A health economic evaluation of concomitant surgical ablation for atrial fibrillation

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Abstract

Objective: Current drug treatment for atrial fibrillation is suboptimal and percutaneous catheter-based ablation techniques may be associated with complications. The aim of this study is to assess the cost-effectiveness of (1) high-intensity focused ultrasound (HIFU)-assisted surgical ablation, (2) the classic 'cut and sew' maze procedure and (3) percutaneous ablation, all concomitant to cardiac surgery (e.g. CABG, valve repair) in comparison with non-interventional (drug) treatment.

Methods: A Markov model was developed to predict the cost-effectiveness of the interventional approaches. The model consisted of four disease states (sinus rhythm without complications, atrial fibrillation without complications, stroke and death), allowing for 3-monthly transitions between these states and using direct UK costs from the National Health Service perspective. Clinical input data are obtained from literature and cost input data from National Health Service sources and literature. Five-year total and incremental costs are calculated. Incremental effects are expressed in quality-adjusted-life-years-gained (QALY).

Results: All interventional treatments show good incremental cost-effectiveness ratios in all atrial fibrillation types, compared to drug treatment. For classic maze the incremental cost-effectiveness ratio compared to non-interventional atrial fibrillation treatment varies from 1343 to 3471 GBP/QALY, for HIFU-assisted surgical ablation from 4005 to 7448 GBP/QALY and for percutaneous ablation from 7041 to 17,372 GBP/QALY depending on the atrial fibrillation type. Sensitivity analyses showed the robustness of the data.

Conclusions: Performing a classic maze procedure or HIFU-assisted surgical ablation concomitant to a scheduled CABG or valve procedure is highly cost-effective. Performing a percutaneous ablation in a subsequent procedure is also cost-effective, but to a lower extent. Both the maze procedure and the HIFU-assisted surgical ablation are cheaper and more effective than percutaneous ablation in a subsequent procedure.

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1. Introduction

Atrial fibrillation (AF) is the most common arrhythmic condition and its prevalence is rising along with the age of the population [1]. There are various treatment options to restore sinus rhythm, including medication therapy, electrical cardioversion (internal and external), pacing, percutaneous and surgical ablation and the classic surgical maze procedure. However, maintaining sinus rhythm is a major challenge, and pharmaceutical treatment to maintain sinus rhythm or to control heart rate in case of recurrence may have complications. Only ablation and surgery offer long-term solutions without the need for further pharmaceutical treatment.

It is well known that the presence of atrial fibrillation increases mortality and the incidence of stroke [1,2]. In addition, anticoagulants, required to reduce the number of ischaemic strokes, increase the risk of bleeding.

Until the publication of the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) and the rate control versus electrical cardioversion (RACE) studies, it was generally thought that restoring sinus rhythm and rhythm maintenance would reduce the number of strokes and have an impact on mortality [3,4]. Unfortunately, this seems not to be the case and long-term anticoagulation remains necessary. However, in both studies, rhythm was maintained with drugs and recurrence of AF occurred frequently. Ablation and surgery provide a more permanent solution and therefore the conclusions drawn from both studies cannot be extrapolated.
to ablation and surgery, both of which seem to reduce the strokes and mortality rate [5—7].

The surgical maze procedure (the Cox maze III operation) is the most effective curative therapy of AF [8]. In the maze procedure, surgical incisions and cryolesions are strategically made to interrupt the multiple re-entrant circuits of AF. In experienced hands, the procedure itself requires 45—60 min but also requires cardiopulmonary bypass. Success rates of 75—95% have been reported [8]. Although this procedure is very effective, the complexity and time associated with the procedure prevent widespread application.

Ablation can be performed either catheter-based (percutaneously) or surgically. The catheter-based procedure aims to focally ablate specific triggers in the pulmonary veins and anatomically isolate all pulmonary veins in order to disconnect all potential triggers from the left atrium [8]. It is a time-consuming procedure (3—6 h in the hands of an experienced electrophysiologist) and has less favourable results in persistent and permanent, compared to paroxysmal, AF [8,9]. Surgical ablation has some potential advantage in that it allows the creation of strategically placed, linear left atrial lesions under direct vision rapidly and safely, but does require general anaesthesia, due to the surgical access to the thoracic cavity [8]. Different surgical ablation techniques are available (e.g. microwave, radio frequency, high-intensity focused ultrasound (HIFU), cryoablation) [10].

While it is possible to perform surgical ablation as a stand-alone procedure, there is much benefit in performing it concomitantly to heart surgery, in patients where AF is associated with valvular or ischaemic heart disease. If device-based surgical ablation is performed alongside a coronary artery bypass graft (CABG), or valvular surgery, the total duration of surgery is increased only by about 15 min [8,10]. Hence, according to Ninet et al., with a small-time investment and without an additional surgical risk, a positive effect on mortality and morbidity (less strokes) may be obtained [11].

The population of this study consists of patients with coronary or valvular disease undergoing CABG or valve replacement/repair and with concomitant AF requiring treatment. It has the objective to determine the cost-effectiveness (cost-utility) of high-intensity focused ultrasound device-assisted surgical ablation concomitant to cardiac surgery, compared to the ‘cut and sew’ maze procedure, percutaneous ablation and non-interventional AF treatment. The case country for this analysis was the UK.

2. Materials and methods

2.1. General

A Markov model was developed in TreeAge™ Pro Suite. In a Markov model, mutually exclusive disease states are defined. The time of evaluation is divided into periods (cycles) [12]. During each cycle the patient can move from one health state to another (transition). The risk of this transition is called a ‘transition probability’. The cycle length in this model is 3 months. The model duration is 5 years.

We considered four different comparators in the model: the classical maze procedure, surgical ablation, percutaneous ablation in a subsequent procedure, and non-interventional treatment for AF.

![Fig. 1. Simplified model structure.](https://academic.oup.com/ejcts/article-abstract/32/5/702/372412)
The model simulates hypothetical patients. The initial procedure will either be complication-free or will prompt short-term complications: mortality, stroke, cardiac tamponade or bleeding leading to surgical intervention and pacemaker implantation. In case the intervention was complication-free, the patient will either be in sinus rhythm or will remain in AF, which will then require drug treatment or a percutaneous ablation at a later stage.

At the end of the first 3-month cycle, the patient will be in one of the following four health states: sinus rhythm without complications, AF without complications, stroke and death. The model assumes that every 3 months (for a total of 5 years) the patient runs the risk of moving from one health state to another, i.e. to die or to have a stroke or an AF recurrence. In Fig. 1, a simplified version of the model is shown. At any time during the model and at the end of the model simulation, each of the patients will be in one of these four health states and the health outcomes and costs of being in these states will have been recorded. The model is run four times, once for each comparative strategy, each time with other transition probabilities. As such, the model calculations will result in cumulative costs and effects for each strategy. Both future costs and effects are discounted at an annual discount rate of 3.5% according to the UK guidelines.

The difference in costs and effects between each interventional strategy and the non-interventional strategy lead then to incremental cost-effectiveness ratios (ICERs).

2.2. Clinical data

The clinical data applied in the model are summarised in Table 1. In the text below, the sources and raw inputs are described. Several of those inputs do not fit with the model structure. For instance, the model requires as input the initial conversion rate after 3 months, while most studies report conversion after a longer period, which may be the result of initial conversion, followed by later recurrence. Hence the raw figures, as reported below, were further adjusted as described in Section 2.2.5.

| Free of AF first cycle (3 months) | No AF surgery (%) | Classic maze (%) | Surgical ablation (%) | Percutaneous ablation (%) |
|----------------------------------|-------------------|------------------|-----------------------|--------------------------|
| Permanent                        | 23 [15]           | 85 [7]           | 81 [10]               | 72 [9]                   |
| Persistent                       | 57 [15]           | 90 [7]           | 95 [10]               | 79 [9]                   |
| Paroxysmal                       | 57 [15]           | 95 [7]           | 100 [10]              | 89 [9]                   |
| Recurrence rates after index per year [6] | | | | |
| First year after cycle 1         | 15                | 5                | 5                     | 5                        |
| Second year recurrence rate      | 15                | 5                | 5                     | 5                        |
| Third year recurrence rate       | 10                | 1                | 1                     | 1                        |
| Early complications              | 10 [7]            | 21 [7]           | 22 [10]               | 11 [9]                   |
| Cardiac tamponade                | 0 [7]             | 0 [7]            | 1 [10]                | 1 [9]                    |
| Early mortality                  | 2 [7]             | 4 [7]            | 4 [10]                | 2 [9]                    |
| Stroke/TIA                       | 2 [7]             | 0 [7]            | 3 [10]                | 2 [9]                    |
| Bleeding leading to re-surgery   | 0 [7]             | 6 [7]            | 6 [10]                | 0 [9]                    |
| Pacemaker implant                | 6 [7]             | 11 [7]           | 8 [10]                | 6 [9]                    |
| Long-term stroke rate per 3 months [2,7] | 1.35           | 1.16 [7]         | 1.14 [10]             | 1.17                     |
| Late mortality per 3 months [2,7] | | | | |
| Year 0–3                         | 0.97              | 0.84             | 0.83                  | 0.85                     |
| Year 4–5                         | 1.13              | 0.98             | 0.97                  | 1.00                     |

To define the clinical trials used to populate the model a Medline search was performed. The key words ‘maze procedure [title/abstract] AND combined’ resulted in 56 hits of which 7 were reviews (November 2006). The articles were related to classic maze and to device-assisted surgical ablation. The only comparative, although post hoc, trial on classic maze was the one centre study of Raanani et al. [7]. Many different devices for surgical ablation are available and studied. Two randomised controlled trials were identified [13,14]. Khargi et al. [13] reported the results with saline-irrigated cooled-tip radio frequency ablation compared to no ablation in a small group of 30 patients, and Doukas et al. [14] described the effects of radio frequency ablation in 101 patients. Since the focus of this study was on HIFU-assisted surgical ablation, results on clinical effectiveness were taken from a multicentre trial published by Ninet et al. [11].

Many publications on percutaneous ablation for AF exist. Here, we selected the studies that provided us with results that were usable in the model without too many adaptations.

2.2.1. Conversion rates

Raanani et al. evaluated post hoc the outcomes of the maze procedure combined with mitral valve (MV) surgery in patients with AF compared to MV surgery alone [7]. The population consisted of 94 patients (47 in each arm) with longstanding AF (58% of patients had >12 months duration of AF), aged 68 years, who were followed after surgery for on average 30 months. The maze procedure that did not seem to increase operative mortality of MV surgery was effective in eliminating AF (75%) and reduced the risk of thromboembolic complications compared to no AF surgery, namely 0% in the maze arm versus 17% in the no AF surgery arm. This study was a post hoc study in which an attempt was made to match the two treatment arms. However, there were differences in the patient characteristics. Left atrial size was significantly bigger in the maze group, and more control arm patients were in New York Heart Association class IV.

Ninet et al. reported the 6-month outcomes of surgical ablation, via epicardial high-intensity focused ultrasound,
concomitant to cardiac surgery, in a non-comparative setting [10]. From September 2002 through February 2004, 103 patients with a mean age of 66.6 years (±9.57) were prospectively enrolled in a multicentre study. Atrial fibrillation duration ranged from 6 to 240 months (mean 44 months) and was permanent in 76 (74%) patients, paroxysmal in 22 (21%) patients and persistent in 5 (5%) patients. There were four (3.8%) early deaths and two late extracardiac deaths. At the 6-month visit, 85% of patients were free of AF (80% of patients with permanent atrial fibrillation and 100% of patients with paroxysmal atrial fibrillation). A pacemaker was implanted in eight patients (7.8%).

Pappone et al. treated 251 consecutive patients with paroxysmal (n = 179, lasting for longer than 1 year) or permanent (n = 72, lasting for longer than 3 months) AF with percutaneous ablation, again in a non-comparative setting [9]. Procedures lasted 148 ± 26 min. Cardiac tamponade occurred in two patients (0.8%). After 10.4 ± 4.5 months, 152 patients with paroxysmal AF (85%) and 49 with permanent AF (68%) were AF-free.

In the control arm of the Raanani et al. study (MV surgery alone), a conversion rate of 36% was observed. Eguchi et al. [15], in a single-centre observational trial, with 109 AF patients, aged 55 years, reported more detailed conversion rates for the different types of AF separately, namely 19% among patients with chronic AF and 53% in patients with intermittent (paroxysmal or persistent) AF after valvular repair, without ablation.

2.2.2. Recurrence

Pappone et al. reported outcomes at 1, 2 and 3 years after the initial procedure in a comparative setting [6]. The clinical course of 1171 consecutive patients with symptomatic AF was followed, whereby 589 percutaneously ablated patients were compared with 582 who received anti-arrhythmic medications for rhythm control. One, 2 and 3 years after the study inclusion, 84%, 79% and 78% of patients treated with ablation were in sinus rhythm compared to, respectively, 61%, 47% and 37% in the pharmacologically treated arm.

2.2.3. Early complications

The different trials described above also reported early complication rates. These are early mortality, early stroke rate, bleeding risk and need of a pacemaker implantation. The unadjusted figures are reported in Table 1. For percutaneous ablation in our setting two procedures are performed; first the cardiac surgery (valve or CABG) followed by a second procedure, the percutaneous ablation. Thus, the procedure-related early complications of the cardiac surgery (valve or CABG) needed to be added to the procedure-related acute side effects of percutaneous ablation.

2.2.4. Mortality and stroke incidence

There was no mortality or stroke in the maze group after the acute phase in Raanani et al.’s study, which is against expectations, and which is probably explained by the low patient number. In the no AF surgery arm, mortality was 5% and the stroke rate was 17%. Wolf et al., in a prospective cohort study on 26,753 Medicare patients, assessed the impact of AF on mortality and stroke rate [2]. These authors reported a relative risk increase due to AF for different age groups and per gender. The relative mortality and stroke risk of the 65–74 age groups were 1.21 (95% CI 1.00–1.46) and 1.20 (95% CI 0.99–1.45) for men and 1.20 (95% CI 1.00–1.45) and 1.23 (95% CI 1.02–1.48) for women, and can therefore provide a reasonable estimate of the relative risk reduction in case of successful ablation.

2.2.5. Adjustments and assumptions

The long-term stroke, mortality and AF-free data were recalculated to 3-monthly risks, using the following formula (example for 1-year data) [16]:

\[ \text{Transition}_{1\text{months}} = 1 - (1 - \text{rate}_{12\text{months}})^{1/4} \]

It was furthermore assumed that the majority of recurrences occur in the first 3 months after the initial procedure. Therefore, as from the second cycle of the first year of follow-up, the same probability of recurrence is applied as in the cycles of the second year. This assumption is supported by earlier clinical studies [17].

It was assumed that if ablation is performed (maze, surgical or percutaneous), the recurrence rate in year 2 and 3 will be as reported by Pappone et al. [6] (i.e. 5% for the second year and 1% for the third year). For the following years (4 and 5) the 1% per year recurrence is used.

Raanani et al. described the success rate for maze ablation in permanent AF at 3 years (75%). Using the above-mentioned assumptions on the recurrence rate in the second and third year after the intervention, the 3-month recurrence-free rate was recalculated and was 85% [7]. Here it is assumed that the acute success rate for the classic surgical maze in paroxysmal AF is 95%, and for persistent AF, the average of paroxysmal and permanent is assumed (90%) [8]. Ninet et al. described the success rate of surgical ablation at 6 months (80% in permanent AF and 100% in paroxysmal AF) [10]. Applying the above assumptions, the 3-month success rate was recalculated to 81% for permanent and 100% for paroxysmal AF. Pappone at al. described the success rate with catheter ablation. Using the same assumptions as described, 3-month recurrence-free rates of, respectively, 72%, 79% and 89% for permanent, persistent and paroxysmal AF were calculated.

There were no statistically significant differences in acute outcomes (early mortality, stroke rate, etc.) between the classic maze group and the no AF surgery group in the study by Raanani et al. [7]. Therefore in the base case, it is assumed that there is no difference in early mortality and stroke, but in the sensitivity analysis the effect of the (non-significant) differences reported by Raanani et al. is also tested.

A stroke can be fatal or not. In a meta-analysis of primary prevention trials including more than 50,000 patients about 13% of cerebrovascular events were fatal [18].

If a recurrence occurs, patients can be treated with drugs or with percutaneous ablation. The latter percentage was derived from the Euro Heart Survey on AF where, respectively, 2%, 4% or 5% with permanent, persistent or paroxysmal AF had a previous ablation [19].

2.3. Cost data

Different costs are needed to populate the model including the cost of the device and the cost of possible...
The case country for this analysis is the UK and the perspective of the National Health Service (NHS) is taken. In the UK, funding and reimbursement of procedures/complications is mainly based on the costs reported by the ‘NHS Reference costs’, providing average costs by Health-Related Groups (HRGs) across the UK. There are four different HRGs relating to a disease. The HRG codes associated are non-elective (emergency) and elective (routine), with and without complications (not always present). Currently a HRG exists for valve surgery and coronary bypass but not for an ablation procedure being performed alongside the above-mentioned surgeries. The cost of surgical ablation is assumed to be 2500 GBP, which industry sources have reported as market average. In the model, this figure was also varied through a sensitivity analysis. Furthermore, there is no HRG available for the maze procedure. It is very rarely performed in the UK, but is nevertheless considered the approach to which new strategies should be compared [25].

To estimate the extra cost of a maze performed alongside CABG or a valve procedure, it is assumed that patients will stay one additional day on the ICU ward [7]. The cost of one day in an ICU unit in the UK is 1025 GBP (http://www.dh.gov.uk/assetRoot/04/13/17/98/04131798.xls). The cost of percutaneous ablation is not included specifically in the HRG system, but subsumed under HRG E38, electrophysiological and other percutaneous cardiac procedures in patients older than 18. At the time of writing this paper, the device cost is not included in the HRG but is to be added (and charged to the NHS) separately. This would mean that an average of 1689 GBP for the device has to be added to the cost of HRG, which would lead to a total cost for percutaneous ablation of 3468 GBP. Similar to the cost for surgical ablation devices, the cost for catheter ablation has been based on averages reported by industry sources, in the absence of specific costing information in the NHS Reference Costs data sets. Again these costs were subject to variation in the sensitivity analysis.

The cost of complications (early and late) can be divided into acute costs and follow-up costs. For the acute costs, the NHS reference costs are used as a source (2006 Admitted Patient Care Mandatory Tariff, http://www.dh.gov.uk/assetRoot/04/13/17/98/04131798.xls).

The starting procedure is a scheduled procedure (valve surgery or CABG) that has to be attributed to all patients. This cost is therefore not applied in the model. The procedural cost does not distinguish between the intervention with or without complications. Hence, complications occurring during the initial surgery like bleeding, stroke or pacemaker implantation would not be taken into account, which is an underestimation of the real cost. Therefore, the HRG cost (non-elective) for pacemaker implantation and stroke was applied when these complications occurred.

The NHS does not provide the cost of a cardiac death, or the cost of follow-up after a non-fatal stroke. Clarke et al. developed a model for estimating the immediate and long-term healthcare costs associated with seven diabetes-related complications in patients with Type 2 diabetes participating in the UK Prospective Diabetes Study (UKPDS) using data on 5102 UKPDS patients [20]. They reported the cost of fatal MI, a cost that is assumed to be the cost of late death after cardiac surgery.

Kavanagh et al. reported that among people living alone after a non-fatal stroke, the major contributors to costs were in-patient care (27 GBP per week) and home help (30 GBP per week). Other services costing more than 5 GBP per week were: general practitioner consultations, hospital outpatient care and day centre attendances. So a conservative approach is to assume that all patients live with others, and thus incurs about 33 GBP per week. After a year, and inflation adjusted to 2005, this would mean 1821 GBP.

Patients with a pacemaker implanted will have extra follow-up costs to ensure the functioning of the device. It is assumed that two cardiologist visits (95 GBP per visit) with ECG (22 GBP) per year are needed (http://www.dh.gov.uk/assetRoot/04/13/17/98/04131798.xls). This leads to a total cost of 234 GBP per year.

It is further assumed that, aside from the use of drugs, there is no difference in resource use in the follow-up of patients continuing in AF compared to those who are in sinus rhythm (extensive cardiac follow-up due to their concomitant disease). For simplicity, we will assume here that patients who are in sinus rhythm no longer take anti-arrhythmics (treatment with digoxin and amiodarone is considered to calculate the drug cost of patients in AF) and are no longer on anticoagulants unless these drugs are needed for the concomitant disease (http://www.bnf.org.uk/bnf/). It can be assumed that anti-platelets and β-blockers are standard treatments for the concomitant disease and will be administered in most patients.

### Table 2

| Item                        | Cost (GBP) | Source                      | Comment                        |
|-----------------------------|------------|-----------------------------|--------------------------------|
| Maze procedure              | 1,025      | NHS                         | 1 day on surgery ward          |
| Percutaneous ablation       | 3,468      | NHS                         | E38 + material cost            |
| Cardiac death               | 1,227      | Clarke et al. [20]           |                                |
| Stroke acute                | 3,978      | NHS                         | A22-23                         |
| Stroke follow-up per 3 months | 455       | Kavanagh et al. [21]         |                                |
| Pacemaker                   | 3,445      | NHS                         | E08                            |
| Surgical ablation           | 2,500      | Assumption                  |                                |
| Pacemaker follow-up per 3 months | 78       | NHS                         | 2 ECG + cardiologist visits    |
| Drug cost for AF per 3 months | 78         | http://www.bnf.org.uk/bnf/   |                                |
2.4. Utility

Results are expressed as cost per quality-adjusted-life-years-gained (QALYG). Patients included in this study have important concomitant disease and are elderly (more than 65). In order to calculate QALYs, the patient’s quality of life needs to be expressed in utilities, which allow for a quantitative expression of the preference for a health state. A utility value is expressed between 0 and 1: 1, perfect health; and 0, dead. By multiplying the utility level with the time during which a person has that level, a QALY is calculated. For instance, a person living at a level of 0.8 during 2 years will have 1.6 QALYs. Kind et al. described the impact of age on utility (based on a visual analogue scale) in the UK population [22]. At the age of 60–69 the average utility is 0.8. The other utility parameters shown further on are used as multipliers of this age-specific utility.

Although the initial report of the Euro Heart Survey on atrial fibrillation does not show data on quality of life, these data, based on the Euro-QoL 5D (EQSD) questionnaire, were gathered and provided to us by the Euro Heart Survey investigators [19]. The mean utilities for paroxysmal, persistent and permanent atrial fibrillation at year 1 inclusion in the Euro Heart Survey were 0.79 (0.69 – 1.00), 0.79 (0.69 – 1.00) and 0.73 (0.62 – 1.00), respectively. The interquartile range shown between brackets is used in the sensitivity analysis.

Tengs and Lin performed a meta-analysis of quality-of-life estimates for stroke [23]. Based on the time trade-off method, they estimated that utility for a major, moderate and minor stroke was 0.52, 0.68 and 0.87, respectively. In the model, it is assumed that the average patient who had a stroke has moderate sequelae. The outer limits are used in a sensitivity analysis.

Bleeding, leading to re-surgery, cardiac tamponade and need for a pacemaker implantation, is assumed only to change utility in the acute phase and not in the long run. To account for the acute impact on utility a penalty is applied (utility of 0 for 1 week) [24].

3. Results

The base case results are shown in Table 3. Over the 5-year modelling period, the three studied treatment options show good ICER values compared to no ablation during surgery in the three types of AF. For classic maze the ICER varies from 1343 to 3471 GBP/QALYG, for surgical ablation from 4005 to 7448 GBP/QALYG and for percutaneous ablation from 7041 to 1343 to 3471 GBP/QALYG, for surgical ablation from 4005 to 7448 GBP/QALYG depending on the type of AF.

3.1. One-way sensitivity analysis

The base case assumptions are described above. Different sensitivity analyses were performed: the annual discount rate was altered between 0% and 6%; the interquartile estimates of utility were used; the cost of complications was decreased and increased by 50%; the procedure cost of maze, surgical and percutaneous ablation was decreased and increased by 50%; the early complication rates of maze as reported by Raanani et al.

| Strategy          | Cost  | Incremental cost | QALY  | QALYG  | ICER |
|-------------------|-------|------------------|-------|--------|------|
| Permanent AF      | No ablation 2,513 | 2,5297 |       |        |      |
|                   | Classic maze 3,233 | 720   | 3,0658 | 0.5361 | 1,334 |
|                   | Surgical ablation 4,567 | 2,054 | 3,0425 | 0.5128 | 4,005 |
|                   | Percutaneous ablation 5,538 | 3,025 | 2,9593 | 0.4926 | 7,041 |
| Persistent AF     | No ablation 2,318 | 2,8835 |       |        |      |
|                   | Classic maze 3,203 | 885   | 3,1385 | 0.2550 | 3,471 |
|                   | Surgical ablation 4,487 | 2,169 | 3,1747 | 0.2912 | 7,448 |
|                   | Percutaneous ablation 5,497 | 3,179 | 3,0665 | 0.1830 | 17,372 |
| Paroxysmal AF     | No ablation 2,317 | 2,8843 |       |        |      |
|                   | Classic maze 3,173 | 856   | 3,1704 | 0.2861 | 2,991 |
|                   | Surgical ablation 4,457 | 2,140 | 3,2056 | 0.3213 | 6,660 |
|                   | Percutaneous ablation 5,438 | 3,121 | 3,1285 | 0.2442 | 12,781 |

were used and a 10-year time horizon instead of 5 years was tested.

1. As explained previously in the base case early mortality and stroke rates are set as equal for the four treatment arms. As a sensitivity analysis, the hard study endpoints of the different clinical trials are used (as shown in Table 1) meaning that early stroke rate and early mortality in the maze and surgical ablation group are slightly higher compared to no intervention and percutaneous ablation. As a consequence, the ICER for device-assisted surgical ablation increases, but remains far below the 20,000 GBP/QALY value (Table 4).

2. Doubling the time horizon from 5 to 10 years decreased ICER by 50% for all treatment options in the three types of AF (see Table 5).

3. In the base case it is assumed that the utility of being in AF was, respectively, 0.73, 0.79, 0.79 for permanent, persistent and paroxysmal AF. If higher utility values are to be applied to AF, the interventions that avoid AF will become less cost-effective, as the utility gain from AF to sinus rhythm is smaller. We varied the utility value between 0.62 and 1.0 in patients with permanent AF and between 0.69 and 1.0 for persistent and paroxysmal AF. Classic maze remains cost-effective for all utility values.

| Strategy          | Cost  | Incremental cost | QALY  | QALYG  | ICER |
|-------------------|-------|------------------|-------|--------|------|
| Permanent AF      | No ablation 2,514 | 2,5297 |       |        |      |
|                   | Classic maze 3,001 | 488   | 3,0314 | 0.5361 | 1,343 |
|                   | Surgical ablation 4,631 | 2,117 | 2,9706 | 0.4409 | 4,802 |
| Persistent AF     | No ablation 2,318 | 2,8835 |       |        |      |
|                   | Classic maze 2,971 | 653   | 3,1013 | 0.2550 | 3,471 |
|                   | Surgical ablation 4,552 | 2,234 | 3,1002 | 0.2167 | 10,309 |
| Paroxysmal AF     | No ablation 2,317 | 2,8843 |       |        |      |
|                   | Classic maze 2,941 | 623   | 3,1331 | 0.2861 | 2,991 |
|                   | Surgical ablation 4,523 | 2,206 | 3,1303 | 0.2460 | 8,967 |
For permanent AF, up to a value of 0.97, surgical ablation remains cost-effective using the most stringent willingness-to-pay value (20,000 GBP per QALY), and up to 0.99 if the upper limit is used (30,000 GBP/QALY). In persistent AF these threshold figures are, respectively, 0.98 and 0.995, in paroxysmal AF 0.98 and 1.0. For percutaneous ablation these figures are lower (see Fig. 2).

Ranging the utility after stroke from 0.52 to 0.87 changes ICER by only 200 GBP.

5. Also, changing discount rate on effects and cost from 0 to 6% or decreasing and increasing the cost of complications only has a small influence on ICER.

6. The cost of the initial procedure has an important impact on the ICER. A 50% increase (or decrease) results in a 50% change of the ICER (Fig. 3).

4. Discussion

The analyses performed show that performing the classic maze procedure is the most cost-effective approach, but HIFU-assisted surgical ablation and percutaneous ablation are also cost-effective treatments in this model.
Although some authors still state that "The Cox maze III procedure remains the standard against which alternative procedures for atrial fibrillation must be judged", surgeons did not adopt the procedure [25]. Only a few experienced surgeons worldwide perform the procedure. In the corresponding absence of exact cost data for the procedure, we applied a cost of 1025 GBP (representing one extra day on intensive care), which is a conservative cost assumption.

The ICER obtained for percutaneous ablation is twice the ICER for HIFU-assisted surgical ablation. This is due to the need of a second procedure and thus re-hospitalisation, but also due to the additive risk of two procedures. In addition, a percutaneous ablation is a time-consuming procedure, and therefore, in patients who are already scheduled for cardiac surgery, less appropriate. In such a concomitant setting, surgical ablation seems the most appropriate approach.

The most sensitive factor for the analysis is the quality of life of a patient with AF. The utility data used in the model were obtained from the Euro Heart Survey, thus derived from a large population [19]. However, even if the highest utility values found in the Euro Heart Survey are applied to AF, surgical ablation and classic maze still remain cost-effective.

Another very sensitive factor is the time horizon. In the base case we applied a conservative time horizon of 5 years. If this is extended to 10 years, maybe more appropriate in a population of about 65 years of age, the ICER decreases by more than 50%.

As explained in the Section 2, the selection of the clinical studies can be discussed. However, we believe the conclusions would not have changed by using other studies. For example, the methodology and therefore the results of the Raanani et al. study can be questioned [7]. It was a post hoc study with a 'match' between two groups, which was not really successful, which the authors admit in their conclusions. Therefore we compared the results with the three series of maze procedures from three institutions in the US: Prasad (Cox’s group), Schaff (Mayo clinic) and McCarthy (Cleveland group) [25—27]. The Raanani et al. results are in line with the results obtained in other experienced centres. After completing our study, Lall et al. published a retrospective comparison of the classic 'cut and sew' technique with bipolar radio frequency energy and cryoablation as performed in their centre between 1992 and 2005 [28]. There was no significant difference in intensive care unit and hospital stay, 30-day mortality, permanent pacemaker placement, early atrial tachyarrhythmias, late stroke and survival between both groups. Freedom from atrial fibrillation recurrence was greater than 90% in both groups at 1 year.

The findings in this study confirm the effectiveness data we used in our model. In the earlier mentioned study by Doukas et al. [14], the restoration of sinus rhythm with radio frequency ablation was about 50% at 1 year [14]. The authors did not comment on this observed low restoration rate; however, the longer duration of AF in the patients included in this study compared to the HIFU-assisted ablation (57 months vs 44 months), the larger left atrium (58 mm vs 51.5 mm) as well as the ablation technique might have played a role [10,11].

In future health economic evaluations it could be of interest to evaluate the use of surgical ablation not concomitant to cardiac surgery in other types of AF, like lone AF, or to compare the different types of surgical ablation (e.g. microwave, radio frequency, HIFU, cryoablation) to the classic 'cut and sew' technique. At this point in time, however, the necessary clinical data to conduct this research are not yet available.

In conclusion, performing a classic maze procedure or HIFU-assisted surgical ablation concomitant to a scheduled CABG or valve surgery is very cost-effective. Performing a percutaneous ablation in a subsequent procedure is also cost-effective, but to a lower extent. Percutaneous ablation is more costly and less effective than the classic maze procedure and the surgical ablation.

This study is the first to assess the health economic consequences of concomitant surgical ablation for the treatment of atrial fibrillation. As ablation technologies are still relatively novel, a modelling approach based on published literature and expert validation seemed appropriate. Additional data from future trials and registries will improve the evidence base for further economic evaluations.

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