777	
Vascular complications	£1,389	
Persistent phrenic nerve injury	£325	
Healthcare contact costs		
CV-related hospitalisations (excluding re-ablation procedures)	£1,362	[20] Weighted average: Non-elective long and short stays: HRG EB07A to EB07E.
CV-related A&E department visits (excluding re-ablation procedures)	£332	[20] Weighted average: HRG VB01Z to VB09Z.
CV-related outpatient appointments (excluding re-ablation procedures)	£191	[20] Total outpatient attendance. Service code: 320 - Cardiology.
Pharmaceutical cardioversion	£1,528	[20] Weighted average: HRG codes: EB07A-EB07E (Day case). Consultant led; Cardiology; Currency code: WF01A
Electrical cardioversion	£1,528	
Atrial fibrillation adverse event costs (per cycle)		
Non-disabling stroke	£2,196	[20] Weighted average of currency codes AA35E and AA35F (Stroke with CC score 0-3 and 4-6).
Moderately disabling stroke	£3,622	[20] Weighted average of currency codes AA35C and AA35D (Stroke with CC score 7-9 and 10-12).
Severely disabling stroke	£6,812	[20] Weighted average of currency codes AA35A and AA35B (Stroke with CC score 13-15 and 16+).
Stroke long-term cost	£293	[21]
Heart failure (NYHA class I)	£125	[22]
Heart failure (NYHA class II)	£159	
Heart failure (NYHA class III)	£183	
Heart failure (NYHA class IV)	£218	
Pharmaceutical costs (per cycle) ***		
Cryoablation arm	£38.37	Derived from per cycle pharmaceutical costs weighted by resource use at 12

Parameter	Value	Source
AAD Arm	£48.69	months.
Utility Decrements		
Health state decrements		
LT-persistent	0.08	Assumption based on clinical expert opinion.
Permanent	0.11	[6]
Adverse event decrements		
Non-disabling stroke – short-term	0.00	[23]
Moderately disabling stroke – short-term	0.23	
Severely disabling stroke – short-term	0.60	
Non-disabling stroke – long-term	0.00	
Moderately disabling stroke – long-term	0.17	
Severely disabling stroke – long-term	0.35	
Heart failure (NYHA class I) – long-term	0.00	[23]
Heart failure (NYHA class II) – long-term	0.05	[22]
Heart failure (NYHA class III) – long-term	0.15	
Heart failure (NYHA class IV) – long-term	0.33	

Abbreviations: AAD, antiarrhythmic drug; LT, long-term; NYHA, New York Heart Association; ST, short-term.
* The cited parameters include those that were not derived from analysis of the individual patient data.
** The ablation procedure cost calculation is detailed in the Supplementary Material (Section 1).
*** The per cycle pharmaceutical cost calculations are detailed in the Supplementary Material (Section 2).

Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was conducted to generate the mean cost and QALY outcomes per patient across 5000 model iterations. The 95% credible intervals (CrI) around these mean values, mean incremental cost-effectiveness ratio (ICER) and the probability of cryoablation being cost-effective were also reported. To generate the input values for each iteration, distributions were fitted to uncertain parameters within the model. For probabilities and utilities, beta distributions were used, while cost parameters were fitted with gamma distributions. Uncertainty around estimates provided by the regression equations was incorporated into the model by utilising the Cholesky matrix derived from the regression variance-covariance matrix.

Scenario Analysis

Scenario analyses, where base case input parameters were changed to those obtained from alternative sources or varied according to clinical expert opinion or where a 12-week blanking period was applied, were conducted to explore parameter uncertainty. The following parameters were explored in the scenario analyses: AF recurrence risk, AF resolution rate, ablation success rate, stroke incidence, HRQoL measures, the relative risk for stroke, the relative risk for heart failure and procedure costs.

6. RESULTS

Results of the Statistical Analysis

The results of the statistical analyses are reported in Section 5 of the Supplementary Material. Cryoablation is associated with a statistically significant reduction in the three-monthly rate of AF recurrence ($p<0.001$). On average, the three-monthly AF recurrence rate was 46.7% lower than those receiving AADs. However, as there was no statistically significant treatment impact on AF resolution in those who failed initial treatment, the treatment effect covariable was consequently removed from the regression model during model refinement via stepwise deletion ($p>0.05$).

Patients receiving cryoablation have, on average, a monthly rate of re-ablation that is 72.8% lower than those receiving AADs, a monthly rate of pharmaceutical cardioversion that is 82.5% lower and a monthly rate of electrical cardioversion that is 48.9% lower than those receiving AADs. A statistically significant treatment effect was observed for the monthly rate of re-ablation ($p<0.001$) and electrical ($p = 0.021$) and pharmaceutical ($p<0.001$) cardioversion.

After stepwise selection, treatment arm ($p = 0.025$) and utility at baseline ($p<0.001$) remained the only statistically significant predictors of utility at 12 months. Those with ST-episodic AF were not found to be significantly different to those in the NSR health state ($p=0.115$). However, there is a non-significant trend of decreased utility associated with the ST-episodic state over the NSR state in the AAD and cryoablation group, with decrements of 0.10 and 0.08, respectively.

Cost-effectiveness Results

The probabilistic results (Table 3) showed that cryoablation is estimated to yield 0.17 incremental QALYs [CrI: 0.04 to 0.35]) and a higher cost (incremental costs = £641 [CrI: -£1,210 to £2,364]) per person than AADs. This produced an ICER of £3,783 per QALY gained (CrI: £710 to £36,753).

Table 3: Probabilistic cost-effectiveness results

Treatment	Cryoablation	AADs	Incremental
Cost (per patient)	£21,301 (£19,432 to £23,264)	£20,661 (£18,395 to £23,174)	£641 (-£1210 to £2364)
QALYs (per patient)	11.47 (10.88 to 11.99)	11.30 (10.65 to 11.88)	0.17 (0.04 to 0.35)
ICER			**£3,783 (£710 to £36,753)**
NMB			**£2,746 (-£665 to £7023)**
Probability of cost-effectiveness at a threshold of £20,000 per QALY gained			**89.5%**
Probability of cost-effectiveness at a threshold of £30,000 per QALY gained			**94.3%**

Abbreviations: AADs, antiarrhythmic drugs; CrI, credible interval; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY quality adjusted life-year.

Most PSA iterations fell in the North-east quadrant of the plane, indicating that cryoablation is more effective and more costly than AADs (Figure 2a).

Cryoablation is the economically preferred intervention at a willingness-to-pay (WTP) threshold of approximately £4,000 or higher (Figure 2b). The cost-acceptability analysis indicated that, at the £20,000 WTP threshold (used by NICE), 89.5% of iterations were cost-effective. Additionally, at a WTP threshold of £30,000 (the upper threshold accepted by NICE), 94.3% of iterations were cost-effective (Table 3).

Figure 2: Cost-effectiveness plane and cost-effectiveness acceptability curve

A summary of the deterministic results and additional model outcomes, including time spent in each state, life years, lifetime adverse event rates and the lifetime number of re-ablations, is reported in Section 6 of the Supplementary Material. Patients in the cryoablation arm had higher predicted life years gained and a lower lifetime rate of stroke. They also spent less time in AF health states and received fewer re-ablations.

In the scenario analysis (Table 4), cryoablation was found to be cost-effective versus AADs in all scenarios explored, including when the 'blanking period' was implemented and where additional utility decrements were applied to higher European Heart Rhythm Association (EHRA) classes. The incremental QALYs per patient remained positive, and cryoablation remained cost-increasing in all scenarios.

Table 4: Scenario Analyses Results

Scenario	Incremental Costs	Incremental QALYs	ICER
Base case	£641	0.17	£3,783
Blanking period implemented	£298	0.09	£3,219
Increased relative risk of AF recurrence relative to the number of previous ablations by 10%	£317	0.18	£1,722
Increased relative risk of AF resolution relative to the number of previous ablations by 10%	£899	0.16	£5,619
Decreased ablation success rate of 30% (proportionally)	£572	0.18	£3,252
Decreased incidence of stroke by 30% (proportionally)	£667	0.17	£3,977
EQ-5D form was replaced by AF Quality of Life Survey (AFEQT) form with additional utility decrement for higher European Heart Rhythm Association (EHRA) class	£614	0.08	£7,759
Changed health state specific stroke relative risk values to values sourced from published literature	£383	0.23	£1,690
Increased relative risk of developing heart failure for those in the permanent health state by 10%	£653	0.17	£3,830
Average selling price used for all procedure costs	£596	0.17	£3,565
2022/23 cost used for ablation procedure cost	£790	0.17	£4,686

Abbreviations: EQ-5D, EuroQoL 5 Dimensions; ICER, incremental cost-effectiveness ratio; QALY quality adjusted life-year.

7. DISCUSSION

Model and Statistical Analyses Results Discussion

The aim of this study was to explore the clinical and economic implications of implementing cryoablation as an alternative first-line therapy for symptomatic PAF versus first-line AADs from an English NHS perspective.

The results from the economic analysis indicated that cryoablation is estimated to be more costly than AADs over a patient's lifetime. However, cryoablation is predicted to yield higher QALYs, resulting in an ICER of £3,783 per QALY gained. Similarly, these findings were consistent with the scenario analyses (Table 4), with cryoablation predicted to be cost-effective in all scenarios explored. This suggests that the results are robust to parameter uncertainty. Thus, the ICER for cryoablation (using the pooled trials efficacy data) was below the lower threshold used in the UK cost-effectiveness decision-making (£20,000 per QALY gained) [24], indicating that cryoablation would be considered a highly cost-effective alternative to AADs as an initial rhythm control therapy.

Statistical modelling using the pooled clinical trial data showed that cryoablation was associated with a statistically significant reduction in the rate of re-ablation and AF recurrence. There were 0.89 fewer re-ablations per person and a 45% relative reduction in the amount of time spent in AF health states over a lifetime for patients who had cryoablation compared with those who received AADs. Additionally, it was predicted that those receiving cryoablation in the ST-episodic health state would have a 4.26% higher 12-month utility than those receiving AADs. Consequently, patients in the cryoablation arm incurred lower utility decrements in the ST-episodic health state. The higher estimated QALY yield in the cryoablation arm is, therefore, attributable to the reduction in time spent in AF health states that are associated with higher utility decrements. This finding aligns with the Euro Heart Survey, which showed that the decrease in HRQoL associated with AF progression is attributed to a minor effect of the associated symptoms and a major effect of associated adverse events due to AF [25].

Clinical Effectiveness

While the cost-effectiveness of second-line cryoablation compared with second-line AADs has previously been shown to fall within the range that is acceptable to NICE [15], this study highlights that first-line cryoablation treatment is also highly cost-effective and clinically pertinent. Since AF is a progressive disease, minimising the time from diagnosis to treatment is crucial to improve clinical outcomes. Recently, the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) showed that early rhythm control is associated with a significantly lower risk of adverse cardiovascular outcomes compared to usual care [26]. Further cost-effectiveness analysis of a subset of the data generated by the EAST-AFNET 4 trial projected fewer cardiovascular death and hospitalisation and stroke events over a 72-month follow-up period for those receiving early rhythm control [27]. Moreover, as an initial first-line rhythm control strategy, cryoablation is associated with a significant reduction in atrial arrhythmia recurrence and re-hospitalisation compared to AAD therapy in patients with PAF [28]. Cryoablation has also been shown to significantly lower the risk of progression from PAF to persistent AF compared to AAD therapy, suggesting that ablation is disease-modifying [29]. Importantly, AF progression is associated with higher risk for stroke, heart failure and healthcare utilisation, underscoring the clinical and economic importance of intervening early [30-32].

Economic Effectiveness

In addition to the clinical advantages of early ablation, this model shows that ablation is economically advantageous for the UK NHS Setting. A recent economic evaluation by NICE (2021) comparing cryoablation as second-line therapy with AADs concluded that cryoablation was cost-effective, with a reported ICER of £11,687 per QALY gained [33]. The total costs and QALYs from this model also align with those described by Rodgers et al. (2008), who reported stroke risk-dependent lifetime costs of £14,415 to £18,107 for AADs [34].

The results of this model are also similar to the cost-effectiveness outcomes of RFA as a first-line treatment compared to first-line AADs [35]; however, the cited study notes that the cost-effectiveness of RFA in older patients (≥50 years) is uncertain. This outcome was not observed in the current study, which included a lifetime time horizon with a baseline age of 57.5 (i.e., based on the characteristics from the pooled RCT sample), suggesting that cryoablation, as a first-line initial rhythm control strategy, may be a cost-effective intervention in older patients (≥50 years). The cited economic analyses were, however, undertaken before the completion of the three RCTs that informed the analysis conducted in this study. Additionally, it is important to note that the EARLY AF three-year results demonstrate that the clinical effects of ablation persist beyond the 12 months that were analysed for the model [29].

Similar outcomes have been observed for second-line RFA versus AAD therapy. Leung *et al.* demonstrated that, despite the high initial cost associated with ablation, a significant reduction in CV-related AEs and AF recurrence resulted in a higher QALY yield in the ablation arm, ultimately producing a cost-effective result (ICER = £8,614) [36]. The authors note, however, that the model only considered one repeat ablation, in contrast to the maximum of two repeat procedures (i.e. three total procedures) captured in the current study.

The current findings are also consistent with that of cost-effectiveness analyses examining catheter ablation in other regions. Chew *et al.*, in a retrospective analysis of the CABANA clinical trial, evaluating the cost-effectiveness of second-line ablation versus AAD therapy for treating AF in a United States setting, found that, despite ablation being more costly than AADs, the treatment provided a substantial enough improvement in patient HRQoL to generate a cost-effective result [37]. Similarly, supportive economic evidence – demonstrating ablation (RFA and cryoballoon) yields higher costs and QALYs versus AAD therapy - has been observed from the perspective of the Chinese and South Korean healthcare systems in populations with PAF [38, 39]. Therefore, whilst the implementation and cost-effectiveness of an intervention in different regions can vary substantially due to factors such as treatment pathway and source of reimbursement not being directly comparable, the current study joins a growing body of evidence demonstrating the potential economic benefits of adopting catheter ablation as a method of rhythm control in AF populations.

Assumptions

Numerous parameters, including the relative risk of 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. Namely, the cited parameters, which were validated by the clinical authors to ensure clinical plausibility, were included as conservative estimates. Similarly, the stroke rates applied in the model are based on clinical opinion due to a failure to identify appropriate parameters in the literature. Despite a reportedly greater risk of complication from a single instance with ablation, the greater frequency of treatment administration with AADs compounds the risk of complication. This is supported in contemporary literature, where the risk of complication from AAD administration was double that of ablation at a three-year follow-up [29]. The utility decrement applied to the ST-episodic and LT-persistent states was assumed equivalent.

Despite the necessity of adopting assumptions, the scenario analyses (Table 4) demonstrated that the results are robust to parameter uncertainty. A cost-effective result was maintained when the relative risk of AF recurrence and resolution was increased by 10% and when the relative risk of heart failure was increased by 10% in the permanent AF state. A cost-effective result was also maintained when the health state-specific relative risk of stroke was changed to alternative values sourced from the literature, when the success rate of re-ablations was reduced by 30% (proportionally) and when applying alternative EHRA class-specific decrements.

Strengths

A key strength of this model is that the parameter estimates were derived from the statistical analysis of IPD from three RCTs (Cryo-FIRST, STOP AF First and EARLY-AF) where possible.

Despite the necessity of adopting some assumptions, the PSA and scenario analyses showed that the model results were robust across all sets of results and throughout all plausible scenarios. In addition, the model structure, parameter estimates and assumptions were reviewed and validated by clinical experts.

Limitations

The data used to parameterise this model were subject to limitations. The AF health state data were derived by ECG monitoring in the trials. As ECG monitors detect both symptomatic and asymptomatic PAF events, the rate of AF recurrence and, consequently, the re-treatment costs may be overestimated. Additionally, all three RCTs employed different ECG monitoring methods; however, said methods were consistent between treatment arms within each trial. These limitations may be mitigated by the trials' inclusion criteria, which specified the enrolment of symptomatic patients. The analysis also did not estimate cryoablation to be cost-saving (in the base case or scenario analyses). Thus, it is unlikely that the model outcomes were affected by overestimated re-treatment costs. Prior literature has also demonstrated no differences in major clinical outcomes for patients who present as asymptomatic versus symptomatic, suggesting that management strategies should not be based on symptomatic clinical status [40]. Regardless, the ECG monitoring method was included as a confounding effect in the regression models to account for any impact this may have on the results.

Conclusion

This analysis illustrates that cryoablation is cost-effective compared with AADs as a first line therapy in a PAF population. This study also generated results that were consistent with previous economic evaluations of cryoablation versus AADs in a second line setting. The ICER in this study was lower, suggesting that earlier intervention is an even more cost-effective option versus delaying and treating initially with AADs. However, further studies and economic modelling are required to confirm the cost-effectiveness of early versus delayed ablation intervention. In summary, this study has shown that cryoablation is a highly cost-effective option for PAF, compared with first-line AAD treatment in the UK NHS healthcare setting.

8. ACKNOWLEDGMENTS

The authors would like to thank Shufeng Liu for her contribution to the statistical analysis and Ralf Meyer for his support during the development of this research.

9. COMPETING INTERESTS

JP reports consultancy payments and educational support received from Medtronic. JM, SM, TB, EL, DL report that Medtronic provided payment to York Health Economics (YHEC), a wholly owned subsidiary of the University of York, to conduct the statistical and cost-effectiveness analyses and write the manuscript. JA reports grants and personal fees from Medtronic, grants from Baylis, personal fees from Biosense-Webster. MK reports honoraria for teaching, participation in clinical trials, proctoring and lectures/presentations from Medtronic. OW reports grants from Medtronic and personal fees from Biosense Webster and Boston Scientific. GBC reports compensation for teaching purposes and proctoring from Medtronic, Abbott, Biotronik, Boston Scientific, and Acutus Medical. EI, AS, MS, RK report being employees and stockholders of Medtronic. DT reports speaker's fees from Boston Scientific and Abbott.

10. FUNDING

This cost-effectiveness study was funded by Medtronic.

11. DATA AVAILABILITY STATEMENT

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

12. REFERENCES

1. Streur MM, Ratcliffe SJ, Callans DJ, *et al.* Atrial fibrillation symptom profiles associated with healthcare utilization: A latent class regression analysis. Pacing and clinical electrophysiology : PACE. 2018.41(7):741-49. doi: https://dx.doi.org/10.1111/pace.13356

2. Ruddox V, Sandven I, Munkhaugen J, *et al.* Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: a systematic review and meta-analysis. European journal of preventive cardiology. 2017.24(14):1555-66.

3. 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

4. Nishtala A, Piers RJ, Himali JJ, *et al.* Atrial fibrillation and cognitive decline in the Framingham Heart Study. Heart Rhythm. 2018.15(2):166-72.

5. Ladwig K-H, Goette A, Atasoy S, *et al.* Psychological aspects of atrial fibrillation: A systematic narrative review: Impact on incidence, cognition, prognosis, and symptom perception. Current cardiology reports. 2020.22:1-11.

6. 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(12):e0226730. doi: https://dx.doi.org/10.1371/journal.pone.0226730

7. Burdett P, Lip GYH. Atrial fibrillation in the UK: predicting costs of an emerging epidemic recognizing and forecasting the cost drivers of atrial fibrillation-related costs. European Heart Journal - Quality of Care and Clinical Outcomes. 2020.8(2):187-94. doi: 10.1093/ehjqcco/qcaa093

8. National Institute for Health and Care Excellence. NICE Guideline NG196 (Atrial fibrillation: diagnosis and management). 2021. Available from: https://www.nice.org.uk/guidance/ng196/evidence/full-guideline-pdf-9081927326.

9. The National Institute for Cardiovascular Outcomes Research. National Audit of Cardiac Rhythm Managment: 2021 Summary Report. 2021. Available from: https://www.nicor.org.uk/wp-content/uploads/2021/10/NACRM-Domain-Report_2021_FINAL.pdf.

10. National Institute for Health and Care Excellence. Interventional procedures guidance IPG427 (Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation). 2012. Available from: https://www.nice.org.uk/guidance/ipg427.

11. Kuck K-H, Furnkranz A, Chun KRJ, *et al.* Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. European Heart Journal. 2016.37(38):2858-65.

12. Kuniss M, Pavlovic N, Velagic V, *et al.* Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation. EP Europace. 2021.23(7):1033-41. doi: 10.1093/europace/euab029

13. Wazni OM, Dandamudi G, Sood N, *et al.* Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. New England Journal of Medicine. 2020.384(4):316-24. doi: 10.1056/NEJMoa2029554

14. Andrade JG, Wells GA, Deyell MW, *et al.* Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. New England Journal of Medicine. 2021.384(4):305-15. doi: 10.1056/NEJMoa2029980

15. Reynolds MR, Lamotte M, Todd D, *et al.* Cost-effectiveness of cryoballoon ablation for the management of paroxysmal atrial fibrillation. EP Europace. 2014.16(5):652-59. doi: 10.1093/europace/eut380

16. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing; 2022. Available from: https://www.R-project.org.

17. van Hout B, Janssen MF, Feng YS, *et al.* Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012.15(5):708-15. doi: 10.1016/j.jval.2012.02.008

18. 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(10):e275-e444. doi: 10.1016/j.hrthm.2017.05.012

19. 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. European heart journal. 2021.42(5):373-498.

20. National Health Service. National Cost Collection for the NHS. 2022. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/.

21. Xu XM, Vestesson E, Paley L, *et al.* The economic burden of stroke care in England, Wales and Northern Ireland: Using a national stroke register to estimate and report patient-level health economic outcomes in stroke. Eur Stroke J. 2018.3(1):82-91. doi: 10.1177/2396987317746516

22. Shore J, Russell J, Frankenstein L, *et al.* An analysis of the cost-effectiveness of transcatheter mitral valve repair for people with secondary mitral valve regurgitation in the UK. Journal of Medical Economics. 2020.23(12):1425-34. doi: 10.1080/13696998.2020.1854769

23. Luengo-Fernandez R, Yiin GSC, Gray AM, *et al.* Population-Based Study of Acute- and Long-Term Care Costs after Stroke in Patients with AF. International Journal of Stroke. 2012.8(5):308-14. doi: 10.1111/j.1747-4949.2012.00812.x

24. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal (section 5.6.1) [PMG9]. 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword.

25. Dudink EAMP, Erküner Ö, Berg J, *et al.* The influence of progression of atrial fibrillation on quality of life: a report from the Euro Heart Survey. EP Europace. 2017.20(6):929-34. doi: 10.1093/europace/eux217

26. Kirchhof P, Camm AJ, Goette A, *et al.* Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. N Engl J Med. 2020.383(14):1305-16. doi: 10.1056/NEJMoa2019422

27. Gottschalk S, Kany S, König H-H, *et al.* Cost-effectiveness of early rhythm control vs. usual care in atrial fibrillation care: an analysis based on data from the EAST-AFNET 4 trial. Europace. 2023.euad051.

28. Andrade JG, Wazni OM, Kuniss M, *et al.* Cryoballoon ablation as initial treatment for atrial fibrillation: JACC state-of-the-art review. Journal of the American College of Cardiology. 2021.78(9):914-30.

29. Andrade JG, Deyell MW, Macle L, *et al.* Progression of atrial fibrillation after cryoablation or drug therapy. New England Journal of Medicine. 2023.388(2):105-16.

30. Zhang W, Xiong Y, Yu L, *et al.* Meta-analysis of stroke and bleeding risk in patients with various atrial fibrillation patterns receiving oral anticoagulants. The American Journal of Cardiology. 2019.123(6):922-28.

31. Cees B. de Vos RP, Robby Nieuwlaat, Martin H. Prins, Robert G. Tieleman, Robert-Jan S. Coelen, Antonius C. van den Heijkant, Maurits A. Allessie, Harry J.G.M. Crijns,. Progression From Paroxysmal to Persistent Atrial Fibrillation: Clinical Correlates and Prognosis. Journal of the American College of Cardiology. 2010.55(8):725-31. doi: https://doi.org/10.1016/j.jacc.2009.11.040

32. Wong JA, Conen D, Van Gelder IC, *et al.* Progression of device-detected subclinical atrial fibrillation and the risk of heart failure. Journal of the American College of Cardiology. 2018.71(23):2603-11.

33. National Institute for Health and Care Excellence. NICE guideline NG196: Cost-effectiveness analysis J3: Ablation. 2021. Available from: https://www.nice.org.uk/guidance/ng196/evidence/j3-ablation-costeffectiveness-analysis-pdf-326949243734.

34. Rodgers M, McKenna C, Palmer S, *et al.* Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation. 2008.12:34. doi: 10.3310/hta12340

35. Aronsson M, Walfridsson H, Janzon M, *et al.* The cost-effectiveness of radiofrequency catheter ablation as first-line treatment for paroxysmal atrial fibrillation: results from a MANTRA-PAF substudy. EP Europace. 2015.17(1):48-55.

36. Leung LW, Imhoff RJ, Marshall HJ, *et al.* Cost-effectiveness of catheter ablation versus medical therapy for the treatment of atrial fibrillation in the United Kingdom. Journal of Cardiovascular Electrophysiology. 2022.33(2):164-75.

37. 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(7):535-47.

38. Hu M, Han Y, Zhao W, *et al.* Long-term cost-effectiveness comparison of catheter ablation and antiarrhythmic drugs in atrial fibrillation treatment using discrete event simulation. Value in Health. 2022.25(6):975-83.

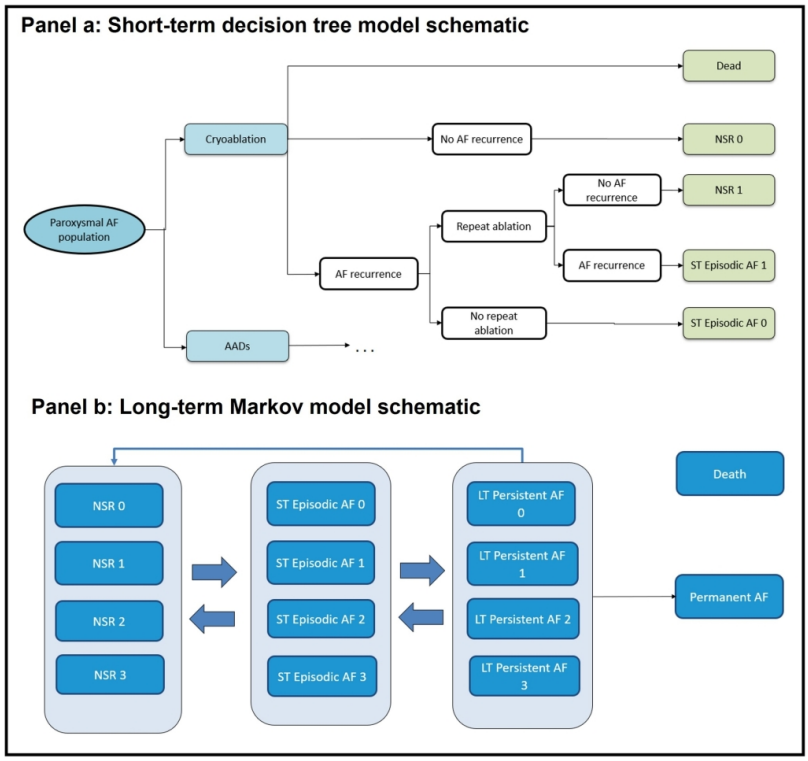
39. Kim W, Kim M, Kim YT, *et al.* Cost-effectiveness of rhythm control strategy: Ablation versus antiarrhythmic drugs for treating atrial fibrillation in Korea based on real-world data. Frontiers in Cardiovascular Medicine. 2023.10:52.

40. Sgreccia D, Manicardi M, Malavasi VL*, et al.* Comparing outcomes in asymptomatic and symptomatic atrial fibrillation: a systematic review and meta-analysis of 81,462 patients. Journal of clinical medicine. 2021.10(17):3979.

13. FIGURE LEGENDS

Figure 1: Schematic of the economic model. (Panel a) Decision tree; (Panel b) Markov model. The decision tree endpoints constitute the initial state allocation in the Markov model. Abbreviations: AAD, antiarrhythmic drugs; AF, atrial fibrillation; LT, long term; NSR, normal sinus rhythm; ST, short term.

Figure 2: Graphical outputs from the probabilistic sensitivity analysis. (Panel a) Cost-effectiveness plane; (Panel b) Cost-effectiveness acceptability curve. The data points presented in the cost-effectiveness plane represent the incremental costs and QALYs produced by 5,000 model iterations generated by the PSA. Most model iterations fell in the North-east quadrant, indicating cryoablation is more effective and more costly. Additionally, most iterations fell below the £20,000 (89.5% of iterations were cost-effective) and £30,000 (94.3% of iterations were cost-effective) threshold lines. The CEAC indicates that cryoablation is the economically preferred intervention at a WTP threshold of approximately £4,000 or higher. Abbreviations: AAD, antiarrhythmic drugs; CEAC, cost-effectiveness acceptability curve; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.



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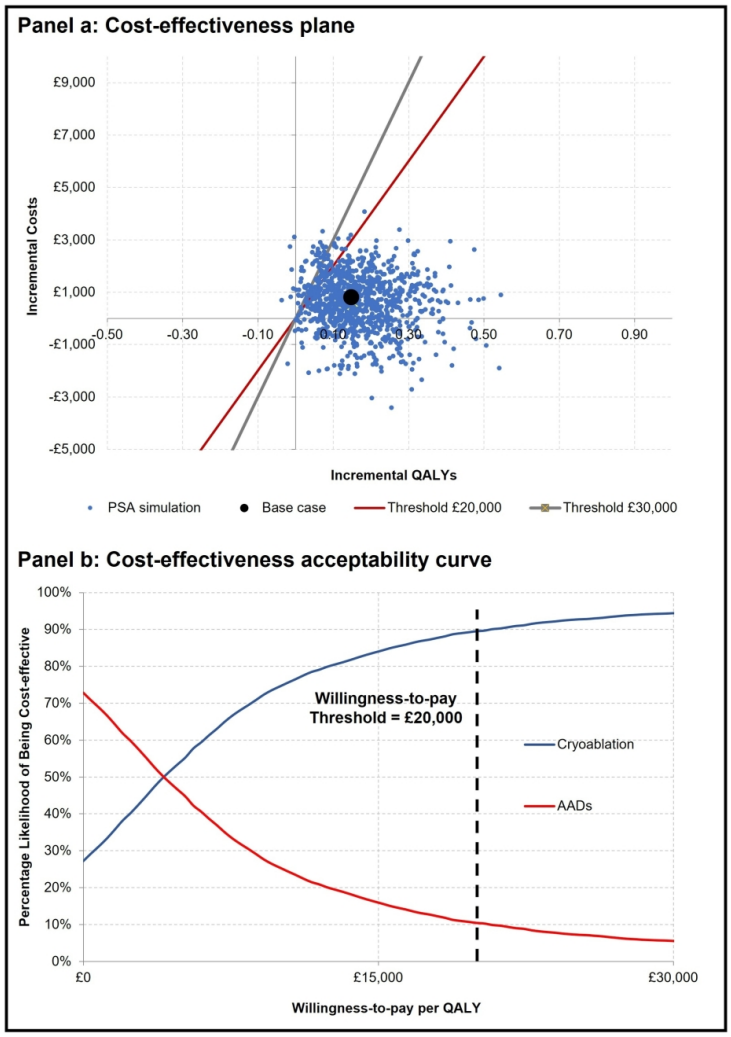

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SUPPLEMENTARY MATERIAL

1. ABLATION PROCEDURE COSTS

The total ablation cost applied in the model was calculated based on HRG codes published in the 2018/19 NHS reference costs and equipment-related costs listed in the NG196 clinical guideline published by NICE [1]. Consistent with the NICE Guideline NG196, reference costs from 2018/19 were applied to account for any confounding influence of the COVID-19 pandemic on the 2020/21 costs. The procedure- and equipment-related costs are displayed in Table S1.

Table S1: Procedure and equipment-related cost parameters

Procedure/equipment	Cost	Source
Ablation HRG	£4,118	[2] Weighted average: Non-elective long and short stays: HRG EY30A to EY30B.
Cryoballoon	£3,552	NICE NG196 [1]
Flexcath sheath	£768	
Achieve catheter	£768	
Introducer (Swartz braided trans-septal)	£130	
Needle	£106	
CS access catheter (diagnostic catheter)	£307	
Cable (decapolar catheter)	£30	
Total Procedure Cost	**£11,514**	

Abbreviations: CS, coronary sinus; HRG, health resource group.

2. PHARMACEUTICAL COSTS

The per cycle (three-monthly) pharmaceutical costs applied in the model (Table 1 in the main text [Cryoablation = £38.37; AADs = £48.69]) reflect an average of the per cycle costs of each pharmacologic agent (anti-coagulation and AADs), weighted by the resource use of said agents in each arm.

The per cycle cost of each agent was derived from the cost per mg (i.e. the unit cost divided by the pack size and indicated dose) multiplied by the total mg administered in 12 months (calculated from the indicated dose) to produce an annual cost. Subsequently, the annual cost was divided by four to generate a per cycle cost. Unit costs were sourced from the British National Formulary (BNF), employing the lowest cost available at the time of model development [3]. Similarly, the indicated doses used to calculate the annual total mg administered were sourced from the BNF and validated by the clinical co-authors [3]. The per cycle costs of each agent are presented in Table S2.

The resource use parameters were generated from the statistical analysis of the available clinical trial data. As these data were only available up to the 12-month follow-up visit, it was assumed that the observed resource use for each pharmaceutical agent was maintained for the entire time horizon. The resource use parameters were stratified according to whether data from the initial 12-month period were included (i.e. whether the blanking period was implemented). The derived resource use is presented in Table S3.

Table S2: Per cycle pharmaceutical costs

Drug	Unit Cost	Indication	Pack Size	Dose (mg)	Cost Per Cycle*
Anti-coagulation Drugs					
Warfarin	£0.61	7.5 mg daily	28	5	£2.97
Aspirin	£0.75	75 mg daily	28	75	£2.44
Rivaroxaban	£180.00	20 mg daily	100	20	£164
Dabigatran	£51.00	110 mg twice daily	60	110	£155
Apixaban	£53.20	5 mg twice daily	56	5	£173
Edoxaban	£49.00	45 mg daily	28	60	£122
Phenprocoumon	£0.00	NA	0	0	£0.00
Ticagrelor	£54.60	90 mg twice daily	56	90	£177
Anti-arrhythmic Drugs					
Amiodarone	£1.67	200mg 3x day for 1 week, 200mg 2x day for 1 week, then 200mg 1x day	28	200	£5.74
Dronedarone	£67.49	400mg twice daily	60	400	£205
Flecainide	£2.52	100mg daily	60	50	£7.64
Propafenone	£7.37	150mg 3 times a day	90	150	£22.36
Sotalol	£0.96	240mg daily	28	40	£18.72

Abbreviations: mg, Milligram.

* The cost per cycle was derived from an annual cost, which was calculated by multiplying the annual total mg administered by the cost per mg (not presented).

Table S3: Pharmaceutical resource use derived from the statistical analysis

Drug	Cryoablation		AADs	
	Blanking Period Not Applied	Blanking Period Applied	Blanking Period Not Applied	Blanking Period Applied
Anti-coagulation Drugs				
Warfarin	3.95%	0.00%	2.58%	0.00%
Aspirin	6.50%	2.56%	4.30%	2.03%
Rivaroxaban	6.78%	1.42%	7.16%	0.00%
Dabigatran	0.56%	0.57%	2.29%	2.32%
Apixaban	14.69%	14.77%	13.75%	20.87%
Edoxaban	0.00%	0.00%	0.00%	0.00%
Phenprocoumon	0.00%	0.00%	0.29%	0.29%
Ticagrelor	0.00%	0.00%	0.29%	0.29%
Anti-arrhythmic Drugs				
Amiodarone	0.00%	0.00%	0.29%	0.29%
Dronedarone	0.28%	0.28%	3.15%	2.61%
Flecainide	1.13%	1.14%	22.35%	22.61%
Propafenone	0.00%	0.00%	0.29%	9.28%
Sotalol	0.28%	0.28%	3.72%	3.77%

Abbreviations: AADs, anti-arrhythmic drugs.

3. ADVERSE EVENT PARAMETERS

Table S4: Probability of intra-operative adverse events

Event	Probability	Source
Oesophageal injury	0.13%	[1]
Cardiac tamponade	0.25%	
Pulmonary vein stenosis	0.25%	
Vascular complications	0.50%	
Persistent phrenic nerve injury	1.72%	

Table S5: Stroke risk by CHA_2DS_2-VASc score

Score	Risk	Source
0	0.2%	[4]
1	0.6%	
2	2.2%	
3	3.2%	
4	4.8%	
5	7.2%	
6	9.7%	
7	11.2%	
8	10.8%	
9	12.2%	

Table S6: CHA_2DS_2-VASc score by age

Age category	Score	Source
15 to 39	1.3	Baseline study data.
40 to 49	1.3	
50 to 59	1.3	Those aged 60 - 79 have their CHA_2DS_2-VASc score increased by 1.
60 to 69	2.3	
70 to 79	2.3	
80 to 89	3.3	Those aged 80+ have their CHA_2DS_2-VASc score increased by 2.
90 and over	3.3	

Table S7: Stroke incidence by age and CHA_2DS_2-VASc score

Age category	Deterministic
15 to 39	1.1%
40 to 49	1.1%
50 to 59	1.1%
60 to 69	2.5%
70 to 79	2.5%
80 to 89	3.7%
90 and over	3.7%

Table S8: Health state-specific relative risk values

Values used in the base case		
Health state	**Relative Risk of Stroke**	**Source**
NSR versus general population	0.34	Assumption.
ST-Episodic versus general population	0.40	
LT-Persistent versus general population	0.60	
Permanent versus general population	1.50	
Values used in the scenario analysis		
Health state	**Relative Risk of Stroke**	**Source**
NSR versus general population	1.00	Assumption.
ST-Episodic versus general population	2.12	[5]
LT-Persistent versus ST-Episodic	1.44	[6]
Permanent versus ST-Episodic	1.83	

Abbreviations: LT, long-term; NSR, normal sinus rhythm; ST, short-term.

Table S9: Heart failure incidence by age in the general population

Age category	Deterministic	Source
15 to 34	0.004%	[7]
35 to 44	0.013%	
45 to 54	0.050%	
55 to 64	0.200%	
65 to 74	0.630%	
75+	1.640%	

Table S10: Heart failure severity distribution

NYHA class	Share	Source
I	22.14%	[8]
II	40.52%	
III	28.99%	
IV	8.34%	

4. MORTALITY PARAMETERS

The following formula was used to calculate mortality rates in the CEM:

*All-cause mortality = [(prob. general mortality * (1- probability of stroke – probability of HF)) + (prob stroke related mortality * probability of stroke) + (prob HF related mortality* probability of HF)].*

Table S11: General mortality rates

Age	Male	Female	Overall	Source
15 - 19	0.02%	0.01%	0.02%	[9]
20 - 24	0.04%	0.02%	0.03%	
25 - 29	0.06%	0.02%	0.05%	
30 - 34	0.08%	0.05%	0.07%	
35 - 39	0.12%	0.07%	0.11%	
40 - 44	0.18%	0.11%	0.16%	
45 - 49	0.29%	0.18%	0.25%	
50 - 54	0.43%	0.26%	0.37%	
55 - 59	0.64%	0.40%	0.56%	
60 - 64	0.99%	0.64%	0.88%	
65 - 69	1.57%	0.97%	1.37%	
70 - 74	2.43%	1.58%	2.14%	
75 - 79	4.21%	2.83%	3.75%	
80 - 84	7.46%	5.24%	6.72%	
85 - 89	13.24%	9.91%	12.13%	
90 +	24.63%	21.66%	23.65%	

Table S12: Stroke mortality rates

Age category	Mortality rate	Source
18 to 24	3.90%	[10]
25 to 34	3.90%	
35 to 44	3.90%	
45 to 54	3.90%	
55 to 64	6.20%	
65 to 74	10.65%	
75+	19.00%	

Table S13: Heart failure mortality rates

Age category	Mortality rate	Source
16 to 24	16.44%	[11]
25 to 34	16.44%	
35 to 44	16.44%	
45 to 54	16.44%	
55 to 64	20.39%	
65 to 74	29.65%	
75+	47.05%	

5. STATISTICAL ANALYSES OUTPUTS

Chi-squared stepwise selection with a cut-off p-value of 0.05, was performed on all outcomes to generate refined statistical models containing only the covariates that were deemed to significantly contribute to the predictive ability of the statistical model. The most appropriate distribution for the statistical models was chosen based on the dependent variable type (e.g., count or continuous) and diagnostic criteria (e.g., Akaike's Information Criteria).

Rate of AF recurrence and resolution

The rate of AF recurrence and resolution were derived using GLM with a Poisson (log link) distribution. To derive a three-monthly rate of recurrence and resolution, an offset variable for the natural log of exposure time was used.

Table S14: Three-monthly rate of AF recurrence (whole study period)

	Coefficient	Standard Error	z-value	*p*-value
Intercept	-2.771	0.175	-15.802	<0.001*
Treatment (Cryo)	-0.629	0.130	-4.843	<0.001*
Ambulatory device (Yes)	0.484	0.216	2.245	0.024*
Implantable loop recorder (Yes)	1.162	0.186	6.234	<0.001*

p * = output reached statistical significance at 95% confidence interval.

Table S15: Three-monthly rate of AF resolution (whole study period)

	Coefficient	Standard Error	z-value	*p*-value
Intercept	-0.441	0.094	-4.665	<0.001*
Implantable loop recorder (Yes)	0.403	0.124	3.259	0.001*

p * = output reached statistical significance at 95% confidence interval.

Rate of repeat ablation (re-ablation)

The rate of repeat ablation was derived from a GLM with a Poisson distribution and log-link. A monthly rate of repeat ablations was derived from an offset variable for the natural log of exposure time.

Table S16: Rate of re-ablation (whole study period)

	Coefficient	Standard Error	z-value	*p*-value
Intercept	-3.843	0.108	-35.639	<0.001*
Treatment (Cryo)	-1.302	0.231	-5.640	<0.001*

p * = output reached statistical significance at 95% confidence interval.

Rate of pharmaceutical and electrical cardioversion

The rates of pharmaceutical and electrical cardioversion were derived from a GLMM with a Poisson distribution and log-link function. An offset variable for time was used, producing monthly rates. A random effect was included to control for variation between patients.

Table S17: Rate of electrical cardioversion (whole study period)

	Coefficient	Standard Error	z-value	*p*-value
Intercept	-4.815	0.171	-28.074	<0.001*
Treatment (Cryo)	-0.672	0.291	-2.304	0.021*

p * = output reached statistical significance at 95% confidence interval.

Table S18: Rate of pharmaceutical cardioversion (whole study period)

	Coefficient	Standard Error	z-value	*p*-value
Intercept	-4.234	0.864	-4.898	<0.001*
Treatment (Cryo)	-1.744	0.489	-3.566	<0.001*
Age	-0.036	0.013	-2.852	0.004*
7-day Holter	1.574	0.538	2.923	0.003*

p * = output reached statistical significance at 95% confidence interval.

Cardiovascular-related hospitalisation and accident and emergency visits

The rates of cardiovascular (CV)-related hospitalisations and A&E visits were derived from a GLMM with a Poisson distribution and log-link function. An offset variable for time was used, producing monthly rates. A random effect was included to control for variation between patients.

Table S19: Rate of CV-related hospitalisation (whole study period)

	Coefficient	Standard Error	z-value	*p*-value
Intercept	-9.235	0.694	-13.307	<0.001*

p * = output reached statistical significance at 95% confidence interval.

Table S20: Rate of CV-related accident and emergency visits (whole study period)

	Coefficient	Standard Error	z-value	*p*-value
Intercept	-2.978	0.283	-10.519	<0.001*

p * = output reached statistical significance at 95% confidence interval.

EQ-5D-3L utility values

Utility values were derived from a generalised linear mixed model (GLMM) with a Beta distribution and a logit link function. A random effect was included to control for variation between patients.

Table S21: Twelve-month EQ-5D-3L utility

	Coefficient	Standard Error	z-value	*p*-value
Intercept	-0.282	0.260	-1.084	0.278
AF status (ST-AF)	-0.747	0.474	-1.576	0.115
Treatment (Cryo)	0.219	0.098	2.234	0.025*
Baseline utility	2.689	0.289	9.319	<0.001*

p * = output reached statistical significance at 95% confidence interval.

Rate of Outpatient Visits

The rate of outpatient visits was derived from a GLM with a Poisson distribution and a log-link function. A random effect was included to control for variation between patients. An offset variable for time was used, producing a monthly rate.

Table S22: Rate of CV-related outpatient appointments (whole study period)

	Coefficient	Standard Error	z-value	*p*-value
Intercept	-9.143	0.650	-14.065	<0.001*

p * = output reached statistical significance at 95% confidence interval.

Probabilities applied in the CEM

Table S23: Per-cycle rates derived from the IPD analysis

	AAD	Cryoablation
Three-monthly rate of AF recurrence	0.12	0.06
Three-monthly rate of AF resolution	0.76	0.76
Monthly rate of re-ablation procedure	0.02	0.01

Abbreviations: AAD, antiarrhythmic drugs; AF, atrial fibrillation; IPD, individual patient data.

6. ADDITIONAL MODEL OUTCOMES

Table S24: Deterministic cost-effectiveness results (per patient)

Outcome	Cryoablation	AADs	Incremental
Initial procedure	£9,779	£0	£9,779
Re-ablations	£1,889	£8,037	-£6,148
Healthcare contact costs	£4,391	£6,507	-£2,116
Pharmaceutical costs	£2,414	£3,062	-£648
AF-related adverse events	£2,558	£2,638	-£80
Intra-operative adverse events	£65	£46	£19
Total cost per patient	**£21,096**	**£20,291**	**£805**
QALYs per patient	**11.71**	**11.56**	**0.15**
Incremental cost-effectiveness ratio (ICER)			**£5,472**

Abbreviations: AADs, antiarrhythmic drugs; AF, atrial fibrillation; ICER, incremental cost-effectiveness ratio; NNT, number needed to treat; QALY, quality-adjusted life years.

Table S25: Additional model results (per patient)

Outcome	Cryoablation	AADs	Incremental	NNT
Time Spent in Each State (Years)				
Normal sinus rhythm	21.64	19.61	2.03	
Short-term episodic	2.21	3.72	-1.51	
Long-term persistent	0.32	0.61	-0.28	
Permanent	0.26	0.48	-0.22	
Life Years				
Undiscounted life years	24.42	24.41	0.01	
Discounted life years	15.73	15.72	0.01	
Lifetime Adverse Event Rates				
Stroke	0.26	0.27	0.01	75
Heart failure	0.10	0.10	0.00	-7,656
Number of Re-ablations				
Twelve months	0.07	0.25	-0.18	
Time horizon (40 years)	0.27	1.16	-0.89	

Abbreviations: AADs, antiarrhythmic drugs; ICER, incremental cost-effectiveness ratio; NNT, number needed to treat; QALY, quality-adjusted life years.

7. REFERENCES

1. National Institute for Health and Care Excellence. NICE Guideline NG196 (Atrial fibrillation: diagnosis and management). 2021. Available from: https://www.nice.org.uk/guidance/ng196/evidence/j3-ablation-costeffectiveness-analysis-pdf-326949243734.

2. National Health Service. 2018/19 National Cost Collection Data Publication. 2019. Available from: https://www.england.nhs.uk/publication/2018-19-national-cost-collection-data-publication/.

3. British National Formulary. British National Formulary. 2022. Available from: https://bnf.nice.org.uk/.

4. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33(12):1500-10.

5. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. European Heart Journal. 2010;31(8):967-75.

6. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M*, et al.* Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. Eur Heart J. 2015;36(5):281-7a.

7. Christiansen MN, Køber L, Weeke P, Vasan RS, Jeppesen JL, Smith JG*, et al.* Age-Specific Trends in Incidence, Mortality, and Comorbidities of Heart Failure in Denmark, 1995 to 2012. Circulation. 2017;135(13):1214-23.

8. Zhang R, Ma S, Shanahan L, Munroe J, Horn S, Speedie S. Discovering and identifying New York heart association classification from electronic health records. BMC Medical Informatics and Decision Making. 2018;18(2):48.

9. Nomis (Office of National Statistics). Official Census and Labour Market Statistics. 2020. Available from: https://www.nomisweb.co.uk/.

10. Saposnik G, Cote R, Phillips S, Gubitz G, Bayer N, Minuk J, *et al.* Stroke outcome in those over 80: a multicenter cohort study across Canada. Stroke. 2008;39(8):2310-7.

11. Vaartjes I, Hoes AW, Reitsma JB, de Bruin A, Grobbee DE, Mosterd A, *et al.* Age- and gender-specific risk of death after first hospitalization for heart failure. BMC Public Health. 2010;10:637.