National Institute for Health and Care Excellence

Final

Atrial fibrillation: diagnosis and management

Cost-effectiveness analysis J3: Ablation

NICE guideline NG196

Economic analysis report

April 2021

Final

Developed by the National Guideline Centre, Royal College of Physicians

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ISBN: 978-1-4731-4043-1

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Cost-effectiveness analysis: What is the clinical and cost effectiveness of different ablative therapies in people with atrial fibrillation?

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1 Introduction

Atrial fibrillation (AF) is a common arrhythmia associated with poor clinical outcomes including reduced overall survival, and an increased risk of major non-fatal cardiovascular adverse events including stroke and heart failure. Some patients with AF report disabling symptoms that can have a significant impact on quality of life. Rhythm control strategies exist to attempt to increase the likelihood of maintenance of sinus rhythm and reduce the symptom burden attributable to arrhythmia in patients with symptomatic AF.

This health economic model aims to determine whether the cost of ablation and possible repeat ablation(s) can be offset by the benefit in quality of life (QoL) as a result of reduced symptoms when compared to usual care: anti-arrhythmic drugs (AADs) with possible cross over to ablation if symptoms recur in first year. In addition, this question aims to determine which ablative therapy is most cost effective. Several ablation techniques exist including surgical (thoracic or open – not as a concomitant treatment) ablation, hybrid ablation (catheter and surgical), radiofrequency catheter ablation (single tip or multi-electrode circumferential), cryoballoon catheter ablation and laser catheter ablation.

A number of health economic (HE) studies have been identified in the literature (7 papers of which 2 were included in the previous guideline, CG180). Four of the HE analyses have a UK NHS perspective. Six of the studies are in people with paroxysmal AF and 6 studies are in people who failed anti-arrhythmic drugs (i.e. second line treatment). None of the studies compare all types of ablation to each other as well as to usual care or placebo. A limitation noted in the current HE literature is the lack of long term follow up, which limits the usefulness of these health economic analyses as ablation is not considered to be permanent and therefore it is not known when AF will return.

Due to the potentially significant resource impact of ablation and the lack of health economic evidence comparing all interventions and on the long-term cost effectiveness of these interventions, the committee agreed this was priority for de novo model.

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2 Methods

2.1 Model overview

2.1.1 Comparators

Twelve comparators were selected for the model:

- Antiarrhythmic drugs (AADs) (split into six comparators to allow for cross over to each ablation technique outlined below if AF symptoms recur within first year)
- Radiofrequency point by point (RF PP) catheter ablation
- Radiofrequency multi-electrode (RF ME) catheter ablation
- Cryoballoon catheter ablation
- Laser catheter ablation
- Thoracoscopy
- Hybrid ablation (thoracoscopy and radiofrequency point by point catheter ablation)

The antiarrhythmic drugs were assumed to be oral amiodarone, flecainide, propafenone, or sotalol based on the drugs used in the clinical evidence informing the network meta-analysis (NMA) conducted as part of the review for this guideline question and current practice (see J2. Ablation NMA).[32, 44, 57, 60, 63, 91, 92] Details of how this was incorporated into the model are provided in **section 2.3.9.2** of this report.

The only comparator listed in the question protocol that is not included in the health economic model is open surgery. There was no clinical data available to include this in the health economic or network meta-analysis.

Of note, in the original health economic plan, cross over from AAD to ablation upon AF symptom recurrence had not been planned. This was changed during the guideline development process to better reflect the clinical trials and what happens in real world practice.

2.1.2 Population

The population in this analysis was people with paroxysmal AF who have previously failed one or more AAD and are ablation naïve with an indication for rhythm control.

Although ablation may also be used in people with persistent AF, there was insufficient clinical evidence to inform a model in this population. Furthermore, the committee anticipated that the treatment effects would be different in persistent AF and paroxysmal AF patients and therefore it was not possible to use the evidence for paroxysmal AF for both populations.

2.1.3 Time horizon, perspective, discount rates used

A lifetime horizon was adopted for this analysis and the perspective was the NHS and Personal and Social Services. A lifetime horizon was selected for the cost-effectiveness analysis because there was evidence that mortality and stroke was impacted with some interventions. In addition, this allowed for modelling of different rates of AF symptom recurrence between those who never received ablation and those receiving any type of ablation over time. The analysis followed the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects, and an incremental analysis was conducted. A sensitivity analysis using a discount rate of 1.5% for costs and health effects was conducted.

ISBN: 978-1-4731-4043-1

2.1.4 Deviations from NICE reference case

None anticipated.

2.2 Approach to modelling

A systematic review of the literature was undertaken to identify existing health economic analyses of ablation in people with AF. This review is summarised in evidence review J1. All existing models were scrutinised to identify possibly relevant and appropriate model structures. These were presented to the committee and the model structure below was agreed. The structure was an adaptation of the two model structures developed by McKenna et al 2009[42] and Blackhouse et al 2013.[8]

The model was made up of two parts: a decision tree to capture the short-term clinical outcomes and costs associated with the different comparators (up to 1 year), and a Markov model to extrapolate clinical outcomes and costs over a lifetime using 1-year cycles. This cycle duration was chosen to account for the acute costs and impact of stroke.

The clinical outcomes incorporated in the model are: serious adverse events (SAEs) of interventions, freedom of symptoms due to AF, recurrence of symptoms due to AF, stroke, major bleed (intracranial haemorrhage and other major bleeds) and death both due to events and background mortality.

People with paroxysmal AF enter the decision tree having received one of the interventions listed in the comparators in **section 2.1.1**. It is assumed that a proportion of patients in the model will be receiving concurrent treatment with anticoagulants; this proportion is the same for all interventions. Estimates of baseline risks with antiarrhythmic drugs (AADs) from the clinical effectiveness review were used to populate the decision tree model and differences in clinical events with ablation techniques were estimated by applying relative treatment effects from the clinical effectiveness review and evidence synthesis (NMA). Costs and clinical events therefore vary by comparator. Probabilities of SAEs were applied by comparator. Details of the decision tree are described in **section 2.2.1** below.

Differential treatment effects that is: SAEs of interventions, freedom of symptoms due to AF, stroke and death were assumed to apply in the first year only. AF symptom recurrence, between those only receiving AADs and those receiving any type of ablation, upfront or as crossover from AADs; and SAEs related to AADs were the only treatment effect to apply beyond the first year. To fully capture the impact of the differences in clinical events in the first year and to capture the differences in rates of AF symptom recurrence between ablation techniques and AADs beyond a year, it was necessary to model the rest of the lifetime of the population. For example, if mortality differs between comparators in the first year this will mean that a different number of people will be alive from each intervention at the end of 1 year. Due to this, costs and QALYs will vary for the population beyond 1 year. A Markov model was used for this extrapolation. Details of the Markov model structure are described in **section 2.2.2.**

In the AAD arms, if AF symptoms recurred within the first year, patients could cross over to ablation. This was modelled for each ablation technique, and therefore 6 AAD comparators were included in the model. This was done to reflect the cross over observed in clinical trials and real-world practice where people who have tried multiple AADs but remain symptomatic would be offered an ablation (see **section 2.3.5** for further details). In the ablation arms, a repeat ablation was permitted in the first year if AF symptoms recurred (see **section 2.3.6** for further detail).In the model the following treatment changes were therefore allowed. In those assigned to the AAD comparator, once AF symptoms recurred, a proportion would cross over to ablation in the first year (assumed to occur at 6 months), and in those who didn't cross over only a proportion would continue to receive AADs (switch drugs) and the others would stop. In those assigned to the ablation comparators, when AF symptoms recur, a

ISBN: 978-1-4731-4043-1

proportion would have a repeat ablation in the first year, and in those who remain symptomatic a proportion would re-start AADs (see **section 2.3.9.2** for more detail). It was assumed that once AF symptoms recurred beyond 12 months no ablative procedures would be provided but a proportion would still receive AADs. The model does not allow for people to move from AF symptoms to AF symptom free after the first year.

The model was run for each of the comparators, with people starting in the decision tree for one year and then entering the Markov model which was run for repeated cycles for a lifetime (for 40 years, by which time most of the cohort had died). The time spent alive in each of the health states was calculated. By attributing costs and quality of life weights (utilities) to the people in each health state, total costs and QALYs were calculated for the population. Comparing the results for each of the comparators allowed us to identify the most cost effective intervention. See **section 2.2.3** for details of how uncertainty was considered.

Full details of all model inputs are described in **section 2.3.**

Summary of key model assumptions:

- *A proportion of patients in the model will be receiving concurrent treatment with anticoagulants.*
- *Differential treatment effects, except for AF symptom recurrence, were assumed to apply in the first year only.*
- *The differential effects in AF recurrence after one year are only between those receiving AADs (with no ablation cross over) and ablation, not between different ablation types.*
- *Once AF symptoms recurred beyond 12 months they would no longer receive ablative procedures.*
- *Patients assigned to drug therapy can "cross-over" to ablation therapy if they have AF symptom recurrence in first year (assumed to occur at 6 months).*
- *Once AF symptoms have recurred at the end of year one, it was not possible for the patient to become free of AF symptoms.*
- *Once AF symptoms recurred, it was assumed that only a proportion of patients in the model would either continue to receive AADs (switch drugs) or start AADs after failed ablation,*
- *All repeat ablations (not cross overs) were assumed to be RF PP ablation and assumed to occur at 6 months.*
- *SAEs vary in nature by comparator. For ablation these were assumed to only occur in year one. It was assumed that these occur at a constant rate and applied it whilst people were alive.*
- *SAEs assumed to include bleeding events when reported and therefore bleeding was not captured separately in the first 12 months.*
- *All events, whether death, AF symptom recurrence or bleed/stroke assumed to occur halfway through the year.*
- *All strokes in tree assumed to be ischaemic strokes.*
- *Model does not account for repeat stroke or repeat ICH.*
- *Model does not account for Mis.*
- *Other non-ICH major bleeds assumed to be GI bleeds.*
- *Base case assumed no difference in the stroke risk for those with and without AF symptoms.*

2.2.1 Model structure: Decision tree

The initial decision tree reflects the period when ablation treatment would occur and establishes whether people are free of AF symptoms as a result of treatment. Following the

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review of the clinical evidence, the committee agreed that the following outcomes needed to be captured in the first year of the model as they potentially vary between interventions:

- Serious adverse events (SAEs)
- All stroke
- All-cause mortality
- AF symptom recurrence

The decision tree included four possible events: all stroke, AF symptoms, freedom of AF symptoms and dead. Following an ablation and AF symptom recurrence, a proportion would receive a repeat ablation in the first year. All repeat ablations were assumed to be RF PP, for more details see **section 2.3.6.** For those assigned to AAD, following AF symptom recurrence, a proportion would receive an ablation in the first year. This was modelled separately for each ablation technique, for more details see **section 2.3.5**.

SAEs vary in nature by comparator. For ablation these were assumed to only occur in year one, whereas for AADs, these could occur over the period these are being taken. They were considered to be transient, having an acute cost and short-term impact on quality of life. They do not determine which health state the people enter the Markov model. These were captured in the decision tree by assigning a cost and QALY loss in the first year. It was assumed that these occur at a constant rate and applied it whilst people were alive. Further details on the type of SAEs incorporated for each comparator are available in **section 2.3.4.2**. Of note, this was assumed to include bleeding events when reported and therefore bleeding was not captured separately in the decision tree to ensure this outcome is not double counted.

All people with AF are at a greater risk of stroke than the general population. In the first year, when they undergo ablation or are treated with AADs, the risk of stroke may differ. The relative risk of stroke reported in the NMA for each intervention was applied here where considered appropriate (see **Section 2.3.4.3** for discussion and interpretation of NMA data). This risk of stroke captured the risk associated with having AF as well as the potential risk of stroke associated with the intervention itself. For modelling purposes, it is assumed that they have a constant rate of stroke. It was therefore assumed that strokes occurred on average at 6 months in the first year. This was important to accurately capture the acute costs and disutility of stroke. All strokes in the first year were assumed to be ischaemic strokes. See Figure 1 for a depiction of the decision tree.

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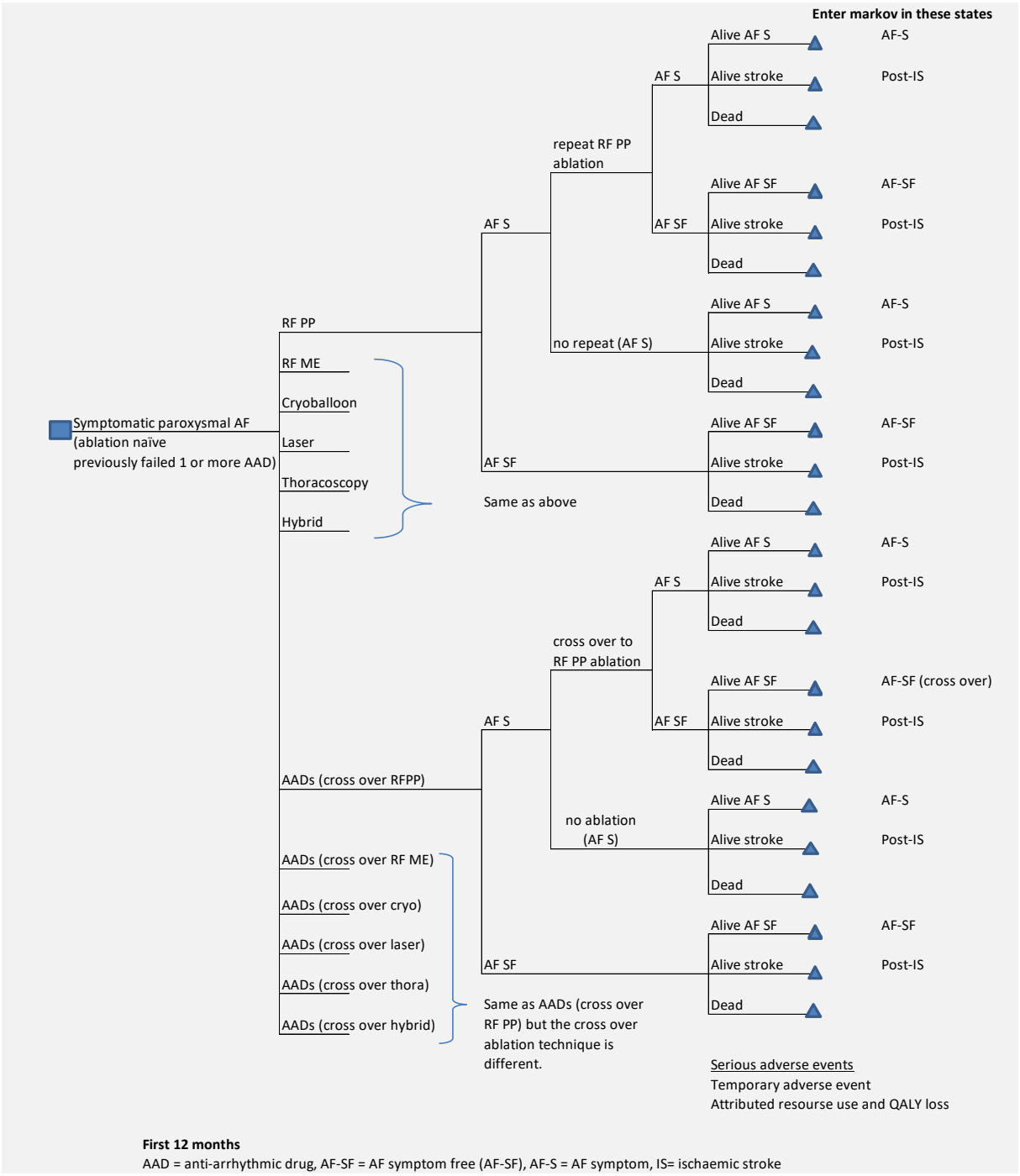
Figure 1: Decision tree



2.2.2 Model structure: post-one year Markov model

At the end of the decision tree, those people alive and free of AF symptoms enter the 'freedom of AF symptoms' state, those alive and with AF symptom recurrence enter the 'AF symptom' state, and finally those who have survived a stroke whether or not they have AF symptoms, enter the 'post-ischaemic stroke' state. For those who were in the AAD comparators but crossed over to ablation in the decision tree, they enter the 'freedom of AF symptom (cross-over)' state.

At each cycle people had a probability of moving between states as depicted in Figure 2.

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From the freedom of AF symptom states people had a chance of reverting back to symptomatic AF, having an ischaemic stroke, having an intracranial haemorrhage (ICH) or dying. Those in the AF symptom state have a chance at each cycle of having an ischaemic stroke, an ICH or dying.

All people with AF are at risk of ischaemic stroke, this was modelled as a tunnel health state, meaning that people only remained in the state for one cycle (one year), at which point they must transition to dead or post-ischaemic stroke state. The reason for including this tunnel state was to account for the short-term higher costs associated with ischaemic stroke as well as the higher risk of mortality. The probability of having an ischaemic stroke was estimated from the NMA of anticoagulation treatment by Sterne 2017[83] (weighted for proportion taking each DOAC based on current prescribing trends in England). The data from the NMA undertaken as part of the guideline was not used, as this may include increased stroke risk associated with the procedures which are not thought to persist beyond 1 year. No direct evidence from the RCTs was available to quantify a differential stroke risk for symptomatic AF versus symptom-free AF. See more detail on this in **section 2.3.7.2**.

Concomitant anticoagulation increases the risk of bleeds. ICH was considered separately to other major bleeds. As with ischaemic stroke, ICH has both an acute and long-term impact on costs and QALYs that needs to be captured in the model. At each cycle all those in the symptomatic and symptom free AF health states were at risk of moving into the ICH state, which like ischaemic stroke was modelled as a tunnel state and people only remain in that state for one cycle to capture the acute cost and effects of that ICH (in terms of higher risk of mortality). They will then move either to the dead state or the post ICH state to account for the lifelong impact on quality of life and costs. People in the post event states remain in these states until death.

At each cycle all those alive in the model, will be at risk of having a major bleed (excluding ICH). This was not modelled as an explicit health state as these types of bleed (assumed to be primarily GI bleeds) would not have a permanent impact on the patients in terms of ongoing costs or ongoing health effects. Instead an acute cost and QALY loss was applied for each non-ICH major bleeding event.

Neither the post-ischaemic stroke nor post-ICH health states account for whether they have AF symptoms or not. This simplification was deemed acceptable as having experienced an ICH or ischaemic stroke will dominate their AF symptom status in terms of costs and QOL (this simplification was also applied for stroke in the decision tree). It is assumed that two thirds of these people will receive AADs, regardless of their original intervention, and therefore the cost of AADs themselves and the impact of SAEs were adjusted accordingly.

The probability of death was increased in the stroke and ICH states compared to those in the AF states. Death in initial 30 days after event was captured in the model; it was assumed no QALYs are contributed by these people, only acute costs of treating a fatal event. Mortality after 30 days following an event was captured using standardised mortality ratios applied to age-dependent mortality rates. Once people moved to the dead state in the model, they could not move elsewhere; this is known as an absorbing state. If the model is run long enough, everyone will eventually be in this state.

Repeat events (ischaemic stroke or ICH bleed) were not explicitly modelled. This is a simplification of reality but was considered reasonable for modelling purposes due to the lack of available data to model downstream further events.

SAEs of the ablation interventions were not modelled beyond one year. It is not expected there would be any relating to ablation beyond the first year. For AADs, these could occur over the period of time these are being taken in the model. Of note, McKenna 2009[42] did model irreversible pulmonary toxicity as a serious adverse event of amiodarone. The committee however felt this was not relevant as pulmonary toxicity is a very rare event[80] and noted that large safety studies of amiodarone showed no evidence of increased risk of

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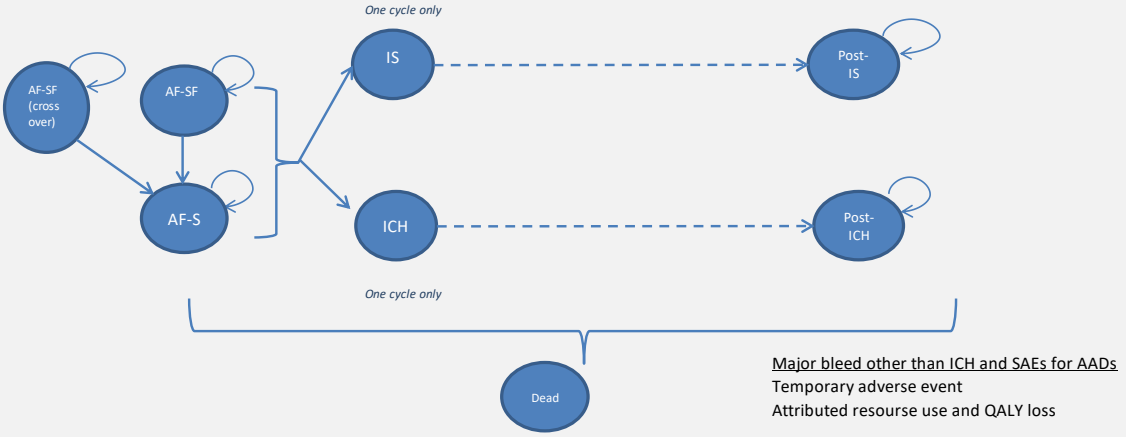
pulmonary toxicity and related mortality when amiodarone is used long term[11, 35]. For more details on which SAEs were captured please **see section 2.3.4.2**.

Figure 2: Markov model



Beyond 1 year
Patients enter model in either AF symptom free (AF-SF), AF symptom (AF-S) or post-ischaemic stroke (Post-IS) health states
For those who had AAD and crossed over to ablation in the first year, they enter the AF-SF (crossover) state.
AF-SF = AF symptom free (AF-SF), AF-S = AF symptom, ICH=Intracranial haemorrhage, IS=Ischaemic stroke
First IS andfirst ICH acute (28 day) fatality modelled as well as all cause mortality

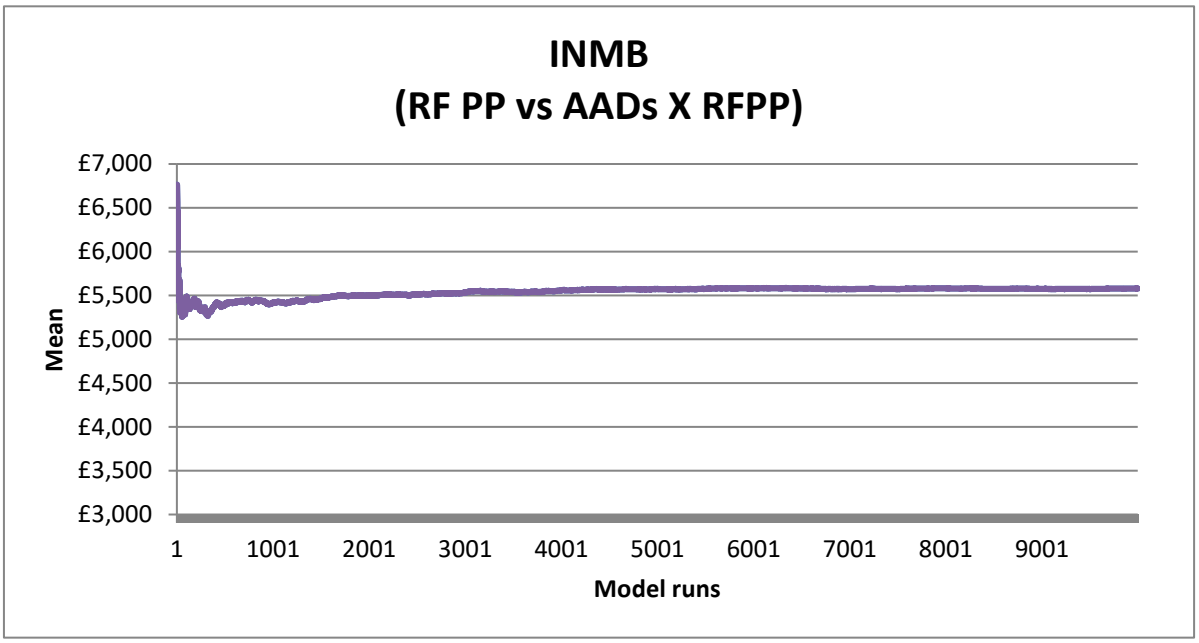
2.2.3 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly –10,000 times for the base case and 5,000 times for each sensitivity analysis – and results were summarised.

When running the probabilistic analysis, multiple runs are required to take into account random variation in sampling. To ensure the number of model runs were sufficient in the probabilistic analysis we checked for convergence in the incremental net monetary benefit at a threshold of £20,000 per QALY gained for each ablation comparator versus AADs (cross over RF PP) and for laser versus RF PP. This was done by plotting the number of runs against the mean outcome at that point (see example in Figure 3) for the base-case analysis. Convergence was assessed visually, and all had stabilised between 3000 and 5000 runs.

Figure 3: Convergence plot for incremental net monetary benefit: RF PP vs. AADs (crossover RFPP)

ISBN: 978-1-4731-4043-1



The way in which distributions are defined reflects the nature of the data, so for example utilities were given a beta distribution, which is bounded by 0 and 1, reflecting that a quality of life weighting will not be outside this range. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 1. Probability distributions in the analysis were parameterised using error estimates from data sources. Where error estimates were unavailable, the standard error was assumed to be 20% of the mean.

Table 1: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Probability of being in a particular subgroup (i.e. having a certain rate of disease progression) (distribution of patients by CHADSVASC subgroup in FIRE and ICE)	Dirichlet	Fitted to multinomial data. Represents a series of conditional distributions, bounded on 0–1 interval. Derived by the number of patients in the sample and the number of patients in a particular subgroup.
Serious adverse event probability, probability of AF recurrence beyond 1 year and utility scores	Beta	Bounded between 0 and 1. Derived from mean and its standard error, using the method of moments: Alpha and Beta values were calculated as follows: $\text{Alpha} = \text{mean}^2 \times [(1-\text{mean})/\text{SE}^2] - \text{mean}$ $\text{Beta} = \text{Alpha} \times [(1-\text{mean})/\text{mean}]$
Relative treatment effects, standardised mortality ratios, transition probability to first fatal IS/ICH	Lognormal	Bounded to positive values so realistic range for rates.
WinBUGS NMA	WinBUGS output	A bespoke distribution where you sample from iterations from the WinBUGs analysis rather than using summary statistics. It ensures that you capture in your model the correlation between the different treatment effect estimates.
Utility	Beta	Bounded between 0 and 1. Derived from mean of a domain or total quality of life score and its standard

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Parameter	Type of distribution	Properties of distribution
		error, using the method of moments. Alpha and Beta values were calculated as follows: $Alpha = mean^2 \times [(1-mean)/SE^2] - mean$ $Beta = Alpha \times [(1-mean)/mean]$
Rate of stroke (Aspberg 2016), Costs and utility decrements	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and Beta values were calculated as follows: $Alpha = (mean/SE)^2$ $Beta = SE^2/Mean$

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE)
- the resource, including time and cost of staff, required to implement each strategy (assumed to be fixed according to national pay scales and programme content)
- NHS reference costs, drug costs and NHS supply chain catalogue costs as these are list prices and represent national costs.
- General population mortality: Rates are based on national data and so the level of uncertainty is considered to be very low and so does not warrant incorporation.
- Probability of having crossed over to ablation following AAD, a repeat ablation and relative efficacy of repeat ablation.
- Prescribing trends from prescription cost analysis.

In addition, various sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed, and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. A description of each of the sensitivity analyses that was conducted is detailed in **section 2.3.11**.

2.3 Model inputs

2.3.1 Summary table of model inputs

Table 2: Model inputs

Input	Data	Source
Initial cohort settings		
Start age	59	Average of RCTs incl. in NMA.
Proportion male	64%	*Note only impacts mortality beyond 1 yr*
CHADSVASC score	1-2	Based on reported means and medians in RCTs incl. in NMA. *Note CHADSVASC score distribution in FIRE and ICE[38] used in Markov to accurately capture ischaemic stroke risk*
Proportion anticoagulated	70%	Estimated looking at FIRE and ICE[38] CHADSVASC score distribution and current recommended thresholds for anticoagulant *Note this reduces to 20% anticoagulated in post-ICH health state*

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Input	Data	Source
Proportion receiving AADs during blanking period (ablation arms only)	50%	GC assumption
Proportion receiving AADs following event (AF symptoms or IS or ICH)	67%	GC assumption *Explored in SA where this is 0% and 100%*
Baseline and treatment effects first year (decision tree) – AADs as baseline		
AF recurrence		
AADs	73%	NMA *Explored in SA where this is 50% and 90%*
RF PP ablation	31%	NMA, uncertainty from NMA included in probabilistic analysis
RF ME ablation	32%	
Cryoballoon ablation	32%	
Laser ablation	36%	
Thoracoscopy	15%	
Hybrid ablation	22%	
Stroke		
AADs	0.7%	No RCT included events. Based on calculations below using FIRE&ICE,[38] Aspberg 2016[5] and Sterne 2017[83]
RF PP ablation	0.7%	Assume same as baseline stroke (AADs)
RF ME ablation	1.4%	Assume double baseline stroke (AADs) *Explore in SA where NMA data used and another SA where assumed to be equal to baseline stroke (AADs)*
Cryoballoon ablation	0.7%	Assume same as baseline stroke (AADs) *Explore in SA where NMA data used*
Laser ablation	0.7%	Assume same as baseline stroke (AADs)
Thoracoscopy		
Hybrid ablation		
Mortality		
AADs	1.2%	Double age-adjusted general population mortality (GC assumption) *Explore in SA where NMA data used instead*
RF PP ablation	1.2%	Assume same as baseline mortality (AADs) *Explore in SA where NMA data used*
RF ME ablation	1.2%	Assume same as baseline mortality (AADs)
Cryoballoon ablation		
Laser ablation		
Thoracoscopy	1.8%	Assume mortality is 50% higher than baseline mortality. *Explore in SA where double baseline mortality assumed*
Hybrid ablation		

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Input	Data	Source
Serious adverse events first year (decision tree)		
Catheter ablation		
Oesophageal injury (perforation/fistula)	0.5%	ESC 2016 guidelines[37]
Cardiac tamponade (all except cryoballoon)	1%	ESC 2016 guidelines[37]
Cardiac tamponade (cryoballoon only)	0.4%	du Fay de Lavallaz 2020,[18] Fortuni 2020 [21]
Pulmonary vein stenosis	1%	ESC 2016 guidelines[37]
Persistent phrenic nerve palsy (cryoballoon and laser ablation only)	1%	ESC 2016 guidelines[37] Tohoku 2020[88] and committee expert opinion
Vascular complication	2%	ESC 2016 guidelines[37]
Other severe complication	1%	ESC 2016 guidelines[37] *Assume these are groin site complications*
Thoracoscopy/hybrid		
Atrial tear requiring sternotomy	10%	Pearman 2019[67]
Phrenic nerve injury	6.7%	Pearman 2019[67]
AADs		
All SAEs	5.5%	Estimated to be equal to total SAEs for catheter ablation (excluding persistent nerve palsy)
Cross over from AAD to ablation if AF symptom recurrence in first year (decision tree)		
All AAD arms	77%	Mean proportion based on Jais, 2008[32] Morillo 2014,[44] Wazni 2005[91] and Wilber 2010[92] *Explored in SA where 25% and 100%*
Repeat RF PP ablation in first year if first failed (decision tree)		
All ablation	80%	GC assumption *Explored in SA where 0% and 100%*
Relative risk applied to probability of AF recurrence following second ablation		
RF PP	1.61	Mean RR based on Pappone 2011[64] and RF PP data from Pokushalov 2013[69] *SA using Pokushalov 2013[69]*
Markov model probabilities and HR		
AF recurrence ablation (including ablation after cross over)	12-6%	Changes over time and based on data from CABANA RCT for yrs1-4[62], Gaita 2018[24] yrs 5-10 and then a constant hazard assumed.
AF recurrence AADs	14-7%	Changes over time and based on data from CABANA for yrs1-4[62] then a constant hazard assumed.
IS	0.7%	Calculated using FIRE&ICE,[38] Aspberg 2016[5] and Sterne 2017[83] and distribution of anticoagulants from prescription cost analysis[30]
HR stroke AF-S vs. AF-SF	*1.6*	*SA only, not in basecase.* *AFFIRM study[82]*

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Input	Data	Source
ICH	0.6%	Sterne NMA,[83] 70% anticoagulated and distribution of anticoagulants from prescription cost analysis[30]
Major non-ICH bleed (all health states)	0.5%	
Major non-ICH bleed (post-ICH health state only)	0.4%	Sterne NMA,[83] 20% anticoagulated and distribution of anticoagulants from prescription cost analysis[30]
Transition probabilities to first fatal IS or ICH (95%CI)		
Death in initial 30 days after event. No QALYs are contributed by these people, only acute costs.		
IS mortality (28 days)	16.8% (13.9% to 20.1%)	Janes 2013[34]
ICH mortality (28 days)	31.6% (22.7% to 42.8%)	Janes 2013[34] supported by Nielsen 2015[58]
Transition probabilities to dead state		
The transition probability of dying for each of the health states was determined by applying relevant standardised mortality ratios (SMRs) to age-dependant general population mortality rates from England life tables (ONS life tables for England 2015-17).[59]		
SMR IS and ICH health states	4.73	Bronnum-Hansen 2001,[10] SMR for non-fatal stroke
SMR post-IS and post ICH health state	2.32	Bronnum-Hansen 2001,[10] SMR for non-fatal stroke
Quality of life (utilities)		
Health states		
AF- SF	0.834 in year one (Age and sex dependant)	Age-adjustment (general population utility by age). Calculated using formula from Ara and Brazier 2010.[2] Applied multiplicatively with health state weights.
AF-S utility decrement	0.04	Berg 2010[7] *SA using Reynolds 2009[76] (0.046)* Decrement applied by using AF-SF utility and subtracting this utility decrement when in AF-S state.
IS	0.628	Tengs 2003,[86] weighted according to Youman 2003[94]
post-IS	0.628	
ICH	0.628	
post-ICH	0.628	
Dead	0	By definition
Adverse event decrements (and duration applied)		
Major non-ICH bleed	0.107 (2 weeks)	Thomson 2000 (as used in TA275 and TA355)[87]
Oesophageal injury	0.5 (1 year)	GC assumption
Vascular complications, cardiac tamponade and other severe complications	0.1 (1 month)	Assumption carried over from Reynolds 2014[74]
Pulmonary vein stenosis	0.1 (6 months)	GC assumption
Phrenic nerve palsy	0.03 (1 year)	Reynolds 2014,[74] taken from STOPAF trial data
Atrial tear requiring sternotomy	0.1 (3 months)	GC assumption
AADs SAEs	0.1 (1 month)	Assumption carried over from Reynolds 2014[74]

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Input	Data	Source
Costs		
Intervention costs		
AADs (annual)	£256	BNF[9] & NHS reference costs,[16, 55] drug and monitoring costs included. Costs applied to all those in AAD arm, 50% ablation for first 3 months (blanking) and a proportion of people in whom AF recurs and who enter stroke/ICH health states (two thirds).
RF PP	£7,707	NHS reference costs2018/2019[55] for procedure, NHS supply chain catalogue[56] for pass through costs. Some laser pass through costs based on expert advice from Dr Scott Gall, these were given a 30% uplift. Assumes 50% catheter ablation have TOE. *Explore proportion having TOE in SA.* *Explore cost of thoracoscopy procedure in SA, using lower HRG code ED31C: Standard, Other Operations on Heart or Pericardium, with CC Score 0-4* *Other SAs conducted around costs.*
RF ME ablation	£9,143	
Cryoballoon ablation	£9,911	
Laser ablation	£10,826	
Thoracoscopy	£12,559	
Hybrid ablation	£20,329	
Anticoagulant costs		
All states except post ICH	£460	BNF[9] and 70% anticoagulated and distribution of anticoagulants from prescription cost analysis
Post ICH only	£136	BNF[9] and 20% anticoagulated and distribution of anticoagulants from prescription cost analysis
Health state costs		
IS	£22,796	Xu 2018[93] SSNAP project Costs for NIHSS (5-15) for IS Costs for NIHSS (16-20) for HS used for ICH *Explore ICH costs where different source used (inflated costs from Wardlaw 2006[90] and Rosand 2004[79])*
Post-IS	£7,296	
ICH	£30,530 (SA: £20,543)	
Post-ICH	£14,414 (SA: £9,854)	
First fatal IS	£14,338	Xu 2018[93] SSNAP project Total cost for those dead before discharge IS and ICH respectively
First fatal ICH	£14,315	
Adverse event costs		
Major non-ICH bleed	£2,142	NHS reference costs 2018/19[55] weighted average of emergency admission with investigation
Oesophageal injury	£24,417	Calculated assuming 7 days in ICU and 14 excess days (ward). NHS reference costs 2017/2018[16] inflated to 2018/2019 (excess bed days)[15] and NHS reference costs 2018/19 (ICU)[55]
Cardiac tamponade	£1,977	Calculated assuming 3 excess days. NHS reference costs

ISBN: 978-1-4731-4043-1

Input	Data	Source
Pulmonary vein stenosis	£2,636	Calculated assuming 4 excess days. NHS reference costs 2017/2018[16] inflated to 2018/2019[55]
Vascular complication	£1,318	Calculated assuming 2 excess days. NHS reference costs 2017/2018[16] inflated to 2018/2019[55]
Other severe complication	£1,318	
Persistent phrenic nerve palsy	£240	NHS reference costs 20118/2019[55] Assume CT scan and outpatient cardiology visit (as per Reynolds 2014[74])
Atrial tear requiring sternotomy	£7,471	NHS reference costs 2018/2019.[55] Total HRG for ED30C
AADs SAEs	£1,318	Assume cost equal to vascular complications /other severe complications above

Abbreviations: AADs = antiarrhythmic drugs; AF = atrial fibrillation; BNF = British national formulary; CT = computerized tomography; HR = hazard ratio; HRG = health resource group; ICH = intracranial haemorrhage; IS = ischaemic stroke; ME = multielectrode; NMA = network meta-analysis; PP = point by point; RF = radiofrequency; SA= sensitivity analysis; SAE =serious adverse events; SF = symptom free; SMR = standardized mortality ratio; SSNAP= Sentinel Stroke National Audit Programme; TOE = transoesophageal echocardiogram

2.3.2 Initial cohort settings

The start age of the model cohort was 59, and the proportion of men to women was 64:56. These settings were based on the mean age and gender split reported in the studies identified in the clinical review that inputted into the NMA. These settings only impact the mortality beyond one year for which lifetables are used.

The cohort was assumed to have a CHADSVASC score between 1 and 2 based on the scores reported in the trials included in the NMA. Of note this was not reported in all trials.

Depending on a person's CHADSVASC score they may receive anticoagulants. Those with a score of 0 would not be anticoagulated and depending on their gender and local practice they may or may not be anticoagulated with a score of 1. All those with a score of 2 or more would likely receive anticoagulants. The committee assumed based on the proportion of people for each CHADSVASC score reported in the FIRE and ICE study[38], that 70% of patients would be anticoagulated.

2.3.3 Baseline event rates in decision tree

AADs were the baseline intervention in the model.

2.3.3.1 Baseline events in first year

Different sources were used for the baseline event rates due to the lack of real-world data in the correct population from which to estimate baseline risks.

For AF recurrence the baseline events were estimated from the AAD arms of the RCTs identified in the clinical review. Three studies provided the baseline data: Jais[32], Pappone[63], and Wazni[91]. These were all with a 1 year follow up from European studies and felt to be the most relevant data to the UK population. The baseline loghazard rate of AF recurrence at one year for AADs was modelled using a cloglog link model in WinBUGS, the data used can be found in Table 3 below and the code is available in the ablation NMA document (J2. Ablation NMA). The aim of this model was to calculate the baseline log hazard rate for these outcomes by pooling event rates for AADs taken from the RCTs. The log hazard rate was then converted to a hazard rate and then to a transition probability. In the deterministic

ISBN: 978-1-4731-4043-1

analysis the mean log hazard rate generated from the model was used. In the probabilistic analysis the CODA for the log hazard rate taken from WinBUGS was used.

For stroke and mortality outcomes, the committee had concerns with using the baseline events from the RCTs as they are rare events and the RCTs were small, therefore the data generated may not accurately reflect true baseline risks. Furthermore, for stroke, only one RCT, Nielsen[57] reported a single stroke related event, a TIA, which would have a less significant impact in terms of QoL for patient and cost to NHS than stroke. The baseline risk of stroke for those receiving AADs was taken from the estimated stroke risk outlined in **Section 2.3.7.2** (this also includes details on how it was made probabilistic).

For mortality, a baseline model was conducted using WinBUGS using data from Jais[32] to estimate a baseline transition probability, the data used can be found in Table 3 below and the code is available in the ablation NMA document (J2. Ablation NMA). However, the committee were concerned that this was an unexpectedly high baseline mortality, and therefore in the base case analysis of the economic model chose to use double the age-adjusted general population mortality. This was not made probabilistic. A sensitivity analysis was conducted using the transition probability generated from WinBUGS using Jais[32] (including using the CODA for the probabilistic analysis).

Table 3: Event rates reported in the trials that informed NMA baseline risk for the AAD arm in the different outcomes

	Jais[32]		Pappone[64]		Wazni[91]	
Outcome	Number events / Total randomised	%	Number events / Total randomised	%	Number of events / Total randomised	%
Recurrence	42/55	76.4	87/99	87.9	22/35	62.9
Mortality	2/59	3.4				

The baseline event probabilities used in the model are summarised in Table 4. A sensitivity analysis was conducted where the baseline AF recurrence was varied (50% and 90%). Further details are available in **section 2.3.11**.

Table 4: Baseline data for AADs

Event	Baseline model data (where applicable)	Mean probability
AF recurrence	Log-hazard (95% CI): 0.282 (0.100;0.459)	73.4% (95% CI: 66.9%; 79.4%)
Stroke	N/A	0.7%
Mortality	N/A	1.2%

2.3.4 Relative treatment effects at 1 year

Treatment effects at 1 year for each intervention relative to AADs were estimated as part of the clinical review. In the model, these relative treatment effects were applied to baseline event probabilities for AADs to generate intervention-specific probabilities.

2.3.4.1 Recurrence of AF

The hazard ratio of AF recurrence compared to AADs was based on the NMA conducted for the guideline. The NMA was conducted in WinBUGS (see J2. Ablation NMA for full data inputs and NMA code). Full trial details are available in chapter J1. In the deterministic analysis, the mean hazard ratios generated from the NMA were used. In the probabilistic analysis the CODA for the hazard ratio was used from WinBUGS.

Table 5: AF recurrence compared to AADs, NMA results

Intervention	mean HR (95% CI)	Transition probability

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Intervention	mean HR (95% CI)	Transition probability
RF PP ablation	0.276 (0.146;0.476)	31%
RF ME ablation	0.292 (0.119; 0.615)	32%
Cryoballoon ablation	0.294 (0.129; 0.595)	32%
Laser ablation	0.339 (0.083;0.961)	37%
Thoracoscopy	0.126 (0.015;0.470)	15%
Hybrid ablation	0.186 (0.036; 0.590)	22%

2.3.4.2 Serious adverse events

An NMA was conducted as part of the clinical review for SAEs. This outcome grouped together many different SAEs (see Appendix A: for full list of SAEs). The NMA results were extremely uncertain; this was demonstrated by the wide credible intervals around each relative risk (see J2. Ablation NMA). Overall, the results suggested that there was little difference between catheter ablation techniques and AADs. Thoracoscopy and hybrid appear to have more SAEs compared to catheter ablation and AADs. Of note only two small studies contributed to the thoracoscopy[85] and hybrid evidence[33] and the credible intervals were very wide. The committee were concerned about using this pooled outcome in the health economic model as it doesn't provide information on the nature and potential differing severity of the adverse events to enable the accurate assignment of a cost and disutility. Using the hospitalisation outcome was considered, which was included in the original clinical review protocol, as a proxy for SAEs in the health economic model. Unfortunately, very few studies reported this outcome and so it was not possible to use the data.

RCT study sizes were often too small to accurately capture the frequency of these rare events, therefore non-RCT data was considered for this outcome.

For catheter ablation, a number of registries report complications rates (these include stroke and mortality). Each registry/study reports a breakdown of individual complications, for comparative purposes these are summarised as total rates of serious adverse events here. Cappato 2010, a worldwide survey of catheter ablations over 20,000 ablations conducted between 2003 and 2006, reported major complication rates of 4.5%.[13] Deskmukh 2013, a US register of 90,000 catheter ablations conducted between 2000-2010, reported an overall procedural complication rate of 6.29%.[17] Arbelo 2017, a more recent European register (ESC/EHRA registry) of approximately 3,000 patients who received catheter ablations between 2012 and 2015, reported an in-hospital complication rate of 7.8% and a 12-month follow-up complication rate of 10.7%, the overall complication rate was 16.3%.[3] In this study the most common technique was RF PP followed by cryoballoon ablation, which has been more commonly associated with phrenic nerve palsy. There is evidence that laser ablation has similar rates of persistent phrenic nerve palsy when compared with cryoballoon ablation.[88] Two studies, du Fay de Lavallaz 2020[18] and Fortuni 2020,[21] reported lower risk of cardiac tamponade or pericardial effusion (RR 0.582 and 0.438 respectively) with cryoballoon when compared to RFPP. Finally, the ESC 2016 AF guideline[37] reported the following rates based on a number of sources (including many of the registries listed): 5-7% for severe complications and 2-3% life-threatening but usually manageable complications.

The committee considered these various sources and chose to use the ESC 2016 guideline for the rates of complications following catheter ablation as this was a synthesis of several the registries listed as well as other sources. It was assumed that all catheter ablation techniques would have the same risk of SAEs, with the exception of: cryoballoon and laser which would be the only ones at risk of phrenic nerve palsy (Tohoku 2020[88]) and that cryoballoon ablation would have a lower risk of cardiac tamponade when compared to other techniques (du Fay de Lavallaz 2020,[18] Fortuni 2020[21])..

Several other sources were identified reporting complications following thoracoscopy and/or hybrid procedures. Pearman 2019,[67] a UK observational study comparing catheter ablation

ISBN: 978-1-4731-4043-1

(n=90) to thoracoscopy (n=30), reported major complication rates of 1% and 16.7%, respectively (excluding stroke and mortality). They also reported complication rates from other studies (RCT and observational) comparing catheter ablation to thoracoscopy: 0-8% and 21-35% respectively (these included death and stroke). A systematic review of observational studies (case series) by Pearman 2017[66] comparing thoracoscopy to hybrid procedures indicated that major complications were more common with hybrid procedures than with thoracoscopy alone (7.3 % [95 % CI 4.2–10.5] vs. 2.9 %; [95 % CI 1.9–3.9] respectively), these major complications are a composite of death, stroke/transient ischemic attack, major bleeding, pericardial effusion requiring drainage, atrio-oesophageal fistula, and sternotomy. These rates of complications for thoracoscopy are much lower than those reported in other studies, the authors suggest there may have been some under-reporting in some case series. Finally, Vos 2018,[89] a large Dutch observation study (n=558) reported intra-operative complications (2.3 %), major post-operative (3.2%) and minor post-operative (8.2%) for people undergoing thoracoscopic ablation. Many of the minor post-operative complications, the committee considered were SAEs. Therefore, the overall serious adverse event rate was circa 13.7%. The guideline NMA did suggest that thoracoscopy and hybrid have more SAEs than AADs and catheter ablation, therefore it was agreed to use Pearman 2019[67] (16.7%) for both thoracoscopy and hybrid techniques in the health economic model.

Finally, for AADs, as the NMA suggested that the rate of SAEs is likely to be similar to catheter ablation, we assumed the same rate. This was done by summing the rate of the separate adverse events that could be experienced with catheter ablation. The trials in the NMA reported the following SAEs: hyperthyroidism; bleeding; atrial flutter, syncope, bradycardia, life-threatening arrhythmias and disabling drug intolerance requiring discontinuation. Many of these SAEs would result in a hospitalisation.

Table 6 summarises the rates of SAEs used in the economic model. No measure of uncertainty was available from the literature and therefore a standard error of 20% of mean was assumed. In the probabilistic analysis a beta distribution was used for this probability as it is bounded between 0 and 1. The distribution is derived from mean and its standard error, using the method of moments.

As detailed in **section 2.3.5**, a proportion of people in the AAD arm will have ablation in the first year. Those people will then be at risk of SAEs associated with the ablation technique they undergo. Furthermore, as noted in **section 2.3.6**, a proportion of people will have repeat ablations; these are assumed to be RF PP. Therefore, for those who initially had thoracoscopy or hybrid ablation, and then have a repeat with RF PP, they will then be at risk of SAEs associated with catheter ablations.

Table 6: Serious adverse event risk

Serious adverse event	Mean probability	SE	Source
Catheter ablation			
Oesophageal injury	0.50%	0.10%	ESC 2016,[37] Tohoku 2020,[88] du Fay de Lavallaz 2020,[18] Fortuni 2020[21] and committee expert opinion
Cardiac tamponade (all except cryoballoon)	1.00%	0.20%	
Cardiac tamponade (cryoballoon only)	0.4%	0.08%	
Pulmonary vein stenosis	1.00%	0.20%	
Vascular complications	2.00%	0.40%	
Other severe complications	1.00%	0.20%	
Persistent phrenic nerve injury (cryoballoon and laser only)	1.00%	0.20%	
Thoracoscopy and hybrid ablation			
Persistent phrenic nerve injury	6.70%	1.34%	Pearman 2019[67]
Atrial tear requiring sternotomy	10.00%	2.00%	

ISBN: 978-1-4731-4043-1

Serious adverse event	Mean probability	SE	Source
AADs			
All SAEs related to AADs	5.50%	1.10%	Committee assumption informed by NMA and ESC 2016[37]

2.3.4.3 Stroke

An NMA was conducted as part of the clinical review to estimate the relative risk of stroke compared to AADs. The NMA was conducted in WinBUGS (see J2. Ablation NMA full data inputs and NMA code). Full trial details are available in the evidence review for Ablation, chapter J. There was insufficient evidence to include thoracoscopy and hybrid ablation in the NMA. This was because the trials that included this intervention reported zero events in both arms of the trials and so could not be analysed as part of an NMA.

As part of this NMA, a sensitivity analysis was conducted, excluding two trials which reported asymptomatic cerebral lesions rather than clinical strokes. These would not have the same impact on the patient and cost to the NHS. In this sensitivity analysis, the NMA results indicated that RF ME ablation, and to a lesser extent cryoballoon ablation, have a higher risk of stroke compared to AADs, the credible intervals were very wide, but did not cross 1. The credible intervals for the other ablation techniques all crossed 1 when compared to AADs. Due to the size of the credible intervals, the committee were not confident about using this NMA data in the base case of the model. Instead they agreed to use this data to guide them on the trend that stroke risk is greater for RF ME ablation compared to AADs. The committee highlighted that this is a known risk associated with RF ME ablation and they noted that the technology has been modified in recent years, reducing peri-procedural stroke risk, but that there is no available RCT evidence supporting this yet. This was explored in a sensitivity analysis, further details in **section 2.3.11**.

Therefore, in the base case, it was assumed that the stroke risk was the same for all catheter ablation techniques as AADs, with the exception of RF ME where it was assumed to be double that of AADs. This is supported by a large observational dataset where the peri-procedural stroke rates are close to 1%.[13, 17, 37] A sensitivity analysis was conducted using the NMA data for the two significant results: RF ME, and cryoballoon ablation.

As no data was available for thoracoscopy and hybrid techniques, the committee where required to make an assumption on the relative treatment effect for thoracoscopy and hybrid approach on stroke compared to AADs. The committee assumed in the base case that the risk of stroke for thoracoscopy and hybrid procedures was likely to be equivalent to RF PP ablation (which was in turn assumed the same as for AADs). The committee discussed that although thoracoscopy is conducted outside the heart, external injury as a result of result of the procedure is less likely to cause stroke but as the procedure involves going through the chest, the patient is less likely to be on anticoagulants and therefore has a greater risk of stroke. On balance therefore it was thought to not increase risk of stroke relative to other techniques.

The table below summarises the transition probabilities stroke used in the economic model base case (see **Section 2.3.7.2** on how this was made incorporated probabilistically).

Table 7: Transition probabilities for stroke base case

Intervention	Transition probability	Source
RF PP ablation	0.7%	Assumption = AADs
RF ME ablation	1.4%	Assumption double AADs

ISBN: 978-1-4731-4043-1

Intervention	Transition probability	Source
Cryoballoon ablation	0.7%	Assumption = AADs
Laser ablation	0.7%	Assumption = AADs
Thoracoscopy	0.7%	Assumption = AADs
Hybrid ablation	0.7%	Assumption = AADs

Of note this outcome, when extracted from the papers for the NMA, was for all stroke, whether haemorrhagic or ischaemic. None of the papers specified which type of stroke patients experienced and in two studies stroke and transient ischaemic attack (TIA) were extracted together.[19, 38] For costing and modelling purposes, it was assumed that these were all ischaemic strokes and therefore they would then enter the post-ischaemic stroke state in the Markov model. This is unlikely to impact the model results as the committee considered that 80% of strokes are likely to be ischaemic strokes. Furthermore, the cost and impact of ischaemic stroke and haemorrhagic stroke are similar.

2.3.4.4 Mortality

An NMA was conducted as part of the clinical review to estimate the relative risk of mortality compared to AADs. The NMA was conducted in WinBUGS (see J2. Ablation NMA for full data inputs and NMA code). Full trial details are available in the ablation evidence review chapter J. There was insufficient evidence to include thoracoscopy, hybrid and RF ME catheter ablation in the NMA. This was because of zero events in both arms for some of the trials and one trial comparing thoracoscopy with RF ME not connecting to the network.[85]

The results indicated that RF PP ablation had the most favourable mortality risk, followed by AADs, cryoballoon and finally laser ablation. Upon discussion of the results of the NMA, the committee expressed concern with the uncertainty demonstrated by the credible intervals which were all crossing 1 when comparing the different techniques to AADs. In particular, for cryoballoon and laser techniques the credible intervals were very wide. The risk ratios for the latter were deemed by the committee to be very high and unlikely to be seen in practice. As a result, in the base case the committee assumed that the probability of mortality would be the same as AADs for laser and cryoballoon. A sensitivity analysis was conducted where the NMA data for RF PP was used as this was the comparator with the least uncertainty, further details in **section 2.3.11**.

The committee where required to make an assumption on the relative treatment effects on mortality compared to AADs for those three comparators not in the NMA (thoracoscopy, hybrid, and RF ME catheter ablation). They assumed that RF ME catheter ablation would be the same as other catheter ablation techniques and therefore the mortality probability equal to that of AADs. This is supported by the pair-wise analysis of ablation RCTs (See Chapter J) showing zero events in both arms of RCTs comparing RF ME to RF PP or cryoballoon.

For hybrid and thoracoscopy, the single RCT that reports mortality is Sugihara 2018,[85] which reports a mortality rate of 5%, however this is based on a small sample size and a single death. Observational data is mixed; Pearman 2019 reports a higher peri-procedural mortality rate for thoracoscopy versus catheter ablation (3.3% vs 0%).[67] Pearman 2017 reports mortality rates between 0% and 6.1% for thoracoscopy and 0% and 12.5% for hybrid procedures.[66] Finally Vos 2018, reported a single death in a cohort of 500 patients receiving thoracoscopy.[89] A conservative approach was taken in the model and it was assumed that thoracoscopy and hybrid procedures would have a 50% higher mortality rate than AADs and catheter ablation, further details in **section 2.3.11**. This was explored in a sensitivity analysis where the mortality rate was double that of AADs for these two interventions (this sensitivity analysis was conducted in conjunction with the sensitivity analysis where the NMA data for RF PP was used).

ISBN: 978-1-4731-4043-1

The table below summarises the transition probabilities for stroke used in the decision tree base case.

Table 8: Risk ratios for mortality NMA results

Intervention	Transition probability	Source
RF PP ablation	1.20%	Assumption = AADs
RF ME ablation	1.20%	Assumption = AADs
Cryoballoon ablation	1.20%	Assumption = AADs
Laser ablation	1.20%	Assumption = AADs
Thoracoscopy	1.80%	Assumption 50% higher than AADs
Hybrid ablation	1.80%	Assumption 50% higher than AADs

2.3.5 Cross over from AAD to ablation

The guideline NMA AF recurrence provided the probability of first AF recurrence after 3 months blanking following initiation of AADs. Four of the RCTs included in this NMA compared AADs to ablation. In these trials a proportion of people in the AAD arm crossed over to ablation once AF symptoms recurred (see Table 9). The mean proportion of cross over from these trials was used in the model. This was explored in a sensitivity analysis where 25% and 100% of those with AF recurrence crossed over. Of note, this proportion was fixed in the probabilistic sensitivity analyses.

Table 9: Proportion crossover from AAD to ablation

Study	N cross over	N AF symptom recurrence	Proportion cross over
Wazni 2005[91]	37	42	88%
Morillo 2014[44]	26	44	59%
Wazni 2005[91]	18	22	82%
Wilber 2010[92]	36	46	78%
Mean cross over			77%

Cross over occurred between 3 months (after the blanking period) and 2 years, however only one trial however reported the mean time (6 months) at which this occurred (Jais 2008[32]). Therefore, in the decision tree it was assumed that cross overs occurred at 6 months.

The probability of AF recurrence following ablation was assumed to be the same as for those in the ablation arms (see **Table 5**). Although these probabilities are annual, rather than 6-month, these were considered acceptable as this would be a way of front loading the AF recurrence.

In the decision tree, the probability of stroke and mortality for AADs was applied for those who did not cross over and the probability of stroke and mortality for each ablation technique was applied for those who do cross over. As noted in **section 2.3.4.2**, those who cross over to ablation will then be at risk of SAEs associated with the ablation technique.

2.3.6 Repeat ablations data

The guideline NMA AF recurrence outcome provided the probability of first recurrence that is after a single ablation. In reality, repeat catheter ablations may be done. To capture this, the decision tree was structured to allow for a repeat ablation in the first year, it was assumed these would occur at 6 months to be consistent with cross overs to ablation. A proportion of those who have AF recurrence in the first year are given a second ablation. It was assumed that all repeat ablations were RF PP as this is what is commonly done in current practice. The committee assumed that 80% of those with AF recurrence in the first year would have a

ISBN: 978-1-4731-4043-1

repeat; this reflects a proportion choosing not to have a repeat and or the clinician deciding they should not have a repeat. Furthermore, this is similar to the proportion reported in the RCTs. This was explored in a sensitivity analysis where 0% and 100% of those with AF recurrence had a repeat.

All the RCTs included in the clinical review were reviewed to see if data was available on the relative efficacy of the first versus second ablation on AF recurrence. Two studies were identified which reported useable data (Pappone 2011[64] and Pokushalov 2013[69]). The AF recurrence following the first ablation and then following the second ablation reported in these studies were 27% and 33% for Pappone 2011[64] and 21% and 42% for Pokushalov 2013[69] respectively. Based on these studies, a mean relative risk was estimated and applied to the probability of AF recurrence for RF PP (Table 10). A sensitivity analysis was conducted using only the Pokushalov 2013[69] data.

In the decision tree, the probability of stroke and mortality for RFPP was applied for those who had repeat ablations. For those who did not, they kept their original ablation technique probabilities. As noted in **section 2.3.4.2**, those who had a repeat ablation will then be at risk of SAEs associated with RFPP.

The data used for repeat ablations and resulting probabilities are summarised below. These values were fixed in the probabilistic sensitivity analysis.

Table 10: Repeat ablation data

Input	Value	Source
Proportion having repeat ablation	80%	GC assumption
Relative risk of AF recurrence with 2nd ablation vs 1st	1.61	Calculated from Pokushalov 2013[69] and Pappone 2011[64]

2.3.7 Markov model transition probabilities

2.3.7.1 Recurrence of AF

Recurrence of AF is the only outcome for which a treatment effect was expected beyond a year. It was expected that the rate of recurrence would be different between ablation compared to medical treatment and even between ablation types.

The clinical review was not able to provide much data for this as it was limited to RCTs, only 4 of which provided data beyond 1 year. Three of the studies compared AADs to RF PP ablation.[44, 57, 64] Of these, MANTRA-PAF had the longest follow up: 5 years, and included 294 patients, and data was reported for 2 years and 5 years.[57] The fourth study compared RF PP to hybrid procedures and had a 36 month follow up.[33] The committee were concerned regarding the applicability of the latter study to inform the difference in rates of recurrence beyond a year, as it was a very small highly selective study, where the baseline rate of recurrence in the catheter ablation was lower than expected.

Due to lack of data to inform the rate of AF recurrence beyond 1 year for ablation techniques other than RF PP, an assumption was made that all ablation techniques would have the same rate of recurrence beyond a year.

In order to identify the most appropriate evidence for recurrence rates of AF following ablation and AADs for use in the model, the MANTRA PAF[57] study was compared to other published data that would not have been identified in the clinical review as it did not meet the protocol. This included longitudinal/observational data, and also RCT studies such as CABANA,[61] that have a longer follow up but did not specify which catheter ablation technique was used.

ISBN: 978-1-4731-4043-1

The committee identified a recent systematic review of longitudinal studies (2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation) which reported AF recurrence following ablation beyond 1 year.[12] Of these studies, the Committee identified Medi 2011,[43] and Sawhney 2009,[81] as the most widely referenced studies which reported the recurrence of AF following radiofrequency catheter ablation in paroxysmal AF patients.[43, 81] A more recent (Gaita 2018)[24] longitudinal study was identified, which reported freedom of AF recurrence over a 10 year follow-up in people who had a catheter ablation (type not specified) in Italy. This was presented in the form of a Kaplan-Meier curve and presented paroxysmal and persistent AF separately. The issue with these studies is that they do not provide recurrence rates for AADs. Furthermore, although they have long term follow-up, they are old studies, and recruitment was over 15 years ago and techniques have evolved over time, so may not accurately reflect current ablation techniques. Finally, how recurrence of AF was measured will impact the rate of recurrence: for example, symptomatic AF, versus implantable loop recorder and 30 second recording of AF versus burden of AF. The committee noted that older studies tended to be symptom driven reporting, this is likely to represent a lower rate of AF recurrence.

CABANA[61] reported the rate of recurrence over 48 months for people receiving either catheter ablation (type not specified) compared to AADs in the form of a Kaplan Meier curve. This study included 1,240 patients. Although CABANA included persistent and paroxysmal AF, sensitivity analyses indicated that rate of AF recurrence was not sensitive to type of AF.

MANTRA-PAF[57] did not report a Kaplan-Meier curve, and it is unclear if the data includes AF recurrences in the blanking period. Due to this poor reporting, this RCT was considered less useful source for AF recurrence over time.

CASTLE AF[41] was another RCT which combined catheter ablation techniques together, compared to AADs. This study however was specifically in a population of AF with heart failure and so was deemed less generalizable than either MANTRA PAF or CABANA.

As CABANA was a much larger RCT and also reported a published Kaplan-Meier curve of freedom of AF symptom recurrence for both ablation and AADs, it was used to model AF recurrence for all ablations and AADs in the model base case. As this study only provided follow-up data for 4 years, the data from Gaita 2018 was used to estimate AF recurrence from years 4 to 10 for those receiving ablation. For those receiving AADs, after 4 years a constant hazard was assumed. The same assumption was made after 10 years for ablation. The cumulative freedom from AF at each year was extracted from the Kaplan Meier curves, using software called GraphIt. This was then converted to a cumulative hazard and then an annual probability of AF recurrence was calculated. The cumulative freedom from AF as extracted from the studies, as well as the number at risk at each time point are reported in Table 11 and Table 12 . A beta distribution was applied to the transition probability for the probabilistic analysis. Alpha and beta were calculated using the number at risk reported in the studies. The resulting transition probabilities for each cycle used in the base case are reported in Table 13. A reminder that for those in the AAD comparators, if they are AF symptom free, they either enter the Markov model in the AF SF (cross over) health state if they had crossed over to ablation in the first year or they enter the AF SF health state if they had AADs throughout. The AF recurrence rates applied to those two states are the ablation arm and AAD arm (from CABANA) respectively.

Table 11: Freedom from AF following ablation from CABANA and Gaia 2018

Year	Cumulative freedom of AF	N at risk	Source
1	0.636	381	CABANA[61]
2	0.557	291	
3	0.507	201	
4	0.483	134	

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Year	Cumulative freedom of AF	N at risk	Source
5	0.742	82	Gaita 2018[24]
6	0.719	79	
7	0.675	76	
8	0.668	74	
9	0.657	59	
10	0.617	36	

Table 12: Freedom from AF following AADs from CABANA

Year	Cumulative freedom of AF	N at risk	Source
1	0.408	252	CABANA[61]
2	0.349	181	
3	0.313	131	
4	0.291	94	

Table 13: Freedom from AF following ablation from CABANA and Gaita 2018

Cycle	Probability of AF recurrence (ablation/AAD with cross over to ablation)	Probability of AF recurrence (AADs)	Source
1	12%	14%	CABANA[61]
2	9%	10%	
3	5%	7%	
4	2%	7%	
5	3%	7%	For ablation: Gaita 2018[24] For AADs: Assume constant hazard
6	6%	7%	
7	1%	7%	
8	2%	7%	
9	6%	7%	
10-39	6%	7%	Assume constant hazard

Of note in CABANA, 39% of those in the AAD arm and with AF symptom recurrence cross over to ablation. Therefore, the AF recurrence data for this arm may underestimate the true probability of AF recurrence if they had only had AADs.

A sensitivity analysis was conducted where only the CABANA data was used, and after 4 years a constant hazard is assumed for both AADs and ablation. Due to the potential underestimation of AF recurrence in the AAD arms in CABANA due to cross over to ablation, a sensitivity analysis was conducted where the AF recurrence was adjusted to account for this (for more information see **section 2.3.11**). Finally, an extreme scenario analysis was conducted were no further AF recurrence was modelled beyond 1 year. That is, all those free from AF symptoms at the end of year one, remain in that state until they experience an event (ICH or ischaemic stroke) or die.

2.3.7.2 Transition probability for ischaemic stroke

The probability of ischaemic stroke beyond one year was assumed to be the same for all those with symptoms of AF, irrespective of the intervention they initially received.

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Baseline ischaemic stroke risk for a population with the distribution of CHADSVASC scores reported in FIRE and ICE (Table 14), was estimated using stroke rates reported by CHADSVASC score from a large Swedish cohort of untreated AF patients (Table 15). The model assumed 30% of the population was untreated. These would be lower risk individuals, that is all those with a CHADSVASC of 0 and some with a score of 1. The baseline probability of stroke was therefore estimated accounting for all those being untreated having a score of 0 or 1, and all those treated having a score of 1 or more. The baseline probability was then adjusted for the remaining 70% of the cohort who are treated with anticoagulants using the HR from Sterne 2017 (Table 16). The anticoagulant distribution was based on Prescription cost analysis data (see section 2.3.9.2, Table 34).

A weighted average annual rate of stroke was derived by weighting the rate of stroke per CHADSVASC by the distribution of patients per CHADSVASC score, and then using this to determine the rate of stroke by drug. As the treatments other than warfarin were compared to warfarin, then the rate of stroke was multiplied by both the HR of warfarin vs no treatment and the HR of the relevant drug vs warfarin to derive the HR of the relevant drug vs no treatment. See Table 17 for final probabilities by anticoagulant and weighted probability used in model for ischaemic stroke.

Table 14: FIRE and ICE baseline CHADSVASC distribution[39]

CHA2DS2-VASc	% patients at each score taken from FIRE and ICE baseline Kuck 2016
0	16.7%
1	28.9%
2	25.6%
3	16.3%
4	9.7%
5	2.3%
6	0.5%

Table 15: Aspberg data for stroke rate by CHADSVASC score (untreated cohort)[5]

CHA2DS2-VASc	Number of events	Person years	Mean rate (per 100 person years)*
0	142	37839.13	0.375273
1	337	45581.64	0.739333
2	1028	54540.93	1.884823
3	1927	65875.49	2.925215
4	2499	59936.04	4.169445
5	2198	39387.13	5.580503
6	1768	23375.56	7.563455
7	840	9974.05	8.421855
8	270	3205.68	8.42255
9	44	507.72	8.666194

Table 16: Ischaemic stroke data from Sterne[83]

HR: warfarin vs no anticoagulant	0.359 (0.213)
HR: apixaban vs warfarin	0.90(0.72 to 1.11)
HR: dabigatran vs warfarin	0.75 (0.58 to 0.97)
HR: edoxaban vs warfarin	1.00 (0.83 to 1.2)
HR: rivaroxaban vs warfarin	0.92 (0.73 to 1.13)

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Table 17: Ischaemic stroke probabilities and weighted average probability using FIRE and ICE[38, 83]

Anticoagulant	Annual probability
Untreated	0.005
Apixaban	0.008
Dabigatran	0.006
Edoxaban	0.008
Rivaroxaban	0.008
Warfarin	0.008
Weighted average (70% treated)	**0.007**

Using the above data, the ischaemic stroke probability overall was 0.007. This probability was not adjusted for increasing age which is a limitation of the model. However as this applies to all comparators it is unlikely to impact the conclusions of the model. The transition probability was made probabilistic by applying a Dirichlet distribution to the proportion of people at each CHADSVASC score reported in FIRE and ICE, a Gamma distribution to the rates of stroke from Aspberg 2016 and a Lognormal distribution to the hazard ratios from Sterne 2017.

A number of limitations were identified with this approach, including that the studies included in the Sterne analyses were not stratified by type of AF, and the authors note that few were likely to be paroxysmal AF, thus the data may not be representative of the model population. Furthermore, the population in the Aspberg observational cohort were hospitalised older patients and thus the stroke rates may have been higher than expected for the target population. The committee however felt that the annual stroke probability calculated was not unexpectedly high.

Observational data sets have suggested that there is a lower stroke rate in ablated patients versus non-ablated patients over time but this may be due to selection bias. Another economic analysis in the area[42] had conducted a systematic review of the literature and identified the AFFIRM study (Sherman 2005).[82] This study examined the occurrence and characteristics of stroke events in the investigation of sinus rhythm management and provided estimates of the hazard of stroke for AF relative to normal sinus rhythm (symptom free AF). Of note however those who received rhythm control therapy received less anticoagulant therapy than the controls (70% versus 90%). It found that patients with AF symptoms had a 1.6 times (95%CI 1.11 to 2.30) greater risk of stroke than those in normal sinus rhythm, when adjusted for warfarin therapy. This relative risk reduction was applied in both McKenna and Blackhouse HE analyses. The committee considered whether or not to do the same but overall agreed there was too much uncertainty as direct clinical data (RCT evidence) and experience suggests that there is no long-term impact of ablation on stroke risk. Furthermore, the AFFIRM study was indirect evidence and reflected out of date clinical practice. Therefore, in the base case it was assumed there was no difference in the stroke risk for those with and without AF symptoms. A sensitivity analysis was conducted where this risk reduction from the AFFIRM trial was incorporated.

2.3.7.3 Transition probabilities for ICH and capturing major bleeding as an adverse event

The transition probability for ICH beyond one year was assumed to be the same for those in the symptom free and symptomatic AF states, irrespective of the intervention they initially received. An HTA which included an NMA and HE model of all DOACs and warfarin (Sterne 2017)[83] provided rates of ICH and other clinically relevant bleed. They utilised a published meta-analysis of warfarin vs placebo by Hart 2007 for their baseline. Both of these sources were used in the model to estimate weighted probabilities of ICH and other major bleed

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(other clinically relevant bleed). An assumption was made that major bleeds were most comparable to 'clinically relevant bleeds', as defined in Sterne 2017.

The probability of ICH was calculated from the Sterne 2017 NMA and weighted according the current prescribing trends in England for anticoagulants.[83] It was applied to the proportion of patients receiving anticoagulants that is 70% of the cohort. The anticoagulant distribution was based on Prescription cost analysis data (see **section 2.3.9.2**, Table 34). See Table 18 for Sterne data used and Table 19 final probabilities by anticoagulant and weighted probability used in model for ICH. Of note, there was no HR available for no treatment vs warfarin, therefore it was assumed to be equal to the reciprocal of the HR for warfarin vs no treatment for other clinically relevant bleeds (see Table 20), as was done in the Sterne 2017 HE analysis. Due to the uncertainty with this assumption, a sensitivity analysis was conducted where the HR of warfarin vs no treatment was equal to 1.

Table 18: ICH data from Sterne[83]

Intervention	Rate/HR (95% CI/SD)
Rate: warfarin	0.0094 (0.0057 to 0.17)
HR: warfarin vs no anticoagulant	Not possible to estimate due to 0 events in placebo arms. For model, assumed HR for clinically relevant bleed 2.3 (3.53).
HR: apixaban vs warfarin	0.46 (0.36 to 0.58)
HR: dabigatran vs warfarin	0.36 (0.26 to 0.49)
HR: edoxaban vs warfarin	0.49 (0.39 to 0.61)
HR: rivaroxaban vs warfarin	0.65 (0.46 to 0.89)

Table 19: ICH probabilities by intervention and weighted by prescribing trends[83]

Anticoagulant	Annual probability
Untreated	0.004
Apixaban	0.004
Dabigatran	0.003
Edoxaban	0.005
Rivaroxaban	0.006
Warfarin	0.009
Weighted average	**0.006**

The probability of having a major bleed was calculated in the same way taking data for other clinically relevant bleed from the Sterne 2017 NMA.[83] See Table 20 for Sterne data used and Table 21 for final probabilities by anticoagulant, and weighted probability used in model for major bleed. This probability was applied to all those alive in the model irrespective of their health state and initial treatment to calculate acute costs and QALY loss. Following an ICH, the committee noted that many people would discontinue anticoagulants. Therefore, in the post-ICH state it was assumed that only 20% would receive anticoagulants (instead of the base case of 70%) and so the probability of major bleed was adjusted for this health state. See Table 21 for the adjusted weighted average probability.

Table 20: Bleed data from Sterne[83]

Intervention	Rate/HR (95% CI/SD)
Rate: warfarin	0.0066 (0.031 to 0.13)
HR: warfarin vs no anticoagulant	2.3 (3.53)
HR: apixaban vs warfarin	0.82 (0.70 to 0.94)
HR: dabigatran vs warfarin	1.07 (0.92 to 1.24)
HR: edoxaban vs warfarin	0.88 (0.82 to 0.94)

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Intervention	Rate/HR (95% CI/SD)
HR: rivaroxaban vs warfarin	1.05 (0.98 to 1.13)

Table 21: Major bleed probabilities and weighted average probability using FIRE and ICE[38, 83]

Anticoagulant	Annual probability
Untreated	0.003
Apixaban	0.005
Dabigatran	0.007
Edoxaban	0.006
Rivaroxaban	0.007
Warfarin	0.007
Weighted average (70% treated)	0.005
Weighted average (20% treated)	0.004

The transition probabilities for ICH and major bleed were made probabilistic by applying a lognormal distribution to the rates and hazard ratios from Sterne 2017. The prescribing trends used for the weighting were kept fixed.

2.3.7.4 Transition probabilities for mortality

National life tables for England were used to estimate age-dependent baseline mortality rates.[59] The committee considered adjusting this rate to account for any increased mortality rate for people with paroxysmal AF versus the general population. A large Swedish observational study[22] with a 4.6 year follow up indicated of those with paroxysmal AF, the standardised mortality ratio (SMR) was 1.6 (95% CI 1.4 to 1.8) for all-cause mortality versus the general population. In this study, they found that those with a low risk age (≤75 years) and no significant comorbidity, had no excess mortality (SMR 0.9, 95% CI 0.5–1.5) compared to the general population. They also found that the SMR increased as the CHADS2 score increased (CHADS2 0-1: SMR 1.3; CHADS2 2-3: 1.6; CHADS2 4-6: 2.3). When they looked at cause specific SMR, there was an increased SMR for MI, heart failure, and cardiovascular disease in general (SMRs 2.4; 2.6 and 2.1 respectively). In those treated with warfarin, the SMR was 1.1 (95% CI 0.8 to1.4). In those not anticoagulated the SMR was 2.2 (95%CI 1.6 to 2.8). Overall, this data suggests that in lower risk patients, and in those that are anticoagulated, the all-cause mortality SMR versus the general population indicates no increase in mortality. As our population is generally lower risk, and those with moderate stroke risk being anticoagulated, it was deemed appropriate to not apply an SMR for all-cause mortality in the AF symptom and AF symptom-free states.

Of note, it was assumed that having symptoms of AF would not impact all-cause mortality.

The ischaemic stroke, post-ischaemic stroke and ICH and post-ICH standardised mortality ratios were based on SMRs reported in Bronnum-Hansen 2001.[10] This study looked at long-term survival following a non-fatal stroke (those who survive 30 days) in people in Denmark. The SMRs were reported separately for different time intervals, initially for years 0 – 1 and also for different intervals between years 2 – 15. To calculate the SMR for the post-ischaemic stroke health state, a straight average was used as the model reflects a lifetime perspective. A confidence interval for the average SMR was obtained using Monte Carlo simulation. Of note these SMRs were for all strokes rather than ischaemic stroke or intracranial haemorrhage specifically and therefore it was felt appropriate to use them for both ischaemic stroke and ICH in the model. Therefore, these SMRs may be over or underestimates of the true mortality rates.

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Table 22: SMR data

Health state	SMR	Source
AF	None	See discussion of Friberg 2007 above.
Ischaemic stroke (first year)	4.73 (95%CI 4.34, 5.15)	Bronnum-Hansen 2001
Post-ischaemic stroke (after first year)	2.32 (95%CI 2.17 to 2.49)	Bronnum-Hansen 2001
ICH (first year)	Same as ischaemic stroke	Assume same as stroke as no data was identified, this approach was taken in Sterne 2017 and will be explored in SA
Post-ICH (after 1 year)	Same as ischaemic stroke	

As these SMRs were for those who survived first 30 days following a stroke event, it was necessary to model acute ischaemic stroke and ICH mortality. The probability of death in the first 30 days was estimated using data from Janes 2013,[34] which was used in the edoxaban NICE TA[48]. This Italian population-based prospective study reported 28-day stroke case fatality rates. Table 23 summarises the data used in the model. These rates of acute mortality following ICH are supported by Nielen 2015.[58] In the model it was assumed that those who die in the first 30 days contribute no QALYs in that time period between the event occurring and dying, only acute costs.

Table 23: Transition probabilities to first fatal IS or ICH

Health state	Transition probability (95% CI)	Source
Ischaemic stroke mortality (28 days)	16.8% (13.9% to 20.1%)	Janes 2013[34]
ICH mortality (28 days)	31.6% (22.7% to 42.8%)	Janes 2013[34]

The SMRs and transition probabilities to first fatal ICH or IS were included in the probabilistic analysis by applying a Lognormal distribution using the 95% CI reported above.

2.3.8 Utilities

A systematic review of quality of life literature was conducted to identify utility data related to AF. The search strategy is available in Evidence review J1_Ablation, Appendix B. In addition, a review of utility data used in other AF models and technology appraisals, and recent NICE clinical guideline health economic models, was conducted.

A summary of the utility values used in the model can be seen in Table 24, with discussion on the sources below. In the probabilistic analysis, a Gamma distribution was applied to all utility decrements and beta distribution was applied to utility values.

2.3.8.1 AF symptom free

A number of studies have demonstrated that freedom of AF symptoms as a result of successful ablation or receiving AADs is correlated with improvements in QoL.[25, 26, 36, 70, 72, 75] In both Blackhouse 2013[8] and McKenna 2009,[42] they used the gender and age specific general population utility values for those who are free of AF symptoms (in normal sinus rhythm). The same approach was taken in this model. This is supported by prospective study evidence indicating that patient in sinus rhythm at 12 months follow up showed improvements in all subscales of SF-36 approximating the normative levels.[71]

Therefore, for the freedom of AF symptoms health state, general population utility values were used. These utilities were age-adjusted in order to account for the fact that as people age their quality of life decreases. This is a method that is adopted by many other economic

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models and was also highlighted in the recent rivaroxaban NICE TA for acute coronary syndrome[50] evidence review group report as being something that should be incorporated. Not adjusting utilities for increasing age can lead to QALYs potentially being overestimated for older people.

Age-specific general population EQ-5D-3L utilities were derived using the following formula based on regression from Ara 2010:[2]

$$Utility = 0.9508566 + 0.0212126 * Male - 0.0002587 * age - 0.0000332 * age\text{^}2$$

These were then combined with the health-state specific utilities using the multiplicative method. Age-specific utilities were not varied probabilistically.

2.3.8.2 Symptomatic AF

Berg 2010,[7] reported EQ-5D data from the Euroheart Survey. They conducted an ordinary least squares (OLS) regression, to derive coefficients for prediction for different variables including for AF symptoms (palpitations, chest pain, syncope or dizziness). They measured these both at baseline and at 12-month follow up. As the baseline was conducted in relation to a hospitalisation for a cardiac event, it was considered the 1 year follow up would be more appropriate as it represents a more stable population. This was applied as a decrement to the general population age adjusted utility vales to estimate the utility of those in the AF symptomatic health state. The utility decrement from this analysis was 0.04 (95% CI 0.006 to 0.074).

The value from Berg is not dissimilar to the disutility of having AF symptoms used in the Blackhouse 2013[8] model taken from Reynolds 2009: 0.046 (95% CI: 0.014,0.095).[76] Reynolds et al. specifically transformed patient level SF-12 responses for patients enrolled in the FRACTAL registry to utility scores using the Brazier algorithm. The FRACTAL registry included over 1000 patients with a first-time diagnosis of AF. Reynolds et al. reported the average change in utility in patients with no documented recurrences of AF over 12 months to be 0.046. Based on this data, a disutility of 0.046 was applied to patients while being in the AF symptomatic health state. Berg 2010 was used in the base case as it was EQ-5D data. Reynolds 2009 was used in a sensitivity analysis.

2.3.8.3 Utility for ischaemic stroke and ICH health states

A number of sources of utilities were considered for acute stroke and ICH and the post-event states that were identified in previous TAs (Robinson 2001, Gage 1996, Haacke 2006).[23, 27, 77] These provided utilities by severity and level of disability. As the model structure did not separate out stroke severity, alternative sources were considered. The health economic models in NICE clinical guidelines NG136 (Hypertension)[49] and CG181 (lipid modification)[46] used a mean stroke utility value taken from a published meta-analysis weighted by severity using a UK data set (0.628, SE=0.04).[86,94] In these models the same utility was applied to both the acute event state and the post event state as the original sources did not distinguish between the two time points and therefore it assumed that the quality of life did not differ. The same assumption was made in two of the four anticoagulant NICE technology appraisals.[48, 51] Furthermore, evidence from an acute coronary syndrome population suggests that there is no evidence that health related quality of life improves over time.[53] Of note, this utility was applied multiplicatively to the age-adjusted general population utilities for ICH and ischaemic stroke in both the acute and post event health states.

2.3.8.4 Utility decrement for major bleed (other than ICH)

Two possible sources for utility decrements for major bleed were considered. Some published HE analyses including Pink 2011[68] and Stevanovic 2014[84] used a utility decrement of 0.1385 (applied for 1 month and 2 weeks respectively) for other major bleed; however, the

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original source for this value was difficult to trace. TA355[48] and TA275[51] both use a utility decrement of 0.1070 for major bleed. This was taken from a health economic analysis by Thomson 2000.[87] This was elicited by standard gamble and was applied in the model for 2 weeks. The source used by the two TAs was considered the more appropriate estimate to use in the model by the committee.

2.3.8.5 Utility decrement for serious adverse events

For SAEs associated with the interventions (ablation and AADs), a QALY loss is calculated from a utility decrement and the estimated duration of the event. The utility decrements used in other health economic models of ablation were reviewed and based on those reported in Reynolds 2014[74] and GC expert opinion, the utility decrements and durations summarised in Table 24 were applied in the model. Where an estimate of uncertainty was not available, the standard error was assumed to be 20% of the mean.

Table 24: Summary of utility decrements and utility weights used in model

Health State	Utility (SE)	Duration (for decrements)	Source
AF SF health state	Age adjusted general population utility	N/A	Ara 2010[2]
Ischaemic stroke (acute)	0.628 (0.04)	N/A	Tengs 2003,[86] Youman 2003[94]
Post-IS	0.628 (0.04)	N/A	
ICH (acute)	0.628 (0.04)	N/A	
Post-ICH	0.628 (0.04)	N/A	
ICH	0.628 (0.04)	N/A	
Utility decrements			
AF S health state	0.04 (0.017)	Ongoing whilst in state	Berg 2010[7]
Major bleed	0.107 (0.021)[(a)]	2 weeks	Thomson 2000,[87] TA355[48] and TA275[51]
Oesophageal injury	0.5 (0.1)[(a)]	1 year	GC expert advice
Vascular complications, cardiac tamponade and other sever complications	0.1 (0.02)[(a)]	1 month	Reynolds 2014[74] and GC expert advice
Pulmonary vein stenosis	0.1 (0.02)[(a)]	6 months	GC expert advice
Phrenic nerve palsy	0.03 (0.006)[(a)]	1 year	Utility Reynolds 2014[74] and Packer 2013,[60] duration GC expert advice
Atrial tear requiring sternotomy	0.1 (0.02)[(a)]	3 months	GC expert advice
SAEs related to AADs	0.1 (0.02)[(a)]	1 month	Reynolds 2014[74]

(a) Estimated SE, 20% of mean

ISBN: 978-1-4731-4043-1

2.3.9 Resource use and costs

2.3.9.1 Ablation procedures

The cost of ablation is made up of the NHS reference costs[55] for the relevant HRG procedure codes and the additional equipment costs provided by the NHS supply chain catalogue.[56] These costs were fixed in the probabilistic analysis. Capital equipment was not included in the costing as these are not publicly available and the committee stated that in most cases this is provided free of charge by manufacturers as part of a contractual agreement in exchange for the purchase of a minimum volume of equipment.

For all catheter ablation types (that is all except thoracoscopic ablations) the following HRG procedure is included: complex ablation (HRG EY30A & EY30B) and for a proportion of people a trans-oesophageal echocardiogram (HRG EY50Z). The committee acknowledged that different catheter ablation techniques may require different resource use due to differences in procedural time, type of anaesthesia and whether they require an overnight stay and that this may lead to differences in procedural costs which are not accounted in the use of a single NHS reference cost. The NHS reference costs are an average cost of catheter ablation, accounting for the current distribution of catheter ablation techniques within the NHS. The committee suggested that approximately 70% of ablation is RFPP, 30% cryoballoon, and approximately 1-2% RFME and laser ablation. Below is more detail regarding potential variations between the different ablation techniques in terms of procedure resource use.

Procedural time

Studies have reported that cryoballoon ablation can be quicker than RFPP.[1, 18, 73] Observational studies report up to 31 minutes and an RCT reports 25 minutes difference in procedural time.[38] Furthermore, cryoballoon procedure time is reportedly more predictable. Laser ablation may also be a quicker procedure than RFPP and comparable to cryoballoon but this is uncertain as the evidence relates to the third generation of laser equipment which is less established.[31] A reduction in procedure duration may subsequently lead to different procedural costs. With regards to cryoballoon, the committee noted that the “proven” 25 minutes procedural time reduction from the FIRE and ICE RCT[38] and its predictability might equate to a 100% difference in the number of ablation cases that can be completed in an electrophysiology laboratory day. Committee experience suggests 3 to 4 cryoballoon cases can be completed in a day versus a maximum of 2 RFPP cases, with potentially some time spare for a shorter case. We have calculated the potential saving in terms of staff time for cryoballoon relative to RFPP using the reported 25 minutes procedural time saving from FIRE and ICE RCT[38] and the unit costs for each staff member required for a catheter ablation (based on committee advice). This is reported in Table 25 below. Adjusting the reference costs for this difference in procedural time is challenging as the reference costs represent the average cost of all catheter ablation and so they will already account in part for the reduced procedural time for cryoballoon.

Table 25: Staff savings associated with shorter procedure

Staff	Unit cost (per hour) (a)	Cost (per minute)	Number of staff	Total cost (per minute)
Consultant electrophysiologist	£109	£1.82	2	£3.63
Consultant cardiologist	£109	£1.82	1	£0.98
Radiographer	£59(b)	£0.98	1	£0.92
Sedation nurse	£55(c)	£0.92	1	£0.78
Catheter laboratory nurse	£47(d)	£0.78	1	£1.82
Average procedure duration saving (minutes)				25

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Staff	Unit cost (per hour) (a)	Cost (per minute)	Number of staff	Total cost (per minute)
Total saving from shorter procedure				**£203**

(a) PSSRU 2018/2019[15]
(b) Hospital-based scientific and professional staff/Band 7
(c) Hospital-based nurse/Band 7
(d) Hospital-based nurse/Band 6

Anaesthesia

Another area that may influence the procedural cost is the choice of anaesthesia. RFPP is generally done under general anaesthetic and less frequently using conscious sedation. For laser and cryoballoon ablation the use of sedation is more common. The committee noted that the choice of anaesthesia is very variable nationally and can depend on a number of factors unrelated to the ablation technique such as availability of general anaesthesia in a given hospital, physician preference and patient related factors (e.g. contraindications for general anaesthesia or sedation). The impact of using conscious sedation on procedural cost may include eliminating the need for a consultant anaesthetist and an Operating Department Practitioner (ODP), based on an average procedure time of 143 minutes for RFPP in FIRE and ICE RCT[38] this equates to savings of £260 and £83 for each staff member respectively (NHS PSSRU 2018/19 for a consultant physician, £109 per hour and for a Hospital-based scientific and professional staff/Band 5, £35 per hour).[15] This could equate to a saving of £343 in terms of staff time for ablations that do not require general anaesthesia, the cost of the drugs would increase the saving further. A committee member noted that in their hospital the cost of general anaesthesia for one session (4 hours) is £500 including consultant anaesthetist, ODP, drugs and equipment.

Same day discharge

Finally, stakeholders during the guideline consultation reported that national data from NHS Digital Hospital Episode Statistics (HES) (March 2019 to February 2020) suggests that same day discharge is more common for those receiving cryoballoon ablation compared to RFPP. The committee were cautious about the ability of HES data to accurately capture same day discharge and that it may be misleading due to reasons for admission the day before the procedure but discharge the same day as the procedure, transfers, or a less than 23 hour stay. However, they agreed that from their own experience same day discharge may occur more frequently for cryoballoon than with RFPP due to the reduced use of general anaesthetic however they said it varied hugely between hospitals and is very dependent on local discharge policies. Same day discharge may save £742, based on the unit cost of an elective inpatient excess bed day for catheter ablation (weighted average of EY30A and B from NHS Reference costs 2017/2018, inflated to 2018/2019, note excess bed days not reported in 2018/2019).[15, 16]

An alternative way to consider the potential procedural savings associated with cryoballoon compared to other catheter ablation techniques as a result of no general anaesthetic and same days discharge is to consider using the NHS reference costs for day cases as opposed to using the total HRG for catheter ablation. Given the distribution of ablation techniques in current practice and that more cryoballoon ablations are reported to have same day discharge according to HES, the majority of the activity for day cases may be cryoballoon. The different unit costs available in the NHS reference costs for this HRG are below in Table 26.

Table 26: NHS reference costs for catheter ablation

Currency	Currency Description	Total HRG		Elective		Day Case	
		Activity	Unit Cost	Activity	Unit Cost	Activity	Unit Cost

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		Total HRG		Elective		Day Case	
EY30A	Complex Percutaneous Transluminal Ablation of Heart with CC Score 3+	2831	£4,856	2001	£4,838	512	£3,037
EY30B	Complex Percutaneous Transluminal Ablation of Heart with CC Score 0-2	5892	£3,494	3931	£3,751	1858	£2,869
Weighted average cost (based on activity)			**£3,936**		**£4,118**		**£2,905**

Despite the limitations of using the total HRG NHS reference costs for all the catheter ablation techniques, it was agreed that there was insufficient evidence to accurately capture these differences for each procedure to allow for an equitable adjustment of the procedure costs. Therefore in the base case the total HRG NHS reference costs were used for the catheter ablation techniques and a number of sensitivity analyses were conducted specifically relating to the possible savings associated with cryoballoon procedure (for more information see **section 2.3.11**).

In current practice, the trans-oesophageal echocardiogram is conducted pre- or intra-operatively for some (e.g. CHADSVASC >1) or all patients depending on the centre. In the model it was assumed that 50% of people received one, and so the cost was adjusted accordingly. This assumption was explored in a sensitivity analysis by varying proportion (0% and 100%).

See Table 27 for HRG costs for catheter ablation. Note these are total HRGs which include all HRG activity with the exception of excess bed days.

Table 27: Catheter ablation HRG costs use in model

Currency	Currency Description	Activity	Unit Cost
EY30A	Complex Percutaneous Transluminal Ablation of Heart with CC Score 3+	2831	£4,856
EY30B	Complex Percutaneous Transluminal Ablation of Heart with CC Score 0-2	5892	£3,494
Weighted average cost (based on activity)			**£3,936**
EY50Z	Complex Echocardiogram	97961	£257
Weighted average cost (based on 50% having trans-oesophageal echocardiogram)			**£128**
Total procedure costs for endocardial ablation			**£4,064**

Thoracoscopy as defined in our model refers to minimally invasive surgical epicardial ablation. Different approaches can be used; either bilaterally totally thoracoscopic epicardial ablation with radiofrequency or right monolateral totally thoracoscopic epicardial ablation with radiofrequency. There was uncertainty as to which HRG code was most relevant for this procedure. The manufacturers of the thoracoscopy equipment Atricure provided HRG ED31C whereas; a committee member provided a reference of a local business case which utilised HRG ED30C for thoracoscopy. The committee were sceptical that thoracoscopy was accurately captured in either cost as they represent ‘other’ catch all HRG codes. Due to this uncertainty, in the base case the higher cost of ED30C was used, and a sensitivity analysis was conducted using the lower cost from ED31C. See Table 28 for the total HRG unit cost for both codes. Note that this would also affect the cost of hybrid ablation below.

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Table 28: Thoracoscopy ablation HRG costs

Currency	Currency Description	Activity	Unit Cost
ED30C	Complex, Other Operations on Heart or Pericardium, with CC Score 0-4	268	£7,471
ED31C	Standard, Other Operations on Heart or Pericardium, with CC Score 0-4	888	£3,057

Hybrid ablation as defined in our model refers to minimally invasive surgical epicardial ablation and catheter endocardial ablation, based on the study informing this comparator in the NMA.[33] The HRG codes are assumed to be the equivalent of thoracoscopy plus catheter ablation, thus the unit cost would be the sum of the two (Table 29)

Table 29: Hybrid ablation HRG costs

Procedures	Unit cost
Total cost for thoracoscopy ablation	£7,471
Total procedure costs for catheter ablation	£3,057
Total cost for hybrid ablation	**£11,535**

The committee, Dr Scott Gall (laser ablation specialist in Blackpool), and Atricure (manufacturer of thoracoscopic equipment) advised on which equipment from the NHS supply chain catalogue was required for each ablation type. The cost of most of the laser equipment was based on local costs from Dr Scott Gall as list prices from the NHS Supply Chain Catalogue were not identified. As these costs may include locally negotiated discounts, the committee agreed to include a 30% uplift to these costs to account for any potential discounts. This was explored further in a sensitivity analysis (for more information see **section 2.3.11**).

It was noted that cables for point by point ablation can be sterilised and reused and so it was assumed this was done 10 times, the manufacturer instructions suggest this can be done up to 20 times, but based on committee experience this is not done in practice and the sterilising companies will only allow 10 times. For laser ablation the endoscope can be sterilised and reused 10 times, this is based on manufacturer guidance. These costs were adjusted accordingly. Dr Gall noted that the cost of sterilising is primarily the cost of the sterilising box, which was estimated at £149. This box can be used for 100 to 150 times; therefore, it costs at most £1.49 per use. In the model this unit cost was added to each item that can be reused.

For thoracoscopy the equipment is different for each approach and therefore an average of the total cost of the two approaches was used in the model. In a hybrid procedure the thoracoscopy approach could be either of the following three:

- Bilateral totally thoracoscopic epicardial ablation with radiofrequency
- Right monolateral totally thoracoscopic epicardial ablation with radiofrequency
- Subxiphoid or trans-diaphragmatic totally thoracoscopic epicardial ablation with radiofrequency

The equipment is different for each approach and therefore an average of the total cost of the three approaches was used in the model. For the catheter ablation element of the hybrid procedure it was assumed to be RF PP and so the total cost of the equipment for that procedure was used in the model.

The committee noted that there was significant variability in the equipment costs locally compared to those listed in the NHS supply chain catalogue. These differences may be down to locally negotiated prices with manufacturers. A sensitivity analysis was conducted where all catheter ablation techniques were assumed to be equal to the cost of RFPP (for more information see **section 2.3.11**). For laser ablation, the circular mapping catheter and

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accompanying cable are recommended for this procedure in the NICE IPG563.[47] Dr Gall noted however that in his experience it is not necessary. A sensitivity analysis was conducted excluding this catheter and cable (for more information see **section 2.3.11**).

See Table 30 for a summary of the total equipment costs, these costs exclude VAT. A detailed breakdown of the costs is available in Appendix A: Table 53.

Table 30: Total equipment costs

Intervention	Total equipment cost (a)
RF PP ablation	£ 3,643
RF ME ablation	£ 5,078
Cryoballoon ablation	£ 5,846
Laser ablation	£ 6,762(b)
Thoracoscopy	£ 5,088
Hybrid ablation	£ 8,795

(a) including sterilising where relevant
(b) including 30% uplift in costs provided by Dr Gall from single centre.

Summarised below are the total costs for each intervention, including HRG and equipment costs.

Table 31: Total ablation costs

Intervention	Cost
RF PP ablation	£7,707
RF ME ablation	£9,143
Cryoballoon ablation	£9,911
Laser ablation	£10,826
Thoracoscopy	£12,559
Hybrid ablation	£20,329

2.3.9.2 Drugs

Antiarrhythmic drugs

In the model, for who undergo an ablation procedure, a proportion of people (GC assumption: 50%) will continue AADs for 3 months post ablation (known as the blanking period).

Once AF symptoms recurred, whether they were assigned to AADs or an ablation intervention or cross over to ablation, it was assumed that only a proportion of patients in the model would continue to receive AADs (switch to another AAD) or start AADs after ablation. The committee assumed two thirds of people would switch or re-start AADs following AF recurrence or after experiencing a stroke. Due to the uncertainty regarding this, a sensitivity analysis was conducted where 0% and 100% take AADs following AF recurrence or after an event.

Note, there is no opportunity to go back to a symptom free state after symptom recurrence or a stroke or ICH. This is a simplification of reality, but there was insufficient data to populate sequencing of treatment. This assumption is likely to bias in favour of ablation as there are more people experiencing AF recurrence with AADs.

The AADs used in the clinical trials that inform the NMA do not provide sufficient detail to calculate the weighted average AADs used. In most cases, a list of approved drugs was provided and the choice of AAD was at the discretion of the investigator. In all cases they

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were oral AADs. The AADs that were available were the following alone and sometimes in combination: amiodarone, quinidine, disopyramide, flecainide, propafenone, cibenzoline, dofetilide, and sotalol. Dosage was either defined or reference to local guidelines was made. The most commonly cited AADs were: amiodarone, flecainide, propafenone, and sotalol. These also represent frequently prescribed drugs in NHS current practice for second or third line rhythm control.

On this basis, the unit cost for AADs in the model was assumed to be equal to the mean unit costs of these four drugs, using BNF recommended dosages.

In Table 32 is a summary of the daily cost of AADs used in the model. The unit costs are taken from BNF.[9]

Table 32: Unit cost of AADs

Drug	Maximum daily dosage	Cost per day	Cost/ year (£)
Amiodarone	200mg	£0.12	£ 42.50
Flecainide acetate	300mg	£0.20	£ 74.28
Propafenone hydrochloride	900mg	£0.49	£ 179.34
Sotalol hydrochloride	320mg	£0.35	£ 126.97
Average cost of AADs		£0.29	£ 105.77

Source: Dosage and unit cost taken from BNF online, accessed July 2020[9]

There are some monitoring costs associated with these specialist drugs. Based on information provided in the BNF and GC expert advice, the following monitoring costs were included: annual cardiology appointment when taking AADs, bi-annual liver and thyroid function tests for those taking amiodarone (25% of people as using a straight average of 4 drugs) and annual ECG for those taking propafenone (25% of people as using a straight average of 4 drugs).

Table 33: Monitoring costs for AADs

Item and frequency	Unit cost	Source
Annual cardiology appointment (HRG: WF01A)	£135	NHS reference costs 2018-19[55]
Electrocardiogram (HRG EY51Z) for those on propafenone	£49	NHS reference costs 2018-19[55]
Liver and thyroid function tests, 6 monthly for those on amiodarone (HRG DAPS05)	£3	NHS reference costs 2018-19[55]
Total annual AAD monitoring costs	**£150**	Based on assumptions on frequency outlined in table

Anticoagulants

The committee noted that current practice in terms of whether anticoagulants are prescribed depends on whether or not people are already receiving anticoagulants. Those who are not currently receiving anticoagulants will be given them for a short period prior before and after the ablation procedure (4 weeks prior and 6 weeks post). For those who are already receiving anticoagulants they will continue these after the procedure. The committee noted that the decision on whether a person received anticoagulants is driven by the stroke risk level and in current practice they will continue to receive them if their CHADSVASC score is >1. The reported mean CHADSVASC score was >1 in most of the trials included in the NMA. The committee considered that 70% of these people would be receiving anticoagulants.

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For costing purposes, a weighted average of the anticoagulants used in current practice in the UK was used and their relative costs applied.

Two sources were identified to estimate the respective proportion of anticoagulants currently prescribed in the NHS in England. The first source is the Prescription Cost Analysis 2018. This provides the total number of prescriptions of each drug in England for that year. It is important to note that it does not discriminate by prescription indication and so for anticoagulants, some of the prescriptions will be for other indications such as venous thrombotic embolism and other approved indications.

The second source is the NHS BSA Medicines Optimisation Dashboard (April-June 2018 data)[54] which provides the number of prescription items for apixaban, dabigatran etexilate, edoxaban and rivaroxaban as a percentage of the total number of prescription items for apixaban, dabigatran etexilate, edoxaban, rivaroxaban and warfarin sodium. In the specifications for this source it is noted that the comparator is likely to highlight prescribing of DOACs for atrial fibrillation, and possibly treatment and prevention of deep vein thrombosis and pulmonary embolism in primary care. Use of DOACs for prevention of venous thromboembolism post hip or knee surgery will be mostly or entirely within secondary care and therefore not reflected in the comparator.

Weightings from both sources are summarised in Table 34 below:

Table 34: Weighting of anticoagulants

Drug	Weighting from Prescription Cost Analysis	Weighting from NHS BSA Medicines Optimisation Dashboard
Apixaban	26%	n/a
Edoxaban	2%	n/a
Dabigatran	3%	n/a
Rivaroxaban	22%	n/a
All DOACs	53%	52%
Warfarin	47%	48%

Source: Prescription Cost Analysis 2018 and NHS BSA Medicines Optimisation Dashboard[30]
Abbreviations: NA=not available.

There was little difference between the two sources in terms of the percentage of warfarin prescriptions versus DOAC prescriptions. Therefore, for the purposes of this model, the proportion receiving each drug was taken from the Prescription Cost Analysis as this provided detail on individual DOACs.

The calculations of the daily unit cost for anticoagulation are reported in Table 35. This includes the unit cost of each drug based on dosage and costs reported the BNF as well as the weighting from the Prescription Cost Analysis. For warfarin a maintenance dose of 3-9mg is recommended. For the model the committee assumed an average dose of 5mg daily.

Table 35: Unit cost of anticoagulants

Drug	Daily dosage	Unit cost per month	Unit cost per year
Apixaban	5 mg BD	£58	£694
Edoxaban	60mg OD	£52	£621
Dabigatran	110/150mg BD	£53	£639
Rivaroxaban	20mg OD	£55	£657
Warfarin	5mg OD	£0.48	£6

Source: Dosage and unit cost taken from BNF online, accessed July 2020[9]. For warfarin the committee assumed an average daily dose of 5mg.Weighting using Prescription Cost Analysis 2018 data.[30]

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In addition to the drug costs for anticoagulants, the cost of anticoagulation clinics for those taking warfarin needs to be accounted for. The estimated annual unit cost for this was £258. This was taken from the cost reported in the NICE AF CG180 guideline (2014) cost impact analysis report and was inflated to 2018/19 cost year using NHS cost inflation index. This cost will be applied to 47% of the patients receiving anticoagulants to reflect the weighting from the Prescription Cost Service.

2.3.9.3 Serious adverse events

The unit costs for SAEs were calculated by considering the excess bed days or hospitalisation the person may experience because of the serious adverse event. This is a similar approach to that taken in another economic analysis of ablation by Reynolds 2014.[74] The unit costs for hospitalisations (excess bed days following ablation procedures and critical care stays) were taken from the NHS reference 2017/2018 costs[16] as the 2018/2019 NHS reference costs no longer report excess bed days. These were inflated to 2018/2019 costs using NHS cost inflation index.[15]

For phrenic nerve injury, as done in Reynolds 2014,[74] it was assumed that no additional hospitalisation would occur but rather the person would require a CT scan and an additional cardiology outpatient appointment (NHS reference costs 2018/2019[55]).

For SAEs related to AADs, it was assumed that these would be equal to the cost of vascular complications /other severe complications following catheter ablation.

Table 36: Serious adverse events costs

Adverse event costs		
Oesophageal injury	£24,417	Calculated assuming 14 days in ICU and 7 excess days (ward). NHS reference costs HRG: CCU06 (critical care) and EY30A/B (weighted elective and non-elective excess bed days)
Cardiac tamponade	£1,977	Calculated assuming 3 excess days. NHS reference costs: EY30A/B (weighted elective and non-elective excess bed days).
Pulmonary vein stenosis	£2,636	Calculated assuming 4 excess days. NHS reference costs: EY30A/B (weighted elective and non-elective excess bed days)
Vascular complication	£1,318	Calculated assuming 2 excess days. NHS reference costs: EY30A/B (weighted elective and non-elective excess bed days)
Other severe complication	£1,318	
Persistent phrenic nerve palsy	£240	NHS reference costs Assume CT scan (RD20A/RD21A) and outpatient cardiology visit (WF01A/B) (as per Reynolds 2014)
Atrial tear requiring sternotomy	£7,471	NHS reference costs. Total HRG for ED30C
AADs SAEs	£1,318	Assume cost equal to vascular complications /other severe complications above

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2.3.9.4 Health states

2.3.9.4.1 Ischaemic stroke & ICH

Costs of stroke were based on Xu 2018[93] who undertook a patient level simulation using audit data from the UK Sentinel Stroke National Audit Programme to generate estimates of the financial burden of Stroke to the NHS and social care services. The estimates of costs attributable to stroke from resulting health and social care provision were estimated up to 5 years after the first stroke. The total of 1-year and 5-year costs were reported with NHS and social care costs being reported separately. Social care costs included both local authority and private social care costs. Recurrent strokes were also included in the costs.

As this analysis takes an NHS and personal social services perspective, non-publicly funded costs should not be included. A recent report published by the Stroke Association (Patel 2017[65]) used the assumption that approximately 50% of social care costs are publicly funded. Therefore, an assumption was made in the model that 50% of these costs were publicly funded. The costs of the post-event state were calculated based on the difference in costs between the 1-year and 5-year period, so as not to double count, and the difference in average life-years between years 1 and 5 in order to derive the cost per-life-year. All published costs above were inflated to 2018/19 costs using the NHS cost Inflation Index.[15]

In addition, it was possible to disaggregate the ischaemic and haemorrhage stroke costs as well as by severity in the SSNAP audit, thus allowing us to assign costs for ischaemic stroke and ICH by initial NIHSS score. The committee noted that the severity of strokes in people with AF compared to others. The committee assumed that on average ischaemic strokes had an initial NIHSS score of 5-15 and haemorrhage stroke of 16-20. This is supported by a costing report by the stroke association[65], the Dublin stroke audit,[29] and a stroke audit in Surrey, England.[28]

Furthermore, the SNAPP audit also reports the costs associated with those who die before discharge by stroke type. This was used to capture the costs of those who die in the first 30 days of having a stroke. A summary of the costs used in the model are in Table 37.

In the decision tree, strokes were assumed to be IS for costing purposes. Instead of halving the 1-year cost of stroke, it was deemed appropriate to assume that the majority of costs in the first year happen in the first 6 months. Therefore, the annual cost of stroke after year 1 was halved and removed from the first-year stroke cost to obtain a higher cost. This was done to ensure no costs were lost once people entered the Markov model in the post-stroke health state

Table 37: Ischaemic stroke and ICH costs used in model

Health state/event	Annual cost	Source
IS	£22,796	Xu 2018 1 year costs for IS with NIHSS (5-15). 50% of social care costs removed
Post-IS	£7,296	Xu 2018 5 year costs adjusted to remove 1 year cost and annualised for IS with NIHSS (5-15). 50% of social care costs removed
ICH	£30,530	Xu 2018 1 year costs for HS with NIHSS (16-20). 50% of social care costs removed
Post-ICH	£14,414	Xu 2018 5 year costs adjusted to remove 1 year cost and annualised for HS with NIHSS (16-20). 50% of social care costs removed
Fatal IS	£14,338	Xu 2018 Total cost for those dead before discharge IS
Fatal ICH	£14,315	Xu 2018 Total cost for those dead before discharge HS

Source/Note: All published costs that were inflated above were inflated to 2017/18 costs using the NHS cost Inflation Index (PSSRU 2019).[15]

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A sensitivity analysis was conducted where the costs of ICH were taken from the anticoagulation model conducted for this guideline update.

2.3.9.4.2 Major bleed costs

These were assumed to be primarily gastrointestinal bleeds and therefore an average of NHS reference costs 2018/2019[55] for all categories of gastrointestinal bleed admission (weighted by number of attendances including excess bed days) was used; this is shown in **Table 38**. The HRG codes were: FD03A; FD03B; FD03C; FD03D; FD03E; FD03F and FD03G. Due to lack of excess bed day reporting in the 2018/2019 NHS reference costs, the data for excess bed days was taken from NHS reference costs 2017/2018[16] and inflated to 2018/2019 prices using NHS cost inflation index.[15]

Table 38: Major bleeding costs based on gastrointestinal bleed

Calculated combining short and long stay	Activity	Weighted average
Long stay weighted average (including excess bed days)	21,616	£2,961
Short stay weighted average	11,284	£573
Total weighted average		£2,142

2.3.10 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohorts age as a respective risk factor for mortality. Baseline utility was also time dependent and was conditional on the number of years after entry to the model.

Patients start in cycle 0 in an alive health state. Patients moved to the dead health state at the end of each cycle as defined by the mortality transition probabilities.

All rates were converted into transition probabilities for the respective cycle length (1 year in the base case) before inputting into the Markov model. The above conversions were done using the following formulae:

$$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$$	Where *P*=probability of event over time *t* *t*=time over which probability occurs (1 year)

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent in the alive state of the model was weighted by a utility value that is dependent on the time spent in the model and the treatment effect. A half-cycle correction was applied. QALYs were then discounted to reflect time preference (discount rate 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle, C(t), were calculated in the same way as QALYs. Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discounting formula:

$$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$$	Where: *r*=discount rate per annum *n*=time (years)

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2.3.11 Sensitivity analyses

Cohort settings:

SA1&2: Proportion receiving AADs post event

Two sensitivity analyses were conducted where the proportion of people receiving AADs following AF symptom recurrence or an event was changed from two thirds (67%) to 0% and 100%.

Decision tree parameters:

SA3&4: Vary baseline (AAD) AF recurrence

To explore the influence of baseline AF recurrence on the results of the model, this was varied to 50% and 90%.

SA5: Vary baseline (AADs) mortality, using NMA data

A sensitivity analysis was conducted using the transition probability generated from WinBUGS (including using the CODA for the probabilistic analysis) for baseline mortality in the decision tree, rather than the base case of double general population mortality. See Table 39.

Table 39: Baseline mortality (AADs)

Mean log-odds (95% CI)	Transition probability
-3.612 (-5.47; -2.281)	2.6%

When using NMA data, in the deterministic analysis the mean log odds ratio generated from the NMA was used. In the probabilistic analysis, the CODA for the log odds ratio was used from WinBUGS. Please note log odds ratios were used in the model to ensure when converted to probabilities they remain between 0 and 1.

SA6: Apply stroke treatment effects for RF ME and cryoballoon ablation, using NMA data

A sensitivity analysis was conducted using the NMA data for stroke for the two significant results: RF ME, and cryoballoon ablation. See Table 40 for data used in this sensitivity analysis. When using NMA data, in the deterministic analysis the mean log odds ratios generated from the NMA were used. In the probabilistic analysis, the CODA for the log odds ratio was used from WinBUGS. Please note log odds ratios were used in the model to ensure when converted to probabilities they remain between 0 and 1.

Table 40: Transition probabilities for stroke sensitivity analysis

Intervention	Mean logOR (95% CI)	Transition probability
RF PP ablation	N/A	0.7%
RF ME ablation	4.041 (0.140; 9.918)	29.2%
Cryoballoon ablation	1.945 (0.213; 4.161)	4.8%
Laser ablation	N/A	0.7%
Thoracoscopy	N/A	0.7%
Hybrid ablation	N/A	0.7%

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SA7: Remove increased stroke risk associated with RF ME

Although the NMA indicated that there was an increased risk of peri-procedural stroke for RF ME, the committee noted that the technology has been modified in recent years to reduce the peri-procedural stroke risk but there is no RCT evidence supporting this yet. To explore this uncertainty, a sensitivity analysis was conducted where all comparators had a stroke transition probability equal to AADs (0.7%).

SA8: Apply mortality treatment effects for RFPP, using NMA data, and thoracoscopy and hybrid = double baseline

A sensitivity analysis was conducted where the NMA data for RF PP was used for mortality and the mortality for thoracoscopy and hybrid was double that of the baseline mortality (AADs).

As with stroke, when the NMA data was used, in the deterministic analysis the mean log odds ratios generated from the model were used. In the probabilistic analysis the CODA for the log odds ratio was used from WinBUGS. Please note log odds ratios were used in the model to ensure when converted to probabilities they remain between 0 and 1.

Table 41: Transition probabilities for mortality sensitivity analysis

Intervention	Mean logOR (95% CI)	Transition probability
RF PP ablation	-0.455 (-1.646; 0.695)	0.76%
RF ME ablation	N/A	1.20%
Cryoballoon ablation	N/A	1.20%
Laser ablation	N/A	1.20%
Thoracoscopy	N/A	2.40%
Hybrid ablation	N/A	2.40%

SA9&SA10: Proportion crossing over from AAD to ablation in first year

A sensitivity analysis was conducted where the proportion of people crossing over from AAD to ablation after AF symptom recurrence in first year was reduced to 25% and increased to 100%.

SA11&12: Proportion having a repeat ablation

A sensitivity analysis was conducted where the proportion of people having a repeat ablation after AF symptom recurrence was varied to 0% and 100% respectively.

SA13: Efficacy of repeat ablation data

A sensitivity analysis was conducted using only the Pokushalov 2013[69] data (relative risk = 2).

Markov model parameters:

SA14: AF recurrence beyond 1 year: no AF recurrence

An extreme scenario analysis was conducted were no further AF recurrence was modelled beyond 1 year. That is, all those free from AF symptoms at the end of year one, remain in that state until they experience an event (ICH or ischaemic stroke) or die.

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SA15: AF recurrence beyond 1 year: CABANA data and no AF recurrence after 4 years

A sensitivity analysis was conducted where only the CABANA data was used, and after 4 years no further AF recurrence occurs.

SA16: AF recurrence beyond 1 year: AAD adjusted for 0% cross over

As the CABANA[62] AAD arm included 39% of people crossing over to ablation after AF symptom recurrence, the AF recurrence data for this arm may underestimate the true probability of AF recurrence if they had only had AADs. A sensitivity analysis was conducted where the CABANA AAD AF recurrence data was adjusted to account for this underestimation. This was done by calculating the relative probabilities of AF recurrence beyond year one, using the probability of AF recurrence from the NMA (which gave us the AF recurrence at 1 year with 0% crossing over) as the starting point and the CABANA data. The resulting transition probabilities are outlined in Table 42 below. Please note that these transition probabilities were not made probabilistic in this sensitivity analysis as there was insufficient data to do so.

Table 42: Transition probabilities for mortality sensitivity analysis

Year	Probability AF recurrence (CABANA data + constant hazard assumed after year 4)		Probability AF recurrence for AAD (assuming 0% cross over) (a)
	Ablation	AAD (this includes 39% crossing over to ablation)	
1	36%	59%	73%
2	12%	14%	18%
3	9%	10%	13%
4	5%	7%	9%
5 to 40	Same as above respectively. Post year 4 we assume a constant hazard.		

a) *Year 1 using NMA AAD AF recurrence data. Year 2,3 and 4 are the relative probabilities compared to CABANA data.[62]*

SA17: Stroke risk reduction for AF symptom free health state

A sensitivity analysis was conducted where the risk reduction from the AFFIRM trial was applied to those in the AF symptom free health state. This was to reflect a potential link between ablation, reduced symptoms of AF and a reduced stroke risk, as was reported in the observational studies. The stroke risk reduction applied for AF symptom vs AF symptom free state was 1.6 (95%CI: 1.11; 2.3).[82] In the probabilistic analysis, a Lognormal distribution was applied to this hazard ratio.

SA18: ICH beyond a year, HR of warfarin vs no treatment equal to 1

As noted in the inputs section, there was no HR available for no treatment vs warfarin for ICH, therefore it was assumed to be equal to the reciprocal of the HR for warfarin vs no treatment for other clinically relevant bleeds (see Table 20), as was done in the Sterne 2017 HE analysis. Due to the uncertainty with this assumption, a sensitivity analysis was conducted where the HR of warfarin vs no treatment was equal to 1.

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Utility inputs:

SA19: Utility data AF symptom recurrence use Reynolds 2009

Due to the uncertainty regarding the choice of data the utility decrement for AF symptom recurrence an alternative source was used in a sensitivity analysis: 0.046 (95% CI: 0.014;0.095) from Reynolds 2009.[76]

Cost inputs:

SA20: Cost of thoracoscopy procedure

A sensitivity analysis was conducted where the lower cost from HRG code ED31C was used instead of ED30C.[55]

Table 43: Cost of thoracoscopy sensitivity analysis

Intervention	Base case cost(a)	Sensitivity analysis cost(b)
Thoracoscopy	£12,559	£8,145
Hybrid ablation	£20,329	£15,916

(a) Using HRG ED30C procedure cost: £7,471
(b) Using HRG ED31C procedure cost: £3,057

SA21: Cost of laser ablation equipment (unadjusted)

The costs of laser ablation equipment (pass through costs) were in part provided by Dr Scott Gall and represent local cost rather than national costs. National costs from the NHS Supply Chain Catalogue were not identified. These local costs may include discounting negotiated by the hospital and therefore may not reflect the nationally available costs. In the base case these were inflated by 30% to account for this. Due to the uncertainty of whether or not this uplift is representative of the true undiscounted values, a sensitivity analysis was conducted where the equipment costs were unadjusted. The total costs of laser ablation decreased from £10,826 in the base case to £9,562 in this sensitivity analysis.

SA22: Cost of laser ablation equipment (excluding circular mapping catheter)

The costs of laser ablation equipment included in the base case included a circular mapping catheter and associated cable which are recommended for this procedure in the NICE IPG563.[47] Dr Gall noted however that in his experience it is not necessary to use this catheter or cable. A sensitivity analysis was conducted excluding these from the costing. The total costs of laser ablation decreased from £10,826 in the base case to £9,875 in this sensitivity analysis.

SA23: Change NHS reference costs for cryoballoon and RFPP

The cryoballoon procedure NHS reference cost was changed from total HRG to day case. This was done to account for more cases being done as day cases compared to other techniques. The RFPP procedure cost was changed to elective cases. All other catheter ablation techniques were kept unchanged. The total cost of cryoballoon decreased from £9,911 to £5,846 and the cost of RFPP increased from £7,707 to £7,889.

SA24: Adjust cost of catheter ablation to equal RF PP

An exploratory sensitivity analysis was conducted where the cost of all catheter ablation was made equal to that of RFPP. This was done as there was some concern expressed by the committee that their locally negotiated costs for ablation equipment varied and were at times lower than the costs reported in the NHS supply chain catalogue. Thus, this exploratory

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sensitivity analysis was done to see what the most cost effective intervention would be if all the catheter ablation techniques cost the same.

SA25: Cost of ICH event using an alternative source

A sensitivity analysis was conducted where the costs of ICH were taken from the anticoagulation model conducted for this guideline update. The management costs for ICH were derived from annual 1st and post 2nd year cost estimates in Wardlaw 2006[90]; this paper provided estimates for patients in dependent and independent states, which we averaged using a proportion reported in Rosand 2004[79]. See Table 44. These costs were inflated to 2018/2019 prices using the NHS cost inflation index (PSSRU 2019[15])

In the probabilistic analysis, a beta distribution was assumed for the proportion of patients in independent states.

Table 44: ICH costs used in models

Event	Mean	Source
First year - dependent state	£31,004	Wardlaw 2006
First year - independent state	£5,175	Wardlaw 2006
Second year onwards - dependent state	£15,731	Wardlaw 2006
Second year onwards - independent state	£1,219	Wardlaw 2006
Proportion of patients in independent state (GOS >3)*	0.405 (SE=0.024)	Rosand 2004
ICH management cost (year 1)	£20,543	Average of first year dependent and independent using proportion patients independent
ICH management cost (after year 1)	£9,854	Average of first year dependent and independent using proportion patients independent

SA26&27: Vary proportion receiving trans-oesophageal echocardiogram (TOE)

Sensitivity analyses were conducted where the proportion of people who have a TOE was varied to 0% and 100% respectively to reflect the variability in current practice.

NHS reference case edits:

SA28: Discounting rate 1.5%

As recommended in the reference case, a sensitivity analysis using a discount rate of 1.5% for costs and health effects was conducted.

SA29: 5-year time horizon

A deterministic sensitivity analysis was conducted using a 5-year time horizon rather than a lifetime, in order to compare our model results to other published health economic analyses of ablation procedures.

Data validation:

SA30&31: Validating the utility data in the model with CABANA EQ5D data

No direct utility data was available by AF symptom health state for people who had received our interventions of interest. Therefore, indirect utility values were used. In this probabilistic

ISBN: 978-1-4731-4043-1

sensitivity analysis we validate the difference in utility values we generate in our model for RF PP versus AAD (with cross over to RFPP) by comparing them to the difference in EQ5D reported in CABANA. This was done by dividing the total QALYs by the life years for years 1 to 5 and comparing the resulting utility to that reported in CABANA. This sensitivity analysis was done using both the basecase data and using the Reynolds utility decrement for AF symptom health state (SA19). To accurately reflect the CABANA trial, the proportion of people having a repeat ablation and crossing over from AAD to ablation was adjusted to that reported in the trial (34% and 39% respectively). Furthermore, if the results of the model are sensitive to SA16 (adjusting the ADD AF recurrence post year 1 for 0% cross over) then this was included as part of this sensitivity analysis.

Table 45: CABANA EQ-5D data[40]

Year	Difference in utility between ablation and AAD (95% CI)
Year 1	0.0260 (0.012 to 0.040)
Year 2	0.0220 (0.007 to 0.036)
Year 3	0.0230 (0.007 to 0.040)
Year 4	0.0100 (-0.007 to 0.027)
Year 5	0.0150 (0.005 to 0.036)
All follow up	0.0200 (0.010 to 0.031)

An extension of this validation exercise was conducted in SA35 below.

Threshold analyses:

In these analyses one input parameter is varied until the conclusions of the model results change. This was done deterministically to identify the value at which the results changed. Once the value was identified, the model was run probabilistically using this new value to get an estimate of uncertainty.

SA32: Threshold analysis on proportion crossing over to ablation after AAD in year 1

A threshold analysis was conducted to see what the proportion of crossover from AAD to ablation would need to be in the first year for the conclusions of the model to change.

SA33: Threshold analysis on the procedural cost of cryoballoon ablation

A threshold analysis was conducted to see what reduction in procedural costs for cryoballoon would be needed for the conclusions of the model to change.

SA34: Threshold analysis on utility decrement for AF symptom health state

A threshold analysis was conducted to see what the utility decrement for the AF symptom health state would need to be in order for the difference in utility values we generate in our model for RFPP versus AADs (crossing over to RFPP) to be similar to the difference in EQ5D reported in CABANA (as done is SA30).

SA35: AF S utility decrement from SA34

The model was rerun changing the utility decrement for AFS using the value identified in SA34. The probabilistic results were compared with the basecase probabilistic results to see whether this led to a change in the model conclusions.

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2.3.12 Model validation

The model was developed in consultation with the committee; model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NGC; this included systematic checking of the model calculations.

As part of model validation, probabilistic and deterministic results were compared. There was some difference between the two sets of results, this was explored by using hazard ratios for AF recurrence (NMA data) rather than log HR. The reason for this was because Markov models are by nature non-linear, as are logHR, and thus by using HR instead, the difference between the probabilistic and deterministic is expected to be less pronounced. This adjustment did reduce the difference between the results. Small differences remained but these differences did not change the conclusion of the results. As expected, in instances of non-linearity, the ICERs are greater in the probabilistic compared to the deterministic results. The probabilistic results are the most reflective of the evidence are these are reported in the results.

2.3.13 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$ Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	Cost effective if: • ICER < Threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary\ Benefit(X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$ *Where: λ = threshold (£20,000 per QALY gained)*	Cost effective if: • Highest net benefit

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Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy.

The difference in the mean NMB between the interventions and the baseline comparator (AADs cross over to RFPP) is equal to the incremental net benefit (INMB);

$NMB_A - NMB_B = INMB$ *Where A = ablation intervention, B baseline comparator (AADs cross over to RFPP)*	Cost effective compared to AAD (cross over RFPP) if: • INMB is positive

INMB is very useful when comparing more than two strategies. If the INMB is positive, then the intervention is cost effective compared to AAD (cross over to RFPP).

Results are also presented graphically where incremental costs and QALYs for each comparator compared to AAD (cross over RFPP) are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

2.3.14 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[52] sets out the principles that committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have several interventions, we use the NMB to rank the strategies on the basis of their relative cost effectiveness. The highest NMB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained.

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2.4 Results

2.4.1 Base case

The base case probabilistic results are reported in Table 46 and Table 47 and shown graphically in Figure 4. Breakdowns of clinical events and costs are presented in Table 48 and Table 49.

In the base case analysis, RFPP ablation was the most cost-effective option both at a threshold of £20,000 per QALY and £30,000 per QALY as it had the highest net monetary benefit, with a probability of being the most cost-effective option of 98% and 97% respectively.

A full incremental analysis was also conducted and is depicted graphically in Figure 4. Interventions that were ruled out by dominance were AAD (RFME), , AAD (thoracoscopy), AAD (hybrid), RF ME, laser, thoracoscopy, cryoballoon and hybrid, they were all dominated by AAD (RFPP) or RF PP. AAD (laser) and AAD (cryoballoon) were ruled out as they were subject to extended dominance. The ICER was estimated between the remaining non-dominated interventions as represented by the lines. The ICER for RFPP versus AAD (RFPP) was £9,764.

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Table 46: Base case probabilistic results and NMB at £20,000

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
AAD RFPP	£42,904	£28,606	21.84	14.77	15.65	10.84	£188,184	6	2	6	1%
AAD RFME	£44,262	£29,828	21.84	14.77	15.63	10.83	£186,675	8	5	9	0%
AAD Cryo	£44,181	£29,867	21.85	14.78	15.66	10.84	£186,984	7	5	9	0%
AAD Laser	£44,763	£30,424	21.88	14.79	15.67	10.85	£186,530	9	5	9	0%
AAD Thora	£45,423	£31,383	21.55	14.62	15.50	10.76	£183,796	10	9	10	0%
AAD Hybrid	£50,005	£35,881	21.63	14.66	15.54	10.78	£179,631	12	11	12	0%
RF PP	£48,900	£33,891	23.24	15.47	16.68	11.38	£193,725	1	1	1	98%
RF ME	£51,314	£36,091	23.21	15.45	16.62	11.34	£190,809	3	2	7	0%
Cryoballoon	£51,191	£36,178	23.24	15.47	16.67	11.38	£191,382	2	2	6	0%
Laser	£52,262	£37,242	23.24	15.47	16.67	11.37	£190,251	4	2	9	1%
Thoracoscopy	£52,823	£37,963	23.10	15.38	16.62	11.35	£188,938	5	3	9	0%
Hybrid	£61,083	£46,200	23.10	15.38	16.60	11.33	£180,447	11	11	12	0%

Table 47: Base case probabilistic results and NMB at £30,000

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£30K	Rank @£30K	Rank @£30K LCI	Rank @£30K UCI	% Rank 1 (CE @£30K)
AAD RFPP	£42,904	£28,606	21.84	14.77	15.65	10.84	£296,579	6	5	7	0%

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Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£30K	Rank @£30K	Rank @£30K LCI	Rank @£30K UCI	% Rank 1 (CE @£30K)
AAD RFME	£44,262	£29,828	21.84	14.77	15.63	10.83	£294,927	9	7	10	0%
AAD Cryo	£44,181	£29,867	21.85	14.78	15.66	10.84	£295,410	7	6	0	0%
AAD Laser	£44,763	£30,424	21.88	14.79	15.67	10.85	£295,007	8	6	10	0%
AAD Thora	£45,423	£31,383	21.55	14.62	15.50	10.76	£291,385	11	10	11	0%
AAD Hybrid	£50,005	£35,881	21.63	14.66	15.54	10.78	£287,387	12	11	12	0%
RF PP	£48,900	£33,891	23.24	15.47	16.68	11.38	£307,533	1	1	2	97%
RF ME	£51,314	£36,091	23.21	15.45	16.62	11.34	£304,258	3	2	5	0%
Cryoballoon	£51,191	£36,178	23.24	15.47	16.67	11.38	£305,162	2	2	5	0%
Laser	£52,262	£37,242	23.24	15.47	16.67	11.37	£303,997	4	2	6	2%
Thoracoscopy	£52,823	£37,963	23.10	15.38	16.62	11.35	£302,389	5	2	5	1%
Hybrid	£61,083	£46,200	23.10	15.38	16.60	11.33	£293,771	10	6	12	0%

Table 48: Event breakdown

Intervention	First year			Post year 1			
	Stroke	AADs SAEs	Ablation SAEs	IS	ICH	Major bleeds	AADs SAEs
AAD RFPP	7	46	31	134	107	110	705
AAD RFME	11	46	31	133	107	110	708
AAD Cryo	7	46	33	134	107	110	708
AAD Laser	7	47	37	134	107	110	713
AAD Thora	7	45	125	132	106	109	657

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Intervention	First year			Post year 1			
AAD Hybrid	7	46	125	132	106	109	675
RF PP	7	12	68	143	115	117	542
RF ME	14	12	69	142	114	117	545
Cryoballoon	7	12	73	143	115	117	545
Laser	7	12	75	143	115	117	549
Thoracoscopy	7	9	174	142	114	117	498
Hybrid	7	10	176	142	114	117	514

Table 49: Cost breakdown

Intervention	First year costs per person									Health state costs (post 1 year, per person)				
	Intervention cost	Drug cost	Stroke cost	SAEs cost	AF SF costs	AF S costs	IS costs	Post-IS costs	ICH costs	Post-ICH costs	IS fatal costs	ICH fatal costs	Bleeding costs	AAD SAE costs
AAD RFPP	£4,541	£458	£138	£178	£3,498	£7,859	£2,603	£9,199	£2,261	£10,200	£321	£484	£236	£929
AAD RFME	£5,350	£458	£215	£178	£3,460	£7,871	£2,594	£9,750	£2,253	£10,162	£320	£482	£236	£933
AAD Cryo	£5,782	£458	£138	£173	£3,464	£7,915	£2,605	£9,203	£2,263	£10,205	£322	£485	£236	£933
AAD Laser	£6,298	£458	£138	£180	£3,414	£8,000	£2,609	£9,208	£2,265	£10,211	£322	£485	£236	£940
AAD Thora	£7,269	£457	£138	£608	£3,920	£7,114	£2,566	£9,123	£2,229	£10,107	£317	£477	£232	£866
AAD Hybrid	£11,647	£457	£138	£609	£3,751	£7,395	£2,577	£9,142	£2,239	£10,130	£318	£479	£233	£890
RF PP	£9,577	£508	£138	£274	£3,911	£7,338	£2,791	£9,524	£2,418	£10,594	£345	£518	£252	£714
RF ME	£11,070	£508	£276	£275	£3,856	£7,320	£2,771	£10,495	£2,400	£10,516	£342	£514	£251	£719
Cryoballoon	£11,857	£508	£138	£266	£3,876	£7,387	£2,791	£9,524	£2,418	£10,594	£345	£518	£252	£718
Laser	£12,888	£509	£138	£281	£3,825	£7,456	£2,791	£9,524	£2,418	£10,594	£345	£518	£252	£724

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Intervention	First year costs per person									Health state costs (post 1 year, per person)				
	Intervention cost	Drug cost	Stroke cost	SAEs cost	AF SF costs	AF S costs	IS costs	Post-IS costs	ICH costs	Post-ICH costs	IS fatal costs	ICH fatal costs	Bleeding costs	AAD SAE costs
Thoracoscopy	£13,438	£497	£138	£802	£4,359	£6,647	£2,774	£9,472	£2,403	£10,529	£343	£515	£250	£657
Hybrid	£21,595	£500	£138	£813	£4,177	£6,897	£2,774	£9,472	£2,403	£10,529	£343	£515	£250	£677

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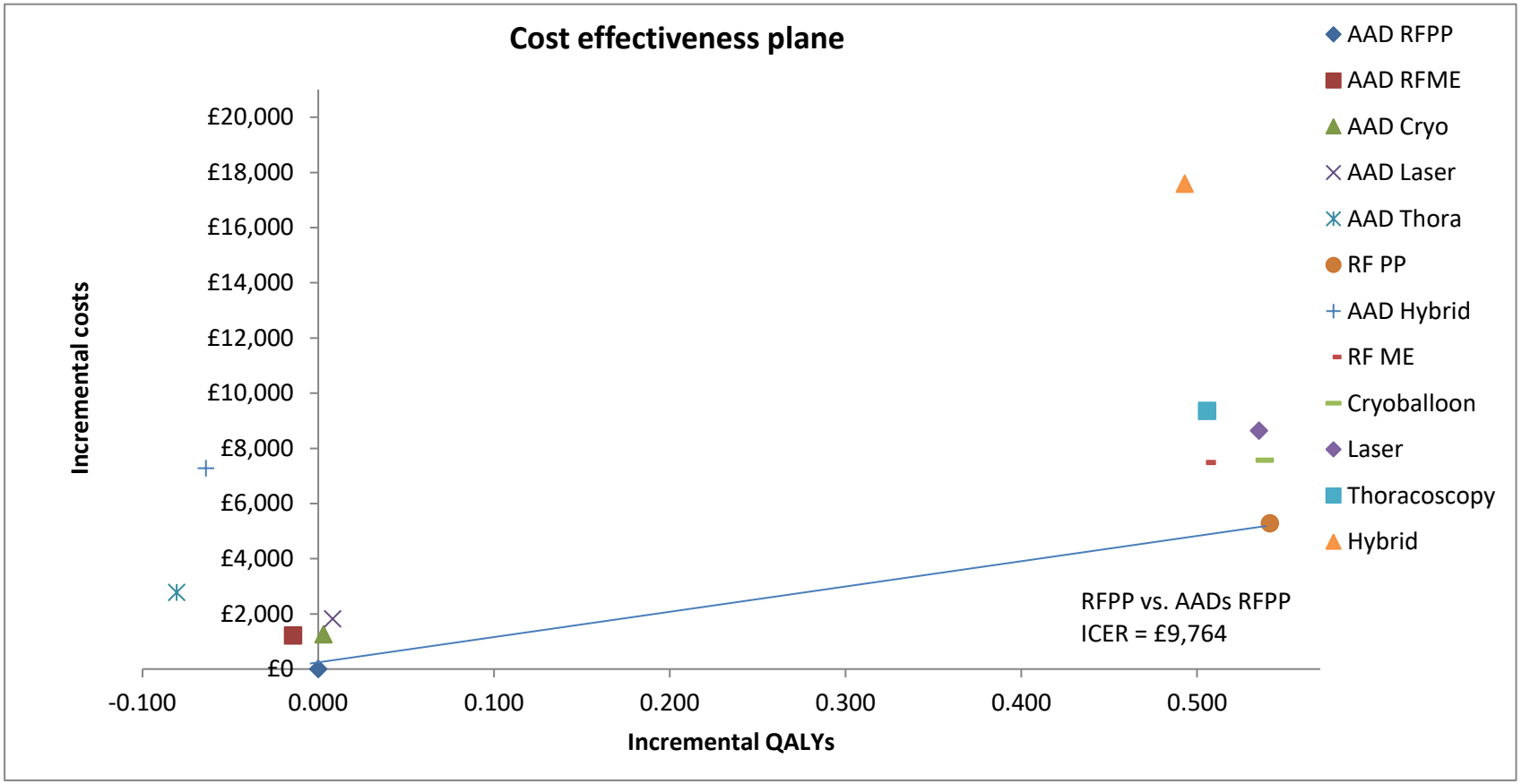
Figure 4: Cost effectiveness plane base case



ISBN: 978-1-4731-4043-1

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2.4.2 Sensitivity analyses

A number of sensitivity analyses were conducted and are described in detail in **section 2.3.11**. The results of the sensitivity analyses SA1 to SA35 are presented in Table 50 and Table 51 below and graphically below. Conclusions about RFPP being the most cost-effective intervention were unchanged in most sensitivity analyses. The exception being the sensitivity analysis SA29.

SA29 (deterministic analysis) used a 5-year time horizon rather than a lifetime horizon and showed that AAD with cross over to RFPP became the most cost-effective option. Results are presented in Table 51.

Although the conclusions of the model did not change, the certainty of the results was reduced in sensitivity analyses conducted around the cost of the ablation techniques. Of note, when the cost of thoracoscopy was reduced in SA20 (using different HRG code), RFPP remained the most cost effective option, but the probability of it being the most cost effective option reduced to 60%. Thoracoscopy was ranked second with a probability of being the most cost effective of 39%. Similarly, when the cost of laser ablation was reduced in SA21 (removing 30% uplift), RFPP remained the most cost effective option but the probability reduced to 95% . Laser was ranked second with a probability of being the most cost effective of 4%. Again, in SA23, where the cost of cryoballoon was adjusted to use day case costs and RFPP using elective case costs as opposed to the total HRG cost for the procedure, RFPP remained the most cost effective but the probability reduced to 70%. Cryoballoon was ranked second with a probability of being the most cost effective of 29%. Finally, in SA24 was an exploratory sensitivity analysis where the cost of all catheter ablation was made equal to that of RFPP. In this analysis the RFPP remained the most cost effective, followed by cryoballoon and then laser ablation. These results were highly uncertain with the probability of each being the most cost effective being: 28%, 30% and 40% respectively.

SA30 was a data validation exercise to see whether the mean treatment difference in terms of utility values by year were similar in our model to those seen in CABANA. This sensitivity analysis was done using both the base case and also using the Reynolds 2009 utility decrement for AF symptom health state (SA31). As SA16 (adjusting the AAD AF recurrence data post 1 year for 0% cross over) did not result in a change in conclusions, this was not incorporated in these validation analyses. The results are represented graphically in Figure 5 and Figure 6. They show that our resultant utility treatment difference year by year was aligned with the lower confidence interval of the CABANA data. When comparing the mean utility difference between RFPP ablation and AAD (with RF PP cross over) over time, our model was very similar to the lower confidence interval of CABANA. When using Reynolds 2009 for the utility decrement for AF symptom health state our model was a little closer to the mean of CABANA. A threshold analysis was undertaken to identify what the utility decrement for AF symptoms would need to be to better reflect CABANA (SA34). This analysis indicated that a utility decrement of 0.08, rather than 0.04 in the base case would result in similar resultant utility values to CABANA (see figure 7). The model was run using this utility decrement of 0.08 to see if it resulted in a change in the conclusions of the model (SA35, Table 50). This analysis resulted in no change in the conclusions of the model, RFPP remained the most cost effective option.

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Overall therefore, these results indicate that we may have underestimated the benefit of ablation, but our results are within the confidence intervals reported by CABANA (see Table 45) and when the utility decrement for AF symptoms is increased, the model conclusions are unchanged.

Figure 5: Utility validation base case versus CABANA (SA30)

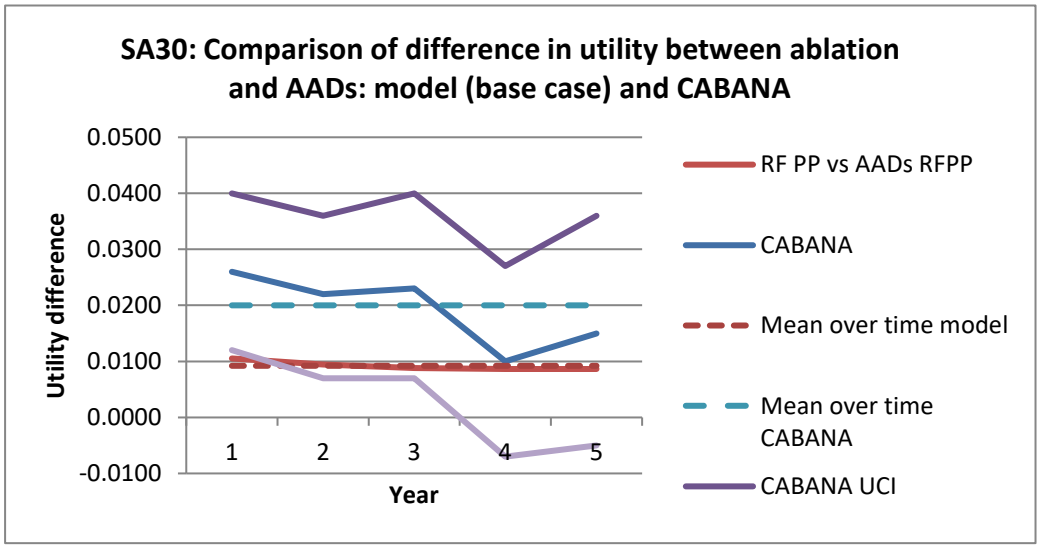

Figure 6: Utility validation Reynolds versus CABANA (SA31)

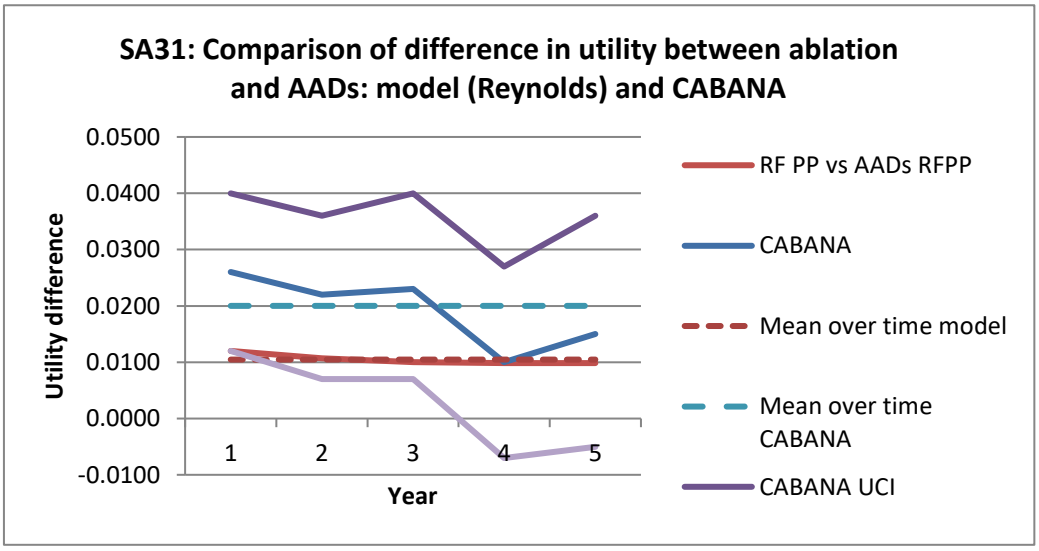

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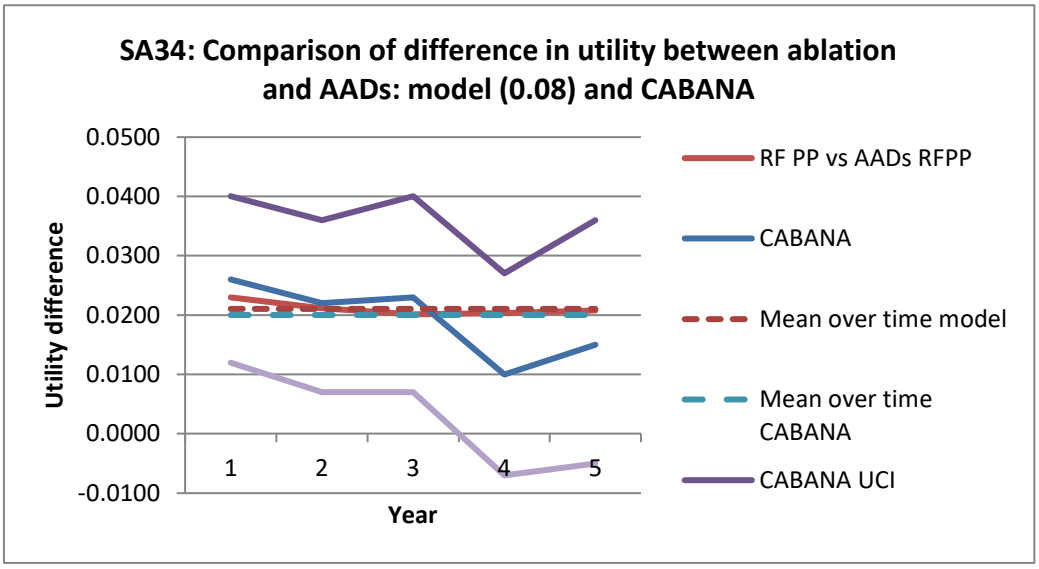
Figure 7: Utility validation using threshold value (0.08) versus CABANA (SA34)



SA32 was a threshold analysis on the proportion crossing over in year 1 from AAD to ablation following symptom recurrence. The full results including the ranking of interventions are summarised in Table 50. This analysis found that the proportion cross over would need to be 14% (same for all AAD arms) for RFPP ablation to no longer be the most cost effective option. AAD with cross over to RFPP ablation would be the most cost effective option.

SA33 was a threshold analysis on the procedural cost for cryoballoon ablation. A cost reduction of 61% of the ablation procedure cost resulted in cryoballoon becoming the most cost-effective intervention (probability of 59%). This equates to a reduction of £2,401. As detailed in section 2.3.9.1., cryoballoon maybe associated with savings related to not requiring a general anaesthetic (up to £500), a shorter procedure (£203) and same day discharge (£742). Together these equate to £1,289 in savings which is not enough for cryoballoon to become more cost effective than RFPP.

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Table 50: Sensitivity analyses results

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
Basecase												
AAD RFPP	£42,904	£28,606	21.837	14.769	15.652	10.840	£188,184	£0	6	2	6	1%
AAD RFME	£44,262	£29,828	21.838	14.770	15.632	10.825	£186,675	-£1,509	8	5	9	0%
AAD Cryo	£44,181	£29,867	21.853	14.777	15.660	10.843	£186,984	-£1,200	7	5	9	0%
AAD Laser	£44,763	£30,424	21.878	14.790	15.672	10.848	£186,530	-£1,654	9	5	9	0%
AAD Thora	£45,423	£31,383	21.551	14.615	15.495	10.759	£183,796	-£4,388	10	9	10	0%
AAD Hybrid	£50,005	£35,881	21.635	14.656	15.535	10.776	£179,631	-£8,553	12	11	12	0%
RF PP	£48,900	£33,891	23.240	15.469	16.677	11.381	£193,725	£5,541	1	1	1	98%
RF ME	£51,314	£36,091	23.208	15.454	16.620	11.345	£190,809	£2,625	3	2	7	0%
Cryoballoon	£51,191	£36,178	23.240	15.469	16.673	11.378	£191,382	£3,198	2	2	6	0%
Laser	£52,262	£37,242	23.240	15.469	16.669	11.375	£190,251	£2,067	4	2	9	1%
Thoracoscopy	£52,823	£37,963	23.102	15.378	16.620	11.345	£188,938	£754	5	3	9	0%
Hybrid	£61,083	£46,200	23.102	15.378	16.603	11.332	£180,447	-£7,737	11	11	12	0%
SA1 Vary proportion receiving AADs post event (0%)												
AAD RFPP	£39,679	£26,586	21.831	14.766	15.651	10.839	£190,194	£0	6	2	6	1%
AAD RFME	£41,018	£27,794	21.829	14.766	15.630	10.824	£188,693	-£1,501	8	5	9	0%

ISBN: 978-1-4731-4043-1

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
AAD Cryo	£40,938	£27,834	21.847	14.774	15.659	10.842	£189,012	-£1,182	7	4	9	0%
AAD Laser	£41,492	£28,372	21.873	14.787	15.671	10.847	£188,576	-£1,619	9	4	9	0%
AAD Thora	£42,473	£29,555	21.544	14.611	15.493	10.758	£185,605	-£4,589	10	9	10	0%
AAD Hybrid	£46,956	£33,988	21.625	14.651	15.532	10.774	£181,492	-£8,702	12	11	12	0%
RF PP	£45,851	£32,064	23.233	15.466	16.675	11.380	£195,541	£5,347	1	1	1	98%
RF ME	£48,233	£34,236	23.201	15.451	16.620	11.345	£192,664	£2,470	3	2	7	0%
Cryoballoon	£48,126	£34,339	23.233	15.466	16.672	11.378	£193,212	£3,018	2	2	6	0%
Laser	£49,175	£35,388	23.233	15.466	16.667	11.374	£192,089	£1,895	4	2	9	1%
Thoracoscopy	£50,021	£36,317	23.095	15.375	16.618	11.345	£190,574	£380	5	3	10	0%
Hybrid	£58,179	£44,474	23.095	15.375	16.601	11.332	£182,164	-£8,030	11	11	12	0%
SA2 Vary proportion receiving AADs post event (100%)												
AAD RFPP	£44,466	£29,588	21.838	14.770	15.658	10.843	£187,279	£0	6	2	6	1%
AAD RFME	£45,831	£30,816	21.837	14.770	15.638	10.829	£185,759	-£1,520	8	5	9	0%
AAD Cryo	£45,758	£30,859	21.855	14.778	15.666	10.847	£186,072	-£1,207	7	4	8	0%
AAD Laser	£46,368	£31,435	21.883	14.792	15.680	10.852	£185,605	-£1,673	9	5	9	0%
AAD Thora	£46,856	£32,275	21.554	14.616	15.501	10.763	£182,980	-£4,299	10	9	11	0%
AAD Hybrid	£51,481	£36,807	21.633	14.656	15.540	10.779	£178,766	-£8,513	12	11	12	0%

ISBN: 978-1-4731-4043-1

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
RF PP	£50,356	£34,756	23.244	15.471	16.685	11.386	£192,959	£5,680	1	1	1	98%
RF ME	£52,768	£36,953	23.212	15.456	16.629	11.350	£190,054	£2,775	3	2	7	0%
Cryoballoon	£52,663	£37,056	23.244	15.471	16.681	11.383	£190,598	£3,320	2	2	6	0%
Laser	£53,763	£38,146	23.244	15.471	16.676	11.379	£189,430	£2,152	4	2	9	1%
Thoracoscopy	£54,160	£38,741	23.105	15.380	16.627	11.349	£188,247	£969	5	2	10	0%
Hybrid	£62,438	£46,986	23.105	15.380	16.611	11.337	£179,759	-£7,520	11	10	12	0%
SA3 Vary baseline (AAD) AF recurrence (50%)												
AAD RFPP	£41,793	£27,473	21.704	14.698	15.599	10.819	£188,913	£0	6	2	6	1%
AAD RFME	£42,720	£28,307	21.706	14.699	15.586	10.810	£187,887	-£1,026	8	4	9	0%
AAD Cryo	£42,662	£28,331	21.715	14.703	15.604	10.821	£188,095	-£818	7	3	8	0%
AAD Laser	£43,067	£28,716	21.735	14.713	15.614	10.826	£187,794	-£1,119	9	4	9	0%
AAD Thora	£43,520	£29,371	21.513	14.594	15.493	10.765	£185,922	-£2,991	10	8	10	0%
AAD Hybrid	£46,631	£32,431	21.565	14.620	15.518	10.775	£183,072	-£5,841	11	11	12	0%
RF PP	£48,858	£33,864	23.232	15.465	16.678	11.382	£193,779	£4,866	1	1	1	98%
RF ME	£51,276	£36,069	23.200	15.450	16.621	11.346	£190,858	£1,945	3	2	8	0%
Cryoballoon	£51,144	£36,146	23.232	15.465	16.675	11.380	£191,445	£2,532	2	2	7	0%
Laser	£52,241	£37,235	23.232	15.465	16.669	11.376	£190,276	£1,363	4	2	10	1%
Thoracoscopy	£52,807	£37,961	23.094	15.374	16.619	11.345	£188,945	£32	5	3	10	0%

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Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
Hybrid	£61,028	£46,161	23.094	15.374	16.604	11.334	£180,512	-£8,401	12	11	12	0%
SA4 Vary baseline (AAD) AF recurrence (90%)												
AAD RFPP	£43,842	£29,505	21.913	14.811	15.681	10.850	£187,491	£0	6	3	6	0%
AAD RFME	£45,502	£31,001	21.912	14.811	15.656	10.832	£185,637	-£1,853	8	6	9	0%
AAD Cryo	£45,412	£31,054	21.934	14.821	15.691	10.854	£186,026	-£1,465	7	5	9	0%
AAD Laser	£46,124	£31,737	21.963	14.836	15.706	10.860	£185,465	-£2,026	9	5	9	0%
AAD Thora	£46,931	£32,911	21.563	14.622	15.488	10.751	£182,102	-£5,389	10	10	11	0%
AAD Hybrid	£52,535	£38,422	21.658	14.669	15.534	10.770	£176,976	-£10,515	12	11	12	0%
RF PP	£49,078	£33,997	23.230	15.464	16.669	11.377	£193,537	£6,046	1	1	1	98%
RF ME	£51,479	£36,185	23.198	15.449	16.613	11.341	£190,640	£3,149	3	2	6	0%
Cryoballoon	£51,376	£36,291	23.230	15.464	16.665	11.374	£191,185	£3,694	2	2	6	0%
Laser	£52,439	£37,347	23.230	15.464	16.661	11.371	£190,064	£2,573	4	2	9	1%
Thoracoscopy	£52,995	£38,065	23.092	15.374	16.611	11.341	£188,752	£1,261	5	3	9	0%
Hybrid	£61,224	£46,272	23.092	15.374	16.596	11.329	£180,306	-£7,185	11	10	12	0%
SA5 Vary baseline (AAD) mortality												
AAD RFPP	£42,352	£28,261	21.347	14.445	15.302	10.602	£183,782	£0	5	2	6	1%
AAD RFME	£43,701	£29,478	21.345	14.444	15.280	10.587	£182,266	-£1,516	7	5	9	0%
AAD	£43,632	£29,523	21.365	14.454	15.310	10.606	£182,587	-£1,195	6	4	8	0%

ISBN: 978-1-4731-4043-1

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
Cryo												
AAD Laser	£44,210	£30,079	21.387	14.465	15.320	10.610	£182,113	-£1,669	8	5	9	0%
AAD Thora	£44,667	£30,911	20.941	14.208	15.055	10.459	£178,263	-£5,519	10	9	10	0%
AAD Hybrid	£49,236	£35,404	21.018	14.246	15.092	10.474	£174,079	-£9,704	11	11	12	0%
RF PP	£48,335	£33,542	22.718	15.129	16.299	11.128	£189,017	£5,235	1	1	1	98%
RF ME	£50,724	£35,720	22.686	15.114	16.244	11.093	£186,138	£2,355	3	2	7	0%
Cryoballoon	£50,633	£35,836	22.718	15.129	16.296	11.125	£186,668	£2,885	2	2	6	0%
Laser	£51,691	£36,888	22.718	15.129	16.291	11.122	£185,548	£1,766	4	2	9	1%
Thoracoscopy	£51,849	£37,369	22.330	14.874	16.058	10.967	£181,974	-£1,808	9	3	10	0%
Hybrid	£60,090	£45,589	22.330	14.874	16.043	10.956	£173,526	-£10,257	12	11	12	0%
SA6 Apply stroke treatment effects												
AAD RFPP	£42,760	£28,520	21.842	14.771	15.661	10.844	£188,364	£0	4	2	6	1%
AAD RFME	£68,623	£48,426	21.310	14.529	14.431	10.043	£152,430	-£35,935	11	6	11	0%
AAD Cryo	£48,701	£33,338	21.756	14.733	15.437	10.697	£180,606	-£7,759	8	6	11	0%
AAD Laser	£44,626	£30,343	21.886	14.793	15.681	10.853	£186,710	-£1,655	5	3	8	0%
AAD Thora	£45,270	£31,289	21.554	14.616	15.502	10.763	£183,967	-£4,397	6	5	10	0%
AAD Hybrid	£49,851	£35,788	21.639	14.658	15.543	10.780	£179,806	-£8,558	9	7	12	0%

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Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
RF PP	£48,743	£33,796	23.246	15.472	16.686	11.386	£193,920	£5,555	1	1	1	98%
RF ME	£93,935	£68,822	21.706	14.748	14.089	9.750	£126,186	-£62,179	12	2	12	0%
Cryoballoon	£59,176	£42,331	22.958	15.337	16.198	11.078	£179,237	-£9,127	10	2	12	0%
Laser	£52,121	£37,162	23.246	15.472	16.677	11.379	£190,416	£2,052	2	2	6	1%
Thoracoscopy	£52,643	£37,845	23.107	15.381	16.629	11.350	£189,158	£794	3	2	7	0%
Hybrid	£60,913	£46,092	23.107	15.381	16.611	11.337	£180,647	-£7,718	7	7	12	0%
SA7 Stroke ME risk = AADs												
AAD RFPP	£43,028	£28,686	21.821	14.761	15.645	10.836	£188,044	£0	6	3	6	1%
AAD RFME	£43,861	£29,510	21.830	14.766	15.650	10.839	£187,260	-£784	7	4	8	0%
AAD Cryo	£44,304	£29,946	21.836	14.769	15.653	10.840	£186,846	-£1,198	8	5	9	0%
AAD Laser	£44,890	£30,507	21.862	14.782	15.665	10.845	£186,388	-£1,656	9	5	9	0%
AAD Thora	£45,545	£31,462	21.536	14.607	15.488	10.756	£183,653	-£4,391	10	9	11	0%
AAD Hybrid	£50,116	£35,955	21.613	14.646	15.526	10.771	£179,472	-£8,572	12	11	12	0%
RF PP	£49,026	£33,970	23.224	15.461	16.670	11.378	£193,581	£5,537	1	1	2	96%
RF ME	£50,518	£35,459	23.224	15.461	16.668	11.376	£192,065	£4,021	2	1	5	3%
Cryoballoon	£51,312	£36,252	23.224	15.461	16.666	11.375	£191,248	£3,204	3	2	7	0%
Laser	£52,389	£37,322	23.224	15.461	16.661	11.371	£190,104	£2,060	4	2	9	1%
Thoracoscopy	£52,946	£38,040	23.086	15.370	16.612	11.342	£188,792	£748	5	3	10	0%

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Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
Hybrid	£61,172	£46,244	23.086	15.370	16.597	11.330	£180,352	-£7,692	11	10	12	0%
SA8 Apply mortality treatment effects												
AAD RFPP	£42,890	£28,601	21.880	14.797	15.689	10.864	£188,670	£0	5	2	7	1%
AAD RFME	£44,186	£29,786	21.844	14.773	15.643	10.831	£186,838	-£1,833	8	5	9	0%
AAD Cryo	£44,110	£29,827	21.861	14.781	15.672	10.849	£187,157	-£1,513	7	4	8	0%
AAD Laser	£44,694	£30,386	21.886	14.793	15.683	10.854	£186,694	-£1,976	9	5	9	0%
AAD Thora	£45,242	£31,276	21.490	14.572	15.456	10.730	£183,323	-£5,347	10	9	10	0%
AAD Hybrid	£49,806	£35,766	21.565	14.609	15.492	10.745	£179,132	-£9,539	12	11	12	0%
RF PP	£48,936	£33,917	23.315	15.518	16.737	11.420	£194,486	£5,815	1	1	2	95%
RF ME	£51,230	£36,043	23.214	15.457	16.630	11.350	£190,963	£2,293	3	2	7	1%
Cryoballoon	£51,122	£36,143	23.246	15.472	16.683	11.383	£191,520	£2,850	2	2	6	2%
Laser	£52,194	£37,209	23.246	15.472	16.678	11.379	£190,381	£1,711	4	2	9	1%
Thoracoscopy	£52,538	£37,802	22.970	15.290	16.528	11.282	£187,830	-£840	6	4	10	0%
Hybrid	£60,751	£45,993	22.970	15.290	16.513	11.270	£179,409	-£9,261	11	11	12	0%
SA9 Vary proportion cross over to ablation 100%												
AAD RFPP	£43,498	£29,502	21.557	14.630	15.524	10.788	£186,253	£0	6	4	6	0%
AAD RFME	£45,254	£31,086	21.554	14.630	15.497	10.769	£184,284	-£1,969	8	7	9	0%
AAD	£45,162	£31,143	21.579	14.641	15.535	10.792	£184,697	-£1,556	7	6	9	0%

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Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
Cryo												
AAD Laser	£45,920	£31,870	21.612	14.657	15.551	10.799	£184,103	-£2,150	9	6	9	0%
AAD Thora	£46,763	£33,106	21.181	14.428	15.317	10.681	£180,523	-£5,730	11	10	11	0%
AAD Hybrid	£52,731	£38,964	21.292	14.483	15.370	10.703	£175,104	-£11,148	12	11	12	0%
RF PP	£48,833	£33,851	23.240	15.469	16.685	11.386	£193,865	£7,612	1	1	1	99%
RF ME	£51,227	£36,032	23.209	15.454	16.629	11.351	£190,981	£4,729	3	2	5	0%
Cryoballoon	£51,127	£36,141	23.240	15.469	16.681	11.383	£191,519	£5,266	2	2	5	0%
Laser	£52,199	£37,206	23.240	15.469	16.676	11.379	£190,382	£4,129	4	2	8	1%
Thoracoscopy	£52,730	£37,899	23.102	15.378	16.628	11.350	£189,109	£2,856	5	2	8	0%
Hybrid	£61,005	£46,150	23.102	15.378	16.610	11.337	£180,591	-£5,662	10	9	12	0%
SA10 Vary proportion cross over to ablation 25%												
AAD RFPP	£41,354	£26,467	22.469	15.082	15.973	10.977	£193,070	£0	2	1	6	30%
AAD RFME	£41,797	£26,865	22.470	15.082	15.967	10.972	£192,580	-£489	4	2	8	0%
AAD Cryo	£41,769	£26,877	22.475	15.084	15.976	10.978	£192,681	-£389	3	2	7	0%
AAD Laser	£41,960	£27,059	22.483	15.089	15.980	10.979	£192,531	-£539	5	2	9	1%
AAD Thora	£42,172	£27,369	22.375	15.031	15.921	10.950	£191,633	-£1,437	7	5	10	0%
AAD Hybrid	£43,664	£28,835	22.403	15.045	15.934	10.956	£190,278	-£2,792	10	7	11	0%

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Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
RF PP	£48,806	£33,828	23.248	15.473	16.694	11.391	£193,987	£917	1	1	7	68%
RF ME	£51,225	£36,033	23.216	15.458	16.637	11.355	£191,065	-£2,004	8	2	11	0%
Cryoballoon	£51,095	£36,112	23.248	15.473	16.690	11.388	£191,653	-£1,417	6	2	10	0%
Laser	£52,168	£37,179	23.248	15.473	16.686	11.385	£190,512	-£2,557	9	2	11	0%
Thoracoscopy	£52,714	£37,886	23.110	15.382	16.636	11.355	£189,208	-£3,862	11	4	11	0%
Hybrid	£60,979	£46,127	23.110	15.382	16.619	11.342	£180,710	-£12,360	12	12	12	0%
SA11 Repeat ablation proportion = 100%												
AAD RFPP	£42,997	£28,662	21.831	14.766	15.649	10.838	£188,099	£0	6	2	6	1%
AAD RFME	£44,357	£29,886	21.833	14.767	15.630	10.824	£186,595	-£1,504	8	5	9	0%
AAD Cryo	£44,274	£29,923	21.847	14.774	15.657	10.841	£186,900	-£1,199	7	4	8	0%
AAD Laser	£44,857	£30,481	21.873	14.787	15.669	10.846	£186,444	-£1,655	9	5	9	0%
AAD Thora	£45,521	£31,441	21.548	14.613	15.492	10.757	£183,707	-£4,392	10	9	10	0%
AAD Hybrid	£50,081	£35,927	21.624	14.651	15.530	10.773	£179,532	-£8,567	12	11	12	0%
RF PP	£49,408	£34,377	23.233	15.466	16.685	11.388	£193,385	£5,287	1	1	2	97%
RF ME	£51,840	£36,596	23.201	15.451	16.629	11.353	£190,455	£2,356	3	2	8	0%
Cryoballoon	£51,718	£36,683	23.233	15.466	16.682	11.386	£191,030	£2,931	2	2	7	0%
Laser	£52,814	£37,775	23.233	15.466	16.678	11.383	£189,882	£1,783	4	2	9	1%
Thoracoscopy	£53,126	£38,236	23.095	15.375	16.620	11.347	£188,698	£600	5	2	10	0%

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Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
Hybrid	£61,421	£46,512	23.095	15.375	16.607	11.337	£180,227	-£7,872	11	11	12	0%
SA12 Repeat ablation proportion = 0%												
AAD RFPP	£42,986	£28,659	21.834	14.768	15.653	10.840	£188,141	£0	6	4	6	0%
AAD RFME	£44,341	£29,880	21.833	14.768	15.632	10.825	£186,628	-£1,513	8	7	9	0%
AAD Cryo	£44,267	£29,922	21.852	14.776	15.661	10.843	£186,943	-£1,198	7	6	9	0%
AAD Laser	£44,867	£30,491	21.883	14.792	15.676	10.850	£186,502	-£1,639	9	6	9	0%
AAD Thora	£45,508	£31,438	21.549	14.614	15.495	10.759	£183,739	-£4,402	10	10	11	0%
AAD Hybrid	£50,090	£35,941	21.629	14.653	15.534	10.775	£179,564	-£8,577	12	11	12	0%
RF PP	£47,336	£32,227	23.233	15.465	16.624	11.343	£194,630	£6,489	1	1	1	100%
RF ME	£49,693	£34,370	23.201	15.450	16.568	11.307	£191,767	£3,626	3	2	4	0%
Cryoballoon	£49,562	£34,445	23.233	15.465	16.618	11.338	£192,320	£4,179	2	2	4	0%
Laser	£50,545	£35,413	23.233	15.465	16.608	11.331	£191,206	£3,065	4	2	7	0%
Thoracoscopy	£52,123	£37,200	23.095	15.375	16.593	11.326	£189,319	£1,178	5	3	9	0%
Hybrid	£60,039	£45,081	23.095	15.375	16.567	11.307	£181,054	-£7,088	11	10	12	0%
SA13 Efficacy repeat ablation												
AAD RFPP	£42,602	£28,422	21.854	14.778	15.668	10.848	£188,541	£0	6	2	6	1%
AAD RFME	£43,961	£29,646	21.854	14.778	15.648	10.834	£187,025	-£1,517	8	5	9	0%
AAD	£43,878	£29,683	21.870	14.786	15.676	10.851	£187,341	-£1,201	7	4	9	0%

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Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
Cryo												
AAD Laser	£44,476	£30,250	21.900	14.801	15.690	10.857	£186,890	-£1,651	9	5	9	0%
AAD Thora	£45,122	£31,201	21.566	14.623	15.510	10.767	£184,139	-£4,402	10	9	10	0%
AAD Hybrid	£49,717	£35,710	21.652	14.665	15.551	10.784	£179,972	-£8,570	12	11	12	0%
RF PP	£48,667	£33,762	23.259	15.479	16.680	11.380	£193,834	£5,293	1	1	2	97%
RF ME	£51,078	£35,958	23.227	15.464	16.624	11.344	£190,918	£2,377	3	2	8	0%
Cryoballoon	£50,956	£36,046	23.259	15.479	16.676	11.377	£191,489	£2,948	2	2	7	0%
Laser	£52,061	£37,142	23.259	15.479	16.670	11.372	£190,292	£1,750	4	2	9	1%
Thoracoscopy	£52,540	£37,795	23.121	15.388	16.631	11.350	£189,202	£661	5	2	10	0%
Hybrid	£60,832	£46,059	23.121	15.388	16.611	11.334	£180,630	-£7,911	11	10	12	0%
SA14 AF recurrence after 1 yr: no AF recurrence after 1 yr												
AAD RFPP	£39,127	£26,929	19.370	13.760	14.359	10.345	£179,978	£0	7	6	8	0%
AAD RFME	£40,544	£28,180	19.402	13.774	14.355	10.337	£178,565	-£1,413	9	7	10	0%
AAD Cryo	£40,443	£28,208	19.409	13.777	14.378	10.353	£178,848	-£1,130	8	7	10	0%
AAD Laser	£41,083	£28,792	19.464	13.802	14.406	10.364	£178,482	-£1,496	10	7	10	0%
AAD Thora	£41,093	£29,451	18.784	13.484	14.044	10.205	£174,652	-£5,326	11	10	11	0%
AAD Hybrid	£45,875	£34,042	18.977	13.570	14.141	10.243	£170,818	-£9,160	12	12	12	0%

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Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
RF PP	£46,956	£32,775	23.252	15.475	17.007	11.569	£198,601	£18,623	1	1	2	96%
RF ME	£49,403	£34,996	23.220	15.460	16.945	11.530	£195,607	£15,629	3	2	5	0%
Cryoballoon	£49,256	£35,064	23.252	15.475	17.000	11.564	£196,225	£16,247	2	2	5	0%
Laser	£50,333	£36,126	23.252	15.475	16.992	11.559	£195,055	£15,077	4	2	5	2%
Thoracoscopy	£50,705	£36,756	23.114	15.384	16.986	11.554	£194,320	£14,342	5	2	5	2%
Hybrid	£59,007	£45,004	23.114	15.384	16.955	11.533	£185,660	£5,682	6	6	10	0%
SA15 AF recurrence after 1 yr: CABANA + no AF recurrence post yr 4												
AAD RFPP	£40,570	£27,600	20.361	14.195	14.876	10.553	£183,467	£0	6	6	8	0%
AAD RFME	£41,960	£28,837	20.379	14.202	14.865	10.543	£182,013	-£1,454	9	7	10	0%
AAD Cryo	£41,873	£28,872	20.392	14.209	14.891	10.559	£182,314	-£1,153	8	7	10	0%
AAD Laser	£42,501	£29,451	20.443	14.231	14.917	10.570	£181,943	-£1,524	10	6	10	0%
AAD Thora	£42,773	£30,242	19.891	13.970	14.620	10.436	£178,484	-£4,983	11	10	11	0%
AAD Hybrid	£47,479	£34,794	20.048	14.039	14.699	10.467	£174,547	-£8,920	12	11	12	0%
RF PP	£47,679	£33,237	23.255	15.477	16.865	11.477	£196,313	£12,846	1	1	1	98%
RF ME	£50,108	£35,445	23.223	15.461	16.806	11.441	£193,366	£9,899	3	2	5	0%
Cryoballoon	£49,977	£35,527	23.255	15.477	16.860	11.474	£193,950	£10,484	2	2	5	0%
Laser	£51,071	£36,607	23.255	15.477	16.853	11.469	£192,779	£9,312	4	2	5	1%
Thoracoscopy	£51,506	£37,263	23.117	15.386	16.826	11.451	£191,757	£8,290	5	2	5	1%

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Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
Hybrid	£59,803	£45,516	23.117	15.386	16.801	11.434	£183,163	-£303	7	6	11	0%
SA16 AAD AF recurrence post 1 yr adjusted to represent 0% cross over												
AAD RFPP	£42,950	£28,613	21.915	14.804	15.698	10.860	£188,580	£0	6	2	6	1%
AAD RFME	£44,305	£29,834	21.915	14.805	15.678	10.845	£187,074	-£1,506	8	5	9	0%
AAD Cryo	£44,221	£29,870	21.929	14.812	15.705	10.862	£187,377	-£1,203	7	4	9	0%
AAD Laser	£44,808	£30,430	21.956	14.825	15.717	10.867	£186,917	-£1,663	9	5	9	0%
AAD Thora	£45,457	£31,383	21.625	14.648	15.538	10.778	£184,169	-£4,411	10	9	10	0%
AAD Hybrid	£50,042	£35,883	21.710	14.690	15.579	10.795	£180,014	-£8,566	12	11	12	0%
RF PP	£48,856	£33,856	23.241	15.470	16.689	11.389	£193,920	£5,340	1	1	1	98%
RF ME	£51,263	£36,050	23.210	15.455	16.633	11.353	£191,016	£2,436	3	2	7	0%
Cryoballoon	£51,133	£36,129	23.241	15.470	16.686	11.386	£191,597	£3,017	2	2	6	0%
Laser	£52,210	£37,199	23.241	15.470	16.681	11.382	£190,450	£1,870	4	2	9	1%
Thoracoscopy	£52,769	£37,920	23.103	15.379	16.632	11.353	£189,143	£563	5	3	9	0%
Hybrid	£61,032	£46,160	23.103	15.379	16.615	11.340	£180,646	-£7,934	11	11	12	0%
SA17 Stroke risk reduction for AF symptom free health state												
AAD RFPP	£41,702	£27,838	21.891	14.798	15.726	10.882	£189,802	£0	6	3	6	1%
AAD RFME	£43,060	£29,061	21.887	14.796	15.703	10.866	£188,267	-£1,536	8	6	9	0%
AAD	£42,985	£29,102	21.904	14.804	15.732	10.884	£188,580	-£1,223	7	5	8	0%

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Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
Cryo												
AAD Laser	£43,593	£29,676	21.929	14.817	15.743	10.888	£188,091	-£1,711	9	6	9	0%
AAD Thora	£44,044	£30,501	21.613	14.648	15.580	10.808	£185,662	-£4,140	10	9	11	0%
AAD Hybrid	£48,702	£35,049	21.694	14.688	15.616	10.822	£181,396	-£8,406	12	11	12	0%
RF PP	£47,356	£32,893	23.370	15.532	16.814	11.455	£196,197	£6,394	1	1	2	97%
RF ME	£49,756	£35,075	23.336	15.516	16.757	11.419	£193,302	£3,500	3	2	6	0%
Cryoballoon	£49,643	£35,173	23.369	15.532	16.809	11.451	£193,857	£4,055	2	2	5	0%
Laser	£50,740	£36,256	23.367	15.531	16.803	11.447	£192,678	£2,876	4	2	9	1%
Thoracoscopy	£51,090	£36,839	23.247	15.449	16.774	11.428	£191,728	£1,926	5	2	9	1%
Hybrid	£59,431	£45,131	23.241	15.446	16.750	11.411	£183,097	-£6,705	11	10	12	0%
SA18 HR warfarin vs no treatment ICH												
AAD RFPP	£45,550	£30,214	21.669	14.685	15.499	10.758	£184,937	£0	6	2	6	1%
AAD RFME	£46,892	£31,427	21.668	14.685	15.479	10.743	£183,439	-£1,498	8	5	9	0%
AAD Cryo	£46,820	£31,470	21.682	14.691	15.505	10.760	£183,731	-£1,206	7	4	8	0%
AAD Laser	£47,398	£32,026	21.704	14.702	15.516	10.764	£183,261	-£1,677	9	5	9	0%
AAD Thora	£48,044	£32,976	21.387	14.532	15.344	10.677	£180,573	-£4,364	10	9	10	0%
AAD Hybrid	£52,613	£37,467	21.462	14.569	15.380	10.693	£176,388	-£8,550	12	11	12	0%

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RF PP	£51,650	£35,558	23.038	15.370	16.498	11.287	£190,185	£5,248	1	1	1	98%
RF ME	£54,030	£37,733	23.008	15.356	16.444	11.253	£187,320	£2,382	3	2	7	0%
Cryoballoon	£53,924	£37,828	23.038	15.370	16.495	11.285	£187,871	£2,934	2	2	7	0%
Laser	£54,981	£38,879	23.038	15.370	16.491	11.282	£186,755	£1,817	4	2	9	1%
Thoracoscopy	£55,542	£39,606	22.901	15.280	16.442	11.252	£185,428	£490	5	3	10	0%
Hybrid	£63,769	£47,811	22.901	15.280	16.426	11.240	£176,990	-£7,947	11	11	12	0%
SA19 Utility decrement AF symptoms use Reynolds data												
AAD RFPP	£42,660	£28,457	21.850	14.776	15.595	10.801	£187,560	£0	6	2	6	1%
AAD RFME	£44,012	£29,675	21.849	14.776	15.574	10.786	£186,050	-£1,510	8	5	9	0%
AAD Cryo	£43,930	£29,712	21.864	14.783	15.601	10.803	£186,350	-£1,211	7	5	9	0%
AAD Laser	£44,524	£30,277	21.894	14.797	15.614	10.808	£185,890	-£1,670	9	5	9	0%
AAD Thora	£45,172	£31,227	21.563	14.621	15.443	10.724	£183,261	-£4,300	10	9	11	0%
AAD Hybrid	£49,747	£35,721	21.644	14.661	15.480	10.739	£179,058	-£8,502	12	11	12	0%
RF PP	£48,655	£33,745	23.255	15.477	16.626	11.348	£193,215	£5,654	1	1	1	98%
RF ME	£51,056	£35,932	23.223	15.462	16.571	11.313	£190,324	£2,764	3	2	7	0%
Cryoballoon	£50,930	£36,017	23.255	15.477	16.622	11.345	£190,889	£3,328	2	2	6	0%
Laser	£52,031	£37,109	23.255	15.477	16.616	11.340	£189,696	£2,135	4	2	9	1%
Thoracoscopy	£52,565	£37,805	23.117	15.386	16.576	11.317	£188,544	£983	5	2	10	1%

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Hybrid	£60,817	£46,034	23.117	15.386	16.557	11.303	£180,029	-£7,531	11	10	12	0%
SA20 Cost of thoracoscopy procedure												
AAD RFPP	£42,948	£28,632	21.832	14.767	15.650	10.839	£188,148	£0	6	3	7	0%
AAD RFME	£44,300	£29,850	21.831	14.767	15.630	10.824	£186,635	-£1,513	8	6	10	0%
AAD Cryo	£44,222	£29,890	21.847	14.774	15.658	10.842	£186,946	-£1,202	7	6	9	0%
AAD Laser	£44,804	£30,448	21.872	14.787	15.670	10.847	£186,487	-£1,660	9	6	11	0%
AAD Thora	£42,976	£28,918	21.545	14.612	15.493	10.758	£186,241	-£1,907	10	6	11	0%
AAD Hybrid	£47,548	£33,410	21.626	14.652	15.532	10.774	£182,073	-£6,074	12	11	12	0%
RF PP	£48,944	£33,916	23.236	15.467	16.676	11.381	£193,697	£5,549	1	1	2	60%
RF ME	£51,345	£36,104	23.204	15.452	16.620	11.345	£190,800	£2,652	4	3	8	0%
Cryoballoon	£51,230	£36,197	23.236	15.467	16.672	11.378	£191,359	£3,211	3	2	7	0%
Laser	£52,301	£37,261	23.236	15.467	16.668	11.374	£190,229	£2,081	5	2	10	0%
Thoracoscopy	£48,443	£33,565	23.098	15.376	16.619	11.345	£193,336	£5,188	2	1	5	39%
Hybrid	£56,690	£41,788	23.098	15.376	16.602	11.332	£184,861	-£3,286	11	6	12	0%
SA21 Laser equipment costs unadjusted (no 30% uplift)												
AAD RFPP	£42,817	£28,554	21.838	14.770	15.656	10.842	£188,281	£0	6	3	6	1%
AAD RFME	£44,173	£29,776	21.838	14.770	15.635	10.827	£186,770	-£1,512	9	6	9	0%
AAD	£44,091	£29,813	21.854	14.778	15.663	10.845	£187,081	-£1,200	8	6	9	0%

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Cryo												
AAD Laser	£43,974	£29,667	21.883	14.792	15.677	10.850	£187,343	-£939	7	4	9	0%
AAD Thora	£45,333	£31,329	21.551	14.615	15.498	10.761	£183,885	-£4,397	10	9	10	0%
AAD Hybrid	£49,916	£35,831	21.633	14.656	15.537	10.777	£179,713	-£8,569	12	11	12	0%
RF PP	£48,793	£33,817	23.247	15.472	16.685	11.385	£193,890	£5,609	1	1	2	95%
RF ME	£51,199	£36,010	23.215	15.457	16.629	11.350	£190,987	£2,706	4	2	7	0%
Cryoballoon	£51,075	£36,096	23.247	15.472	16.681	11.383	£191,563	£3,281	3	2	6	0%
Laser	£50,910	£35,923	23.247	15.472	16.675	11.379	£191,647	£3,366	2	1	9	4%
Thoracoscopy	£52,705	£37,879	23.108	15.382	16.628	11.350	£189,117	£836	5	3	9	0%
Hybrid	£60,956	£46,108	23.108	15.382	16.611	11.337	£180,638	-£7,644	11	10	12	0%
SA22 Laser costs without circular mapping catheter												
AAD RFPP	£42,919	£28,617	21.835	14.768	15.653	10.840	£188,176	£0	6	2	6	1%
AAD RFME	£44,277	£29,840	21.836	14.769	15.633	10.825	£186,668	-£1,508	9	6	9	0%
AAD Cryo	£44,192	£29,875	21.850	14.775	15.659	10.842	£186,972	-£1,204	8	5	9	0%
AAD Laser	£44,242	£29,900	21.876	14.788	15.672	10.848	£187,051	-£1,125	7	4	9	0%
AAD Thora	£45,446	£31,399	21.553	14.616	15.497	10.760	£183,793	-£4,384	10	9	10	0%
AAD Hybrid	£50,010	£35,889	21.629	14.653	15.533	10.775	£179,606	-£8,571	12	11	12	0%

ISBN: 978-1-4731-4043-1

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
RF PP	£48,908	£33,896	23.238	15.468	16.677	11.381	£193,728	£5,552	1	1	2	96%
RF ME	£51,320	£36,095	23.206	15.453	16.621	11.345	£190,814	£2,638	4	2	8	0%
Cryoballoon	£51,186	£36,171	23.238	15.468	16.674	11.379	£191,405	£3,229	2	2	6	0%
Laser	£51,315	£36,292	23.238	15.468	16.669	11.375	£191,207	£3,030	3	1	9	3%
Thoracoscopy	£52,848	£37,985	23.100	15.377	16.619	11.345	£188,911	£735	5	3	10	0%
Hybrid	£61,064	£46,180	23.100	15.377	16.604	11.333	£180,485	-£7,691	11	10	12	0%
SA23 Catheter ablation procedure cost changed: 'elective case' for RFPP and 'day case' for cryoballoon, others 'total HRG'												
AAD RFPP	£42,798	£28,543	21.843	14.772	15.660	10.843	£188,327	£0	6	3	7	1%
AAD RFME	£44,156	£29,766	21.844	14.773	15.640	10.829	£186,822	-£1,505	8	6	9	0%
AAD Cryo	£42,967	£28,695	21.860	14.780	15.668	10.847	£188,239	-£88	7	3	7	0%
AAD Laser	£44,650	£30,357	21.881	14.791	15.678	10.851	£186,657	-£1,670	9	6	9	0%
AAD Thora	£45,327	£31,326	21.560	14.619	15.503	10.763	£183,935	-£4,392	10	9	10	0%
AAD Hybrid	£49,899	£35,821	21.639	14.658	15.542	10.779	£179,760	-£8,566	12	11	12	0%
RF PP	£48,780	£33,816	23.246	15.472	16.685	11.385	£193,887	£5,561	1	1	2	70%
RF ME	£51,193	£36,015	23.214	15.457	16.629	11.350	£190,977	£2,651	3	3	7	0%
Cryoballoon	£49,105	£34,136	23.246	15.472	16.681	11.382	£193,512	£5,185	2	1	3	29%
Laser	£52,121	£37,147	23.246	15.472	16.677	11.379	£190,438	£2,111	4	2	9	1%
Thoracos	£52,718	£37,902	23.108	15.381	16.627	11.349	£189,073	£746	5	3	10	0%

ISBN: 978-1-4731-4043-1

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
copy												
Hybrid	£60,954	£46,117	23.108	15.381	16.611	11.337	£180,618	-£7,709	11	10	12	0%
SA24 Cost of all catheter ablation = RFPP												
AAD RFPP	£42,898	£28,606	21.839	14.770	15.660	10.844	£188,275	£0	8	5	8	0%
AAD RFME	£43,440	£29,016	21.837	14.770	15.639	10.829	£187,572	-£703	9	6	9	0%
AAD Cryo	£42,931	£28,624	21.855	14.778	15.668	10.847	£188,321	£46	7	4	8	0%
AAD Laser	£42,998	£28,667	21.879	14.790	15.679	10.852	£188,374	£99	6	4	9	1%
AAD Thora	£45,417	£31,385	21.552	14.615	15.501	10.762	£183,865	-£4,410	10	9	10	0%
AAD Hybrid	£49,999	£35,887	21.632	14.655	15.540	10.779	£179,689	-£8,586	12	11	12	0%
RF PP	£48,895	£33,894	23.241	15.470	16.683	11.384	£193,793	£5,517	1	1	3	28%
RF ME	£49,856	£34,642	23.209	15.455	16.627	11.349	£192,342	£4,067	4	2	7	1%
Cryoballoon	£48,978	£33,973	23.241	15.470	16.680	11.382	£193,662	£5,387	2	1	4	30%
Laser	£49,131	£34,119	23.241	15.470	16.675	11.378	£193,447	£5,172	3	1	7	40%
Thoracoscopy	£52,805	£37,954	23.103	15.379	16.626	11.349	£189,017	£742	5	4	10	0%
Hybrid	£61,056	£46,182	23.103	15.379	16.609	11.336	£180,536	-£7,739	11	11	12	0%
SA25 Cost of ICH event, alternative source												
AAD RFPP	£38,936	£26,267	21.841	14.771	15.659	10.843	£190,602	£0	6	2	6	1%
AAD RFME	£40,307	£27,498	21.840	14.771	15.638	10.829	£189,081	-£1,521	8	6	9	0%

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Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
AAD Cryo	£40,216	£27,531	21.859	14.780	15.668	10.847	£189,409	-£1,193	7	5	9	0%
AAD Laser	£40,794	£28,087	21.882	14.791	15.679	10.852	£188,945	-£1,657	9	5	9	0%
AAD Thora	£41,492	£29,064	21.553	14.616	15.501	10.762	£186,181	-£4,421	10	9	11	0%
AAD Hybrid	£46,077	£33,570	21.639	14.658	15.542	10.779	£182,020	-£8,582	12	11	12	0%
RF PP	£44,748	£31,456	23.245	15.472	16.684	11.385	£196,246	£5,644	1	1	1	98%
RF ME	£47,179	£33,662	23.213	15.457	16.629	11.350	£193,337	£2,735	3	2	7	0%
Cryoballoon	£47,047	£33,750	23.245	15.472	16.681	11.382	£193,893	£3,291	2	2	6	0%
Laser	£48,109	£34,806	23.245	15.472	16.676	11.379	£192,770	£2,167	4	2	9	1%
Thoracoscopy	£48,679	£35,526	23.107	15.381	16.628	11.350	£191,468	£866	5	3	9	0%
Hybrid	£56,955	£43,778	23.107	15.381	16.610	11.336	£182,948	-£7,654	11	10	12	0%
SA26 Vary TOE proportion (0%)												
AAD RFPP	£42,815	£28,525	21.831	14.766	15.655	10.841	£188,303	£0	6	2	6	1%
AAD RFME	£44,167	£29,744	21.830	14.766	15.634	10.827	£186,789	-£1,515	8	5	9	0%
AAD Cryo	£44,091	£29,785	21.847	14.774	15.662	10.844	£187,101	-£1,202	7	5	8	0%
AAD Laser	£44,675	£30,344	21.872	14.786	15.674	10.849	£186,640	-£1,663	9	5	9	0%
AAD Thora	£45,401	£31,370	21.544	14.611	15.496	10.760	£183,826	-£4,478	10	9	11	0%
AAD Hybrid	£49,915	£35,800	21.628	14.653	15.537	10.777	£179,737	-£8,566	12	11	12	0%

ISBN: 978-1-4731-4043-1

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
RF PP	£48,719	£33,718	23.234	15.466	16.679	11.382	£193,932	£5,629	1	1	1	98%
RF ME	£51,116	£35,902	23.203	15.451	16.623	11.347	£191,042	£2,739	3	2	7	0%
Cryoballoon	£51,006	£36,001	23.234	15.466	16.676	11.380	£191,593	£3,290	2	2	6	0%
Laser	£52,072	£37,060	23.234	15.466	16.671	11.376	£190,463	£2,159	4	2	9	1%
Thoracoscopy	£52,771	£37,920	23.096	15.375	16.622	11.346	£189,009	£706	5	3	10	0%
Hybrid	£60,905	£46,030	23.096	15.375	16.605	11.334	£180,643	-£7,660	11	10	12	0%
SA27 Vary TOE proportion (100%)												
AAD RFPP	£42,999	£28,694	21.827	14.764	15.645	10.835	£188,014	£0	6	2	6	1%
AAD RFME	£44,353	£29,914	21.826	14.764	15.624	10.821	£186,506	-£1,508	8	5	9	0%
AAD Cryo	£44,280	£29,957	21.844	14.773	15.653	10.839	£186,817	-£1,197	7	4	8	0%
AAD Laser	£44,866	£30,517	21.870	14.785	15.666	10.844	£186,365	-£1,650	9	5	9	0%
AAD Thora	£45,446	£31,398	21.542	14.610	15.488	10.755	£183,706	-£4,308	10	9	10	0%
AAD Hybrid	£50,094	£35,967	21.622	14.650	15.527	10.771	£179,452	-£8,563	12	11	12	0%
RF PP	£49,074	£34,057	23.231	15.464	16.670	11.377	£193,488	£5,473	1	1	1	98%
RF ME	£51,477	£36,247	23.199	15.449	16.614	11.342	£190,592	£2,578	3	2	7	0%
Cryoballoon	£51,375	£36,353	23.231	15.464	16.666	11.374	£191,129	£3,115	2	2	6	0%
Laser	£52,453	£37,424	23.231	15.464	16.661	11.371	£189,988	£1,974	4	2	9	1%
Thoracoscopy	£52,852	£37,984	23.092	15.373	16.613	11.342	£188,852	£837	5	2	10	0%

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Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
Hybrid	£61,228	£46,338	23.092	15.373	16.596	11.329	£180,245	-£7,769	11	11	12	0%
SA28 Change discounting to 1.5%												
AAD RFPP	£42,933	£35,611	21.831	18.238	15.654	13.220	£228,791	£40,777	6	5	7	0%
AAD RFME	£44,292	£36,903	21.832	18.240	15.635	13.203	£227,163	£39,149	9	7	10	0%
AAD Cryo	£44,208	£36,878	21.846	18.249	15.662	13.225	£227,625	£39,610	7	6	9	0%
AAD Laser	£44,789	£37,448	21.869	18.266	15.673	13.232	£227,199	£39,185	8	6	10	0%
AAD Thora	£45,457	£38,270	21.547	18.024	15.497	13.103	£223,799	£35,785	11	10	11	0%
AAD Hybrid	£50,037	£42,808	21.626	18.082	15.536	13.130	£219,798	£31,784	12	11	12	0%
RF PP	£48,930	£41,217	23.234	19.266	16.679	13.988	£238,549	£50,535	1	1	1	98%
RF ME	£51,343	£43,525	23.202	19.243	16.623	13.943	£235,333	£47,319	3	2	5	0%
Cryoballoon	£51,214	£43,499	23.234	19.266	16.676	13.986	£236,212	£48,198	2	2	5	0%
Laser	£52,274	£44,556	23.234	19.266	16.671	13.981	£235,072	£47,057	4	2	7	1%
Thoracoscopy	£52,857	£45,219	23.096	19.152	16.621	13.941	£233,609	£45,595	5	2	7	0%
Hybrid	£61,100	£53,451	23.096	19.152	16.605	13.927	£225,099	£37,084	10	6	12	0%
SA34 Cryoballoon ablation procedure costs reduced 61%												
AAD RFPP	£42,830	£28,559	21.838	14.769	15.655	10.841	£188,259	£244	7	4	7	0%
AAD RFME	£44,183	£29,778	21.837	14.769	15.634	10.826	£186,747	-£1,267	8	6	9	0%
AAD	£42,752	£28,465	21.853	14.777	15.662	10.844	£188,412	£398	6	3	7	1%

ISBN: 978-1-4731-4043-1

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
Cryo												
AAD Laser	£44,682	£30,372	21.876	14.788	15.673	10.848	£186,595	-£1,419	9	6	9	0%
AAD Thora	£45,350	£31,334	21.554	14.616	15.498	10.760	£183,870	-£4,144	10	9	10	0%
AAD Hybrid	£49,921	£35,826	21.633	14.655	15.536	10.776	£179,696	-£8,318	12	11	12	0%
RF PP	£48,825	£33,844	23.241	15.470	16.679	11.382	£193,800	£5,786	2	1	2	40%
RF ME	£51,228	£36,033	23.209	15.455	16.623	11.347	£190,902	£2,888	3	3	7	0%
Cryoballoon	£48,709	£33,724	23.241	15.470	16.676	11.380	£193,868	£5,853	1	1	3	59%
Laser	£52,168	£37,177	23.241	15.470	16.672	11.376	£190,352	£2,337	4	3	9	0%
Thoracoscopy	£52,750	£37,918	23.103	15.379	16.622	11.346	£189,002	£988	5	3	10	0%
Hybrid	£60,989	£46,135	23.103	15.379	16.606	11.334	£180,545	-£7,470	11	10	12	0%
SA35 CABANA validation and threshold on utility decrement AF symptom free (0.08)												
AAD RFPP	£42,591	£28,416	21.857	14.779	15.142	10.506	£181,695	-£6,319	6	3	6	0%
AAD RFME	£43,944	£29,636	21.855	14.779	15.120	10.490	£180,173	-£7,841	8	6	8	0%
AAD Cryo	£43,871	£29,679	21.874	14.788	15.146	10.506	£180,446	-£7,569	7	5	7	0%
AAD Laser	£44,456	£30,239	21.899	14.800	15.153	10.507	£179,909	-£8,105	9	7	9	0%
AAD Thora	£45,117	£31,198	21.570	14.625	15.032	10.458	£177,967	-£10,048	10	9	11	0%
AAD Hybrid	£49,696	£35,699	21.650	14.664	15.053	10.462	£173,542	-£14,473	12	11	12	0%

ISBN: 978-1-4731-4043-1

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	INMB @20K vs AADs RFPP	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
RF PP	£48,571	£33,689	23.264	15.481	16.208	11.089	£188,092	£78	1	1	2	94%
RF ME	£50,967	£35,871	23.231	15.466	16.154	11.055	£185,219	-£2,795	3	2	7	1%
Cryoballoon	£50,865	£35,978	23.264	15.481	16.201	11.084	£185,696	-£2,318	2	2	6	1%
Laser	£51,935	£37,042	23.264	15.481	16.191	11.076	£184,487	-£3,527	4	2	10	2%
Thoracoscopy	£52,492	£37,759	23.125	15.390	16.198	11.088	£184,005	-£4,009	5	2	9	2%
Hybrid	£60,728	£45,972	23.125	15.390	16.165	11.064	£175,303	-£12,712	11	10	12	0%

Table 51: 5 year time horizon (deterministic analysis SA29)

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	Rank @£20K	NMB @£30K	Rank @£30K
AAD RFPP	£9,478	£9,122	4.84	4.53	3.84	3.60	£62,811	1	£98,778	1
AAD RFME	£10,483	£10,118	4.84	4.53	3.84	3.59	£61,706	2	£97,618	2
AAD Cryo	£10,723	£10,366	4.84	4.53	3.84	3.60	£61,547	3	£97,503	3
AAD Laser	£11,264	£10,906	4.84	4.53	3.84	3.59	£60,964	4	£96,898	4
AAD Thora	£12,564	£12,214	4.82	4.51	3.84	3.59	£59,616	5	£95,531	5
AAD Hybrid	£16,977	£16,624	4.82	4.51	3.83	3.59	£55,135	10	£91,015	10
RF PP	£14,318	£13,989	4.87	4.55	3.89	3.64	£58,761	6	£95,136	6
RF ME	£16,185	£15,839	4.87	4.55	3.88	3.63	£56,715	7	£92,992	7
Cryoballoon	£16,621	£16,290	4.87	4.55	3.89	3.64	£56,427	8	£92,786	8
Laser	£17,814	£17,482	4.87	4.55	3.88	3.63	£55,170	9	£91,496	9
Thoracoscopy	£18,662	£18,339	4.84	4.53	3.88	3.63	£54,232	11	£90,517	11
Hybrid	£26,871	£26,546	4.84	4.53	3.87	3.62	£45,917	12	£82,149	12

ISBN: 978-1-4731-4043-1

ISBN: 978-1-4731-4043-1

2.5 Discussion

2.5.1 Summary of results

The base case and most sensitivity analyses found RFPP ablation was the most cost effective option at a threshold of £20,000 per QALY (probability of being most cost effective 98% in base case). The ICER of RFPP compared to AAD (RFPP) was £9,764 per QALY. All other options were dominated. AAD with cross over to RFPP had the lowest costs and RF PP had the highest QALYs. Hybrid ablation had the highest costs.

A data validation exercise was undertaken to compare the utility data in our model to the EQ5D data reported in a large mixed population RCT comparing catheter ablation to AADs (CABANA)[40]. We compared the utility difference between RF PP ablation and AADs (with cross over to RF PP) generated from our model with the difference in EQ5D from CABANA. This indicated that we may have underestimated the benefit of ablation, but our results are within the confidence intervals reported by CABANA. Furthermore, when the model was run using a greater utility decrement for AF S to better reflect CABANA, this analysis resulted in no change in the conclusions of the model, RFPP remained the most cost effective option.

The model was sensitive to the proportion of AAD cross over to ablation in the first year following AF symptom recurrence. When this was reduced to 14% or less, AAD with cross over to RFPP ablation became the most cost-effective option.

Finally, although RFPP remained the most cost effective option, the model was sensitive to changes in the cost of the ablation interventions such as reducing the cost of thoracoscopy, laser, cryoballoon. This was reflected in a reduction in the probability of RFPP being the most cost effective. Similarly, an exploratory analysis found that if all catheter ablation techniques costed the same as RF PP, the results became highly uncertain with the probability of RFPP, cryoballoon and laser each being the most cost effective being: 28%, 30% and 40% respectively.

2.5.2 Limitations and interpretation

This analysis had a number of limitations. Most notably, no direct evidence that could estimate the benefit of being free from AF symptoms in people who following ablation or AADs was identified and therefore indirect estimates were sought. A utility decrement associated with having AF symptoms of 0.04 was used in the model, based on evidence from the EuroHeart survey. A large number of sensitivity analyses were conducted to explore uncertainty around model parameters and model assumptions. A validation of the utility data was undertaken against the CABANA RCT, which represented a broad AF population. This validation exercise in combination with the threshold analysis conducted around this input, indicated that our base case utility data was likely to be representative of the broader symptomatic AF population. Using the higher utility decrement of 0.08 for AF symptom health state, as identified in the threshold analysis, the conclusions of the model remained unchanged.

There was uncertainty regarding the following areas:

- impact of ablation on stroke and mortality in the short term as denoted by the wide credible intervals from the NMA data
- impact of being symptom free on stroke risk

ISBN: 978-1-4731-4043-1

- AF recurrence over time (limited longitudinal evidence on the rate of AF recurrence beyond 1 year in the RCTs, and so assumptions were required, and other published sources were used to estimates rates of recurrence beyond the first year (CABANA trial and observational data from Gaia 2018)
- Costs of thoracoscopy, laser and cryoballoon ablation

These were explored in multiple sensitivity analyses, but the model conclusions were generally robust.

The model was sensitive to the proportion of people crossing over to ablation from AAD in the first year. When the proportion was reduced to 14%, AAD with cross over to RFPP became the most cost effective option. CABANA had a cross over rate of 39%, whereas our included RCTs had a mean cross over of 77%. The committee noted that in people who have failed 1 or more AAD and remained symptomatic, more than 14% would be considered for ablation in current practice.

An exploratory analysis where the cost of all catheter ablation was made equal to that of RFPP changed the cost effectiveness ranking to RFPP, followed by cryoballoon and then laser ablation. As this exploratory analysis was not based on evidence of equivalent overall cost, the committee could not make recommendations based on this exploratory analysis.

The committee noted that because of the way the NHS reference cost group procedures together under single HRGs, all catheter ablation procedures had the same procedural cost. As a result, potential savings that could be incurred from procedures that have a shorter duration, have same day discharge or that do not require general anaesthetic, such as cryoballoon ablation, are not captured in the analysis. This was explored in a threshold analysis to see by how much the procedure costs for cryoballoon would need to reduce for cryoballoon to be cost effective. A reduction of 61% (£2,401) is required. When estimating what the total savings may be if all people with cryoballoon ablation had sedation, shorter procedure time and same day discharge this equated to £1,289 in savings which is not enough for cryoballoon to become more cost effective than RFPP. The committee considered it would be an extreme scenario to assume all cryoballoon cases would be done using sedation and all RFPP would be under general anaesthetic. Similarly, it is unlikely all cryoballoon cases would be day cases and all RFPP would require overnight stay. Furthermore they noted that people who had sedation but required a trans-oesophageal echocardiogram then this would need to be done as a separate visit prior to ablation (day case) rather than during the allocated theatre time for the ablation procedure, thus possibly negating some of the procedural time savings associated with cryoballoon.

The committee also highlighted that there is a smaller evidence base for laser ablation, which may not fully capture rarer complications.

2.5.3 Generalisability to other populations or settings

The model was conducted in people with paroxysmal AF rather than all people with AF. It was not possible to model persistent AF as there was insufficient data. The clinical evidence in the evidence review did include a mixed population and studies such as CABANA have included mixed populations. These studies indicate that there may not be a significant difference in efficacy of ablation techniques between populations. Therefore, with caution, it may be possible to extrapolate the findings of this health economic analysis to a persistent AF population.

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This analysis does not compare first line rhythm control and therefore cannot inform recommendations for this specific population, but rather can inform recommendations for a population that has failed 1 or more AAD.

2.5.4 Comparisons with published studies

Seven health economic studies with relevant comparisons were included in the ablation evidence review (J1). One study included compared radiofrequency catheter ablation to alternative strategies as first line therapy for AF.[4] Four studies were included that compared ablation to alternative strategies as second line therapy for AF.[6, 8, 20, 42, 74, 78] Two studies compared cryoballoon ablation to radiofrequency ablation as second line therapy.[14, 45]

One Swedish study compared RF ablation to AADs as first line therapy for AF and found that ablation was not cost-effective compared to AADs (ICER £45,385).[4] A sensitivity analysis stratifying by age, suggested that ablation was cost effective for people younger than 50. This was a lifetime model based on a single RCT (MANTRA-PAF). The economic analysis had unclear methodological reporting, did not include all comparators of interest and effectiveness data was based on a single RCT, which was not included in our NMA review due to poor methodological reporting. Overall, this study was considered to be partially applicable with potential serious limitations.

Four studies were included that compared catheter ablation to AADs as second line therapy for AF.[6, 8, 20, 42, 74, 78] Each found that subject to certain assumptions, catheter ablation was cost effective compared to AADs (either dominates AADs or ICER between £7,000 and £21,000). All of these studies were considered to be partially applicable with potentially serious limitations. In particular, none of these studies included all comparators and none included the full body of clinical evidence identified in our clinical review. The assumptions made in these models regarding the rate of AF symptom recurrence were considered to be very favourable towards ablation and not reflective of current evidence. Most of these models assumed that being free of AF symptoms resulted in a reduction in stroke risk, which the committee considered to not be supported by current clinical evidence. Overall therefore the committee were not confident in the conclusion of these studies.

Finally, two studies compared cryoballoon ablation to RF ablation as second line therapy.[14, 45] Both were UK studies with very short time horizons (1-1.5years). One was a within trial cost consequence analysis which suggested that cryoballoon dominated (less costly and more effective) RF PP and the other was a cost utility analysis which found that cryoballon was not cost-effective when compared to RF ablation (ICER >£150,000 per QALY). Both studies were judged to be partially applicable with potentially serious limitations. The committee did not think either study provided valuable information to inform decision making.

As seen in the published models (Reynolds, Blackhouse and McKenna), when a short time horizon of 5 years is taken in this model, ablation interventions are no longer cost effective options and AAD (with cross over to RFPP) is the most cost effective option. This highlights the importance of fully capturing the long-term benefits of ablation in order to offset the upfront cost of the procedure.

2.5.5 Conclusions

RFPP ablation is the most cost effective rhythm control for people with paroxysmal AF who have previously failed one or more AAD. Conclusion is heavily dependent on rate of

ISBN: 978-1-4731-4043-1

crossover to ablation in those initially treated with AADs and are sensitive to the cost of ablation techniques.

ISBN: 978-1-4731-4043-1

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Appendices

Appendix A: Additional information

Table 52: Serious adverse events reported by comparator in RCTs

Intervention	Serious adverse events
Radiofrequency point by point ablation	• Cardiac tamponade • Pulmonary vein stenosis • Bradychardia, pacemaker insertion • Significant effusion requiring drainage • Major vascular events (incl MI) • Arteriovenous fistula (requiring surgical repair) • Bleeding • Pneumonia • Atrial/cardiac perforation • Diaphragmatic paralysis beyond BP • AF requiring cardioversion • Atrial flutter/tachycardia • Groin site complications • Transient neurological complications • Dyspnoea • GI complications • Pulmonary oedema • Heart failure
Radiofrequency multielectrode catheter ablation	• Pericardial drainage for pericardial tamponade due to perforation by mesh system • Retinal infarction • Transient global amnesia • Pneumonia • Pseudoaneurysm requiring thrombin injection but no long term sequelae • Cardiac tamponade that required additional 24 hr stay but no long term sequelae
Thoracoscopy	• Sternotomy for bleeding • Symptomatic pleural effusion • Post op lower respiratory tract infection
Cryoballoon catheter ablation	• Phrenic nerve injuries resolving in 3-17 months • Major vascular events • Major pericardial effusions • Retroperitoneal hematoma requiring surgery • Atrial flutter/tachycardia • Groin site complications • Cardiac tamponade • Pulmonary/bronchial complications

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Intervention	Serious adverse events
	• Transient neurological complications • Dyspnoea • GI complications
Laser ablation	• Need for later atrial septal closure after failure of atrial septal puncture site • Cardiac perforation • Tamponade • Significant effusion • PV stenosis • Diaphragmatic paralysis beyond BP • Atrio-esophageal fistula • Major bleeding • MI • AF requiring cardioversion
Medical management	• Hyperthyroidism • Bleeding • Atrial flutter • Syncope • Bradycardia • Life-threatening arrhythmias • Disabling drug intolerance requiring discontinuation

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Table 53: Ablation equipment costs

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NPC	Base description	SecondaryDescription	Unit of issue	Band 1 price	Unit price	Unit price excl. VAT	Number of uses*	Unit cost per use	RF PP total cost	RF ME total cost	Cryo total cost	Laser total cost	Thoracoscopy total cost	Hybrid total cost
FKD3348	Needle	Transseptal Guidewire with radiopaque coil 0.014inch Diam &135cm Length	5	£1,164	£233	£186	1	£186	£186	£186	£186			£186
FRH1206	Introducer	Swartz braided transseptal sl 8.5f/ 63cm	Each	£162	£162	£130	1	£130	£130	£130	£130	£130		£130
FRZ3453	Needle	71cm trans brk xs	Each	£132	£132	£106	1	£106	£106	£106	£106	£106		£106
FRB16791	Diagnostic Mapping Catheter	bw lasso 2515 nav eco variable ep 7f 02	Each	£761	£761	£609	1	£609	£609					£609
FRJ24442	Catheter	8f d curve 3 5mm 2 5 2mm 115cm	Each	£2,010	£2,010	£1,608	1	£1,608	£1,608					£1,608
FRJ24523	Cable*	Ez steer nav ablation	Each	£354	£354	£283	10	£28	£30					£30
FRJ24525	Accessories	Carto3 ref patches	Each	£714	£714	£571	1	£571	£571					£571
FRJ24570	Cable*	Lasso nav eco connection	Each	£354	£354	£283	10	£28	£30			£30		£30
FYU3251	Connecting Tubing	Coolflow pump tubing	Each	£46	£46	£36	1	£36	£36					£36
FRJ24571	Diagnostic Catheter	Webster deflectable 10 pole cs cath d curve 6f	Each	£384	£384	£307	1	£307	£307	£307	£307			£307
FCB15351	Cable*	Decapolar caths auto id	Each	£354	£354	£283	10	£28	£30	£30	£30			£30

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FRB14468	Ablation Catheter	Specialist catheters for pulmonary vein isolation either multipolar radiofrequency ablation or cryo-ablation 28mm	Each	£4,440	£4,440	£3,552	1	£3,552			£3,552			
FRB14471	Guiding Catheter	Steerable / deflectable flexible ep introducer sheath sets	Each	£960	£960	£768	1	£768			£768			
FVI2269	Mapping Catheter	Achieve mapping catheter 20mm	Each	£960	£960	£768	1	£768			£768			
FRB15597	Ablation Catheter	Pvac gold ablation bundle single pack includes pvac gold and greatbatch sheath	Each	£5,400	£5,400	£4,320	1	£4,320		£4,320				
From Dr Scott Gall		Laser kit (including sheaths, all connectors etc)				£3,500	1	£3,500				£3,500		
		Circatemp oesophageal temperature probe				£450	1	£450				£450		
		Endoscope (reusable)				£2,000	10	£200				£201		
		Abbott Livewire catheter				£160	1	£160				£160		

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		Sterilising box (100-150 uses)				£149	100	£1.49						
FRJ24335	Deflectable Catheter	7f 20 halo 2 8 2mm 110cm	Each	£1,152	£1,152	£922	1	£922				£922		
	Bilateral totally thoracoscopic epicardial ablation with radiofrequency													
FRP1369	Ablation Catheter	isolator linear pen	Each	£1,800	£1,800		1	£1,440					£720	£480
FRP1362	Accessories	isolator synergy clamp left curve	Each	£2,220	£2,220		1	£1,776					£888	£592
FRP1361	Accessories	isolator synergy clamp right curve	Each	£2,220	£2,220		1	£1,776					£888	£592
FRP1370	Ablation Catheter	lumitip dissector 27cm	Each	£1,800	£1,800		1	£1,440					£720	£480
	Right monolateral totally thoracoscopic epicardial ablation with radiofrequency													
FRP1377	Ablation Catheter	cobra fusion 150 epicardial probe with magnetic instrument set	Each	£4,680	£4,680		1	£3,744					£1,872	£1,248
	Subxiphoid or trans-diaphragmatic totally thoracoscopic epicardial ablation with radiofrequency													
FRP1385	Ablation Catheter	1x cdk 1413 epi sense guided coagulation system 3cm eu 1x csk 2000 cable kit rf coagulation 1x csk 6130 cannula w guide 30cm1x 017 m004 354 0 valley lab r ground pad	Each	£6,600	£6,600		1	£5,280						£1,760

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	Total ablation pass through cost (used in base case except laser ablation)	**£3,643**	**£5,078**	**£5,846**	**£5,498**	**£5,088**	**£8,795**
	Including 30% uplift on costs provided by single centre (Dr Gall estimates) – used in base case				**£6,762**		
	Excluding circular mapping catheter & cable and including uplift (sensitivity analysis)				**£5,810**		

*Source: NHS Supply chain catalogue,[56] unless otherwise stated. *Some of the equipment (cables) can be sterilised and reused (approx. 10 times). Therefore, those costs were divided by 10 and cost of sterilisation added.*

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