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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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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 (Catheter Cryoablation Versus Antiarrhythmic Drug as First-Line Therapy of Paroxysmal Atrial Fibrillation), STOP AF First (Cryoballoon Catheter Ablation in an Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation) and EARLY-AF (Early Aggressive Invasive Intervention for Atrial Fibrillation) 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 1-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; 3-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 £3783 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.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Ablation by cryo balloon is a clinically and cost-effective treatment for paroxysmal atrial fibrillation.
⇒ It is superior to antiarrhythmic drug therapy as an initial treatment as measured by atrial fibrillation recurrence.

WHAT THIS STUDY ADDS

⇒ Cryoablation is a highly cost-effective strategy for paroxysmal atrial fibrillation, compared with first-line antiarrhythmic drug treatment in the UK National Health Service (NHS) healthcare setting (£3783 per quality-adjusted life years).
⇒ Statistical analysis of pooled individual patient data from three randomised controlled trials showed a statistically significant reduction in the 3 monthly rate of atrial fibrillation recurrence for patients receiving cryoablation compared with antiarrhythmic drugs.
⇒ Patients receiving cryoablation reported a statistically significant reduction in the monthly rate of reablation and electrical and pharmaceutical cardioversion compared with antiarrhythmic drugs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The option to offer ablation before antiarrhythmic drugs may be offered to patients as a cost-effective strategy.

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 paroxysmal atrial fibrillation (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.

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 V.4.1.1 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 UK. Any missing data were assumed missing completely at random.

The following outcomes were incorporated in the CEM:
► AF recurrence and resolution.
► Rate of ablation after index treatment (reablation; reablation may represent an index ablation for patients randomised to AAD).
► EuroQol 5-Dimensions 3-Levels (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

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%						

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

clinical relevance were used to produce adjusted mean estimates. Statistical models (generalised linear models and generalised linear mixed models), 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 (eg, count or continuous) and diagnostic criteria (eg, 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 3 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 1000 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 3-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 1-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 3 months; short-term (ST)-episodic AF ('ST-Episodic'), defined as at least one AF episode (either paroxysmal or persistent)

documented within 3 months, and death. The definitions of all the health states used in both parts of the CEM were agreed on 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 3-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.

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 2018/2019. Where appropriate, costs were inflated using the PSSRU 2020/2021 inflation indices (table 2).[8] The ablation procedure costs are available in Section 1 of the online supplemental 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
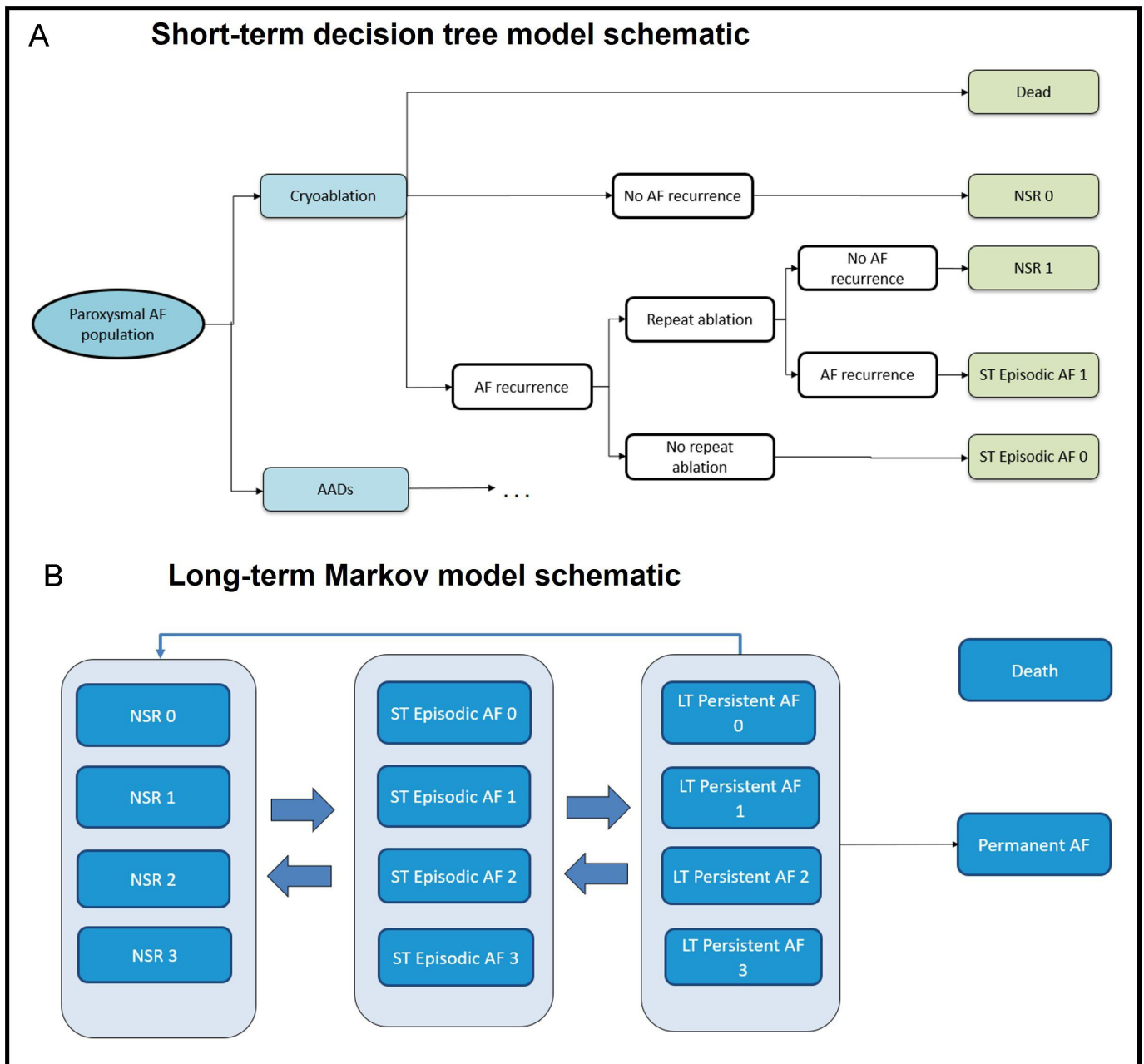
Figure 1 Schematic of the economic model. (A) Decision tree. (B) Markov model. The decision tree endpoints constitute the initial state allocation in the Markov model. AAD, antiarrhythmic drugs; AF, atrial fibrillation; LT, long term; NSR, normal sinus rhythm; ST, short term.

of intraoperative events, including oesophageal injury, cardiac tamponade, pulmonary vein stenosis, vascular complications and persistent phrenic nerve injury, was sourced from the NICE guideline NG196. As these intraoperative 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' congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age, sex category (CHA2DS2-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

Table 2 Key model input parameters

Parameter	Value	Source
Unit costs		
Procedure-related costs		
Ablation procedure	£9779	Derived from ablation HRG procedure cost and average list prices provided by Medtronic.[8]*
Intraoperative adverse event costs (per event)		
Oesophageal injury	£26 733	[8]
Cardiac tamponade	£2083	
Pulmonary vein stenosis	£2777	
Vascular complications	£1389	
Persistent phrenic nerve injury	£325	
Healthcare contact costs		
CV-related hospitalisations (excluding reablation procedures)	£1362	[38]Weighted average: non-elective long and short stays: HRG EB07A to EB07E.
CV-related A&E department visits (excluding reablation procedures)	£332	[38]Weighted average: HRG VB01Z to VB09Z.
CV-related outpatient appointments (excluding reablation procedures)	£191	[38]Total outpatient attendance. Service code: 320—cardiology.
Pharmaceutical cardioversion	£1528	[38]Weighted average: HRG codes: EB07A-EB07E (day case).
Electrical cardioversion	£1528	Consultant led; cardiology; currency code: WF01A
Atrial fibrillation adverse event costs (per cycle)		
Non-disabling stroke	£2196	[38]Weighted average of currency codes AA35E and AA35F (stroke with CC score 0–3 and 4–6).
Moderately disabling stroke	£3622	[38]Weighted average of currency codes AA35C and AA35D (stroke with CC score 7–9 and 10–12).
Severely disabling stroke	£6812	[38]Weighted average of currency codes AA35A and AA35B (stroke with CC score 13–15 and 16+).
Stroke long-term cost	£293	[39]
Heart failure (NYHA class I)	£125	[40]
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 months.
AAD Arm	£48.69	
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	[41]
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	[41]
Heart failure (NYHA class II)—long-term	0.05	[40]
Heart failure (NYHA class III)—long-term	0.15	
Heart failure (NYHA class IV)—long-term	0.33	

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

trial data. These final annual rates were then converted to 3 monthly rates for use in the CEM.

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 using 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.

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 3 monthly rate of AF recurrence ($p<0.001$). On average, the 3 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 reablation 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 reablation ($p<0.001$) 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: -£1210 to £2364)) per person than AADs. This produced an ICER of £3783 per QALY gained (CrI: £710 to £36 753).

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 £4000 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).

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 reablations, is reported in Section 6 of the online supplemental material. Patients in the cryoablation arm had higher predicted life years gained and a

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			**£3783 (£710 to £36 753)**
NMB			**£2746 (-£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%**

AADs, antiarrhythmic drugs; CrI, credible interval; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY quality adjusted life-year.
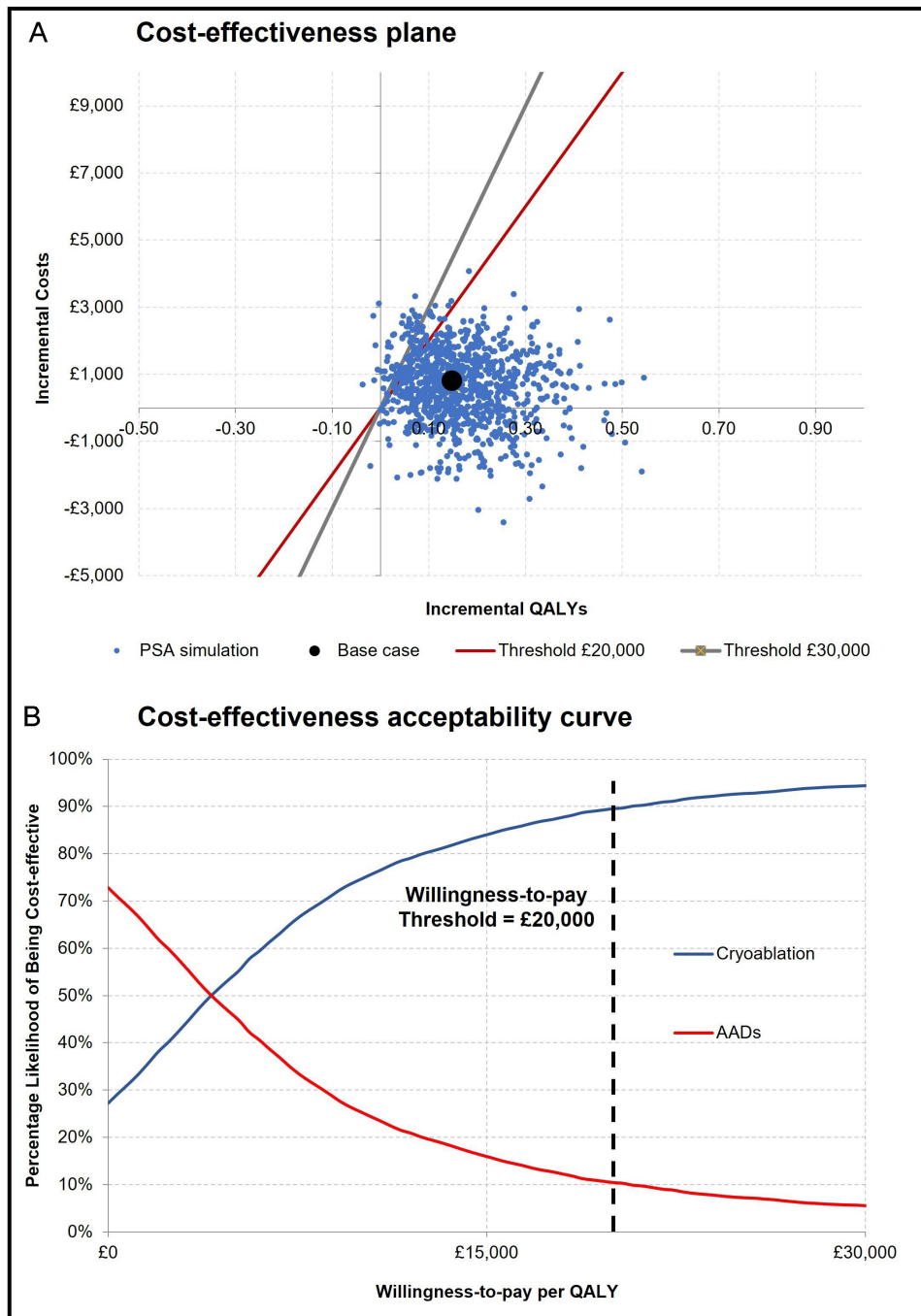
Figure 2 Graphical outputs from the probabilistic sensitivity analysis (PSA). (A) Cost-effectiveness plane. (B) Cost-effectiveness acceptability curve. The data points presented in the cost-effectiveness plane represent the incremental costs and QALYs produced by 5000 model iterations generated by the 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 willingness-to-pay threshold of approximately £4000 or higher. AAD, antiarrhythmic drugs; CEAC, cost-effectiveness acceptability curve; QALY, quality-adjusted life-year.

lower lifetime rate of stroke. They also spent less time in AF health states and received fewer reablations.

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	£3783
Blanking period implemented	£298	0.09	£3219
Increased relative risk of AF recurrence relative to the number of previous ablations by 10%	£317	0.18	£1722
Increased relative risk of AF resolution relative to the number of previous ablations by 10%	£899	0.16	£5619
Decreased ablation success rate of 30% (proportionally)	£572	0.18	£3252
Decreased incidence of stroke by 30% (proportionally)	£667	0.17	£3977
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	£7759
Changed health state specific stroke relative risk values to values sourced from published literature	£383	0.23	£1690
Increased relative risk of developing heart failure for those in the permanent health state by 10%	£653	0.17	£3830
Average selling price used for all procedure costs	£596	0.17	£3565
2022/2023 cost used for ablation procedure cost	£790	0.17	£4686

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

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 £3783 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),[20] 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 reablation and AF recurrence. There were 0.89 fewer reablations 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.[21]

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 with usual care.[22] 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.[23] Moreover, as an initial first-line rhythm control strategy, cryoablation is associated with a significant reduction in atrial arrhythmia recurrence and rehospitalisation compared with AAD therapy in patients with PAF.[24] Cryoablation has also been shown to significantly lower the risk of progression from PAF to persistent AF compared with AAD therapy, suggesting that ablation is disease modifying.[25] Importantly, AF progression is associated with higher risk for stroke, heart failure and healthcare utilisation,

underscoring the clinical and economic importance of intervening early.[26–28]

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.[29] 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.[30]

The results of this model are also similar to the cost-effectiveness outcomes of RFA as a first-line treatment compared with first-line AADs[31]; 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 (ie, 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 3-year results demonstrate that the clinical effects of ablation persist beyond the 12 months that were analysed for the model.[25]

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 = £8614).[32] The authors note, however, that the model only considered one repeat ablation, in contrast to the maximum of two repeat procedures (ie, three total procedures) captured in the current study.

The findings of this analysis can be generalised to other healthcare systems. A recently published adaptation of this economic model from a United States Medicare perspective also found that first-line cryoballoon ablation is cost-effective compared with first-line AAD therapy.[33] Further adaptations of the economic model from a Canadian and German healthcare perspective are in preparation for publication. 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 (Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial) clinical trial, evaluating the cost-effectiveness of second-line ablation versus AAD therapy for treating AF in a US 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.[34] 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.[35 36] Therefore, while 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 reablation 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 3-year follow-up.[25] 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 reablations 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 retreatment costs may be overestimated. However, it should be noted that this overestimation will be present in both treatment arms. 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 retreatment 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.[37] 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.

In addition, variation may exist between guideline recommendations and clinical practice (eg, regarding AAD prescription) that could affect the applicability of the methods used in the economic model to clinical practice. However, to minimise this, the opinions of clinical experts were used in the design of this model. Clinical coauthors were interviewed until a consensus for all inputs was achieved and based on their clinical experience these inputs were considered both reasonable and conservative. The same panel of clinical experts also validated the structure of the economic model to ensure it was reflective of the clinical pathway for PAF. Scenario analyses were used where there was variation between clinical expert opinions to ensure that the economic model covered a broad range of real-world practices.

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.

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