National Institute for Health and Care Excellence

Draft for consultation

Atrial fibrillation

Cost-effectiveness analysis: Ablation

NICE guideline

Economic analysis report

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Draft for Consultation

This guideline was developed by the National Guideline Centre

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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.

2 1 Methods

2.1 2 Model overview

3 2.1.1 Comparators

4 Twelve comparators were selected for the model:

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

13 The antiarrhythmic drugs were assumed to be oral amiodarone, flecainide, propafenone, or
14 sotalol based on the drugs used in the clinical evidence informing the network meta-analysis
15 (NMA) conducted as part of the review for this guideline question and current practice (see
16 J2. Ablation NMA).[28, 40, 52, 55, 58, 84, 85] Details of how this was incorporated into the model are
17 provided in **section 2.3.9.2** of this report.

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

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

25 2.1.2 Population

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

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

32 2.1.3 Time horizon, perspective, discount rates used

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

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[38]and Blackhouse et al 2013.[7]

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

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

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:

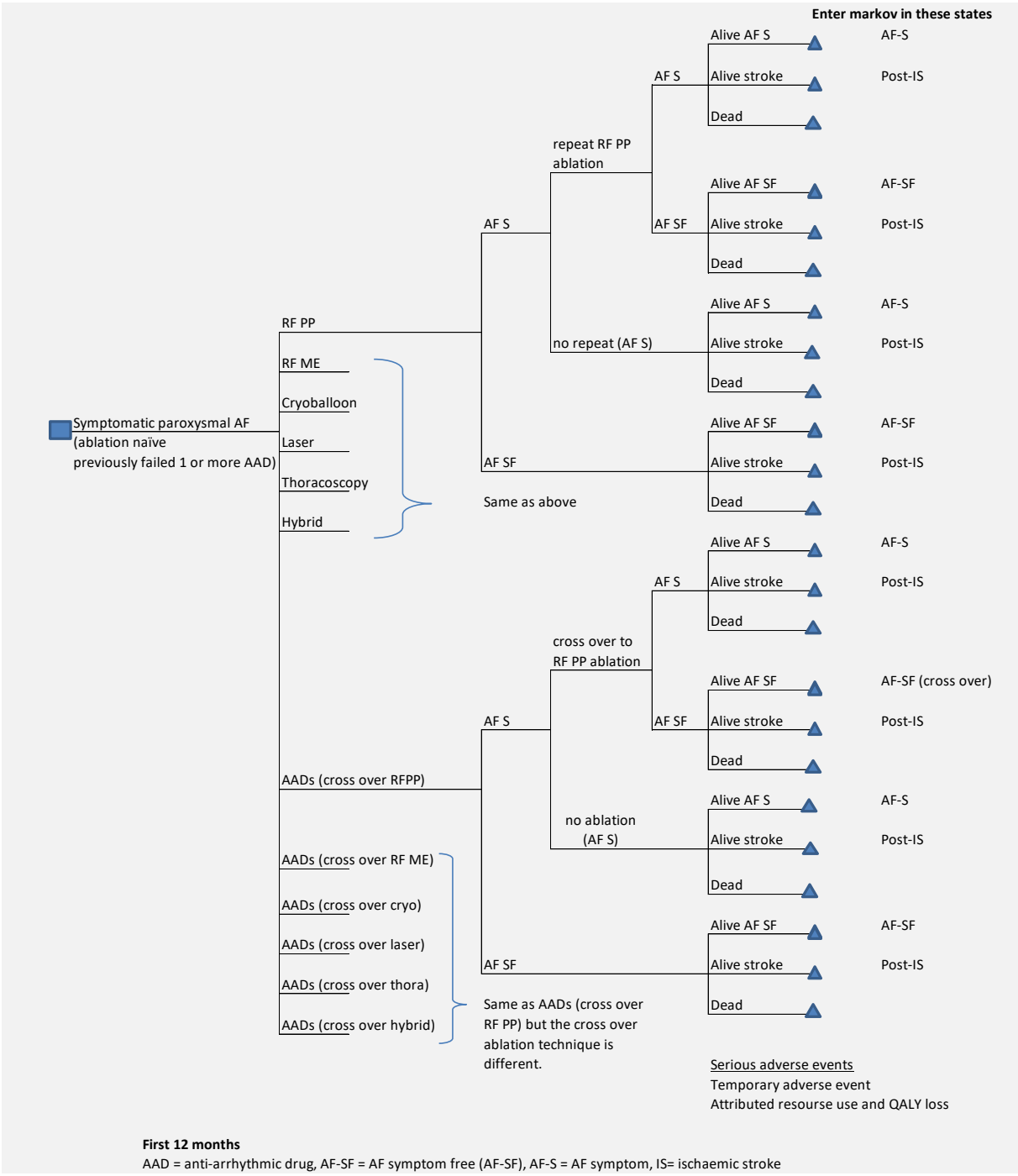
- Serious adverse events (SAEs)
- All stroke
- All-cause mortality
- AF symptom recurrence

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.

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.

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[77] (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.

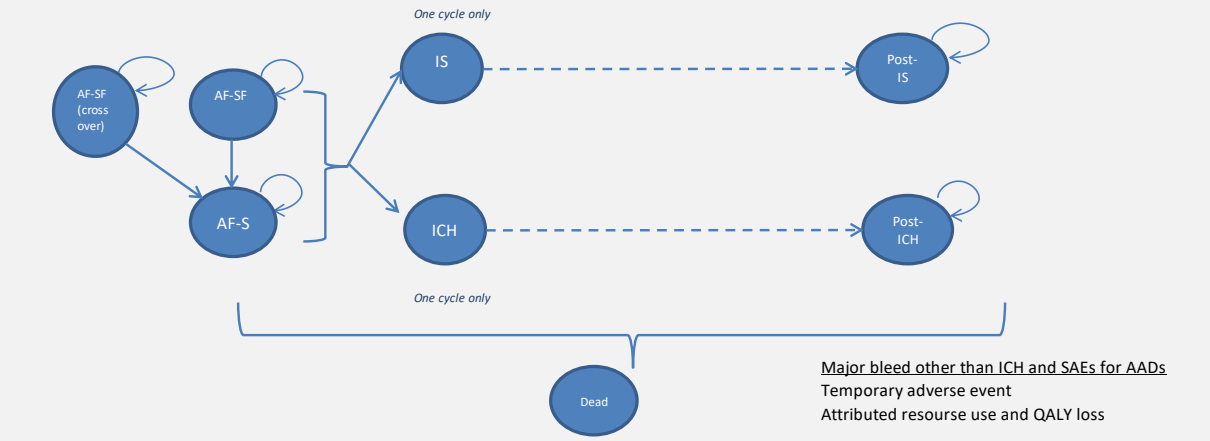
The probability of death was increased in the stroke and ICH states compared to those in the AF states. Death in initial 30 days after event was captured in the model; it was assumed no QALYs are contributed by these people, only acute costs of treating a fatal event. Mortality after 30 days following 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[38] 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[74] and noted that large safety studies of amiodarone showed no evidence of increased risk of

pulmonary toxicity and related mortality when amiodarone is used long term[10, 31]. For more details on which SAEs were captured please **see section 2.3.4.2**.

Figure 2: Markov model



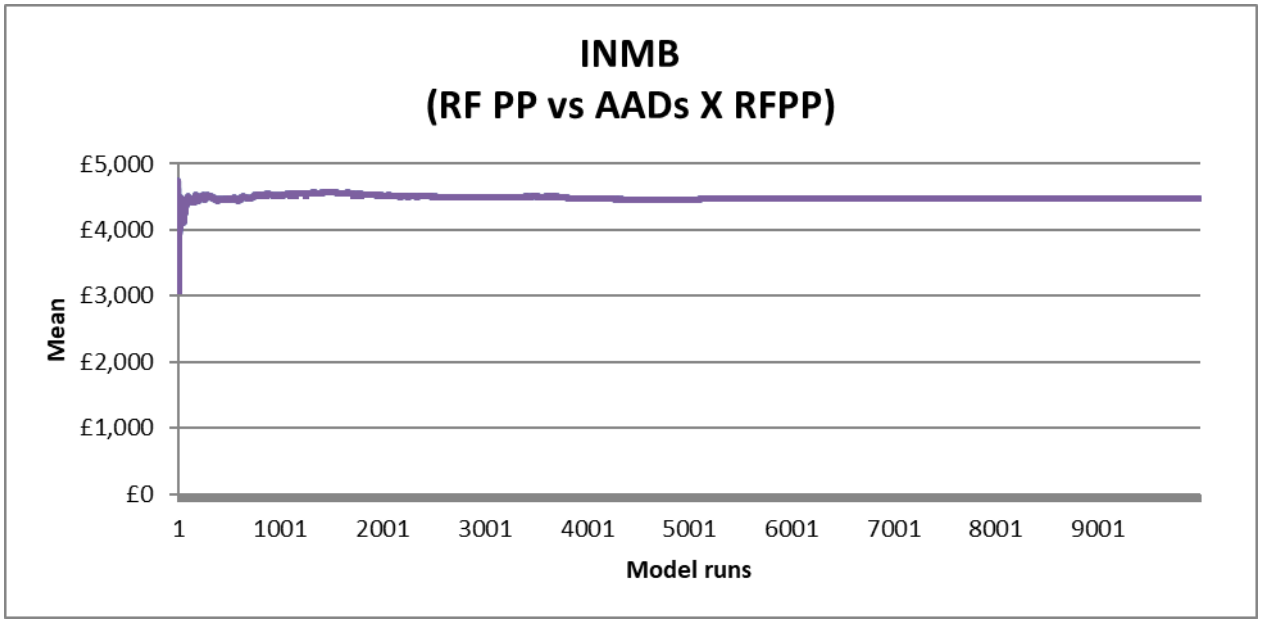
Beyond 1 year
Patients enter model in either AF symptom free (AF-SF), AF symptom (AF-S) or post-ischaemic stroke (Post-IS) health states
For those who had AAD and crossed over to ablation in the first year, they enter the AF-SF (crossover) state.
AF-SF = AF symptom free (AF-SF), AF-S = AF symptom, ICH=Intracranial 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)



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

Parameter	Type of distribution	Properties of distribution
		effect estimates.
Utility	Beta	Bounded between 0 and 1. Derived from mean of a domain or total quality of life score and its standard 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. *Note only impacts mortality beyond 1 yr*
Proportion male	64%	
CHADSVASC score	1-2	Based on reported means and medians in RCTs incl. in NMA. *Note CHADSVASC score distribution in FIRE and ICE[34] used in Markov to accurately capture ischaemic stroke risk*
Proportion anticoagulated	70%	Estimated looking at FIRE and ICE[34] CHADSVASC score distribution and current recommended thresholds for anticoagulant

Input	Data	Source
		Note this reduces to 20% anticoagulated in post-ICH health state
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,[34] Aspberg 2016[4] and Sterne 2017[77]
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.
Hybrid ablation		

Input	Data	Source
		Explore in SA where double baseline mortality assumed
Serious adverse events first year (decision tree)		
Catheter ablation		
Oesophageal injury (perforation/fistula)	0.5%	ESC 2016 guidelines[33]
Cardiac tamponade	1%	ESC 2016 guidelines[33]
Pulmonary vein stenosis	1%	ESC 2016 guidelines[33]
Persistent phrenic nerve palsy (cryoballoon ablation only)	1%	ESC 2016 guidelines[33]
Vascular complication	2%	ESC 2016 guidelines[33]
Other severe complication	1%	ESC 2016 guidelines[33] *Assume these are groin site complications*
Thoracoscopy/hybrid		
Atrial tear requiring sternotomy	10%	Pearman 2019[62]
Phrenic nerve injury	6.7%	Pearman 2019[62]
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[28], Morillo 2014,[40] Wazni 2005[84] and Wilber 2010[85] *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[59] and RF PP data from Pokushalov 2013[64] *SA using Pokushalov 2013[64]*
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[57], Gaita 2018[21] 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[57] then a constant hazard assumed.
IS	0.7%	Calculated using FIRE&ICE,[34] Aspberg 2016[4] and Sterne 2017[77] and distribution of anticoagulants from prescription cost analysis[27]
HR stroke AF-S vs. AF-SF	*1.6*	*SA only, not in basecase.* *AFFIRM study[76]*
ICH	0.6%	Sterne NMA,[77] 70% anticoagulated and distribution of anticoagulants from prescription cost analysis[27]
Major non-ICH bleed (all health states)	0.5%	

Input	Data	Source
Major non-ICH bleed (post-ICH health state only)	0.4%	Sterne NMA,[77] 20% anticoagulated and distribution of anticoagulants from prescription cost analysis[27]
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[30]
ICH mortality (28 days)	31.6% (22.7% to 42.8%)	Janes 2013[30] supported by Nielsen 2015[53]
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).[54]		
SMR IS and ICH health states	4.73	Bronnum-Hansen 2001,[9] SMR for non-fatal stroke
SMR post-IS and post ICH health state	2.32	Bronnum-Hansen 2001,[9] 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.[1] Applied multiplicatively with health state weights.
AF-S utility decrement	0.04	Berg 2010[6] *SA using Reynolds 2009[70] (0.046)* Decrement applied by using AF-SF utility and subtracting this utility decrement when in AF-S state.
IS	0.628	Tengs 2003,[80] weighted according to Youman 2003[87]
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)[81]
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[68]
Pulmonary vein stenosis	0.1 (6 months)	GC assumption
Phrenic nerve palsy	0.03 (1 year)	Reynolds 2014,[68] 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[68]
Costs		
Intervention costs		

Input	Data	Source
AADs (annual)	£256	BNF[8] & NHS reference costs,[15, 50] 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	£9,286	NHS reference costs2018/2019[50] for procedure, NHS supply chain catalogue[51] for pass through costs. Some laser pass through costs based on expert advice from Dr Scott Gall. 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*
RF ME ablation	£9,991	
Cryoballoon ablation	£10,951	
Laser ablation	£8,510	
Thoracoscopy	£13,831	
Hybrid ablation	£23,196	
Anticoagulant costs		
All states except post ICH	£460	BNF[8] and 70% anticoagulated and distribution of anticoagulants from prescription cost analysis
Post ICH only	£136	BNF[8] and 20% anticoagulated and distribution of anticoagulants from prescription cost analysis
Health state costs		
IS	£22,796	Xu 2018[86] 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[83] and Rosand 2004[73])*
Post-IS	£7,296	
ICH	£30,530 (SA: £20,543)	
Post-ICH	£14,414 (SA: £9,854)	
First fatal IS	£14,338	Xu 2018[86] 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[50] 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[15] inflated to 2018/2019 (excess bed days)[14] and NHS reference costs 2018/19 (ICU)[50]
Cardiac tamponade	£1,977	Calculated assuming 3 excess days. NHS reference costs
Pulmonary vein stenosis	£2,636	Calculated assuming 4 excess days. NHS reference costs 2017/2018[15] inflated to 2018/2019[50]
Vascular complication	£1,318	Calculated assuming 2 excess days. NHS

Input	Data	Source
Other severe complication	£1,318	reference costs 2017/2018[15] inflated to 2018/2019[50]
Persistent phrenic nerve palsy	£240	NHS reference costs 20118/2019[50] Assume CT scan and outpatient cardiology visit (as per Reynolds 2014[68])
Atrial tear requiring sternotomy	£7,471	NHS reference costs 2018/2019.[50] 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[34], 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[28], Pappone[58], and Wazni[84]. 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 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[52] 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[28] 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[28] (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[28]		Pappone[59]		Wazni[84]	
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
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%

Intervention	mean HR (95% CI)	Transition probability
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[79] and hybrid evidence[29] 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%.[12] Deskmukh 2013, a US register of 90,000 catheter ablations conducted between 2000-2010, reported an overall procedural complication rate of 6.29%.[16] 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%.[2] In this study the most common technique was RF PP followed by cryoballoon ablation, which unlike other catheter ablation techniques can lead to phrenic nerve palsy. Finally, the ESC 2016 AF guideline[33] 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 which would be the only type to be at risk of phrenic nerve palsy.

Several other sources were identified reporting complications following thoracoscopy and/or hybrid procedures. Pearman 2019,[62] a UK observational study comparing catheter ablation (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[61] 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,[82] 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[62] (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[33]
Cardiac tamponade	1.00%	0.20%	
Pulmonary vein stenosis	1.00%	0.20%	
Vascular complications	2.00%	0.40%	
Other severe complications	1.00%	0.20%	
Persistent phrenic nerve injury (cryoablation only)	1.00%	0.20%	
Thoracoscopy and hybrid ablation			
Persistent phrenic nerve injury	6.70%	1.34%	Pearman 2019[62]
Atrial tear requiring sternotomy	10.00%	2.00%	
AADs			
All SAEs related to AADs	5.50%	1.10%	Committee assumption informed by NMA and ESC 2016[33]

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%.[12, 16, 33] 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
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.[17, 34] 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.[79]

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,[79] 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%).[62] Pearman 2017 reports mortality rates between 0% and 6.1% for thoracoscopy and 0% and 12.5% for hybrid procedures.[61] Finally Vos 2018, reported a single death in a cohort of 500 patients receiving thoracoscopy.[82] 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).

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[84]	37	42	88%
Morillo 2014[40]	26	44	59%
Wazni 2005[84]	18	22	82%
Wilber 2010[85]	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[28]). 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 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[59] and Pokushalov 2013[64]). The AF recurrence following the first ablation and then following the second ablation reported in these studies were 27% and 33% for Pappone 2011[59] and 21% and 42% for Pokushalov 2013[64] 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[64] 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[64] and Pappone 2011[59]

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.[40, 52, 59] 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.[52] The fourth study compared RF PP to hybrid procedures and had a 36 month follow up.[29] 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[52] 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,[56] that have a longer follow up but did not specify which catheter ablation technique was used.

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.[11] Of these studies, the Committee identified Medi 2011,[39] and Sawhney 2009,[75] as the most widely referenced studies which reported the recurrence of AF following radiofrequency catheter ablation in paroxysmal AF patients.[39, 75] A more recent (Gaita 2018)[21] 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[56] 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[52] 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[37] 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[56]
2	0.557	291	
3	0.507	201	
4	0.483	134	
5	0.742	82	Gaita 2018[21]
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[56]
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[56]
2	9%	10%	
3	5%	7%	
4	2%	7%	
5	3%	7%	For ablation: Gaita 2018[21] 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.

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 32).

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[35]

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)[4]

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[77]

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)

Table 17: Ischaemic stroke probabilities and weighted average probability using FIRE and ICE[34, 77]

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[38] had conducted a systematic review of the literature and identified the AFFIRM study (Sherman 2005).[76] 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)[77] 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 (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.[77] 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 32). 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[77]

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

Intervention	Rate/HR (95% CI/SD)
	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[77]

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.[77] 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[77]

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)
HR: rivaroxaban vs warfarin	1.05 (0.98 to 1.13)

Table 21: Major bleed probabilities and weighted average probability using FIRE and ICE[34, 77]

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.[54] 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[19] 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.[9] 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.

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,[30] which was used in the edoxaban NICE TA[43]. 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.[53] 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[30]
ICH mortality (28 days)	31.6% (22.7% to 42.8%)	Janes 2013[30]

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.[22, 23, 32, 65, 67, 69] In both Blackhouse 2013[7] and McKenna 2009,[38] 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.[66]

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 models and was also highlighted in the recent rivaroxaban NICE TA for acute coronary syndrome[44] 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:[1]

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

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,[6] 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[7] model taken from Reynolds 2009: 0.046 (95% CI: 0.014,0.095).[70] 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).[20, 24, 71] 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)[45] and CG181 (lipid modification)[42] 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).[80,87] 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.[43, 48] Furthermore, evidence from an acute coronary syndrome population suggests that there is no evidence that health related quality of life improves over time.[47] 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[63] and Stevanovic 2014[78] used a utility decrement of 0.1385 (applied for 1 month and 2 weeks respectively) for other major bleed; however, the original source for this value was difficult to trace. TA355[43] and TA275[48] both use a utility decrement of 0.1070 for major bleed. This was taken from a health economic analysis by Thomson 2000.[81] 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[68] 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

Health State	Utility (SE)	Duration (for decrements)	Source
AF SF health state	Age adjusted general population utility	N/A	Ara 2010[1]
Ischaemic stroke (acute)	0.628 (0.04)	N/A	Tengs 2003,[80] Youman 2003[87]
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[6]
Major bleed	0.107 (0.021)[(a)]	2 weeks	Thomson 2000,[81] TA355[43] and TA275[48]
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[68] 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[68] and Packer 2013,[55] 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[68]

(a) Estimated SE, 20% of mean

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[50] for the relevant HRG procedure codes and the additional equipment costs provided by the NHS supply chain catalogue.[51] These costs were fixed in the probabilistic analysis.

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

Table 25: Catheter ablation HRG costs

Currency	Currency Description	Activity	Unit Cost

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 26 for the total HRG unit cost for both codes. Note that this would also affect the cost of hybrid ablation below.

Table 26: 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.[29] 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 27)

Table 27: 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, a sensitivity analysis was conducted around these costs (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 4 times. For laser ablation the endoscope can be sterilised and reused 50 times. 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**).

See Table 28 for a summary of the total equipment costs. A detailed breakdown of the costs is available in Appendix A: Table 51.

Table 28: Total equipment costs

Intervention	Total equipment cost (a)
RF PP ablation	£ 5,221
RF ME ablation	£ 5,927
Cryoballoon ablation	£ 6,887
Laser ablation	£ 4,455
Thoracoscopy	£ 6,360
Hybrid ablation	£ 11,661

(a) including sterilising where relevant

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

Table 29: Total ablation costs

Intervention	Cost
RF PP ablation	£9,286
RF ME ablation	£9,991
Cryoballoon ablation	£10,951
Laser ablation	£8,510
Thoracoscopy	£13,831
Hybrid ablation	£23,196

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 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 30 is a summary of the daily cost of AADs used in the model. The unit costs are taken from BNF.[8]

Table 30: 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[8]

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 31: Monitoring costs for AADs

Item and frequency	Unit cost	Source
Annual cardiology appointment (HRG: WF01A)	£135	NHS reference costs 2018-19[50]
Electrocardiogram (HRG EY51Z) for those on propafenone	£49	NHS reference costs 2018-19[50]
Liver and thyroid function tests, 6 monthly for those on amiodarone (HRG DAPS05)	£3	NHS reference costs 2018-19[50]
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.

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)[49] 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 32 below:

Table 32: 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

Drug	Weighting from Prescription Cost Analysis	Weighting from NHS BSA Medicines Optimisation Dashboard
All DOACs	53%	52%
Warfarin	47%	48%

Source: Prescription Cost Analysis 2018 and NHS BSA Medicines Optimisation Dashboard[27]
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 33. 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 33: 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[8]. For warfarin the committee assumed an average daily dose of 5mg.Weighting using Prescription Cost Analysis 2018 data.[27]

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.[68] The unit costs for hospitalisations (excess bed days following ablation procedures and critical care stays) were taken from the NHS reference 2017/2018 costs[15] 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.[14]

For phrenic nerve injury, as done in Reynolds 2014,[68] 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[50]).

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 34: Serious adverse events costs

Adverse event costs		
Oesophageal injury	£24,417	Calculated assuming 14 days in ICU and 7 excess days (ward). NHS reference

Adverse event costs		
		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

2.3.9.4 Health states

2.3.9.4.1 Ischaemic stroke & ICH

Costs of stroke were based on Xu 2018[86] 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[60]) 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.[14]

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[60], the Dublin stroke audit,[26] and a stroke audit in Surrey, England.[25]

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 35.

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 35: 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).[14]

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[50] for all categories of gastrointestinal bleed admission (weighted by number of attendances including excess bed days) was used; this is shown in **Table 36**. 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[15] and inflated to 2018/2019 prices using NHS cost inflation index.[14]

Table 36: 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)

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 37.

Table 37: 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 38 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 38: 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%

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 39: 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[64] 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.

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[57] 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 40 below. Please note that these transition probabilities were not made probabilistic in this sensitivity analysis as there was insufficient data to do so.

Table 40: 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.[57]*

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).[76] 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.

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.[70]

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.[50]

Table 41: Cost of thoracoscopy sensitivity analysis

Intervention	Base case cost(a)	Sensitivity analysis cost(b)
Thoracoscopy	£13,831	£9,417
Hybrid ablation	£23,196	£18,783

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

SA21: Cost of laser ablation equipment

The costs of laser ablation equipment (pass through costs) were 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. A sensitivity analysis was conducted where the equipment costs was increased by 30% to account for this. The total costs of laser ablation increased from £8,510 in the base case to £9,844 in this sensitivity analysis.

SA22: 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 analysis was

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

SA23: Cost of ICH evet 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[83]; this paper provided estimates for patients in dependent and independent states, which we averaged using a proportion reported in Rosand 2004[73]. See Table 42. These costs were inflated to 2018/2019 prices using the NHS cost inflation index (PSSRU 2019[14])

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

Table 42: 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

SA24&25: 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:

SA26: 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.

SA27: 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:

SA28&29: 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

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 43: CABANA EQ-5D data[36]

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 SA31 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.

SA30: 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.

SA31: 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 SA28).

SA32: AF S utility decrement from SA31

The model was rerun changing the utility decrement for AFS using the value identified in SA31. The probabilistic results were compared with the basecase probabilistic results to see whether this led to a change in the model conclusions.

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

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*	Cost effective compared to AAD (cross over RFPP) if:

RFPP)	• 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'[46] 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.

2.4 Results

2.4.1 Base case

The base case probabilistic results are reported in Table 44 and Table 45 and shown graphically in Figure 4. Breakdowns of clinical events and costs are presented in Table 46 and Table 47.

In the base case analysis, laser 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 66% and 67% respectively.

A full incremental analysis was also conducted and is depicted graphically in Figure 4. Interventions that were ruled out by dominance were AAD (RFPP), AAD (RFME), AAD (cryoballoon), AAD (thoracoscopy), AAD (hybrid), RF ME, thoracoscopy, cryoballoon and hybrid, they were all dominated by RF PP. The ICER was estimated between the remaining non-dominated interventions as represented by the lines. The ICER for laser versus AAD (laser) was £11,754 and for RF PP versus laser was £90,684.

Table 44: 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	£43,560	£29,349	21.847	14.774	15.661	10.844	£187,536	7	3	7	0%
AAD RFME	£44,506	£30,160	21.847	14.775	15.641	10.830	£186,437	9	5	9	0%
AAD Cryo	£44,540	£30,313	21.863	14.782	15.669	10.847	£186,635	8	5	9	0%
AAD Laser	£43,216	£28,967	21.885	14.793	15.679	10.852	£188,066	5	2	7	2%
AAD Thora	£45,919	£31,962	21.563	14.621	15.505	10.764	£183,319	10	9	10	0%
AAD Hybrid	£51,390	£37,355	21.642	14.660	15.543	10.780	£178,240	11	11	12	0%
RF PP	£50,631	£35,709	23.251	15.475	16.687	11.386	£192,016	2	1	3	31%
RF ME	£52,324	£37,187	23.219	15.460	16.631	11.351	£189,823	4	2	8	0%
Cryoballoon	£52,410	£37,483	23.251	15.475	16.683	11.384	£190,187	3	2	8	0%
Laser	£50,114	£35,182	23.251	15.475	16.679	11.380	£192,427	1	1	7	66%
Thoracoscopy	£54,066	£39,291	23.113	15.384	16.630	11.350	£187,716	6	3	10	0%
Hybrid	£63,965	£49,169	23.113	15.384	16.614	11.338	£177,596	12	11	12	0%

Table 45: 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	£43,560	£29,349	21.847	14.774	15.661	10.844	£295,978	7	6	8	0%

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	£44,506	£30,160	21.847	14.775	15.641	10.830	£294,736	9	7	10	0%
AAD Cryo	£44,540	£30,313	21.863	14.782	15.669	10.847	£295,108	8	6	0	0%
AAD Laser	£43,216	£28,967	21.885	14.793	15.679	10.852	£296,583	6	4	8	0%
AAD Thora	£45,919	£31,962	21.563	14.621	15.505	10.764	£290,960	11	10	11	0%
AAD Hybrid	£51,390	£37,355	21.642	14.660	15.543	10.780	£286,037	12	11	12	0%
RF PP	£50,631	£35,709	23.251	15.475	16.687	11.386	£305,879	2	1	2.025	34%
RF ME	£52,324	£37,187	23.219	15.460	16.631	11.351	£303,329	4	2	5	0%
Cryoballoon	£52,410	£37,483	23.251	15.475	16.683	11.384	£304,022	3	2	5	1%
Laser	£50,114	£35,182	23.251	15.475	16.679	11.380	£306,232	1	1	5	64%
Thoracoscopy	£54,066	£39,291	23.113	15.384	16.630	11.350	£301,219	5	3	9	1%
Hybrid	£63,965	£49,169	23.113	15.384	16.614	11.338	£290,978	10	8	12	0%

1 **Table 46: Event breakdown**

Intervention	First year			Post year 1			
	Stroke	AADs SAEs	Ablation SAEs	IS	ICH	Major bleeds	AADs SAEs
AAD RFPP	7	43	31	134	106	109	655
AAD RFME	11	43	31	133	105	109	658
AAD Cryo	7	43	37	134	106	109	658
AAD Laser	7	43	31	134	106	110	663
AAD Thora	7	42	125	132	104	108	611

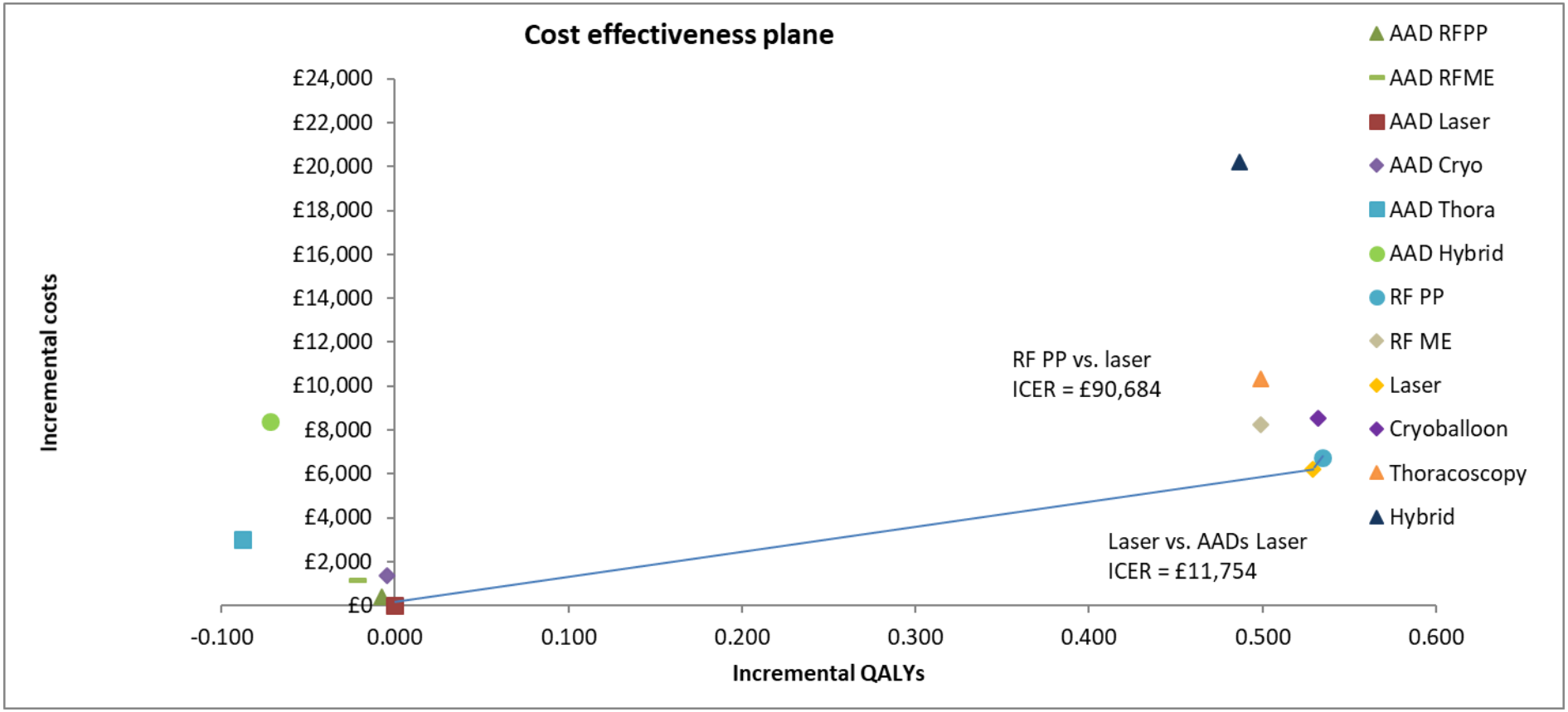
Intervention	First year			Post year 1			
AAD Hybrid	7	43	125	132	105	108	627
RF PP	7	11	68	143	113	117	504
RF ME	14	11	69	142	112	117	507
Cryoballoon	7	11	79	143	113	117	507
Laser	7	11	70	143	113	117	510
Thoracoscopy	7	9	174	142	112	116	464
Hybrid	7	9	176	142	112	116	477

Table 47: 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	£5,436	£458	£138	£174	£3,498	£7,869	£2,605	£9,203	£2,231	£10,051	£322	£478	£234	£863
AAD RFME	£5,834	£458	£216	£174	£3,461	£7,879	£2,596	£9,755	£2,223	£10,012	£321	£477	£234	£867
AAD Cryo	£6,375	£458	£138	£175	£3,465	£7,924	£2,607	£9,207	£2,233	£10,055	£322	£479	£234	£868
AAD Laser	£4,999	£458	£138	£174	£3,421	£7,998	£2,610	£9,212	£2,235	£10,061	£323	£479	£235	£873
AAD Thora	£7,994	£457	£138	£604	£3,917	£7,129	£2,568	£9,127	£2,200	£9,959	£317	£472	£231	£806
AAD Hybrid	£13,276	£457	£138	£605	£3,757	£7,395	£2,579	£9,145	£2,208	£9,980	£319	£473	£232	£826
RF PP	£11,535	£508	£138	£272	£3,919	£7,341	£2,793	£9,528	£2,386	£10,440	£345	£512	£250	£664
RF ME	£12,306	£508	£276	£274	£3,866	£7,321	£2,773	£10,500	£2,369	£10,363	£343	£508	£250	£668
Cryoballoon	£13,291	£508	£138	£277	£3,884	£7,390	£2,793	£9,528	£2,386	£10,440	£345	£512	£250	£668
Laser	£10,973	£509	£138	£278	£3,839	£7,451	£2,793	£9,528	£2,386	£10,440	£345	£512	£250	£672

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	£14,901	£497	£138	£800	£4,362	£6,656	£2,776	£9,476	£2,372	£10,376	£343	£509	£248	£611
Hybrid	£24,703	£500	£138	£811	£4,189	£6,894	£2,776	£9,476	£2,372	£10,376	£343	£509	£248	£629

Figure 4: Cost effectiveness plane base case



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 SA32 are presented in Table 48 and Table 49 below and graphically below. Conclusions about laser being the most cost effective intervention were unchanged in most sensitivity analyses. The exception being the sensitivity analyses SA8, SA10, SA21, SA22 and SA27.

In SA8, this analysis utilised the mortality NMA data for RF PP (reduced mortality risk) and the mortality for thoracoscopy and hybrid was double that of the baseline mortality (AADs). This sensitivity analysis resulted in RFPP being the most cost effective option, followed by laser, with the probability being most cost effective at £20,000 per QALY being 50% and 47% respectively.

SA10 was a sensitivity analysis where the probability of AAD cross over to ablation in the first year following AF symptom recurrence was reduced from 77% in base case to 25%. This resulted in AAD with cross over to laser ablation being the most cost-effective option (49% probability cost effective at £20,000 per QALY).

SA21 was a sensitivity analysis where the costs of laser ablation equipment were increased by 30% to account for potential locally negotiated cost reductions. This analysis resulted in RFPP being the most cost effective option, followed by laser ablation (68% and 29% probability most cost effective respectively).

SA22 was a sensitivity analysis where the cost of all catheter ablation was made equal to that of RFPP. In this analysis the ranking changed and RFPP was 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: 27%, 29% and 41% respectively.

SA27 (deterministic analysis) used a 5-year time horizon rather than a lifetime horizon and showed that AAD with cross over to laser became the most cost-effective option. Results are presented in Table 49.

SA28 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 (SA29). As SA19 (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 (SA31). 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 (SA32, Table 48). This analysis resulted in no change in the conclusions of the model, laser remained the most cost effective option.

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 43) and when the utility decrement for AF symptoms is increased, the model conclusions are unchanged.

Figure 5: Utility validation base case versus CABANA (SA28)

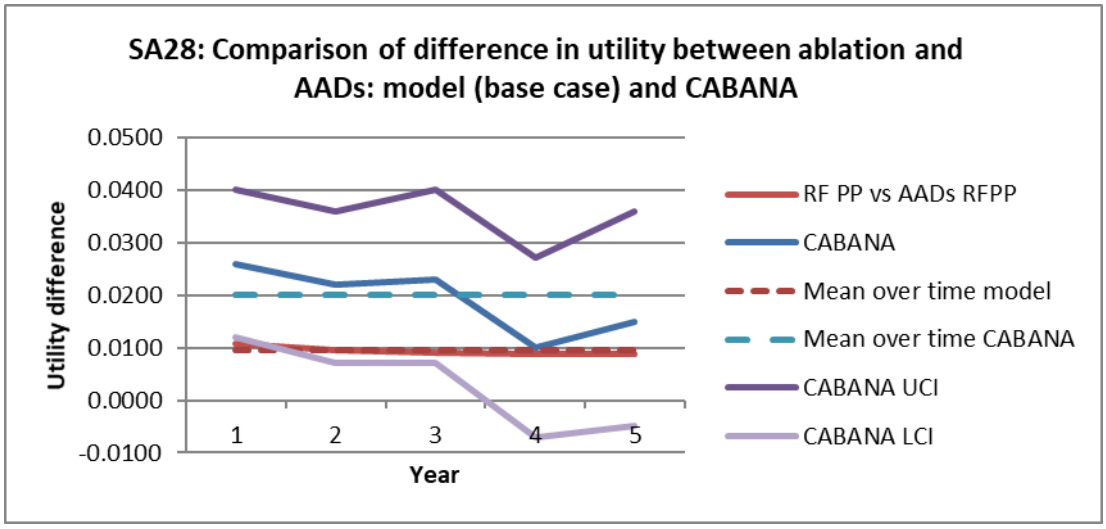


Figure 6: Utility validation Reynolds versus CABANA (SA29)

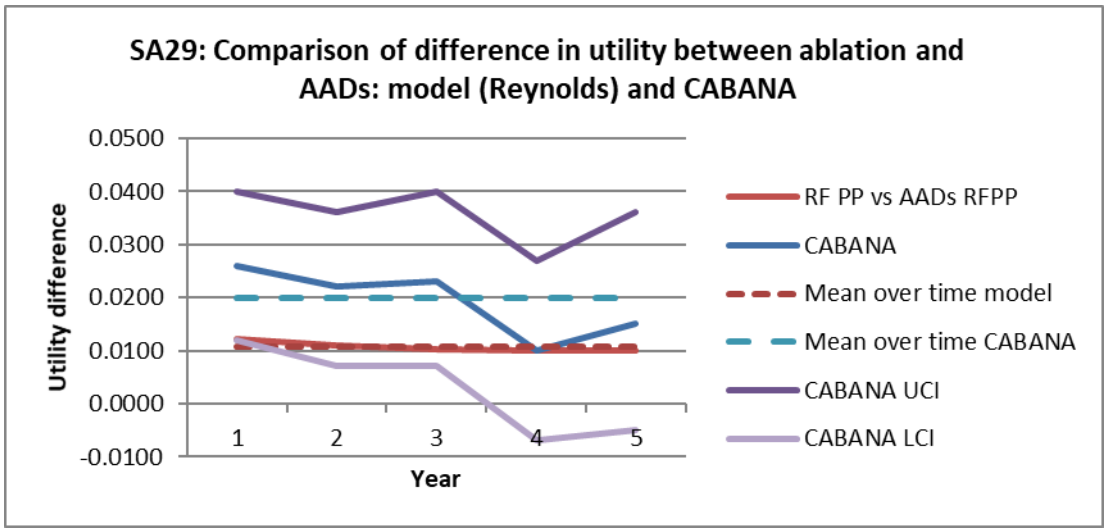
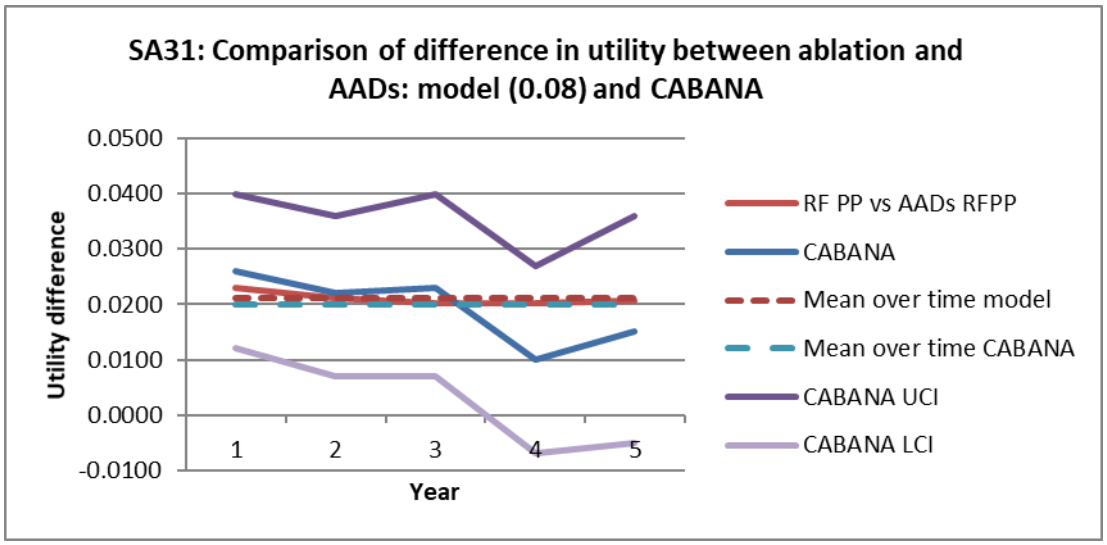


Figure 7: Utility validation using threshold value (0.08) versus CABANA (SA31)



SA30 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 48. This analysis found that the proportion cross over would need to be 30% (same for all AAD arms) for laser ablation to no longer be the most cost effective option. AAD with cross over to laser ablation would be the most cost effective option.

1 **Table 48: 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	£43,560	£29,349	21.847	14.774	15.661	10.844	£187,536	£0	7	3	7	0%
AAD RFME	£44,506	£30,160	21.847	14.775	15.641	10.830	£186,437	-£1,098	9	5	9	0%
AAD Cryo	£44,540	£30,313	21.863	14.782	15.669	10.847	£186,635	-£901	8	5	9	0%
AAD Laser	£43,216	£28,967	21.885	14.793	15.679	10.852	£188,066	£531	5	2	7	2%
AAD Thora	£45,919	£31,962	21.563	14.621	15.505	10.764	£183,319	-£4,216	10	9	10	0%
AAD Hybrid	£51,390	£37,355	21.642	14.660	15.543	10.780	£178,240	-£9,296	11	11	12	0%
RF PP	£50,631	£35,709	23.251	15.475	16.687	11.386	£192,016	£4,481	2	1	3	31%
RF ME	£52,324	£37,187	23.219	15.460	16.631	11.351	£189,823	£2,288	4	2	8	0%
Cryoballoon	£52,410	£37,483	23.251	15.475	16.683	11.384	£190,187	£2,652	3	2	8	0%
Laser	£50,114	£35,182	23.251	15.475	16.679	11.380	£192,427	£4,891	1	1	7	66%
Thoracoscopy	£54,066	£39,291	23.113	15.384	16.630	11.350	£187,716	£180	6	3	10	0%
Hybrid	£63,965	£49,169	23.113	15.384	16.614	11.338	£177,596	-£9,940	12	11	12	0%
SA1 Vary proportion receiving AADs post event (0%)												
AAD RFPP	£40,550	£27,459	21.833	14.767	15.654	10.841	£189,356	£0	6	3	7	0%
AAD RFME	£41,474	£28,255	21.832	14.767	15.633	10.826	£188,271	-£1,085	9	5	9	0%

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	£41,511	£28,410	21.850	14.776	15.662	10.844	£188,469	-£887	8	5	9	0%
AAD Laser	£40,165	£27,048	21.876	14.788	15.674	10.849	£189,940	£584	5	1	7	3%
AAD Thora	£43,163	£30,250	21.543	14.611	15.494	10.759	£184,929	-£4,427	10	9	10	0%
AAD Hybrid	£48,551	£35,584	21.629	14.654	15.536	10.776	£179,943	-£9,413	11	11	12	0%
RF PP	£47,803	£34,015	23.238	15.468	16.680	11.383	£193,646	£4,290	2	1	3	30%
RF ME	£49,464	£35,465	23.206	15.453	16.624	11.348	£191,491	£2,135	4	2	8	0%
Cryoballoon	£49,566	£35,778	23.238	15.468	16.676	11.380	£191,826	£2,470	3	2	8	0%
Laser	£47,273	£33,485	23.238	15.468	16.672	11.377	£194,050	£4,694	1	1	7	67%
Thoracoscopy	£51,441	£37,736	23.100	15.377	16.623	11.348	£189,218	-£138	7	4	10	0%
Hybrid	£61,299	£47,593	23.100	15.377	16.606	11.335	£179,099	-£10,257	12	11	12	0%
SA2 Vary proportion receiving AADs post event (100%)												
AAD RFPP	£45,327	£30,452	21.839	14.770	15.655	10.841	£186,373	£0	7	3	7	0%
AAD RFME	£46,277	£31,267	21.838	14.770	15.634	10.827	£185,265	-£1,107	9	6	9	0%
AAD Cryo	£46,315	£31,421	21.854	14.778	15.662	10.844	£185,463	-£910	8	5	9	0%
AAD Laser	£45,020	£30,095	21.881	14.791	15.675	10.849	£186,893	£521	5	2	7	2%
AAD Thora	£47,536	£32,961	21.551	14.615	15.497	10.760	£182,243	-£4,130	10	9	10	0%
AAD Hybrid	£53,066	£38,393	21.635	14.657	15.537	10.777	£177,141	-£9,232	11	11	12	0%

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	£52,332	£36,734	23.241	15.470	16.679	11.382	£190,903	£4,530	2	1	3	33%
RF ME	£54,023	£38,211	23.210	15.455	16.623	11.346	£188,715	£2,342	4	2	9	0%
Cryoballoon	£54,115	£38,511	23.241	15.470	16.675	11.379	£189,072	£2,700	3	2	8	0%
Laser	£51,867	£36,252	23.241	15.470	16.670	11.375	£191,251	£4,879	1	1	7	64%
Thoracoscopy	£55,607	£40,192	23.103	15.379	16.622	11.346	£186,737	£364	6	3	10	0%
Hybrid	£65,587	£50,137	23.103	15.379	16.604	11.333	£176,528	-£9,844	12	11	12	0%
SA3 Vary baseline (AAD) AF recurrence (50%)												
AAD RFPP	£42,524	£28,147	21.702	14.697	15.592	10.815	£188,157	£0	6	2	7	0%
AAD RFME	£43,162	£28,696	21.701	14.696	15.577	10.805	£187,406	-£751	8	4	9	0%
AAD Cryo	£43,192	£28,804	21.714	14.703	15.597	10.817	£187,543	-£614	7	4	9	0%
AAD Laser	£42,300	£27,893	21.733	14.712	15.607	10.821	£188,535	£378	5	1	7	4%
AAD Thora	£44,120	£29,919	21.507	14.592	15.484	10.760	£185,278	-£2,879	10	8	10	0%
AAD Hybrid	£47,856	£33,600	21.563	14.619	15.511	10.771	£181,821	-£6,336	11	11	11	0%
RF PP	£50,994	£35,937	23.228	15.463	16.669	11.377	£191,597	£3,440	2	1	5	31%
RF ME	£52,663	£37,393	23.196	15.448	16.613	11.342	£189,440	£1,284	4	2	9	0%
Cryoballoon	£52,776	£37,714	23.228	15.463	16.665	11.374	£189,763	£1,607	3	2	9	0%
Laser	£50,522	£35,453	23.228	15.463	16.660	11.370	£191,947	£3,791	1	1	8	64%
Thoracoscopy	£54,389	£39,480	23.090	15.372	16.612	11.341	£187,341	-£815	9	4	10	0%

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	£64,324	£49,393	23.090	15.372	16.595	11.328	£177,170	-£10,987	12	12	12	0%
SA4 Vary baseline (AAD) AF recurrence (90%)												
AAD RFPP	£44,692	£30,449	21.922	14.815	15.688	10.853	£186,615	£0	7	4	7	0%
AAD RFME	£45,851	£31,442	21.922	14.815	15.663	10.835	£185,268	-£1,348	9	6	9	0%
AAD Cryo	£45,895	£31,632	21.942	14.825	15.698	10.857	£185,512	-£1,103	8	6	9	0%
AAD Laser	£44,283	£29,988	21.973	14.840	15.713	10.864	£187,283	£668	6	2	7	2%
AAD Thora	£47,585	£33,653	21.574	14.627	15.497	10.755	£181,447	-£5,168	10	9	10	0%
AAD Hybrid	£54,304	£40,273	21.675	14.677	15.546	10.775	£175,227	-£11,388	12	11	12	0%
RF PP	£50,803	£35,819	23.238	15.468	16.675	11.380	£191,780	£5,165	2	1	3	32%
RF ME	£52,489	£37,292	23.206	15.453	16.619	11.344	£189,596	£2,981	4	2	8	0%
Cryoballoon	£52,583	£37,595	23.238	15.468	16.672	11.377	£189,950	£3,335	3	2	7	0%
Laser	£50,312	£35,318	23.238	15.468	16.667	11.374	£192,155	£5,540	1	1	6	65%
Thoracoscopy	£54,230	£39,394	23.100	15.377	16.618	11.344	£187,491	£876	5	3	9	0%
Hybrid	£64,157	£49,298	23.100	15.377	16.601	11.331	£177,330	-£9,285	11	11	12	0%
SA5 Vary baseline (AAD) mortality												
AAD RFPP	£43,014	£29,007	21.350	14.445	15.303	10.602	£183,039	£0	6	3	7	0%
AAD RFME	£43,955	£29,815	21.349	14.446	15.283	10.588	£181,942	-£1,098	8	5	9	0%
AAD	£43,994	£29,970	21.367	14.454	15.311	10.605	£182,139	-£900	7	5	9	0%

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	£42,678	£28,630	21.393	14.466	15.325	10.611	£183,592	£553	5	1	6	3%
AAD Thora	£45,150	£31,480	20.938	14.206	15.054	10.458	£177,672	-£5,368	10	9	10	0%
AAD Hybrid	£50,617	£36,869	21.018	14.245	15.092	10.473	£172,597	-£10,442	11	11	12	0%
RF PP	£50,094	£35,387	22.721	15.129	16.301	11.128	£187,170	£4,131	2	1	3	31%
RF ME	£51,777	£36,858	22.689	15.115	16.245	11.092	£184,991	£1,952	4	2	8	0%
Cryoballoon	£51,877	£37,165	22.721	15.129	16.297	11.125	£185,337	£2,298	3	2	8	0%
Laser	£49,608	£34,890	22.721	15.129	16.293	11.122	£187,553	£4,514	1	1	7	65%
Thoracoscopy	£53,085	£38,690	22.330	14.872	16.059	10.966	£180,635	-£2,404	9	4	10	0%
Hybrid	£63,009	£48,592	22.330	14.872	16.043	10.954	£170,494	-£12,545	12	11	12	0%
SA6 Apply stroke treatment effects												
AAD RFPP	£43,784	£29,488	21.830	14.766	15.652	10.840	£187,308	£0	5	3	7	0%
AAD RFME	£69,473	£49,168	21.293	14.521	14.410	10.031	£151,455	-£35,853	11	6	11	0%
AAD Cryo	£49,232	£33,861	21.747	14.728	15.437	10.699	£180,111	-£7,198	7	6	11	0%
AAD Laser	£43,447	£29,111	21.872	14.786	15.672	10.848	£187,852	£544	3	1	6	3%
AAD Thora	£46,128	£32,092	21.543	14.611	15.493	10.758	£183,076	-£4,233	6	5	10	0%
AAD Hybrid	£51,607	£37,489	21.625	14.652	15.533	10.775	£178,012	-£9,297	9	7	12	0%

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	£50,870	£35,859	23.232	15.465	16.675	11.380	£191,743	£4,435	2	1	3	31%
RF ME	£95,706	£70,454	21.678	14.734	14.057	9.732	£124,186	-£63,122	12	3	12	1%
Cryoballoon	£60,436	£43,610	22.957	15.336	16.208	11.086	£178,101	-£9,208	8	3	12	0%
Laser	£50,371	£35,350	23.232	15.465	16.667	11.374	£192,134	£4,826	1	1	5	65%
Thoracoscopy	£54,270	£39,409	23.094	15.374	16.618	11.344	£187,479	£171	4	3	8	0%
Hybrid	£64,199	£49,315	23.094	15.374	16.601	11.332	£177,323	-£9,985	10	7	12	0%
SA7 Stroke ME risk = AADs												
AAD RFPP	£43,722	£29,450	21.834	14.767	15.655	10.841	£187,380	£0	7	4	7	0%
AAD RFME	£44,139	£29,859	21.842	14.771	15.659	10.843	£187,005	-£375	8	4	9	0%
AAD Cryo	£44,701	£30,412	21.850	14.775	15.663	10.845	£186,479	-£902	9	6	9	0%
AAD Laser	£43,385	£29,072	21.875	14.788	15.675	10.850	£187,923	£543	5	2	7	3%
AAD Thora	£46,069	£32,053	21.547	14.613	15.497	10.760	£183,148	-£4,232	10	9	10	0%
AAD Hybrid	£51,542	£37,446	21.629	14.653	15.536	10.776	£178,084	-£9,297	11	11	12	0%
RF PP	£50,804	£35,819	23.237	15.467	16.679	11.382	£191,827	£4,447	2	1	4	26%
RF ME	£51,565	£36,577	23.237	15.467	16.677	11.381	£191,046	£3,666	3	1	7	7%
Cryoballoon	£52,584	£37,594	23.237	15.467	16.675	11.379	£189,994	£2,614	4	3	9	0%
Laser	£50,304	£35,308	23.237	15.467	16.671	11.376	£192,218	£4,838	1	1	7	64%
Thoracoscopy	£54,208	£39,371	23.098	15.376	16.621	11.346	£187,554	£174	6	4	10	0%

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	£64,133	£49,274	23.098	15.376	16.605	11.334	£177,402	-£9,979	12	11	12	0%
SA8 Apply mortality treatment effects												
AAD RFPP	£43,590	£29,369	21.884	14.798	15.691	10.864	£187,909	£0	6	3	8	0%
AAD RFME	£44,470	£30,139	21.847	14.774	15.644	10.832	£186,500	-£1,408	9	5	9	0%
AAD Cryo	£44,507	£30,293	21.864	14.782	15.673	10.850	£186,699	-£1,209	7	5	9	0%
AAD Laser	£43,207	£28,962	21.895	14.798	15.688	10.856	£188,161	£252	5	2	7	2%
AAD Thora	£45,755	£31,860	21.488	14.571	15.455	10.730	£182,735	-£5,173	10	9	10	0%
AAD Hybrid	£51,242	£37,263	21.575	14.614	15.497	10.747	£177,678	-£10,231	11	11	12	0%
RF PP	£50,726	£35,775	23.317	15.518	16.737	11.420	£192,621	£4,712	1	1	4	51%
RF ME	£52,289	£37,168	23.219	15.459	16.634	11.352	£189,875	£1,966	4	2	8	0%
Cryoballoon	£52,383	£37,471	23.251	15.474	16.686	11.385	£190,227	£2,318	3	2	8	0%
Laser	£50,153	£35,233	23.251	15.474	16.680	11.381	£192,377	£4,468	2	1	7	46%
Thoracoscopy	£53,775	£39,105	22.975	15.293	16.533	11.284	£186,584	-£1,324	8	5	10	0%
Hybrid	£63,735	£49,042	22.975	15.293	16.515	11.271	£176,375	-£11,533	12	11	12	0%
SA9 Vary proportion cross over to ablation 100%												
AAD RFPP	£44,585	£30,610	21.565	14.635	15.525	10.788	£185,142	£0	7	5	7	0%
AAD RFME	£45,822	£31,669	21.568	14.637	15.500	10.769	£183,717	-£1,425	9	7	9	0%
AAD	£45,856	£31,863	21.585	14.644	15.534	10.791	£183,960	-£1,182	8	7	9	0%

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	£44,150	£30,121	21.620	14.662	15.552	10.799	£185,850	£708	6	3	7	1%
AAD Thora	£47,645	£34,003	21.193	14.434	15.320	10.682	£179,642	-£5,500	10	10	11	0%
AAD Hybrid	£54,772	£41,028	21.298	14.486	15.370	10.703	£173,035	-£12,108	12	11	12	0%
RF PP	£50,741	£35,779	23.246	15.472	16.684	11.385	£191,915	£6,773	2	1	2	32%
RF ME	£52,442	£37,266	23.214	15.457	16.627	11.349	£189,709	£4,567	4	2	6	0%
Cryoballoon	£52,510	£37,544	23.246	15.472	16.680	11.382	£190,095	£4,952	3	2	6	0%
Laser	£50,252	£35,279	23.246	15.472	16.675	11.378	£192,288	£7,145	1	1	6	66%
Thoracoscopy	£54,152	£39,339	23.108	15.381	16.627	11.349	£187,640	£2,497	5	3	9	0%
Hybrid	£64,066	£49,231	23.108	15.381	16.610	11.336	£177,497	-£7,646	11	10	12	0%
SA10 Vary proportion cross over to ablation 25%												
AAD RFPP	£41,505	£26,668	22.472	15.083	15.961	10.969	£192,705	£0	2	1	6	3%
AAD RFME	£41,812	£26,932	22.472	15.083	15.954	10.964	£192,347	-£359	5	3	8	0%
AAD Cryo	£41,825	£26,982	22.477	15.086	15.964	10.970	£192,411	-£294	3	3	7	0%
AAD Laser	£41,392	£26,543	22.484	15.089	15.967	10.971	£192,877	£172	1	1	5	48%
AAD Thora	£42,270	£27,517	22.379	15.033	15.910	10.942	£191,331	-£1,374	7	5	10	0%
AAD Hybrid	£44,053	£29,274	22.405	15.046	15.923	10.948	£189,679	-£3,026	10	6	11	0%

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	£50,679	£35,745	23.250	15.474	16.683	11.384	£191,938	-£767	6	1	8	9%
RF ME	£52,363	£37,215	23.218	15.459	16.627	11.349	£189,756	-£2,949	9	3	11	0%
Cryoballoon	£52,461	£37,521	23.250	15.474	16.680	11.381	£190,102	-£2,603	8	3	11	0%
Laser	£50,150	£35,206	23.250	15.474	16.676	11.379	£192,365	-£340	4	1	10	40%
Thoracoscopy	£54,088	£39,302	23.112	15.383	16.627	11.349	£187,675	-£5,030	11	7	11	0%
Hybrid	£64,012	£49,203	23.112	15.383	16.610	11.336	£177,514	-£15,191	12	12	12	0%
SA11 Repeat ablation proportion = 100%												
AAD RFPP	£43,626	£29,387	21.844	14.773	15.658	10.842	£187,462	£0	7	3	7	0%
AAD RFME	£44,567	£30,195	21.843	14.773	15.638	10.828	£186,366	-£1,096	9	5	9	0%
AAD Cryo	£44,604	£30,349	21.860	14.780	15.666	10.846	£186,564	-£899	8	5	9	0%
AAD Laser	£43,281	£29,005	21.882	14.791	15.676	10.850	£187,990	£528	5	1	7	4%
AAD Thora	£45,974	£31,992	21.558	14.618	15.501	10.762	£183,243	-£4,220	10	9	10	0%
AAD Hybrid	£51,451	£37,387	21.642	14.660	15.541	10.778	£178,180	-£9,282	11	11	12	0%
RF PP	£51,218	£36,285	23.247	15.473	16.694	11.393	£191,569	£4,107	2	1	4	30%
RF ME	£52,912	£37,767	23.215	15.458	16.639	11.358	£189,387	£1,925	4	2	9	0%
Cryoballoon	£53,011	£38,074	23.247	15.473	16.692	11.391	£189,738	£2,276	3	2	9	0%
Laser	£50,743	£35,802	23.247	15.473	16.688	11.388	£191,959	£4,496	1	1	8	65%
Thoracoscopy	£54,354	£39,561	23.109	15.382	16.631	11.352	£187,488	£25	6	3	10	0%

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	£64,398	£49,585	23.109	15.382	16.616	11.341	£177,241	-£10,221	12	11	12	0%
SA12 Repeat ablation proportion = 0%												
AAD RFPP	£43,585	£29,370	21.846	14.773	15.660	10.843	£187,500	£0	7	5	7	0%
AAD RFME	£44,529	£30,180	21.846	14.774	15.640	10.829	£186,398	-£1,102	9	7	9	0%
AAD Cryo	£44,567	£30,335	21.863	14.782	15.668	10.847	£186,602	-£898	8	7	9	0%
AAD Laser	£43,257	£28,997	21.891	14.795	15.682	10.852	£188,050	£550	6	4	7	0%
AAD Thora	£45,939	£31,980	21.560	14.619	15.503	10.762	£183,269	-£4,231	10	10	10	0%
AAD Hybrid	£51,421	£37,382	21.641	14.659	15.542	10.779	£178,195	-£9,304	12	11	12	0%
RF PP	£48,629	£33,634	23.248	15.473	16.634	11.348	£193,320	£5,821	2	1	2	25%
RF ME	£50,258	£35,048	23.216	15.458	16.577	11.311	£191,179	£3,679	4	3	5	0%
Cryoballoon	£50,327	£35,325	23.248	15.473	16.629	11.343	£191,544	£4,044	3	2	5	0%
Laser	£47,934	£32,919	23.248	15.473	16.620	11.337	£193,815	£6,315	1	1	4	74%
Thoracoscopy	£53,116	£38,306	23.110	15.382	16.603	11.331	£188,315	£815	5	4	9	0%
Hybrid	£62,626	£47,781	23.110	15.382	16.577	11.312	£178,452	-£9,047	11	11	12	0%
SA13 Efficacy repeat ablation												
AAD RFPP	£43,704	£29,438	21.843	14.772	15.655	10.841	£187,381	£0	7	3	7	0%
AAD RFME	£44,647	£30,247	21.843	14.772	15.635	10.826	£186,283	-£1,098	9	5	9	0%
AAD	£44,681	£30,400	21.858	14.779	15.663	10.844	£186,475	-£905	8	5	9	0%

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	£43,365	£29,059	21.883	14.792	15.675	10.849	£187,922	£541	5	1	7	4%
AAD Thora	£46,056	£32,045	21.559	14.619	15.499	10.761	£183,170	-£4,211	10	9	10	0%
AAD Hybrid	£51,527	£37,439	21.638	14.658	15.537	10.776	£178,091	-£9,290	11	11	12	0%
RF PP	£50,871	£35,875	23.243	15.471	16.664	11.371	£191,540	£4,160	2	1	4	30%
RF ME	£52,556	£37,347	23.211	15.456	16.608	11.335	£189,355	£1,975	4	2	9	0%
Cryoballoon	£52,643	£37,643	23.243	15.471	16.660	11.368	£189,716	£2,335	3	2	8	1%
Laser	£50,376	£35,368	23.243	15.471	16.654	11.364	£191,905	£4,524	1	1	8	65%
Thoracoscopy	£54,251	£39,414	23.105	15.380	16.614	11.340	£187,395	£14	6	3	10	1%
Hybrid	£64,173	£49,310	23.105	15.380	16.595	11.326	£177,212	-£10,168	12	11	12	0%
SA14 AF recurrence after 1 yr: no AF recurrence after 1 yr												
AAD RFPP	£40,028	£27,821	19.367	13.758	14.358	10.345	£179,081	£0	8	6	9	0%
AAD RFME	£41,023	£28,654	19.394	13.770	14.352	10.336	£178,069	-£1,012	10	7	10	0%
AAD Cryo	£41,058	£28,809	19.410	13.777	14.379	10.354	£178,263	-£819	9	7	10	0%
AAD Laser	£39,771	£27,479	19.454	13.797	14.403	10.363	£179,784	£703	7	6	10	0%
AAD Thora	£41,792	£30,156	18.763	13.474	14.032	10.200	£173,845	-£5,236	11	10	11	0%
AAD Hybrid	£47,508	£35,664	18.974	13.568	14.139	10.242	£169,177	-£9,905	12	12	12	0%

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	£48,965	£34,767	23.246	15.472	17.004	11.567	£196,580	£17,499	2	1	3	33%
RF ME	£50,676	£36,255	23.214	15.457	16.944	11.529	£194,333	£15,252	4	2	5	1%
Cryoballoon	£50,766	£36,557	23.246	15.472	16.997	11.563	£194,698	£15,617	3	2	5	1%
Laser	£48,456	£34,236	23.246	15.472	16.992	11.560	£196,957	£17,876	1	1	5	64%
Thoracoscopy	£52,155	£38,194	23.108	15.381	16.984	11.553	£192,872	£13,791	5	2	5	2%
Hybrid	£62,184	£48,162	23.108	15.381	16.951	11.531	£182,454	£3,373	6	6	11	0%
SA15 AF recurrence after 1 yr: CABANA + no AF recurrence post yr 4												
AAD RFPP	£41,818	£28,707	20.355	14.191	14.861	10.544	£182,164	£0	7	6	8	0%
AAD RFME	£42,793	£29,531	20.372	14.198	14.850	10.533	£181,121	-£1,043	9	7	10	0%
AAD Cryo	£42,826	£29,684	20.387	14.205	14.877	10.550	£181,311	-£853	8	6	10	0%
AAD Laser	£41,559	£28,364	20.441	14.229	14.905	10.561	£182,853	£689	6	5	9	0%
AAD Thora	£43,846	£31,179	19.880	13.964	14.603	10.426	£177,334	-£4,830	11	10	11	0%
AAD Hybrid	£49,475	£36,646	20.045	14.037	14.686	10.458	£172,520	-£9,643	12	11	12	0%
RF PP	£50,041	£35,449	23.231	15.464	16.837	11.462	£193,794	£11,631	2	1	3	34%
RF ME	£51,744	£36,932	23.199	15.450	16.779	11.425	£191,577	£9,414	4	2	5	1%
Cryoballoon	£51,831	£37,231	23.231	15.464	16.832	11.459	£191,940	£9,776	3	2	5	1%
Laser	£49,592	£34,977	23.231	15.464	16.824	11.453	£194,090	£11,927	1	1	5	63%
Thoracoscopy	£53,344	£38,953	23.093	15.374	16.800	11.437	£189,781	£7,617	5	2	6	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)
Hybrid	£63,345	£48,908	23.093	15.374	16.774	11.419	£179,472	-£2,691	10	6	12	0%
SA16 AAD AF recurrence post 1 yr adjusted to represent 0% cross over												
AAD RFPP	£43,502	£29,293	21.931	14.813	15.709	10.865	£188,016	£0	7	3	7	0%
AAD RFME	£44,443	£30,100	21.930	14.812	15.688	10.851	£186,914	-£1,102	9	5	9	0%
AAD Cryo	£44,478	£30,254	21.947	14.820	15.717	10.868	£187,114	-£902	8	5	9	0%
AAD Laser	£43,151	£28,907	21.967	14.830	15.727	10.873	£188,548	£532	5	1	7	3%
AAD Thora	£45,835	£31,888	21.639	14.656	15.549	10.783	£183,780	-£4,237	10	9	10	0%
AAD Hybrid	£51,323	£37,290	21.726	14.699	15.591	10.801	£178,725	-£9,291	11	11	12	0%
RF PP	£50,489	£35,620	23.259	15.479	16.702	11.395	£192,284	£4,268	2	1	3	30%
RF ME	£52,167	£37,084	23.227	15.464	16.646	11.360	£190,111	£2,095	4	2	9	0%
Cryoballoon	£52,257	£37,384	23.259	15.479	16.699	11.393	£190,470	£2,454	3	2	8	0%
Laser	£49,947	£35,068	23.259	15.479	16.695	11.390	£192,734	£4,718	1	1	7	66%
Thoracoscopy	£53,878	£39,158	23.121	15.388	16.646	11.360	£188,047	£31	6	3	10	0%
Hybrid	£63,832	£49,089	23.121	15.388	16.628	11.347	£177,845	-£10,171	12	11	12	0%
SA17 Stroke risk reduction for AF symptom free health state												
AAD RFPP	£42,401	£28,603	21.900	14.803	15.734	10.887	£189,135	£0	7	4	7	0%
AAD RFME	£43,358	£29,421	21.898	14.803	15.713	10.872	£188,017	-£1,117	9	6	9	0%
AAD	£43,391	£29,573	21.915	14.810	15.741	10.889	£188,212	-£922	8	6	9	0%

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	£42,113	£28,257	21.944	14.824	15.753	10.894	£189,630	£496	6	2	7	1%
AAD Thora	£44,578	£31,098	21.622	14.653	15.589	10.813	£185,163	-£3,972	10	9	10	0%
AAD Hybrid	£50,109	£36,529	21.698	14.690	15.622	10.826	£179,995	-£9,139	12	11	12	0%
RF PP	£49,139	£34,744	23.383	15.539	16.826	11.461	£194,478	£5,344	2	1	3	34%
RF ME	£50,840	£36,224	23.350	15.523	16.768	11.425	£192,273	£3,138	4	2	8	1%
Cryoballoon	£50,924	£36,520	23.382	15.539	16.821	11.458	£192,636	£3,502	3	2	8	1%
Laser	£48,709	£34,288	23.380	15.537	16.813	11.452	£194,754	£5,620	1	1	7	62%
Thoracoscopy	£52,380	£38,194	23.261	15.456	16.786	11.435	£190,500	£1,365	5	3	10	1%
Hybrid	£62,348	£48,117	23.255	15.453	16.763	11.419	£180,263	-£8,871	11	11	12	0%
SA18 HR warfarin vs no treatment ICH												
AAD RFPP	£46,352	£31,048	21.664	14.682	15.501	10.759	£184,133	£0	6	3	7	0%
AAD RFME	£47,286	£31,852	21.665	14.683	15.482	10.745	£183,050	-£1,083	9	5	9	0%
AAD Cryo	£47,332	£32,012	21.680	14.690	15.508	10.762	£183,225	-£907	8	5	9	0%
AAD Laser	£46,024	£30,676	21.707	14.703	15.522	10.768	£184,674	£542	5	1	7	4%
AAD Thora	£48,687	£33,646	21.386	14.531	15.348	10.680	£179,946	-£4,187	10	9	10	0%
AAD Hybrid	£54,156	£39,039	21.461	14.568	15.384	10.695	£174,858	-£9,275	11	11	12	0%

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	£53,536	£37,474	23.032	15.367	16.499	11.288	£188,288	£4,156	2	1	4	31%
RF ME	£55,204	£38,937	23.002	15.353	16.445	11.253	£186,132	£2,000	4	2	9	0%
Cryoballoon	£55,310	£39,245	23.032	15.367	16.496	11.285	£186,463	£2,330	3	2	8	0%
Laser	£53,058	£36,985	23.032	15.367	16.491	11.281	£188,644	£4,511	1	1	8	65%
Thoracoscopy	£56,942	£41,034	22.896	15.277	16.442	11.252	£184,003	-£129	7	3	10	0%
Hybrid	£66,832	£50,904	22.896	15.277	16.427	11.240	£173,905	-£10,228	12	11	12	0%
SA19 Utility decrement AF symptoms use Reynolds data												
AAD RFPP	£43,551	£29,347	21.839	14.770	15.578	10.791	£186,471	£0	7	3	7	0%
AAD RFME	£44,492	£30,156	21.837	14.770	15.557	10.776	£185,367	-£1,105	9	6	9	0%
AAD Cryo	£44,535	£30,314	21.857	14.779	15.586	10.794	£185,568	-£903	8	5	9	0%
AAD Laser	£43,206	£28,965	21.878	14.789	15.596	10.798	£186,992	£521	5	2	7	2%
AAD Thora	£45,899	£31,953	21.551	14.615	15.427	10.715	£182,346	-£4,125	10	9	10	0%
AAD Hybrid	£51,376	£37,351	21.632	14.655	15.463	10.729	£177,225	-£9,246	11	11	12	0%
RF PP	£50,626	£35,711	23.246	15.472	16.611	11.340	£191,082	£4,611	2	1	3	32%
RF ME	£52,302	£37,174	23.214	15.457	16.556	11.304	£188,915	£2,444	4	2	9	0%
Cryoballoon	£52,416	£37,495	23.246	15.472	16.607	11.336	£189,231	£2,760	3	2	8	1%
Laser	£50,109	£35,183	23.246	15.472	16.603	11.333	£191,482	£5,010	1	1	7	65%
Thoracoscopy	£54,030	£39,263	23.107	15.381	16.562	11.309	£186,927	£455	6	3	10	0%

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	£63,946	£49,157	23.107	15.381	16.542	11.295	£176,739	-£9,733	12	11	12	0%
SA20 Cost of thoracoscopy procedure												
AAD RFPP	£43,827	£29,510	21.828	14.765	15.643	10.835	£187,185	£0	7	4	7	0%
AAD RFME	£44,771	£30,320	21.829	14.765	15.623	10.820	£186,087	-£1,098	9	6	10	0%
AAD Cryo	£44,808	£30,474	21.845	14.773	15.651	10.838	£186,283	-£902	8	6	9	0%
AAD Laser	£43,486	£29,130	21.868	14.784	15.663	10.843	£187,727	£542	6	2	7	1%
AAD Thora	£43,687	£29,628	21.542	14.610	15.486	10.754	£185,448	-£1,738	10	7	10	0%
AAD Hybrid	£49,163	£35,023	21.624	14.651	15.525	10.770	£180,381	-£6,805	12	11	12	0%
RF PP	£50,919	£35,888	23.230	15.464	16.667	11.376	£191,627	£4,442	3	1	4	13%
RF ME	£52,607	£37,362	23.198	15.449	16.611	11.340	£189,439	£2,254	5	3	10	0%
Cryoballoon	£52,700	£37,664	23.230	15.464	16.663	11.373	£189,793	£2,608	4	3	9	0%
Laser	£50,409	£35,367	23.230	15.464	16.659	11.370	£192,032	£4,847	1	1	7	53%
Thoracoscopy	£49,914	£35,031	23.092	15.373	16.610	11.340	£191,768	£4,583	2	1	6	33%
Hybrid	£59,839	£44,933	23.092	15.373	16.593	11.327	£181,615	-£5,570	11	11	12	0%
SA21 Laser equipment costs increase (30%)												
AAD RFPP	£43,479	£29,303	21.847	14.774	15.669	10.849	£187,685	£0	6	3	7	1%
AAD RFME	£44,418	£30,110	21.845	14.773	15.648	10.834	£186,577	-£1,108	9	5	9	0%
AAD	£44,458	£30,266	21.863	14.782	15.677	10.852	£186,781	-£904	8	5	9	0%

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	£43,880	£29,669	21.883	14.792	15.687	10.857	£187,463	-£222	7	2	8	1%
AAD Thora	£45,823	£31,906	21.558	14.618	15.510	10.768	£183,446	-£4,239	10	9	10	0%
AAD Hybrid	£51,299	£37,302	21.640	14.659	15.550	10.784	£178,380	-£9,305	11	11	12	0%
RF PP	£50,548	£35,663	23.253	15.476	16.696	11.391	£192,159	£4,474	1	1	3	67%
RF ME	£52,221	£37,122	23.221	15.460	16.640	11.356	£189,994	£2,309	4	2	8	0%
Cryoballoon	£52,323	£37,434	23.253	15.476	16.692	11.388	£190,334	£2,648	3	2	8	1%
Laser	£51,347	£36,453	23.253	15.476	16.689	11.386	£191,266	£3,580	2	1	9	30%
Thoracoscopy	£53,942	£39,206	23.115	15.385	16.638	11.355	£187,902	£217	5	3	10	0%
Hybrid	£63,863	£49,105	23.115	15.385	16.622	11.343	£177,758	-£9,927	12	11	12	0%
SA22 Cost of all catheter ablation = RFPP												
AAD RFPP	£43,802	£29,497	21.835	14.768	15.654	10.841	£187,313	£0	8	4	8	0%
AAD RFME	£44,349	£29,909	21.835	14.769	15.633	10.826	£186,613	-£700	9	6	9	0%
AAD Cryo	£43,842	£29,521	21.851	14.776	15.661	10.843	£187,347	£34	7	3	8	0%
AAD Laser	£43,904	£29,558	21.877	14.789	15.674	10.849	£187,419	£105	6	3	9	1%
AAD Thora	£46,146	£32,100	21.547	14.613	15.495	10.759	£183,085	-£4,228	10	9	10	0%
AAD Hybrid	£51,627	£37,498	21.631	14.654	15.535	10.776	£178,021	-£9,293	11	11	12	0%

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	£50,893	£35,874	23.235	15.467	16.676	11.380	£191,736	£4,422	1	1	4	27%
RF ME	£51,875	£36,643	23.203	15.452	16.620	11.345	£190,257	£2,943	4	2	8	2%
Cryoballoon	£51,001	£35,978	23.235	15.467	16.672	11.378	£191,576	£4,263	2	1	6	30%
Laser	£51,178	£36,148	23.235	15.467	16.667	11.374	£191,332	£4,019	3	1	9	39%
Thoracoscopy	£54,291	£39,421	23.097	15.376	16.619	11.345	£187,478	£165	5	4	10	0%
Hybrid	£64,226	£49,333	23.097	15.376	16.602	11.332	£177,307	-£10,006	12	11	12	0%
SA23 Cost of ICH event, alternative source												
AAD RFPP	£39,953	£27,231	21.823	14.762	15.639	10.832	£189,408	£0	7	3	7	0%
AAD RFME	£40,912	£28,050	21.824	14.763	15.619	10.818	£188,306	-£1,102	9	5	9	0%
AAD Cryo	£40,930	£28,193	21.839	14.770	15.646	10.835	£188,505	-£902	8	5	9	0%
AAD Laser	£39,612	£26,852	21.865	14.783	15.659	10.840	£189,949	£541	5	1	7	3%
AAD Thora	£42,343	£29,859	21.539	14.609	15.482	10.752	£185,173	-£4,235	10	9	10	0%
AAD Hybrid	£47,804	£35,247	21.617	14.647	15.520	10.767	£180,100	-£9,307	11	11	12	0%
RF PP	£46,867	£33,518	23.224	15.461	16.662	11.373	£193,937	£4,529	2	1	3	32%
RF ME	£48,588	£35,012	23.192	15.446	16.606	11.337	£191,732	£2,324	4	2	9	0%
Cryoballoon	£48,644	£35,290	23.224	15.461	16.658	11.370	£192,108	£2,700	3	2	8	0%
Laser	£46,375	£33,014	23.224	15.461	16.653	11.366	£194,309	£4,901	1	1	7	65%
Thoracoscopy	£50,309	£37,097	23.086	15.370	16.605	11.337	£189,643	£235	6	3	10	0%

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	£60,213	£46,980	23.086	15.370	16.589	11.325	£179,523	-£9,884	12	11	12	0%
SA24 Vary TOE proportion (0%)												
AAD RFPP	£43,541	£29,311	21.839	14.770	15.658	10.843	£187,549	£0	7	3	7	0%
AAD RFME	£44,488	£30,122	21.840	14.771	15.639	10.829	£186,458	-£1,091	9	5	9	0%
AAD Cryo	£44,514	£30,271	21.853	14.777	15.665	10.846	£186,643	-£906	8	5	9	0%
AAD Laser	£43,196	£28,929	21.876	14.788	15.677	10.851	£188,089	£539	5	2	7	2%
AAD Thora	£45,958	£31,986	21.551	14.615	15.500	10.762	£183,247	-£4,303	10	9	10	0%
AAD Hybrid	£51,364	£37,310	21.634	14.656	15.540	10.778	£178,256	-£9,293	11	11	12	0%
RF PP	£50,533	£35,592	23.243	15.470	16.684	11.385	£192,099	£4,550	2	1	3	31%
RF ME	£52,230	£37,074	23.211	15.455	16.627	11.349	£189,903	£2,354	4	2	8	1%
Cryoballoon	£52,295	£37,349	23.243	15.470	16.681	11.382	£190,295	£2,746	3	2	8	1%
Laser	£50,014	£35,062	23.243	15.470	16.677	11.379	£192,522	£4,973	1	1	7	66%
Thoracoscopy	£54,076	£39,283	23.105	15.379	16.627	11.349	£187,696	£147	6	4	10	0%
Hybrid	£63,878	£49,062	23.105	15.379	16.610	11.336	£177,660	-£9,889	12	11	12	0%
SA25 Vary TOE proportion (100%)												
AAD RFPP	£43,759	£29,500	21.834	14.768	15.654	10.841	£187,313	£0	7	3	7	0%
AAD RFME	£44,697	£30,306	21.832	14.767	15.632	10.826	£186,211	-£1,102	9	5	9	0%
AAD	£44,744	£30,466	21.853	14.777	15.662	10.844	£186,418	-£895	8	5	9	0%

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	£43,422	£29,122	21.876	14.788	15.674	10.849	£187,861	£547	5	1	7	3%
AAD Thora	£46,032	£32,029	21.548	14.614	15.496	10.760	£183,167	-£4,147	10	9	10	0%
AAD Hybrid	£51,579	£37,496	21.630	14.654	15.536	10.776	£178,033	-£9,281	11	11	12	0%
RF PP	£50,922	£35,948	23.241	15.470	16.681	11.383	£191,711	£4,398	2	1	3	31%
RF ME	£52,593	£37,406	23.209	15.455	16.625	11.348	£189,552	£2,239	4	2	8	0%
Cryoballoon	£52,718	£37,739	23.241	15.470	16.677	11.380	£189,859	£2,545	3	2	8	0%
Laser	£50,429	£35,445	23.241	15.470	16.673	11.377	£192,097	£4,783	1	1	7	65%
Thoracoscopy	£54,182	£39,357	23.103	15.379	16.624	11.347	£187,590	£276	6	3	10	0%
Hybrid	£64,245	£49,397	23.103	15.379	16.607	11.335	£177,301	-£10,013	12	11	12	0%
SA26 Change discounting to 1.5%												
AAD RFPP	£43,747	£36,437	21.833	18.240	15.655	13.220	£227,966	£0	7	5	8	0%
AAD RFME	£44,695	£37,317	21.835	18.242	15.635	13.204	£226,756	-£1,210	9	7	9	0%
AAD Cryo	£44,732	£37,412	21.852	18.254	15.663	13.226	£227,112	-£854	8	6	9	0%
AAD Laser	£43,408	£36,077	21.873	18.269	15.674	13.233	£228,589	£623	6	4	8	0%
AAD Thora	£46,101	£38,924	21.549	18.025	15.498	13.104	£223,152	-£4,814	10	10	11	0%
AAD Hybrid	£51,573	£44,355	21.630	18.084	15.537	13.130	£218,254	-£9,712	12	11	12	0%

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	£50,821	£43,118	23.236	19.268	16.679	13.988	£236,643	£8,677	2	1	2	33%
RF ME	£52,518	£44,710	23.204	19.245	16.623	13.943	£234,144	£6,178	4	2	5	0%
Cryoballoon	£52,614	£44,909	23.236	19.268	16.675	13.984	£234,781	£6,815	3	2	5	1%
Laser	£50,314	£42,606	23.236	19.268	16.671	13.981	£237,021	£9,056	1	1	5	65%
Thoracoscopy	£54,243	£46,614	23.098	19.154	16.621	13.941	£232,213	£4,247	5	3	9	1%
Hybrid	£64,160	£56,521	23.098	19.154	16.604	13.927	£222,016	-£5,949	11	9	12	0%
SA32 CABANA validation and threshold on utility decrement AF symptom free (0.08)												
AAD RFPP	£43,704	£29,437	21.839	14.770	15.126	10.497	£180,497	£0	7	4	7	0%
AAD RFME	£44,647	£30,247	21.838	14.770	15.105	10.482	£179,388	-£1,109	9	6	9	0%
AAD Cryo	£44,682	£30,401	21.854	14.778	15.129	10.497	£179,544	-£953	8	6	9	0%
AAD Laser	£43,369	£29,061	21.881	14.791	15.137	10.499	£180,913	£416	6	3	6	1%
AAD Thora	£46,061	£32,051	21.553	14.616	15.016	10.450	£176,940	-£3,557	10	9	10	0%
AAD Hybrid	£51,545	£37,455	21.634	14.656	15.038	10.453	£171,611	-£8,885	12	11	12	0%
RF PP	£50,775	£35,795	23.242	15.470	16.190	11.079	£185,793	£5,296	2	1	3	35%
RF ME	£52,455	£37,262	23.210	15.455	16.136	11.045	£183,630	£3,133	4	2	9	1%
Cryoballoon	£52,543	£37,559	23.242	15.470	16.184	11.075	£183,933	£3,437	3	2	8	1%
Laser	£50,284	£35,294	23.242	15.470	16.173	11.067	£186,046	£5,549	1	1	8	61%
Thoracoscopy	£54,196	£39,364	23.104	15.379	16.179	11.078	£182,193	£1,696	5	2	10	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)
Hybrid	£64,113	£49,259	23.104	15.379	16.146	11.053	£171,803	-£8,694	11	11	12	0%

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2 **Table 49: 5 year time horizon (deterministic analysis SA27)**

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	£10,354	£9,999	4.84	4.53	3.84	3.60	£61,936	2	£97,904	2
AAD RFME	£10,947	£10,582	4.84	4.53	3.84	3.59	£61,243	3	£97,156	3
AAD Cryo	£11,302	£10,946	4.84	4.53	3.84	3.60	£60,968	4	£96,925	4
AAD Laser	£9,941	£9,583	4.84	4.53	3.84	3.59	£62,291	1	£98,228	1
AAD Thora	£13,268	£12,919	4.82	4.51	3.84	3.59	£58,913	5	£94,828	5
AAD Hybrid	£18,580	£18,228	4.82	4.51	3.83	3.59	£53,533	10	£89,413	10
RF PP	£16,279	£15,949	4.87	4.55	3.89	3.64	£56,801	7	£93,176	7
RF ME	£17,432	£17,087	4.87	4.55	3.88	3.63	£55,467	8	£91,745	8
Cryoballoon	£18,074	£17,745	4.87	4.55	3.89	3.64	£54,973	9	£91,331	9
Laser	£15,947	£15,616	4.87	4.55	3.88	3.63	£57,041	6	£93,369	6
Thoracoscopy	£20,124	£19,801	4.84	4.53	3.88	3.63	£52,770	11	£89,055	11
Hybrid	£30,008	£29,684	4.84	4.53	3.87	3.62	£42,780	12	£79,012	12

3

2.5 Discussion

2.5.1 Summary of results

The base case and most sensitivity analyses found laser ablation was the most cost effective option at a threshold of £20,000 per QALY (probability of being most cost effective 66% in base case). RF PP was ranked second most cost effective at £20,000 per QALY, compared to laser ablation, the ICER was £90,684 per QALY. All other options were dominated. AAD with cross over to laser 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)[36]. 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, laser remained the most cost effective option.

The model was sensitive to changes to changes to the mortality data used in the decision tree. When the mortality NMA data for RF PP (reduced mortality risk) was used and the mortality for thoracoscopy and hybrid was double that of the baseline mortality (AADs), RFPP was the most cost effective option.

In addition, 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 30% or less, AAD with cross over to laser ablation became the most cost-effective option.

Finally, the results are sensitive to the cost of laser ablation, when this was increased by 30%, RF PP became the most cost effective option followed by laser ablation. Furthermore, an exploratory analysis found that if all catheter ablation techniques costed the same as RF PP then the ranking changed and RFPP was the most cost effective, followed by cryoballoon and then laser ablation. These results however were highly uncertain with the probability of each being the most cost effective being: 27%, 29% and 41% 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
- 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 and laser 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 30%, AAD with cross over to laser 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 30% 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. However, 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 or that do not require general anaesthetic, such as cryoballoon ablation, are not captured in the analysis.

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.

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.[3] Four studies were included that compared

ablation to alternative strategies as second line therapy for AF.[5, 7, 18, 38, 68, 72] Two studies compared cryoballoon ablation to radiofrequency ablation as second line therapy.[13, 41]

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).[3] 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.[5, 7, 18, 38, 68, 72] 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.[13, 41] 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 laser) 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

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

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1 Appendices

2 Appendix A: Additional information

3 **Table 50: 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

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 51: Ablation equipment costs

NPC	Base description	SecondaryDescription	Unit of issue	Band 1 price	Unit price	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	1	£233	£233	£233	£233			£233
FRH1206	Introducer	Swartz braided transseptal sl 8.5f/ 63cm	Each	£162	£162	1	£162	£162	£162	£162	£162		£162
FRZ3453	Needle	71cm trans brk xs	Each	£132	£132	1	£132	£132	£132	£132	£132		£132
FRB16791	Diagnostic Mapping Catheter	bw lasso 2515 nav eco variable ep 7f 02	Each	£761	£761	1	£761	£761					£761
FRJ24442	Catheter	8f d curve 3 5mm 2 5 2mm 115cm	Each	£2,010	£2,010	1	£2,010.00	£2,010					£2,010
FRJ24523	Cable*	Ez steer nav ablation	Each	£354	£354	4	£89	£90					£90
FRJ24525	Accessories	Carto3 ref patches	Each	£714	£714	1	£714	£714					£714
FRJ24570	Cable*	Lasso nav eco connection	Each	£354	£354	4	£89	£90					£90
FYU3251	Connecting Tubing	Coolflow pump tubing	Each	£46	£46	1	£46	£46					£46
FRJ24577	Diagnostic Catheter	Dcurve decanav catheter d for carto 7f	Each	£960	£960	1	£960	£960					£960
FCB15351	Cable*	10 pin DX connecting cable deca	Each	£90	£90	4	£23	£24					£24

FRB14468	Ablation Catheter	Specialist catheters for pulmonary vein isolation either multipolar radiofrequency ablation or cryo-ablation 28mm	Each	£4,440	£4,440	1	£4,440			£4,440			
FRB14471	Guiding Catheter	Steerable / deflectable flexible ep introducer sheath sets	Each	£960	£960	1	£960			£960			
FVI2269	Mapping Catheter	Achieve mapping catheter 20mm	Each	£960	£960	1	£960			£960			
FRB15597	Ablation Catheter	Pvac gold ablation bundle single pack includes pvac gold and greatbatch sheath	Each	£5,400	£5,400	1	£5,400		£5,400				
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	50	£40				£41		
		Abbott Livewire catheter			£160	1	£160				£160		

		Sterilising box (100-150 uses)			£149	100	£1.49						
Bilateral totally thoracoscopic epicardial ablation with radiofrequency													
FRP1369	Ablation Catheter	isolator linear pen	Each	£1,800	£1,800	1	£1,800					£900	£600
FRP1362	Accessories	isolator synergy clamp left curve	Each	£2,220	£2,220	1	£2,220					£1,110	£740
FRP1361	Accessories	isolator synergy clamp right curve	Each	£2,220	£2,220	1	£2,220					£1,110	£740
FRP1370	Ablation Catheter	lumitip dissector 27cm	Each	£1,800	£1,800	1	£1,800					£900	£600
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	£4,680					£2,340	£1,560
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	£6,600						£2,200
Total ablation pass through cost								£5,221	£5,927	£6,887	£4,445	£6,360	£11,661

1 *Source: NHS Supply chain catalogue,[51] unless otherwise stated. *Some of the equipment (cables) can be sterilised and reused (approx. 4 times). Therefore,*
2 *those costs were quartered.*

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