

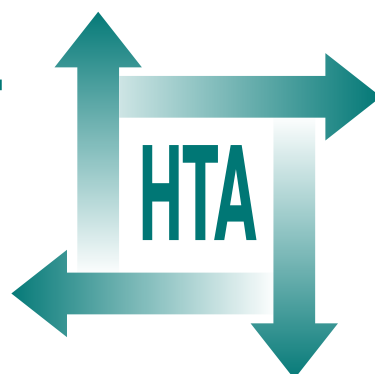
Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation

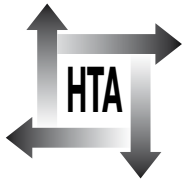
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Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation

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Abstract

Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation

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Objectives: To determine the safety, clinical effectiveness and cost-effectiveness of radio frequency catheter ablation (RCFA) for the curative treatment of atrial fibrillation (AF) and typical atrial flutter.

Data sources: For the systematic reviews of clinical studies 25 bibliographic databases and internet sources were searched in July 2006, with subsequent update searches for controlled trials conducted in April 2007. For the review of cost-effectiveness a broad range of studies was considered, including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases.

Review methods: Systematic reviews of clinical studies and economic evaluations of catheter ablation for AF and typical atrial flutter were conducted. The quality of the included studies was assessed using standard methods. A decision model was developed to evaluate a strategy of RCFA compared with long-term antiarrhythmic drug (AAD) treatment alone in adults with paroxysmal AF. This was used to estimate the cost-effectiveness of RCFA in terms of cost per quality-adjusted life-year (QALY) under a range of assumptions. Decision uncertainty associated with this analysis was presented and used to inform future research priorities using the value of information analysis.

Results: A total of 4858 studies were retrieved for the review of clinical effectiveness. Of these, eight controlled studies and 53 case series of AF were included. Two controlled studies and 23 case series of typical atrial flutter were included. For atrial fibrillation, freedom from arrhythmia at 12 months in case series ranged from 28% to 85.3% with a weighted mean of 76%. Three RCTs suggested that RCFA is more effective than long-term AAD therapy in patients with drug-refractory paroxysmal AF. Single RCTs

also suggested superiority of RCFA over electrical cardioversion followed by long-term AAD therapy and of RCFA plus AAD therapy over AAD maintenance therapy alone in drug-refractory patients. The available RCTs provided insufficient evidence to determine the effectiveness of RCFA beyond 12 months or in patients with persistent or permanent AF. Adverse events and complications were generally rare. Mortality rates were low in both RCTs and case series. Cardiac tamponade and pulmonary vein stenosis were the most frequently recorded complications. For atrial flutter, freedom from arrhythmia at 12 months in case series ranged from 85% to 92% with a weighted mean of 88%. Neither of the atrial flutter RCTs reported freedom from arrhythmia at 12 months. One RCT found a statistically significant benefit favouring ablation over AADs in terms of freedom from arrhythmia at a mean follow-up of 22 months. A second RCT reported a more modest effect favouring ablation in terms of freedom from atrial flutter at follow-up in older patients (mean age 78 years) after their first episode of flutter. In the atrial flutter case series, mortality was rare and the most frequent complications were atrioventricular block and haematomas. Complications in the RCTs were similar, except for those events likely to have been caused by AAD therapy (e.g. thyroid dysfunction). The review of cost-effectiveness evidence found one relevant study, which from a UK NHS perspective had a number of important limitations. The base-case analysis in the decision model demonstrated that if the quality of life benefits of RCFA are maintained over the remaining lifetime of the patient then the cost-effectiveness of RCFA appears clear. These findings were robust over a wide range of alternative assumptions, being between £7763 and £7910 per additional QALY with very little

uncertainty. If the quality of life benefits of RFCA are assumed to be maintained for no more than 5 years, cost-effectiveness of RFCA is dependent on a number of factors. Estimates of cost-effectiveness that explored the influence of these factors ranged from £23,000 to £38,000 per QALY.

Conclusions: RFCA is a relatively safe and efficacious procedure for the therapeutic treatment of AF and typical atrial flutter. There is some randomised evidence to suggest that RFCA is superior to AADs in patients with drug-refractory paroxysmal AF in terms of freedom from arrhythmia at 12 months. RFCA appears to be cost-effective if the observed quality of life benefits are assumed to continue over a patient's lifetime. However, there remain uncertainties around longer-term effects of the intervention and the extent to which published

effectiveness findings can be generalised to 'typical' UK practice. All catheter ablation procedures for the treatment of AF or atrial flutter undertaken in the UK should be recorded prospectively and centrally and measures to increase compliance in recording RFCA procedures may be needed. This would be of particular value in establishing the long-term benefits of RFCA and the true incidence and impact of any complications. Collection of appropriate quality of life data within any such registry would also be of value to future clinical and cost-effectiveness research in this area. Any planned multicentre RCTs comparing RFCA against best medical therapy for the treatment of AF and/or atrial flutter should be conducted among 'non-pioneering' centres using the techniques and equipment typically employed in UK practice and should measure relevant outcomes.



Contents

Glossary and list of abbreviations	vii	Assessment of factors relevant to the NHS and other parties	83
Executive summary	xi	6 Conclusions	85
1 Background	1	Implications for service provision	85
Description of health problem	1	Suggested research priorities	85
Current service provision	3	Acknowledgements	87
Description of technology under assessment	6	References	89
2 Definition of decision problem	9	Appendix 1 Literature search strategies ...	101
Decision problem	9	Appendix 2 Quality assessment of included studies	125
Overall aims and objectives of the assessment	9	Appendix 3 Review of clinical effectiveness	127
3 Assessment of clinical effectiveness	11	Appendix 4 Clinical evaluation of RFCA in atrial fibrillation: additional analyses	169
Methods for reviewing clinical effectiveness	11	Appendix 5 Excluded studies	173
Results of review of clinical effectiveness – atrial fibrillation	13	Appendix 6 Ongoing and not yet published studies	175
Results of review of clinical effectiveness – atrial flutter	37	Appendix 7 Economic evaluation	177
Discussion of clinical evaluation	47	Health Technology Assessment reports published to date	199
4 Assessment of cost-effectiveness evidence	51	Health Technology Assessment Programme	217
Systematic review of existing cost- effectiveness evidence	51		
Decision model	53		
Value of information analysis	73		
5 Discussion	79		
Statement of principal findings	79		
Strengths and limitations of the assessment	80		
Uncertainties	81		



Glossary and list of abbreviations

Glossary

Accessory pathway An abnormal conduction circuit of electrical activity within the heart.

Arrhythmia An abnormality of the normal rhythm of the heart.

Atrial fibrillation An arrhythmia characterised by rapid and irregular beating of the atria (upper chambers of the heart) and absence of regular 'P waves' on the electrocardiogram.

Atrial flutter An arrhythmia related to atrial fibrillation and characterised by a 'sawtooth' pattern of 'flutter waves' on the electrocardiogram.

Atrioventricular node ablation and pacing A procedure to treat atrial fibrillation by selective destruction of the atrioventricular node to prevent conduction of electrical signals, together with implantation of a pacemaker to take over control of heart rate.

Cardioversion Treatment to restore the heart to normal sinus rhythm using drugs (pharmacological cardioversion) or electric shock (electrical cardioversion).

Catheter ablation An invasive procedure using a catheter to target energy for selective destruction of small areas of tissue within the heart.

Cavotricuspid isthmus ablation The most common procedure for catheter ablation intended to cure atrial flutter.

Case series A report of a number of cases of a disease, its treatment and the outcome, with no comparison (control) group.

Controlled clinical trial A clinical study in which the effectiveness of a treatment is evaluated by comparing outcomes in a group of

people who received the treatment with those of a control group who received an alternative treatment, an inactive treatment (placebo) or no treatment.

Cost-effectiveness The consequences of the alternatives are measured in natural units, such as years of life gained. The consequences are not given a monetary value.

Cost-utility The consequences of alternatives are measured in 'health state preferences', which are given a weighting score. In this type of analysis, different consequences are valued in comparison with each other, and the outcomes (e.g. life-years gained) are adjusted by the weighting assigned. In this way an attempt is made to value the quality of life associated with the outcome so that life-years gained become quality-adjusted life-years gained.

Cox maze procedure See Maze procedure.

Decision model A quantitative framework used to synthesise evidence on the costs and health outcomes of different treatments under conditions of uncertainty.

Electrocardiogram A recording of electrical activity within the heart.

Incidence The rate of occurrence of new cases of a disease in a population.

Lone atrial fibrillation Atrial fibrillation occurring in the absence of evidence of structural heart disease or other known predisposing factors.

Mapping In the context of catheter ablation, the use of various systems for identifying areas of tissue to be ablated and positioning and guiding of catheters within the heart.

continued

Maze procedure A surgical procedure for the curative treatment of atrial fibrillation, normally performed at the same time as surgery for other co-existing heart disease.

Odds ratio The ratio of the odds of an event in the intervention group to the odds of an event in the control group. Within each group the odds is the ratio of the number of people in the group with an event to the number without an event.

Pacemaker A device for the control of heart rate.

Paroxysmal atrial fibrillation Atrial fibrillation characterised by recurrent episodes that terminate spontaneously.

Permanent atrial fibrillation Long-standing atrial fibrillation that is not terminated by cardioversion or for which cardioversion is not pursued.

Persistent atrial fibrillation Atrial fibrillation characterised by recurrent episodes that do not terminate spontaneously.

Pill-in-the-pocket therapy A management strategy in which the patient carries medication to be taken on the onset of symptoms.

Prevalence The proportion of people in a population who have a particular disease.

Pulmonary vein isolation A common procedure for curative catheter ablation of atrial fibrillation involving creation of ablation lines to prevent abnormal electrical activity originating in the pulmonary veins from spreading within the heart.

Pulmonary vein stenosis Narrowing of the pulmonary veins.

Quality-adjusted life-year A measure of health-care outcomes that adjusts gains (or losses) in years of life subsequent to a health-care intervention by the quality of life during those years. Quality-adjusted life-years can provide a common unit for comparing cost-utility across different interventions and health problems.

Quality of life A measure of overall well-being taking into account both the physical effects of a disease and its wider effects on the patient's life (e.g. ability to work, effect on personal relationships, etc.).

Randomised controlled trial A controlled clinical trial in which participants are randomly assigned to treatment groups.

Rate control A management strategy for arrhythmia that focuses on control of heart rate rather than restoration of normal sinus rhythm.

Relative risk The ratio of the risk in the intervention group to the risk in the control group. Within each group the risk (proportion, probability or rate) is the ratio of people with an event in the group to the total in the group.

Rhythm control A management strategy for arrhythmia that focuses on the restoration and maintenance of normal sinus rhythm.

(Normal) Sinus rhythm The normal rhythm of the heart.

Structural heart disease Heart disease caused by abnormality of structures in the heart, for example the valves or heart muscle (myocardium).

Transient ischaemic attack A 'minor stroke' not resulting in disability or cognitive impairment beyond 24 hours.

Abbreviations

AAD	antiarrhythmic drug	NICE	National Institute for Health and Clinical Excellence
AF	atrial fibrillation	NSR	normal sinus rhythm
AV node	atrioventricular node	OR	odds ratio
CCT	controlled clinical trial (non-randomised)	PP	per protocol
CI	confidence interval	PSS	Personal Social Services
CRD	Centre for Reviews and Dissemination	PV	pulmonary vein
CTI	cavotricuspid isthmus	PVI	pulmonary vein isolation
CVA	cerebrovascular accident	QALY	quality-adjusted life-year
DCC	direct current cardioversion	QoL	quality of life
ECG	electrocardiogram	RA	right atrium
EVPI	expected value of perfect information	RCT	randomised controlled trial
GI	gastrointestinal	RFCA	radio frequency catheter ablation
HRG	Health Resource Group	RR	risk ratio
ICER	incremental cost-effectiveness ratio	SD	standard deviation
ITT	intention to treat	SHD	structural heart disease
LA	left atrium	TIA	transient ischaemic attack
NHS	National Health Service	VOI	value of information
		WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS) or it has been used only once or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.



Executive summary

Background

Atrial fibrillation (AF) and typical atrial flutter are common and debilitating abnormalities of the heart rhythm (arrhythmias).

There are two broad strategies for the management of AF and atrial flutter. Rhythm control strategies attempt to control the arrhythmia by restoring and maintaining a normal heart rhythm (sinus rhythm) whereas rate control strategies aim to control heart rate without attempting to remove the underlying arrhythmia. Both strategies are normally combined with anticoagulants or antiplatelet drugs to reduce the risk of stroke. Long-term rhythm and rate control strategies typically involve treatment with antiarrhythmic drugs (AADs). Acute conversion of an arrhythmia to sinus rhythm ('cardioversion') can be achieved using AADs or by controlled application of direct electrical current.

Radio frequency catheter ablation (RFCA) for the treatment of cardiac arrhythmias involves the percutaneous insertion of catheters that are guided by fluoroscopy to the heart. Small areas of tissue responsible for the propagation of abnormal electrical activity through the heart are selectively destroyed (ablated) using radio frequency energy to restore normal sinus rhythm. In recent years, focus has been on ablating tissue around the pulmonary veins in the left atrium for the treatment of AF and in an area of the right atrium called the cavotricuspid isthmus (CTI) for typical atrial flutter.

Technical aspects of RFCA continue to evolve such that the clinical studies represent experience with many variations in equipment and technique.

Objectives

The aim of this project was to determine the safety, clinical effectiveness and cost-effectiveness of RFCA for the curative treatment of (1) AF and (2) typical atrial flutter.

Methods

This technology assessment comprises the following sections: systematic reviews of clinical studies and economic evaluations of catheter ablation for AF and typical atrial flutter. In addition we developed a de novo economic model of catheter ablation in the treatment of AF.

For the systematic reviews of clinical studies we searched 25 bibliographic databases and internet sources, and checked the references of all included studies. The database searches were originally conducted in July 2006, with subsequent update searches for controlled trials conducted in April 2007.

We included randomised (RCTs) and non-randomised controlled trials comparing RFCA with alternative treatment strategies (i.e. AAD therapy and/or cardioversion) in adults with symptomatic AF or typical atrial flutter. We also included case series of at least 100 patients as well as studies comparing two or more variations on the RFCA approach. The latter were treated as uncontrolled RFCA case series.

An 18-item checklist was used to assess the quality of the included studies. All 18 items were applicable to controlled studies and a subgroup of eight of these items was applicable to case series.

The primary outcome was the proportion of patients free of arrhythmia at 12 months' follow-up; relative risks (RR) and related 95% confidence intervals (CIs) were calculated and, when considered sufficiently homogenous, statistically pooled using a fixed-effects model. When studies failed to report freedom from arrhythmia at 12 months, mean follow-up data were shown but not included in any pooled analyses. Secondary outcomes were the occurrence of complications or adverse events and quality of life.

A broad range of studies was considered for inclusion in the review of cost-effectiveness,

including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) were included. The quality of studies was assessed according to a checklist updated from that developed by Drummond and Jefferson.¹

A decision model was developed to evaluate a strategy of RFCA (without long-term AAD use) compared with long-term AAD treatment alone (amiodarone) in adults with paroxysmal AF. This was used to estimate the cost-effectiveness of RFCA in terms of cost per QALY under a range of assumptions. Decision uncertainty associated with this analysis was presented and used to inform future research priorities using the value of information analysis.

Results

Review of clinical effectiveness

A total of 4858 studies were retrieved from the searches. Of these, eight controlled studies and 53 case series of AF were included. Two controlled studies and 23 case series of typical atrial flutter were included. The majority of case series were judged to be of 'poor' quality; six of the ten included controlled studies were rated as 'satisfactory'.

Clinical effectiveness of RFCA for atrial fibrillation

Freedom from arrhythmia at 12 months in case series (when reported) ranged from 28% to 85.3% with a weighted mean of 76%.

Three RCTs (298 patients) suggested that RFCA is more effective than long-term AAD therapy in patients with drug-refractory paroxysmal AF [per-protocol RR 2.36 (95% CI 1.89–2.95)]. A large non-randomised trial had similar findings. Single RCTs also suggested superiority of RFCA over electrical cardioversion followed by long-term AAD (amiodarone) therapy and of RFCA plus AAD therapy over AAD maintenance therapy alone in drug-refractory patients.

The available RCTs provided insufficient evidence to determine the effectiveness of RFCA beyond 12 months or in patients with persistent or permanent AF.

Adverse events and complications were generally rare. Some events were specific to ablation (tamponade, pericardial effusion, groin haematoma) whereas others were specific to AADs (corneal microdeposit, thyroid dysfunction, pro-arrhythmia, sexual impairment). Mortality rates were low in both RCTs and case series. Cardiac tamponade and pulmonary vein stenosis were the most frequently recorded complications.

Clinical effectiveness of RFCA for typical atrial flutter

Freedom from arrhythmia at 12 months in case series (when reported) ranged from 85% to 92% with a weighted mean of 88%.

Neither of the atrial flutter RCTs reported freedom from arrhythmia at 12 months. One RCT found a statistically significant benefit favouring ablation over AADs in terms of freedom from arrhythmia at a mean follow-up of 22 months [RR 2.2 (95% CI 1.33–3.63)]. This study suggested a very large effect favouring ablation in terms of freedom from atrial flutter [RR 14.03 (95% CI 3.67–53.7)] and a smaller, but also significant, effect in terms of freedom from AF during follow-up [RR 1.77 (95% CI 1.08–2.90)].

A second RCT reported a more modest effect favouring ablation in terms of freedom from atrial flutter at follow-up in older patients (mean age 78 years) after their first episode of flutter [RR 1.36 (95% CI 1.13–1.64)]. No significant effect was observed for freedom from occurrence of significant AF [intention to treat RR 1.44 (95% CI 0.68–3.08)].

In the atrial flutter case series, mortality was rare and the most frequent complications were atrioventricular block and haematomas. Across case series, no single complication occurred at a rate of more than 0.5%. Complications during longer-term follow-up were rarely reported. Complications in the RCTs were similar, except for those events likely to have been caused by AAD therapy (i.e. thyroid dysfunction).

Review of cost-effectiveness and decision model

The review of cost-effectiveness evidence found one relevant study, which from a UK NHS perspective had a number of important limitations.

The base-case analysis in the decision model demonstrated that if the quality of life benefits of

RFCA are maintained over the remaining lifetime of the patient then the cost-effectiveness of RFCA appears clear. These findings were robust over a wide range of alternative assumptions, being between £7763 and £7910 per additional QALY with very little uncertainty.

If the quality of life benefits of RFCA are assumed to be maintained for no more than 5 years, cost-effectiveness of RFCA is dependent on a number of factors, including: (1) any prognostic benefits associated with normal sinus rhythm (NSR); (2) the magnitude of any quality of life differences between RFCA and AADs; and (3) the long-term reduction in risk of recurrent AF following RFCA. Estimates of cost-effectiveness that explored the influence of these factors ranged from £23,000 to £38,000 per QALY.

Conclusions

The available evidence suggests that RFCA is a relatively safe and efficacious procedure for the therapeutic treatment of AF and typical atrial flutter. There is some randomised evidence to suggest that RFCA is superior to AADs in patients with drug-refractory paroxysmal AF in terms of freedom from arrhythmia at 12 months. RFCA appears to be cost-effective if the observed

quality of life benefits are assumed to continue over a patient's lifetime. However, there remain uncertainties around longer-term effects of the intervention and the extent to which published effectiveness findings can be generalised to 'typical' UK practice.

Recommendations for research

All catheter ablation procedures for the treatment of AF or atrial flutter undertaken in the UK should be recorded prospectively and centrally. A Central Cardiac Audit Database already exists, but measures to increase compliance in recording RFCA procedures may be needed. This would be of particular value in establishing the long-term benefits of RFCA and the true incidence and impact of any complications. Collection of appropriate quality of life data within any such registry would also be of value to future clinical and cost-effectiveness research in this area.

Any planned multicentre RCTs comparing RFCA against best medical therapy for the treatment of AF and/or atrial flutter should be conducted among 'non-pioneering' centres using the techniques and equipment typically employed in UK practice and should measure relevant outcomes.

Chapter I

Background

Description of health problem

Atrial fibrillation (AF) and typical atrial flutter are common and debilitating abnormalities of the heart rhythm (arrhythmias). They are related but distinct conditions.

AF is characterised by irregular and rapid beating of the atria (the upper chambers of the heart). It may cause symptoms including palpitations, dizziness, chest pain and, in severe cases, loss of consciousness, but patients may also have AF without experiencing any symptoms.

An international consensus group has produced a definition and classification of AF and related arrhythmias² that has also been used in recent international guidelines for the management of AF³ and in the UK guidelines produced by the National Collaborating Centre for Chronic Conditions on behalf of the National Institute for Health and Clinical Excellence (NICE).⁴ This classification recognises four different patterns of AF (*Table 1*).

AF may be progressive: for example, paroxysmal AF may deteriorate with an increase in the frequency of episodes or may change to persistent

or permanent AF, whereas persistent AF may progress to permanent AF. Reversion of permanent AF to normal sinus rhythm is also possible in some cases, particularly when an underlying disease responsible for AF is treated successfully.⁴ The term 'lone AF' is sometimes used to refer to AF that occurs in the absence of clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension.

Atrial flutter is also an arrhythmia of the atria, which usually occurs paroxysmally, lasting from a few seconds to several hours.⁵ Symptoms are most prevalent when the flutter is paroxysmal and the ventricular rate in response to the flutter is rapid.⁵ The most common symptoms are palpitations, dyspnoea, chest discomfort, dizziness and weakness.⁵ Syncope is not a common symptom unless significant cardiac disease is also present.⁵ Patients who have both atrial flutter and AF are usually more symptomatic.⁵

Aetiology, pathology and prognosis

The normal beating rhythm of the heart involves propagation of electrical activity from the sinoatrial node of the heart to stimulate contraction of the heart muscle (myocardium). Regular and ordered

TABLE 1 Classification of atrial fibrillation

Terminology	Clinical features	Pattern
Initial event (first detected episode)	Symptomatic	May or may not recur
	Asymptomatic (first detected)	
	Onset unknown (first detected)	
Paroxysmal	Spontaneous termination within 7 days (usually within 48 hours)	Recurrent
Persistent	Not self-terminating Lasting over 7 days or requiring cardioversion	Recurrent
Permanent ('accepted')	Not terminated	Established
	Terminated but relapsed	
	No cardioversion attempt	

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stimulation of the myocardium produces efficient contraction of the heart, which in turn maintains the pumping of blood around the body.

In AF, the normal rhythmic pattern of electrical impulses in the heart is replaced by a more random pattern produced by larger areas of atrial tissue. This can be detected on an electrocardiogram (ECG) by the absence of characteristic 'P waves' and their replacement by unorganised electrical activity. The propagation of irregular electrical activity in AF is complex and may involve more than one mechanism. The substrate for AF is diffuse and it may involve the whole atrium. Initial interventional approaches, for example the Maze operation (see Current service provision), attempted to address this. An important milestone was the observation of Haissaguerre and colleagues⁶ that focal triggers within the pulmonary veins (PVs) served to initiate AF and were potential targets for therapeutic intervention.

In contrast to AF, atrial flutter is caused by a single wave of electrical activation that follows a consistent path around the atria as the result of an intra-atrial macroreentry. The circuit involved in typical atrial flutter passes through an area of the right atrium called the cavotricuspid isthmus (CTI) between the tricuspid valve and the inferior vena cava and this observation underlies the development of catheter ablation strategies for the treatment of atrial flutter.⁷ On the ECG, atrial flutter is characterised by a 'sawtooth' pattern of electrical activity known as 'flutter waves'. Atrial flutter is subdivided into typical (also known as type

I and common atrial flutter) and atypical (type II) forms, which can be distinguished by differences in the flutter waves. Atypical flutter is not included in this report. Typical atrial flutter is divided into counterclockwise (the more common) and clockwise forms.

The irregular beating of the heart in AF and atrial flutter affects blood flow and increases the risk of formation of blood clots in the atria, which may subsequently be dislodged and travel to other parts of the body, disrupting the blood flow there (embolism). An embolism in the brain results in a stroke. Embolism to the lungs (pulmonary embolism) can also be life-threatening, although this is rarely seen in patients with AF. Population studies suggest that the risk of stroke is five times higher in people with AF compared with the general population,⁸ and mortality risk is also increased.⁹ Similarly, studies have reported an increased mortality with atrial flutter, although lower than that with AF or a combination of AF and flutter.^{10,11}

Epidemiology and risk factors

AF is the common outcome of a wide range of pathological processes and a wide range of factors predispose to its development (*Table 2*). Increasing age, male sex, diabetes, hypertension and heart valve disease were associated with increased risk of developing AF in the Framingham (USA) epidemiological study.¹² AF is often associated with various other types of heart disease (e.g. ischaemic heart disease, rheumatic heart disease,

TABLE 2 Common causes of atrial fibrillation

Cardiac causes	Non-cardiac causes
<i>Common</i>	Acute infections, especially pneumonia
Ischaemic heart disease	Electrolyte depletion
Rheumatic heart disease	Lung cancer
Hypertension	Other thoracic pathology (e.g. pleural effusion)
Sick sinus syndrome	Pulmonary embolism
Pre-excitation syndromes (e.g. Wolff–Parkinson–White)	Thyrotoxicosis
<i>Less common</i>	
Cardiomyopathy or heart muscle disease	
Pericardial disease	
Atrial septal defect	
Atrial myxoma	

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hypertension and sick sinus syndrome). AF may also result from non-cardiac causes (e.g. infections such as pneumonia, and various chest and lung diseases). Surgery, particularly cardiothoracic surgery, may also lead to the development of AF. When AF results from an acute underlying condition, treatment of the underlying condition may resolve AF. Lifestyle factors associated with an increased risk of AF include excessive alcohol and caffeine consumption and stress.

Atrial flutter is associated with old age and male gender.⁵ Medical conditions that are associated with atrial flutter include valvular heart disease, previous stroke, myocardial infarction, congenital heart disease and surgical repair of congenital heart disease, pericardial disease and thyrotoxicosis, cardiac tumours, hypertrophic cardiomyopathy, cardiothoracic surgery, major non-cardiac surgery, chronic pulmonary disease, pulmonary embolism and acute alcohol intoxication.⁵

Incidence/prevalence

AF is the most common arrhythmia. Prevalence increases with age (from about 0.5% in people aged 50–59 years to 9% in those aged 80–89 years) and is higher in men than in women. Prevalence of AF in the Renfrew–Paisley study in Scotland (a cohort aged 45–64 years, therefore typical of the population undergoing catheter ablation of AF) was 6.5 cases per 1000 examinations, with increased risk being associated with age and male gender (around 14 cases per 1000 males and 8 cases per 1000 females at 60–64 years of age).¹³ The incidence of new cases of AF was 54 per 100,000 person-years.¹³

Most data on prevalence and incidence of AF come from predominantly white populations and data on other ethnic groups are limited. A study in Birmingham found a prevalence of AF of 0.6% among Indo-Asian people aged over 50 years compared with an overall prevalence of 2.4%.⁴ Overall prevalence is rising because of an aging general population and increased longevity resulting from improved medical care among patients with chronic cardiac conditions that predispose to AF.¹⁴ This poses a major health-care challenge for the future.

The incidence of atrial flutter in the USA is reported to be 88 per 100,000 person-years.^{15,16} The incidence increases with age: 5 per 100,000 at age less than 50 years increasing to 587 per 100,000 at age 80 years or more.¹⁶ The incidence

of atrial flutter is two to five times higher in men than in women.

Impact of health problem

Symptomatic AF and atrial flutter or their combination can have a marked negative effect on a patient's quality of life (QoL). Symptoms impact on QoL particularly by reducing exercise tolerance and in some cases cognitive function,⁴ which may reduce the patient's ability to work and take part in other everyday activities. Episodes of AF may require emergency treatment to improve symptoms such as breathlessness and chest pain. Treatment of AF also impacts on the patient through increased rates of consultation in primary and secondary care, hospitalisations and the adverse effects associated with AADs and other treatments. Many patients with AF and atrial flutter receive anticoagulation with warfarin, which requires regular monitoring to prevent over- and underdosing.

AF and atrial flutter are linked to other conditions such as stroke and heart failure. The presence of AF worsens the prognosis following a stroke, with increased disability, longer hospital stays and a reduced chance of being discharged home.⁴

The fact that AF and atrial flutter are common and increasing in prevalence means that the cost to health-care systems of managing these conditions is high. A 2004 study¹⁷ (using 1995 data extrapolated to 2000) estimated the direct cost of AF to the UK NHS in 2000 as £459 million, equivalent to 0.97% of total NHS expenditure. AF and atrial flutter have an impact on all sectors of the NHS, from emergency care to primary and secondary care to specialist tertiary referral.

Current service provision

Management of atrial fibrillation and atrial flutter

There are two broad strategies for the management of AF and atrial flutter. Rhythm control strategies attempt to control the arrhythmia by restoring and maintaining a normal heart rhythm (sinus rhythm) whereas rate control strategies involve control of heart rate without attempting to remove the underlying arrhythmia. Both strategies are normally combined with anticoagulants or antiplatelet drugs such as aspirin to reduce the risk of stroke.

In recent UK guidelines it is recommended that patients with paroxysmal AF should be treated first with a rhythm control strategy, whereas a rate control strategy should be used first for patients with permanent AF. For those with persistent AF the choice between rhythm and rate control depends on a number of factors including age, severity of symptoms and presence of complicating factors, as well as patient preference.⁴

Short-term treatment options for typical atrial flutter are similar to those for AF and include pharmacological rate and rhythm control, electric shock treatment to restore normal heart rhythm, and pacing (using a pacemaker to interrupt the flutter rhythm).⁵ Standard options for longer-term management are continuing drug treatment and catheter ablation.

AADs may be used for both rate control and rhythm control. An imperfect but commonly used classification of AADs (Vaughan Williams classification) divides them into four classes (I–IV; class I has three subclasses, Ia–Ic) according to their effect on the different phases of electrical conduction in the myocardium.¹⁸ Some AADs fall outside this classification (see *Table 3*).

Rhythm control

The general term for restoration of AF or atrial flutter to normal sinus rhythm is ‘cardioversion’. Cardioversion may be carried out using drugs (pharmacological cardioversion) or by administering an electric shock to the heart (electrical cardioversion). Clinical trials suggest that electrical and pharmacological cardioversion are equally effective for restoration of sinus

rhythm in patients with AF.¹⁹ In UK clinical practice, electrical cardioversion is generally preferred to pharmacological cardioversion for relatively prolonged AF (over 48 hours) whereas pharmacological cardioversion may be preferred for AF of more recent onset.⁴ Electrical cardioversion is associated with relatively high rates of reversion to AF and AADs are often given before and after the procedure.

A range of AADs in classes Ia, Ic and III are commonly used for pharmacological cardioversion and subsequently to maintain sinus rhythm in patients with AF or atrial flutter. Beta-blockers (class II) are also commonly used to maintain sinus rhythm following cardioversion. Such therapy has to be lifelong and, furthermore, is at best palliative as nearly all patients will continue to experience some degree of AF or flutter. In addition, AADs are associated with significant adverse events.²⁰ Some AADs can precipitate arrhythmia in patients with underlying heart disease. Therefore, careful monitoring of AAD therapy is required. Amiodarone in particular is associated with a range of adverse effects including pulmonary fibrosis, liver dysfunction, corneal deposits, thyroid problems, photosensitivity, peripheral neuropathy and central nervous system effects. Although there is evidence that amiodarone is more effective than some other AADs for maintenance of sinus rhythm,⁴ the risk of adverse effects means that in clinical practice amiodarone is generally reserved for use when other agents [e.g. beta-blockers, class Ic AADs and sotalol (class III)] have failed. This is the treatment sequence recommended in the UK national guidelines for patients with persistent or paroxysmal AF treated with a rhythm control strategy.⁴

TABLE 3 Vaughan Williams classification of antiarrhythmic drugs

Class	Action	Drugs
I	Sodium channel blockade	
Ia	Prolong repolarisation	Quinidine, procainamide, disopyramide
Ib	Shorten repolarisation	Lidocaine, mexiletine, tocainide, phenytoin
Ic	Little effect on repolarisation	Encainide, flecainide, propafenone
II	Beta-adrenergic blockade	Propranolol, esmolol, acebutolol, L-sotalol
III	Prolong repolarisation (potassium channel blockade; other)	Amiodarone, bretylium, D,L-sotalol, ibutilide
IV	Calcium channel blockade	Verapamil, diltiazem, bepridil
Miscellaneous	Miscellaneous actions	Adenosine, digitalis, magnesium

Pharmacological rhythm control in atrial flutter also commonly involves AADs from classes Ia, Ic and III. However, long-term efficacy of AADs in atrial flutter is less well established than in AF, partly because patients with AF and flutter have been grouped together in many clinical trials.⁵ The risks of AAD treatment in patients with AF also apply to those with flutter.

Another option for rhythm control for some patients with paroxysmal AF is 'pill-in-the-pocket' therapy. This approach may be used with patients who have infrequent symptoms but the number of patients managed in this way in the UK is thought to be small.

Rate control

Rate control for the management of AF is most appropriate for patients with permanent AF and some patients with persistent AF. Drugs used for rate control include beta-blockers and rate-limiting calcium antagonists. Atrioventricular (AV) node ablation and pacing is a rate control procedure that involves ablation of the AV node to eliminate conduction of electrical signals from the atria to the ventricles, combined with implantation of a permanent pacemaker to control heart rate. Studies suggest that AV node ablation and pacing provides effective control of heart rate and improves symptoms in selected patients with AF.³ A meta-analysis of studies published between 1989 and 1998 concluded that the procedure improved cardiac symptoms and QoL and reduced health-care resource use in patients with symptomatic AF resistant to medical treatment.²¹ However, patients treated with this approach still need anticoagulation because the underlying arrhythmia and risk of stroke remains, and they are dependent on a pacemaker for life.

Surgical ablation of atrial fibrillation and atrial flutter

Initial attempts to cure AF by selective creation of lesions within the atria used a surgical approach. The Maze procedure was pioneered by J. L. Cox and involved interrupting all of the circuits that could be involved in AF using a 'cut and sew' method. High rates of maintenance of sinus rhythm were reported following the Maze procedure but the procedure was technically difficult and was associated with relatively high mortality [30-day mortality of 0–7.2% in large case series (mean 2.1%)] and morbidity (including

sinus node dysfunction, bleeding and stroke).²² Modified versions of the Maze procedure were developed that involved creating a more limited set of lesions, and selected areas of tissue were ablated as an alternative to the 'cut and sew' approach. Cryoablation and radio frequency ablation can be performed using hand-held probes or clamp devices. Other energy sources for surgical ablation include laser, microwave and ultrasound. The vast majority of surgical procedures for ablation of AF are performed in conjunction with other heart surgery, particularly mitral valve surgery.²² Surgical ablation may also be an option for a minority of cases of atrial flutter but is less important for this arrhythmia than for AF.

Current service cost

A recent report¹⁷ estimated that about 1% of all NHS expenditure is the result of AF. In total, 50% of this expenditure was associated with hospital admissions and 20% with the costs of drug treatment. Implementation of the 2006 NICE guidance on management of AF is expected to result in increased expenditure, primarily through increased use of ECG to confirm diagnosis and increased use of anticoagulants. These increased costs are anticipated to be offset by savings resulting from strokes and deaths avoided by improved treatment.⁴ Costs directly associated with atrial flutter are likely to be lower than those for AF because the condition is much less common, but the close relationship between the two arrhythmias makes it difficult to separate them in terms of their cost to the health-care system.

Relevant national guidelines

Management of AF and related arrhythmias is covered in Chapter 8 of the *National service framework for coronary heart disease*.²³ There are NICE guidelines for the management of AF in primary and secondary care;⁴ most of the recommendations are stated to apply to atrial flutter as well as AF. NICE has also issued an interventional procedure overview specifically of RFCA for AF.²⁴ This is based on a rapid evidence review and expert opinion and is not intended as a definitive assessment of the procedure. The guidelines on management of AF recommend that patients with the following characteristics may benefit from referral for catheter ablation (PV isolation): patients with AF resistant to pharmacological treatment; younger rather than older patients (not defined); and those with 'lone AF'.

Description of technology under assessment

Catheter ablation is a relatively new, invasive technique for the treatment of cardiac arrhythmias. Curative percutaneous catheter ablation developed from the surgical ablation techniques briefly described above. The most well-established approach involves the percutaneous insertion of catheters, which are guided by fluoroscopy to the heart. Ablation for atrial flutter and fibrillation is now well understood with defined targets for ablation of the arrhythmia substrate. There are well-defined end points for atrial flutter ablation that predict high (80–90%) success rates.⁷ The end points for ablation of AF are less well defined, but success rates of 50–70% were reported by most centres in an early survey.²⁵

Catheter ablation for atrial flutter is a highly standardised technique. Atrial flutter is most commonly caused by a specific reentrant circuit in the right atrium, and the approach to ablating this typical form of atrial flutter is well established, with ablation of a line between the tricuspid valve and the inferior vena cava [cavotricuspid isthmus (CTI) ablation].²⁶

Catheter ablation in AF has developed in recent years such that it now primarily involves ablation of atrial tissue around the PVs.²⁷ The procedure has changed over time because of changes in technology and increased knowledge of aetiology. Variations can relate to the type of catheter (standard or irrigated), type of ablation energy (e.g. radio frequency, cryoablation, microwave, laser, ultrasound), type of mapping technique used to locate and guide the catheters within the heart (e.g. intracardiac electrogram, intracardiac echocardiography, electroanatomical mapping), and the ablation approach itself (e.g. linear, focal, PV isolation). The two main types of approach are three-dimensional (3D)-guided compartmentalisation techniques and electrical disconnection of the PVs, sometimes referred to as circumferential and segmental ablation respectively.

Circumferential ablation uses a 3D guidance system to visualise the anatomical structure and ablation lines. This approach involves the creation of a continuous ablation line in the left atrium (LA) that surrounds and completely encloses the PVs. The end point of this type of procedure is completion of the planned ablation lines. Segmental ablation is an electrophysiological approach in which energy is applied near the PV–LA junction to destroy the

electrical connections between the PV and LA. The end point of the procedure is achieved when all PV potentials are abolished or potentials are dissociated from the rest of the LA. Techniques that combine elements of both approaches, or that combine PV ablation with additional ablation lines in the LA, are increasingly used.

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) commissioned a systematic review²⁸ (published in 2002) that covered RFCA for all types of arrhythmia. For atrial flutter, this review found one small RCT²⁹ reporting reduced symptoms, a lower rate of complications and rehospitalisation, and improved QoL compared with drug therapy with almost 2 years' mean follow-up. Case series^{30–44} suggested acute procedural success rates of 83–100% in patients with atrial flutter alone, but also suggested that up to 15% of patients may experience a recurrence. In relation to AF, the review summarised some of the earliest case series reporting PV isolation.^{6,45–49} It concluded that the observed short-term clinical success rates of 62–88% in these series were 'encouraging' but that PV isolation for AF must, at that time, be considered an experimental procedure.

More recently, the NICE Interventional Procedures Programme published an overview of RFCA for AF to support guidance issued in April 2006.²⁴ This guidance concluded that current evidence 'appears adequate to support the use of this procedure in appropriately selected patients', defined as 'symptomatic patients with atrial fibrillation refractory to anti-arrhythmic drug therapy or where medical therapy is contraindicated because of co-morbidity or intolerance'. We are not aware of any recent systematic reviews or guidelines of catheter ablation for typical atrial flutter.

An international survey on catheter ablation for AF was published by Cappato and colleagues in 2005.²⁵ The survey questionnaire was sent to 777 electrophysiology centres, of which 181 (23.3%) responded. The participating centres were considered by the authors to be representative of contemporary good clinical practice in interventional electrophysiology. Of the 181 centres that responded, 100 had ongoing programmes for catheter ablation of AF and they provided data on 11,762 procedures performed on 9370 patients between 1995 and 2002. The median number of procedures per centre was 37.5 (range 1–600). Complete data for assessment of efficacy of catheter ablation were provided for 8745 patients

who were followed up for a median of 12 months (range 1–98 months).

Table 4 summarises the details and key findings of the study. Of the patients for whom full data were available, 52% became free of symptoms without AADs and a further 23.9% became free of symptoms on a previously ineffective AAD regimen. In total, 24.3% of patients required two ablation procedures and 3.1% required three procedures. The success rate free of AADs was 52.7% for 65 centres that treated patients with paroxysmal AF only, 48.5% for 17 centres that treated patients with paroxysmal or persistent AF, and 57.3% for eight centres that treated patients with all forms of AF.

Techniques used for catheter ablation of AF captured by the Cappato survey varied between centres and over time within centres. PV disconnection was the most prevalent technique overall and in the most recent years covered by the survey (2000–2002). Of 4918 patients for whom the energy source used for catheter ablation was known, 89% received radio frequency current ablation, 5% cryotherapy, 2% ultrasound, 2% laser ablation and 2% ablation using other

energy sources. The most common techniques for mapping and ablation were CARTO™ (BioSense Webster; 1846 patients in 43% of centres), Lasso (BioSense Webster; 3385 patients, 77% of centres), EnSite® (Endocardial Solutions; 141 patients, 12% of centres) and basket-shaped electrode catheters (317 patients, 21% of centres).

Success rates tended to increase with volume of procedures performed, overall success increasing from 59.9% in centres performing 1–30 procedures to 91% in those performing 231–300 and 87.9% in those performing more than 300 procedures in total. Success rates remained relatively constant across follow-up times ranging from less than 3 months to more than 24 months (*Table 5*).

Major complications, including periprocedural death, cardiac tamponade, stroke, transient ischaemic attack and PV stenosis, occurred in 6% of patients. New-onset atypical atrial flutter was reported in 3.9% of patients; this phenomenon was significantly more frequent in centres using 3D-guided compartmentalisation techniques than in those that performed ablation of the triggering substrate or PV electrical disconnection.

TABLE 4 Summary of the international survey of catheter ablation for atrial fibrillation²⁵

Study details	Main efficacy findings	Main safety findings
Worldwide survey (181 centres)	Freedom from AF without AADs: 4550/8745 (52%, range among centres 14.5–76.5%)	All major complications: 524/8745 (6%)
Procedures performed 1995–2002		Periprocedural death: 4/8745 (0.05%)
9370 patients (11,762 procedures)	Freedom from AF with previously ineffective AADs: 2094/8745 (23.9%, range among centres 8.8–50.3%)	Cardiac tamponade: 107/8745 (1.2%)
Efficacy data for 8745 patients (68.3% male, age range 16–86 years)		Stroke: 20/8745 (0.2%)
Inclusion criteria: paroxysmal AF 100% of centres; drug refractory 93%; persistent AF 53%; permanent AF 20%	Resolution of symptoms with or without AADs: 6644/8745 (76%, range among centres 22.3–91%)	Transient ischaemic attack: 47/8745 (0.5%)
Exclusion criteria: lower limit of left ventricular ejection fraction between 30% and 35% (65% of centres); previous heart surgery (64%); upper limit of left atrial size between 50 and 60mm of maximal transverse diameter (46%)		PV stenosis: 117/8745 (1.3%)
		Sepsis, abscess or endocarditis: 1/8745 (0.01%)
		Pneumothorax: 2/8745 (0.02%)
		Haemothorax: 14/8745 (0.02%)
		Permanent diaphragmatic paralysis: 10/8745 (0.1%)
		Femoral pseudoaneurysm: 47/8745 (0.5%)
		Arteriovenous fistulae: 37/8745 (0.4%)
		Valve damage: 1/8745 (0.01%)
		Aortic dissection: 3/8745 (0.03%)
		New-onset atypical atrial flutter: 340/8745 (3.9%)

Adapted from NICE.⁵⁰

TABLE 5 Success rates of catheter ablation for atrial fibrillation by follow-up duration²⁵

Range of follow-up duration (months)	Number of centres	Overall success rate
0–3	4	122/179 (68.2%)
4–6	16	615/906 (67.8%)
7–9	14	939/1271 (73.9%)
10–12	15	1383/1537 (89.9%)
13–18	17	2035/2607 (78.1%)
19–24	8	326/467 (69.8%)
> 24	6	1125/1619 (69.5%)

The Cappato survey provides valuable information about success and complication rates of RFCA for AF in a worldwide sample of centres. It provides evidence of the range of techniques employed and the volume of procedures at different centres and their relationship to success rates. Potentially, the data relate to everyday clinical practice rather than to the sometimes highly selected populations included in clinical trials. On the other hand, the survey has a number of limitations:

- Given the low response rate of around 23%, the centres that responded to the survey are unlikely to be a representative sample.
- The survey reports procedures performed between 1995 and 2002; in view of the rapid developments in RFCA for AF, these results may not be representative of current practice.
- The survey provides uncontrolled data and gives no indication of the effectiveness of RFCA relative to other treatment strategies.
- The authors do not report any longer-term follow-up data on important clinical outcomes such as mortality and stroke.

Chapter 2

Definition of decision problem

Decision problem

RFCA is generally indicated for the treatment of those patients with AF or atrial flutter for whom AAD therapy has proven ineffective, intolerable or unsafe. When successful, RFCA can eliminate the need for AADs or prevent patients having to progress to more powerful but more toxic agents such as amiodarone. However, the procedure also carries a risk of complications and morbidity, in particular an increased risk of stroke. It is unclear how well these risks are offset by the level of benefit achieved.

When successful, RFCA restores and maintains normal sinus rhythm (NSR). Thus, it should be considered as a rhythm control strategy and compared with rhythm control strategies, i.e. AADs for cardioversion and maintenance of NSR.

Within the patient populations being evaluated there are important subgroups of patients for whom the differential effects of catheter ablation need to be investigated. AF and atrial flutter must be considered separately. With AF there is a distinction between patients with the paroxysmal form of AF (in which AF comes and goes by itself) and patients with persistent (in which AF can only be stopped by cardioversion) or permanent (either AF cannot be stopped or the clinician has elected not to attempt to do so) AF. The distinction is drawn because of the higher success rates of ablation for treating paroxysmal AF.²² There is no similar distinction within atrial flutter.

Outcome measures to evaluate effectiveness and safety vary between studies and can include acute procedural success (e.g. re-established sinus rhythm), long-term maintenance of sinus rhythm, relief from symptoms, need for repeat ablation procedures, complications (e.g. cardiac tamponade), adverse events (e.g. sudden death, stroke), morbidity, mortality and QoL.

Possible modifiers of the effect of RFCA include the precise technology used for mapping and ablation, the experience of the team performing the procedure and follow-up care after the procedure.

RFCA is currently provided by the NHS at specialist tertiary referral centres. The technical aspects of the procedure are developing rapidly and its use is expanding worldwide.²⁵ RFCA is strongly advocated by many clinicians and recently there has been discussion of its use as a first-line treatment as an alternative to AAD therapy in selected patients. In view of the potential promise and uncertainties surrounding RFCA for AF and atrial flutter, an up-to-date review of the evidence for its clinical effectiveness, safety and cost-effectiveness is clearly justified.

Overall aims and objectives of the assessment

The aim of this project is to determine the safety, clinical effectiveness and cost-effectiveness of RFCA for the curative treatment of (1) AF and (2) typical atrial flutter. It aims to examine the available evidence regarding the clinical and cost-effectiveness of catheter ablation compared with relevant comparator treatments.

For the clinical review, comparative clinical studies have been supplemented with observational studies, as these constitute much of the evidence base for RFCA. A specific aim is to focus on evidence from the setting of the NHS and to consider evidence from other sources in relation to its generalisability to NHS practice. Gaps in the evidence are highlighted and recommendations presented for further research.

The specific objectives of the cost-effectiveness analysis are to: (1) structure an appropriate decision model to characterise patients' care and subsequent prognosis and the impacts of alternative therapies; (2) populate this model using the most appropriate data identified systematically from published literature and routine sources; (3) relate intermediate outcomes to final health outcomes, expressed in terms of quality-adjusted life-years (QALYs); (4) estimate the mean cost-effectiveness of catheter ablation; and (5) characterise the uncertainty in the data used to populate the model and to present the

uncertainty in these results to decision-makers. To inform future research priorities in the NHS, the model will be used to undertake analyses of the expected value of information. The model focuses

on the treatment of AF but consideration is given to extending the analysis to the treatment of typical atrial flutter.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing clinical effectiveness

Search strategy

Literature searches were conducted in 25 bibliographic databases and internet sources. They were originally conducted in July 2006, with subsequent update searches for controlled trials conducted in April 2007. Our review aimed to build on the findings of the previous CCOHTA systematic review,²⁸ but with a focus on research evidence of higher quality or of relevance to current practice. Therefore, any controlled trials from the earlier review were obtained for screening and the search strategies used in the CCOHTA review were rerun from the year 2000 onwards. No language restrictions were applied to any of the search strategies; however, terms referring to issues beyond the scope of the current review (e.g. ventricular tachycardia) were excluded. A variety of keywords and search strategies were used (details of the search strategies for all of the databases are presented in Appendix 1). The bibliographies of all relevant reviews and guidelines and all included studies were checked for further potentially relevant studies. Citation searching was also undertaken for selected papers. The following databases were searched:

Guidelines databases

- BMJ Clinical Evidence. URL: www.clinicalevidence.com/ceweb/index.jsp
- Cardiovascular Diseases Specialist Library. URL: www.library.nhs.uk/cardiovascular
- Health Evidence Bulletin Wales. URL: <http://hebw.cf.ac.uk>
- HSTAT. URL: www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
- National Guidelines Clearing House. URL: www.guideline.gov
- NICE. URL: www.nice.org.uk
- NLH Guidelines Finder. URL: www.library.nhs.uk/guidelinesFinder
- Scottish Intercollegiate Guidelines Network (SIGN). URL: www.sign.ac.uk
- TRIP. URL: www.tripdatabase.com/index.html

Databases of systematic reviews

- Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library). URL: www.library.nhs.uk/
- Database of Abstracts of Reviews of Effects (DARE) [Centre for Reviews and Dissemination (CRD) Internal Database]

Health-/medical-related databases

- BIOSIS (DIALOG). URL: <http://library.dialog.com/>
- CENTRAL (Cochrane Central Register of Controlled Trials) (Cochrane Library). URL: www.library.nhs.uk
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (OvidWeb). URL: <http://gateway.ovid.com/athens>
- EMBASE (OvidWeb). URL: <http://gateway.ovid.com/athens>
- Health Technology Assessment Database (HTA) (CRD Internal Database)
- MEDLINE (OvidWeb). URL: <http://gateway.ovid.com/athens>
- MEDLINE In-Process and other non-indexed citations (OvidWeb). URL: <http://gateway.ovid.com/athens>
- Science Citation Index (SCI) (Web of Knowledge). URL: <http://wos.mimas.ac.uk/>

Databases of conference proceedings

- ISI Proceedings: Science and Technology (Web of Knowledge). URL: <http://wos.mimas.ac.uk/>
- Zetoc Conferences (MIMAS). URL: <http://zetoc.mimas.ac.uk/>

Databases for ongoing and recently completed research

- ClinicalTrials.gov. URL: www.clinicaltrials.gov
- ESRC SocietyToday Database. URL: www.esrc.ac.uk/ESRCInfoCentre/index.aspx
- MetaRegister of Controlled Trials. URL: www.controlled-trials.com
- National Research Register (NRR). URL: www.update-software.com/national

- Research Findings Electronic Register (ReFeR).
URL: www.info.doh.gov.uk/doh/refr_web.nsf/Home?OpenForm

Inclusion and exclusion criteria

Studies were included in the review if they met the following inclusion criteria:

Population

Adults with symptomatic AF or adults with typical atrial flutter. For AF, patients had to be refractory to at least one AAD. Studies with a mixed group of patients with both AF and atrial flutter, without reporting separate outcomes for each arrhythmia, were excluded.

Interventions

Percutaneous RFCA for the curative treatment of AF or typical atrial flutter. Non-RF techniques were excluded. Similarly, evaluations of ablation techniques no longer in use or considered obsolete (i.e. pre-1998)⁶ were excluded, as were studies evaluating surgical ablation (i.e. variations on the Maze procedure) and AV node ablation and pacing.

Comparators

When controlled studies were identified, AAD treatment (e.g. flecainide, sotalol, amiodarone) and/or cardioversion were considered relevant comparators. Controlled studies comparing catheter ablation with no therapy, when standard therapy in the form of AADs was given to all patients in both treatment arms, were also eligible for inclusion. Studies were excluded if the comparator was not intended to achieve rhythm control.

Outcomes

Studies were included if they reported any of the following outcomes: acute (in hospital) and long-term procedural success (i.e. freedom from recurrence of arrhythmia), incidence of symptoms, need for repeat ablation procedures, assessment of QoL, or complications (e.g. cardiac tamponade, stroke).

Study designs

The following study designs were included: RCTs comparing RFCA against a comparator and including at least 20 patients; non-randomised controlled studies (CCTs) with at least 100 patients comparing RFCA against a comparator; and case series reporting at least 100 consecutive cases. RCTs and CCTs comparing different variations in RFCA technique or equipment were treated

as uncontrolled studies of catheter ablation and included if they reported at least 100 consecutive patients. This was a practical decision reflecting the fact that: (1) RFCA techniques are evolving rapidly and (2) our primary objective was to assess the effectiveness of RFCA relative to alternative approaches for the management of AF. When the same centre reported multiple case series, each of the series was included in the review and, when possible, those with potential overlaps in patient populations were identified before analysis.

Animal models, preclinical and biological studies, reviews, editorials, opinions and non-English language papers were excluded.

Data extraction strategy

Titles and abstracts were independently screened for relevance by two reviewers and all potentially relevant papers were ordered. Full papers were independently screened by two reviewers and the decision to include studies or not made according to the inclusion criteria detailed above. Disagreements were resolved by consensus, consulting a third reviewer if necessary.

Data were extracted on participants (including age, gender distribution, proportion of drug-refractory patients, proportion with concomitant structural heart disease, etc.), interventions (e.g. technique used, mapping system, type of catheter tip), comparators (e.g. type of AAD, dosage), outcomes (e.g. freedom from arrhythmia, complications/adverse events, QoL, mortality) and study design/quality. Data were extracted into a predefined Microsoft Access database. All data extraction was performed by one reviewer and checked by a second.

Quality assessment strategy

An 18-item checklist was used to assess the quality of the included studies (see Appendix 2). All 18 items were applicable to controlled studies and a subgroup of eight of these items was applicable to case series. The items specific to controlled studies related to issues such as randomisation, concealment of allocation, baseline comparability of groups and blinding. Items common to both the case series and controlled studies addressed issues such as appropriateness of patient selection criteria, reporting of variability and loss to follow-up. These criteria were derived from CRD's guidance on undertaking reviews of effectiveness⁵¹ and previously published reviews

incorporating case series data.^{52,53} Depending upon which specific quality criteria were met and the subsequent potential for bias, controlled studies could receive an overall quality rating of 'poor', 'satisfactory', 'good' or 'excellent' and case series could be rated as 'poor', 'satisfactory' or 'good'. Each included study was quality assessed by one reviewer and the quality assessment was checked by a second reviewer. Disagreements were resolved by consensus, consulting a third reviewer if necessary.

Role of clinical advisors

Clinical experts (DT, CP) collaborated closely throughout the review of clinical effectiveness, helping to refine the review question, identify all of the relevant evidence and interpret results.

Data analysis

As the aim of the review was to evaluate RFCA as a curative procedure in the management of AF and typical atrial flutter, the primary outcome was the proportion of patients free of arrhythmia at 12 months' follow-up. The US Food and Drug Administration (FDA) has defined this as the preferred outcome for trials of catheter ablation.⁵⁴ Secondary outcomes were the occurrence of complications or adverse events and QoL. In addition, freedom from arrhythmia at other time points was also summarised. The results of RCTs reporting this outcome were displayed as risk ratios (RR) and related 95% confidence intervals (CIs) in forest plots and, when considered sufficiently homogenous, these were pooled in a meta-analysis using a fixed-effects model. Inconsistency was investigated using the standard chi-squared test for statistical heterogeneity and expressed as the I^2 statistic. Where studies failed to report freedom from arrhythmia at 12 months, mean follow-up data were shown but not included in any pooled analyses.

To assess the impact of withdrawals and crossovers on trial results, the data were presented in three forms: per protocol (i.e. patients who remained on the protocol to which they were randomised and were available at follow-up); 'worst case' (in which withdrawals from the ablation group were assumed to have arrhythmia and those from the comparison group were assumed to be free of arrhythmia); and intention to treat (in which patients were analysed according to the group to which they were originally randomised, regardless of withdrawals or crossovers). FDA clinical study design guidance suggests that crossover from comparator to RFCA arm be treated as treatment failure in the

comparator arm.⁵⁴ Therefore, we have placed greater emphasis on the estimates based on the per protocol results.

Some studies reported time-to-event data, such as hazard ratios (HR) or arrhythmia-free Kaplan–Meier survival curves. Where possible, HRs were either extracted from the paper or indirectly estimated using the methods described by Parmar *et al.*⁵⁵

From the case series, rates of freedom from arrhythmia at 12 months and at mean follow-up were presented and discussed in a narrative synthesis. Where reported, we calculated a weighted average for this outcome at 12 months using a random-effects model.

Data on complications were extracted from the case series and controlled studies and were tabulated and discussed in a narrative synthesis.

Results of review of clinical effectiveness – atrial fibrillation

Quantity and quality of research available

A total of 4860 studies were retrieved from the searches (see *Figure 1*). Of these, 483 were ordered and 86 studies (89 publications) met the inclusion criteria for the review. In total, 61 of these related to RFCA for AF (eight controlled studies and 53 case series).

Of the eight controlled studies evaluating the effectiveness of RFCA for AF, one was rated 'good',⁵⁶ four were rated 'satisfactory',^{57–60} and three were rated 'poor'.^{61–63} Two studies were non-randomised, one of which reported clear differences between groups at baseline.⁶¹ The third 'poor' study was rated as such because of the very limited information available in the published abstract.⁶³ The study rated as 'good' was the only randomised study to blind outcome assessors to group allocation⁵⁶ (see *Table 6*). One randomised⁶⁰ and one large non-randomised⁶¹ controlled study included patients who had not been proven to be drug refractory. However, it was decided that these studies could provide important evidence on the relative effects of RFCA and so they were included in the review, but any potential impact of their patient populations on outcomes was emphasised where relevant.

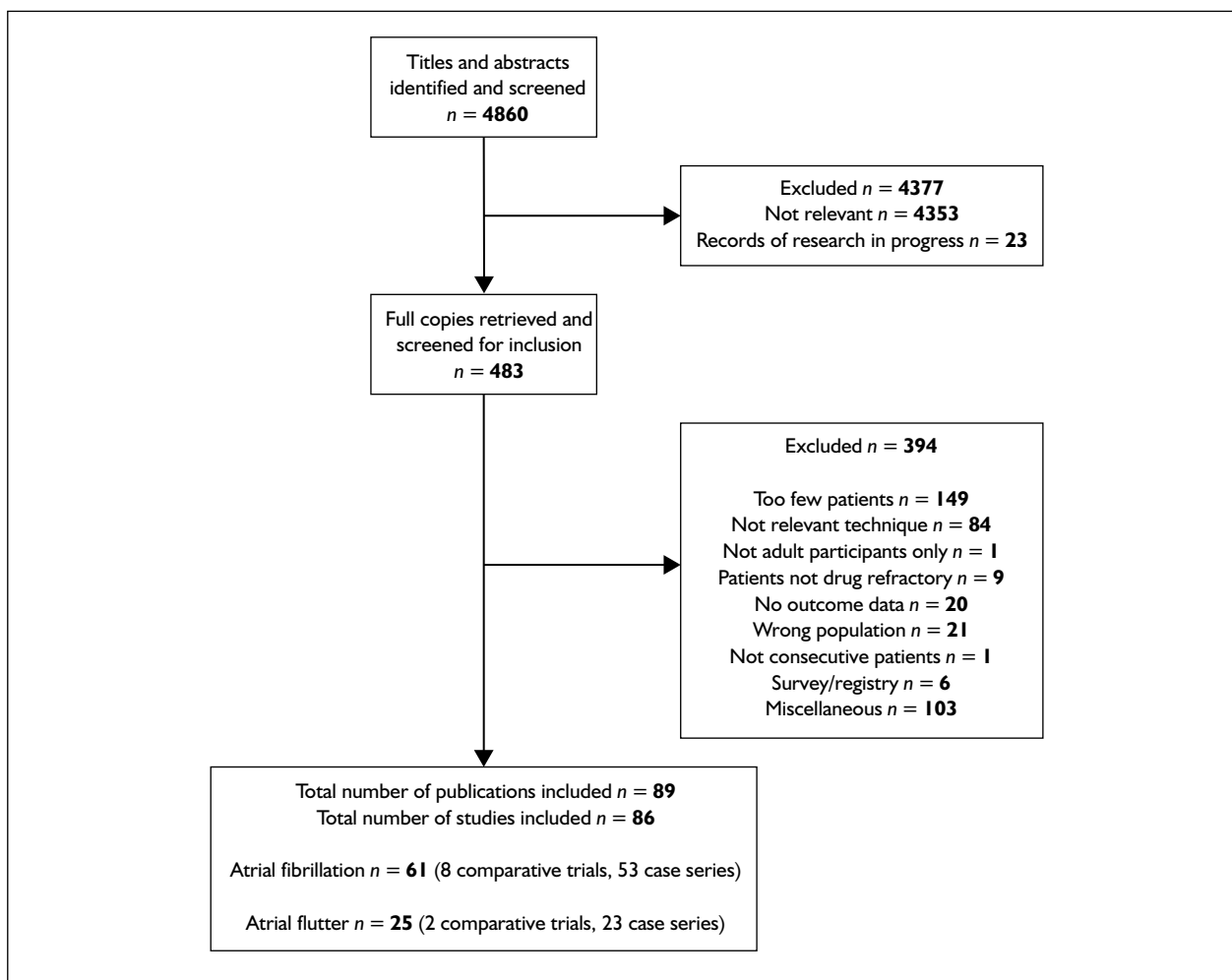


FIGURE 1 Flow chart of studies through the review process.

TABLE 6 Quality ratings of controlled studies

Study	Study design	Criteria met	Overall quality rating
Krittayaphong <i>et al.</i> , 2003 ⁵⁷	RCT	1, 4, 11–16, 18	Satisfactory
Pappone <i>et al.</i> , 2003 ⁶¹	CCT	4, 7, 9, 11, 13–18	Poor
Wazni <i>et al.</i> , 2005 ⁶⁰	RCT	1, 2, 4, 9, 11–16, 18	Satisfactory
Oral <i>et al.</i> , 2006 ⁵⁶	RCT	1, 2, 4, 7, 9–18	Good
Pappone <i>et al.</i> , 2006 (APAF) ⁵⁸	RCT	1, 4, 9–11, 13–18	Satisfactory
Stabile <i>et al.</i> , 2006 ⁵⁹	RCT	1, 2, 4, 10–18	Satisfactory
Lakkireddy <i>et al.</i> , 2006 ⁶²	CCT	4, 9, 11	Poor
Jais <i>et al.</i> , 2006 ⁶³	RCT	1, 9, 11, 12, 16, 17	Poor

See Appendix 2 for an explanation of the ratings and criteria used in quality assessment.

Of 53 case series in AF, only two were rated as 'good'^{64,65} and three as 'satisfactory'⁶⁶⁻⁶⁸ (Table 7). The UK case series by Bourke and colleagues⁶⁶ was one of those rated 'satisfactory'. The remaining 48 series were rated as 'poor', most commonly because details of follow-up were lacking.

Ongoing research

The search of research registers for ongoing studies produced 23 records. Following contact with investigators, there were four studies which appeared relevant to the review that were in progress or completed but with no results available at the time of the review (Appendix 6).

In addition, the CABANA (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial^{69,70} began its pilot phase in late

2006. This large RCT (planned to follow 3000 patients for an estimated 5 years) is designed to determine whether there is a mortality benefit from catheter ablation compared with pharmacological rate and rhythm control strategies and will also evaluate effects on QoL, costs and resource use. Unfortunately, it will be some time before any results are available from this study.

Assessment of effectiveness from controlled trials

Trial characteristics

Six RCTs^{56-60,63} and two non-randomised studies^{61,62} compared the effects of RFCA against an alternative treatment strategy for AF (see Appendix 3.1). Patient characteristics are summarised in Table 8 with a brief summary of each study given below.

TABLE 7 Quality ratings of case series

Study	Criteria met	Overall quality rating
Berkowitsch <i>et al.</i> , 2005 ⁷¹	11, 13, 16, 17, 18	Poor
Bertaglia <i>et al.</i> , 2005 ⁷³	11, 12, 13, 15, 17, 18	Poor
Beukema <i>et al.</i> , 2005 ⁷⁵	12, 13, 17, 18	Poor
Bhargava <i>et al.</i> , 2004 ⁷⁷	12, 13, 15, 18	Poor
Bourke <i>et al.</i> , 2005 ⁶⁶	11, 12, 14, 15, 16, 17, 18	Satisfactory
Cha <i>et al.</i> , 2005 ⁸⁰	13, 18	Poor
Chen <i>et al.</i> , 2004 ⁸²	11, 12, 13, 15, 17, 18	Poor
Daoud <i>et al.</i> , 2006 ⁶⁷	11, 12, 13, 14, 15, 16, 17	Satisfactory
Deisenhofer <i>et al.</i> , 2004 ⁸⁴	11, 12, 15, 16, 17, 18	Poor
Della Bella <i>et al.</i> , 2005 ⁶⁸	12, 13, 14, 15, 16, 17, 18	Satisfactory
Dong <i>et al.</i> , 2005 ⁸⁷	11, 13, 17, 18	Poor
Ernst <i>et al.</i> , 2003 ⁸⁹	12, 13, 18	Poor
Essebag <i>et al.</i> , 2005 ⁹¹	12, 13, 15, 17, 18	Poor
Fassini <i>et al.</i> , 2005 ⁹³	11, 12, 13, 15, 16, 17, 18	Poor
Herweg <i>et al.</i> , 2005 ⁹⁵	11, 12, 13, 15, 17, 18	Poor
Hindricks <i>et al.</i> , 2005 ⁹⁷	11, 12, 13, 15, 16, 17, 18	Poor
Hsieh <i>et al.</i> , 2003 ⁹⁹	15	Poor
Hsu <i>et al.</i> , 2004 ¹⁰¹	11, 13, 14, 15, 16, 18	Poor
Jais <i>et al.</i> , 2004 ¹⁰³	11, 12, 13, 15, 16, 17, 18	Poor
Karch <i>et al.</i> , 2005 ¹⁰⁵	11, 12, 13, 14, 15, 16, 18	Poor
Kilicaslan <i>et al.</i> , 2005 ¹⁰⁶	11, 12, 13, 15, 18	Poor
Kilicaslan <i>et al.</i> , 2006 ¹⁰⁸	11, 12, 13, 17, 18	Poor
Kobza <i>et al.</i> , 2004 ¹¹⁰	11, 12, 16, 17, 18	Poor

continued

TABLE 7 Quality ratings of case series

Study	Criteria met	Overall quality rating
Kottkamp <i>et al.</i> , 2004 ¹¹²	11, 12, 13, 16, 17, 18	Poor
Kumagai <i>et al.</i> , 2005 ¹¹⁴	11, 12, 13, 15, 16, 17, 18	Poor
Lee <i>et al.</i> , 2004 ¹¹⁶	13, 15, 18	Poor
Liu <i>et al.</i> , 2005 ¹¹⁸	11, 13, 14, 15, 17, 18	Poor
Ma <i>et al.</i> , 2006 ⁷²	11, 12, 17, 18	Poor
Macle <i>et al.</i> , 2002 ⁷⁴	11, 12, 13, 15, 17, 18	Poor
Marchlinski <i>et al.</i> , 2003 ⁷⁶	12, 17	Poor
Marrouche <i>et al.</i> , 2002 ⁷⁸	12, 13, 14, 15, 16, 18	Poor
Nademanee <i>et al.</i> , 2002 ⁷⁹	15	Poor
Nademanee <i>et al.</i> , 2004 ⁸¹	12, 13, 18	Poor
Nilsson <i>et al.</i> , 2006 ⁶⁴	11, 12, 13, 14, 15, 16, 17, 18	Good
Oral <i>et al.</i> , 2004 ⁸³	12, 13, 14, 15, 17, 18	Poor
Oral <i>et al.</i> , 2004 ⁸⁵	12, 13, 14, 15, 17, 18	Poor
Pappone <i>et al.</i> , 2001 ⁸⁶	11, 12, 14, 15, 17, 18	Poor
Pappone <i>et al.</i> , 2001 ⁸⁸	12, 13, 14, 15, 17, 18	Poor
Pappone <i>et al.</i> , 2004 ⁹⁰	11, 12, 13, 15, 16, 17, 18	Poor
Purerfellner <i>et al.</i> , 2006 ⁹²	13, 18	Poor
Ren <i>et al.</i> , 2004 ⁹⁴	12, 13, 18	Poor
Saad <i>et al.</i> , 2003 ⁹⁶	12, 13, 15, 18	Poor
Saad <i>et al.</i> , 2003 ⁹⁸	12, 13, 15, 18	Poor
Shah <i>et al.</i> , 2001 ¹⁰⁰	11, 12, 13, 15, 17, 18	Poor
Shah <i>et al.</i> , 2003 ¹⁰²	11, 12, 15, 17, 18	Poor
Trevisi <i>et al.</i> , 2003 ¹⁰⁴	12, 13, 18	Poor
Verma <i>et al.</i> , 2005 ⁶⁵	11, 12, 13, 14, 15, 16, 17, 18	Good
Wazni <i>et al.</i> , 2005 ¹⁰⁷	12, 13, 15, 17, 18	Poor
Weerasooriya <i>et al.</i> , 2003 ¹⁰⁹	11, 12, 13, 15, 16, 17, 18	Poor
Weerasooriya <i>et al.</i> , 2003 ¹¹¹	11, 12, 15, 17, 18	Poor
Yamada <i>et al.</i> , 2006 ¹¹³	12, 13, 17, 18	Poor
Yamane <i>et al.</i> , 2002 ¹¹⁵	11, 12, 13, 15, 17, 18	Poor
Yu <i>et al.</i> , 2001 ¹¹⁷	11	Poor

See Appendix 2 for an explanation of the ratings and criteria used in quality assessment.

Results by trial**Krittayaphong *et al.*, 2003⁵⁷**

RCT (rated 'satisfactory') of RFCA versus amiodarone in patients with paroxysmal or persistent AF (70% paroxysmal, mean duration 4.6 years). All patients were refractory to at least one AAD but had never received amiodarone.

A total of 15 patients randomised to RFCA underwent circumferential PV ablation, with an additional line connecting the circular line to the

mitral annulus. In addition, CTI ablation was performed, plus a horizontal line at the level of the mid right atrium. RFCA could not be performed in one patient because of failure of trans-septal puncture. Electrical cardioversion was performed in two patients still in AF following ablation, and all patients received amiodarone for 3 months post procedure.

A total of 15 patients were randomised to long-term amiodarone treatment. Cardioversion was

performed in patients with persistent AF. When serious side effects occurred, amiodarone was discontinued in favour of class Ia or Ic agents.

At 12 months post randomisation, 11/15 patients in the RFCA group were free of AF compared with 6/15 patients in the amiodarone group.

Frequency of symptoms decreased from 42.8 (SD 22.6) attacks per month at baseline to 0.9 (2.8) attacks per month at 12 months in the RFCA group. There was a non-significant decrease over the same period in the amiodarone group. Differences between groups were not statistically significant.

SF-36 (Short Form 36) general health and physical functioning scores improved significantly at 12 months compared with baseline in the RFCA group but not in the amiodarone group. Between-group differences for general health score favoured ablation.

One stroke and one groin haematoma were associated with the ablation procedure. In the amiodarone group, seven patients experienced at least one adverse effect attributed to amiodarone: six had gastrointestinal (GI) adverse effects (mainly nausea), two each had corneal microdeposit, hypothyroidism and abnormal liver function test, and one had hyperthyroidism and sinus node dysfunction. Three patients in the RFCA group had amiodarone-attributed adverse effects during the 3-month amiodarone treatment period: two had GI adverse effects and one had sinus node dysfunction.

Pappone *et al.*, 2003⁶¹

Large non-randomised controlled study (rated 'poor') comparing RFCA with long-term AAD treatment in patients with symptomatic AF (70% paroxysmal, mean duration 4.6 years).

A total of 589 consecutive patients underwent circumferential PV ablation. In total, 19.5% of patients were given previously ineffective AADs if they had in-hospital AF episodes or required cardioversion. AADs were discontinued 3 months after ablation in the absence of recurrences.

A control group of 582 patients received AAD therapy (33% amiodarone, 17% propafenone, 15% flecainide, 13% sotalol, 9% quinidine, 6% disopyramide and 7% combined AAD therapy).

At 12 months, an estimated 84% of patients in the RFCA group and 61% of patients in the AAD group were free of AF. At 2 years these values were 79% and 47%, respectively, and at 3 years they were 78% and 37% respectively. There were a total of 120 AF recurrences in the ablation group and 340 in the AAD group.

After a median follow-up of 29.6 months there were more deaths overall in the AAD group (83 versus 38). The difference remained apparent for deaths due to cardiovascular causes (59 versus 18).

Four patients in the RFCA group (0.7%) required pericardiocentesis for cardiac tamponade. A total of 46 ablated patients (8%) and 98 AAD-treated patients (19%) were managed for a total of 54 and 117 adverse events respectively. Sinus rhythm was associated with significantly lower mortality rates [HR 0.24 (95% CI 0.16–0.37)] and adverse event rates [HR 0.22 (95% CI 0.15–0.31)].

SF-36 physical and mental composite scores from a subgroup of patients improved significantly from baseline to 1 year in ablated patients ($n = 109$) but not in medically treated patients ($n = 102$).

Wazni *et al.*, 2005⁶⁰

RCT (rated 'satisfactory') comparing RFCA with long-term AAD treatment as first-line therapy in patients with symptomatic AF (96% paroxysmal, mean duration 5 months).

A total of 33 patients were randomised to receive segmental PV ablation. AADs were not given as part of the treatment protocol, but beta-blocker therapy was continued in 43% of patients. There were no repeat ablation procedures within the first year of follow-up. One patient was lost to follow-up.

A total of 37 patients were randomised to receive the maximum tolerable dose of AAD chosen by the treating physician (typically flecainide, propafenone or sotalol). Amiodarone was given only when two other drugs had previously failed. Two patients were lost to follow-up.

At 12 months, 87.5% of patients in the RFCA group were in sinus rhythm after a single procedure. For the same time period in the AAD group, 37% of patients were in sinus rhythm at follow-up. Sensitivity analyses accounting for patients lost to follow-up did not substantially change these results. There were no crossovers during the 12-month follow-up.

TABLE 8 Population details: controlled studies – atrial fibrillation

Study	Country	Quality rating	Number randomised (treated): RFCA	Number randomised (treated): control	Mean age (years) (SD): RFCA	Mean age (years) (SD): control	Male (%)
Jais <i>et al.</i> , 2006 ⁶³	France, Canada, USA	Poor	53 (53)	59 (59)	51 (11) (overall)	51 (11) (overall)	83
Krittayaphong <i>et al.</i> , 2003 ⁵⁷	Thailand	Satisfactory	15 (14)	15 (15)	55.3 (10.5)	48.6 (15.4)	63
Lakkireddy <i>et al.</i> , 2006 ⁶²	USA	Poor	138 (138)	139 (139)	70.6 (5.2)	70.2 (5.5)	67
				133 (133)		70.3 (5.5)	
Oral <i>et al.</i> , 2006 ⁵⁶	Italy, USA	Good	77 (77)	69 (69)	55 (9)	58 (8)	88
Pappone <i>et al.</i> , 2003 ⁶¹	Italy	Poor	589 (589)	582 (582)	65 (9)	65 (10)	59
Pappone <i>et al.</i> , 2006 (APAF) ⁵⁸	Italy	Satisfactory	99 (99)	99 (99)	55 (10)	57 (10)	67
Stabile <i>et al.</i> , 2006 ⁵⁹	Italy	Satisfactory	68 (68)	69 (69)	62.2 (9)	62.3 (10.7)	59
Wazni <i>et al.</i> , 2005 ⁶⁰	USA, Italy, Germany	Satisfactory	33 (33)	37 (37)	53 (8)	54 (8)	–

NR, not reported; SD, standard deviation.

There was a significantly greater improvement in the ablation group than in the AAD group at 6 months on five of the eight subscales of the SF-36 questionnaire (general health, physical functioning, role physical, bodily pain, social functioning).

Two patients in the RFCA group developed mild to moderate PV stenosis. Three patients in the AAD group developed bradycardia. There were significantly more patients hospitalised in the AAD treatment group than in the RFCA group (54% versus 9%; $p < 0.001$).

Oral *et al.*, 2006⁵⁶

RCT (rated 'good') comparing the effect of 3 months' treatment with amiodarone and cardioversion with or without the addition of RFCA on long-term maintenance of sinus rhythm in patients with persistent AF (mean duration approximately 4.5 years).

A total of 77 patients were randomised to receive circumferential PV ablation followed by 3 months of amiodarone treatment, plus cardioversion if AF recurred within those 3 months. In total, 25 of

these patients underwent a repeat ablation (20 for AF, five for flutter).

A total of 69 patients were randomised to receive amiodarone treatment for 3 months, plus cardioversion if AF recurred. In total, 53 of these patients (77%) ultimately elected to cross over into the RFCA group because of recurrent AF.

According to intention to treat analysis at 12 months, 74% of patients in the RFCA group were in sinus rhythm without AAD therapy, compared with 58% in the amiodarone group ($p = 0.05$). If the need for any treatment (ablation or drugs) after 3 months was considered a treatment failure, 74% of patients in the RFCA group were in sinus rhythm without AAD therapy, compared with 4% of those in the amiodarone group.

Patients in sinus rhythm had greater improvements in symptom severity score than those with recurrent AF or atrial flutter ($p = 0.002$).

In the RFCA group, five patients required further ablation for atypical atrial flutter. No other

Mean (SD) duration of symptoms: RFCA	Mean (SD) duration of symptoms: control	Previous AAD, mean (SD): RFCA	Previous AAD, mean (SD): control	Paroxysmal/chronic (%): RFCA	Paroxysmal/chronic (%): control	Heart disease (%): RFCA/control
NR	NR	At least 1	At least 1	100/0	100/0	NR
62.9 (58.3) months	48.2 (63.7) months	1.7 (0.6)	1.9 (0.7)	73/27	67/33	13/13
2.5 (2.1) years	6.5 (3.3) years	3 (1)	2.4 (0.8)	NR	NR	NR
	6.5 (3.6) years		1.6 (1.4)			
5 (4) years	4 (4) years	2 (1.2)	2.1 (1.2)	0/100	0/100	8/9
5.5 (2.8) years	3.6 (1.9) years	3.1 (2.1)	2.3 (1.5)	69/31	71/29	37/34
6 (4) years	6 (6) years	2 (1)	2 (1)	100/0	100/0	7/4
5.1 (3.9) years	7.1 (5.9) years	NR	NR	61.8/38.2	72.5/27.5	63/62
5 (2) months	5 (2.5) months	0	0	97/3	95/5	25/28

complications related to ablation or drug therapy were reported.

Pappone *et al.*, 2006 (APAF)⁵⁸

RCT (rated 'satisfactory') comparing RFCA with long-term AAD treatment in patients with drug-refractory paroxysmal AF (mean duration 6 years).

A total of 99 patients were randomised to receive circumferential PV ablation. Patients received AADs for 6 weeks post procedure, after which drug treatment was stopped. Nine of these patients underwent a repeat ablation (six for recurrent AF, of which five were successful, and three for atrial tachycardia, all successful). Five patients went on to have AAD therapy to maintain sinus rhythm.

A total of 99 patients were randomised to receive AADs (amiodarone, flecainide or sotalol, either singly or in combination) at the maximum tolerable doses. In total, 42 of these patients (42%) elected to cross over into the RFCA group after two failed AADs over 3 months. Of the 42 crossovers to RFCA, 36 were successful in terms of subsequent freedom from arrhythmia.

At 12 months, 86% of patients in the RFCA group were in sinus rhythm after a single procedure and without the need for AAD therapy. Including repeat ablations and patients on adjunctive AADs, 93% of patients in the RFCA group were in sinus rhythm at 12 months. For the same time period in the AAD group, 24% of patients were in sinus rhythm after the first tested AAD and 35% were in sinus rhythm after combination therapy.

No serious complications occurred in the RFCA group, although three patients developed post-ablation atrial tachycardia requiring further ablation. Significant adverse events leading to permanent drug withdrawal occurred in 23 patients. There were significantly more hospital admissions in the AAD treatment group than in the RFCA group (167 versus 24; $p < 0.001$).

Stabile *et al.*, 2006⁵⁹

RCT (rated 'satisfactory') comparing long-term AAD treatment with or without RFCA in patients with paroxysmal or persistent AF for which AAD therapy had already failed (66% paroxysmal, mean duration 6.1 years).

A total of 68 patients were randomised to receive an AAD chosen by the physician (preferentially amiodarone, or class Ic if amiodarone could not be tolerated) and also undergo circumferential PV ablation, with an additional line connecting the left inferior PV to the mitral annulus. In addition, CTI ablation was performed when considered appropriate. There were no repeat ablations. Two patients were lost to follow-up.

A total of 69 patients were randomised to receive an AAD chosen by the physician without ablation. The AAD was only changed if the patient experienced a recurrence of arrhythmia. In total, 36 patients (52%) with AF relapses eventually crossed over to receive ablation while continuing the previously ineffective AAD regime. Two patients were lost to follow-up.

According to the authors' analysis, at 12 months 56% of patients in the AAD plus ablation group were in sinus rhythm after a single procedure. For the same time period in the AAD therapy alone group, 9% of patients remained in sinus rhythm during follow-up.

Three major complications were related to the ablation procedure: one stroke (patient died 9 months later of a brain haemorrhage), one transient phrenic paralysis, and one pericardial effusion requiring pericardiocentesis. In the control group there was one transient ischaemic attack and two deaths (one sudden death, one cancer). There was no significant difference in the median number of hospitalisations needed between groups (one versus two; $p = 0.34$).

Jais *et al.*, 2006⁶³

An unpublished RCT (rated 'poor', mainly because of the limited reporting of trial details) comparing RFCA with long-term AAD treatment in patients with drug-refractory paroxysmal AF.

A total of 53 patients were randomised to receive segmental PV ablation. A mean of 1.8 PV ablation procedures were conducted. In addition, 64% of patients were reported to have had CTI ablation, 30% had mitral isthmus ablation and 17% had ablation of the roof line.

A total of 59 patients were randomised to receive AADs (including beta-blockers and classes I, III and IV AADs, alone or in combination; amiodarone was used in 22 patients). In total, 37 patients (63%) elected to cross over into the RFCA group.

The primary end point was absence of AF for 3 minutes or more (either symptomatic or documented). At the 12-month follow-up, 75% of patients in the RFCA group and 6% of patients in the AAD group were AF free. RFCA was also favoured in terms of duration of recurrent AF episodes [8 minutes (SD 55) versus 150 minutes (SD 350)].

One tamponade and one PV stenosis (> 50%) occurred in the RFCA group. There was one case of amiodarone-induced hyperthyroidism.

Lakkireddy *et al.*, 2006⁶²

An unpublished, non-randomised study (rated 'poor') comparing RFCA in older patients with AF (aged 60–80 years) with AV node ablation or direct current cardioversion (DCC) in age-matched control subjects.

The authors of this study concluded that PV ablation had significant mortality and morbidity benefits against the other therapeutic strategies; however, because of the inadequate and inconsistent data currently available for this study, it will not be discussed further here. For the sake of completeness, the available details are presented in Appendix 3.1.

Results by outcome

Freedom from arrhythmia at 12 months

Figure 2 shows the RR and associated 95% confidence intervals for freedom from arrhythmia at 12 months for the six RCTs reporting sufficient data to calculate this outcome.

The forest plots show that all of the included controlled studies favour ablation over AAD-based management, but the extremely high degree of statistical heterogeneity observed between the studies (I^2 85.8–91.7%) indicates clearly that a pooled value for the group of studies as a whole is not considered appropriate. The heterogeneity can be partly explained by variation in patient populations and interventions: one study (Oral *et al.*⁵⁶) was limited to patients with persistent AF; one (Stabile *et al.*⁵⁹) evaluated combined RFCA/AAD treatment versus AADs alone (see Figure 2). The remaining randomised evidence included four RCTs^{57,58,60,63} comparing ablation with long-term AAD treatment (predominantly amiodarone, sotalol and class Ic agents, when reported) for the maintenance of sinus rhythm. However, when these four trials were pooled, highly significant statistical heterogeneity (I^2 74%) remained (Appendix 4). One RCT⁶³ intensively followed up arrhythmia in

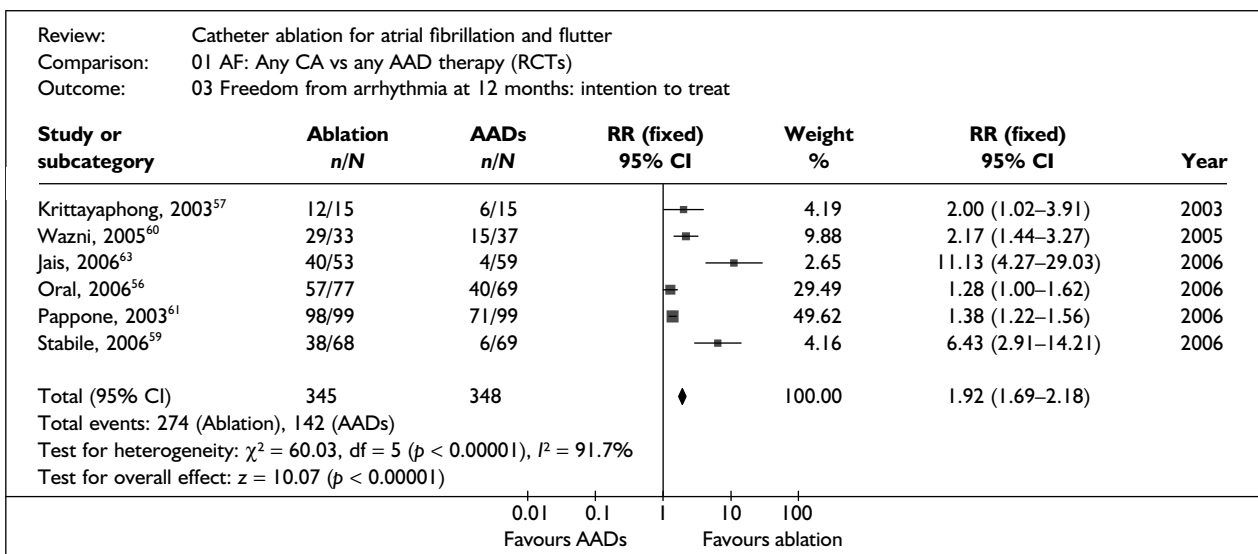
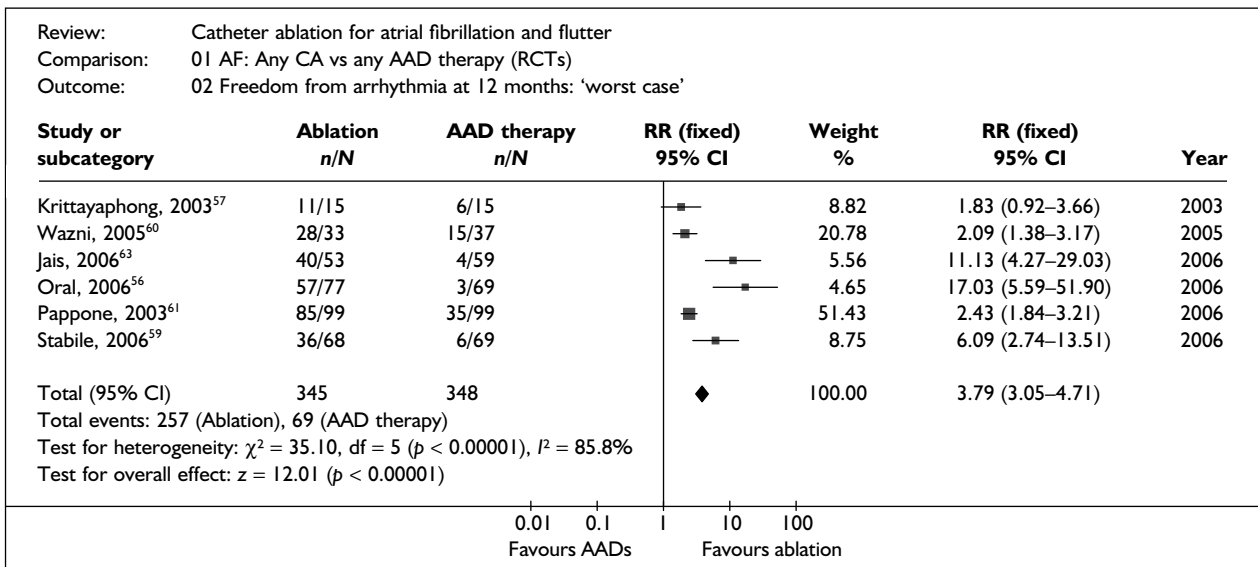
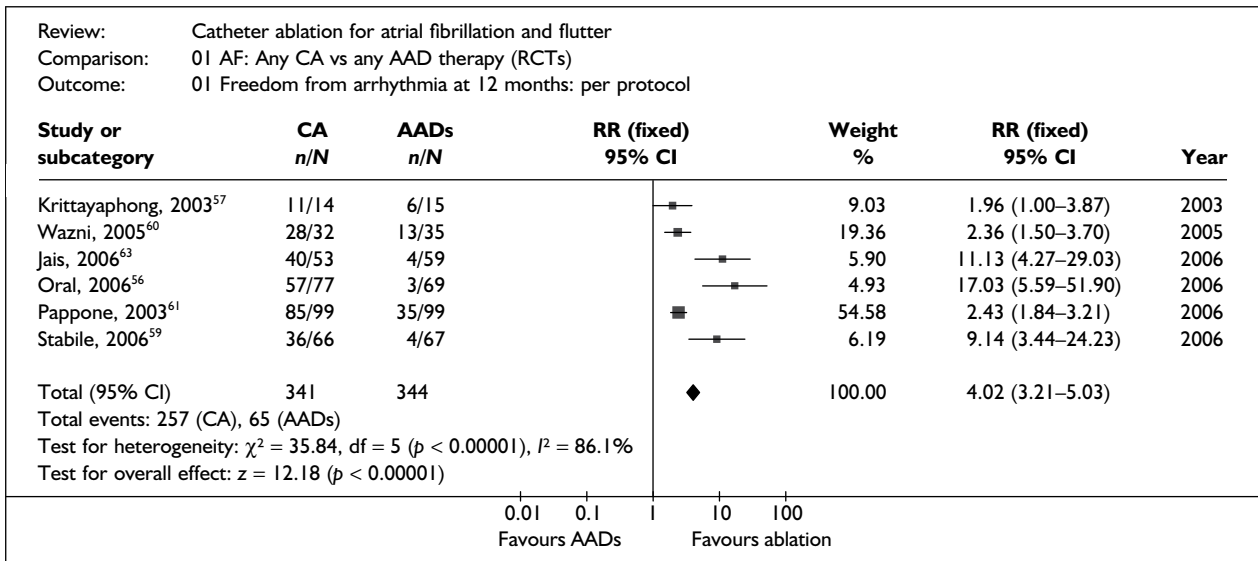


FIGURE 2 Freedom from arrhythmia at 12 months: all atrial fibrillation randomised controlled trials.

a way that differs from typical clinical practice and from follow-up protocols in other trials making the same comparison. This trial reported an unusually high rate of failures associated with AAD use,

resulting in a very different relative effect from other RCTs. Removal of this study from the pooled comparison removed all statistical heterogeneity (I^2 0%; see Figure 3).

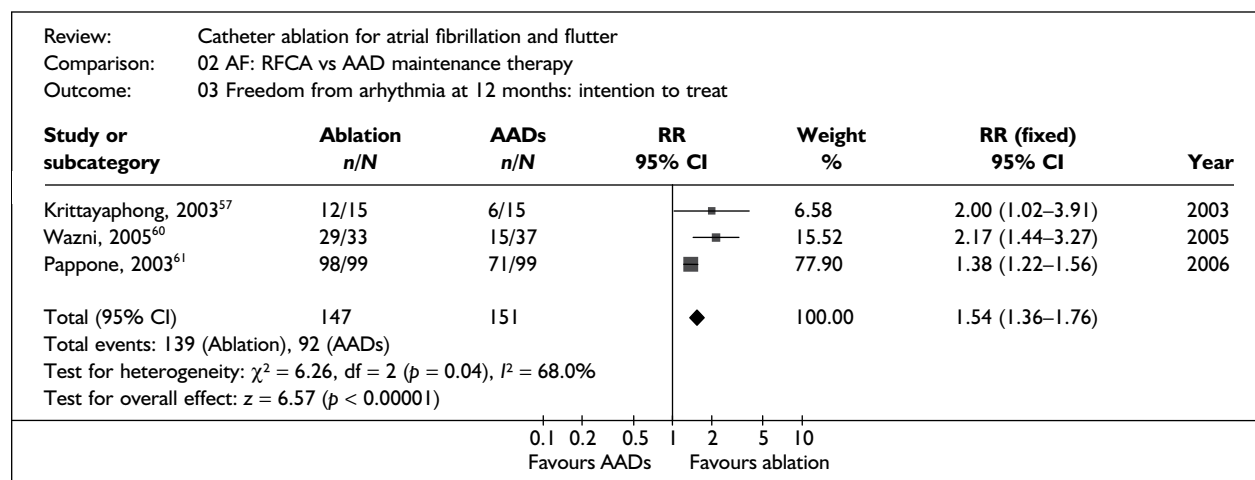
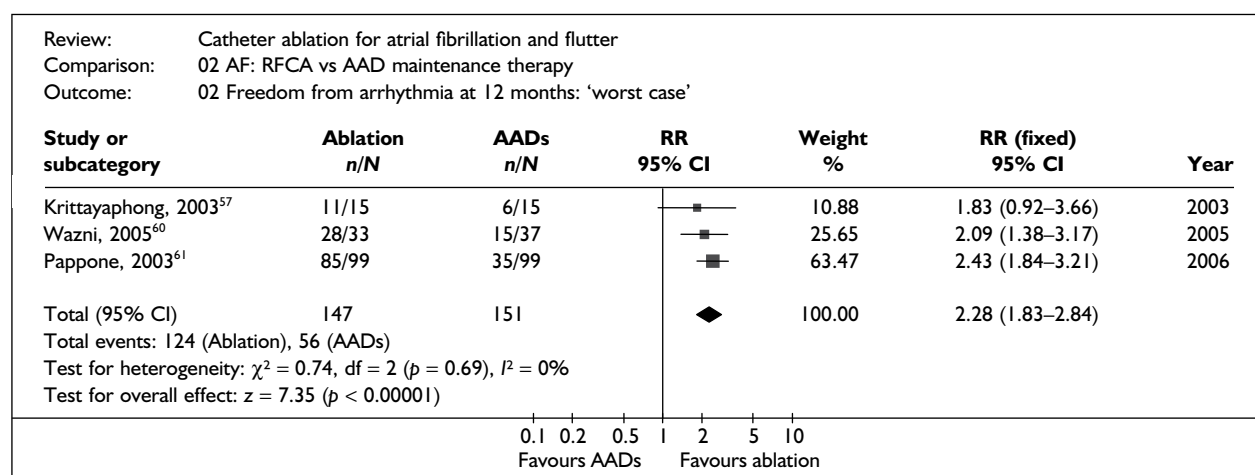
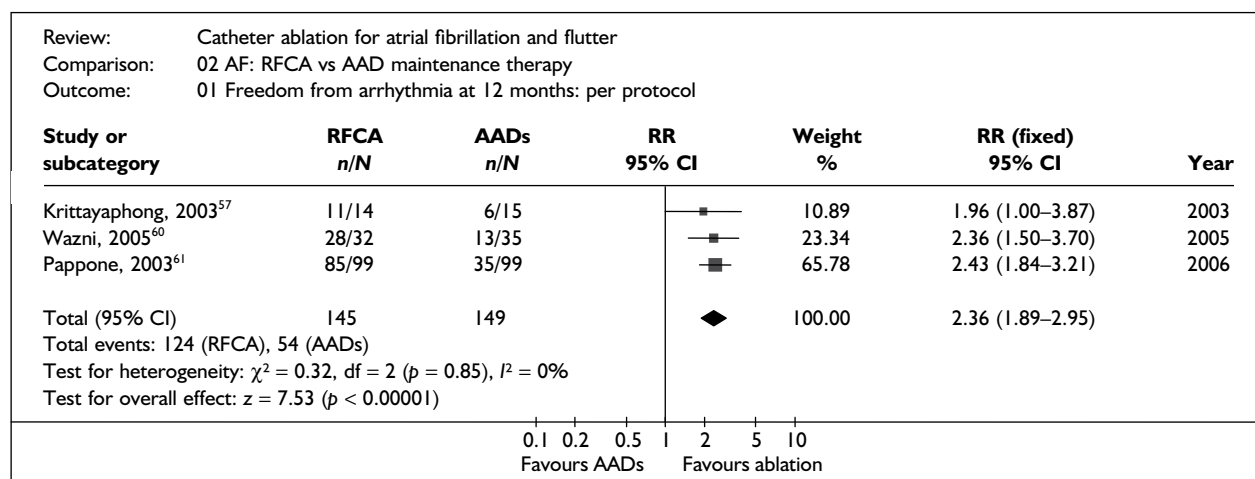


FIGURE 3 Freedom from arrhythmia at 12 months: RFCA vs long-term AAD therapy in paroxysmal atrial fibrillation.

Within the three remaining RCTs comparing ablation with long-term AAD treatment that could be pooled in a meta-analysis,^{57,58,60} 97% of the patients (Figure 3) were diagnosed with paroxysmal AF (ten patients in the Krittayaphong *et al.*⁵⁷ study had chronic AF) and the majority of patients (75%, 87%, 93%, respectively) were free of structural heart disease in the three trials. Only nine repeat ablation procedures were reported (all in the APAF study). The pooled per protocol results showed that significantly more patients undergoing RFCA were free of arrhythmia (without AADs) at 12 months' follow-up than those receiving AAD maintenance therapy alone [RR 2.36 (95% CI 1.89–2.95)]. There were only four patients lost to follow-up across the three studies; assuming that data from these patients would be unfavourable to ablation had little influence on the pooled estimate [RR 2.28 (95% CI 1.83–2.84)]. The pooled intention to treat analysis ignoring crossovers indicated a smaller but statistically significant effect in favour of ablation [RR 1.54 (95% CI 1.36–1.76)]. As the study of Wazni *et al.*⁶⁰ was limited to patients undergoing first-line therapy, the mean duration of AF was considerably shorter in this trial (5 months) than in the other two trials (4.6 years and 6 years). However, sensitivity analyses involving the removal of the Krittayaphong and Wazni studies had little influence on the overall estimate of effect (see Appendix 4).

One RCT by Oral *et al.*⁵⁶ compared the effect of adding ablation to a short-term (3 month) amiodarone/cardioversion treatment strategy on subsequently achieving sinus rhythm without the need for AADs in patients with persistent AF. The majority of patients in the amiodarone/cardioversion treatment arm (77%) crossed over into the ablation arm before the 12-month follow-up. Forest plots showing the effect on sinus rhythm without AADs at 12 months are given in Appendix 4. Disregarding the very large crossover and analysing the data by original treatment allocation gives a relatively small effect, of borderline statistical significance, in favour of ablation [RR 1.28 (95% CI 1.00–1.62)]. If the need for additional treatment for recurrent AF after the initial 3 months was considered a failure of short-term therapy, the effect was much larger and significantly favoured the group that had received ablation [RR 17.03 (95% CI: 5.59–51.90)].

Stabile *et al.*⁵⁹ evaluated the effect of adding ablation to a long-term AAD maintenance strategy in patients for whom previous AAD therapy had already failed. As in the Oral *et al.* trial, a high

proportion of patients (52%) crossed over from the AADs alone group to receive ablation after recurrence of AF. For freedom from arrhythmia at 12 months, the intention to treat analysis reported by the study authors showed a large, statistically significant effect in favour of ablation [RR 6.43 (95% CI 2.91–14.21)]. Assuming that data from patients lost to follow-up would have been unfavourable to ablation gave a slightly smaller pooled estimate [RR 6.09 (95% CI 2.74–13.51)], and per protocol analysis increased the pooled estimate [RR 9.14 (95% CI 3.44–24.23); see Appendix 4]. It is not entirely clear why the relative effect for this comparison (RFCA plus AADs versus AADs alone) should be noticeably larger than that typically seen in the RCTs comparing RFCA against AADs alone, although the very low success rate seen in the AADs alone arm of Stabile *et al.* may be attributable to the intensive follow-up (patients had daily ECG recordings for 3 months) undertaken in this study.

The preliminary findings of a trial by Jais *et al.* were reported in a conference abstract.⁶³ This study appeared to have intensive follow-up of arrhythmia, similar to the trial by Stabile *et al.*, and similarly reported a large, statistically significant effect in favour of RFCA over ongoing AAD therapy [RR 11.13 (95% CI 4.27–29.03)].

For reference, Table 9 shows these results for the meta-analysis and trials that could not be pooled when calculated as odds ratios and related confidence intervals. However, our discussion of the findings will be limited to the RR estimates as relative probabilities are more easily interpreted than relative odds.

Freedom from arrhythmia at other follow-up points

Of the studies reporting adequate freedom from arrhythmia data at other follow-up points, five were randomised and one was non-randomised. By far the largest of the studies was the non-randomised comparison of ablation against AAD therapy conducted by Pappone *et al.*⁶¹ A lack of randomisation means that the two treatment arms are more likely to be unbalanced at baseline in terms of key participant characteristics. This appears to be true in the case of this particular study; at baseline the ablation group had longer duration of AF, a greater number of failed AADs and more frequent hospitalisation than the medical treatment group. However, survival analysis (mean follow-up of 900 days) indicated a significantly lower overall rate of AF recurrence in the ablation

TABLE 9 Atrial fibrillation – relative risks and odds ratios for freedom from arrhythmia at 12 months

	Relative risk (95% confidence interval)	Odds ratio (95% confidence interval)
Any RFCA vs AAD maintenance therapy (three pooled studies)		
Per protocol	2.36 (1.89–2.95)	10.35 (5.85–18.32)
'Worst case'	2.28 (1.83–2.84)	9.11 (5.23–15.86)
Intention to treat	1.54 (1.36–1.76)	14.63 (6.13–34.95)
RFCA vs short-term amiodarone and cardioversion (one study)		
Per protocol	17.03 (5.59–51.90)	62.7 (17.71–221.97)
Intention to treat	1.28 (1.00–1.62)	2.07 (1.03–4.15)
RFCA plus AAD therapy versus AAD maintenance therapy alone (one study)		
Per protocol	9.14 (3.44–24.23)	18.9 (6.16–57.97)
'Worst case'	6.09 (2.74–13.51)	11.81 (4.51–30.95)
Intention to treat	6.43 (2.91–14.21)	13.30 (5.07–34.89)

group [HR 0.30 (95% CI 0.24–0.37; $p < 0.001$)]. The difference in the estimated proportion of patients free from AF between the groups increased over time: 0.23 (95% CI 0.18–0.28) at 1 year, 0.32 (95% CI 0.28–0.38) at 2 years, and 0.41 (95% CI 0.33–0.49) at 3 years.

None of the randomised studies explicitly reported the number of patients free from arrhythmia before 12 months' follow-up. When Kaplan–Meier analyses of AF recurrence were presented, these broadly indicated a steady rate of recurrences over time associated with AAD treatment, whereas recurrences associated with RFCA treatment tended to occur in the first 2–3 months post procedure before stabilising.

Complications, adverse events and mortality

Table 10 summarises the complications, adverse events and deaths reported in the controlled AF studies. A total of 1860 patients (932 ablation, 928 control) were included in these seven studies. Adverse events and complications were rarely reported; where data on major events/complications were not reported, we assumed that such an event/complication did not occur during the study. Some events were specific to ablation (tamponade, PV stenosis, groin haematoma) whereas others were specific to AADs (corneal microdeposit, thyroid dysfunction, pro-arrhythmia, sexual impairment).

A total of 30 strokes were reported. Eight were in patients receiving RFCA, and two of these were related to the ablation procedure itself.

Seven patients undergoing ablation had cardiac tamponade or pericardial effusion and three had PV stenosis (one mild, two moderate).

Deaths were reported in three of the studies.^{56,59,61} Brain haemorrhage caused death in one patient, 9 months after having had a stroke during an ablation procedure.⁵⁹ One patient who had received RFCA died from pneumonia.⁵⁶ The majority of deaths ($n = 121$) were reported in the single largest study⁶¹ with the longest follow-up (median 29.6 months).

Quality of life

Three controlled studies evaluated participants' QoL using the SF-36 health survey.^{57,60,61} This is made up of 36 questions that contribute to eight subscales: four within physical health (physical functioning, role physical, bodily pain and general health) and four within mental health (vitality, social functioning, role emotional and mental health).

Wazni *et al.*⁶⁰ and Krittayaphong *et al.*⁵⁷ found a significantly greater improvement on the general health subscale in patients randomised to RFCA compared with control subjects at 6 and 12 months respectively. In addition, Wazni *et al.*⁶⁰ reported that RFCA patients attained significantly higher scores on the physical functioning, role physical and bodily pain subscales.

In terms of within-group changes from baseline for RFCA treatment, Krittayaphong *et al.* reported a significant increase in both physical functioning and general health scores. Pappone *et al.*⁶¹ reported

a significant improvement in scores from baseline but did not state on which subscales.

Further QoL data, in relation to utility estimates, were considered in the development of the decision model (see Chapter 4, Decision model).

Summary of results for atrial fibrillation from controlled trials

There is a small amount of moderate-quality randomised evidence to suggest that PV ablation is more effective than long-term AAD treatment in patients with drug-refractory paroxysmal AF. Evidence from one small RCT suggests that RFCA may also be more effective than AADs as first-line treatment in patients with paroxysmal AF. In fact, the results of this trial were consistent with those of the trials with nominally 'drug refractory' populations.

Where reported, the rates of freedom from arrhythmia at 12 months ranged from 74% to 87.5% in the RFCA arms of RCTs included in the AF meta-analysis. Intention to treat meta-analysis suggests that RFCA is 36–76% more effective than AAD treatment in terms of freedom from arrhythmia at 12 months; analysis by actual treatment received suggests a larger two- to threefold improvement in this outcome for patients treated with RFCA.

The pooled RCT estimates for AF are dominated by the APAF trial, which was conducted by one of the world's leading catheter ablation centres. Consequently, the pooled effect estimates from the RCTs may overestimate the levels of success that could be achieved by less experienced groups.

There were relatively few repeat procedures reported among the RCTs comparing RFCA with AADs in patients with paroxysmal AF (6%, all in a single trial⁵⁸). However, in the trial evaluating the addition of RFCA to a short-term amiodarone/cardioperfusion treatment strategy in patients with persistent AF, 32% of patients underwent a repeat procedure. On this basis it is not possible to establish a clear pattern in the need for repeat ablation procedures.

Although one large non-randomised study⁶¹ suggested that the effects of RFCA observed at 12 months remain fairly stable at 2–3 years post procedure, there is no randomised evidence comparing the effects of RFCA against pharmacological therapy in paroxysmal AF beyond a year. Furthermore, there is insufficient evidence to assess the effectiveness of RFCA relative to other

treatment strategies in patients with persistent or permanent AF.

There is very little evidence from randomised trials on the impact of RFCA relative to AAD treatment on QoL. The small amount of evidence that is available from RCTs suggests that RFCA treatment might be associated with improvements in self-rated physical and/or general health from baseline.

RCTs provide limited evidence on mortality, adverse events and complications. The available controlled trials suggest the possibility of a relatively small risk of complications associated with RFCA (e.g. cardiac tamponade, PV stenosis) and adverse events associated with long-term use of certain antiarrhythmic agents (e.g. thyroid dysfunction associated with amiodarone). The evidence does not suggest that RFCA is associated with increased mortality.

Assessment of effectiveness from case series

Case series characteristics

Populations

Details of the populations in the case series are presented in *Table 11*. The populations were relatively uniform in terms of average age and proportion of men, but other characteristics (proportion with paroxysmal AF and structural heart disease, duration of symptoms and number of unsuccessful AADs) varied substantially.

Of the 53 case series, 26 were from centres in Europe, 15 were from the USA, eight were from Asia and four reported experience from centres in more than one country. Several expert centres contributed multiple case series, including the Cleveland Clinic Foundation (ten publications), the Hôpital Haut-Leveque, France (eight publications) and the San Raffaele Hospital, Milan, Italy (four publications).

The number of treated patients ranged from 100 (the minimum required to meet inclusion criteria) to 1125. In total, the 53 case series included 11,908 patients (mean 224.7, median 158) but because of multiple publications from some centres it is likely that this overestimates the total number of unique patients. Mean age was in the 50s in 89% of the series. Age range was reported in 18 case series, with most series including a wide range of ages from young (in the teens or 20s) to elderly adults (in their 70s or 80s). Almost all case series (51/53) were made up of a majority of male participants; two case series did not report gender balance.

TABLE 10 Complications, adverse events and mortality in atrial fibrillation controlled studies

Study		Stroke/ CVA	Tamponade/ pericardial effusion	Mild/ moderate PV stenosis	Death	Thyroid dysfunction	Liver dysfunction	Sinus node dysfunction	Atypical atrial flutter	Groin haematoma
Krittayaphong <i>et al.</i> , 2003 ⁵⁷	RFCA	1/14 (7%)	–	–	–	–	–	1/15 (7%)	–	1/14 (7%)
	Amio	–	–	–	–	4/15 (27%)	2/15 (13%)	1/14 (7%)	–	–
Pappone <i>et al.</i> , 2003 ⁶¹	RFCA	6/589 (1%)	4/589 (0.7%)	–	38/589 (6.5%)	–	–	–	–	–
	AAD (LT)	22/582 (3.8%)	–	–	83/582 (14%)	–	–	–	–	–
Wazni <i>et al.</i> , 2005 ⁶⁰	RFCA	–	–	2/33 (6%)	–	–	–	–	–	–
	AAD (LT)	–	–	–	–	–	–	–	–	–
Pappone <i>et al.</i> , 2006 (APAF) ⁵⁸	RFCA	–	1/99 (1%)	–	–	–	–	–	–	–
	AAD (LT)	–	–	–	–	7/99 (7%)	–	–	–	–
Oral <i>et al.</i> , 2006 ⁵⁶	RFCA + ST amio + CVN	–	–	–	1/77 (1.3%)	–	–	–	5/77 (7%)	–
	ST amio + CVN	–	–	–	–	–	–	–	–	–
Stabile <i>et al.</i> , 2006 ⁵⁹	RFCA + AAD (LT)	1/68 (2%)	1/68 (2%)	–	1/68 (2%)	–	–	–	–	–
	AAD (LT)	–	–	–	2/69 (1%)	–	–	–	–	–
Jais <i>et al.</i> , 2006 ⁶³	RFCA	–	1/53 (1.9%)	1/53 (1.9%)	–	–	–	–	–	–
	AAD (LT)	–	–	–	–	1/59 (1.9%)	–	–	–	–

Amio, amiodarone; CVA, cardiovascular accident; CVN, cardioversion; GI, gastrointestinal; LT, long-term maintenance therapy; PV, pulmonary vein; RFCA, radio frequency catheter ablation; ST, short-term maintenance therapy.

Pro-arrhythmia	Sexual impairment	GI adverse events	Bradycardia	Tachycardia	'Bleeding'	Transient phrenic paralysis	Transient ischaemic attack	Congestive heart failure	Myocardial infarction	Peripheral embolism	Corneal micro-deposit
-	-	2/15 (13%)	-	-	-	-	-	-	-	-	-
-	-	6/15 (40%)	-	-	-	-	-	-	-	-	2/15 (13%)
-	-	-	-	-	-	-	8/589 (1.4%)	32/589 (5.4%)	7/589 (1.2%)	1/589 (0.2%)	-
-	-	-	-	-	-	-	27/582 (4.6%)	57/582 (9.8%)	8/582 (1.4%)	3/582 (0.5%)	-
-	-	-	-	-	2/33 (6%)	-	-	-	-	-	-
-	-	-	3/37 (8%)	-	1/37 (3%)	-	-	-	-	-	-
-	-	-	-	3/99 (3%)	-	-	-	-	-	-	-
3/99 (3%)	11/99 (11%)	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	1/68 (2%)	-	-	-	-	-
-	-	-	-	-	-	-	1/69 (1%)	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-

TABLE 11 Population details: case series – atrial fibrillation

Study	Country	Quality rating	Number enrolled	Number ablated	Age (years), mean (SD)	Age range (years)
Berkowitsch <i>et al.</i> , 2005 ⁷¹	Germany	Poor	104	104	55	46–61
Bertaglia <i>et al.</i> , 2005 ⁷³	Italy	Poor	158	143	61.4 (8.1)	35–78
Beukema <i>et al.</i> , 2005 ⁷⁵	Netherlands	Poor	105	105	52 (9.5)	27–75
Bhargava <i>et al.</i> , 2004 ⁷⁷	USA	Poor	323	323	54.3	18–79
Bourke <i>et al.</i> , 2005 ⁶⁶	UK	Satisfactory	100	100	52	23–73
Cha <i>et al.</i> , 2005 ⁸⁰	USA	Poor	395	395	54 (10)	
Chen <i>et al.</i> , 2004 ⁸²	USA	Poor	377	377	55.5	
Daoud <i>et al.</i> , 2006 ⁶⁷	USA	Satisfactory	112	112	58 (10)	
Deisenhofer <i>et al.</i> , 2004 ⁸⁴	Germany	Poor	115	115	58.2 (10.1)	
Della Bella <i>et al.</i> , 2005 ⁶⁸	Italy	Satisfactory	234	234	55.9 (10.6)	22–78
Dong <i>et al.</i> , 2005 ⁸⁷	China	Poor	151	151	56 (11.2)	18–79
Ernst <i>et al.</i> , 2003 ⁸⁹	Germany	Poor	196	196	56.5 (9.8)	
Essebag <i>et al.</i> , 2005 ⁹¹	USA	Poor	102	102	53 (11)	
Fassini <i>et al.</i> , 2005 ⁹³	Italy	Poor	187	187	55 (11)	
Herweg <i>et al.</i> , 2005 ⁹⁵	USA	Poor	170	170	56 (11)	25–85
Hindricks <i>et al.</i> , 2005 ⁹⁷	Germany	Poor	114	114	54 (9)	
Hsieh <i>et al.</i> , 2003 ⁹⁹	Taiwan	Poor	227	227		
Hsu <i>et al.</i> , 2004 ¹⁰¹	France	Poor	116	116	56 (10)	
Jais <i>et al.</i> , 2004 ¹⁰³	France	Poor	200	200	53.5 (10)	
Karch <i>et al.</i> , 2005 ¹⁰⁵	Germany	Poor	100	100	60	52–65
Kilicaslan <i>et al.</i> , 2005 ¹⁰⁶	USA	Poor	1345	1125	55.1	
Kilicaslan <i>et al.</i> , 2006 ¹⁰⁸	USA	Poor	202	202	57.1	
Kobza <i>et al.</i> , 2004 ¹¹⁰	Germany	Poor	150	150	52 (10)	
Kottkamp <i>et al.</i> , 2004 ¹¹²	Germany	Poor	100	100	53 (10)	
Kumagai <i>et al.</i> , 2005 ¹¹⁴	Japan	Poor	100	100	58.5	
Lee <i>et al.</i> , 2004 ¹¹⁶	Taiwan	Poor	227	207	62 (13)	
Liu <i>et al.</i> , 2005 ¹¹⁸	China	Poor	130	130	57.9 (11.5)	24–79
Ma <i>et al.</i> , 2006 ⁷²	China	Poor	200	200	57.3 (9.6)	18–79
Macle <i>et al.</i> , 2002 ⁷⁴	France	Poor	136	136	52 (10)	22–77

Male (%)	Duration of symptoms	Previous AADs, mean (SD)	Paroxysmal AF (%)	Chronic AF (%)	Heart disease (%)
67.3	Not reported		100	0	8
65.7	Mean 5.0 years (SD 4.0, range 0.5–20)	3.2 (0.8)	45	55	12
70.5	Paroxysmal AF: 6.0 years (SD 5.1); persistent AF: 7.6 years (SD 6.0)	2.8 (0.7)	49.5	50.5	5.7
80.2	Mean 6.2 years	3.1	53.9	46.1	32.2
81.0	53 months (range 6–180)	3	36	64	0
84.3	6.3 years (SD 5.9) men, 6.0 years (SD 4.5) women	2.1 (1.2)	60.5		
78.8	Mean 5.2 years	2.7	51.4	48.5	52.8
60.7	46 months (SD 19)	2.2 (1.1)	73	27	4
69.6	Not reported				
77.8	6.2 years (SD 5.3)		78	22	47
72.2	86.5 months (range 1–380)		85.4	14.6	34.4
78.6	Mean 8.3 years	3.8 (1.5)	80	20	
73.5	Not reported	1.5 (1.1)	59	41	59
80.2			67	33	5.9
72.9	6.9 years (SD 7.6)		82	18	22
71.1	Median 5 years (range 1.5–8)		84	16	19
			100		
87.9	Mean 6.6 years (79.5 months)	3 (1)	9	91	
86.5	Mean 6.5±6 years	4 (2)			23
64.0	Mean 4.5 years (range 2–7)	2	89	11	57
80.1	Mean 6.6 years	2.7	56.8	43.2	
83.2	Mean 7.7 years	2.4	51	49	
71.3	6.9 years (SD 6.8)	2.3 (1.1)	83	17	20
67.0	7.3 years (SD 7)	2.2 (1.2)	80	20	25
75.0	79 months	3 (1.1)	100	0	4
74.9	5.1 years (SD 0.4)	2.2 (1.3)	100	0	
73.1	7.1 years (SD 5.7, range 0.3–30)		70	30	
72.5	5.4 years (SD 3.6, range 0.3–19)		72.5	27.5	17.5
80.1	Mean 7±5.8 years	3.9 (1.6)	90	10	17

continued

TABLE 11 Population details: case series – atrial fibrillation

Study	Country	Quality rating	Number enrolled	Number ablated	Age (years), mean (SD)	Age range (years)
Marchlinski <i>et al.</i> , 2003 ⁷⁶	USA	Poor	159	107	51.4	
Marrouche <i>et al.</i> , 2002 ⁷⁸	USA, Italy	Poor	211	211	53 (11)	
Nademanee <i>et al.</i> , 2002 ⁷⁹	USA	Poor	214	214	68	
Nademanee <i>et al.</i> , 2004 ⁸¹	Thailand, USA	Poor	121	121	63 (12)	
Nilsson <i>et al.</i> , 2006 ⁶⁴	Denmark	Good	100	100	55.9	
Oral <i>et al.</i> , 2004 ⁸⁵	USA	Poor	188	188	52.8	
Oral <i>et al.</i> , 2004 ⁸³	USA	Poor	176	176	53 (12)	19–73
Pappone <i>et al.</i> , 2001 ⁸⁸	Italy	Poor	251	251	51.5 (11.4)	
Pappone and Santinelli, 2001 ⁸⁶	Italy	Poor	127	127	51.4	
Pappone <i>et al.</i> , 2004 ⁹⁰	Italy	Poor	560	560	56.5 (7.3)	
Purerfellner <i>et al.</i> , 2006 ⁹²	Austria	Poor	117	117	51 (11)	25–73
Ren <i>et al.</i> , 2004 ⁹⁴	USA	Poor	232	232	55 (11)	17–80
Saad <i>et al.</i> , 2003 ⁹⁸	USA, Italy, Germany	Poor	608	608	51.3	
Saad <i>et al.</i> , 2003 ⁹⁶	USA	Poor	335	335	54	18–79
Shah <i>et al.</i> , 2001 ¹⁰⁰	France	Poor	200	200	52.6	18–80
Shah <i>et al.</i> , 2003 ¹⁰²	France	Poor	160	160	53 (11)	
Trevisi <i>et al.</i> , 2003 ¹⁰⁴	Italy	Poor	158	158	57 (10)	
Verma <i>et al.</i> , 2005 ⁶⁵	USA	Good	700	700	53.4 (13)	
Wazni <i>et al.</i> , 2005 ¹⁰⁷	USA, Italy, Germany	Poor	785	785	54	
Weerasooriya <i>et al.</i> , 2003 ¹⁰⁹	France	Poor	152	152	50 (11)	
Weerasooriya <i>et al.</i> , 2003 ¹¹¹	France	Poor	118	118	52 (18)	
Yamada <i>et al.</i> , 2006 ¹¹³	Japan	Poor	108	108	57 (12)	
Yamane <i>et al.</i> , 2002 ¹¹⁵	France	Poor	157	157	54.4	
Yu <i>et al.</i> , 2001 ¹¹⁷	Taiwan	Poor	102	102	65 (13)	29–86

SD, standard deviation.

Male (%)	Duration of symptoms	Previous AADs, mean (SD)	Paroxysmal AF (%)	Chronic AF (%)	Heart disease (%)
78.5	94 patients with AF for > 2 years	3.8	87	13	
77.3	5.5 years (SD 3.6)	3 (1)	54	46	24
	Not reported		48	52	
76.0	4 years (SD 3.3)	2.4 (1.3)	47	53	65
71.0	Mean 4.1 years	3.2	51	49	27
81.4	Mean 7.4 years		100	0	11.7
81.3	Mean 7 years (SD 7)	2 (1)	100	0	13
	8.1 years (range 1–28)	2.9 (1)	71.3	28.7	15
83.5		2.9 (1)	77	23	26
52.0	Mean 7.2 years		63	37	40
82.1	Mean 73 months (SD 67); median 48 months	3.1 (1.4)	94.7	5.3	3.4
79.3		3.7	91	9	9
81.1	Mean 5.3 years	3	52.3	47.7	25.6
81.2	Mean 5.4±3.6 years	3	52	48	27
79.5	Mean 5.2 years (range 1–26)	5 (2)	100		30.2
81.3	Not reported		100		27
77.8			79	21	
77.9	Mean 6.15 years	2.2	39.1	60.9	44.1
83.4	Not reported		53	47	48
80.9	Mean 6±5 years		100	0	25
69.5	Not reported	2	100		
84.3	Mean 4 years (SD 4)	4 (1)	100	0	0
59.9	Mean 4.7 years	5	100		8.9
87.3	Not reported	2 (1)	100	0	10

Duration of symptoms was reported in 40 case series, normally as the mean. The reported measure was 5 years or less in nine case series, 5–6 years in nine, 6–7 years in 13, 7–8 years in six and over 8 years in two. Based on reports in 36 case series, the mean number of unsuccessful AADs ranged from 1.5 to 5. The proportion of patients with paroxysmal AF (reported in 51 case series) ranged from 9% to 100%; 13 case series included only patients with paroxysmal AF. Presence of structural heart disease was reported in 40 case series and ranged from 0% to 65%; only four series had a majority of patients with structural heart disease. Hypertension was not included as structural disease when these were reported separately.

Interventions

Intervention characteristics varied widely between case series, the most fundamental division being between segmental and circumferential techniques for PV ablation. Of the 53 studies treated as case series, 24 used segmental PV isolation uniformly in all patients, eight used circumferential PV isolation, three used a combination of approaches, two used other PV isolation techniques and two used other approaches. The catheter sizes used, mapping technique, definition of end point, number of PVs ablated and other details varied across the case series. This variation of intervention characteristics needs to be interpreted in light of our decision to treat all techniques of RFCA as a single intervention. Of 14 studies (true case series and trials) that compared ablation techniques, seven compared different techniques within one basic approach (e.g. different catheter types or mapping systems) and seven compared results of two or more different approaches. Appendix 3.3 summarises details of the interventions in the included case series (including RCTs and CCTs that compared ablation techniques).

Relevant details regarding how AADs were used with RFCA were not well reported. For example, in 30 of the 53 case series it was unclear whether or not AADs were withdrawn before RFCA. Where it was reported most series did withdraw AADs. Similarly, details of AADs after the procedure were frequently not reported: in 26 out of 53 series it was unclear; in 18 out of 27 series patients did receive AADs. A total of 20 case series either did not use anticoagulants after the procedure or did not report details. When the time on anticoagulants was reported (32 series), it ranged from 1 to 6 months.

The UK series by Bourke and colleagues⁶⁶ was fairly typical in terms of average age of participants (52 years) and percentage of male patients (81%) but it had a relatively high proportion of patients with chronic AF (64%) while excluding patients with structural heart disease. Mean duration of symptoms was 53 months (range 6–180) and patients had been treated unsuccessfully with an average of three AADs. The intervention was classified as segmental PV isolation using a 4-mm tip ablation catheter. The mean number of PVs isolated (2.41 ± 0.79) was relatively low in case series in which this outcome was reported. The authors adapted their technique later in the series by drawing additional ablation lines if necessary. Patients were returned to AAD treatment after RFCA and those with persistent AF were treated with anticoagulants for a minimum of 3 months after the procedure.

Results for case series by outcome

Freedom from arrhythmia at 12 months

Eleven of the 53 case series reported data for freedom from arrhythmia (AF) at 12 months. The rates reported ranged from 28% to 85.3%; 9/11 of the case series reported rates of over 60% (*Table 12*). The weighted pooled estimate of freedom from arrhythmia at 12 months was 76% (95% CI 74–77%) (*Table 13*).

Two case series^{64,90} reported on occurrence of arrhythmias other than AF, reporting rates of atrial tachycardia of 12% and 7% respectively.

Whether freedom from AF was achieved as a result of a single ablation procedure or whether it required repeat ablations was reported for 10 of the 11 case series reporting this outcome; for two the rates were achieved with repeat ablation and for seven they were achieved without. The rates achieved with repeat ablation were not necessarily higher than the rates achieved without repeat ablation. One case series reported on whether freedom from arrhythmia was achieved with or without AADs; 71/100 patients were free of AF without AADs, and a further 11/100 patients achieved sinus rhythm with additional AAD treatment.

Two series^{68,81} reported on freedom from both paroxysmal and chronic AF. In both series, freedom from paroxysmal AF (73.2% and 82.5% respectively) was higher than freedom from chronic AF (51% and 70.3% respectively).

TABLE 12 Summary of freedom from arrhythmia at 12 months: atrial fibrillation case series

Study	Number ablated	Overall freedom as reported	Freedom without AADs	Freedom with AADs	Freedom from paroxysmal AF	Freedom from chronic AF	Occurrence of AFI or another arrhythmia	Freedom from any arrhythmia (calculated)	Main outcome includes repeat ablation	Freedom after repeat ablation
Chen et al., 2004 ⁸²	377	316/377 (83.8%)	UC	UC	UC	UC	UC	UC	No	356/377 (94.4%)
Deisenhofer et al., 2004 ⁸⁴	115	59/86 (69%)	NR	NR	NR	NR	NR	NR	NR	NR
Della Bella et al., 2005 ⁶⁸	234	160/234 (68.4%)	UC	UC	134/183 (73.2%)	26/51 (51.0%)	NR	NR	Yes	NR
Herweg et al., 2005 ⁹⁵	170	136/170 (80.0%)	136/170 (80.0%)	UC	UC	UC	UC	UC	No	NR
Hindricks et al., 2005 ⁹⁷	114	45/70 (64.3%)	UC	UC	UC	UC	UC	UC	No	NR
Jais et al., 2004 ¹⁰³	200	119/200 (59.5%)	119/200 (59.5%)	NR	NR	NR	UC	UC	No	NR
Kumagai et al., 2005 ¹¹⁴	100	71/100 (71.0%)	71/100 (71.0%)	82/100 (82.0%)	NR	NR	NR	NR	Yes	NR
Marrouche et al., 2002 ⁷⁸	190 (Just group 1)	162/190 (85.3%)	UC	UC	NR	NR	NR	NR	No	UC
Nademanee et al., 2004 ⁸¹	121	92/121 (76%)	UC	UC	47/57 (82.5%)	45/64 (70.3%)	NR	NR	No	110/121 (91%)
Nilsson et al., 2006 ⁶⁴	100	28/100 (28%)	28/100 (28%)	NR	NR	NR	12/100 (12%) AT	16/100 (16%)	No	UC
Pappone et al., 2004 ⁹⁰	560	444/560 (79.2%)	NR	NR	NR	NR	39/560 (7.0%), AT	NR	No	NR

AFI, atrial flutter; AT, atrial tachycardia; NR, not reported; UC, unclear.

TABLE 13 Freedom from atrial fibrillation at 12 months: proportions with 95% confidence intervals and pooled estimate of effect

Study	n	N	Proportion	LCI	HCI
Chen et al., 2004 ⁸²	316	377	0.838	0.801	0.875
Deisenhofer et al., 2004 ⁸⁴	59	86	0.686	0.588	0.784
Della Bella et al., 2005 ⁶⁸	160	234	0.683	0.624	0.743
Herweg et al., 2005 ⁹⁵	136	170	0.800	0.740	0.860
Hindricks et al., 2005 ⁹⁷	45	70	0.643	0.531	0.755
Jais et al., 2004 ¹⁰³	119	200	0.595	0.527	0.663
Kumagai et al., 2005 ¹¹⁴	71	100	0.710	0.621	0.799
Marrouche et al., 2002 ⁷⁸	162	190	0.853	0.802	0.903
Nademanee et al., 2004 ⁸¹	92	121	0.760	0.684	0.836
Nilsson et al., 2006 ⁶⁴	28	100	0.280	0.192	0.368
Pappone et al., 2004 ⁹⁰	444	560	0.793	0.759	0.826
Total	1632	2208			
Weighted pooled (random effects) estimate of proportion			0.76	0.74	0.77

HCI, higher confidence interval; LCI, lower confidence interval.

Freedom from arrhythmia at mean follow-up

A total of 26 case series reported on freedom from arrhythmia (freedom AF) at a mean follow-up point (Appendix 3.7). Mean follow-up ranged from 5.5 to 30 months. Freedom from arrhythmia as reported in publications ranged from 52% to 98%, with freedom from arrhythmia above 70% achieved in 19 case series. The series with the longest mean follow-up (30 months) reported 66.2% freedom from AF.^{99,116} The results were comparable with those reported in the survey by Cappato and colleagues²⁵ (Table 14).

Whether freedom from AF at mean follow-up was achieved as a result of a single ablation procedure or whether it required repeat ablations was reported for only 10 of the 26 case series. Freedom from AF was based on numbers of patients

undergoing a single ablation procedure in just two case series.^{75,82} In eight other case series, substantial numbers of patients required a repeat procedure to achieve freedom from AF.

Only two case series that reported overall freedom from AF also explicitly reported the occurrence of other arrhythmias, essentially atrial flutter. Treating these arrhythmias as treatment failures, the rate of freedom from arrhythmia is reduced from 316/377 (83.8%) to 311/377 (82.5%) in one case series⁸² and from 911/1125 (81%) to 617/1125 (54.8%) in the other.¹⁰⁶ A subgroup of patients in this latter study had undergone previous cardiac surgery and had a higher incidence of atrial flutter during follow-up. Three case series that did not report overall freedom from AF reported the occurrence of atrial

TABLE 14 Comparison of freedom from arrhythmia at mean follow-up reported from case series and freedom from arrhythmia at mean follow-up from the Cappato survey²⁵

Mean follow-up time	Number of series	Range as reported (%)	Range worst case (%)	Cappato success rate (%)
0–6 months	2	71–80	71–80	68
> 6–12 months	8	52–98	52–88	74–90
> 12–18 months	12	67–83	67–83	78
> 18–24 months	3	61–81	21–81	70
> 24 months	1	66	60	69.5

TABLE 15 Summary of frequency of major complications by study follow-up: atrial fibrillation case series

	Stroke/CVA		Tamponade		PV stenosis		Death	
	Explicit ^a	All series ^b	Explicit	All series	Explicit	All series	Explicit	All series
Immediate	18/2443 (0.74%); 11 series	18/5260 (0.34%); 22 series	29/4219 (0.69%); 15 series	29/5260 (0.55%); 22 series	8/836 (0.96%); five series	8/5260 (0.15%); 22 series	NR	0/5260 (0%); 22 series
3 months	NR	NR	NR	NR	101/985 (10.3%); two series	101/985 (10.3%); two series	NR	0/2346 (0%); 11 series
6 months	1/210 (0.48%); two series	1/410 (0.24%); four series	7/310 (2.3%); three series	7/410 (1.7%); four series	9/308 (2.9%); three series	9/410 (2.2%); four series	0/202 (0%); two series	0/2414 (0%); 16 series
12 months	0/121 (0%); one series	0/660 (0%); four series	0/121 (0%); one series	0/660 (0%); four series	54/660 (8.2%); four series	54/660 (8.2%); four series	0/560 (0%); one series	0/3159 (0%); 18 series
Mean	6/754 (0.8%); four series	6/3180 (0.19%); 13 series	8/877 (0.91%); five series	8/3180 (0.25%); 13 series	68/2751 (2.5%); ten series	68/3180 (2.1%); 13 series	1/116 (0.9%); one series	1/6510 (0.02%); 30 series
Cappato et al. survey ⁵	20/7154 (0.28%)		107/8745 (1.22%)		117/7154 (1.63%) stenosis	117/7154 (1.63%) with > 50% stenosis	4/8745 (0.05%) periprocedural deaths	

CVA, cerebrovascular accident; NR, not reported; PV, pulmonary vein.

a Explicit: only includes series reporting the event or specifying that it did not occur (or 'no complications').

b All series: includes all series reporting complications, assuming that the complication did not occur if not reported. For mortality, includes all series reporting any outcome at that time point.

All reported events were considered to occur postoperatively, unless specifically stated otherwise.

flutter at highly variable rates of 28/112 (25%),⁶⁷ 28/150 (18.7%)¹¹⁰ and 2/176 (1.1%).⁸³

Fifteen case series reported on whether AF-free patients were receiving AAD treatment. In all except one series the majority of patients did not receive AADs and in five series all patients who were AF free were also free of AAD treatment.

Freedom from paroxysmal and chronic AF was reported separately in eight case series. Freedom from paroxysmal AF ranged from 75% to 87.4% and was higher than freedom from chronic AF (range 57.6%–80.6%) in all but one series.

Quality of life

Only three studies treated as case series reported on QoL in patients with AF before and after RFCA. Hsu and colleagues¹⁰¹ administered the SF-36 questionnaire at baseline and at 1 and 12 months after ablation. SF-36 summary scores (physical and mental) increased significantly over time. In the series by Cha and colleagues,⁸⁰ the SF-36 total score increased significantly from 63 ± 18 before ablation to 79 ± 17 3 months after ablation ($p < 0.0001$). In the case series by Chen and colleagues,⁸² 193 patients (out of 377 treated patients) completed the SF-36 questionnaire before and after ablation and showed significant improvements on all subscales. Purerfellner and colleagues⁹² reported that standardised questionnaires were used to evaluate QoL but no results were presented.

It should be noted that, because the studies mentioned here present only SF-36 physical and mental component scores or an overall summary score, a separate review focused on obtaining utility-based QoL evidence was undertaken (see Appendix 7.4).

Complications and mortality

The main complications and mortality rates reported in the case series of RFCA in AF are summarised in *Table 15*. When case series specifically stated that there were no complications, events are inserted as zeros in the tables. The figures in this table also assume no duplication of patients across the included series and should therefore be treated cautiously. For comparison, the findings of Cappato and colleagues²⁵ in their survey of procedures performed between 1995 and 2002 are included. Detailed results by time period of reporting are presented in Appendices 3.5–3.8.

Mortality

Mortality was rarely reported in the published papers. Of the 18 case series that included follow-up at 12 months, only one reported on mortality at 12 months; this case series of 560 ablated patients reported that no deaths had occurred.⁹⁰ Among 30 case series reporting at mean follow-up (5.5–18.7 months), one reported a single death among 116 ablated patients during follow-up.¹⁰¹ Of the 16 case series that included follow-up at 6 months, the UK case series by Bourke and colleagues⁶⁶ reported no deaths among 100 ablated patients and there were also no deaths in the 102-patient case series reported by Essebag and colleagues.⁹¹ Overall, only one death was reported; when expressed as a proportion of those patients included in the case series for whom mortality information was reported this is 1/878 (0.1%).

Stroke

Stroke/cerebrovascular accident was reported as an immediate complication in 11 case series at frequencies ranging from less than 1% to 2%. Related complications [e.g. cerebroembolic complications, transient ischaemic attack (TIA)] were reported at similar frequencies in some case series (Appendix 3.5). If all cerebrovascular events are pooled their rate, where reported, is 1%. At mean follow-up (Appendix 3.7) the frequency of stroke where reported was 0.5–1.7% and that of TIA or cerebroembolic complications was 0.6–1%. One case series reported a single stroke among 102 patients at 6 months (Appendix 3.8).

Cardiac tamponade

A total of 15 case series reported cardiac tamponade as a procedural complication, occurring in up to 2% of cases. Pericardial effusion (0.3–3.9%) and/or haemopericardium (1.6–2.3%) were reported as procedural complications in four case series (Appendix 3.5). Pericardial effusion was reported in one patient (1%) in one case series¹¹⁴ at 12 months. At mean follow-up (Appendix 3.7), four case series reported tamponade at frequencies of 0.6–1.7%. Pericardial effusion occurred in five case series^{92,102,106} at frequencies of 0.2–1.7%. Haemopericardium was reported in 2/200 patients (1%) in one series.¹⁰⁰ The 100-patient UK series by Bourke and colleagues⁶⁶ reported tamponade in 6% of patients at 6 months (Appendix 3.8). Tamponade (1%) and pericardial effusion (2%) were reported in one other case series⁹¹ at this time point.

Pulmonary vein stenosis

Three case series reported PV stenosis as an immediate complication of RFCA, at frequencies of less than 1–2.4% (Appendix 3.5). PV stenosis was the main complication reported at 12 months (Appendix 3.6); severe stenosis occurred in 5% and 17% of patients in two series, whereas Kumagai *et al.*¹¹⁴ reported at least 50% stenosis in 18% of patients. The highest rate of stenosis at mean follow-up (33%) was seen in a series that specifically investigated this outcome.¹¹⁷ In six other series, stenosis at varying degrees of severity was reported in less than 1–1.9% of patients (Appendix 3.5). In the case series by Oral and colleagues,⁸³ asymptomatic narrowing of PVs occurred in 5/176 patients (2.8%). Two case series reported on PV stenosis 3 months after ablation, giving overall rates of 1.6% and 16% respectively (Appendix 3.8). The only case series to report stenosis at 6 months found the complication in 9/100 patients.

Other complications

Other immediate complications reported in more than one case series included haematomas (three case series; 0.6–0.9%), AV block (three series; 0.8–12%), thrombus/thrombosis (three series; 0.6–10.3%) and pulmonary oedema (two series; 0.3–0.8%) (Appendix 3.5). The only other complication at 12 months was unilateral quadrantopsia in one patient in a single series. Embolism (2–4%) and bleeding/haemorrhage (1–4%) were each reported in two series at 6 months (Appendix 3.8). At mean follow-up (Appendix 3.7), complications other than those listed above were reported at low frequencies in a single series only.

Summary of results from case series

The AF case series included in this review represent the experience of several thousand patients followed for up to 2–3 years after ablation. Success rates defined as freedom from arrhythmia at 12 months ranged from 28% to 85.3% with a weighted mean of 76%, reflecting differences in patients, techniques, expertise and methods of measuring and reporting outcomes across centres. Data post 12 months were rarely reported; data from case series with a mean follow-up of up to 30 months

reported rates of 61–81% for freedom from arrhythmia. It was not always clear from published reports whether success was dependent on the use of repeat procedures when necessary or not.

The majority of patients, and all arrhythmia-free patients in some series, no longer required AADs to remain arrhythmia free. In general, freedom from arrhythmia was somewhat less common in patients with chronic AF than in those with paroxysmal AF.

Mortality rates in the case series that reported on mortality were very low: only one death from 878 patients. Many series did not report mortality; however, it is likely that any periprocedural deaths would have been reported, at least in the 22 case series that reported other complications associated with RFCA. Stroke, cardiac tamponade and PV stenosis were the most frequently recorded complications.

Some centres published multiple case series reports covering overlapping time periods. Without access to individual patient data it is difficult to determine the degree of overlap in terms of patients being included in more than one case series. However, it is likely that some degree of overlap exists and this should be taken into account in evaluating the evidence of these case series.

The results from these case series are comparable with the findings of the international survey by Cappato and colleagues²⁵ covering procedures carried out between 1995 and 2002 (see *Table 5*). It is likely that there is overlap between the centres and patients included in the Cappato survey and this review.

These case series represent the bulk of the evidence for the effectiveness of RFCA for AF in clinical practice. A high percentage of the series come from a number of pioneering centres that have specialised in RFCA. Results achieved at such centres are unlikely to be generalisable to routine practice elsewhere. The only evidence from a UK, non-pioneering setting that met inclusion criteria for this review was the case series by Bourke and

TABLE 16 Quality ratings of controlled studies

Study	Criteria met	Overall quality rating
Da Costa <i>et al.</i> , 2006 ¹²¹	1, 4, 10, 11, 13–16, 18	Satisfactory
Natale <i>et al.</i> , 2000 ²⁹	1, 4, 11–13, 14–18	Satisfactory
See Appendix 2 for an explanation of the ratings and criteria used in quality assessment.		

TABLE 17 Quality ratings of case series

Study	Criteria met	Overall quality rating
Andronache et al., 2003 ¹²⁵	11–13, 15–18	Poor
Bertaglia et al., 2004 ¹¹⁹	11–18	Good
Calkins et al., 2004 ¹²⁶	11–14, 16–18	Poor
Chen et al., 2002 ¹²⁷	11–13, 15–18	Poor
Da Costa et al., 2002 ¹²⁸	12, 15, 17, 18	Poor
Da Costa et al., 2003 ¹²²	11–18	Good
Da Costa et al., 2004 ¹²⁹	11–13, 15–18	Poor
Da Costa et al., 2005 ¹²³	11–18	Good
Feld et al., 2004 ¹²⁰	11–16, 18	Poor
Gilligan et al., 2003 ¹³⁰	11–14, 16–18	Poor
Heidbuchel et al., 2006 ¹³¹	11–14, 17, 18	Poor
Hsieh et al., 2002 ¹³²	11–14, 18	Poor
Jais et al., 2001 ¹³³	11–13, 15, 17, 18	Poor
Loutrianakis et al., 2002 ¹³⁴	11–14, 16–18	Poor
Mantovan et al., 2002 ¹³⁵	17	Poor
Marrouche et al., 2003 ¹³⁶	11–13, 15, 17, 18	Poor
Ozaydin et al., 2003 ¹³⁷	12–15, 17, 18	Poor
Paydak et al., 1998 ³⁰	11–15, 17, 18	Poor
Schmieder et al., 2003 ¹³⁸	11–15, 17, 18	Poor
Schreieck et al., 2002 ¹²⁴	11–18	Good
Stovicek et al., 2006 ¹³⁹	17	Poor
Ventura et al., 2003 ¹⁴⁰	11–13, 15–18	Poor
Ventura et al., 2004 ¹⁴¹	11–13, 15–18	Poor

See Appendix 2 for an explanation of the ratings and criteria used in quality assessment.

colleagues,⁶⁶ who reported outcomes for 100 patients 6 months after ablation. A total of 55 patients were free of AF at that point but only 17 were also not receiving AAD treatment. Longer-term follow-up data from this series are awaited.

Results of review of clinical effectiveness – atrial flutter

Quantity and quality of research available

A total of 4860 studies were retrieved from the searches (see *Figure 1*). Of these, 483 were ordered and 86 studies (89 publications) met the inclusion criteria for the review. A total of 25 of these related to RFCA for typical atrial flutter (two controlled studies and 23 case series). Atrial flutter case series by Bertaglia and colleagues¹¹⁹ and Feld

and colleagues¹²⁰ were represented in multiple publications.

Both of the controlled studies evaluating the effectiveness of RFCA for atrial flutter were rated as ‘satisfactory’ (*Table 16*).^{29,121} Four out of 23 case series of atrial flutter^{119,122–124} were rated as ‘good’ quality (*Table 17*). The other 19 series were rated ‘poor’. Most series rated ‘poor’ failed to report or explain losses to follow-up, or followed up less than 90% of treated patients.

Assessment of effectiveness from controlled trials

Trial characteristics

Two RCTs^{29,121} (both rated ‘satisfactory’) compared the effects of RFCA against an alternative treatment strategy for atrial flutter (*Appendix 3.2*).

TABLE 18 Population details: controlled studies – atrial flutter

Study	Country	Quality rating	Number randomised (treated): RCFA	Number randomised (treated): control	Mean age (years) (SD): RFCA	Mean age (years) (SD): control	Male (%)	Mean (SD) duration of symptoms: RFCA	Mean (SD) duration of symptoms: control	Heart disease (%): RFCA/control
Da Costa et al., 2006 ²¹	France	Satisfactory	52 (52)	52 (51)	78.5 (5)	78 (5)	81	First symptomatic episode	First symptomatic episode	58/65
Natale et al., 2000 ²⁹	USA, Italy	Satisfactory	31 (31)	30 (30)	67 (8)	66 (11)	69	–	–	48/43

Patient characteristics are presented in *Table 18* with a summary of each study given below.

Results from controlled trial by trial

Natale *et al.*, 2000²⁹

RCT comparing RFCA with long-term drug treatment in patients with at least two episodes of symptomatic atrial flutter in the preceding 2 months.

A total of 31 patients were randomised to receive CTI ablation. All rate-control drugs were discontinued following ablation. After 12 months, two of these patients underwent a repeat ablation because of recurrence of atrial flutter.

A total of 30 patients were randomised to receive drug therapy. These patients tried a mean of 3.4 drugs, with 11 remaining on AADs at follow-up (eight on amiodarone, one on propafenone plus atenolol, and two on procainamide plus digoxin). In total, 16 patients received rate-control drugs after AADs failed to maintain sinus rhythm. Two patients crossed over into the ablation group before 12 months, and one required AV node ablation and pacing.

After a mean follow-up of 22 months, 25 (80%) patients in the RFCA group were in sinus rhythm without the need for AADs. For the same time period in the AAD group, 11 (36%) patients remained in sinus rhythm. Atrial flutter was seen in two patients (6%) in the RFCA group compared with 28 (93%) in the drug therapy group. AF was seen in nine patients (29%) in the RFCA group compared with 18 (60%) in the drug therapy group.

One patient experienced chest discomfort and another had a haematoma in the RFCA group. There were significantly more hospital admissions for severely symptomatic arrhythmia in the drug treatment group than in the RFCA group (19 versus 7; $p < 0.01$).

QoL and symptom scores significantly improved from baseline for all measures in the RFCA group at 6 and 12 months. Significant improvement over time in the drug therapy group was seen only for palpitations.

Da Costa *et al.*, 2006¹²¹

RCT comparing RFCA with cardioversion plus long-term amiodarone treatment in older patients (mean age 78 years) after their first episode of symptomatic atrial flutter.

A total of 52 patients were randomised to receive CTI ablation. Seven patients went on to have AAD therapy following occurrence of AF (six patients) or ventricular tachycardia (one patient).

A total of 52 patients were randomised to receive cardioversion (after attempting intracardiac stimulation) followed by amiodarone treatment. One patient was excluded after being diagnosed with a left reentrant atrial tachycardia.

After a mean follow-up of 13 months (SD 6 months), 96% of patients randomised to the RFCA group were free from recurrence of atrial flutter. Of patients randomised to cardioversion plus amiodarone, 71% of patients were free from recurrence of atrial flutter. All patients with recurrent atrial flutter went on to be successfully treated with RFCA, with the exception of one patient who refused the procedure. For the same time period, the occurrence of significant symptomatic AF beyond 10 minutes did not significantly differ between the RFCA and the amiodarone groups (25% versus 18%, $p = 0.3$).

Five patients in the amiodarone group had adverse events requiring discontinuation. No procedural-related complications occurred in the RFCA group. Six patients in the RFCA group died, compared with eight in the amiodarone group.

Results by outcome

Freedom from arrhythmia at 12 months

Neither of the atrial flutter RCTs reported freedom from arrhythmia at 12 months.

Freedom from arrhythmia at mean follow-up

The two RCTs evaluating CTI ablation for atrial flutter^{29,121} were conducted in clinically distinct populations and so were not combined statistically.

The trial by Natale *et al.*²⁹ found a statistically significant benefit favouring ablation in terms of freedom from arrhythmia without the need for AADs at a mean follow-up of 22 months [RR 2.2 (95% CI 1.33–3.63); see *Figure 4*]. Broken down by type of arrhythmia, this study suggested a very large statistically significant effect favouring ablation in terms of freedom from atrial flutter [RR 14.03 (95% CI 3.67–53.7)] and a smaller, but also significant, effect in terms of freedom from occurrence of AF during follow-up [RR 1.77 (95% CI 1.08–2.90)] (*Figures 5 and 6*).

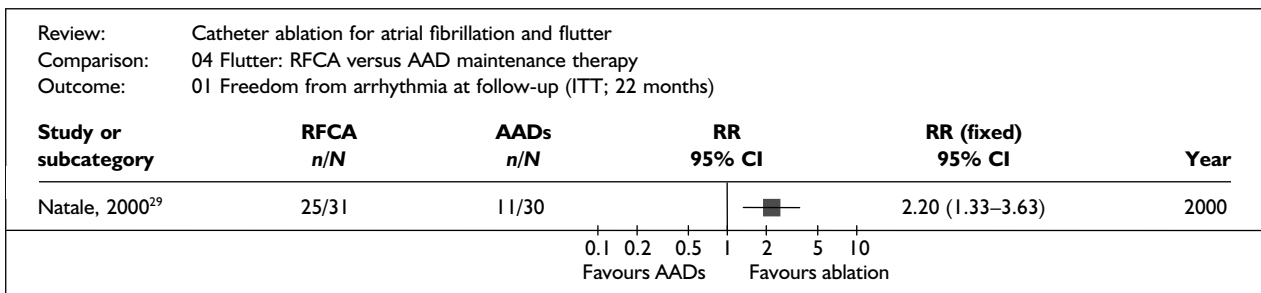


FIGURE 4 RFCA versus long-term AADs – freedom from arrhythmia. Refers to number of patients in sinus rhythm at follow-up, as reported by study authors.

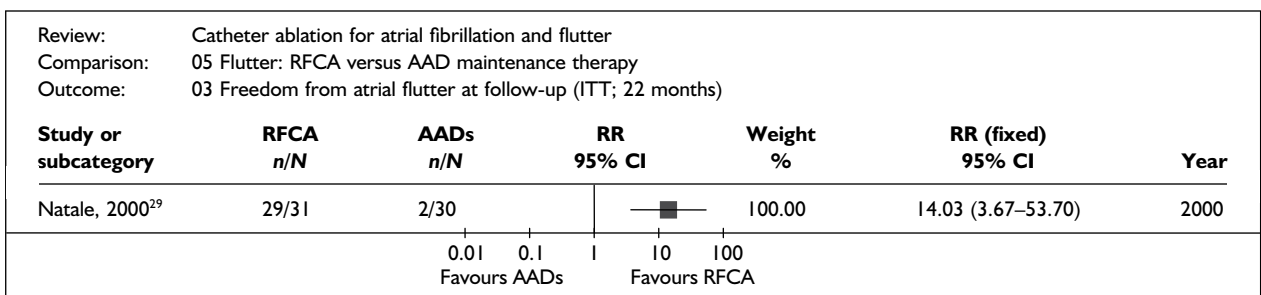


FIGURE 5 RFCA versus long-term AADs – freedom from atrial flutter. Refers to number of patients without occurrence of flutter during follow-up period.

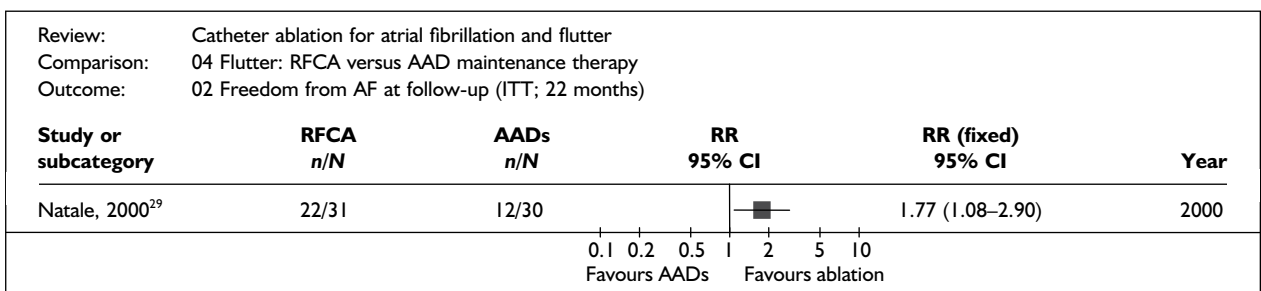


FIGURE 6 RFCA versus long-term AADs – freedom from atrial fibrillation. Refers to number of patients without occurrence of atrial fibrillation during follow-up period.

Da Costa *et al.*¹²¹ reported a more modest effect favouring ablation in terms of freedom from atrial flutter at follow-up in older patients (mean age 78 years) after their first episode of flutter [ITT 1.35 (95% CI 1.13–1.62); per protocol 1.36 (95% CI 1.13–1.64); see *Figure 7*]. The groups did not significantly differ in terms of freedom from occurrence of significant AF [intention to treat RR 1.44 (95% CI 0.68–3.08); see *Figure 8*].

The difference between the two RCTs in terms of treatment effects on freedom from atrial flutter results from a lower rate of recurrence in the AAD arm in the Da Costa *et al.* study and reflects the fact that this study recruited patients with a first episode of atrial flutter rather than the more drug-refractory patients recruited by Natale *et al.*

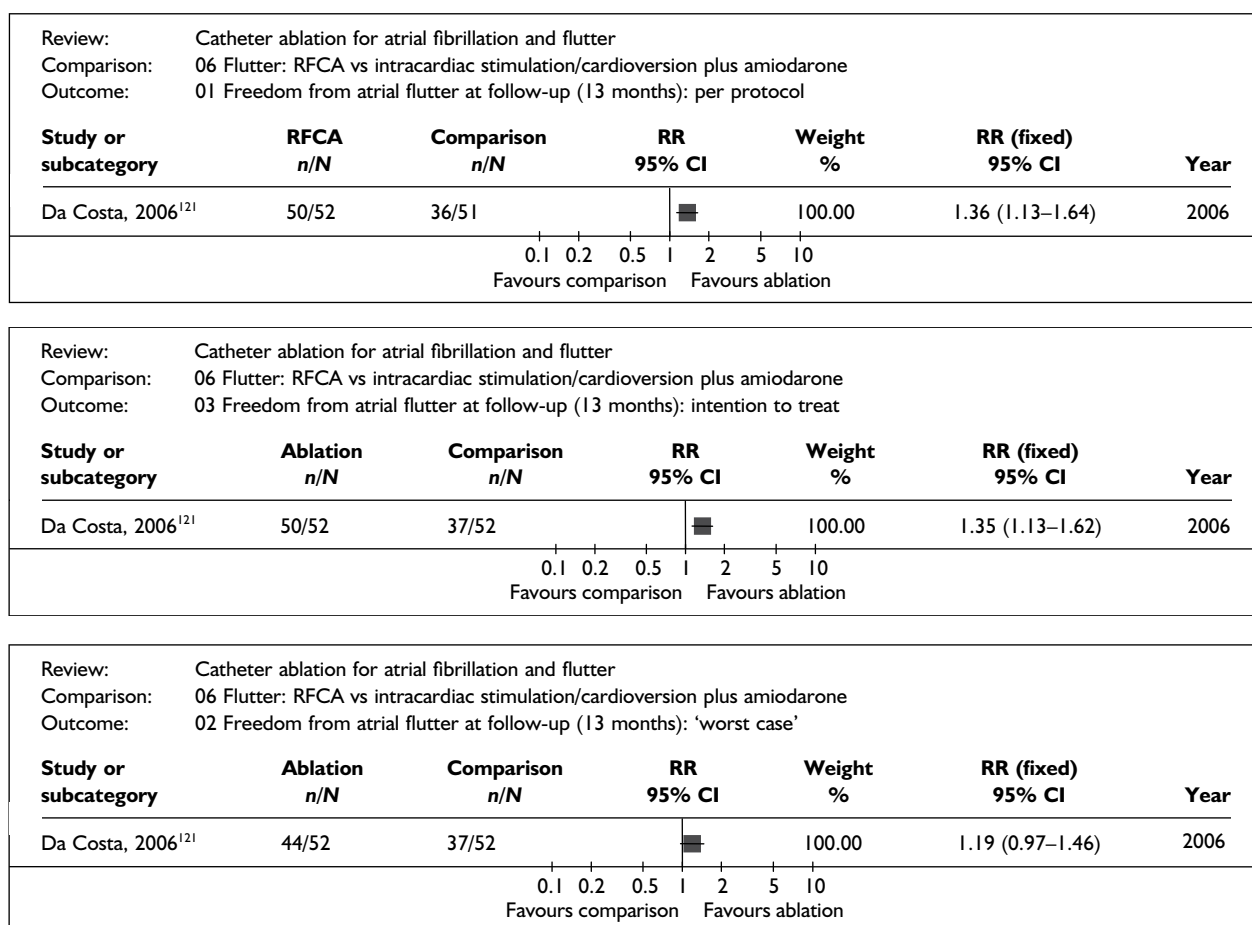


FIGURE 7 RFCA versus intracardiac stimulation/amiodarone: freedom from atrial flutter. 'Worst case' analysis assumes that all six patients in the RFCA group who died had recurrence of flutter; per protocol analysis assumes that these patients did not have recurrence of flutter.

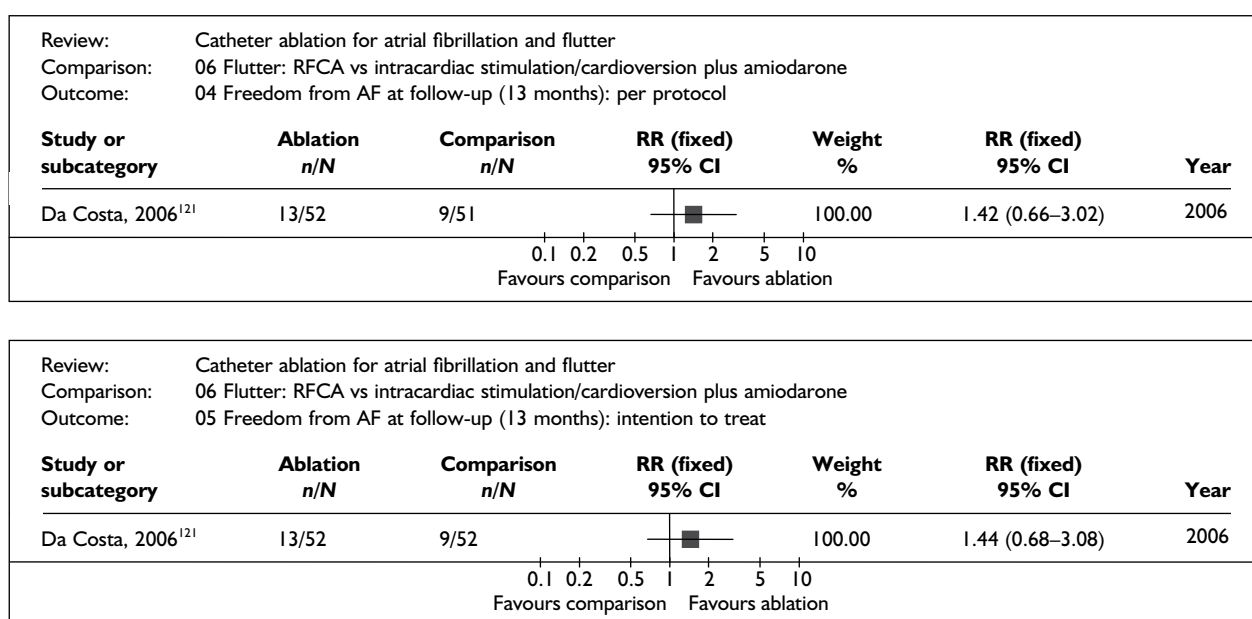


FIGURE 8 RFCA versus intracardiac stimulation/amiodarone: freedom from atrial fibrillation.

For reference, *Table 19* shows the outcomes from the two RCTs when calculated as relative risks and odds ratios and related confidence intervals.

Complications, adverse events and mortality

Table 20 summarises the complications, adverse events and deaths reported in the two atrial flutter RCTs.

These studies included a total of 164 patients and reported a total of seven adverse events or complications. Natale *et al.*²⁹ reported one patient with groin haematoma and one with chest discomfort among 31 patients receiving ablation. Da Costa *et al.*¹²¹ reported two occurrences of hypothyroidism, one of hyperthyroidism and two of symptomatic sick sinus syndrome among 51 patients receiving long-term amiodarone treatment.

The Da Costa *et al.* study reported six deaths in the ablation group (11.5%; one refractory heart failure, one sudden death, four non-cardiovascular causes) and eight deaths in the amiodarone group (15.7%; one pulmonary embolism, one death during coronary artery bypass graft surgery, four non-cardiovascular causes, two unknown).

Quality of life

In the study by Natale *et al.*,²⁹ QoL and symptom scores significantly improved from baseline for all measures in the RFCA group at 6 and 12 months. Significant improvement over time in the drug therapy group was seen only for palpitations.

Summary of results from controlled trials

There is very little randomised evidence available to assess the effectiveness of RFCA for the curative treatment of atrial flutter. That which is available suggests that a high proportion of patients who undergo RFCA are free from atrial flutter at follow-up in the medium term. RFCA has been shown to be superior to AAD therapy in terms of freedom from flutter in one small RCT of moderate quality and, in a larger moderate quality RCT, superior to cardioversion followed by long-term amiodarone in a selected group of older patients.

Only two repeat procedures were mentioned, in one of the two trials.²⁹

There is very little evidence from trials on the impact of RFCA on QoL in patients with atrial flutter. Where this has been reported, RFCA was associated with a general increase in self-reported health scores from baseline.

Where reported, complications associated with RFCA were rare. The currently available evidence does not show a significant relationship between RFCA and mortality.

Assessment of effectiveness from case series

Case series characteristics

Populations

Twenty-three case series with a total of 4238 participants were included (*Table 21*). The number of treated patients in each case series ranged

TABLE 19 Relative risks and odds ratios for freedom from arrhythmia at follow-up in atrial flutter RCTs

	Relative risk (95% confidence interval)	Odds ratio (95% confidence interval)
RFCA vs AAD maintenance therapy (one study)		
Freedom from arrhythmia (intention to treat)	2.20 (1.33–3.63)	7.20 (2.26–22.95)
Freedom from flutter (intention to treat)	14.03 (3.67–53.70)	203 (26.73–1541.94)
Freedom from AF (intention to treat)	1.77 (1.08–2.90)	3.67 (1.26–10.64)
RFCA vs intracardiac stimulation/cardioversion plus amiodarone (one study)		
Freedom from flutter (per protocol)	1.36 (1.13–1.64)	10.42 (2.24–48.41)
Freedom from flutter ('worst case')	1.19 (0.97–1.46)	2.23 (0.85–5.84)
Freedom from flutter (intention to treat)	1.35 (1.13–1.62)	10.14 (2.18–47.06)
Freedom from AF (per protocol)	1.42 (0.66–3.02)	1.56 (0.60–4.04)
Freedom from AF (intention to treat)	1.44 (0.68–3.08)	1.59 (0.61–4.13)

TABLE 20 Complications, adverse events and mortality in controlled studies of catheter ablation for atrial flutter

Study		Groin haematoma	Chest discomfort	Thyroid dysfunction	Sinus node dysfunction	Death
Natale et al., 2000 ²⁹	RFCA	1/31 (3%)	1/31 (3%)	–	–	–
	Drug treatment (LT)	–	–	–	–	–
Da Costa et al., 2006 ¹²¹	RFCA	–	–	–	–	6/52 (11.5%)
	CVN + amiodarone (LT)	–	–	3/51 (6%)	2/51 (4%)	8/51 (15.7%)

CVN, cardioversion; LT, long-term maintenance therapy.

from 100 to 417. Seven case series originated from the USA, 15 from Western Europe (mainly France, Germany and Italy) and one from Taiwan. Although obvious duplicate reports have been excluded, the case series included multiple publications from centres in France^{122,123,128,129} and Germany^{140,141} and so there may be some overlap of populations.

Of the 23 case series, 19 had an average patient age of 60 years or more. With one exception,¹³⁶ all the case series had a majority of male patients. Duration of symptoms was reported in ten case series and ranged from 13 months to 4.1 years; this was shorter than for most of the AF case series. Patient populations were classified as drug refractory in nine of the 23 atrial flutter case series, mixed (drug refractory and first line) in nine and unclear in five. The number of unsuccessful AADs was reported for five of the case series with drug-refractory patient populations^{119,133,136,140,141} and ranged from 1.7 to 2.2. Prevalence of structural heart disease (excluding hypertension where possible) was reported for 18 case series and ranged from 22% to 72%.

Interventions

All of the case series used CTI ablation. A variety of different catheter types and mapping techniques were used but only three studies treated as case series were trials of different ablation techniques.^{123,124,141} Most case series used bidirectional conduction block as the end point of the procedure, often requiring the block to last for at least 30 minutes. AAD treatment was stopped before the procedure in seven case series and continued in one; in the remaining series the situation was unclear. Patients returned to AADs after the procedure in one case series, AADs were withheld in three and in the other 19 series the situation was unclear. Of the eight case series that

reported anticoagulant use, six used heparin and two used warfarin. Time on anticoagulants after ablation, when reported, ranged from 7 days to 3 months. Details are presented in Appendix 3.9.

Freedom from arrhythmia at 12 months

The results of the case series are reported as two outcomes: freedom from atrial flutter and occurrence of other arrhythmias, mainly AF. The results for freedom from atrial flutter and other arrhythmias at 12 months are summarised in *Tables 22 and 23*.

Freedom from atrial flutter at 12 months' follow-up was reported to range from 72% to 95% with a weighted mean of 88% (95% CI 85–92%). None of the series reported whether the results at these time points were due to single or repeat procedures.

Freedom from arrhythmia at mean follow-up

Most studies reported data for a mean follow-up period (*Table 24*). Across all durations of follow-up freedom from atrial flutter was maintained in 68.3–97.8% of patients ablated. At the longest duration of mean follow-up (30 months) the reported rate of freedom from atrial flutter was 85.1%.¹³¹ However, these values are not easily interpreted as we do not know how many patients were at risk over the follow-up periods. Although the success rates for freedom from atrial flutter appear high, the proportion of patients with AF or atrial tachycardia or atypical atrial flutter at the end of follow-up is noteworthy; ignoring the data from the study that included repeat ablation¹²⁴ the proportion of patients with another arrhythmia ranged from 8.7% to 53.2%. Thus, the proportion of patients who achieve freedom from arrhythmia following RFCA for atrial flutter is calculated to range from 31.7% to 86.9%.

TABLE 21 Population details case series – atrial flutter

Study	Country	Quality rating	Number enrolled	Number ablated	Age (years), mean (SD)	Age range (years)	Male (%)	Duration of symptoms	Previous AADs, mean (SD)	Heart disease (%)
Andronache et al., 2003 ¹²⁵	France	Poor	100	100	62 (10)		85	Not reported		46
Bertaglia et al., 2004 ¹¹⁹	Italy	Good	383	383	61.7 (11.1)		75.4	Mean 4.1 ± 4.0 years	1.9 (1)	47.6
Calkins et al., 2004 ¹²⁶	USA	Poor	194	150	63.7 (10.7)		80	Mean 1.6 ± 2.8 years		
Chen et al., 2002 ¹²⁷	Norway, France	Poor	124	124	58 (11)		84.7	Not reported		35.5
Da Costa et al., 2002 ¹²⁸	France	Poor	161	161	66 (12)		82	Mean 13.1 months		40.2
Da Costa et al., 2003 ¹²²	France	Good	248	248	66.3 (12)	21–96	81.1	Mean 13 ± 23 months (range 1–120)		49.6
Da Costa et al., 2004 ¹²⁹	France, Netherlands	Poor	219	185	67 (11)	20–88	82.7	Not reported		41
Da Costa et al., 2005 ¹²³	France	Good	318	176	63 (11)		81.2	13 months (SD 23)		45.5
Feld et al., 2004 ¹²⁰	USA	Poor	1076	169	61 (12)		81.7	Not reported		49
Gilligan et al., 2003 ¹³⁰	USA	Poor	126	126	66 (11)	25–98	93.5	Not reported		65
Heidbuchel et al., 2006 ¹³¹	Belgium	Poor	219	154	58 (10)		83.2	Not reported		29
Hsieh et al., 2002 ¹³²	Taiwan	Poor	380	333	63 (16)	17–90	76.9	Not reported		

continued

TABLE 21 Population details case series – atrial flutter (continued)

Study	Country	Quality rating	Number enrolled	Number ablated	Age (years), mean (SD)	Age range (years)	Male (%)	Duration of symptoms	Previous AADs, mean (SD)	Heart disease (%)
Jais et al., 2001 ¹³³	France	Poor	221	221	62 (13)		81	Mean 30 ± 47 months	2.2 (1)	46
Loutrianakis et al., 2002 ¹³⁴	USA	Poor	117	104	65 (13)		79.8	Not reported		
Mantovan et al., 2002 ¹³⁵	Italy	Poor	417	417	62	21–86	75.3	Not reported		
Marrouche et al., 2003 ¹³⁶	USA	Poor	103	102	60 (7)	25–78	47.1	2.3 years	2 (1)	22
Ozaydin et al., 2003 ¹³⁷	USA	Poor	100	100	59 (13)		76	Not reported		31
Paydak et al., 1998 ³⁰	USA	Poor	110	110	62 (14)		78.2	25 months (SD 36)		65
Schmieder et al., 2003 ¹³⁸	Germany	Poor	363	363	58 (16)	2–86	73	Not reported		72
Schreieck et al., 2002 ¹²⁴	Germany	Good	100	100	62.4		82	Not reported		49
Stovicek et al., 2006 ¹³⁹	Czech Republic	Poor	108	108	63 (15)		78.7	Not reported		
Ventura et al., 2003 ¹⁴⁰	Germany	Poor	174	174	61 (9)		78.7	Mean 27 ± 15 months	2 (1.3)	46
Ventura et al., 2004 ¹⁴¹	Germany	Poor	130	130	61 (11)		80	Mean 21 months	1.7 (0.7)	51

SD, standard deviation.

TABLE 22 Efficacy data at 12 months' follow-up

Author	Number ablated	Overall freedom from AFI as reported	Overall freedom from AFI (assuming dropouts AFI)	Occurrence of AF or other arrhythmia ^a
Bertaglia <i>et al.</i> , 2002 ⁷³	383	NR	NR	AF: 148/383 (38.6%)
Calkins <i>et al.</i> , 2004 ¹²⁶	150	47/59 (79.7%)	47/150 (31.3%)	AF: 107/150 (71.3%)
Feld <i>et al.</i> , 2004 ¹²⁰	169	93/98 (95%) ^b	93/169 (55%) ^b	NR
Gilligan <i>et al.</i> , 2003 ¹³⁰	126	91/126 (72.2%)	91/126 (72.2%)	NC

AFI, atrial flutter; NC, not calculable; NR, not reported.
 a Calculated as 'worst case' ITT, assuming that patients not successfully ablated did not develop AF or atypical AFI later.
 b Freedom from symptoms.

TABLE 23 Freedom from atrial flutter at 12 months: proportions with 95% confidence intervals and pooled estimate of effect

	<i>n</i>	<i>N</i>	Proportion	LCI	HCI
Calkins <i>et al.</i> , 2004 ¹²⁶	47	59	0.797	0.69	0.90
Feld <i>et al.</i> , 2004 ¹²⁰	93	98	0.949	0.91	0.99
Gilligan <i>et al.</i> , 2003 ¹³⁰	91	126	0.722	0.60	0.70
Total	231	354			
Weighted pooled (random effects) estimate of proportion			0.88	0.85	0.92

HCI, higher confidence interval; LCI, lower confidence interval.

TABLE 24 Freedom from arrhythmia at mean follow-up

Mean follow-up time	Number of series	Range as reported (%)	Range worst case (%)
0–6 months	1	96	86
> 6–12 months	9	96–98	76–98
> 12–18 months	7	68–98	68–98
> 18–24 months	6	78–96	78–96
> 24 months	4	88–96	85–95

Quality of life

Only two case series reported on QoL before and after ablation of atrial flutter. Feld and colleagues¹²⁰ used three health-related QoL instruments that were administered at baseline and 3 and 6 months after ablation. Significant improvements over baseline were seen in 10/13 items reported. In the series by Calkins and colleagues,¹²⁶ the SF-36 questionnaire and a symptom checklist were administered at baseline and 6 months

after ablation. Improvements were seen in six of the eight SF-36 domains, in general physical and mental health and in 13 out of 16 cardiac symptoms.

Complications and mortality

The reported complications and mortality rates are summarised in *Table 25* with further details in Appendices 3.11 and 3.12.

Mortality

Of the 23 case series, six reported some data on mortality rates. Only two reported mortality rates for the periprocedural and immediate postprocedural period; both specifically reported mortality rates of 0%.^{120,134} One case series reported mortality of 4/169 ablated patients at 6 months (2.4%).^{120,142} One series reported mortality at 12 months: five deaths unrelated to the procedure among 150 patients (3.3%).¹²⁶ Four case series reported mortality at mean follow-up, with mortality rates that ranged from less than 1% to 12.5% over 16–29 months. No case series reported on mortality at 3 months, 9 months, 15 months, 18 months or 24 months. Summed across case series (Table 25) this represents a mortality rate of 4.5% in those case series reporting mortality (3.5% across all series reporting at that time point). Deaths during follow-up may reflect the relatively high prevalence of structural heart disease in some case series. One series¹²⁶ specifically reported that the deaths that occurred were unrelated to the ablation procedure.

Complications

A substantial proportion of case series that reported on complications reported that there were none or no significant complications: five out of 13 for the periprocedural and immediate postprocedural period and one out of three at mean follow-up. No case series reported on complications at 3 months, 9 months, 12 months, 15 months, 18 months or 24 months.

Atrioventricular block AV block was reported as a procedural complication in four series at a frequency of 0.5–1%. One series¹⁴³ reported two cases of AV block among 383 patients at mean follow-up.

Haematomas Haematomas as a procedural complication were reported in 0.5–2.3% of ablated patients in three case series; two patients with groin haematomas in one series also had false femoral aneurysms.¹³³ One series reporting outcomes at mean follow-up noted an accidental arterial puncture leading to groin haematoma,¹²³ probably a procedural complication.

Other complications For the periprocedural and immediate postprocedural period, ventricular arrhythmias (tachycardia or fibrillation) were reported in one patient in each of three case series. Pericardial effusion was reported in 2/363 patients in one series¹³⁸ and 2/100 in another.¹²⁴

Summary of results from case series

Freedom from atrial flutter at 12 months' follow-up was reported to range from 72% to 95% with a weighted mean of 88% (95% CI 85–92%) (Table 23). When the occurrence of AF or other arrhythmias was taken into account the proportion of patients free from arrhythmia appears to be nearer 30%; however, it should be noted that this estimate is derived from just three poor-quality case series with differing study characteristics. None of the series reported whether or not the results at these time points were due to single or repeat procedures.

For longer duration of follow-up, freedom from atrial flutter at mean follow-up was reported to be approximately 68–98%.

RFCA for atrial flutter differs from ablation for AF in having a less clear pattern of complications that may be associated with the procedure. The most frequent complications in these case series were AV block and haematomas, most commonly reported in the periprocedural and immediate postprocedural period. Across case series, assuming no duplication of patients between case series, no single complication occurred at a rate of more than 0.5%. Complications during longer-term follow-up were rarely reported and further research is needed to gain a more complete picture.

Discussion of clinical evaluation

The evidence reviewed here suggests that RFCA is an efficacious procedure for the treatment of AF and atrial flutter, with controlled studies typically reporting it to be more effective than long-term antiarrhythmic medical therapy. RFCA has not really been evaluated against other treatments with the exception of one unpublished non-randomised study comparing RFCA against direct current cardioversion and AV node ablation in AF.⁶² Most of the evidence for the effectiveness of RFCA in AF is in patients in whom pharmacological therapy has failed, reflecting current guidelines and recommendations.^{4,70} However, one small RCT⁶⁰ that investigated RFCA as first-line treatment found that its effectiveness relative to long-term AAD therapy did not differ substantially from the RCTs conducted in patients refractory to drug treatment. In most studies of atrial flutter the populations were not strictly drug refractory.

Although the evidence also suggests that RFCA is effective for atrial flutter, the lack of high-

TABLE 25 Summary of complications and mortality at different time points: atrial flutter case series

	AV block		Ventricular tachycardia/fibrillation		Haematoma		False femoral aneurysm		Pericardial effusion		Other complications		Mortality	
	Explicit ^a	All series ^b	Explicit	All series	Explicit	All series	Explicit	All series	Explicit	All series	Explicit	All series	Explicit	All series
Immediate	8/2013 (0.4%); nine series	8/2738 (0.3%); 13 series	3/1700 (0.2%); eight series	3/2738 (0.1%); 13 series	8/1504 (0.5%); eight series	8/2738 (0.3%); 13 series	4/1156 (0.3%); seven series	4/2738 (0.1%); 13 series	4/1213 (0.3%); seven series	4/2738 (0.1%); 13 series	19/2232 (0.9%); ten series	19/2738 (0.7%); 13 series	0/273 (0%); two series	0/2738 (0%); 13 series
Mean	2/544 (0.4%); two series	2/1520 (0.1%); six series	NR	NR	1/337 (0.3%); two series	1/1520 (0.07%); six series	NR	NR	NR	NR	4/544 (0.7%); two series	4/1520 (0.3%); six series	53/1183 ^c (4.5%); four series	53/1520 ^c (3.5%); six series

AV, atrioventricular; NR, not reported.

a Explicit: only includes series reporting the event or specifying that it did not occur (or 'no complications').

b All series: includes all series reporting complications; assumes that the complication did not occur if not reported. For mortality, includes all series reporting any outcome at that time point.

c Total deaths during follow-up, not procedure related.

quality randomised data means that there are real uncertainties around the estimate for the effectiveness of RFCA in atrial flutter. Furthermore, most of the case series of atrial flutter also failed to report freedom from arrhythmia at 12 months. Thus, the evidence base for RFCA in atrial flutter is very limited. Case series evidence suggests that a significant proportion of patients develop new-onset AF following flutter ablation; however, the small amount of published randomised evidence does not suggest that this occurs any more frequently in ablated patients than in patients receiving other treatments, with one study suggesting a lower rate of new-onset AF in patients undergoing RFCA than in those receiving AADs.²⁹

Importantly, it is not clear to what extent success rates depend on repeat ablations. Repeat procedures were rare in the small number of included RCTs, but this was often unclear or not reported in case series. In addition, the available data were not sufficient to enable us to determine the influence of the proportion of patients with structural heart disease or mean duration of arrhythmia on success rates.

Although relief from symptoms is one of the goals of treatment, there is little evidence from randomised trials on the impact of RFCA relative to AAD treatment on QoL. The small amount of

evidence that is available from RCTs and case series does however suggest that RFCA treatment might be associated with improvements in self-rated physical and/or general health from baseline in AF and atrial flutter.

The available data indicate that there is a relatively small risk of serious complications associated with RFCA, with a low risk of operative mortality. The risk of such complications needs to be balanced against that of potential adverse events associated with long-term use of certain antiarrhythmic agents. It should be noted that estimates of overall complication rates are associated with high uncertainty because of limited reporting. For example, only 22 out of 52 AF case series reported on immediate complications, and rates of reporting at other follow-up points were even lower. However, we considered it reasonable to assume that, when complications were not reported, they did not occur.

As a final point it should be noted that the published evidence may not be entirely generalisable to practice; much of the evidence comes from pioneering centres and it is these centres that have produced a disproportionately large number of the included case series and which have been the first to undertake randomised trials.

Chapter 4

Assessment of cost-effectiveness evidence

Systematic review of existing cost-effectiveness evidence

Methods

A broad range of studies was considered for inclusion in the assessment of cost-effectiveness, including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) were included.

The following databases were searched for relevant published literature: Cochrane Controlled Trials Register (CCTR), EMBASE, Health Economic Evaluations Databases (HEED), MEDLINE, National Research Register (NRR), NHS Economic Evaluation Database (NHS EED), PsycINFO and Science Citation Index. Full details of the main search strategy for this review are presented in Appendix 1.

Two reviewers independently assessed all obtained titles and abstracts for inclusion. Any discrepancies were resolved by discussion. The quality of the cost-effectiveness studies was assessed according to a checklist updated from that developed by Drummond *et al.*¹

Results

The systematic literature search identified only one study¹⁴⁴ that met the inclusion criteria for the cost-effectiveness review. The following sections provide a detailed critique of the cost-effectiveness evidence from the included study and an assessment of the quality and relevance of the data from the perspective of the UK NHS. A quality assessment checklist is provided in Appendix 7.1.

Review of Chan *et al.*, 2006:¹⁴⁴ cost-effectiveness of RFCA for atrial fibrillation Overview

The study was designed to compare the cost-effectiveness of left atrial catheter ablation (LACA) with the cost-effectiveness of two alternative treatment strategies for the management of AF.

The two alternative strategies were (1) rhythm control with amiodarone therapy and (2) rate control with a combination of digoxin and atenolol therapy. The main outcome measure was the degree of stroke reduction evaluated according to different baseline risks of stroke (low or moderate). In addition, short- and long-term outcomes including haemorrhage, drug toxicity, adverse events and procedural complications for each treatment strategy were incorporated. In all of the strategies patients also received antithrombotic or anticoagulant therapy. Those at moderate risk of stroke received warfarin whereas those at low risk received warfarin or aspirin.

The study was based on a deterministic Markov decision-analytic model of AF in a hypothetical 65-year-old US population at risk of stroke, evaluated over a cycle length of 3 months with patients modelled until death. A moderate risk of stroke was defined as having one risk factor (hypertension, diabetes mellitus, coronary artery disease or congestive heart failure), a low risk of stroke was defined as having no risk factors, and a high risk of stroke (\geq two risk factors) was excluded from the analysis. An additional cohort of 55-year-old patients at moderate risk was also considered. The study reports a societal perspective, although the exclusion of productivity costs means that the analysis is closer to a US payer perspective.

Summary of effectiveness data

An efficacy rate for LACA of 80% was derived from a number of large studies including a worldwide survey of the methods, safety and efficacy of curative catheter ablation of AF.²⁵ The rate incorporates a 30% redo ablation rate from AF recurrences or post-ablation atrial flutters during the first year. Because of the absence of long-term data on the relapse rate to AF for patients successfully restored to sinus rhythm with LACA, a 2% annual rate was assumed. The model incorporated complication rates due to LACA for tamponade, stroke, atriopharyngeal fistula, death and other events.

The rate of restoration to sinus rhythm with rate control therapy was based on findings from a 5-year follow-up of the AFFIRM trial.¹⁴⁵ The

relapse rate back to AF was conservatively assumed to be 5% annually. Rates for amiodarone efficacy, adverse events and relapse to AF were derived from a large number of literature sources.

The annual baseline stroke risks (without antithrombotic therapy) were based on conservative estimates from two previous decision-analytic models and a more recent meta-analysis.^{146,147} The additional use of aspirin or warfarin therapy in conjunction with AF treatment was modelled on the basis of an annual stroke risk reduction with aspirin therapy of 22% (for both risk groups), and an annual stroke risk reduction with warfarin therapy of 45% and 35% compared with aspirin therapy at moderate and low risk respectively. The annual risk of stroke in patients with AF restored to sinus rhythm was unknown. The study assumed a rate of 0.5% for the cohort at low risk of stroke, representing a 29% relative risk reduction compared with low-risk AF patients on warfarin therapy. A similar relative risk reduction in the moderate risk cohorts was assumed. The model incorporated differential mortality and disability rates associated with stroke severity for patients on aspirin and warfarin therapy, and the rates for these were derived from a number of published literature sources. Patients who experienced a stroke were modelled to be twice as likely to have a recurrent stroke.

The annual baseline risks of haemorrhage for aspirin and warfarin therapy were based on results from a recent meta-analysis of pooled data from six randomised clinical trials.¹⁴⁸ A 1.5 relative risk of rehaemorrhage was based on data from the SPAF I–III clinical trials.¹⁴⁹

Summary of resource utilisation and cost data

Costs associated with treatment (single event and annual costs), cardiac events, annual care, intracranial bleed, stroke and adverse events associated with treatment were based on Medicare reimbursement rates, hospital accounting information, previously published studies and the *Red Book* for wholesale drug costs. Costs were reported in US dollars for the year 2004 and discounted at an annual rate of 3%. Productivity and personal care costs were not included in the analysis.

The cost associated with a single ablation was US\$16,500. The cost of repeat ablation was assumed to be the same as the cost of the first procedure. The cost of complications from

ablation was estimated to be the average of complication costs from tamponade and stroke with LACA at US\$11,000. A rare atrioesophageal fistula complication with a 50% mortality rate was estimated to cost US\$50,000 per event. The annual cost of warfarin therapy included the cost of regular 4-week serum monitoring and an office visit. Patients receiving rate control treatment were assigned atenolol and digoxin therapy. The cost of digoxin therapy included 6-month monitoring costs.

Summary of cost-effectiveness data

Quality of life for warfarin and aspirin therapies and individual health states were obtained from published studies. For clinical events (stroke, haemorrhage, drug toxicity and LACA complications) a disutility of 0.5 was applied for the duration of the event.

For 65-year-old patients with AF at moderate risk of stroke and on warfarin therapy, LACA (with an 80% efficacy rate) was estimated to be more effective but more costly than the alternative treatment strategies. The corresponding incremental cost-effectiveness ratio (ICER) was US\$51,800 per QALY gained when compared with the use of rate control therapy. The use of amiodarone therapy was both less effective and more costly, and was dominated by rate control therapy. Similarly, for 55-year-old patients with AF at moderate risk of stroke, LACA was more costly and more effective with an ICER of US\$28,700 per QALY gained relative to rate control therapy, which dominated amiodarone therapy. For 65-year-old patients at low risk for stroke and on aspirin therapy, LACA had an ICER of US\$98,900 per QALY gained compared with rate control therapy, which dominated amiodarone therapy.

The ICERs above US\$50,000 are driven largely by the significant upfront costs of LACA surgery. Any time horizon shorter than a lifetime would make LACA appear less cost-effective. The study estimated that for 65-year-old moderate stroke risk patients and an 80% LACA efficacy rate, relative stroke risk reductions with long-term sinus rhythm restoration of 42% and 11% would yield ICERs of less than US\$50,000 and US\$100,000 per QALY gained respectively. For the same patient population at low risk of stroke, LACA therapy could never be cost-effective unless the reduction in stroke risk was improbably large. The LACA efficacy rate is inversely related to the relative stroke risk reductions with sinus rhythm restoration, i.e. higher and lower LACA efficacy

rates require correspondingly lower and higher stroke risk reductions to achieve the required cost-effective thresholds.

A series of univariate and multivariate sensitivity analyses were performed over a range of estimates for patients at moderate risk of stroke. The one-way analyses indicated that the ICER was most sensitive to the risk of stroke in AF with warfarin therapy, the discount rate, the cost of LACA, the utility and haemorrhage risk with warfarin therapy, the rate of recurrence of AF after LACA, and the conversion rate to sinus rhythm with rate control therapy. The multivariate sensitivity analyses were conducted using Monte Carlo simulation methods. The results indicate that, for 55-year-old moderate stroke risk patients, there is an 82% probability that the ICER comparing LACA treatment with rate control therapy is below US\$50,000 per QALY gained. Among the 65-year-old moderate stroke risk population the cost-effectiveness is less certain with a 40% probability that the ICER falls below US\$50,000 per QALY gained.

Discussion

The study is comprehensive and well conducted but suffers from a number of limitations. It focuses primarily on the long-term benefit of stroke risk reduction rather than considering a broader set of potential treatment benefits including palliative benefits from improved symptoms. This distinction may have an important impact on the overall estimate of cost-effectiveness. Recurrent arrhythmias occur in the vast majority of patients with AF whereas stroke occurs in a minority of patients. Thus, symptomatic benefits from catheter ablation should be considered in an assessment of the cost-effectiveness of the procedure. The study focused on first-line use of LACA for maintaining sinus rhythm in patients with AF; however, the majority of patients referred for LACA therapy have failed previous antiarrhythmic therapy. As such, the study may have underestimated the relative efficacy of LACA compared with pharmacological strategies for these patients.

From a UK NHS perspective the study has a number of additional limitations. The data are mostly sourced from a variety of US studies and the costs are specific to the US. As such, it is difficult to assess the generalisability and transferability of the data to a UK setting in which the pattern of care and number of surgeons undertaking catheter ablation differs. For example, in the UK

catheter ablation is usually performed only on the most highly symptomatic patients. The exclusion of potential QoL benefits due to symptomatic improvements in this study is potentially a key omission in relation to current UK management. The following section presents a new decision-analytic model that has been developed to provide a more appropriate analysis in the context of the UK NHS.

Decision model

Overview

The review of cost-effectiveness studies in the previous section identified a number of potential limitations of previously published studies in relation to the cost-effectiveness of RFCA in the UK NHS. A new decision-analytic model was therefore developed to more formally assess the cost-effectiveness of RFCA in this setting. This model provides a framework for the synthesis of data from the clinical effectiveness review and other relevant parameters in order to evaluate the potential long-term cost-effectiveness of RFCA. The model was developed using Microsoft Excel.

The model was populated using data from the systematic review and synthesis of clinical effectiveness data reported in Chapter 3 in the section on summary of results from case series of AF. The model considers the potential long-term costs and consequences associated with the primary outcome of the review: freedom from arrhythmia at 12 months. The model evaluates costs from the perspective of the NHS and Personal Social Services (PSS), expressed in UK pounds sterling at a 2006 price base. Outcomes in the model are expressed in terms of QALYs. As appropriate utility values could not be identified in the studies meeting the inclusion criteria for the clinical or cost-effectiveness reviews (see section on quality of life under Model inputs), a series of additional searches were required to relate the primary outcome from the clinical effectiveness review to QALYs and to identify additional data required to quantify the potential long-term costs and consequences required for the cost-effectiveness analysis. Both costs and outcomes are discounted using a 3.5% annual discount rate, in line with current guidelines.¹⁵⁰ All stages of the work were informed by discussion with our clinical advisors to provide feedback on specific aspects of the analysis such as the model structure, data inputs and assumptions.

The model is probabilistic in that input parameters are entered into the model as probability distributions to reflect second order uncertainty – that is, uncertainty in the mean estimates.^{151,152} Monte Carlo simulation is used to propagate uncertainty in input parameters through the model in such a way that the results of the analysis can also be presented with their uncertainty. The probabilistic analysis also provides a formal approach to quantifying the consequences associated with the uncertainty surrounding the model results and can be used to identify priorities for future research.

The following sections outline the decision problem and the structure of the model and also provide an overview of the key assumptions and data sources used to populate the model in more detail.

Treatment strategies and population

The decision problem addressed by the model relates to the cost-effectiveness of RFCA in adults with AF refractory to at least one AAD. During the review process consideration was given to extending the model to consider typical atrial flutter as well. However, although the general structure of the model was considered to be generalisable across the different patient groups, it was unclear whether the data inputs required for the long-term modelling (particularly in relation to subsequent prognosis) could be generalised in the same manner. Given that the majority of data required to populate the long-term model were reported only for subjects with AF, a decision was made to constrain the analysis to subjects with AF only.

The decision model therefore evaluates a strategy of RFCA (without long-term AAD use) compared with long-term AAD treatment alone in adults with AF refractory to at least one AAD. It should be recognised that the majority of subjects included in the RCTs of this comparison had paroxysmal AF as opposed to persistent or permanent forms. This needs to be taken into account when generalising the results from the cost-effectiveness analysis to the management of AF. For the evaluation of long-term AAD treatment the model evaluates the use of amiodarone. Amiodarone was selected on the basis that this was the AAD most likely to be given after patients had previously failed on other AADs in routine practice. It was also the most common AAD evaluated in the RCTs comparing the strategies considered in the model.

Model structure

The model is made up of two components: a short-term element, which characterises a period of 12 months, and a long-term element, which considers the costs and outcomes over the remaining lifetime of a patient. The period represented by the short-term model mirrors the primary outcome considered in the clinical effectiveness review (freedom from AF at 12 months), ensuring consistency between the clinical and economic analyses.

Short-term model

The short-term model is structured as a decision tree as shown in *Figure 9*, reflecting the short-term clinical outcomes and adverse events associated with the two treatment strategies. For the RFCA strategy, patients are exposed to a risk of operative death or procedural complications. The major complications include cardiac tamponade, stroke and PV stenosis, each of which influence the management costs and QoL attributed to RFCA. For AADs, patients face a risk of adverse drug toxicity. This risk may represent time-limiting symptoms that require evaluation and management of the toxic event, but which may be reversed without the need for discontinuation of the drug therapy. This is represented by ‘reversible general toxicity’ in *Figure 9*. However, patients may have an acute episode of toxicity that requires permanent withdrawal from treatment. These patients face an additional risk of pulmonary complications given that they have withdrawn. These complications in turn can either be reversed or lead to acute irreversible pulmonary toxicity, with an elevated risk of mortality assumed to be associated with the latter event.

Several competing risks including stroke, adverse bleeding events (due to concomitant medications) and other causes of mortality are also included in the short-term model for both treatment strategies. At the end of the 12-month period patients are either restored to NSR or they revert back to AF (after accounting for mortality and the risk of stroke over this period). These outcomes represent the main starting health states for the long-term Markov model (denoted by M in *Figure 9*).¹⁵³

Long-term model

The long-term model considers the subsequent prognosis (beyond 12 months) of patients with NSR/AF or stroke, quantifying the potential costs and QoL incurred by patients over their remaining lifetime. In addition to considering any potential QoL and cost differences between the separate

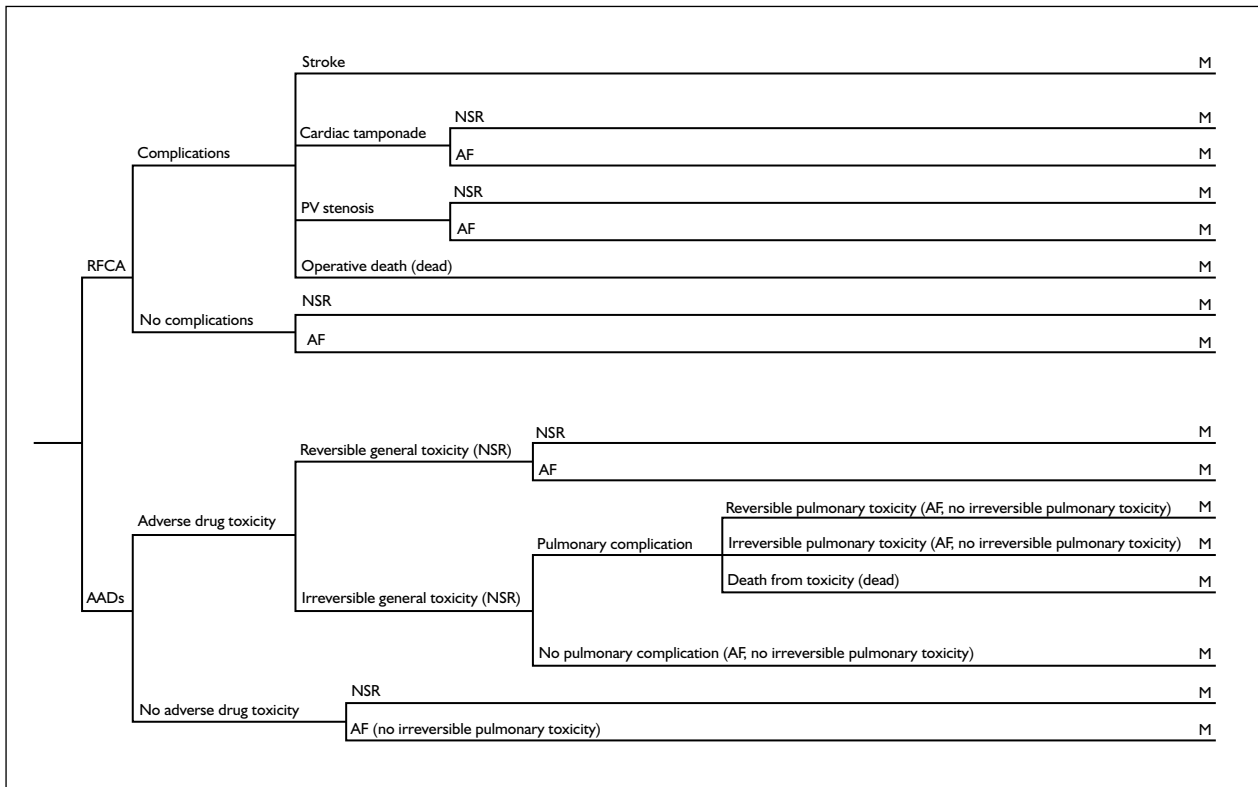


FIGURE 9 Schematic of the short-term model showing pathways for adverse events and complications from treatment leading to the two main starting health states (normal sinus rhythm and atrial fibrillation) of the long-term Markov model.

states, the model also allows the subsequent prognosis to differ according to the longer-term risks of fatal and non-fatal events (in particular the risk of stroke).

The long-term models for the two treatment strategies take slightly different forms and are illustrated in *Figures 10* and *11*. The same general structure is applied to both strategies, although the potential adverse drug toxicity events associated with the use of AADs require additional states in the model. Both models take the form of a Markov process with key health states for NSR, AF, stroke and death (represented using circles). The arrows represent possible pathways (transitions) that a patient may follow over each cycle of the model (annual cycles are applied).

For RFCA (*Figure 10*), patients enter the model at the end of 12 months in the NSR, AF or stroke state. Patients entering the NSR state face an annual probability of reversion back to AF. In addition, they face an elevated risk of stroke compared with the general population. Patients entering the AF state are assumed to face a higher risk of stroke than NSR patients (see later sections

for details). If patients survive the first year of a stroke they then enter a post-stroke state in which the risk of death due to stroke and the costs incurred from stroke are lower than in the first year of the event. In each yearly cycle all patients, regardless of their current health state, face an annual risk of mortality from other causes (non-stroke mortality).

For AADs (*Figure 11*), patients enter the model at the end of 12 months in the NSR, AF or stroke state but can also enter with irreversible pulmonary toxicity. Irreversible pulmonary toxicity incurs an annual cost and QoL decrement for each year that the patient remains alive and so the model must keep track of these patients. Patients in the NSR state continue receiving AADs and therefore have an annual probability of general toxicity. If this toxicity occurs and is reversible and non-fatal, an additional cost and QoL decrement is incurred only for the duration of the event. If this risk is non-reversible then patients face longer-term costs and QoL implications. Patients who stayed in the AF state after the first year of treatment, or reverted back to the AF state from NSR, were assumed to be withdrawn from AAD treatment

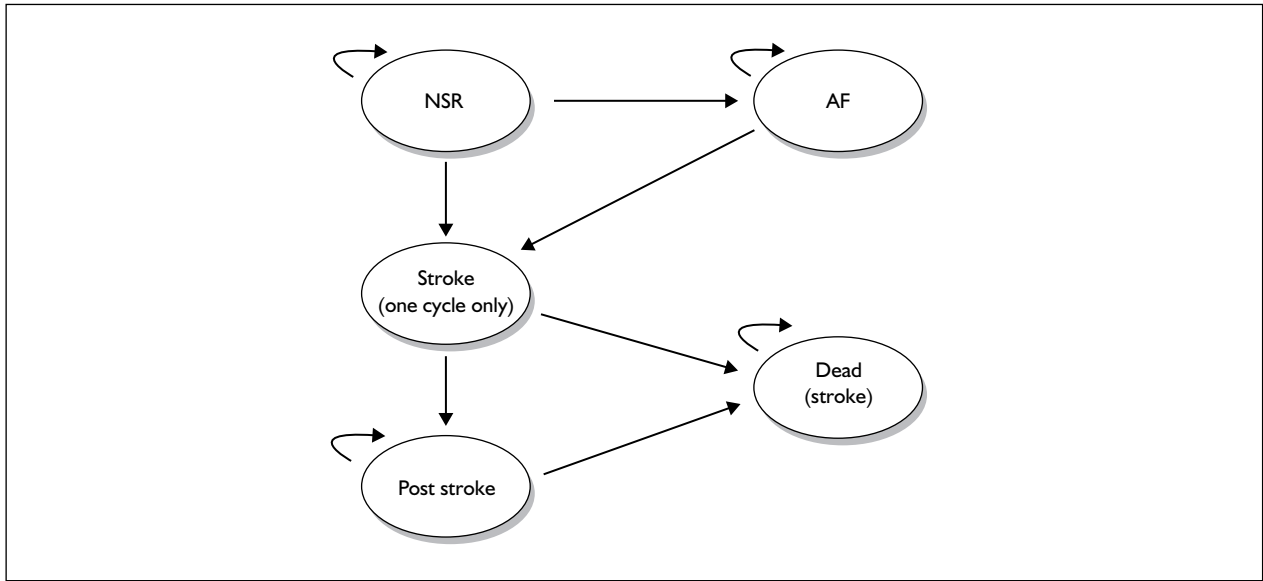


FIGURE 10 Structure of the long-term model for RFCA.

at this point. The subsequent prognosis for these patients included a higher risk of stroke than for NSR patients, and a risk of other-cause mortality. The subsequent movement between the NSR, AF and stroke states for patients having received AADs are assumed to be the same as for RFCA patients in a number of aspects. However, the strategies will differ according to the proportion of patients who leave the short-term model in the different states (a higher proportion of patients are assumed to leave

the short-term model in the NSR state for RFCA) and the long-term risk of reverting back to AF from the NSR state. Both models also include a cost and QoL decrement linked to the risks of major and minor bleeding events associated with the use of anticoagulants. These are assumed to be the same for both strategies and will only differ in the long term if there are mortality differences between the strategies. That is, patients who live longer will continue to accrue these costs over a longer period.

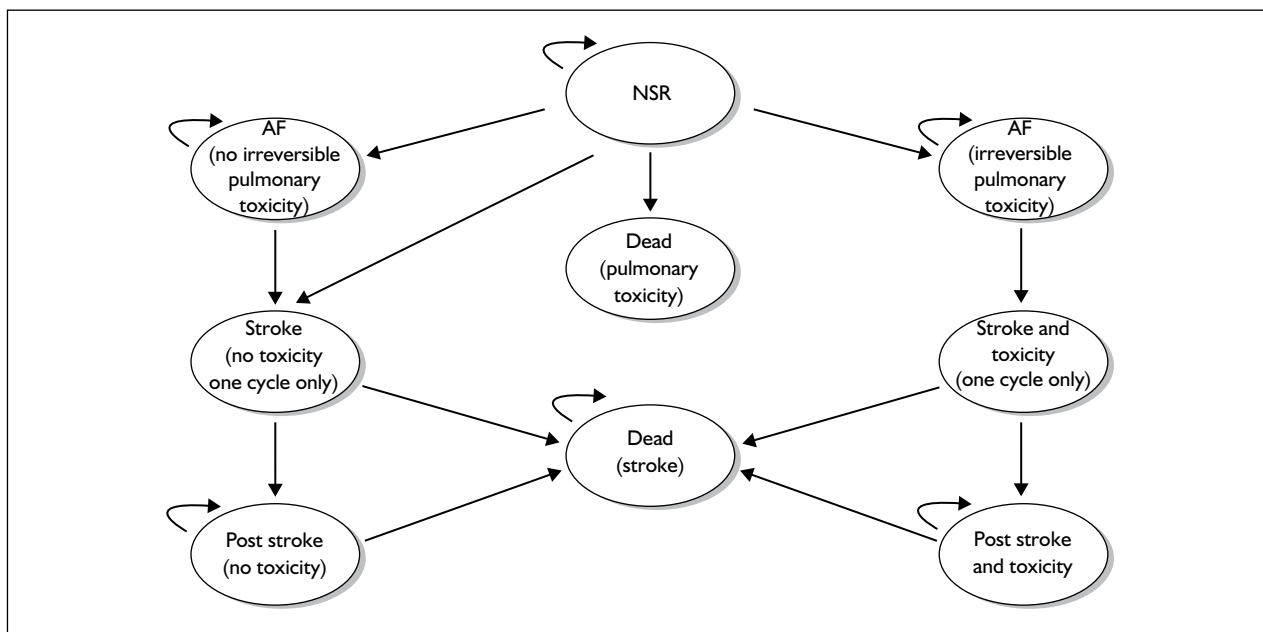


FIGURE 11 Structure of the long-term model for AADs.

Key assumptions

The cost-effectiveness of RFCA in the NHS will be determined by a number of potential factors. These factors relate to both short-term and longer-term issues and also to the generalisability of the existing clinical evidence base to the NHS. In the short term the use of RFCA will incur significant additional upfront costs compared with AADs in terms of the initial procedure costs and the management of any associated complications. There will also be a potential increase in the short-term risk of major adverse events due to the operative risk of mortality and stroke. For RFCA to be considered cost-effective in the long term it will be important to demonstrate that these additional costs result in potential long-term gains in QoL and/or that subsequent management costs are reduced compared with the use of AADs. There also remains an important question of whether the RCT evidence on the clinical effectiveness of RFCA can be applied to a UK setting.

The model makes a number of key assumptions in considering the cost-effectiveness of RFCA in the UK NHS. These include:

- *QoL* Potential QoL gains associated with RFCA are examined in relation to a number of factors: (1) improved symptomatic benefits in both the short term and long term and the duration that these are likely to be maintained; (2) the avoidance of the use of AADs and the impact that potential side effects may have on QoL; (3) the impact of RFCA on the longer-term risk of stroke and/or mortality due to any prognostic benefit compared with the use of AADs.
- *Costs* In addition to the initial upfront costs associated with the use of RFCA, potential differences in the subsequent management of patients are also considered. These include: (1) the avoidance of the acquisition costs of AADs themselves and the costs of managing side effects; (2) the potential for RFCA to reduce the frequency and/or severity of recurrent episodes of AF in both the short term and longer term, thereby potentially reducing subsequent management costs; (3) a reduction in the costs associated with major clinical events such as stroke due to any prognostic benefits compared with the use of AADs.
- *Generalisability of evidence to the UK* In addition to ensuring that the management costs and underlying risks associated with AF are relevant to UK patients, consideration is given to whether the existing RCT evidence itself,

related to the use of RFCA, can be transferred directly to a UK setting.

Clearly there exists significant uncertainty in relation to each of these separate aspects. The use of decision analysis provides a number of advantages in exploring these uncertainties in more detail: (1) it provides a framework for identifying the potential risks and benefits (short and long term) associated with each strategy; (2) it makes each of these assumptions explicit and can highlight where the current uncertainties exist; (3) it provides a quantitative approach to synthesising evidence from separate sources and the use of probabilistic analysis means that the precision of each source can be reflected in the distribution assigned (reflecting the degree of uncertainty surrounding particular inputs); and (4) the potential impact of each of the assumptions on the cost-effectiveness results can be considered in detail.

The following sections provide a detailed overview of the model inputs and the main assumptions. A base-case analysis is then undertaken using a particular set of assumptions. A series of detailed sensitivity analyses follows, exploring the impact of a range of alternative assumptions on the overall cost-effectiveness results.

Model inputs

A full list of parameter inputs applied in the model is reported in Appendix 7.3. Each of the main parameter groups (e.g. clinical effectiveness parameters, costs, QoL, etc.) is discussed in detail in the following sections.

Baseline events rates (RFCA) and relative treatment effect (versus AADs)

The clinical effectiveness review identified three RCTs in which RFCA was compared directly with AADs for patients with predominantly paroxysmal AF. The primary health outcome considered in these trials was freedom from AF at 12 months. These data are used to estimate the probability of NSR and AF for RFCA and AADs applied in the short-term model. However, the generalisability of the RCT evidence to the NHS is an important issue. In many respects, treatment patterns in the centres involved in the trials may differ from those in the UK. Consequently, it is unclear whether the success rates of RFCA from the RCTs are likely to be representative of UK practice or not. One approach to dealing with this in decision models is to incorporate external evidence relevant to the

setting of interest. This is commonly carried out by using external evidence to estimate the event rates associated with one particular strategy, the external evidence itself acting as a 'baseline' representing UK practice. The relative treatment effect measure derived from the RCTs (e.g. odds ratio, relative risk – either unadjusted or adjusted for the revised baseline event rates) is then applied to the baseline data to estimate the absolute event rates for the other comparator(s). To consider this issue within the decision model, a range of alternative sources were considered as a potential basis for providing an alternative source of baseline data for RFCA to that reported in the RCTs.

The clinical effectiveness review identified one UK case series that met the inclusion criteria and which could potentially provide alternative data with which to estimate a baseline for RFCA. This study by Bourke and colleagues⁶⁶ was based on a relatively small number of patients ($n = 36$, paroxysmal AF; $n = 64$, persistent AF) and the outcome of freedom from AF was reported at 6 months' follow-up. Given the small patient numbers and the short follow-up period, this study was not considered to provide a suitable alternative to the RCT data. In the absence of a single study with which to populate a UK baseline event rate for RFCA, evidence from a wider range of case series and survey data were considered. The clinical effectiveness review identified a number of individual case series reporting the primary outcome at 12 months following RFCA. In addition, the review also identified a worldwide survey on the efficacy of RFCA, with data collected from 181 separate centres, including results at 12 months' follow-up.²⁵ As it was possible that data from the individual case series may have been incorporated into the worldwide survey, the survey and case series data were treated as separate sources and were not combined.

Meta-analytic approaches were used to synthesise the RCT evidence and the non-RCT data. Separate analyses were undertaken using the RCT data alone and also combining the RCT evidence with the non-RCT data. In this manner, the alternative scenarios could be evaluated within the decision model, allowing separate analyses of the RCT evidence with or without the external evidence. A random baseline fixed-effect model was used as the basis for the meta-analysis for each scenario, with the inputs varying according to whether the RCT evidence only, or a combination of the RCT and case series or survey data, was used. The random-effects baseline allows some exchangeability

between the absolute effect and the relative treatment effect. By specifying a distribution on the study baselines, an overall common distribution across studies can be estimated. Thus, the estimate for the baseline is effectively being pooled by the weighting of each study. In doing so it incorporates both the within-study variability and the between-study heterogeneity in the baseline event rates. The model therefore provides an explicit analytical framework that combines the weight of evidence from the RCTs and the external evidence. The model was conducted using Markov chain Monte Carlo simulations implemented in specialist software (WinBUGS¹⁵⁴). Full details of the statistical code are reported in Appendix 7.2. The simulated output (10,000 iterations) from WinBUGS was exported directly into Microsoft Excel to maintain correlation between the event rates estimated for the separate strategies.

The impacts of the different analyses on the cost-effectiveness estimates were explored as part of a wider set of alternative assumptions considered in the sensitivity analysis section (see Base-case analysis). Sensitivity analysis was undertaken to explore the robustness of the results based on the RCT evidence alone (employed in the base-case analysis) compared with the impact of using additional evidence from the case series and worldwide survey. Details of the alternative event rates applied in the different scenarios are reported in Appendix 7.5.

Side effects (AADs) and complications (RFCA)

All patients could experience some form of adverse effect related to the treatment received. For RFCA, patients were subject to procedural complications including operative death. The systematic review of the case series evidence outlined in Chapter 3 indicated that the major complications most frequently reported were stroke, cardiac tamponade and PV stenosis. Furthermore, the international survey by Cappato *et al.*,²⁵ covering procedures carried out over a 7-year period, revealed that the most significant complications included death (four out of 8745 procedures), cardiac tamponade (107 episodes out of 8745), stroke (20 out of 7154) and PV stenosis (53 requiring intervention out of 7154). The results of the Cappato survey, which were comparable with the case series evidence, were used for the baseline RFCA complication and mortality rates.

Patients receiving AADs were at a risk for drug toxicity. This toxicity may represent an acute event

that is reversible under management or it may result in permanent withdrawal from treatment. The baseline risk of a toxic event and the need for discontinuation of AAD therapy was informed by Owens *et al.*¹⁵⁵ Based on a review of 11 randomised trials of amiodarone therapy they estimated that 10% of patients would discontinue therapy during the first year as a result of intolerable side effects and that 5% would discontinue in each subsequent year. These risks were applied to the reversion rates back to AF, where it was assumed that transitions to this state resulted in withdrawal from treatment. Upon withdrawing, patients face an additional risk of a pulmonary complication. This risk was also informed by Owens *et al.*,¹⁵⁵ in which it was estimated that 15% of withdrawals would result in a pulmonary complication. Furthermore, this pulmonary toxicity would be irreversible in 25% of these patients, and 20% of this group would face a risk of dying from the toxicity.¹⁴⁶ The remainder of patients with permanent irreversible pulmonary toxicity had an additional cost and QoL decrement applied for each year of their life.

Long-term reversion rates (normal sinus rhythm to atrial fibrillation)

Central to the long-term model are the subsequent event rates (and costs and QoL estimates) for patients who leave the short-term model free of arrhythmia (NSR) or not (AF) at 12 months. Clearly any additional benefit assigned to the NSR state relative to the AF state will be maintained in the long term only if patients continue to remain free of arrhythmia. The long term reversion rates back to AF after 12 months represent important parameters in the model. In the absence of data from the RCTs of RFCA beyond 12 months' follow-up, these estimates were obtained from other sources. The annual rate of reversion for patients who receive RFCA was estimated from the large controlled study by Pappone *et al.*⁶¹ with a median follow-up of 900 days. Kaplan–Meier survival curves enabled estimates of the percentage of patients remaining free of AF recurrence over a period of 1080 days. After adjusting for censoring, 31 events out of 479 were observed over a follow-up of 720 days after the first year of treatment. This equates to a mean risk of AF recurrence of 3.35% per annum. A beta distribution was used to characterise the uncertainty in the mean estimate.

The annual reversion rate for patients receiving AADs was estimated from a multicentre trial¹⁵⁶ examining the long-term efficacy of amiodarone in preventing recurrent AF. Over a mean follow-up of 485 days, 35% of patients receiving amiodarone

experienced recurrence of AF. This rate was converted to an annual probability to give a 29% risk of recurrent AF in years 2 and above. Uncertainty in the mean estimate was characterised by a beta distribution.

Once patients in either strategy reverted back to the AF state it was assumed that subsequent transitions in the model would be identical for both groups. For the AAD strategy, patients were assumed to be withdrawn from AAD treatment at this point. For the RFCA strategy, the model did not allow for repeat ablation procedures after the first 12 months. Transitions back to the NSR state were not allowed in the model although it should be recognised that, because of the episodic nature of AF, subsequent risks (i.e. the risk of stroke in the AF state) are derived from sources in which patients are likely to have been in and out of episodes for periods of time. The use of concomitant medications, in particular the use of oral anticoagulants/antiplatelets, was assumed to be continued on reversion back to AF in both strategies.

Stroke

The baseline risk of stroke in AF was based on the CHADS₂ index.¹⁵⁷ The CHADS₂ stroke risk score combines the stroke risk classification schemes of the Stroke Prevention in Atrial Fibrillation (SPAF) trial investigators¹⁵⁸ and the AF investigators,¹⁵⁹ and has been validated in the National Registry of Atrial Fibrillation cohort. A numerical CHADS₂ score is given to each of five risk factors (recent congestive heart failure, hypertension, age, diabetes mellitus, history of stroke or transient ischaemic attack) and the total score (≤ 6) equates to a stroke risk for AF patients. A risk stratification algorithm proposed by NICE stratifies subjects into low-, moderate- and high-risk categories, and this scheme has been shown to be broadly similar to the CHADS₂ scoring system.¹⁶⁰

In addition to estimating the risk of stroke in AF, consideration was also given to whether this risk was different according to NSR/AF. No direct evidence was available in the RCTs to quantify the differential stroke risk for NSR based on a risk stratification scheme. A separate search of the literature was therefore undertaken to identify additional evidence related to the prognostic value of NSR in patients with AF. The search identified one study, based on the AFFIRM study, that examined the occurrence and characteristics of stroke events in the investigation of sinus rhythm management and provided an estimate of the

hazard of stroke for AF relative to NSR. Using a Cox proportional hazards regression analysis, the presence of AF was found to be significantly associated with a 60% increase in the risk of stroke after adjusting for several covariates including the use of warfarin therapy. The reciprocal of the hazard ratio of 1.60 for AF provided an estimate of the stroke risk reduction for NSR. Thus, the stroke risk for NSR was lower than the risk for AF but remained higher than the general population.

To reduce thromboembolism in AF, most patients, regardless of treatment strategy, receive some form of anticoagulants or antiplatelets. The Euro Heart Survey on Atrial Fibrillation¹⁶¹ analysed current antithrombotic drug prescriptions. These data were used to estimate the proportion of patients likely to receive warfarin, aspirin or no anticoagulants in the UK. The corresponding stroke risk reduction for NSR and AF with the use of anticoagulants was derived from a systematic review and meta-analysis of stroke prevention with warfarin and aspirin in patients with AF.¹⁶⁰ This study found that warfarin significantly reduced the risk of stroke compared with aspirin [RR 0.59 (95% CI 0.40–0.86)] or placebo [RR 0.33 (95% CI 0.24–0.45)]. These adjustments for the use of anticoagulants were applied to the stroke risk for NSR and AF derived from the CHADS₂ index.

Mortality from stroke

The mortality risk from stroke was assumed to be higher in the first year of the event than in subsequent years. Therefore, once patients survive the first year of a stroke they enter a post-stroke state in which the risk of death is lower. The mortality rates were derived from a UK-based community stroke project,¹⁶² which examined the long-term prognosis after acute stroke. In the first year the relative risk of dying compared with the general population was 7.4 (95% CI 6.5–8.5). In subsequent years this relative risk was reduced to 2.3 (95% CI 2.0–2.7). To incorporate uncertainty in the estimates of the relative risk, a log-normal distribution was used.

Other-cause mortality

The model separates deaths into those caused by stroke, drug toxicity and other-cause mortality. The baseline risks for stroke and toxicity were informed by the observational cohort study and toxicity data respectively. The age-dependent risk of other-cause mortality was based on standard UK age- and sex-specific mortality rates.¹⁶³ These were adjusted to exclude those deaths recorded with an ICD (International Classification of Diseases)

code pertaining to stroke. The treatments were assumed not to infer a differential mortality effect, except through their reduction in the risk of stroke through NSR or AF. A sensitivity analysis was used to explore an additional mortality risk in patients with AF compared with the general population.

Resource use and unit costs

Resource utilisation and cost data were based on the short-term and long-term events associated with each strategy. The main short-term costs associated with RFCA relate to the procedure cost itself, the need for repeat procedures and the management of any complications. For AADs, the short-term costs comprise the drug acquisition and administration costs of amiodarone including the management of side effects. In the longer term there are the ongoing costs associated with the use of amiodarone and, in addition to the ongoing management costs of all patients (other medications, routine consultations, attendance at anticoagulant clinics), there are also the longer-term costs associated with the Markov states themselves. The costs were derived from a variety of sources for differing years and so all costs were updated to a common year of 2006.

The procedure costs for RFCA have been the subject of considerable debate. Under the current payment by results (PbR) system trusts receive payment according to a national schedule of fees. Particular procedures and interventions are categorised into particular groups (Health Resource Groups – HRGs) according to similar resource implications. Under the current HRG classification (HRG v3.5), all ablation procedures are classified within a single code and hence receive the same level of reimbursement (E38 – £2511 at 2005 prices). Consequently, simple and more complex procedures are not differentiated within the current system. Concern has been expressed that current HRG costs are likely to significantly underestimate the costs of the more complex ablation procedures undertaken in patients with AF. This concern appears to have been acknowledged within the recent update to the HRG system (HRG 4), which lists four separate HRGs for ablation procedures, with separate codes for complex procedures and for those involving catheterisation or percutaneous coronary intervention; however, the reimbursement fee for each of these separate codes has not yet been finalised:

- Root HRG (EA27), final HRG (EA27Z): cardiac procedures – standard electrophysiology (EP) or ablation

- EA28, EA28Z: cardiac procedures – standard EP or ablation with catheterisation or percutaneous coronary intervention
- EA29, EA29Z: cardiac procedures – complex ablation (includes atrial fibrillation or ventricular tachycardia)
- EA30, EA30Z: cardiac procedures – complex ablation (includes atrial fibrillation or ventricular tachycardia) with catheterisation or percutaneous coronary intervention.

In the absence of suitable reference cost estimates for the NHS, the costs of catheter ablation were based on estimates provided by Dr Adam Fitzpatrick (Consultant Cardiologist, Manchester Heart Centre, 2007, personal communication). The total cost of RFCA consisted of three main components, consumables and laboratory and ward costs, and was estimated to be £7848 per procedure, significantly higher than current tariffs. Allowing for overheads and assuming that some patients may receive a repeat or ‘top-up’ procedure (assuming a mean number of procedures of 1.30²⁵), this resulted in an overall mean cost of RFCA applied in the short-term model of approximately £11,538.

In addition to the procedural costs, the costs of procedural-related complications were also considered, namely cardiac tamponade and PV stenosis. Estimates for these were derived from the reference costs schedules.¹⁶⁴ The cost of complications relating to stroke was assumed to be included in the annual cost associated with the first year of stroke applied in the Markov process (see below).

Amiodarone was assumed to be initiated in an outpatient setting for all patients. The dosage of amiodarone was assumed to be 200 mg taken daily, which resulted in an annual cost of £32 incurred for each year that the patient continues to receive the drug. All patients, regardless of the strategy, were assumed to receive anticoagulants and/or aspirin. A 5-mg daily dose of warfarin costs £19 per annum, and a 75-mg daily dose of aspirin costs £20. Additional costs were also applied for the use of amiodarone and anticoagulants in relation to the management of adverse events such as toxicity and bleeding. The total cost of managing a toxic event with amiodarone was estimated to be £1497.¹⁶⁵ In addition, a specific cost associated with pulmonary complications was applied. A daily cost of £0.43, based on 50 mg of a high-dose corticosteroid, was applied for the duration of the toxicity (short term for reversible and lifetime for irreversible). All

drug costs were obtained from the *British National Formulary*.¹⁶⁶ The cost of a major and minor bleed was £1573 and £87 respectively.¹⁶⁷

In addition to the intervention costs and other related costs (including other forms of medical management), the annual costs of the main health states in the Markov model were also estimated based on published literature. The annual costs associated with the two underlying AF health states, namely NSR and AF, were estimated from a recent study examining the cost of AF in the UK.¹⁷ The study estimates the costs of community and hospital-based care related to AF, including general practitioner consultations, anticoagulation visits and hospital costs. An annual amount of £646 was estimated for these costs. Additional costs of hospital admissions when stroke was listed as the principal diagnosis were excluded to avoid double counting this particular component. In the absence of cost data that discriminated between the NSR and AF states, we applied a conservative assumption towards RFCA by applying the same annual costs to both of these states for the remaining lifetime of the patients. The impact of applying differential costs was explored using sensitivity analysis. In the sensitivity analysis a lower cost was applied to the NSR state (£331) by excluding the costs of hospital admission related to a principal diagnosis of AF. That is, we assumed that patients would only be hospitalised in the AF state itself. The annual cost associated with stroke was derived from a separate source.¹⁶⁸ A higher cost was applied for the first year of the event to reflect the additional management costs and resources used when the event first occurs. The cost of stroke in year 1 was estimated as £9431 (standard error £315) and the yearly cost of patients who survive 1 year event free was estimated as £2488 (standard error £303). The uncertainty in the cost of stroke was reflected by assigning a gamma distribution to the annual costs.

Quality of life

To estimate QALYs it is necessary to quality adjust the period of time that the average patient is alive within the model using an appropriate utility or preference score. Ideally, utility data are required that quantify the potential health status of patients with AF and which can also be used to quantify the impact of the different treatment regimens (RFCA and AADs) in terms of QoL, i.e. adverse events and/or palliative benefits. In the absence of suitable utility values identified in the clinical and cost-effectiveness reviews, we conducted a separate review of other potential sources that could be

used to inform this part of the economic analysis. Full details of the search strategy are reported in Appendix 1. The review of this evidence is reported in detail in Appendix 7.4 and is summarised below.

The review focused on three specific aspects related to QoL associated with AF:

1. Studies evaluating the QoL of patients with AF (regardless of the intervention).
2. Studies evaluating the impact of RFCA on the QoL of patients with AF.
3. Studies evaluating the impact of NSR on the QoL of patients with AF.

The review focused on studies reporting utility data in relation to these aspects. However, given the lack of published utility data in relation to the second and third areas, consideration was also given to studies reporting other generic measures of health that could potentially be converted into a utility score for the model. The review focused on studies reporting results using the SF-36 instrument.¹⁶⁹ An algorithm was applied to map between studies reporting summary scores using the SF-36 instrument and a utility instrument (the EuroQol EQ-5D).¹⁷⁰ This algorithm provided an approach to estimating utility values associated with changes in the domains of SF-36 reported following RFCA or AADs. These were used to estimate incremental changes in utility over a 12-month period for the main states of the model (i.e. for patients free of arrhythmia following RFCA or AADs and for patients experiencing a recurrent episode).

The main review of studies reporting the QoL of patients with AF (regardless of the intervention) was used to identify relevant sources of baseline utility estimates to apply these utility changes. However, despite the large number of studies that were considered, no single source was identified that could provide a suitable reference value to which to apply the utility changes. Typically, previous studies had assigned a value of 1 (i.e. equivalent to full health) to patients with AF and then applied particular decrements reflecting specific events (e.g. side effects, bleeding events, etc.). However, assuming a value of 1 does not reflect the fact that the overall health of the general population (i.e. those without AF) will be lower than this and also that the underlying health status of the general population naturally deteriorates over time. To encapsulate this in the model, the underlying utility of the general population, derived from a nationally representative UK sample using EQ-5D, was used as a reference

point.¹⁷¹ We assumed that patients restored to NSR following catheter ablation (estimated to be associated with the largest improvement in utility) would revert back to having the same QoL as the general population. For the other main health states specific decrements were then estimated (i.e. AF following RFCA and NSR/AF following AADs) relative to the utility value estimated for patients restored to NSR following catheter ablation. These decrements were then applied to the general population utility values assumed to represent the QoL in the NSR state for RFCA.

In addition to estimating utility values for the NSR and AF states in the model, utility values were also estimated for the other states or events in the model. Utility values for stroke were based on previous work undertaken in this area.¹⁶⁸ In addition, utility decrements were also estimated for irreversible pulmonary toxicity (ascribing a decrement reported for chronic bronchitis¹⁷²). Finally, a utility decrement was also applied for other general side effects and for major and minor bleeding events. No relevant utility estimates were found for these events and hence we assumed that each event would incur loss equivalent to a full day of health for the duration of these events (mean 1 day, range 0–30 days).¹⁵⁵

Base-case analysis

The model results are presented according to a particular set of assumptions employed as part of the base-case analysis. The impact of employing alternative assumptions to those proposed in the base-case analysis is then explored using sensitivity analysis. The base-case assumes an average starting age in the model of 52 years and that 80% of subjects are male.⁶⁶ Heterogeneity in patients is explored by undertaking separate analyses according to different baseline risks of stroke (according to the CHADS₂ score). CHADS₂ scores between 0 and 3 are considered in the base-case analysis.

Within the base-case approach, separate analyses have been undertaken assuming that QoL improvements with RFCA compared with AADs are either (1) maintained for a lifetime (lifetime analysis) or (2) are maintained for a maximum of 5 years (5-year analysis). Both the lifetime and 5-year analyses model cost-effectiveness over a patient's lifetime (a maximum of 60 annual cycles are modelled), but the approaches differ in the duration for which the QoL benefits for RFCA are maintained. The results for each of the different

scenarios considered in the sensitivity analysis are presented for both the lifetime and 5-year analyses. A 5-year horizon was chosen in consultation with our clinical advisors based on the lack of long-term evidence for QoL following RFCA.

The base-case analysis derives estimates of the primary outcome (freedom from arrhythmia at 12 months) from the RCT evidence alone. Hence, estimates of the absolute event rate with RFCA and the relative effect compared with AADs are informed entirely from the trial evidence. The impact of incorporating additional observational evidence for RFCA from the Cappato *et al.* survey²⁵ and the individual case series is investigated in the sensitivity analysis.

Sensitivity analysis

The sensitivity analysis is undertaken to assess the robustness of the base-case model results to variation in (1) the sources of data used to populate the model and (2) alternative assumptions related to key parameters in the model. A number of alternative scenarios are considered as part of the sensitivity analysis (*Table 26*). For each element the position in the base-case analysis is outlined alongside the alternative assumption applied. Each of the different scenarios explored as part of the sensitivity analysis is then undertaken assuming a CHADS₂ score of 1, considered to provide the most representative risk for this patient group.

Cost-effectiveness results

The results of the model are presented in two ways. First, the mean lifetime costs and QALYs of the two strategies are presented and their cost-effectiveness compared, estimating ICERs where appropriate.¹⁷³ The ICER compares the additional costs that one strategy incurs over another with the additional benefits and represents the additional cost required to achieve one additional unit of outcome (QALY). To provide a reference point, NICE uses a threshold cost per QALY of around £20,000–30,000 to determine whether an intervention represents good value for money in the NHS.¹⁵⁰ Consequently, if the ICER for RFCA is less than £20,000 then RFCA should be considered potentially cost-effective. ICERs within the range itself (i.e. between £20,000 and £30,000) are considered borderline and an ICER above £30,000 is not typically considered cost-effective.

Second, the results of the probabilistic analysis using Monte Carlo simulation are then used to calculate the combined impact of the model's

various uncertainties on the overall uncertainty surrounding the cost-effectiveness results themselves. To present the uncertainty in the cost-effectiveness of the alternative strategies, cost-effectiveness acceptability curves (CEACs) are used.¹⁷⁴ The CEAC shows the probability that RFCA is cost-effective using alternative values for the threshold cost per QALY (tabulated results are presented for each analysis for select values of the threshold between £10,000 and £40,000).

Results of the base-case analysis

Table 27 reports the base-case results according to the baseline risk of stroke, modelled using different CHADS₂ scores. The results of the lifetime analysis show that the ICER for RFCA is well below the conventional thresholds used to determine whether a particular treatment is considered cost-effective. As expected, the mean costs (QALYs) for each strategy increase (decrease) as the baseline risk of stroke increases according to the CHADS₂ score. However, there appears to be little variation across the different CHADS₂ scores in terms of the ICER itself (ranging from £7763 to £7910 per additional QALY). At a threshold of £20,000 per QALY there is very little uncertainty surrounding the cost-effectiveness results. The probability that RFCA is cost-effective at this threshold varies from 0.981 to 0.992 across the separate risk groups.

As the threshold cost per QALY increases, the probability that RFCA is cost-effective also increases. The relationship between the threshold ICER and the probability that RFCA is cost-effective is shown more clearly in the CEAC in *Figure 12*, based on a CHADS₂ score of 1. The figure demonstrates how the probability that RFCA is cost-effective increases markedly as the threshold ICER increases (reaching close to 1 around a threshold of £20,000).

The results of the 5-year analysis of the base-case model are reported in *Table 28*. These results show that the ICER for RFCA is within the range of conventional thresholds used to identify whether a particular treatment is considered to be cost-effective in the NHS. As such, the cost-effectiveness of RFCA appears to be more finely balanced. In comparison to the lifetime analysis, there appears to be more variation in the ICER across the different CHADS₂ scores. The cost-effectiveness of RFCA appears more favourable the higher the CHADS₂ risk of stroke, with an associated ICER of £27,745 and £20,831 per additional QALY in patients with a CHADS₂ score of 0 and 3 respectively.

TABLE 26 Details of the key elements of the base-case analysis and how these are varied in the sensitivity analysis

Scenario	Element	Position in base-case analysis	Variation in sensitivity analysis
1	Source of data used to estimate baseline event rates (catheter ablation) and relative effects	Evidence from RCTs only	Evidence synthesis combining RCTs with observational evidence on RFCA from Cappato et al. 2005 ²⁵ Evidence synthesis combining RCTs with observational evidence on RFCA from individual case series
2	Duration of QoL benefit with catheter ablation	Lifetime and 5 years	10, 15 and 20 years
3	Additional mortality risk for AF compared with general population	Elevated mortality because of increased risk of stroke only. Risk of non-stroke mortality assumed to be equivalent to that in the general population	Risk of non-stroke mortality increased to between 1.5 and 2.5 times that in the general population
4	Prognostic impact of NSR	Restoration of NSR reduces the risk of stroke compared with patients with AF	Prognosis for patients with NSR and AF assumed to be equivalent. QALY gains realised only through improved symptoms
5	QoL (utilities)	Separate utilities assigned to NSR and AF states for patients receiving catheter ablation and AADs. QoL for patients in both NSR and AF states following catheter ablation assumed to be higher than in patients in both states following AADs [i.e. QoL of NSR(RFCA) > AF(RFCA) > NSR(AADs) > AF(AADs)]	QoL of AF and NSR states for RFCA and AADs, respectively, assumed to be equivalent [i.e. QoL of NSR(RFCA) > AF(RFCA) = NSR(AADs) > AF(AADs)] QoL of NSR states following RFCA and AADs assumed to be higher than that of AF states following RFCA and AADs [i.e. QoL NSR(RFCA) > NSR(AADs) > AF(RFCA) > AF(AADs)] Separate QoL assigned to NSR and AF states but assumed to be the same for RFCA and AADs [i.e. QoL NSR(RFCA) = NSR(AADs) > AF(RFCA) = AF(AADs)]
6	Population	Male 80%, female 20%; average age 52 years	Separate analysis for males and females
7	Discount rate	3.5% applied to both costs and outcomes	Alternative starting ages assumed from 50 to 65
8	Initiation costs of amiodarone	Assumed to be initiated in an outpatient setting	6% applied to costs, 1.5% to outcomes
9	Costs of NSR and AF states	Assumed to be identical (£646)	57.5% assumed to be administered in an outpatient setting, 42.5% in an inpatient setting
10	Transition probabilities – reversion back to AF for patients receiving RFCA	Approximately 3% per annum	Lower cost applied to NSR state (£331) Increased to 5–15% per annum
11	Costs of catheter ablation	Consumables costed at £5687 per procedure	Lower and higher costs assumed (from £500 to £1000)

NSR, normal sinus rhythm; QoL, quality of life; RCT, randomised controlled trial.

TABLE 27 Base-case estimates of mean lifetime costs and quality-adjusted life-years according to baseline risk of stroke (lifetime analysis)

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
CHADS₂ = 0							
RFCA	£25,240	12.37	£7763	0.700	0.983	0.996	0.999
AADs	£14,415	10.98		0.300	0.017	0.004	0.001
CHADS₂ = 1							
RFCA	£26,027	12.14	£7780	0.717	0.981	0.996	0.998
AADs	£15,367	10.77		0.283	0.019	0.004	0.002
CHADS₂ = 2							
RFCA	£26,987	11.87	£7765	0.728	0.986	0.999	1.000
AADs	£16,517	10.52		0.272	0.014	0.001	0.000
CHADS₂ = 3							
RFCA	£28,343	11.49	£7910	0.706	0.992	1.000	1.000
AADs	£18,107	10.19		0.294	0.008	0.000	0.000

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, willingness to pay.

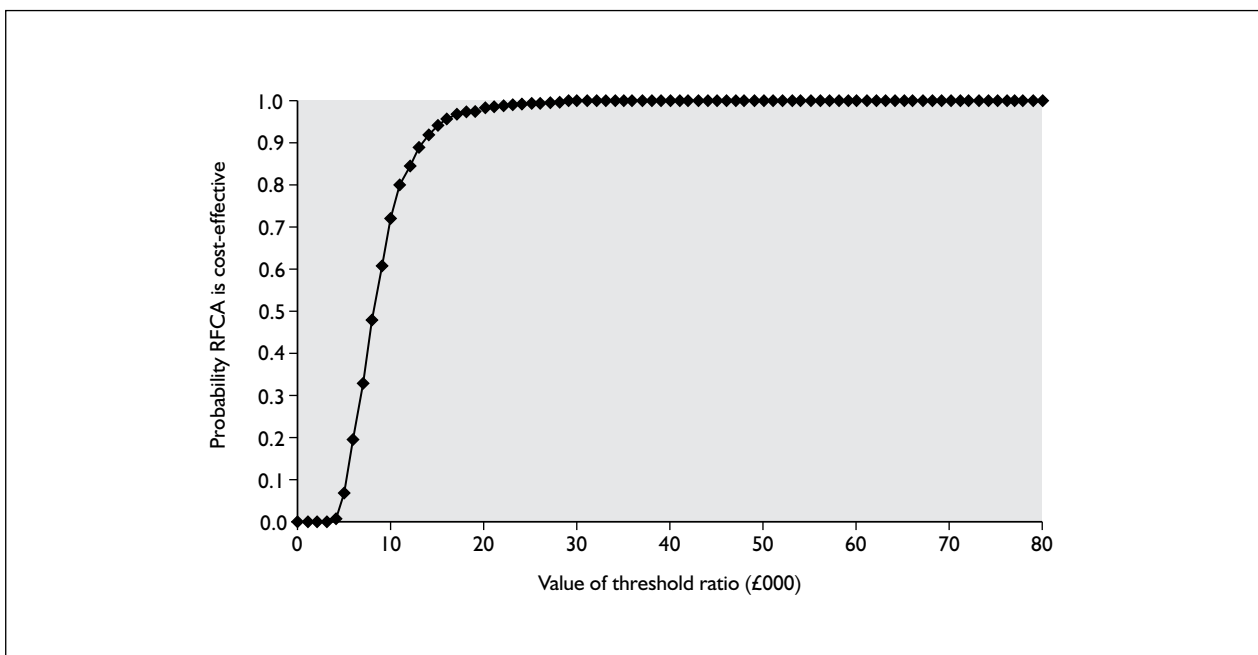


FIGURE 12 Cost-effectiveness acceptability curve for a CHADS₂ score of 1, lifetime analysis.

TABLE 28 Base-case estimates of mean lifetime costs and quality-adjusted life-years according to baseline risk of stroke (5-year analysis)

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
CHADS₂ = 0							
RFCA	£25,251	11.35	£27,745	0.000	0.091	0.577	0.854
AADs	£14,429	10.96		1.000	0.909	0.423	0.146
CHADS₂ = 1							
RFCA	£26,016	11.18	£25,510	0.000	0.165	0.686	0.902
AADs	£15,352	10.76		1.000	0.835	0.314	0.098
CHADS₂ = 2							
RFCA	£26,972	10.97	£23,202	0.000	0.265	0.786	0.942
AADs	£16,499	10.52		1.000	0.735	0.214	0.058
CHADS₂ = 3							
RFCA	£28,366	10.67	£20,831	0.000	0.418	0.881	0.968
AADs	£18,133	10.18		1.000	0.582	0.119	0.032

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, willingness to pay.

The more marked variation in the ICER (and the consistent direction of these changes) across the risk subgroups is not unexpected in the 5-year analysis. In this scenario the ICER after 5 years in the model is affected only by the prognostic impact of NSR on reducing the risk of stroke. Hence, as the absolute risk of stroke increases, the incremental benefit potentially associated with reducing the risk of stroke through NSR becomes greater (assuming the same relative risk reduction associated with NSR holds across the different risk groups). Consequently, the ICER becomes more favourable as the baseline risk of stroke increases.

The relationship between the ICER and the risk subgroups is less obvious in the lifetime analysis as there are competing factors at play, each working in opposite directions. Although the impact of NSR on reducing the risk of stroke applies equally to both the 5-year and lifetime analyses (and will improve the ICER for higher risk groups), these additional gains attributed to the higher risk groups are partially or wholly offset by the higher overall life expectancy achieved in the lower risk groups. As patients in the lifetime analysis are assumed to benefit from the QoL improvements associated with RFCA for a lifetime, this will improve the cost-effectiveness in the risk groups with the lowest mortality risk. Given that the mean

life expectancy across all subgroups is markedly higher than 5 years, differences in the ICER attributed to QoL improvements through a higher overall life expectancy offset the lower incremental gains achieved through the reduction in the risk of stroke.

Each risk subgroup in the 5-year analysis has a mean ICER of more than £20,000. Hence, at a threshold ICER of £20,000 per QALY there is clearly a much lower probability that RFCA is cost-effective in the 5-year analysis than in the lifetime analysis (between 0.09 and 0.4, i.e. equivalent to a percentage probability of between 9% and 40%). As the threshold ICER increases, the probability that RFCA is considered cost-effective rises accordingly. At a threshold ICER of £30,000 (or £40,000) per QALY, the probability that RFCA is cost-effective varies from 0.58 to 0.89 (or from 0.85 to 0.97). The relationship between the threshold ICER and the probability that RFCA is cost-effective is shown in more detail in *Figure 13*. The figure shows a much greater uncertainty surrounding the cost-effectiveness of RFCA in the 5-year analysis than in the lifetime analysis. However, as the threshold increases, the probability that RFCA is cost-effective still approaches 1 (although at a much higher value of the ICER than previously illustrated for the lifetime analysis).

The cost-effectiveness results for RFCA appear to be highly sensitive to the duration assigned to the QoL benefits that are assumed to be achieved with RFCA. Although the lifetime analysis suggests that RFCA is likely to be considered highly cost-effective based on conventional thresholds used to establish value for money by the NHS, the results from the 5-year analysis are less clear-cut. The ICERs presented for each of the subgroups still fall within the range of acceptable thresholds; however, it should also be recognised that other factors (aside from the ICER itself) may be considered in cases of interventions with a cost-effectiveness ratio above the lower bound of the threshold itself. Although by no means comprehensive, these factors may include the strength of evidence (i.e. the uncertainty surrounding the point estimates themselves), the size of the affected population, equity considerations, and whether a suitable comparator exists.¹⁷⁵

Results of the sensitivity analysis

Given the paucity of long-term evidence on the maintenance of the QoL benefits with RFCA, each of the scenarios explored as part of the sensitivity analysis is reported using both the lifetime and the 5-year analyses. Given the number of potential scenarios considered, the sensitivity analyses have only been undertaken on the subgroup of patients with a baseline risk of stroke equivalent to a

CHADS₂ score of 1. This group has been chosen to be the most representative of the stroke risk faced by patients with AF. For this subgroup, the ICERs of £7780 per additional QALY (lifetime analysis) and £25,510 per additional QALY (5-year analysis) provide the benchmarks for assessing whether the cost-effectiveness results appear robust to particular assumptions made in the base-case analysis.

Table 29 details the results of each of the alternative scenarios considered within the sensitivity analysis. This table reports the ICER and the probability that RFCA is cost-effective at a threshold ICER of £30,000 per additional QALY. More detailed tables summarising the mean costs, QALYs and the probability that RFCA is cost-effective at alternative threshold ICERs for each of the separate scenarios are given in Appendix 7.5.

The sensitivity analysis on the sources of evidence used to estimate both the *absolute* success rate of RFCA (freedom from arrhythmia at 12 months) and the *relative* treatment effect compared with AADs appears to have little effect on the cost-effectiveness of RFCA. Combining the trial evidence with the observational evidence for RFCA from the Cappato *et al.* study²⁵ or the individual case series data resulted in a marginal increase in the ICER; however, the results of both the lifetime

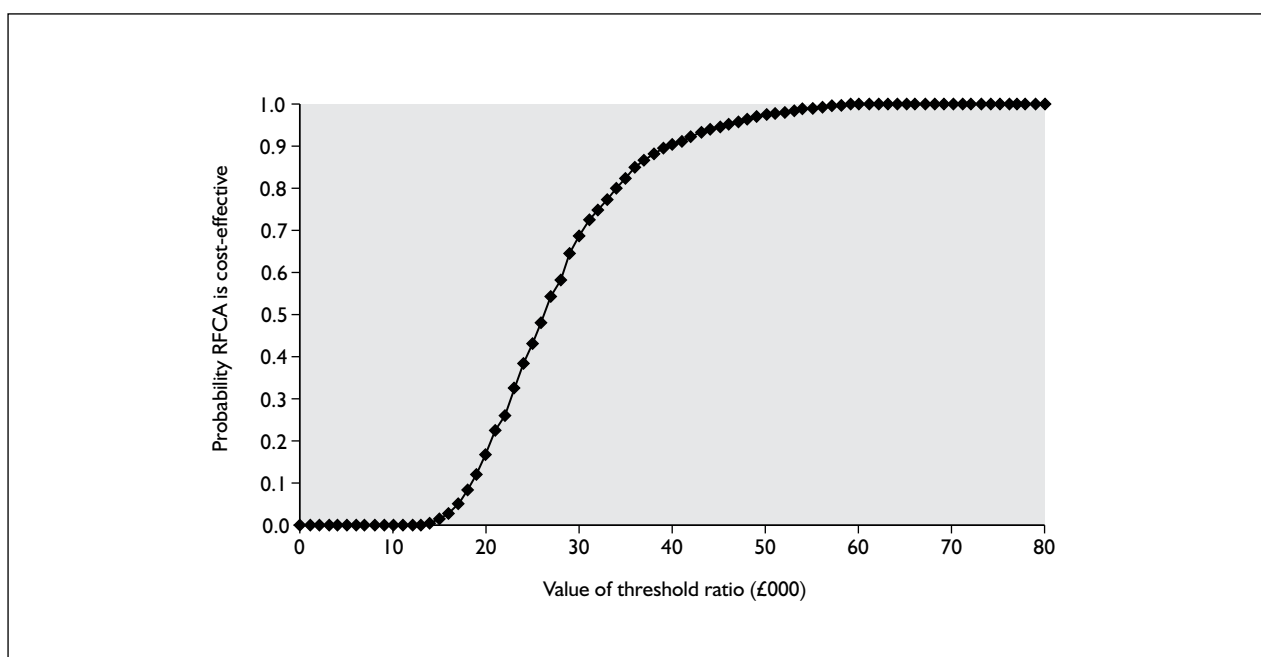


FIGURE 13 Cost-effectiveness acceptability curve for a CHADS₂ score of 1, 5-year analysis.

TABLE 29 Summary of sensitivity analysis results

Scenario	Element	Variation in sensitivity analysis	Lifetime analysis		5-Year analysis	
			ICER	Probability cost-effective at £30,000	ICER	Probability cost-effective at £30,000
1	Base-case Source of data used to estimate baseline event rates (catheter ablation) and relative effects	NA	£7780	0.996	£25,510	0.686
		(a) Evidence synthesis combining RCTs with observational evidence on RFCA from Cappato et al. ²⁵	£7814	1	£25,623	0.701
2	Duration of QoL benefit with catheter ablation	(b) Evidence synthesis combining RCTs with observational evidence on RFCA from individual case series	£7851	0.999	£25,573	0.634
		(a) 10 years	£14,771	0.973	NA	NA
		(b) 15 years	£11,237	0.993		
3	Additional mortality risk for AF compared with the general population	(c) 20 years	£9,492	0.997		
		Risk of non-stroke mortality increased to between 1.5 and 2.5 times that in the general population				
		(a) 1.5	£8577	0.999	£27,362	0.607
4	Prognostic impact of NSR	(b) 2	£9415	0.992	£28,794	0.501
		(c) 2.5	£9990	0.992	£29,908	0.435
		Prognosis for patients with NSR and AF assumed to be equivalent. QALY gains only realised through improved symptoms	£9327	0.996	£37,997	0.204
5	QoL (utilities)	(a) QoL of AF and NSR states for RFCA and AADs, respectively, assumed to be equivalent [i.e. QoL of NSR(RFCA) > AF(RFCA) = NSR(AADs) > AF(AADs)]	£7872	0.999	£26,298	0.659
		(b) QoL of NSR states following RFCA and AADs assumed to be higher than that of AF states following RFCA and AADs [i.e. QoL NSR(RFCA) > NSR(AADs) > AF(RFCA) > AF(AADs)]	£8463	0.991	£27,216	0.599
		(c) Separate QoL assigned to NSR and AF states but assumed to be the same for RFCA and AADs [i.e. QoL NSR(RFCA) = NSR(AADs) > AF(RFCA) = AF(AADs)]	£12,840	0.963	£32,524	0.399

Scenario	Element	Variation in sensitivity analysis	Lifetime analysis		5-Year analysis	
			ICER	Probability cost-effective at £30,000	ICER	Probability cost-effective at £30,000
6	Population	Separate analysis for males and females				
	(a) Males (100%)		£7921	0.997	£25,527	0.690
	(b) Females (100%)		£7322	0.999	£25,450	0.685
	Alternative starting ages from 50 to 65 years					
	(c) 50 years		£7549	1	£25,152	0.720
	(d) 55 years		£8300	0.997	£26,234	0.627
	(e) 60 years		£9443	0.994	£27,531	0.569
	(f) 65 years		£11,223	0.990	£29,394	0.492
7	Discount rate	6% costs, 1.5% outcomes	£5984	1	£21,452	0.858
8	Initiation costs of amiodarone	57.5% assumed to be administered in an outpatient setting, 42.5% in an inpatient setting	£6822	1	£22,155	0.853
9	Costs of NSR and AF states	Lower cost applied to NSR state (£331)	£5978	0.998	£19,673	0.899
10	Transition probabilities – reversion back to AF for patients receiving RFCA	Increased to 5–15% per annum				
	(a) 5%		£7999	0.999	£26,969	0.618
	(b) 10%		£8401	0.970	£29,910	0.441
	(c) 15%		£8703	0.944	£32,035	0.374
11	Costs of catheter ablation	Lower and higher costs assumed (from £500 to £1000)				
	(a) Reduced by £500		£7213	1	£23,638	0.773
	(b) Increased by £500		£8347	0.998	£27,377	0.610
	(c) Increased by £1000		£8894	0.997	£29,283	0.517

ICER, incremental cost-effectiveness ratio; NA, not applicable; NSR, normal sinus rhythm; QALY, quality-adjusted life-year; RCT, randomised controlled trial.

and 5-year analyses appeared remarkably robust to the evidence used for these parameters.

In the base-case analysis results were presented for two alternative scenarios related to the maintenance of QoL benefits associated with RFCA: (1) an assumption that the QoL improvements would be maintained for a lifetime (although the QoL of patients who received RFCA was still allowed to alter as patients progressed over time to the AF state) and (2) an assumption that the QoL benefits relative to AAD therapy would be realised for a maximum of 5 years only. Given the marked difference between these results, additional scenarios were explored between these two assumptions by varying the duration from 10 to 20 years that the QoL advantage conferred by RFCA would be achieved. The ICER for RFCA ranged from £9492 to £14,771, well under conventional threshold values considered to be cost-effective. Indeed, at a threshold of £30,000 per QALY, the probability that RFCA appears cost-effective exceeded 0.973 across these alternative time horizons.

In the base-case analysis we assumed that patients faced an elevated risk of mortality compared with the general population through a higher risk of stroke (modelled via the particular CHADS₂ risk score). Although the specific additional mortality risks associated with the interventions themselves were considered (i.e. the operative mortality rate associated with RFCA and the potentially fatal toxicities associated with AADs), the remaining risk of mortality was assumed to be the same as for the general population. However, if this patient group also faces an elevated risk of other causes of mortality (i.e. non-stroke) compared with the general population, the base-case analysis may overestimate overall life expectancy. This could introduce a possible source of bias in favour of RFCA as the base-case analysis may overestimate the number of years that patients could achieve the QoL improvements associated with RFCA. A sensitivity analysis was therefore undertaken by adjusting the all-cause mortality rate compared with the general population (adjusted for the risk of stroke mortality using cause-elimination approaches to UK life tables). A range of risks was considered between 1.5 and 2.5 times higher than the risk for the general population.^{176,177} As anticipated, the application of a higher mortality rate resulted in an increase in the ICER for RFCA compared with the base-case analysis. However, even assuming that the risk of all-cause mortality (excluding stroke) was 2.5 times that in the general

population did not result in either the lifetime or 5-year analyses exceeding the upper bound of the £20,000–30,000 threshold. It should also be noted that this particular sensitivity analysis did not allow for the potential prognostic value of NSR in reducing the risks associated with non-stroke mortality. Although the prognostic value of NSR remains highly uncertain, if achieving NSR could reduce the risk of other events (and in doing so reduce the risk of other causes of mortality), the results presented here could be considered highly conservative towards RFCA. Indeed, these benefits (if real) could potentially more than offset the potential bias that could have been introduced by overestimating life expectancy and hence could result in lower ICERs than considered in any of the scenarios considered here.

Clearly the prognostic value of NSR itself in reducing the risk of stroke (or any other event) remains a highly contentious issue. Much of the evidence appears contradictory and to date there exists no firm evidence on which to base this assumption. Indeed, the approach applied in the base-case analysis is based on a number of indirect links between separate sources:

1. The probability of stroke for patients with AF is based on CHADS₂ scores.
2. This probability is then adjusted by (a) accounting for the proportion of patients receiving different anticoagulant strategies (based on the recent Euro Heart Survey on Atrial Fibrillation reporting patients receiving aspirin, warfarin, both or neither) and (b) adjusting the CHADS₂ scores based on the treatment effect of the different anticoagulant strategies (relative risks obtained from a recent meta-analysis). This allows the risk of stroke to be recalculated based on current anticoagulant use.
3. Regression results from the AFFIRM study, which reports on the impact of NSR versus AF on stroke, are used to estimate the relative risk reduction (RR approximately 0.6) associated with NSR.
4. The impact of stroke on mortality compared with that in the general population is estimated using data from the Oxfordshire Community Stroke Project. The costs and QoL impact of non-fatal strokes are also considered.

To examine the robustness of the results to the prognostic value of NSR we undertook a sensitivity analysis which assumed that the risks of stroke from the NSR and AF states were the same. That is,

we assumed that the risks of stroke were identical for both treatments and therefore the subsequent cost-effectiveness results are based entirely on the symptomatic benefit of RFCA compared with AAD, realised through improvements in QoL. This assumption had a greater impact on the cost-effectiveness results for the 5-year analysis than on the results for the lifetime analysis. In the lifetime analysis the ICER increased to £9237 per additional QALY (compared with £7780 in the base-case analysis), still well under the current threshold for cost-effectiveness. However, the ICER for the 5-year analysis increased to £37,997 per QALY, clearly above current thresholds of cost-effectiveness. Indeed, at the maximum threshold considered to be cost-effective (£30,000 per additional QALY) the probability that RFCA is cost-effective was only 0.204 (compared with 0.686 in the base-case 5-year analysis). As such, the overall conclusions regarding the cost-effectiveness of RFCA appear to require that the QoL benefits are maintained for more than 5 years and/or that NSR has prognostic value in preventing the risk of stroke. If neither of these is considered to be realistic then the cost-effectiveness of RFCA remains highly uncertain.

The base-case analysis applied separate utility estimates to patients in the NSR and AF health states according to whether patients received RFCA or AADs. Separate assumptions were then applied according to the duration that these benefits were maintained (5 years or a lifetime). The utility values applied assumed that the QoL following catheter ablation would be higher for patients in both the NSR and AF states than in the same states following AADs [i.e. QoL for NSR(RFCA) > AF(RFCA) > NSR(AADs) > AF(AADs)]. However, it should be recognised that the utility values assigned to the NSR and AF states for RFCA and AADs were derived from separate studies. Hence, the different utility values may not be directly comparable and the differences may not simply be due to the impact of the different health states following successful treatment (or not) with RFCA or AADs but may also be due to other characteristics of the patients within the separate studies that cannot be adequately controlled for in our analysis. Although the approach of using incremental, as opposed to the absolute, values for estimating the utility values of the different states is likely to minimise the impact of combining estimates from separate studies, sensitivity analyses were undertaken to explore this issue in more detail.

Three alternative scenarios were considered to examine the robustness of the base-case estimates for QoL. These scenarios explored the impact of the following assumptions:

1. QoL of AF and NSR states for RFCA and AADs, respectively, assumed to be equivalent [i.e. QoL of NSR(RFCA) > AF(RFCA) = NSR(AADs) > AF(AADs)]
2. QoL of NSR state for AADs assumed to be higher than that of AF state for RFCA [i.e. QoL NSR(RFCA) > NSR(AADs) > AF(RFCA) > AF(AADs)].
3. Separate QoL assigned to NSR and AF states but assumed to be the same for RFCA and AADs [i.e. QoL of NSR(RFCA) = NSR(AADs) > AF(RFCA) = AF(AADs)].

In scenario 1, assuming that the QoL of the AF and NSR states were equivalent for both RFCA and AADs had only a minor impact on the overall cost-effectiveness results for both the lifetime and 5-year analyses. Similarly, in scenario 2, assuming that the QoL of the NSR states for both RFCA and AADs was higher than the QoL of the AF states for both treatments did not qualitatively impact on the results. Scenario 3 had the greatest impact on the cost-effectiveness results for RFCA. Although the ICER for RFCA in the lifetime analysis increased to £12,840 per additional QALY (compared with £7780 in the base-case analysis), the ICER remained under the conventional threshold of cost-effectiveness. However, the ICER for the 5-year analysis increased to £32,524 per additional QALY, which is above conventional threshold values. Hence, the results of the 5-year analysis were more sensitive to alternative assumptions related to the impact of the alternative treatments on the QoL estimates following successful treatment or not. Consequently, the cost-effectiveness of RFCA requires that the QoL benefits are maintained for more than 5 years and/or that RFCA confers additional QoL benefits to patients following a successful treatment compared with patients receiving AADs.

The results of the base-case analysis were based on the average patient characteristics from a recent UK study (average age 52 years, approximately 80% of the sample male). Clearly the cost-effectiveness results may also vary according to different patient characteristics (e.g. males versus females, alternative ages). Heterogeneity in patients' characteristics was explored using

a series of separate scenarios. In the absence of reliable evidence related to a possible interaction between the relative treatment effect of the different interventions and these characteristics (and alternative assumptions pertaining to the QoL and prognostic benefits associated with RFCA), these scenarios were explored by varying the general population mortality rate according to the particular age and sex characteristics considered. Using this approach, cost-effectiveness estimates in these scenarios are affected solely by the life expectancy of the different subgroups (*ceteris paribus*, subgroups with a higher life expectancy should be more cost-effective as they potentially stand to gain for longer from any QoL improvements associated with RFCA in the lifetime analysis). As expected, the results demonstrated that cost-effectiveness was marginally improved in subgroups with the highest life expectancy (females, age 50 years, etc.). However, differences between the subgroups were relatively minor and the ICER for RFCA remained below £30,000 per additional QALY across each of the subgroups for both the lifetime and 5-year analyses.

Applying an alternative discount rate of 6% for costs and 1.5% for outcomes (compared with 3.5% for both in the base-case analysis) improved the cost-effectiveness in both the 5-year and lifetime analyses. The results from the 5-year analysis improved the ICER to £21,452 per additional QALY. In addition, the probability that RFCA is cost-effective at £30,000 per QALY increased from 0.686 in the base-case 5-year analysis to 0.858 for the 5-year analysis when the alternative discount rates were applied.

The base-case analysis assumed that amiodarone would be administered in an outpatient setting for all patients. Clearly some controversy exists as to the risks and benefits of initiating therapy in an outpatient setting versus an inpatient setting. As a sensitivity analysis we assumed that a proportion of patients would be initiated in an inpatient setting (43%, cost £3360) as opposed to an outpatient setting (57%, cost £154).¹⁶⁵ As this results in higher costs associated with the AAD strategy, the resulting ICERs for RFCA were more favourable (£6822 and £22,155 in the lifetime and 5-year analyses respectively).

In the base-case analysis the same costs were assigned to the NSR and AF states. That is, long-term cost differences between the RFCA and AAD strategies were assumed to vary only according to the subsequent risks of stroke from

the separate health states (and the costs associated with any adverse events). This was assumed to be a conservative assumption towards RFCA as a higher proportion of patients achieve NSR with the RFCA strategy. A less conservative assumption would be that patients in the NSR state (i.e. patients who have not experienced a recurrent AF episode) are likely to be less costly as the subsequent management of these patients may be less intensive than that of patients experiencing recurrent episodes. The costs assigned to the NSR and AF states in the base-case analysis comprised the routine costs associated with the long-term monitoring and management of patients with AF but also included an element of secondary care utilisation due to hospitalisations, etc. As part of the sensitivity analysis we assumed that only patients in the AF state would incur these additional secondary care elements, thus resulting in lower costs for the NSR state (£331 versus £646 per annum).¹⁷ Applying differential costs to the AF and NSR states resulted in significant improvement in the ICER estimates for RFCA. This was most evident in the 5-year analysis, in which the resulting ICER was £19,673 per QALY (below the £20,000–30,000 threshold) and the associated probability that RFCA is cost-effective at a threshold of £30,000 increased to 0.899 (compared with 0.686 in the base-case analysis).

In the base-case analysis there was a marked difference between the long-term transition probabilities applied in relation to the long-term risk of recurrent AF in patients who were free of AF at 12 months for RFCA and AADs. The base-case estimates assumed an annual probability of approximately 3.3% for RFCA and 28.8% for AADs. A number of additional scenarios were therefore explored to estimate the robustness of the results to increasing the long-term risk following RFCA (to between 5% and 15% per annum). Assuming an annual probability of 5% per annum resulted in only marginal changes to the ICER for RFCA. At an annual probability of 10%, the ICER in both the lifetime and 5-year analyses still remained just below the upper bound of the conventional threshold. However, when the probability was increased to 15%, the ICER increased to £8703 per QALY (lifetime analysis) and £32,035 per QALY (5-year analysis), with the latter result above the threshold range considered to be cost-effective.

As a final sensitivity analysis a series of scenarios were considered by increasing/decreasing the costs of the RFCA procedure itself. These were

undertaken by varying the cost of consumables (£5687 per procedure). Clearly if the costs are lower than those applied in the base-case analysis then the results will appear conservative to RFCA. Reducing the costs by £500 improved the cost-effectiveness in both the lifetime and 5-year analyses (ICER £7213 and £23,638 per QALY respectively). However, even if the costs of RFCA were increased by an additional £1000, the results of the 5-year analysis were still within the threshold range considered to be potentially cost-effective.

Summary of cost-effectiveness results

The results of the base-case analysis clearly demonstrate that the long-term maintenance of the QoL benefits of RFCA appear central to the cost-effectiveness estimates. If these are maintained over the remaining lifetime of the patient then the cost-effectiveness of RFCA appears clear, with the resulting ICERs well below conventional thresholds across a range of different baseline risks (defined according to CHADS₂ risk scores). These findings were also robust to a wide range of alternative assumptions. However, if the assumption of lifetime benefits is considered unrealistic then the question of how long these benefits are likely to be maintained becomes a key consideration. The results of the 5-year analysis suggest that the cost-effectiveness of RFCA is not clear-cut with an ICER of £25,510 falling just below the upper bound of conventional thresholds. Any shorter duration of QoL benefits would result in an ICER above acceptable thresholds (e.g. 4-year QoL duration results in an ICER of £30,102; 3-year duration, ICER of £37,385; 2-year duration, ICER of £49,355). The overall cost-effectiveness of RFCA for a shorter duration of benefits is likely to be determined by a number of factors. These include: (1) whether there are additional prognostic benefits associated with NSR (i.e. via a reduction in the long-term risk of stroke); (2) the magnitude of the QoL difference between RFCA and AADs; and (3) the long-term reduction in the risk of recurrent AF following RFCA. Clearly the importance of these other factors will decline the longer any QoL advantage associated with RFCA is maintained beyond 5 years.

Value of information analysis

Methods

This section explores the implications of the uncertainty associated with the cost-effectiveness

of RFCA by undertaking value of information (VOI) analysis. This analysis produces an upper limit on the value of future research that could be undertaken to reduce the uncertainty associated with a decision to adopt RFCA routinely in the NHS. VOI analysis provides a formal quantitative approach to establishing whether further primary research is indicated and can also provide an indication of areas in which research would be most worthwhile. The results of the VOI analysis can therefore be used to prioritise future research in relation to this decision and to identify particular areas in which this appears most valuable.^{178,179}

Assuming that the objectives of the NHS are consistent with maximising health gains from available NHS resources, adoption/implementation decisions should be based on the expected value of the ICER (i.e. the mean ICER) associated with the intervention.¹⁸⁰ The ICER indicates whether a particular intervention is cost-effective depending upon the threshold/maximum willingness to pay for an additional QALY. However, decisions based on expected values will be uncertain, and there will always be a chance that the wrong decision will be made. If the wrong decision is made there will be costs in terms of health benefits and resources forgone. Therefore, the expected cost of uncertainty can be determined jointly by the probability that a decision based on existing information will be incorrect and the consequences of a wrong decision. Uncertainty in the model results has been represented using cost-effectiveness acceptability curves. These demonstrate that at particular threshold values of the ICER there exists significant uncertainty surrounding the cost-effectiveness of RFCA. Although this uncertainty is considered irrelevant to the adoption/implementation decision with respect to RFCA, it has significant implications for the value of conducting further research to support this decision.¹⁸⁰

The expected costs of decision uncertainty can also be interpreted as the expected value of perfect information (EVPI) as perfect information would eliminate the possibility of making the wrong decision. Furthermore, the EVPI also represents the maximum amount that a decision-maker should be willing to pay for additional evidence to inform this decision in the future. EVPI is used to provide an upper bound on the value of additional research to that provided by the model. This valuation can then be used as a necessary requirement for determining the potential efficiency of further primary research. Applying this decision rule,

additional research should only be considered if the EVPI exceeds the expected cost of the research. In addition to providing a global estimate of the total cost of uncertainty related to all inputs in the model, EVPI can also be estimated for individual parameters (and groups of parameters) contained in the model. The objective of this analysis (termed partial EVPI) is to identify the model parameters for which it would be most worthwhile obtaining more precise estimates.

The use of Monte Carlo simulation allows the expected costs of uncertainty associated with the initial adoption decision to be expressed as the proportion of iterations that result in an adoption decision other than that arising from maximising expected cost-effectiveness. The benefits forgone are simply the difference in the costs and outcomes (net benefit) between the optimal strategy for a given iteration and the strategy identified as optimal in the adoption decision (i.e. based on the expected cost-effectiveness estimates). The expectation of benefits forgone over all iterations represents the EVPI per individual.

Clearly, as information can be of value to more than one individual, EVPI can also be expressed for the total population who stand to benefit over the expected lifetime of the programme/technology. If the EVPI for the population of current and future patients exceeds the expected costs of additional research then it is potentially cost-effective to conduct further research. The overall VOI for a population is determined by applying the individual EVPI estimate to the number of people who would be affected by the information over the anticipated lifetime of the technology:

$$\text{EVPI} * \sum_{t=1}^T \frac{I_t}{(1+r)^t}$$

where I is the incidence in the period, t is the period, T is the total number of periods for which information from research would be useful and r is the discount rate.

As our analysis focuses on the results of one particular subgroup (patients with a CHADS₂ score of 1) we have not attempted to aggregate the individual per patient EVPI results to a population level. However, to put the results into context we have scaled these up to provide results per 1000 patients per annum who could be affected by the decision. This provides a clearer basis to assist decision-makers in applying these results to the potential sizes of their own populations of interest.

Results

Total expected value of perfect information

The individual total per patient EVPI is illustrated in *Figure 14*. Separate estimates are provided for the lifetime analysis and the 5-year analysis. The figure clearly shows that the EVPI estimates are closely related to the threshold cost-effectiveness ratio and the associated probability that RFCA is cost-effective. When the threshold for cost-effectiveness is low (e.g. less than £5000 per QALY), RFCA is not considered to be cost-effective under any scenario and the associated probability that RFCA is cost-effective is also low (and hence there is minimal decision uncertainty that a policy of AAD treatment appears optimal). Given the low uncertainty surrounding this decision, additional information is unlikely to change this decision and hence the estimates of EVPI are low. Similarly, when the threshold is considerably higher (e.g. above £50,000 per QALY), RFCA is expected to be cost-effective in both scenarios and again this decision is less likely to be changed by further research (and hence EVPI falls). The total EVPI reaches a maximum when the threshold for cost-effectiveness is equal to the expected ICER of RFCA. In other words, the EVPI reaches a maximum when the decision is most uncertain whether to adopt or reject RFCA based on existing evidence (£7780 and £25,510 per QALY for the lifetime and 5-year analyses respectively).

Table 30 provides a summary of the total EVPI estimates for a select number of threshold values. The results indicate a considerable range in the individual (and population) EVPI estimates depending on the threshold WTP value and the assumption concerning the maintenance of QoL benefits. For example, assuming a threshold of £30,000 per QALY, the population EVPI (per 1000 patients eligible per annum) ranges from £17,288 to £5,465,967 across the two scenarios.

Partial expected value of perfect information

Although estimates of the total EVPI provide a useful global estimate of the uncertainty surrounding the adoption decision, this estimate does not provide an indication of where further research would be of most value. The value of reducing the uncertainty surrounding particular input parameters in the decision model can be established by estimating partial EVPI. This type of analysis can be used to focus further research by identifying those inputs for which more precise estimates would be most valuable. The analysis of the VOI associated with each of the model inputs

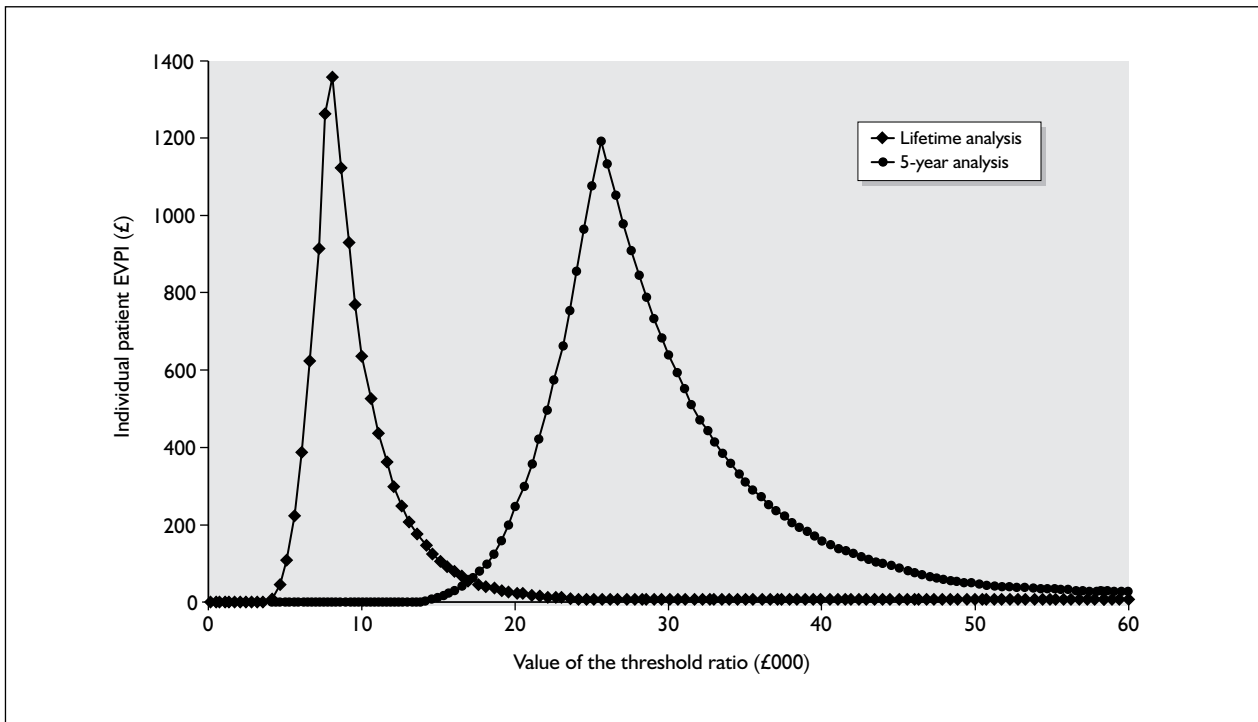


FIGURE 14 Value of information analysis (lifetime and 5-year analyses).

can be conducted in a very similar way to the analysis of the EVPI for the decision as a whole in cases in which a linear relationship between the inputs and the expected costs and outcomes exists. However, when the relationship is non-linear, partial EVPI estimates require substantial additional computation. Because of the complexity of the model presented here, a linear relationship has been assumed for ease of exposition and the partial EVPI results are presented for a single subgroup. Although estimates are only presented for one subgroup (CHADS₂ score of 1), the relative

ordering of importance is likely to be similar across alternative subgroups/scenarios.

Table 31 provides the partial EVPI estimates for a series of different parameter groups at select values of the threshold ICER. In both the lifetime and 5-year scenarios, the EVPI associated with the QoL estimates for patients with and without recurrent AF following treatment with either RFCA or AADs is extremely high and appears to account for the majority of uncertainty surrounding the model. Other parameters that appear to have a

TABLE 30 Individual and population total expected value of perfect information estimates

Base-case scenario	£10,000	£20,000	£30,000	£40,000
Individual patient EVPI for maximum WTP				
Lifetime analysis	£638.43	£22.52	£2.02	£0.46
5-Year analysis	£0.10	£242.06	£635.01	£159.26
Population EVPI for maximum WTP				
Lifetime analysis	£5,495,405	£193,845	£17,388	£3960
5-Year analysis	£861	£2,083,577	£5,465,967	£1,370,860

EVPI, expected value of perfect information; WTP, willingness to pay.
 a. Assuming information valuable for 10 years (estimates for an annual incidence of 1000 patients).

TABLE 31 Individual partial expected value of perfect information estimates

Parameters	Individual patient EVPI for maximum WTP: lifetime analysis				Individual patient EVPI for maximum WTP: 5-year analysis			
	£10,000	£20,000	£30,000	£40,000	£10,000	£20,000	£30,000	£40,000
Base-case	£638.43	£22.52	£2.02	£0.46	£0.10	£242.06	£635.01	£159.26
1 Utilities of NSR and AF health states	£599.12	£15.10	£0.25	£0.00	£0.00	£189.70	£371.47	£21.33
2 Utilities of other health states	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
3 Prognostic benefit of NSR	£0.32	£0.00	£0.00	£0.00	£0.00	£0.92	£94.12	£2.38
4 Baseline and treatment effect	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£11.36	£0.00
5 Long-term AF reversion rates (RFCA)	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
6 Toxicity parameters	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
7 RFCA complications	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00

EVPI, expected value of perfect information; NSR, normal sinus rhythm; WTP, willingness to pay.

more moderate influence on the overall decision uncertainty include the prognostic benefit associated with NSR (and its impact on reducing the probability of stroke) and the success rates at 12 months for RFCA and the relative effect compared with treatment with AADs over this period. The estimates of partial EVPI for these parameters are illustrated graphically in *Figures 15* and *16*, based on a wider range of threshold values. Only those parameters with a sufficient value to illustrate graphically are included. Interestingly, consideration of a wider set of threshold values indicates that, in the 5-year analysis, the long-term reversion rates (i.e. the probability of having recurrent AF) following RFCA appear to demonstrate some value, which was previously not apparent in the select values considered.

Summary of value of information results

The results from the model indicate that there is significant variation in both the ICER and the uncertainty surrounding the decision over a range of key threshold values across the two scenarios.

This uncertainty results in a significant cost of uncertainty reflected in the high EVPI estimates at particular threshold values. The population EVPI estimates suggest that further research in this area is likely to be of significant value. The EVPI for individual parameters highlighted that potential future research would be of most value directed towards obtaining more precise estimates of the QoL of patients following RFCA and AAD treatment (and, in particular, the QoL of patients following successful treatment or not). The different scenarios considered reveal marked variations in the EVPI estimates based on alternative assumptions (lifetime and 5 years). As these have been considered as separate scenarios, partial EVPI estimates for the assumption related to the duration of any benefit cannot be quantified. However, it should be recognised that this assumption resulted in marked differences in estimates of both cost-effectiveness and VOI. Hence, it is likely that further research on how long these QoL benefits are maintained is likely to be important (recognising that follow-up of at least 5 years is likely to be key).

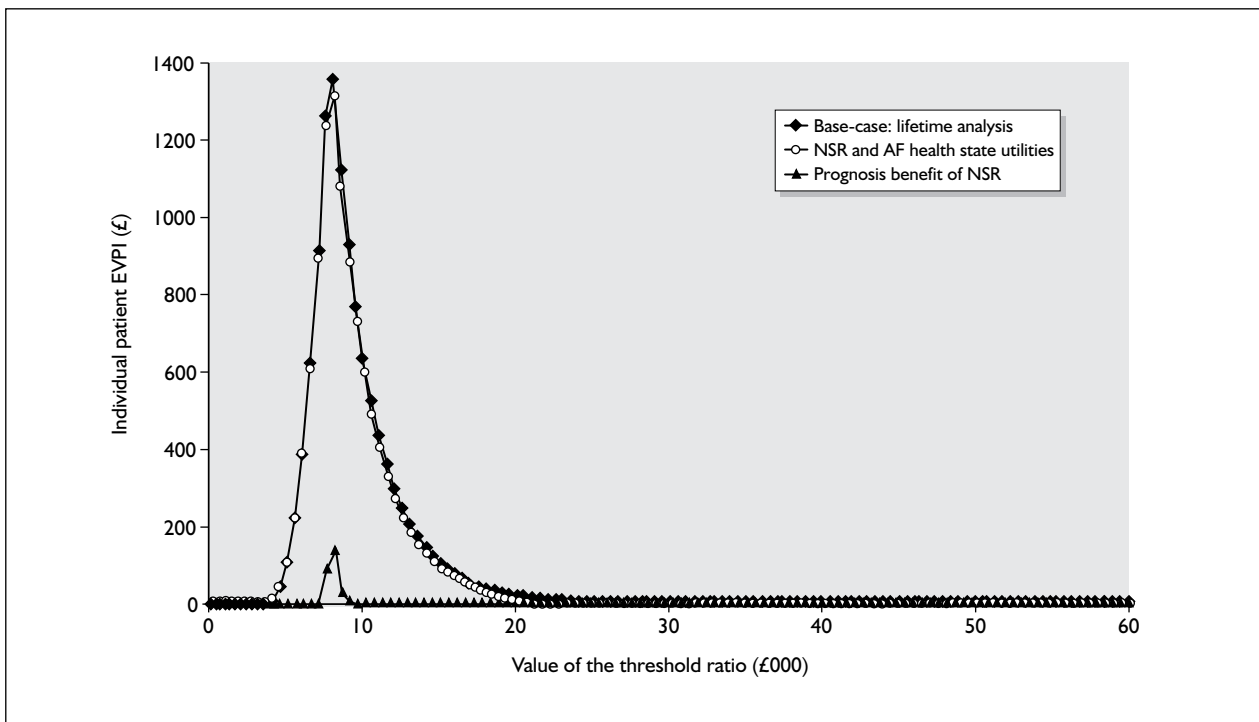


FIGURE 15 Partial expected value of perfect information results (lifetime analysis).

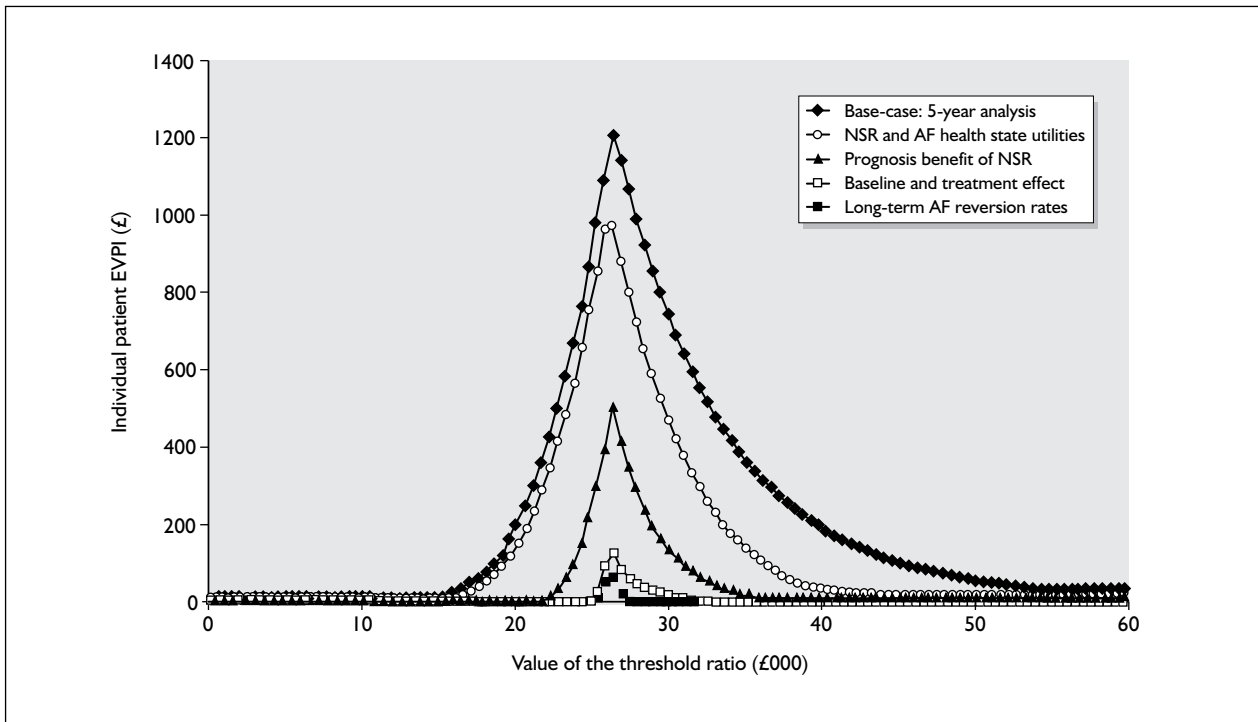


FIGURE 16 Partial expected value of perfect information results (5-year analysis).

Chapter 5

Discussion

Statement of principal findings

Clinical evaluation

As stated in the decision problem (see Chapter 2), the aim of catheter ablation is to achieve NSR. Importantly, catheter ablation offers the potential to eliminate the arrhythmia completely, without the need for ongoing antiarrhythmic therapy, although this cannot always be achieved. In contrast, AADs used to achieve sinus rhythm can only work if they continue to be taken. Furthermore, the maintenance of NSR with drugs is not a realistic expectation.⁷⁰ The other option for the management of arrhythmia, rate control, although alleviating symptoms, cannot offer a return to NSR and therefore cannot offer the potential beneficial prognostic effects of NSR.

RFCA for atrial fibrillation

There is a substantial amount of case series data to suggest that RFCA is an efficacious intervention for the treatment of AF. The rates of freedom from arrhythmia at follow-up vary widely, but in most series the majority of patients are free of AF at 12 months.

There is a small amount of moderate-quality randomised evidence to suggest that PV ablation is more effective than long-term AAD treatment in patients with drug-refractory paroxysmal AF. Evidence from one small RCT suggests that RFCA may also be more effective than AADs as first-line treatment in patients with paroxysmal AF. Intention to treat meta-analysis suggests that RFCA is 36–76% more effective than AAD treatment in terms of freedom from arrhythmia at 12 months; analysis by actual treatment received suggests a larger two- to threefold improvement on this outcome for patients treated with RFCA.

There is insufficient evidence to assess the effectiveness of RFCA in patients with persistent or permanent AF.

Some limited RCT evidence indicates that RFCA is associated with improvements in self-rated physical and/or general health from baseline in AF patients.

Where reported, there is a small risk of serious complications associated with RFCA (e.g. cardiac tamponade, PV stenosis). However, the risk of such complications needs to be balanced against that of potential adverse events associated with long-term use of certain antiarrhythmic agents (e.g. thyroid dysfunction associated with amiodarone). The currently available evidence does not show a significant relationship between RFCA and mortality, although existing trials have not been powered to assess this outcome.

RFCA for typical atrial flutter

Data from uncontrolled case series suggest that RFCA is an efficacious intervention for the treatment of typical atrial flutter, with the majority of patients in most series being free from flutter at follow-up. There is a very small amount of moderate-quality randomised evidence which suggests that a significantly higher proportion of patients who undergo RFCA than those receiving AAD-based therapy are free from atrial flutter during follow-up in the medium term.

Case series suggest that a significant proportion of patients develop new-onset AF following flutter ablation although the randomised evidence does not suggest that this occurs any more frequently in ablated patients than in patients receiving other treatments.

In the infrequent instances in which it has been reported, RFCA was associated with a general increase in self-reported health scores from baseline in patients with atrial flutter.

Where reported, complications associated with RFCA of atrial flutter were rare. The currently available evidence does not show a significant relationship between RFCA and mortality.

Economic evaluation

The decision model evaluates a strategy of RFCA (without long-term AAD use) compared with long-term AAD treatment alone (amiodarone) in adults with paroxysmal AF.

The base-case analysis clearly demonstrates that, if the QoL benefits of RFCA are maintained over the remaining lifetime of the patient, the cost-effectiveness of RFCA appears clear, with the resulting ICERs well below conventional thresholds across a range of different baseline stroke risks. These findings were also robust to a wide range of alternative assumptions.

If the QoL benefits of RFCA are assumed to be maintained for no more than 5 years, the overall cost-effectiveness of RFCA is dependent on a number of factors. These include: (1) whether there are additional prognostic benefits associated with NSR (i.e. via a reduction in the long-term risk of stroke); (2) the magnitude of the QoL difference between RFCA and AADs; and (3) the long-term reduction in the risk of recurrent AF following RFCA. Clearly, the importance of these other factors will decline the longer any QoL advantage associated with RFCA is maintained beyond 5 years.

Strengths and limitations of the assessment

We have conducted a rigorous review of the research literature on the effects of RFCA for the curative treatment of AF and typical atrial flutter, capturing the most recent evidence relating to RFCA. This is a relatively new technology (PV isolation for AF was first described in 1998⁶) and one that continues to evolve rapidly. This is reflected in the evidence base, which is dominated by uncontrolled evidence, with randomised evidence only recently beginning to emerge. An earlier systematic review of RFCA in AF²⁸ had been conducted, but the search period covered by that review meant that it included only the earliest, and now mostly obsolete, case series relating to AF ablation.

The other major source of data summarising the risks and benefits of RFCA (for AF) is the worldwide survey conducted by Cappato *et al.*²⁵ However, as this survey had only a 23% response rate, the findings have a clear potential for bias, most likely in favour of RFCA (i.e. by overestimating success rates and/or underestimating complications). Our review included both controlled studies and case series to build on this previous work.

Our review has found that success rates and complications varied widely between case series,

but on average these were generally consistent with the findings of Cappato *et al.* However, this could be due to the review of case series operating under similar biases to the survey, i.e. publication bias may mean that only centres with better success rates or fewer complications published their findings. In addition, a disproportionately large number of series come from a small group of highly experienced 'pioneering' centres, who are likely to have better outcomes than less experienced centres. Further to this, although we attempted to avoid double counting of patients across series, potential overlap between some reports could not be entirely discounted, which might have compounded any overestimates.

It is likely that variation in success rates between studies could be attributable to differences in ablation techniques and technologies. Restricting inclusion to a limited subset of RFCA techniques might have reduced some of this between-study heterogeneity. However, any evaluation of RFCA (for AF in particular) is likely to incorporate a number of variations because of changes in the technology over time, including ablation patterns, mapping techniques, catheter tips, etc. It was not the aim of this review to establish the most effective variation on the RFCA approach but to determine its effectiveness relative to alternative treatment options. Therefore, we treated RCTs comparing variations in ablation techniques (circumferential versus segmental) and technologies (catheters, mapping techniques, etc.) as case series, and focused on the relatively few comparisons of RFCA against alternative treatment modalities.

Given the potential limitation of existing cost-effectiveness evidence in providing a basis for informing policy decisions regarding the use of RFCA in the NHS, a new decision model was developed to explore these issues in more detail. The model evaluated the cost-effectiveness of RFCA compared with long-term AADs for patients with predominantly paroxysmal AF. The model considered the short-term and long-term costs and outcomes of the alternative strategies from an NHS perspective. The study also examined the generalisability of the clinical data to NHS practice. The model focused on quantifying the potential QoL gains that may be achieved using RFCA through symptomatic improvements and also through any reduction in the longer-term risk associated with major clinical events (e.g. stroke).

Although the cost-effectiveness model addressed a number of the key limitations of existing studies,

the model also has several potential limitations that need to be considered in conjunction with the main results. First, it should be recognised that the QoL estimates applied in the model remain highly uncertain. Although there have been a large number of studies reporting on the QoL of patients following catheter ablation, their direct application within a cost-effectiveness analysis poses several problems. To date, no single study has attempted to quantify the impact of RFCA using a generic utility measure such as the EQ-5D. This represents a major limitation when trying to establish the cost-effectiveness of an intervention, as the use of these measures provides a clearer basis for establishing value for money in the NHS. This is a particularly important consideration for the use of RFCA. The routine use of RFCA in the NHS is likely to generate significant additional upfront costs compared with current management strategies. In a resource-constrained system such as the NHS this will inevitably mean that other interventions (potentially in different patient populations altogether) will have to be displaced to fund the use of RFCA. Consequently, it is important to establish that the additional value provided by RFCA to the NHS will more than offset any benefits lost through resource displacement. The absence of reliable data using a generic utility instrument represents a major omission from the existing evidence base for RFCA. In the absence of this data, alternative approaches were used to attempt to map between the QoL measures that have been used (SF-36) and a utility-based measure (EQ-5D). The process of mapping between these different instruments itself introduces a source of uncertainty, and it should be recognised that the approach employed in the model is far from ideal. However, in the absence of more reliable data the current estimates represent the best data that were available to us. Clearly it is possible that the current estimates may over- or underestimate the QoL gains associated with RFCA. However, a number of separate scenarios demonstrated that the overall results remained fairly robust to the different estimates applied in the sensitivity analysis, suggesting that the duration of any benefits is likely to be the key determinant of cost-effectiveness. This highlights another potential limitation of the model. Evidence for longer-term benefits of RFCA (i.e. for periods potentially beyond 5 years) is lacking and hence extrapolating the potential benefits reported over shorter time horizons becomes increasingly uncertain. The model results clearly demonstrate that the cost-effectiveness estimates are extremely sensitive to the duration over which these benefits are likely to be maintained.

It should be noted that the decision model only considers the cost-effectiveness of RFCA in patients with predominantly paroxysmal AF. Because of the limitations of existing RCT evidence in relation to patients with persistent AF and those with atrial flutter, separate cost-effectiveness analyses were not undertaken. Consequently, the generalisability of these findings to a broader range of patients should be undertaken with caution. Clearly, as new evidence emerges, the current model can be adapted to consider these other populations using more robust evidence than exists at present.

Uncertainties

Despite our systematic review of the available research evidence a number of uncertainties remain. It is uncertain how generalisable to the UK context the findings of our clinical evaluation are. There are very few UK-based data represented in the research literature. We found a single UK case series, on RFCA for AF.⁶⁶ Even though UK-based, it is unclear how representative this study is; it reported only for a predominantly chronic AF population without any structural heart disease.

The available trials and case series did not provide useful information on the efficacy of RFCA in important subgroups of AF patients. The majority of AF patients who undergo RFCA in the published literature are those with paroxysmal AF. The limited evidence from case series suggests that, in general, recurrence is more common in patients with chronic forms of AF than in those with paroxysmal AF. Evidence from controlled studies is even less clear. Within-trial results were not presented separately for these subgroups and only one RCT (Oral *et al.*⁵⁶) has been conducted solely in patients with persistent AF and this found a benefit associated with adding RFCA to a short-term amiodarone/cardioversion treatment strategy. Similarly, our review has been unable to investigate the impact of concomitant structural heart disease and mean duration of arrhythmia on the relative effectiveness of RFCA.

One important aspect in determining the clinical and cost-effectiveness of RFCA is the need for repeat procedures to achieve or maintain sinus rhythm. Such repeat procedures have clear implications for costs and patients' QoL, but there has been little focus on this issue in the published research literature. This represents a very important uncertainty relating to the effectiveness of catheter ablation. It has been

recognised by experts in the field, who, in their consensus statement,⁷⁰ indicated that future study reports should be explicit and trials should avoid reablation for at least 3 months post procedure so that the success of a single procedure can be determined.

Typically, RFCA has been considered a treatment option for patients in whom pharmacological therapy has failed, and most of the evidence for the effectiveness of RFCA is in this population. In addition, current NICE guidelines⁴ recommend that this is one of the patient groups (along with those with lone AF or an underlying electrophysiological disorder) appropriate for specialist referral. However, confidence in RFCA has grown in recent years and certain centres have offered the procedure as first-line therapy. We included one small RCT⁶⁰ that gave RFCA as first-line treatment, and the effect of RFCA compared with long-term AAD therapy did not differ substantially from that seen in the RCTs conducted in patients refractory to drug treatment. However, it is likely that further evidence of effectiveness and safety in this population will be necessary before RFCA can be considered first-line therapy on a general basis.

Another uncertainty relates to the primary outcome upon which our assessment has been based. The primary outcome in this review was freedom from arrhythmia at 12 months, which is the outcome recommended in FDA guidelines for the evaluation of AF and the one used in most RCTs of RFCA for AF. However, this outcome ignores any benefit gained from a near elimination of symptoms or from a clinically significant reduction in arrhythmia episodes. It also ignores the success of a patient previously refractory to AAD therapy who can now be controlled on AAD. The RCTs included in the meta-analysis in this review measured freedom from arrhythmia without AADs in patients undergoing RFCA at follow-up. However, the extent to which AADs are used post RFCA varies between centres and between publications. A recent RCT found that continuing AAD therapy in patients who underwent RFCA for AF did not lower the rate of AF recurrences.¹⁸¹ The impact of maintaining or discontinuing post-ablation anticoagulation has also yet to be established, although this was outside the scope of the current review. This issue is also raised in the 2007 expert consensus statement, which considered one outstanding question to be the identification of patient subgroups in whom warfarin could be discontinued.⁷⁰

Freedom from arrhythmia at 12 months also ignores longer-term data. Given the results of the economic model, together with the clinical importance, it is very important to be confident that the benefits of RFCA are long lasting. Unfortunately, to date the evidence is rather limited, particularly regarding the longer-term risks of patients reverting back to AF having been free of arrhythmia for 12 months and the degree to which this risk differs between patients treated with RFCA or long-term AADs. One large non-randomised study,⁶¹ which followed patients for a median of 900 days, suggested that the effects of RFCA observed at 12 months remain fairly stable at 2–3 years post procedure. The small number of case series following patients for up to 2 years suggested a similar pattern, but there is insufficient evidence to determine what happens to RFCA-treated AF and typical atrial flutter patients beyond this period. A recently started large-scale RCT of RFCA in AF (the CABANA trial) is planned to follow up 3000 patients for 5 years^{69,70} and will go some way towards reducing this uncertainty.

Another hugely important uncertainty relates to the potential impact of RFCA on long-term prognosis for stroke or cardiovascular outcomes and mortality. The future findings of the CABANA trial should also go some way to addressing this question.

The cost-effectiveness model revealed a number of other uncertainties surrounding some of the key inputs, which led to important uncertainties in the overall estimates of cost-effectiveness. The analysis suggests that future research appears most valuable directed toward obtaining more precise estimates of QoL following RFCA and AAD treatment (and, in particular, the QoL of patients following successful treatment or not) and the overall duration that these benefits are maintained in the long term.

It should also be recognised that the procedural cost of RFCA itself remains highly uncertain. Current HRG estimates do not appear to adequately reflect the resources required for complex ablation procedures for AF. In the absence of suitable HRG estimates our costs were based on a reasonable approximation of the real resource costs associated with these procedures. The subsequent estimates appear markedly higher than the existing HRG-based estimates. Further work is therefore required (and is ongoing as part of the revision to the current HRG coding system) to more accurately reflect the costs of the ablation procedure. Despite these concerns, the estimates

applied are considered more appropriate than the existing HRG costs. In addition, sensitivity analysis revealed that the cost-effectiveness results remained robust to higher costs than the estimates applied in the base-case analysis. Clearly, if the true costs of RFCA are lower than the estimates applied, then the cost-effectiveness advantage of RFCA is even greater.

Assessment of factors relevant to the NHS and other parties

AF in particular is common and so any increase in the availability of RFCA would have considerable implications for the NHS. At present there is a lack of capacity within the NHS for an expansion in demand for a highly complex and time-consuming procedure. Any expansion would be a long-term process and would require investment in training for both cardiac electrophysiologists

and support staff, as well as in infrastructure. Even with such an expansion there will be considerable difficulties, particularly in the short term, of ensuring equal access to care. There will also be some practical difficulties if some procedural guidelines are incorporated (e.g. a requirement for transoesophageal echocardiography in all patients before the procedure and that patients should remain in hospital post procedure until warfarin levels are therapeutic).

The current HRG estimates do not appear to adequately reflect the resources required for complex ablation procedures for AF. Hence, current remuneration is unlikely to truly reflect the costs incurred by NHS providers. Further work is therefore required (and is ongoing as part of the revision to the current HRG coding system) to more accurately reflect the costs of the ablation procedure to ensure that providers receive appropriate remuneration.

Chapter 6

Conclusions

Implications for service provision

- The published data suggest that RFCA is an efficacious intervention for the treatment of AF and typical atrial flutter, with the majority of patients remaining free from arrhythmia at 12 months post procedure.
- There is a small amount of moderate-quality randomised evidence to suggest that RFCA is more effective than long-term AAD treatment in patients with drug-refractory paroxysmal AF, with a two- to threefold increase in freedom from arrhythmia associated with RFCA.
- There is a very small amount of moderate-quality randomised evidence which suggests that a significantly higher proportion of patients who undergo RFCA for typical atrial flutter than those receiving AAD-based therapy are free from atrial flutter during follow-up in the medium term.
- Where reported, complications associated with RFCA for either AF or atrial flutter were rare. The currently available evidence does not show a significant relationship between RFCA and mortality, although existing trials have not been powered to assess this outcome.
- Assuming that the QoL benefits of RFCA for paroxysmal AF are maintained over the remaining lifetime of the patient, the cost-effectiveness of RFCA appears clear, with the resulting ICERs well below conventional thresholds across a range of different baseline stroke risks and robust to a wide range of alternative assumptions. If QoL benefits of RFCA are assumed to be maintained for only 5 years, the cost-effectiveness is likely to be influenced by several other assumptions.

Suggested research priorities

Research is required to address the following uncertainties detailed in our report:

- generalisability of findings to UK practice
- efficacy in persistent AF
- efficacy in atrial flutter
- efficacy in subgroups such as patients with structural heart disease, long-standing AF, etc.
- duration of beneficial effects – in terms of arrhythmias and symptoms/QoL
- impact on mortality
- difference between symptoms/QoL after RFCA or AAD
- effect of NSR on stroke prognosis.

The CABANA trial^{69,70} should, when completed, provide data to address at least some of these issues in AF, i.e. cardiovascular death, occurrence of disabling stroke, serious bleeding, cardiac arrest and QoL data. It will hopefully also provide some insight into the relative effects of RFCA and AAD treatment strategies in key subgroups of patients (i.e. those with concomitant heart disease or long-standing AF).

The question of the applicability of research findings to UK practice warrants the collection of UK data. Therefore, we would suggest that a prospective UK registry of such catheter ablation procedures is needed. Cardiac ablation is one of the domains covered by the existing national Central Cardiac Audit Database (CCAD), but additional measures may be required to ensure input from all UK centres. A further set of standards for data collection in this area has been published by the ACC/AHA.¹⁸² Such a registry would provide basic information on the number of procedures conducted per centre and per operator and ablation techniques and mapping technologies used, as well as the indications for the procedure for each centre and how these compare against existing guidance. In addition, it would also be of enormous value in establishing the long-term benefits of RFCA and the true incidence and impact of any rare and/or late complications.

Several key areas of uncertainty were identified by the economic evaluation, including whether there are additional prognostic benefits associated with NSR via a reduction in the long-term risk of stroke, and what is the long-term reduction in the risk of recurrent AF following RFCA. Both of these areas of uncertainty could be addressed with appropriately collected registry data. In addition, the long-term QoL achieved following RFCA relative to that achieved with AAD needs to be established. Collection of QoL data within

the proposed registry could partially inform any evaluation of the magnitude of the QoL difference following RFCA and AAD treatment.

Alternatively, any future RCT comparing RFCA with AAD therapy for the treatment of AF or typical atrial flutter should:

- follow standards for studies on the evaluation of catheter ablation as outlined in recent expert consensus recommendations (e.g. employ a 3-month 'blanking period', delineate the extent of cardiac and non-cardiac disease, use appropriate monitoring methods to detect recurrence during follow-up, etc.)⁷⁰
- be conducted among a group of 'non-pioneering' centres, using the techniques and equipment typically employed in UK practice
- include patients with both paroxysmal and persistent forms of AF when appropriate
- collect QoL and symptom scores
- consider the impact of including newly diagnosed patients – current NICE guidelines

suggest that RFCA is only appropriate for most AF patients once they have failed AAD therapy; however, RFCA has already been evaluated as first-line therapy in one RCT,⁶⁰ and there is likely to be further interest in this area.

The current lack of high-quality published evidence would appear to justify undertaking a multicentre RCT evaluating the effects of catheter ablation for typical atrial flutter, similar to that described above. However, among electrophysiologists, confidence that this procedure is effective is high and there may be ethical objections to the randomisation of patients on this basis.

The impact of withdrawing anticoagulation after successful treatment with RFCA in selected groups of patients was beyond the scope of this review. If there is insufficient evidence to review this question separately, relevant uncontrolled data could be derived from the proposed UK registry and/or incorporated into the design of any future multicentre RCT, if adequately powered.



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CRD/CHE Technology Assessment Group

The technology assessment review team at the University of York is drawn from two specialist centres: the Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE).

CRD undertakes reviews of research about the effects of interventions used in health and social care (www.york.ac.uk/inst/crd). The centre maintains various databases, provides an enquiry service and disseminates results of research to NHS decision-makers.

CHE undertakes research and training in all areas of health economics (www.york.ac.uk/inst/che). The bulk of the input into the technology assessment reviews comes from the programme for economic

evaluation and health technology assessment, which specialises in decision analysis and Bayesian methods in economic evaluations (see www.york.ac.uk/inst/che/teehta.htm).

Contributions of authors

Mark Rodgers was the lead reviewer responsible for study selection, data extraction, validity assessment, data analysis and writing the report. Claire McKenna was responsible for the development of the economic model and contributed to the protocol and report writing. Duncan Chambers contributed to all aspects of the clinical evaluation and report writing. Susan Van Hout was responsible for reviewing the quality of life evidence for the economic evaluation sections of the report. Su Golder devised the search strategy, carried out the literature searches and wrote the search methodology sections of the report. Derrick Todd provided clinical advice and input at all stages, contributed to the protocol, commented on various drafts of the report and contributed to the discussion section of the report. Chris Pepper provided clinical advice and input at all stages, contributed to the protocol, commented on various drafts of the report and contributed to the discussion section of the report. Stephen Palmer provided input at all stages, contributed to the development of the economic model, commented on various drafts of the report and had overall responsibility for the economic evaluation sections of the report. Nerys Woolcott contributed to all aspects of the clinical and economic evaluation and report writing and had overall responsibility for the clinical evaluation sections of the report and project co-ordination.



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Appendix I

Literature search strategies

Databases searched

Guidelines databases

BMJ Clinical Evidence. URL: www.clinicalevidence.com/ceweb/index.jsp

Cardiovascular Diseases Specialist Library. URL: www.library.nhs.uk/cardiovascular/

Health Evidence Bulletin Wales. URL: <http://hebw.cf.ac.uk/>

HSTAT. URL: www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat

National Guidelines Clearing House. URL: www.guideline.gov/

NICE. URL: www.nice.org.uk/

NLH Guidelines Finder. URL: www.library.nhs.uk/guidelinesFinder/

Scottish Intercollegiate Guidelines Network (SIGN). URL: www.sign.ac.uk/

TRIP. URL: www.tripdatabase.com/index.html

Databases of systematic reviews

Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library). URL: www.library.nhs.uk/

Database of Abstracts of Reviews of Effects (DARE) (CRD Internal Database). URL: www.york.ac.uk/inst/crd/crddatabases.htm#DARE

Health-/medical-related databases

BIOSIS (DIALOG). URL: <http://library.dialog.com/>

CENTRAL (Cochrane Central Register of Controlled Trials) (Cochrane Library). URL: www.library.nhs.uk/

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (OvidWeb). URL: <http://gateway.ovid.com/athens>

EMBASE (OvidWeb). URL: <http://gateway.ovid.com/athens>

Health Technology Assessment (HTA) Database (CRD Internal Database).

MEDLINE (OvidWeb). URL: <http://gateway.ovid.com/athens>

MEDLINE In-Process and other non-indexed citations (OvidWeb). URL: <http://gateway.ovid.com/athens>

Science Citation Index (SCI) (Web of Knowledge). URL: <http://wos.mimas.ac.uk/>

Economic databases

EconLit (WebSPIRS). URL: <http://arc.uk.ovid.com/>

Health Economics Evaluation Database (HEED) (CD-ROM).

IDEAS. URL: <http://ideas.repec.org>

NHS Economic Evaluation Database (NHS EED) (CRD Internal Database).

Databases of conference proceedings

ISI Proceedings: Science and Technology (Web of Knowledge). URL: <http://wos.mimas.ac.uk/>

Zetoc Conferences (MIMAS). URL: <http://zetoc.mimas.ac.uk/>

Databases for ongoing and recently completed research

ClinicalTrials.gov. URL: www.clinicaltrials.gov

ESRC SocietyToday Database. URL: www.esrc.ac.uk/ESRCInfoCentre/index.aspx

MetaRegister of Controlled Trials. URL: www.controlled-trials.com/

National Research Register (NRR). URL: www.update-software.com/national/

Research Findings Electronic Register (ReFeR). URL: www.info.doh.gov.uk/doh/refr_web.nsf/Home?OpenForm

Search strategies for studies on the clinical and cost-effectiveness of selected comparators to catheter ablation

To inform the clinical and cost-effectiveness aspects of the study additional searches were carried out for systematic reviews and economic evaluations of the comparators of catheter ablation. These searches were conducted in the following databases:

Systematic reviews

Databases of systematic reviews

Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library). URL: www.library.nhs.uk/

Database of Abstracts of Reviews of Effects (DARE) (CRD Internal Database).

Health-/medical-related databases

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (OvidWeb). URL: <http://gateway.ovid.com/athens>

EMBASE (OvidWeb). URL: <http://gateway.ovid.com/athens>

Health Technology Assessment (HTA) Database (CRD Internal Database).

MEDLINE (OvidWeb). URL: <http://gateway.ovid.com/athens>

MEDLINE In-Process and other non-indexed citations (OvidWeb). URL: <http://gateway.ovid.com/athens>

Economic evaluations

Economic databases

Health Economics Evaluation Database (HEED) (CD-ROM).

NHS Economic Evaluation Database (NHS EED) (CRD Internal Database).

Health-/medical-related databases

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (OvidWeb). URL: <http://gateway.ovid.com/athens>

EMBASE (OvidWeb). URL: <http://gateway.ovid.com/athens>

MEDLINE (OvidWeb). URL: <http://gateway.ovid.com/athens>

MEDLINE In-Process and other non-indexed citations (OvidWeb). URL: <http://gateway.ovid.com/athens>

Additional search strategies for information to inform the decision-analytic model

To help inform the decision-analytic model specific searches were carried out for quality of life studies, prognosis studies and studies on the adverse effects of amiodarone.

Quality of life

Health-/medical-related databases

British Nursing Index (BNI) (OvidWeb). URL: <http://gateway.ovid.com/athens>

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (OvidWeb). URL: <http://gateway.ovid.com/athens>

EMBASE (OvidWeb). URL: <http://gateway.ovid.com/athens>

Health Management Information Consortium (HMIC) (OvidWeb). URL: <http://gateway.ovid.com/athens>

MEDLINE (OvidWeb). URL: <http://gateway.ovid.com/athens>

MEDLINE In-Process and other non-indexed citations (OvidWeb). URL: <http://gateway.ovid.com/athens>

PsycINFO (OvidWeb). URL: <http://gateway.ovid.com/athens>

Prognosis

Health-/medical-related databases

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (OvidWeb). URL: <http://gateway.ovid.com/athens>

EMBASE (OvidWeb). URL: <http://gateway.ovid.com/athens>

Health Management Information Consortium (HMIC) (OvidWeb). URL: <http://gateway.ovid.com/athens>

MEDLINE (OvidWeb). URL: <http://gateway.ovid.com/athens>

MEDLINE In-Process and other non-indexed citations (OvidWeb). URL: <http://gateway.ovid.com/athens>

Adverse effects of amiodarone

Tertiary sources

Aronson JK, editor. *Side effects of drugs annual 27* (SEDA). Amsterdam: Elsevier; 2004.

Dukes MNG, Aronson JK, editors. *Meyler's side effects of drugs*. 14th edn. Amsterdam: Elsevier; 2000.

Sweetman SC, editor. *Martindale: the complete drug reference*. London: Pharmaceutical Press; 2007.

Systematic reviews

Systematic reviews were identified from the searches for comparators and consulted for information on the adverse effects of amiodarone.

Search strategies for studies on the clinical and cost-effectiveness of catheter ablation

All search strategies were limited to publication year 2000 onwards or when this was not possible older references were excluded from the results.

Databases of systematic reviews

Cochrane Database of Systematic Reviews (CDSR)

Cochrane Library – 2006 Issue 3. Searched 25 July 2006. URL: www.library.nhs.uk/

This search strategy retrieved two reviews (two completed and no protocols).

- #1 MeSH descriptor Catheter Ablation, this term only
- #2 catheter NEXT ablation*
- #3 electric* NEXT ablation*
- #4 fulguration*
- #5 electrofulguration*
- #6 cryoablation*
- #7 radiofrecuen* NEXT ablation*
- #8 radio-frecuen* NEXT ablation*
- #9 RFA
- #10 ablation NEXT catheter*
- #11 atrial NEXT flutter NEXT ablation*
- #12 transcatheter NEXT ablation*
- #13 trans-catheter NEXT ablation*
- #14 ablative NEXT cure*
- #15 rf NEXT ablation*
- #16 arrhythmia NEXT ablation*
- #17 atrioventricular NEXT nod* NEXT ablation*

- #18 av NEXT nod* NEXT modification*
- #19 slow NEXT av NEXT nod* NEXT pathway* NEXT ablation*
- #20 his NEXT bundle NEXT ablation*
- #21 radiofrecuen* NEXT linear NEXT ablation*
- #22 radio-frecuen* NEXT linear NEXT ablation*
- #23 auricular NEXT fibrillation*
- #24 MeSH descriptor Atrial Fibrillation, this term only
- #25 atrial NEXT fibrillation*
- #26 atrium NEXT fibrillation*
- #27 MeSH descriptor Atrial Flutter, this term only
- #28 auricular NEXT flutter*
- #29 atrial NEXT flutter*
- #30 atrial NEXT tachycardia*
- #31 atrial NEXT tachyarrhythmia*
- #32 atrium NEXT tachycardia*
- #33 atrial NEXT arrhythmia*
- #34 heart NEXT fibrillation*
- #35 MeSH descriptor Tachycardia, Ectopic Atrial, this term only
- #36 typical NEXT flutter*
 - #37 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
- #38 (#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36)
- #39 (#37 AND #38)

Database of Abstracts of Reviews of Effects (DARE)

CRD Internal Database – July 2006. Searched 26 July 2006.

This search strategy produced two records.

S catheter(w)ablation\$or electric\$(w)ablation\$or fulguration\$or electrofulguration\$or cryoablation\$or radiofrecuen\$(w)ablation\$or radio-frecuen\$(w)ablation\$or RFA or ablation(w) catheter\$or atrial(w)flutter(w)ablation\$or transcatheter(w)ablation\$or trans-catheter(w) ablation\$or ablative(w)cure\$or rf(w)ablation\$or arrhythmia(w)ablation\$or atrioventricular(w) nod\$(w)ablation\$or av(w)nod\$(w)modification\$or slow(w)av(w)nod\$(w)pathway\$(w)ablation\$or his(w) bundle(w)ablation\$or radiofrecuen\$(w)linear(w) ablation\$or radio-frecuen\$(w)linear(w)ablation\$

S auricular(w)fibrillation\$or atrial(w)fibrillation\$or atrium(w)fibrillation\$or auricular(w)flutter\$or atrial(w)flutter\$or atrial(w)tachycardia\$or atrial(w) tachyarrhythmia\$or atrium(w)tachycardia\$or

atrial(w)arrhythmia\$or heart(w)fibrillation\$or
typical(w)flutter\$

S s1 and s2

Health-/medical-related databases

BIOSIS

DIALOG – 1993–present. Searched 28 July 2006.
URL: <http://library.dialog.com/>

This search strategy resulted in 1142 records.

S catheter(w)ablation?
S electric?(w)ablation?
s fulguration?
s electrofulguration?
s cryoablation?
s radiofrequent?(w)ablation?
s radio-frequent?(w)ablation?
s RFA
s ablation(w)catheter?
s atrial(w)flutter(w)ablation?
s transcatheter(w)ablation?
s trans-catheter(w)ablation?
s ablative(w)cure?
s rf(w)ablation?
s arrhythmia(w)ablation?
s atrioventricular(w)nod?(w)ablation?
s av(w)nod?(w)modification?
s slow(w)av(w)nod?(w)pathway?(w)ablation?
s his(w)bundle(w)ablation?
s radiofrequent?(w)linear(w)ablation?
s radio-frequent?(w)linear(w)ablation?
s auricular(w)fibrillation?
s atrial(w)fibrillation?
s atrium(w)fibrillation?
s auricular(w)flutter?
s atrial(w)flutter?
s atrial(w)tachycardia?
s atrial(w)tachyarrhythmia?
s atrium(w)tachycardia?
s atrial(w)arrhythmia?
s heart(w)fibrillation?
s typical(w)flutter?
s s1:s21
s s22:s32
s s33 and s34
S S35/2000:2007

CENTRAL (Cochrane Central Register of Controlled Trials)

Cochrane Library – 2006 Issue 3. Searched 25 July 2006. URL: www.library.nhs.uk/

The same search strategy was used as for CDSR.
This search resulted in 106 records.

Cumulative Index to Nursing and Allied Health Literature (CINAHL)

OvidWeb – 1982 to July Week 3 2006. Searched 25 July 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 381 records.

1. catheter ablation/
2. catheter ablation\$.ti,ab.
3. electric\$ablation\$.ti,ab.
4. fulguration\$.ti,ab.
5. electrofulguration\$.ti,ab.
6. cryoablation\$.ti,ab.
7. radiofrequent\$ablation\$.ti,ab.
8. radio-frequent\$ablation\$.ti,ab.
9. RFA.ti,ab.
10. ablation catheter\$.ti,ab.
11. atrial flutter ablation\$.ti,ab.
12. transcatheter ablation\$.ti,ab.
13. trans-catheter ablation\$.ti,ab.
14. ablative cure\$.ti,ab.
15. rf ablation\$.ti,ab.
16. arrhythmia ablation\$.ti,ab.
17. atrioventricular nod\$ablation\$.ti,ab.
18. av nod\$modification\$.ti,ab.
19. slow av nod\$pathway\$ablation\$.ti,ab.
20. his bundle ablation\$.ti,ab.
21. radiofrequent\$linear ablation\$.ti,ab.
22. radio-frequent\$linear ablation\$.ti,ab.
23. auricular fibrillation\$.ti,ab.
24. Atrial Fibrillation\$.ti,ab.
25. Atrium Fibrillation\$.ti,ab.
26. auricular flutter\$.ti,ab.
27. atrial tachycardia\$.ti,ab.
28. atrial tachyarrhythmia\$.ti,ab.
29. Atrium Tachycardia\$.ti,ab.
30. atrial arrhythmia\$.ti,ab.
31. heart fibrillation\$.ti,ab.
32. typical flutter\$.ti,ab.
33. Atrial Fibrillation/
34. Atrial Flutter/
35. Tachycardia, Atrial/
36. Atrial flutter\$.ti,ab
37. or/1–22
38. or/23–36
39. 37 and 38
40. limit 39 to yr="2000 – 2006"

EMBASE

OvidWeb – 1980 to 2006 Week 29. Searched 25 July 2006. URL: <http://gateway.ovid.com/athens>

This search strategy resulted in 2184 records.

1. catheter ablation/
2. catheter ablation\$.ti,ab.

3. electric\$ablation\$.ti,ab.
4. fulguration\$.ti,ab.
5. electrofulguration\$.ti,ab.
6. cryoablation\$.ti,ab.
7. radiofrecuen\$ablation\$.ti,ab.
8. radio-frecuen\$ablation\$.ti,ab.
9. RFA.ti,ab.
10. ablation catheter\$.ti,ab.
11. atrial flutter ablation\$.ti,ab.
12. transcatheter ablation\$.ti,ab.
13. trans-catheter ablation\$.ti,ab.
14. ablative cure\$.ti,ab.
15. rf ablation\$.ti,ab.
16. arrhythmia ablation\$.ti,ab.
17. atrioventricular nod\$ablation\$.ti,ab.
18. av nod\$modification\$.ti,ab.
19. slow av nod\$pathway\$ablation\$.ti,ab.
20. his bundle ablation\$.ti,ab.
21. radiofrecuen\$linear ablation\$.ti,ab.
22. radio-frecuen\$linear ablation\$.ti,ab.
23. auricular fibrillation\$.ti,ab.
24. Atrial Fibrillation\$.ti,ab.
25. Atrium Fibrillation\$.ti,ab.
26. auricular flutter\$.ti,ab.
27. atrial tachycardia\$.ti,ab.
28. atrial tachyarrhythmia\$.ti,ab.
29. Atrium Tachycardia\$.ti,ab.
30. atrial arrhythmia\$.ti,ab.
31. heart fibrillation\$.ti,ab.
32. typical flutter\$.ti,ab.
33. Heart Atrium Fibrillation/
34. Heart Atrium Flutter/
35. Atrial flutter\$.ti,ab
36. or/1-22
37. or/23-35
38. 36 and 37
39. limit 37 to yr="2000 - 2007" (2184)

Health Technology Assessment (HTA) Database

CRD Internal Database – July 2006. Searched 26 July 2006.

The same search strategy was used as for the DARE database. This search produced nine records.

MEDLINE

OvidWeb – 1966 to July Week 2 2006. Searched 25 July 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 2057 records.

1. catheter ablation/
2. 2 catheter ablation\$.ti,ab.
3. electric\$ablation\$.ti,ab.
4. fulguration\$.ti,ab.

5. electrofulguration\$.ti,ab.
6. cryoablation\$.ti,ab.
7. radiofrecuen\$ablation\$.ti,ab.
8. radio-frecuen\$ablation\$.ti,ab.
9. RFA.ti,ab.
10. ablation catheter\$.ti,ab.
11. atrial flutter ablation\$.ti,ab.
12. transcatheter ablation\$.ti,ab.
13. trans-catheter ablation\$.ti,ab.
14. ablative cure\$.ti,ab.
15. rf ablation\$.ti,ab.
16. arrhythmia ablation\$.ti,ab.
17. atrioventricular nod\$ablation\$.ti,ab.
18. av nod\$modification\$.ti,ab.
19. slow av nod\$pathway\$ablation\$.ti,ab.
20. his bundle ablation\$.ti,ab.
21. radiofrecuen\$linear ablation\$.ti,ab.
22. radio-frecuen\$linear ablation\$.ti,ab.
23. auricular fibrillation\$.ti,ab.
24. Atrial Fibrillation/
25. Atrial Fibrillation\$.ti,ab.
26. Atrium Fibrillation\$.ti,ab.
27. Atrial Flutter/
28. auricular flutter\$.ti,ab.
29. Atrial Flutter\$.ti,ab.
30. atrial tachycardia\$.ti,ab.
31. atrial tachyarrhythmia\$.ti,ab.
32. Atrium Tachycardia\$.ti,ab.
33. atrial arrhythmia\$.ti,ab.
34. heart fibrillation\$.ti,ab.
35. tachycardia, ectopic atrial/
36. typical flutter\$.ti,ab.
37. or/1-22
38. or/23-36
39. 37 and 38
40. limit 39 to yr="2000 - 2006"

MEDLINE In-process and other non-indexed citations

OvidWeb – 24 July 2006. Searched 25 July 2006.

URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 109 records.

1. catheter ablation\$.ti,ab.
2. electric\$ablation\$.ti,ab.
3. fulguration\$.ti,ab.
4. electrofulguration\$.ti,ab.
5. cryoablation\$.ti,ab.
6. radiofrecuen\$ablation\$.ti,ab.
7. radio-frecuen\$ablation\$.ti,ab.
8. RFA.ti,ab.
9. ablation catheter\$.ti,ab.
10. atrial flutter ablation\$.ti,ab.
11. transcatheter ablation\$.ti,ab.
12. trans-catheter ablation\$.ti,ab.

13. ablative cure\$.ti,ab.
14. rf ablation\$.ti,ab.
15. arrhythmia ablation\$.ti,ab.
16. atrioventricular nod\$ablation\$.ti,ab.
17. av nod\$modification\$.ti,ab.
18. slow av nod\$pathway\$ablation\$.ti,ab.
19. his bundle ablation\$.ti,ab.
20. radiofrecuen\$linear ablation\$.ti,ab.
21. radio-frecuen\$linear ablation\$.ti,ab.
22. auricular fibrillation\$.ti,ab.
23. Atrial Fibrillation\$.ti,ab.
24. Atrium Fibrillation\$.ti,ab.
25. auricular flutter\$.ti,ab.
26. Atrial Flutter\$.ti,ab.
27. atrial tachycardia\$.ti,ab.
28. atrial tachyarrhythmia\$.ti,ab.
29. Atrium Tachycardia\$.ti,ab.
30. atrial arrhythmia\$.ti,ab.
31. heart fibrillation\$.ti,ab.
32. typical flutter\$.ti,ab.
33. or/1–21
34. or/22–32
35. 33 and 34
36. limit 36 to yr="2000 – 2006"

Science Citation Index (SCI)

Web of Knowledge – 1956 to present. Searched 26 July 2006. URL: <http://wos.mimas.ac.uk/>

This search strategy retrieved 2889 records.

catheter ablation* OR electric* ablation* OR fulguration* OR electrofulguration* OR cryoablation* OR radiofrecuen* ablation* OR radio-frecuen* ablation* OR RFA OR ablation catheter* OR atrial flutter ablation* OR transcatheter ablation* OR trans-catheter ablation* OR ablative cure* OR rf ablation* OR arrhythmia ablation* OR atrioventricular nod* ablation* OR av nod* modification* OR slow av nod* pathway* ablation* OR his bundle ablation* OR radiofrecuen* linear ablation* OR radio-frecuen* linear ablation*

AND

auricular fibrillation* OR atrial fibrillation* OR atrium fibrillation* OR auricular flutter* OR atrial flutter* OR atrial tachycardia* OR atrial tachyarrhythmia* OR atrium tachycardia* OR atrial arrhythmia* OR heart fibrillation* OR typical flutter*

Databases of conference proceedings

ISI Proceedings: Science and Technology

Web of Knowledge – 1990 to present. Searched 27 July 2006. URL: <http://wos.mimas.ac.uk/>

This database was searched with the same search strategy as for SCI and produced 597 records.

Zetoc Conferences

MIMAS – 1993 to present. Searched 26 July 2006. URL: <http://zetoc.mimas.ac.uk/>

After within-database deduplication this series of individual search strings retrieved 288 records.

“catheter ablation*” – 202 records

“electric* ablation*” – 1 record

fulguration – 14 records

electrofulguration – 0 records

cryoablation – 89 records

“radiofrecuen* ablation*” – 201 records

“radio-frecuen* ablation*” – 19 records

rfa – 29 records

“ablation catheter*” – 6 records

“atrial flutter ablation*” – 2 records

“transcatheter ablation*” – 2 records

“trans-catheter ablation*” – 0 records

“ablative cure*” – 1 record

“rf ablation*” – 26 records

“arrhythmia ablation*” – 0 records

“atrioventricular nod* ablation*” – 3 records

“av nod* modification*” – 2 records

“slow av nod* pathway ablation*” – 0 records

“his bundle ablation*” – 4 records

“radiofrecuen* linear ablation*” – 0 records

“radio-frecuen* linear ablation*” – 0 records

Economic databases

EconLit

WebSPIRS – 1969 to June 2006. Searched 26 July 2006. URL: <http://arc.uk.ovid.com/>

This search retrieved no records.

#1 catheter ablation* OR electric* ablation* OR fulguration* OR electrofulguration* OR cryoablation* OR radiofrecuen* ablation* OR radio-frecuen* ablation* OR RFA OR ablation catheter* OR atrial flutter ablation* OR transcatheter ablation* OR trans-catheter ablation* OR ablative cure* OR rf ablation* OR arrhythmia ablation* OR atrioventricular nod* ablation* OR av nod* modification* OR slow av nod* pathway* ablation* OR his bundle ablation* OR radiofrecuen* linear ablation* OR radio-frecuen* linear ablation*

#2 auricular fibrillation* OR atrial fibrillation* OR atrium fibrillation* OR auricular flutter* OR atrial flutter* OR atrial tachycardia* OR atrial tachyarrhythmia* OR atrium tachycardia* OR atrial arrhythmia* OR heart fibrillation* OR typical flutter*

#1 and #2

Health Economics Evaluation Database (HEED)

CD-ROM – July 2006. Searched 26 July 2006.

This search strategy retrieved 12 records.

ablation* OR fulguration* OR electrofulguration* OR cryoablation* OR ablative OR av OR rfa

AND

fibrillation* OR tachyarrhythmia* OR tachycardia* OR arrhythmia* OR flutter*

IDEAS

Current. Searched 26 July 2006. URL: <http://ideas.repec.org/>

This search strategy retrieved no records.

ablation* fulguration* electrofulguration* cryoablation* ablative av

NHS Economic Evaluation Database (NHS EED)

CRD Internal Database – July 2006. Searched 26 July 2006.

The same search strategy was used as for DARE. This search produced six records.

Guidelines databases

BMJ Clinical Evidence

URL: www.clinicalevidence.com/cweb/index.jsp

No relevant articles (one forthcoming relevant article).

Cardiovascular Diseases Specialist Library

URL: www.library.nhs.uk/cardiovascular/

A search for catheter ablation retrieved seven guidelines.

Health Evidence Bulletin Wales

URL: <http://hebw.cf.ac.uk/>

This database was browsed and no relevant guidelines were identified.

HSTAT

URL: www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat

A search for catheter ablation retrieved two guidelines.

National Guidelines Clearing House

URL: www.guideline.gov/

A search for catheter ablation retrieved 22 guidelines.

NICE

URL: www.nice.org.uk/

A search for catheter ablation retrieved 124 guidelines.

NLH Guidelines Finder

URL: www.library.nhs.uk/guidelinesFinder/

A search for catheter ablation retrieved six guidelines.

Scottish Intercollegiate Guidelines Network (SIGN)

URL: www.sign.ac.uk/

This database was browsed and one potentially relevant guideline was identified.

TRIP

URL: www.tripdatabase.com/index.html

A search for catheter ablation retrieved 32 guidelines.

Databases for ongoing and recently completed research ClinicalTrials.gov

Searched 2 August 2006. URL: www.clinicaltrials.gov/

This search retrieved 35 records, which were all entered into the EndNote library.

(catheter ablation OR electric ablation OR fulguration OR electrofulguration OR cryoablation OR radiofrequency ablation OR radio-frequency ablation OR RFA OR ablation catheter OR atrial flutter ablation OR transcatheter ablation OR trans-catheter ablation OR ablative cure OR rf ablation OR arrhythmia ablation OR atrioventricular nod ablation OR av nod modification OR slow av nod pathway ablation OR his bundle ablation OR radiofrequency linear ablation OR radio-frequency linear ablation) AND (auricular fibrillation OR atrial fibrillation OR atrium fibrillation OR auricular flutter OR atrial flutter OR atrial tachycardia OR atrial tachyarrhythmia OR atrium tachycardia OR atrial arrhythmia OR heart fibrillation OR typical flutter) [ALL-FIELDS]

MetaRegister of Controlled Trials

Searched 9 August 2006. URL: www.controlled-trials.com/

All registers [except ClinicalTrials.gov and the National Research Register (NRR), which were searched directly] were selected. This search strategy retrieved 48 records (six studies were deemed potentially relevant and imported into the EndNote library).

The search was for any of these words:

ablation fulguration electrofulguration cryoablation RFA ablative

National Research Register (NRR)

2006 Issue 3. Searched 9 August 2006. URL: www.update-software.com/national/

This search retrieved 30 records, which were all entered into the EndNote library.

#1 catheter ablation* OR electric* ablation* OR fulguration* OR electrofulguration* OR cryoablation* OR radiofrequen* ablation* OR radio-frequen* ablation* OR RFA OR ablation catheter* OR atrial flutter ablation* OR transcatheter ablation* OR trans-catheter ablation* OR ablative cure* OR rf ablation* OR arrhythmia ablation* OR atrioventricular nod* ablation* OR av nod* modification* OR slow av nod* pathway* ablation* OR his bundle ablation* OR radiofrequen* linear ablation* OR radio-frequen* linear ablation*

#2 auricular fibrillation* OR atrial fibrillation* OR atrium fibrillation* OR auricular flutter* OR atrial flutter* OR atrial tachycardia* OR atrial tachyarrhythmia* OR atrium tachycardia* OR atrial arrhythmia* OR heart fibrillation* OR typical flutter*

#3 #1 and #2

Research Findings Electronic Register (ReFeR)

Searched 9 August 2006. URL: www.info.doh.gov.uk/doh/refr_web.nsf/Home?OpenForm

This search strategy retrieved five records (none of which were relevant and which were therefore not imported into the EndNote library).

ablation OR fulguration OR electrofulguration OR cryoablation OR RFA OR ablative

Results from search strategies for studies on the clinical and cost-effectiveness of catheter ablation

A total of 4860 unique bibliographic records (9902 before deduplication) and 196 guidelines were retrieved.

Update search strategies for studies on the clinical and cost-effectiveness of catheter ablation BIOSIS

DIALOG. Searched 10 April 2007. URL: <http://library.dialog.com/>

The previous search strategy was rerun and restricted to records added to the database since July 2006. This retrieved 226 records.

CENTRAL

Cochrane Library – 2007 Issue 2. Searched 4 April 2007. URL: www.library.nhs.uk/

The previous search strategy was rerun. This retrieved 156 records, which were then deduplicated against the original searches.

Cumulative Index to Nursing and Allied Health Literature (CINAHL)

OvidWeb – 1982 to March Week 5 2007. Searched 4 April 2007. URL: <http://gateway.ovid.com/athens>

The previous search strategy was rerun and restricted to records added to the database since July 2006. This retrieved 112 records.

EMBASE

OvidWeb – 1980 to 2007 Week 13. Searched 4 April 2007. URL: <http://gateway.ovid.com/athens>

The previous search strategy was rerun and restricted to records added to the database since July 2006. This retrieved 448 records.

MEDLINE and MEDLINE In-process and other non-indexed citations

1950 to present. Searched 4 April 2007.

The previous search strategy was rerun and restricted to records added to the database since July 2006. This retrieved 379 records.

Science Citation Index (SCI)

Web of Knowledge – 1956 to present. Searched 4 April 2007. URL: <http://wos.mimas.ac.uk/>

The previous search strategy was rerun and restricted to publications from 2006 and 2007. This retrieved 765 records.

Results from the update search strategies for studies on the clinical and cost-effectiveness of catheter ablation

All of the results of the update searches were entered into an EndNote library and deduplicated against each other and the original searches. This resulted in an EndNote library of 772 records (2086 before deduplication).

Search strategies for studies on the clinical and cost-effectiveness of selected comparators to catheter ablation**Clinical effectiveness of selected comparators to catheter ablation Cochrane Database of Systematic Reviews (CDSR)**

Cochrane Library – 2006 Issue 3. Searched 17 October 2006. URL: www.library.nhs.uk/

This search strategy retrieved 22 reviews (18 completed and four protocols).

- #1 Atrioventricular Node/
- #2 (av near/2 node near/2 ablat*)
- #3 (av near/2 nodal near/2 ablat*).
- #4 (atrioventricular near/2 node near/2 ablat*)
- #5 (atrioventricular near/2 nodal near/2 ablat*)
- #6 (atrio-ventricular near/2 node near/2 ablat*)
- #7 (atrio-ventricular near/2 nodal near/2 ablat*)
- #8 (a-v near/2 node near/2 ablati*)
- #9 (a-v near/2 nodal near/2 ablat*)
- #10 Amiodarone/
- #11 amiodarone
- #12 cordarone
- #13 exp Anti-Arrhythmia Agents/
- #14 antiarrhythmia
- #15 antiarrhythmic
- #16 Anti-Arrhythmia
- #17 Anti-Arrhythmic
- #18 antifibrillatory
- #19 cardiac next depressant*
- #20 myocardial next depressant*
- #21 (rate near/2 control*)
- #22 (rhythm near/2 control*)
- #23 auricular next fibrillation*
- #24 Atrial Fibrillation/
- #25 Atrial next Fibrillation*
- #26 Atrium next Fibrillation*
- #27 Atrial Flutter/
- #28 auricular next flutter*
- #29 Atrial next flutter*
- #30 atrial next tachycardia*
- #31 atrial next tachyarrhythmia*
- #32 Atrium next tachycardia*
- #33 atrial next arrhythmia*
- #34 heart next fibrillation*
- #34 tachycardia, ectopic atrial/
- #35 typical next flutter*

#36 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)

#37 (#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)

#38 (#36 AND #37)

Cumulative Index to Nursing and Allied Health Literature (CINAHL)

OvidWeb – 1982 to October Week 1 2006. Searched 17 October 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 23 records.

1. Atrioventricular Node/
2. (av adj2 node adj2 ablat\$).ti,ab.
3. (av adj2 nodal adj2 ablat\$).ti,ab.
4. (atrioventricular adj2 node adj2 ablat\$).ti,ab.
5. (atrioventricular adj2 nodal adj2 ablat\$).ti,ab.
6. (atrio-ventricular adj2 node adj2 ablat\$).ti,ab.
7. (atrio-ventricular adj2 nodal adj2 ablat\$).ti,ab.
8. (a-v adj2 node adj2 ablati\$).ti,ab.
9. (a-v adj2 nodal adj2 ablat\$).ti,ab.
10. Amiodarone/
11. amiodarone.ti,ab.
12. cordarone.ti,ab.
13. exp Anti-Arrhythmia Agents/
14. antiarrhythmia.ti,ab.
15. antiarrhythmic.ti,ab.
16. Anti-Arrhythmia.ti,ab.
17. Anti-Arrhythmic.ti,ab.
18. antifibrillatory.ti,ab.
19. cardiac depressant\$.ti,ab.
20. myocardial depressant\$.ti,ab.
21. (rate adj2 control\$).ti,ab.
22. (rhythm adj2 control\$).ti,ab.
23. (pace or pacing or pacemaker\$).ti,ab.
24. Pacemaker, Artificial/
25. auricular fibrillation\$.ti,ab.
26. Atrial Fibrillation/
27. Atrial Fibrillation\$.ti,ab.
28. Atrium Fibrillation\$.ti,ab.
29. Atrial Flutter/
30. auricular flutter\$.ti,ab.
31. Atrial Flutter\$.ti,ab.
32. atrial tachycardia\$.ti,ab.
33. atrial tachyarrhythmia\$.ti,ab.
34. Atrium Tachycardia\$.ti,ab.
35. atrial arrhythmia\$.ti,ab.
36. heart fibrillation\$.ti,ab.
37. tachycardia, ectopic atrial/

38. typical flutter\$.ti,ab.
39. or/25–38
40. CARDIAC PACING, ARTIFICIAL/
41. Meta Analysis/
42. systematic review/
43. systematic review.pt.
44. (systematic adj4 (review\$or overview\$)).ti,ab.
45. (literature adj2 review\$).ti,ab.
46. literature review/
47. or/41–46
48. auricular fibrillation.ti,ab.
49. Atrial Fibrillation/
50. Atrial Fibrillation\$.ti,ab.
51. Heart Atrium Fibrillation/
52. Atrium Fibrillation.ti,ab.
53. Atrial Flutter/
54. auricular flutter.ti,ab.
55. Atrial Flutter.ti,ab.
56. atrial tachycardia.ti,ab.
57. atrial tachyarrhythmia\$.ti,ab.
58. exp Tachycardia, Supraventricular/
59. Supraventricular Tachycardia\$.ti,ab.
60. Supraventricular Tachycardia/
61. Atrium Tachycardia.ti,ab.
62. cardiac arrhythmia\$.ti,ab.
63. atrioventricular junction\$.ti,ab.
64. atrial arrhythmia\$.ti,ab.
65. supraventricular arrhythmia\$.ti,ab.
66. premature cardiac complex\$.ti,ab.
67. atrial premature complex\$.ti,ab.
68. paroxysmal tachycardia\$.ti,ab.
69. heart arrhythmia\$.ti,ab.
70. atrium arrhythmia\$.ti,ab.
71. heart fibrillation\$.ti,ab.
72. Arrhythmia/
73. or/48–72
74. (or/1–24) or 40
75. 39 and 47 and 74
76. limit 75 to (english and yr="2000 – 2007")

Database of Abstracts of Reviews of Effects (DARE)

CRD Internal Database – October 2006. Searched 17 October 2006.

This search strategy produced 33 records.

```
s atrioventricular node/kwo
s av(2w)node(2w)ablat$
s av(2w)nodal(2w)ablat$
s atrioventricular(2w)node(2w)ablat$
s atrioventricular(2w)nodal(2w)ablat$
s atrio(w)ventricular(2w)node(2w)ablat$
s atrio(w)ventricular(2w)nodal(2w)ablat$
s a(w)v(2w)node(2w)ablati$
s a(w)v(2w)nodal(2w)ablat$
```

s amiodarone
s cordarone
s antiarrhythmia
s antiarrhythmic
s anti(w)arrhythmia
s anti(w)arrhythmic
s antifibrillatory
s cardiac(w)depressant\$
s myocardial(w)depressant\$
s rate(2w)control\$
s rhythm(2w)control\$
s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or
s10 or s11 or s12 or s13 or s14 or s15 or s16 or
s17 or s18 or s19 or s20
s auricular(w)fibrillation\$
s atrial(w)fibrillation\$
s atrium(w)fibrillation\$
s auricular(w)flutter\$
s atrial(w)flutter\$
s atrial(w)tachycardia\$
s atrial(w)tachyarrhythmia\$
s atrium(w)tachycardia\$
s atrial(w)arrhythmia\$
s heart(w)fibrillation\$
s typical(w)flutter\$
s s22 or s23 or s24 or s25 or s26 or s27 or s28 or
s29 or s30 or s31 or s32
s s21 and s33

EMBASE

OvidWeb – 1996 to 2006 Week 41. Searched 17
October 2006. URL: <http://gateway.ovid.com/athens>

This search strategy resulted in 203 records.

1. Atrioventricular Node/
2. (av adj2 node adj2 ablat\$.ti,ab.
3. (av adj2 nodal adj2 ablat\$.ti,ab.
4. (atrioventricular adj2 node adj2 ablat\$.ti,ab.
5. (atrioventricular adj2 nodal adj2 ablat\$.ti,ab.
6. (atrio-ventricular adj2 node adj2 ablat\$.ti,ab.
7. (atrio-ventricular adj2 nodal adj2 ablat\$.ti,ab.
8. (a-v adj2 node adj2 ablati\$.ti,ab.
9. (a-v adj2 nodal adj2 ablat\$.ti,ab.
10. Amiodarone/
11. amiodarone.ti,ab.
12. cordarone.ti,ab.
13. exp Anti-Arrhythmia Agents/
14. antiarrhythmia.ti,ab.
15. antiarrhythmic.ti,ab.
16. Anti-Arrhythmia.ti,ab.
17. Anti-Arrhythmic.ti,ab.
18. antifibrillatory.ti,ab.

19. cardiac depressant\$.ti,ab.
20. myocardial depressant\$.ti,ab.
21. (rate adj2 control\$.ti,ab.
22. (rhythm adj2 control\$.ti,ab.
23. (pace or pacing or pacemaker\$.ti,ab.
24. Pacemaker, Artificial/
25. cardiac pacing, artificial/
26. auricular fibrillation\$.ti,ab.
27. heart atrium Fibrillation/
28. Atrial Fibrillation\$.ti,ab.
29. Atrium Fibrillation\$.ti,ab.
30. heart atrium Flutter/
31. atrial flutter\$.ti,ab.
32. auricular flutter\$.ti,ab.
33. Atrial Flutter\$.ti,ab.
34. atrial tachycardia\$.ti,ab.
35. atrial tachyarrhythmia\$.ti,ab.
36. Atrium Tachycardia\$.ti,ab.
37. atrial arrhythmia\$.ti,ab.
38. heart fibrillation\$.ti,ab.
39. typical flutter\$.ti,ab.
40. Meta Analysis/
41. systematic review/
42. (systematic adj4 (review\$or overview\$)).ti,ab.
43. (literature adj2 review\$.ti,ab.
44. or/1–25
45. or/26–39
46. or/40–43
47. 44 and 45 and 46
48. limit 47 to (english language and yr="2000 –
2007")

**Health Technology Assessment
(HTA) Database**

CRD Internal Database – October 2006. Searched
17 October 2006.

This search strategy produced one record.

s atrioventricular node/kwo
s av(2w)node(2w)ablat\$
s av(2w)nodal(2w)ablat\$
s atrioventricular(2w)node(2w)ablat\$
s atrioventricular(2w)nodal(2w)ablat\$
s atrio(w)ventricular(2w)node(2w)ablat\$
s atrio(w)ventricular(2w)nodal(2w)ablat\$
s a(w)v(2w)node(2w)ablati\$
s a(w)v(2w)nodal(2w)ablat\$
s amiodarone
s cordarone
s antiarrhythmia
s antiarrhythmic
s anti(w)arrhythmia
s anti(w)arrhythmic
s antifibrillatory
s cardiac(w)depressant\$
s myocardial(w)depressant\$

s rate(2w)control\$
 s rhythm(2w)control\$
 s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or
 s10 or s11 or s12 or s13 or s14 or s15 or s16 or
 s17 or s18 or s19 or s20
 s auricular(w)fibrillation\$
 s atrial(w)fibrillation\$
 s atrium(w)fibrillation\$
 s auricular(w)flutter\$
 s atrial(w)flutter\$
 s atrial(w)tachycardia\$
 s atrial(w)tachyarrhythmia\$
 s atrium(w)tachycardia\$
 s atrial(w)arrhythmia\$
 s heart(w)fibrillation\$
 s typical(w)flutter\$
 s s22 or s23 or s24 or s25 or s26 or s27 or s28 or
 s29 or s30 or s31 or s32
 s s21 and s33

MEDLINE

OvidWeb – 1996 to October Week 1 2006. Searched
 17 October 2006. URL: [http://gateway.ovid.com/
 athens](http://gateway.ovid.com/athens)

This search strategy retrieved 73 records.

1. Atrioventricular Node/
 (av adj2 node adj2 ablat\$).ti,ab.
2. (av adj2 nodal adj2 ablat\$).ti,ab.
3. (atrioventricular adj2 node adj2 ablat\$).ti,ab.
4. (atrioventricular adj2 nodal adj2 ablat\$).ti,ab.
5. (atrio-ventricular adj2 node adj2 ablat\$).ti,ab.
6. (atrio-ventricular adj2 nodal adj2 ablat\$).ti,ab.
7. (a-v adj2 node adj2 ablati\$).ti,ab.
8. (a-v adj2 nodal adj2 ablat\$).ti,ab.
9. Amiodarone/
 amiodarone.ti,ab.
10. cordarone.ti,ab.
11. exp Anti-Arrhythmia Agents/
 antiarrhythmia.ti,ab.
12. antiarrhythmic.ti,ab.
13. Anti-Arrhythmia.ti,ab.
14. Anti-Arrhythmic.ti,ab.
15. antifibrillatory.ti,ab.
16. cardiac depressant\$.ti,ab.
17. myocardial depressant\$.ti,ab.
18. (rate adj2 control\$).ti,ab.
19. (rhythm adj2 control\$).ti,ab.
20. auricular fibrillation\$.ti,ab.
21. Atrial Fibrillation/
 Atrial Fibrillation\$.ti,ab.
22. Atrium Fibrillation\$.ti,ab.
23. Atrial Flutter/
 auricular flutter\$.ti,ab.
24. Atrial Flutter\$.ti,ab.

25. atrial tachycardia\$.ti,ab.
26. atrial tachyarrhythmia\$.ti,ab.
27. Atrium Tachycardia\$.ti,ab.
28. atrial arrhythmia\$.ti,ab.
29. heart fibrillation\$.ti,ab.
30. tachycardia, ectopic atrial/
 typical flutter\$.ti,ab.
31. or/23–36
32. (pace or pacing or pacemaker\$).ti,ab.
33. Cardiac Pacing, Artificial/
 Pacemaker, Artificial/
 (or/1–22) or (or/38–40)
34. 37 and 41
35. meta-analysis.ti,ab.
36. meta-analysis.pt.
37. meta-analysis/
 (systematic\$adj4 (review\$or overview\$)).ti,ab.
38. “review literature”/
 (literature adj2 review\$).ti,ab.
39. or/43–48
40. 42 and 49
41. limit 50 to english language
42. limit 51 to yr=“2000 – 2006”

**MEDLINE In-process and
 other non-indexed citations**

OvidWeb – October 16 2006. Searched 17 October
 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved two records.

1. (av adj2 node adj2 ablat\$).ti,ab.
2. (av adj2 nodal adj2 ablat\$).ti,ab.
3. (atrioventricular adj2 node adj2 ablat\$).ti,ab.
4. (atrioventricular adj2 nodal adj2 ablat\$).ti,ab.
5. (atrio-ventricular adj2 node adj2 ablat\$).ti,ab.
6. (atrio-ventricular adj2 nodal adj2 ablat\$).ti,ab.
7. (a-v adj2 node adj2 ablati\$).ti,ab.
8. (a-v adj2 nodal adj2 ablat\$).ti,ab.
9. amiodarone.ti,ab
10. cordarone.ti,ab.
11. antiarrhythmia.ti,ab.
12. antiarrhythmic.ti,ab.
13. Anti-Arrhythmia.ti,ab.
14. Anti-Arrhythmic.ti,ab.
15. antifibrillatory.ti,ab.
16. cardiac depressant\$.ti,ab.
17. myocardial depressant\$.ti,ab.
18. (rate adj2 control\$).ti,ab.
19. (rhythm adj2 control\$).ti,ab.
20. (pace or pacing or pacemaker\$).ti,ab.
21. auricular fibrillation\$.ti,ab.
22. Atrial Fibrillation\$.ti,ab.
23. Atrium Fibrillation\$.ti,ab.
24. atrial flutter\$.ti,ab.
25. auricular flutter\$.ti,ab.

26. Atrial Flutter\$.ti,ab.
27. atrial tachycardia\$.ti,ab.
28. atrial tachyarrhythmia\$.ti,ab.
29. Atrium Tachycardia\$.ti,ab.
30. atrial arrhythmia\$.ti,ab.
31. heart fibrillation\$.ti,ab.
32. typical flutter\$.ti,ab.
33. (systematic adj4 (review\$or overview\$)).ti,ab.
34. (literature adj2 review\$).ti,ab.
35. meta-analysis.pt.
36. or/1–20
37. or/21–32
38. or/33–35
39. 36 and 37 and 38

Results of search strategies for studies on the clinical effectiveness of selected comparators to catheter ablation

A total of 271 unique bibliographic records were retrieved (357 before deduplication).

Cost-effectiveness of selected comparators to catheter ablation

No date restrictions were applied to any of the searches and, where possible, the searches were limited to English language only.

MEDLINE

OvidWeb – 1966 to November Week 2 2006.
Searched 21 November 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 193 records.

1. Atrioventricular Node/
2. (av adj2 node adj2 ablat\$).ti,ab.
3. (av adj2 nodal adj2 ablat\$).ti,ab.
4. (atrioventricular adj2 node adj2 ablat\$).ti,ab.
5. (atrioventricular adj2 nodal adj2 ablat\$).ti,ab.
6. (atrio-ventricular adj2 node adj2 ablat\$).ti,ab.
7. (atrio-ventricular adj2 nodal adj2 ablat\$).ti,ab.
8. (a-v adj2 node adj2 ablati\$).ti,ab.
9. (a-v adj2 nodal adj2 ablat\$).ti,ab.
10. Amiodarone/
11. amiodarone.ti,ab.
12. cordarone.ti,ab.
13. exp Anti-Arrhythmia Agents/
14. antiarrhythmia.ti,ab.
15. antiarrhythmic.ti,ab.
16. Anti-Arrhythmia.ti,ab.
17. Anti-Arrhythmic.ti,ab.
18. antifibrillatory.ti,ab.
19. cardiac depressant\$.ti,ab.
20. myocardial depressant\$.ti,ab.
21. (rate adj2 control\$).ti,ab.
22. (rhythm adj2 control\$).ti,ab.

23. or/1–22
24. auricular fibrillation\$.ti,ab.
25. Atrial Fibrillation/
26. Atrial Fibrillation\$.ti,ab.
27. Atrium Fibrillation\$.ti,ab.
28. Atrial Flutter/
29. auricular flutter\$.ti,ab.
30. Atrial Flutter\$.ti,ab.
31. atrial tachycardia\$.ti,ab.
32. atrial tachyarrhythmia\$.ti,ab.
33. Atrium Tachycardia\$.ti,ab.
34. atrial arrhythmia\$.ti,ab.
35. heart fibrillation\$.ti,ab.
36. tachycardia, ectopic atrial/
37. typical flutter\$.ti,ab.
38. or/24–37
39. 23 and 38
40. economics/
41. exp “costs and cost analysis”/
42. economic value of life/
43. exp economics,hospital/
44. exp economics, medical/
45. economics, nursing/
46. economics, pharmaceutical/
47. exp models,economic/
48. exp “fees and charges”/
49. exp budgets/
50. ec.fs.
51. (cost or costs or costly or costing\$).ti,ab.
52. (economic\$or price\$or pricing or pharmaco-economic\$).ti,ab.
53. or/40–52
54. 39 and 53
55. 54
56. limit 55 to english language

MEDLINE In-process and other non-indexed citations

OvidWeb – November 15 2006. Searched 21 November 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved ten records.

1. (av adj2 node adj2 ablat\$).ti,ab.
2. (av adj2 nodal adj2 ablat\$).ti,ab.
3. (atrioventricular adj2 node adj2 ablat\$).ti,ab.
4. (atrioventricular adj2 nodal adj2 ablat\$).ti,ab.
5. (atrio-ventricular adj2 node adj2 ablat\$).ti,ab.
6. (atrio-ventricular adj2 nodal adj2 ablat\$).ti,ab.
7. (a-v adj2 node adj2 ablati\$).ti,ab.
8. (a-v adj2 nodal adj2 ablat\$).ti,ab.
9. amiodarone.ti,ab.
10. cordarone.ti,ab.
11. antiarrhythmia.ti,ab.
12. antiarrhythmic.ti,ab.

13. Anti-Arrhythmia.ti,ab.
14. Anti-Arrhythmic.ti,ab.
15. antifibrillatory.ti,ab.
16. cardiac depressant\$.ti,ab.
17. myocardial depressant\$.ti,ab.
18. (rate adj2 control\$.ti,ab.
19. (rhythm adj2 control\$.ti,ab.
20. or/1-19
21. auricular fibrillation\$.ti,ab.
22. Atrial Fibrillation\$.ti,ab.
23. Atrium Fibrillation\$.ti,ab.
24. auricular flutter\$.ti,ab.
25. Atrial Flutter\$.ti,ab.
26. atrial tachycardia\$.ti,ab.
27. atrial tachyarrhythmia\$.ti,ab.
28. Atrium Tachycardia\$.ti,ab.
29. atrial arrhythmia\$.ti,ab.
30. heart fibrillation\$.ti,ab.
31. typical flutter\$.ti,ab.
32. or/21-31
33. 20 and 32
34. ec.fs.
35. (cost or costs or costly or costing\$.ti,ab.
36. (economic\$or price\$or pricing or pharmaco-economic\$.ti,ab.
37. or/34-36
38. 33 and 37
39. 38
40. limit 39 to english language

EMBASE

OvidWeb – 1980 to 2006 Week 46. Searched 21 November 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 417 records.

1. Atrioventricular Node/
2. (av adj2 node adj2 ablat\$.ti,ab.
3. (av adj2 nodal adj2 ablat\$.ti,ab.
4. (atrioventricular adj2 node adj2 ablat\$.ti,ab.
5. (atrioventricular adj2 nodal adj2 ablat\$.ti,ab.
6. (atrio-ventricular adj2 node adj2 ablat\$.ti,ab.
7. (atrio-ventricular adj2 nodal adj2 ablat\$.ti,ab.
8. (a-v adj2 node adj2 ablati\$.ti,ab.
9. (a-v adj2 nodal adj2 ablat\$.ti,ab.
10. Amiodarone/
11. amiodarone.ti,ab.
12. cordarone.ti,ab.
13. exp Anti-Arrhythmia Agents/
14. antiarrhythmia.ti,ab.
15. antiarrhythmic.ti,ab.
16. Anti-Arrhythmia.ti,ab.
17. Anti-Arrhythmic.ti,ab.
18. antifibrillatory.ti,ab.
19. cardiac depressant\$.ti,ab.

20. myocardial depressant\$.ti,ab.
21. (rate adj2 control\$.ti,ab.
22. (rhythm adj2 control\$.ti,ab.
23. or/1-22
24. auricular fibrillation\$.ti,ab.
25. heart atrium Fibrillation/
26. atrial Fibrillation\$.ti,ab.
27. Atrium Fibrillation\$.ti,ab.
28. heart atrium Flutter/
29. atrial flutter\$.ti,ab.
30. auricular flutter\$.ti,ab.
31. Atrial Flutter\$.ti,ab.
32. atrial tachycardia\$.ti,ab.
33. atrial tachyarrhythmia\$.ti,ab.
34. Atrium Tachycardia\$.ti,ab.
35. atrial arrhythmia\$.ti,ab.
36. heart fibrillation\$.ti,ab.
37. typical flutter\$.ti,ab.
38. or/24-37
39. 23 and 38
40. exp health economics/
41. cost/
42. exp health care cost/
43. exp economic evaluation/
44. (cost or costs or costed or costly or costing\$.ti,ab.
45. (economic\$or pharmaco-economic\$or price\$or pricing).ti,ab.
46. or/40-45
47. 39 and 46
48. 47
49. limit 48 to english language

Cumulative Index to Nursing and Allied Health Literature (CINAHL)

OvidWeb – 1982 to November Week 2 2006. Searched 21 November 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 36 records.

1. Atrioventricular Node/
2. (av adj2 node adj2 ablat\$.ti,ab.
3. (av adj2 nodal adj2 ablat\$.ti,ab.
4. (atrioventricular adj2 node adj2 ablat\$.ti,ab.
5. (atrioventricular adj2 nodal adj2 ablat\$.ti,ab.
6. (atrio-ventricular adj2 node adj2 ablat\$.ti,ab.
7. (atrio-ventricular adj2 nodal adj2 ablat\$.ti,ab.
8. (a-v adj2 node adj2 ablati\$.ti,ab.
9. (a-v adj2 nodal adj2 ablat\$.ti,ab.
10. Amiodarone/
11. amiodarone.ti,ab.
12. cordarone.ti,ab.
13. exp Anti-Arrhythmia Agents/
14. antiarrhythmia.ti,ab.
15. antiarrhythmic.ti,ab.

16. Anti-Arrhythmia.ti,ab.
17. Anti-Arrhythmic.ti,ab.
18. antifibrillatory.ti,ab.
19. cardiac depressant\$.ti,ab.
20. myocardial depressant\$.ti,ab.
21. (rate adj2 control\$.ti,ab.
22. (rhythm adj2 control\$.ti,ab.
23. or/1–22
24. auricular fibrillation\$.ti,ab.
25. Atrial Fibrillation/
26. Atrial Fibrillation\$.ti,ab.
27. Atrium Fibrillation\$.ti,ab.
28. Atrial Flutter/
29. auricular flutter\$.ti,ab.
30. Atrial Flutter\$.ti,ab.
31. atrial tachycardia\$.ti,ab.
32. atrial tachyarrhythmia\$.ti,ab.
33. Atrium Tachycardia\$.ti,ab.
34. atrial arrhythmia\$.ti,ab.
35. heart fibrillation\$.ti,ab.
36. tachycardia, atrial/
37. typical flutter\$.ti,ab.
38. or/24–37
39. 23 and 38
40. economics/
41. exp “costs and cost analysis”/
42. economic value of life/
43. economics, pharmaceutical/
44. exp “fees and charges”/
45. exp budgets/
46. ec.fs.
47. (cost or costs or costly or costing\$.ti,ab.
48. (economic\$or price\$or pricing or pharmacoeconomic\$.ti,ab.
49. or/40–48
50. 39 and 49
51. 50
52. limit 51 to English

Health Economics Evaluation Database (HEED)

CD-ROM – November 2006. Searched 21 November 2006.

This search strategy retrieved 21 records.

atrioventricular node or atrioventricular nodal or av node or av nodal or a v node or a v nodal or amiodarone or cordarone or antiarrhythmia or antiarrhythmic or anti arrhythmia or anti arrhythmic or antifibrillatory or cardiac depressant or cardiac depressants or myocardial depressant or myocardial depressants or rate control or rhythm control

AND

auricular fibrillation or atrial fibrillation or atrium fibrillation or auricular flutter or atrial flutter or atrial tachycardia or atrial tachyarrhythmia or atrium tachycardia or atrial arrhythmia or heart fibrillation or typical flutter

NHS Economic Evaluation Database (NHS EED)

CRD Internal Database – November 2006. Searched 21 November 2006.

This search strategy retrieved 21 records.

s atrioventricular node/kwo
s av(2w)node(2w)ablat\$
s av(2w)nodal(2w)ablat\$
s atrioventricular(2w)node(2w)ablat\$
s atrioventricular(2w)nodal(2w)ablat\$
s atrio(w)ventricular(2w)node(2w)ablat\$
s atrio(w)ventricular(2w)nodal(2w)ablat\$
s a(w)v(2w)node(2w)ablati\$
s a(w)v(2w)nodal(2w)ablat\$
s amiodarone
s cordarone
s antiarrhythmia
s antiarrhythmic
s anti(w)arrhythmia
s anti(w)arrhythmic
s antifibrillatory
s cardiac(w)depressant\$
s myocardial(w)depressant\$
s rate(2w)control\$
s rhythm(2w)control\$
s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or s19 or s20
s auricular(w)fibrillation\$
s atrial(w)fibrillation\$
s atrium(w)fibrillation\$
s auricular(w)flutter\$
s atrial(w)flutter\$
s atrial(w)tachycardia\$
s atrial(w)tachyarrhythmia\$
s atrium(w)tachycardia\$
s atrial(w)arrhythmia\$
s heart(w)fibrillation\$
s typical(w)flutter\$
s s22 or s23 or s24 or s25 or s26 or s27 or s28 or s29 or s30 or s31 or s32
s s21 and s33
s english/xla
s s34 and s35

Results of search strategies for studies on the cost-effectiveness of selected comparators to catheter ablation

A total of 496 unique bibliographic records were retrieved (717 before deduplication).

Additional search strategies for information to inform the decision-analytic model

Quality of life searches

British Nursing Index

OvidWeb – 1994 to September 2006. Searched 2 October 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved four records.

1. (utilit\$approach\$or health gain or hui or hui2 or hui3).ti,ab.
2. (health measurement\$scale\$or health measurement\$questionnaire\$).ti,ab.
3. (standard gamble\$or categor\$scal\$or linear scal\$or linear analog\$or visual scal\$or magnitude estimat\$).ti,ab.
4. (time trade off\$or rosser\$classif\$or rosser\$matrix or rosser\$distress\$or hrqol).ti,ab.
5. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
6. (multiattribute\$health ind\$or multi attribute\$health ind\$).ti,ab.
7. (health utilit\$index or health utilit\$indices).ti,ab.
8. (multiattribute\$theor\$or multi attribute\$theor\$or multiattribute\$analys\$or multi attribute\$analys\$).ti,ab.
9. (health utilit\$scale\$or classification of illness state\$).ti,ab.
10. health state\$utilit\$.ti,ab.
11. well year\$.ti,ab.
12. (multiattribute\$utilit\$or multi attribute\$utilit\$).ti,ab.
13. health utilit\$scale\$.ti,ab.
14. (euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.
15. (qualy or qaly or qualys or qalys or quality adjusted life year\$).ti,ab.
16. willingness to pay.ti,ab.
17. (hye or hyes or health\$year\$equivalent\$).ti,ab.
18. (person trade off\$or person tradeoff\$or time tradeoff\$or time trade off\$).ti,ab.
19. theory utilit\$.ti,ab.
20. (sf36 or sf 36).ti,ab.
21. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or

- shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
22. (sf 6d or sf6d or short form 6d or shortform 6d or sf six\$or shortform six\$or short form six\$).ti,ab.
23. or/1–22
24. auricular fibrillation\$.ti,ab.
25. Atrial Fibrillation\$.ti,ab.
26. Atrium Fibrillation\$.ti,ab.
27. auricular flutter\$.ti,ab.
28. Atrial Flutter\$.ti,ab.
29. atrial tachycardia\$.ti,ab.
30. atrial tachyarrhythmia\$.ti,ab.
31. Atrium Tachycardia\$.ti,ab.
32. atrial arrhythmia\$.ti,ab.
33. heart fibrillation\$.ti,ab.
34. typical flutter\$.ti,ab.
35. exp heart disorders/
36. or/24–35
37. 23 and 36

Cumulative Index to Nursing and Allied Health Literature (CINAHL)

OvidWeb – 1982 to September Week 4 2006. Searched 2 October 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 15 records.

1. (utilit\$approach\$or health gain or hui or hui2 or hui3).ti,ab.
2. (health measurement\$scale\$or health measurement\$questionnaire\$).ti,ab.
3. (standard gamble\$or categor\$scal\$or linear scal\$or linear analog\$or visual scal\$or magnitude estimat\$).ti,ab.
4. (time trade off\$or rosser\$classif\$or rosser\$matrix or rosser\$distress\$or hrqol).ti,ab.
5. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
6. (multiattribute\$health ind\$or multi attribute\$health ind\$).ti,ab.
7. (health utilit\$index or health utilit\$indices).ti,ab.
8. (multiattribute\$theor\$or multi attribute\$theor\$or multiattribute\$analys\$or multi attribute\$analys\$).ti,ab.
9. (health utilit\$scale\$or classification of illness state\$).ti,ab.
10. health state\$utilit\$.ti,ab.
11. well year\$.ti,ab.
12. (multiattribute\$utilit\$or multi attribute\$utilit\$).ti,ab.
13. health utilit\$scale\$.ti,ab.
14. (euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.

15. (qualy or qaly or qualys or qalys or quality adjusted life year\$.ti,ab.
16. willingness to pay.ti,ab.
17. (hye or hyes or health\$year\$equivalent\$.ti,ab.
18. (person trade off\$or person tradeoff\$or time tradeoff\$or time trade off\$.ti,ab.
19. theory utilit\$.ti,ab.
20. (sf36 or sf 36).ti,ab.
21. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
22. (sf 6d or sf6d or short form 6d or shortform 6d or sf six\$or shortform six\$or short form six\$.ti,ab.
23. or/1-22
24. auricular fibrillation\$.ti,ab.
25. Atrial Fibrillation/
26. Atrial Fibrillation\$.ti,ab.
27. Atrium Fibrillation\$.ti,ab.
28. Atrial Flutter/
29. auricular flutter\$.ti,ab.
30. Atrial Flutter\$.ti,ab.
31. atrial tachycardia\$.ti,ab.
32. atrial tachyarrhythmia\$.ti,ab.
33. Atrium Tachycardia\$.ti,ab.
34. atrial arrhythmia\$.ti,ab.
35. heart fibrillation\$.ti,ab.
36. typical flutter\$.ti,ab.
37. tachycardia, atrial/
38. or/24-37
39. 23 and 38

EMBASE

OvidWeb – 1980 to 2006 Week 39. Searched 2 October 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 116 records.

1. (utilit\$approach\$or health gain or hui or hui2 or hui3).ti,ab.
2. (health measurement\$scale\$or health measurement\$questionnaire\$.ti,ab.
3. (standard gamble\$or categor\$scal\$or linear scal\$or linear analog\$or visual scal\$or magnitude estimat\$.ti,ab.
4. (time trade off\$or rosser\$classif\$or rosser\$matrix or rosser\$distress\$or hrqol).ti,ab.
5. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
6. (multiattribute\$health ind\$or multi attribute\$health ind\$.ti,ab.
7. (health utilit\$index or health utilit\$indices).ti,ab.
8. (multiattribute\$theor\$or multi attribute\$theor\$or multiattribute\$analys\$or multi attribute\$analys\$.ti,ab.
9. (health utilit\$scale\$or classification of illness state\$.ti,ab.
10. health state\$utilit\$.ti,ab.
11. well year\$.ti,ab.
12. (multiattribute\$utilit\$or multi attribute\$utilit\$.ti,ab.
13. health utilit\$scale\$.ti,ab.
14. (euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.
15. (qualy or qaly or qualys or qalys or quality adjusted life year\$.ti,ab.
16. willingness to pay.ti,ab.
17. (hye or hyes or health\$year\$equivalent\$.ti,ab.
18. (person trade off\$or person tradeoff\$or time tradeoff\$or time trade off\$.ti,ab.
- 19 theory utilit\$.ti,ab.
19. (sf36 or sf 36).ti,ab.
20. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
21. (sf 6d or sf6d or short form 6d or shortform 6d or sf six\$or shortform six\$or short form six\$.ti,ab.
22. or/1-22
23. auricular fibrillation.ti,ab.
24. Atrial Fibrillation/
25. Atrial Fibrillation\$.ti,ab.
26. Heart Atrium Fibrillation/
27. Atrium Fibrillation.ti,ab.
28. Atrial Flutter/
29. auricular flutter.ti,ab.
30. Atrial Flutter.ti,ab.
31. atrial tachycardia.ti,ab.
32. atrial tachyarrhythmia\$.ti,ab.
33. exp Tachycardia, Supraventricular/
34. Supraventricular Tachycardia\$.ti,ab.
35. Supraventricular Tachycardia/
36. Atrium Tachycardia.ti,ab.
37. cardiac arrhythmia\$.ti,ab.
38. atrioventricular junction\$.ti,ab.
39. atrial arrhythmia\$.ti,ab.
40. supraventricular arrhythmia\$.ti,ab.
41. premature cardiac complex\$.ti,ab.
42. atrial premature complex\$.ti,ab.
43. paroxysmal tachycardia\$.ti,ab.
44. heart arrhythmia\$.ti,ab.
45. atrium arrhythmia\$.ti,ab.
46. heart fibrillation\$.ti,ab.
47. Arrhythmia/
48. or/24-48
49. 23 and 49

Health Management Information Consortium (HMIC)

OvidWeb – September 2006. Searched 2 October 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved five records.

1. (utilit\$approach\$or health gain or hui or hui2 or hui3).ti,ab.
2. (health measurement\$scale\$or health measurement\$questionnaire\$).ti,ab.
3. (standard gamble\$or categor\$scal\$or linear scal\$or linear analog\$or visual scal\$or magnitude estimat\$).ti,ab.
4. (time trade off\$or rosser\$classif\$or rosser\$matrix or rosser\$distress\$or hrqol).ti,ab.
5. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
6. (multiattribute\$health ind\$or multi attribute\$health ind\$).ti,ab.
7. (health utilit\$index or health utilit\$indices).ti,ab.
8. (multiattribute\$theor\$or multi attribute\$theor\$or multiattribute\$analys\$or multi attribute\$analys\$).ti,ab.
9. (health utilit\$scale\$or classification of illness state\$).ti,ab.
10. health state\$utilit\$.ti,ab.
11. well year\$.ti,ab.
12. (multiattribute\$utilit\$or multi attribute\$utilit\$).ti,ab.
13. health utilit\$scale\$.ti,ab.
14. (euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.
15. (qualy or qaly or qualys or qalys or quality adjusted life year\$).ti,ab.
16. willingness to pay.ti,ab.
17. (hye or hyes or health\$year\$equivalent\$).ti,ab.
18. (person trade off\$or person tradeoff\$or time tradeoff\$or time trade off\$).ti,ab.
19. theory utilit\$.ti,ab.
20. (sf36 or sf 36).ti,ab.
21. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
22. (sf 6d or sf6d or short form 6d or shortform 6d or sf six\$or shortform six\$or short form six\$).ti,ab.
23. or/1-22
24. exp arrhythmia/
25. auricular fibrillation\$.ti,ab.
26. Atrial Fibrillation\$.ti,ab.
27. Atrium Fibrillation\$.ti,ab.
28. auricular flutter\$.ti,ab.
29. Atrial Flutter\$.ti,ab.

30. atrial tachycardia\$.ti,ab.
31. atrial tachyarrhythmia\$.ti,ab.
32. Atrium Tachycardia\$.ti,ab.
33. atrial arrhythmia\$.ti,ab.
34. heart fibrillation\$.ti,ab.
35. typical flutter\$.ti,ab.
36. or/24-35
37. 23 and 36

MEDLINE

OvidWeb – 1996 to September Week 3 2006. Searched 2 October 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 73 records.

1. auricular fibrillation\$.ti,ab.
2. Atrial Fibrillation/
3. Atrial Fibrillation\$.ti,ab.
4. Atrium Fibrillation\$.ti,ab.
5. Atrial Flutter/
6. auricular flutter\$.ti,ab.
7. Atrial Flutter\$.ti,ab.
8. atrial tachycardia\$.ti,ab.
9. atrial tachyarrhythmia\$.ti,ab.
10. Atrium Tachycardia\$.ti,ab.
11. atrial arrhythmia\$.ti,ab.
12. heart fibrillation\$.ti,ab.
13. tachycardia, ectopic atrial/
14. typical flutter\$.ti,ab.
15. or/1-14
16. (utilit\$approach\$or health gain or hui or hui2 or hui3).ti,ab.
17. (health measurement\$scale\$or health measurement\$questionnaire\$).ti,ab.
18. (standard gamble\$or categor\$scal\$or linear scal\$or linear analog\$or visual scal\$or magnitude estimat\$).ti,ab.
19. (time trade off\$or rosser\$classif\$or rosser\$matrix or rosser\$distress\$or hrqol).ti,ab.
20. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
21. (multiattribute\$health ind\$or multi attribute\$health ind\$).ti,ab.
22. (health utilit\$index or health utilit\$indices).ti,ab.
23. (multiattribute\$theor\$or multi attribute\$theor\$or multiattribute\$analys\$or multi attribute\$analys\$).ti,ab.
24. (health utilit\$scale\$or classification of illness state\$).ti,ab.
25. health state\$utilit\$.ti,ab.
26. well year\$.ti,ab.
27. (multiattribute\$utilit\$or multi attribute\$utilit\$).ti,ab.
28. health utilit\$scale\$.ti,ab.

29. (euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.
30. (qualy or qaly or qualys or qalys or quality adjusted life year\$).ti,ab.
31. willingness to pay.ti,ab.
32. (hyc or hyes or health\$year\$equivalent\$).ti,ab.
33. (person trade off\$or person tradeoff\$or time tradeoff\$or time trade off\$).ti,ab.
34. theory utilit\$.ti,ab.
35. (sf36 or sf 36).ti,ab.
36. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
37. (sf 6d or sf6d or short form 6d or shortform 6d or sf six\$or shortform six\$or short form six\$).ti,ab.
38. or/16-37
39. 15 and 38

MEDLINE(R) In-process and other non-indexed citations

OvidWeb – 29 September 2006. Searched 2 October 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved three records.

1. (utilit\$approach\$or health gain or hui or hui2 or hui3).ti,ab.
2. (health measurement\$scale\$or health measurement\$questionnaire\$).ti,ab.
3. (standard gamble\$or categor\$scal\$or linear scal\$or linear analog\$or visual scal\$or magnitude estimat\$).ti,ab.
4. (time trade off\$or rosser\$classif\$or rosser\$matrix or rosser\$distress\$or hrqol).ti,ab.
5. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
6. (multiattribute\$health ind\$or multi attribute\$health ind\$).ti,ab.
7. (health utilit\$index or health utilit\$indices).ti,ab.
8. (multiattribute\$theor\$or multi attribute\$theor\$or multiattribute\$analys\$or multi attribute\$analys\$).ti,ab.
9. (health utilit\$scale\$or classification of illness state\$).ti,ab.
10. health state\$utilit\$.ti,ab.
11. well year\$.ti,ab.
12. (multiattribute\$utilit\$or multi attribute\$utilit\$).ti,ab.
13. health utilit\$scale\$.ti,ab.
14. (euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.

15. (qualy or qaly or qualys or qalys or quality adjusted life year\$).ti,ab.
16. willingness to pay.ti,ab.
17. (hyc or hyes or health\$year\$equivalent\$).ti,ab.
18. (person trade off\$or person tradeoff\$or time tradeoff\$or time trade off\$).ti,ab.
19. theory utilit\$.ti,ab.
20. (sf36 or sf 36).ti,ab.
21. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
22. (sf 6d or sf6d or short form 6d or shortform 6d or sf six\$or shortform six\$or short form six\$).ti,ab.
23. or/1-22
24. auricular fibrillation.ti,ab.
25. Atrial Fibrillation\$.ti,ab.
26. Atrium Fibrillation.ti,ab.
27. auricular flutter.ti,ab.
28. Atrial Flutter.ti,ab.
29. atrial tachycardia.ti,ab.
30. atrial tachyarrhythmia\$.ti,ab.
31. Supraventricular Tachycardia\$.ti,ab.
32. Atrium Tachycardia.ti,ab.
33. cardiac arrhythmia\$.ti,ab.
34. atrioventricular junction\$.ti,ab.
35. atrial arrhythmia\$.ti,ab.
36. supraventricular arrhythmia\$.ti,ab.
37. premature cardiac complex\$.ti,ab.
38. atrial premature complex\$.ti,ab.
39. paroxysmal tachycardia\$.ti,ab.
40. heart arrhythmia\$.ti,ab.
41. atrium arrhythmia\$.ti,ab.
42. heart fibrillation\$.ti,ab.
43. or/24-42
44. 23 and 43

PsycINFO

OvidWeb – 1982 to September Week 4 2006. Searched 2 October 2006. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved four records.

1. (utilit\$approach\$or health gain or hui or hui2 or hui3).ti,ab.
2. (health measurement\$scale\$or health measurement\$questionnaire\$).ti,ab.
3. (standard gamble\$or categor\$scal\$or linear scal\$or linear analog\$or visual scal\$or magnitude estimat\$).ti,ab.
4. (time trade off\$or rosser\$classif\$or rosser\$matrix or rosser\$distress\$or hrqol).ti,ab.
5. (index of wellbeing or quality of wellbeing or qwb).ti,ab.

6. (multiattribute\$health ind\$or multi attribute\$health ind\$).ti,ab.
7. (health utilit\$index or health utilit\$indices).ti,ab.
8. (multiattribute\$theor\$or multi attribute\$theor\$or multiattribute\$analys\$or multi attribute\$analys\$).ti,ab.
9. (health utilit\$scale\$or classification of illness state\$).ti,ab.
10. health state\$utilit\$.ti,ab.
11. well year\$.ti,ab.
12. (multiattribute\$utilit\$or multi attribute\$utilit\$).ti,ab.
13. health utilit\$scale\$.ti,ab.
14. (euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.
15. (qualy or qaly or qualys or qalys or quality adjusted life year\$).ti,ab.
16. willingness to pay.ti,ab.
17. (hve or hyes or health\$year\$equivalent\$).ti,ab.
18. (person trade off\$or person tradeoff\$or time tradeoff\$or time trade off\$).ti,ab.
19. theory utilit\$.ti,ab.
20. (sf36 or sf 36).ti,ab.
21. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
22. (sf 6d or sf6d or short form 6d or shortform 6d or sf six\$or shortform six\$or short form six\$).ti,ab.
23. or/1-22
24. exp arrhythmia/
25. auricular fibrillation\$.ti,ab.
26. Atrial Fibrillation\$.ti,ab.
27. Atrium Fibrillation\$.ti,ab.
28. auricular flutter\$.ti,ab.
29. Atrial Flutter\$.ti,ab.
30. atrial tachycardia\$.ti,ab.
31. atrial tachyarrhythmia\$.ti,ab.
32. Atrium Tachycardia\$.ti,ab.
33. atrial arrhythmia\$.ti,ab.
34. heart fibrillation\$.ti,ab.
35. typical flutter\$.ti,ab.
36. or/24-35
37. 23 and 36

Results of additional quality of life search strategies for information to inform the decision-analytic model

A total of 131 unique bibliographic records were retrieved (220 before deduplication).

Searches for prognosis studies

Cumulative Index to Nursing and Allied Health Literature (CINAHL)

OvidWeb – 1982 to February Week 2 2007.

Searched 16 February 2007. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 41 records.

1. life expectancy/
2. life expectancy.ti,ab.
3. years of life lost.ti,ab.
4. Survival/
5. prognosis/
6. exp mortality/
7. prognos\$.ti.
8. death.ti,ab.
9. mortality.ti,ab.
10. long-term.ti.
11. survival.ti,ab.
12. follow up.ti.
13. stroke.ti,ab.
14. Cerebral Vascular Accident/
15. (restoration adj2 sinus rhythm).ti,ab.
16. (normal sinus adj2 rhythm\$).ti,ab.
17. (rhythm adj2 control\$).ti,ab.
18. nsr.ti,ab.
19. auricular fibrillation\$.ti,ab.
20. Atrial Fibrillation/
21. Atrial Fibrillation\$.ti,ab.
22. Atrium Fibrillation\$.ti,ab.
23. Atrial Flutter/
24. auricular flutter\$.ti,ab.
25. Atrial Flutter\$.ti,ab.
26. atrial tachycardia\$.ti,ab.
27. atrial tachyarrhythmia\$.ti,ab.
28. Atrium Tachycardia\$.ti,ab.
29. atrial arrhythmia\$.ti,ab.
30. heart fibrillation\$.ti,ab.
31. tachycardia, atrial/
32. typical flutter\$.ti,ab.
33. or/19-32
34. or/1-14
35. or/15-18
36. 33 and 34 and 35
37. limit 36 to english

EMBASE

OvidWeb – 1996 to 2007 Week 6. Searched 16 February 2007. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 316 records.

1. life expectancy/
2. life expectancy.ti,ab.
3. years of life lost.ti,ab.
4. Survival/
5. Survival Rate/
6. prognosis/
7. mortality/
8. prognos\$.ti.
9. death.ti,ab.
10. mortality.ti,ab.
11. long-term.ti.
12. survival.ti,ab.
13. follow up.ti.
14. stroke.ti,ab.
15. Stroke/
16. *follow-up/
17. (restoration adj2 sinus rhythm).ti,ab.
18. (normal sinus adj2 rhythm\$.ti,ab.
19. (rhythm adj2 control\$.ti,ab.
20. nsr.ti,ab.
21. or/17-20
22. auricular fibrillation.ti,ab.
23. Atrial Fibrillation/
24. Atrial Fibrillation\$.ti,ab.
25. Heart Atrium Fibrillation/
26. Atrium Fibrillation.ti,ab.
27. Atrial Flutter/
28. auricular flutter.ti,ab.
29. Atrial Flutter.ti,ab.
30. atrial tachycardia.ti,ab.
31. atrial tachyarrhythmia\$.ti,ab.
32. exp Tachycardia, Supraventricular/
33. Supraventricular Tachycardia\$.ti,ab.
34. Supraventricular Tachycardia/
35. Atrium Tachycardia.ti,ab.
36. cardiac arrhythmia\$.ti,ab.
37. atrioventricular junction\$.ti,ab.
38. atrial arrhythmia\$.ti,ab.
39. supraventricular arrhythmia\$.ti,ab.
40. premature cardiac complex\$.ti,ab.
41. atrial premature complex\$.ti,ab.
42. paroxysmal tachycardia\$.ti,ab.
43. heart arrhythmia\$.ti,ab.
44. atrium arrhythmia\$.ti,ab.
45. heart fibrillation\$.ti,ab.
46. Arrhythmia/
47. or/22-46
48. or/1-16
49. 21 and 47 and 48
50. limit 49 to english language

MEDLINE

OvidWeb – 1996 to February Week 1 2007.
Searched 16 February 2007. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 263 records.

1. auricular fibrillation\$.ti,ab.
2. Atrial Fibrillation/
3. Atrial Fibrillation\$.ti,ab.
4. Atrium Fibrillation\$.ti,ab.
5. Atrial Flutter/
6. auricular flutter\$.ti,ab.
7. Atrial Flutter\$.ti,ab.
8. atrial tachycardia\$.ti,ab.
9. atrial tachyarrhythmia\$.ti,ab.
10. Atrium Tachycardia\$.ti,ab.
11. atrial arrhythmia\$.ti,ab.
12. heart fibrillation\$.ti,ab.
13. tachycardia, ectopic atrial/
14. typical flutter\$.ti,ab.
15. or/1-14
16. life expectancy/
17. life expectancy.ti,ab.
18. years of life lost.ti,ab.
19. Survival/
20. Survival Rate/
21. prognosis/
22. prognos\$.ti.
23. death.ti,ab.
24. mortality.ti,ab.
25. long-term.ti.
26. survival analysis/
27. survival.ti,ab.
28. follow up.ti.
29. stroke.ti,ab.
30. Cerebrovascular Accident/
31. *follow-up studies/
32. mortality/
33. (restoration adj2 sinus rhythm).ti,ab.
34. (normal sinus adj2 rhythm\$.ti,ab.
35. (rhythm adj2 control\$.ti,ab.
36. nsr.ti,ab.
37. or/16-32
38. or/33-36
39. 15 and 37 and 38
40. limit 39 to english language

MEDLINE(R) In-process and other non-indexed citations

OvidWeb – 15 February 2007. Searched 16 February 2007. URL: <http://gateway.ovid.com/athens>

This search strategy retrieved 14 records.

1. auricular fibrillation\$.ti,ab.
2. Atrial Fibrillation\$.ti,ab.
3. Atrium Fibrillation\$.ti,ab.
4. auricular flutter\$.ti,ab.

5. Atrial Flutter\$.ti,ab.
6. atrial tachycardia\$.ti,ab.
7. atrial tachyarrhythmia\$.ti,ab.
8. Atrium Tachycardia\$.ti,ab.
9. atrial arrhythmia\$.ti,ab.
10. heart fibrillation\$.ti,ab.
11. typical flutter\$.ti,ab.
12. or/1-11
13. life expectancy.ti,ab.
14. years of life lost.ti,ab.
15. prognos\$.ti.
16. death.ti,ab.
17. mortality.ti,ab.
18. long-term.ti.
19. survival.ti,ab.
20. follow up.ti.

21. stroke.ti,ab.
22. (restoration adj2 sinus rhythm).ti,ab.
23. (normal sinus adj2 rhythm\$).ti,ab.
24. (rhythm adj2 control\$).ti,ab.
25. nsr.ti,ab.
26. or/22-25
27. or/16-21
28. 12 and 26 and 27
29. limit 40 to english language

**Results of additional searches
for prognosis studies to inform
the decision-analytic model**

A total of 384 unique bibliographic records were retrieved (634 before deduplication).

Appendix 2

Quality assessment of included studies

The following criteria were used to rate the quality of included studies. Criteria could be scored 'Yes', 'No', 'Unclear' or 'Not applicable (NA)'.

1	Was the number of participants randomised stated?	
2	Was the method of randomisation appropriate?	
3	Was allocation concealment adequate?	
4	Were the treatment groups comparable at baseline?	
5	Was the study reported as being at least double blind?	
6	Were patients blinded?	
7	Were outcome assessors blinded?	
8	Were care givers blinded?	
9	Was the study conducted at a 'pioneering' catheter ablation centre?	
10	Was an a priori power calculation for adequate sample size performed?	
11	Were selection/eligibility criteria adequately reported?	
12	Was the selected population representative of that seen in normal practice?	
13	Was an appropriate measure of variability reported?	
14	Was loss to follow-up reported or explained?	
15	Were at least 90% of those included at baseline followed up?	
16	Were patients recruited prospectively?	
17	Were patients recruited consecutively?	
18	Did the study report relevant prognostic factors?	
<p>Controlled study quality rating Excellent: the answer is 'Yes' to all of the following criteria: 1–5, 7, 10–18. Good: the answer is 'Yes' to all of the following criteria: 1, 2, 4, 7, 11–16, 18. Satisfactory: the answer is 'Yes' to all of the following criteria: 1, 4, 11, 13, 14, 16. Poor: the answer is not 'Yes' to one or more of the criteria listed for 'Satisfactory'.</p> <p>Case series quality rating Good: the answer is 'Yes' to all of the following criteria: 11–18 Satisfactory: the answer is 'Yes' to all of the following criteria: 12, 14–17 Poor: the answer is not 'Yes' to one or more of the criteria listed for 'Satisfactory'.</p>		

Appendix 3

Review of clinical effectiveness

Appendix 3.1: Details of controlled studies: atrial fibrillation

Study	Population	Intervention/comparator	Outcomes reported
Jais <i>et al.</i> , 2006 ⁶³ Design: RCT with comparator Overall quality rating: poor (abstract only)	Indication: atrial fibrillation No. randomised/treated (intervention): 53/53 No. randomised/treated (control): 59/59 Mean age (years) (overall): 51 (SD 11) Duration of symptoms (intervention/control): NR Patient population: drug refractory % patients paroxysmal/persistent/permanent (intervention): 100/0/0 % patients paroxysmal/persistent/permanent (control): 100/0/0 % SHD (intervention/control): NR	Intervention: segmental PV ablation (with/without additional linear/focal ablation) Catheter type: NR Mapping technique: Lasso circular mapping catheter Procedure end point: PV isolation/linear block Additional details: mean of 1.8 PVJ procedures were conducted. In addition, 64% of patients had CTI ablation, 30% had mitral isthmus ablation and 17% had ablation of the roof line Comparator: any previously untried AAD, alone or in combination; amiodarone was used in 22/59 patients	Freedom from arrhythmia at any time after 3 months post ablation (arrhythmia of 3 minutes or more symptomatic or documented was counted as a recurrence) Complications
Krittayaphong <i>et al.</i> , 2003 ⁵⁷ Design: RCT with comparator Overall quality rating: satisfactory	Indication: atrial fibrillation No. randomised/treated (intervention): 15/14 No. randomised/treated (control): 15/15 Mean age (years) (intervention/control): 55.3 (SD 10.5)/48.6 (SD 15.4) Duration of symptoms (intervention/control): 62.9 (SD 58.3)/48.2 (SD 63.7) months Patient population: drug refractory % patients paroxysmal/persistent/permanent (intervention): 73/27/0 % patients paroxysmal/persistent/permanent (control): 67/33/0 % SHD (intervention/control): 13/13	Intervention: circumferential PV ablation Catheter type: NAVI-STAR™ (BioSense Webster) ablation catheter Mapping technique: electroanatomic mapping (CARTO) Procedure end point: completion of planned ablation lines Additional details: LA ablation lines included a circular line isolating the ostia of the PVs and a line connecting this line with the mitral annulus Comparator: amiodarone, 1200 mg/day for 1 week, 600 mg/day for 2 weeks, then maintenance dose of 200 mg/day throughout study	Freedom from atrial fibrillation Complications QoL
Lakkireddy <i>et al.</i> , 2006 ⁶² Design: CCT with comparator Overall quality rating: poor	Indication: atrial fibrillation No. treated (intervention): 138 No. treated (control 1): 139 Mean age (years) (intervention/control 1/control 2): 70.6 (SD 5.2)/70.2 (SD 5.5)/70.3 (SD 5.5) Duration of symptoms (intervention/control 1/control 2): 2.5 (SD 2.1)/6.5 (SD 3.3)/6.5 (SD 3.6) years Patient population: drug refractory % patients paroxysmal/persistent/permanent: NR % SHD: NR	Intervention: PV ablation Catheter type: NR Mapping technique: NR Procedure end point: NR Comparators: (1) direct current cardioversion (DCC); (2) AV node ablation (AVNA) with pacing	Freedom from atrial fibrillation Complications Mortality

Study	Population	Intervention/comparator	Outcomes reported
<p>Oral <i>et al.</i>, 2006⁵⁶ Design: RCT with comparator Overall quality rating: good</p>	<p>Indication: atrial fibrillation No. randomised/treated (intervention): 77/77 No. randomised/treated (control): 69/69 Mean age (years) (intervention/control): 55 (SD 9)/58 (SD 8) Duration of symptoms (intervention/control): 5 (SD 4)/4 (SD 4) years Patient population: drug refractory % patients paroxysmal/persistent/permanent (intervention): 0/100/0 % patients paroxysmal/persistent/permanent (control): 0/100/0 % SHD (intervention/control): 7.8/8.7</p>	<p>Intervention: circumferential PV ablation Catheter type: 8-mm quadripolar deflectable catheter (NAVISTAR) Mapping technique: 3D electroanatomical mapping system (CARTO) Procedure end point: 80% reduction in the amplitude of the electrogram or a total of 40 seconds of energy application Additional details: further ablation was performed within the circles, outside the PVs, where local electrogram amplitude > 0.2 mV. If atrial fibrillation still present, ibutilide or trans thoracic cardioversion was used to restore sinus rhythm. CTI ablation to prevent flutter in some patients Comparator: amiodarone and two cardioversions in the first 3 months</p>	<p>Freedom from arrhythmia without AADs Complications Mortality</p>
<p>Pappone <i>et al.</i>, 2002,¹⁸⁹ 2003⁶¹ Design: CCT with comparator Overall quality rating: poor</p>	<p>Indication: atrial fibrillation No. randomised/treated (intervention): 589/589 No. randomised/treated (control): 582/582 Mean age (years) (intervention/control): 65 (SD 9)/65 (SD 10) Duration of symptoms (intervention/control): 5.5 (SD 2.8)/3.6 (SD 1.9) years Patient population: unclear % patients paroxysmal/persistent/permanent (intervention): 69/31/0 % patients paroxysmal/persistent/permanent (control): 71/29/0 % SHD (intervention/control): 37/34</p>	<p>Intervention: circumferential PV ablation Catheter type: not stated Mapping technique: 3D electrogeometric mapping system (CARTO) Procedure end point: creation of circumferential lines of conduction block around each PV Comparator: AAD therapy: at hospital discharge, 33% of patients were on amiodarone, 17% propafenone, 15% flecainide, 13% sotalol, 9% quinidine, 6% disopyramide and 7% > one AAD</p>	<p>Freedom from arrhythmia Complications Mortality</p>
<p>Pappone <i>et al.</i>, 2006,⁵⁸ Nilsson <i>et al.</i>, 2006⁶⁴ Design: RCT with comparator Overall quality rating: satisfactory</p>	<p>Indication: atrial fibrillation No. randomised/treated (intervention): 99/99 No. randomised/treated (control): 99/99 Mean age (years) (intervention/control): 55 (SD 10)/57 (SD 10) Duration of symptoms (intervention/control): 6 (SD 4)/6 (SD 6) years Patient population: drug refractory % patients paroxysmal/persistent/permanent (intervention): 100/0/0 % patients paroxysmal/persistent/permanent (control): 100/0/0 % SHD (intervention/control): 7/4</p>	<p>Intervention: combination of approaches Catheter type: 8-mm standard tip or 3.5-mm irrigated tip Mapping technique: 3D CARTO or NavX Procedure end point: atriovenous electrical disconnection or profound electroanatomic remodelling Additional details: encircling lines > 15 mm from the PV ostia, ipsilateral intravenous lines when possible. Mitral isthmus line from left encircling line to mitral annulus (plus two additional lines connecting contralateral superior and inferior PVs). Also CTI ablation Comparator: AAD therapy: amiodarone, flecainide or sotalol (alone or in combination) at the maximum tolerable doses</p>	<p>Freedom from arrhythmia Complications</p>

continued

Study	Population	Intervention/comparator	Outcomes reported
Stabile <i>et al.</i> , 2006 ⁵⁹ Design: RCT with comparator Overall quality rating: satisfactory	Indication: atrial fibrillation No. randomised/treated (intervention): 68/68 No. randomised/treated (control): 69/69 Mean age (years) (intervention/control): 62.2 (SD 9)/62.3 (SD 10.7) Duration of symptoms (intervention/control): 5.1 (SD 3.9)/7.1 (SD 5.9) years Patient population: drug refractory % patients paroxysmal/persistent/permanent (intervention): 62/38/0 % patients paroxysmal/persistent/permanent (control): 72.5/27.5/0 % SHD (intervention/control): 63.2/62.3	Intervention: combination of approaches Catheter type: 8-mm standard/3.5-mm cooled tip Mapping technique: 3D CARTO Procedure end point: low peak-to-peak bipolar potentials inside lesion on electrogram/voltage maps, mitral isthmus block Additional details: contiguous focal lesions at least 5 mm from PV ostia, forming circumferential line around each PV. Additional line connecting left inferior PV to mitral annulus (mitral isthmus). Plus CTI ablation in patients who had not already received it Comparator: AAD therapy: preferentially amiodarone or class Ic AAD if patient is intolerant to amiodarone, although others given at physician's discretion	Freedom from arrhythmia Complications Mortality
Wazni <i>et al.</i> , 2005 ⁶⁰ Design: RCT with comparator Overall quality rating: satisfactory	Indication: atrial fibrillation No. randomised/treated (intervention): 33/33 No. randomised/treated (control): 37/37 Mean age (years) (intervention/control): 53 (SD 8)/54 (SD 8) Duration of symptoms (intervention/control): 5 (SD 2)/5 (SD 2.5) months Patient population: first line % patients paroxysmal/persistent/permanent (intervention): 97/3/0 % patients paroxysmal/persistent/permanent (control): 95/5/0 % SHD (intervention/control): 25/28	Intervention: segmental PV isolation Catheter type: 8-mm tip catheter Mapping technique: circular mapping catheter guided by intracardiac echocardiography Procedure end point: complete electrical disconnection of PV antrum from the left atrium Comparator: AAD therapy: maximum tolerable dose of AAD chosen by physician (typically flecainide, propafenone or sotalol)	Freedom from arrhythmia Complications

CCT, controlled clinical trial; CTI, cavotricuspid isthmus; NR, not reported; PV, pulmonary vein; PVI, pulmonary vein isolation; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation; SHD, structural heart disease.

Appendix 3.2: Details of controlled studies: atrial flutter

Study	Population	Intervention/comparator	Outcomes reported
<p>Da Costa et al., 2006¹²¹ Design: RCT with comparator Overall quality rating: satisfactory</p>	<p>Indication: atrial flutter No. randomised/treated (intervention): 52/52 No. randomised/treated (control): 52/51 Mean age (years) (intervention/control): 78.5 (SD 5)/78 (SD 5) Duration of symptoms (intervention/control): first symptomatic episode/first symptomatic episode Patient population: first line % SHD (intervention/control): 58/65</p>	<p>Intervention: CTI ablation Catheter type: 8-mm tip or irrigated 5-mm tip Mapping technique: quadripolar and dodecapolar mapping catheters Procedure end point: complete bidirectional isthmus block Comparator: electric intracardiac stimulation followed by internal or external cardioversion if needed to restore sinus rhythm. Amiodarone 400 mg daily for 4 weeks (at least 7 days before sinus rhythm restoration), then 200 mg daily</p>	<p>Freedom from arrhythmia Complications Mortality</p>
<p>Natale et al., 2000²⁹ Design: RCT with comparator Overall quality rating: satisfactory</p>	<p>Indication: atrial flutter No. randomised/treated (intervention): 31/31 No. randomised/treated (control): 30/30 Mean age (years) (intervention/control): 67 (SD 8)/66 (SD 11) Duration of symptoms (intervention/control): NR Patient population: first line % SHD (intervention/control): 48/43</p>	<p>Intervention: CTI ablation Catheter type: 4-mm or 8-mm tip electrode catheter Mapping technique: multipolar catheters in coronary sinus, high RA and His bundle Procedure end point: at least 90% reduction in electrogram amplitude across the isthmus Additional details: in patients in SR, flutter was induced at the time of procedure. Assessment of the continuity of the line of block after ablation was performed in 29 patients Comparator: AAD therapy; AADs chosen by physician. Physicians were required to attempt sinus rhythm maintenance with at least two drugs including amiodarone before resorting to rate control medications</p>	<p>Freedom from arrhythmia Complications</p>

CTI, cavotricuspid isthmus; NR, not reported; RA, right atrium; RCT, randomised controlled trial; SD, standard deviation; SHD, structural heart disease; SR, sinus rhythm.

Appendix 3.3: Intervention details: atrial fibrillation case series

Study	Intervention	Ablation technique	Catheter size	Mapping technique	How was end point of procedure defined?
Berkowitsch <i>et al.</i> , 2005 ⁷¹	RFCA	Segmental PV isolation	7Fr Chilli Cooled Ablation System® (Cardiac Pathways) cooled-tip catheter	10-pole Lasso catheter	NR
Bertaglia <i>et al.</i> , 2005 ⁷³	Circumferential anatomical PV ablation	CPVA	3.5-mm cooled-tip catheter	Non-fluoroscopic navigation system (CARTO)	Low peak-to-peak bipolar potentials (< 0.1 mV) inside the lesion
Beukema <i>et al.</i> , 2005 ⁷⁵	Circumferential PV isolation and LA ablation	CPVA	8-mm tip deflectable or 3.5-mm irrigated tip	Quadripolar deflectable navigation catheter (NAVI-STAR) and non-fluoroscopic navigation system (CARTO)	Completion of ablation lines and bipolar electrogram amplitude 0.5 mV or less in encircled areas
Bhargava <i>et al.</i> , 2004 ⁷⁷	PV isolation	Segmental PV isolation	4-mm cooled-tip catheter	Circular decapolar mapping catheter (Lasso)	NR
Bourke <i>et al.</i> , 2005 ⁶⁶	PV ablation	Segmental PV isolation	Steerable 4-mm tip ablation catheters	PV-left atrial angiograms (first half of series); angiography and Localisa® (Medtronic) intracardiac navigation system (second half of series)	Successful isolation of the culprit veins or see comments
Cha <i>et al.</i> , 2005 ⁸⁰	Wide area circumferential or Lasso-guided PV isolation	CPVA	NR	NR	NR
Chen <i>et al.</i> , 2004 ⁸²	PV isolation	Segmental PV isolation	Cooled-tip ablation catheter	Angiography (56 patients); intracardiac echocardiography (321 patients); 10Fr 64-element phased-array ultrasound imaging catheter and a decapolar Lasso catheter	Abolition of all PV potentials as measured by circular mapping catheter
Daoud <i>et al.</i> , 2006 ⁶⁷	Circumferential LA ablation	CPVA	8-mm tip temperature-controlled catheter	Electroanatomic mapping (CARTO)	Completion of planned lesions
Deisenhofer <i>et al.</i> , 2004 ⁸⁴	Segmental electrical isolation of PVs	Segmental PV isolation	NR	Decapolar circular Lasso catheter	Electrical isolation of PVs

PVs ablated, mean (SD)	Other details	Were AADs discontinued before RFCA?	Return to AADs as part of treatment?	Anti-coagulant	Length on anticoagulant
3.4	RF energy delivered at PV ostium	Unclear	Unclear		NR
3.8 (0.7)	Contiguous focal lesions ≥ 5 mm from ostia of PVs; some patients had additional cavotricuspid isthmus lesions and mitral isthmus lesions	No	Yes		NR
	Left- and right-sided PVs encircled with continuous RF ablation lines, ablation line created as far from ostia as anatomy allowed; in 42 patients also ablation line from left circumferential region to mitral annulus; also other variations	No	Yes	Heparin	3 months (heparin 3 days, then acenocoumarol)
	The SVC was also isolated in patients in whom mapping demonstrated potentials similar to those recorded in the PVs	Yes	Unclear	Heparin	3 months (on warfarin)
2.41 (0.79)	Later in the series, in patients resistant to cardioversion despite PV ablation, lines were drawn to block conduction between the mitral annulus and left lower PV ostium and between ostia of the right and left upper veins	Unclear	Yes	Warfarin	Minimum 3 months (persistent AF)
		Unclear	Unclear		NR
	35 patients underwent isthmus ablation for concomitant typical atrial flutter during the PVI procedure	Yes	Unclear		
	Create ablation lesions in LA to encircle right and left PV ostia, connect encircling lesions along posterior wall, create line of ablation between left-side lesions and lateral aspect of mitral valve annulus, lesion line between tricuspid valve and inferior vena cava	Yes	Yes	Other	Fragmin® (Pharmacia), coumadin, aspirin, not stated how long
3.4		Unclear	Unclear		

continued

Appendix 3.3: Intervention details: atrial fibrillation case series

Study	Intervention	Ablation technique	Catheter size	Mapping technique	How was end point of procedure defined?
Della Bella <i>et al.</i> , 2005 ⁶⁸	PV isolation	Segmental PV isolation	Conventional or irrigated-tip catheter	Lasso catheter (Biosense Webster)	Disconnection of PVs
Dong <i>et al.</i> , 2005 ⁸⁷	CPVA	CPVA	Cool saline irrigated catheter	3D (CARTO or NavX) and circular PV mapping catheter	Electrical isolation of PVs validated by circular mapping catheter
	SPVA	Segmental PV isolation	NR	Circular PV mapping catheter	Electrical isolation of PVs validated by circular mapping catheter
Ernst <i>et al.</i> , 2003 ⁸⁹	Ostial PV isolation	Segmental PV isolation	4-mm solid-tip NAVI-STAR or 4-mm Celsius™ (BioSense Webster)	Electroanatomic mapping system (CARTO)	NR
	Ostial PV isolation	Segmental PV isolation	4-mm solid-tip NAVI-STAR or 4-mm Celsius	Circular PV catheter	NR
Essebag <i>et al.</i> , 2005 ⁹¹	PV isolation	Segmental PV isolation	10- to 14-pole circumferential catheter	TOE or ICE; non-irrigated NAVI-STAR catheter and CARTO and/or EnSite NavX recording systems	Complete bidirectional electrical PV isolation
Fassini <i>et al.</i> , 2005 ⁹³	PV disconnection (PVD)	Segmental PV isolation	Irrigated-tip catheter [Cordis Thermocool (Cordis Webster)]	Circular mapping catheter (Lasso)	Disconnection of the PVs
	PVD plus mitral isthmus line (MIL)	Segmental PV isolation	Irrigated-tip catheter (Cordis Thermocool)	Circular mapping catheter (Lasso)	Disconnection of the PVs and bidirectional block along the mitral isthmus
Herweg <i>et al.</i> , 2005 ⁹⁵	Ultrasound and local electrographic-guided PV-left atrial disconnection	Segmental PV isolation	4-mm tip	10- or 20-pole circumferential mapping catheter (Lasso) guided by intracardiac ultrasound	Complete loss of all PV potentials on the Lasso
Hindricks <i>et al.</i> , 2005 ⁹⁷	RFCA	Combination of approaches	Standard multielectrode catheters	Electroanatomic mapping (CARTO)	Completion of proposed linear and circular lesions

PVs ablated, mean (SD)	Other details	Were AADs discontinued before RFCA?	Return to AADs as part of treatment?	Anti-coagulant	Length on anticoagulant
	Additional CTI ablation was performed in 20 patients with documented atrial flutter	Yes	Yes		2 months
		Yes	Yes	Warfarin	3 months
	Haissaguerre approach	Yes	Yes	Warfarin	3 months
	Target ablation catheter tip temperature limited to 53°C using maximum power of 45 W. Care was taken to avoid dislodging from the ostium into the target vein	Unclear	Unclear	Heparin	3 months
	Target ablation catheter tip temperature limited to 48°C using maximum power of 30 W. Care was taken to avoid dislodging from the ostium into the target vein	Unclear	Unclear	Heparin	3 months
	RF ablation outside the PV ostium near sites with the earliest PV electrograms; all PVs isolated – afterwards induction of AF attempted by burst pacing, isoproterenol used to assess triggers and reconnection; if reconnection observed, vein reisolated	Unclear	Unclear	Heparin	6 months (warfarin), aspirin at least 1 month
		Unclear	Yes	Heparin	3 months
		Unclear	Yes	Heparin	3 months
	PV–LA junction proximal to the earliest bipolar PV recording site targeted for ablation	No	Yes	Heparin	1–6 months
	Ablation performed during sinus rhythm; circumferential lesions around left and right PVs > 5 mm from the orifices; plus two linear lesions: one connecting circular lesions and one connecting left circular lesion with mitral annulus	Unclear	Yes	Heparin	Oral, at least 3 months

continued

Appendix 3.3: Intervention details: atrial fibrillation case series

Study	Intervention	Ablation technique	Catheter size	Mapping technique	How was end point of procedure defined?
Hsieh <i>et al.</i> , 2003 ⁹⁹	PV isolation	Other PV isolation	4-mm distal electrode	Decapolar or circular mapping catheters	Elimination or marked reduction of PV potential amplitude and disconnection of PV
	Focal ablation	Other PV isolation	4-mm distal electrode	Multielectrode mapping catheters	Unclear; procedural success is inability to reinitiate AF with same protocol as used before ablation
Hsu <i>et al.</i> , 2004 ¹⁰¹	RFCA	Segmental PV isolation	4-mm irrigated-tip catheter	Circumferential decapolar mapping catheter (Lasso)	Electrical isolation of all PVs (disappearance or dissociation of PV potentials)
Jais <i>et al.</i> , 2004 ¹⁰³	PV electrical isolation	Segmental PV isolation	4-mm irrigated-tip ablation catheter	Circumferential 10-pole Lasso catheter	Isolation of the PVs as determined by circumferential mapping
Karch <i>et al.</i> , 2005 ¹⁰⁵	Circumferential radio frequency PV ablation	CPVA	8 mm and/or cooled 4 mm	Electroanatomic mapping system (CARTO)	Maximum local bipolar electrogram amplitude reduction by $\geq 80\%$ or ≤ 0.1 mV
	Segmental radio frequency PV ablation	Segmental PV isolation	Irrigated-tip ablation catheter	Circular steerable decapolar mapping catheter (Lasso)	Disappearance or dissociation of distal local PV potentials during sinus or paced rhythm
Kilicaslan <i>et al.</i> , 2005 ¹⁰⁶	PV antrum isolation	Segmental PV isolation	8-mm tip ablation catheter	Guidance by intracardiac echocardiography; mapping by decapolar circular mapping catheter (Lasso)	Abolition of all PV potentials surrounding the vein antrum
Kilicaslan <i>et al.</i> , 2006 ¹⁰⁸	PV antrum isolation	Segmental PV isolation	8-mm tip ablation catheter	Circular mapping catheter (Lasso) guided by intracardiac echocardiography	Abolition of all PV potentials surrounding the vein

PVs ablated, mean (SD)	Other details	Were AADs discontinued before RFCA?	Return to AADs as part of treatment?	Anti-coagulant	Length on anticoagulant
	PV potential in proximal PV and ostial area searched for circumferentially, ablation at ostial region	Yes	No	Heparin	NR
	Ablation sites based on ablation catheter recording of the earliest bipolar activity and/or local unipolar QS pattern of ectopic beats initiating AF	Yes	No	Heparin	NR
4	Additional left atrial linear ablation was performed in 104 patients	Unclear	No	Heparin	3–6 months in SR unless otherwise indicated
4	PV isolation was performed 1 cm from the ostium of the right PVs as well as from the posterior and superior aspects of the left PVs. Cavotricuspid ablation was performed in all 200 patients; 100 patients also had mitral isthmus ablation	Unclear	Unclear	Heparin	1–3 months
	Ablation lines were contiguous focal lesions at a distance > 5 mm from the PV ostia. To prevent left atrial flutter, an additional line was drawn from the circling lesion around the left lower PV to the mitral valve annulus	Yes	No	Heparin	Heparin continued until INR was ≥ 2
		Yes	No	Heparin	Heparin continued until INR was ≥ 2
4		Yes	Yes	Heparin	4–6 months minimum (warfarin)
4	The SVC was isolated as well as the PVs. In 107 patients, RF energy output was titrated according to microbubble formation. In the remaining 95 patients, RF energy output was set to a maximum of 45–50 W at 55°C	Unclear	Unclear	Heparin	NR

continued

Appendix 3.3: Intervention details: atrial fibrillation case series

Study	Intervention	Ablation technique	Catheter size	Mapping technique	How was end point of procedure defined?
Kobza <i>et al.</i> , 2004 ¹¹⁰	Percutaneous radio frequency ablation	Combination of approaches	Standard 8-mm or cooled-tip catheters	Electroanatomic mapping (CARTO)	Completion of proposed circular and linear lesions
Kottkamp <i>et al.</i> , 2004 ¹¹²	Radio frequency energy-induced circular and linear lesions	Combination of approaches	8-mm tip ablation catheter	Electroanatomic mapping (CARTO)	Completion of proposed linear and circular lesions
Kumagai <i>et al.</i> , 2005 ¹¹⁴	Basket catheter-guided PV isolation	Segmental PV isolation	4-mm tip	31-mm 64-pole basket catheter	Bidirectional LA–PV conduction block
	Circular catheter-guided PV isolation	Segmental PV isolation	4-mm tip	Circular 20-electrode catheter (Lasso)	Elimination of all PV potentials
Lee <i>et al.</i> , 2004 ¹¹⁶	Focal ablation	Segmental PV isolation	4-mm tip	Various decapolar catheters, circular catheter	Inability to reinitiate AF with the same protocols used before ablation
	Isolation procedure	Segmental PV isolation	4-mm tip	Various decapolar catheters, circular catheter, basket catheter	Elimination/ marked reduction of PV or SVC potential amplitude (< 0.05 mV), disconnection PV–LA or SVC–RA
Liu <i>et al.</i> , 2005 ¹¹⁸	CPVA	CPVA	3.5-mm irrigated tip	CARTO and circular mapping catheter (Lasso)	Completeness of circular lesions and electrical isolation of all PVs
Ma <i>et al.</i> , 2006 ⁷²	CPVA	CPVA	Cool saline irrigated catheter, size NR	3D (CARTO) or EnSite/NavX	Continuity of circular lesions and PV isolation
Macle <i>et al.</i> , 2002 ⁷⁴	Irrigated-tip PV ablation	Segmental PV isolation	4-mm irrigated-tip catheter	Circumferential decapolar catheter (Lasso) guided by selective PV angiography	Abolition or dissociation of all PV potentials

PVs ablated, mean (SD)	Other details	Were AADs discontinued before RFCA?	Return to AADs as part of treatment?	Anti-coagulant	Length on anticoagulant
	Ablation performed during sinus rhythm (cardioversion if necessary); circumferential lesions around left and right PVs > 5 mm from the orifices; plus two linear lesions: one connecting circular lesions and one connecting left circular lesion with mitral annulus	Unclear	Yes	Heparin	NR
	Ablation performed during sinus rhythm; circumferential lesions around left and right PVs > 5 mm from the orifices; plus two linear lesions: one connecting circular lesions and one connecting left circular lesion with mitral annulus	Unclear	Yes	Warfarin	Oral, at least 3 months
3.8	Ablation of ostial sites with the earliest atrial potentials during distal PV pacing; all PVs targeted (unless < 12 mm diameter to prevent stenosis)	Yes	Unclear	Heparin	Warfarin 3 months
3.9	RF pulses delivered within the first few mm of the PV with the earliest PV potentials; if activation sequence around PV ostium changed, bipole that showed shortest LA–PV conduction was targeted; all PVs targeted (unless < 12 mm diameter)	Yes	Unclear	Heparin	Warfarin 3 months
1.5 (0.6)	Ablation site chosen based on bipolar recording with the earliest activity and/or a local unipolar QS pattern of the ectopic beats initiating AF	No	No	Heparin	NR
1.4 (0.7)	Identification of earliest breakthrough sites from LA to PV, ablation at ostial region. Additional ablation in extravenous areas if necessary	Yes	No	Heparin	NR
	Continuous irrigated RF ablation along the PV antrum to encircle ipsilateral PVs. Additional CTI ablation in patients with typical atrial flutter	Yes	Yes	Warfarin	3 months
3.95	Continuous circular lesion along the PV antrum	No	Yes	Warfarin	3 months
4	CTI ablation was performed in patients who had not previously had this procedure. Linear ablation was performed in the LA for patients with persistent AF	Unclear	Unclear	Heparin	3 months

continued

Appendix 3.3: Intervention details: atrial fibrillation case series

Study	Intervention	Ablation technique	Catheter size	Mapping technique	How was end point of procedure defined?
Marchlinski et al., 2003 ⁷⁶	Focal PV ablation	Other PV isolation	Decapolar catheters with 4-mm tip electrodes	Magnetic electroanatomic mapping catheter (see also comments)	Focal ablation of all PV and non-PV triggers
	PV isolation	Other PV isolation	Decapolar catheters with 4-mm tip electrodes	AcuNav™ (Siemens) diagnostic ultrasound catheter, decapolar Lasso mapping catheter	Elimination of PV atrialisation (absence of PV electrograms) (see also comments)
Marrouche et al., 2002 ⁷⁸	Distal isolation	Segmental PV isolation	Quadripolar 4-mm tip	Custom-made circular catheter or loop catheter (Lasso)	Abolition of PV potentials mapped 5 mm from the ostium of the arrhythmogenic PV
	Ostial isolation	CPVA	Quadripolar 4-mm, 8-mm or cooled tip	Custom-made circular catheter or loop catheter (Lasso)	Inability to record spontaneous or isoproterenol-induced AF originating from targeted veins
Nademanee et al., 2002 ⁷⁹	RFCA guided by multiple fractionated electrograms	Other approach	NR	CARTO	Restoration of sinus rhythm, or organised atrial flutter that ibutilide/ cardioversion converts to sinus rhythm
Nademanee et al., 2004 ⁸¹	RFCA	Other approach	Standard 4-mm tip catheter	Electroanatomic mapping (CARTO)	Complete ablation of CFAEs, conversion of AF to SR; non-inducible AF for paroxysmal patients
Nilsson et al., 2006 ⁶⁴	Segmental ostial PV isolation	Segmental PV isolation	7Fr, 5-mm tip quadripolar saline-irrigated deflectable catheter	Decapolar ring catheter (Lasso)	Elimination of electrical conduction into the PV area distal to the ablation line
	Circumferential extraostial PV isolation	CPVA	3.5-mm tip saline-irrigated deflectable ablation/navigation catheter	Electromagnetic mapping system (CARTO)	Elimination of electrical conduction into the PV area distal to the ablation line

PVs ablated, mean (SD)	Other details	Were AADs discontinued before RFCA?	Return to AADs as part of treatment?	Anti-coagulant	Length on anticoagulant
2.2	Bipolar mapping of spontaneous and provoked triggers, acquire enough points to identify early site surrounded by later sites, isoproterenol used for inducing triggers (or burst atrial pacing)	Yes	Yes	Heparin	At least 6 weeks (on warfarin)
3	Three or four points along circumference of PV targeted for ablation, tagged as reference of location of most ostial aspect, 15- or 20-mm Lasso catheter in ostium of each PV to attempt pacing, identify closest coupled left atrial and PV signals – targeted for RFCA	Yes	Yes	Heparin	At least 6 weeks (on warfarin)
1.6	Ablation targeted to the earliest recorded PV potential during sinus rhythm or coronary sinus pacing, and subsequently, if needed, targeted to contiguous sites showing earlier PV potentials	Yes	Unclear	Warfarin	2–3 months
3.7	PV circumference divided into 16 sectors for documentation purposes	Yes	Unclear	Warfarin	2–3 months
0	Mapping of the electrophysiological substrate was conducted and ablation was performed along the low-frequency multiple fractionated electrogram areas	Unclear	Unclear	Warfarin	Unclear
	Areas with CFAEs ablated	Unclear	Unclear	Heparin	NR
3.4 (0.7)	During the first ablation procedure, three patients underwent ablation of non-PV foci and one patient had a linear ablation line between the superior PVs	No	No	Heparin	3 months
4	During the first ablation procedure, one patient underwent ablation of non-PV foci	No	No	Heparin	3 months

continued

Appendix 3.3: Intervention details: atrial fibrillation case series

Study	Intervention	Ablation technique	Catheter size	Mapping technique	How was end point of procedure defined?
Oral <i>et al.</i> , 2004 ⁸⁵	Segmental ostial ablation	Segmental PV isolation	4-mm tip quadripolar catheter	Decapolar mapping catheter (Lasso)	Elimination of ostial PV potentials and complete entrance block into the PV
Oral <i>et al.</i> , 2004 ⁸³	PV isolation	Segmental PV isolation	4-mm tip quadripolar catheter	Deflectable decapolar Lasso catheter	Elimination of all ostial PV potentials
Pappone <i>et al.</i> , 2001 ⁸⁸	CPVA	CPVA	Not stated	3D (CARTO)	Complete lesions, defined anatomically and electrically
Pappone <i>et al.</i> , 2001 ⁸⁶	Circumferential ablation	CPVA	Not stated	3D (CARTO)	PV isolation determined anatomically and electrically
Pappone <i>et al.</i> , 2004 ⁹⁰	CPVA	CPVA	8-mm tip deflectable ablation catheter	Electroanatomic mapping system (CARTO)	Voltage reduction of local atrial electrogram by 80% or < 0.1 mV
	Modified CPVA (CPVA-M)	CPVA	8-mm tip deflectable ablation catheter	Electroanatomic mapping system (CARTO)	Voltage reduction of local atrial electrogram by 80% or < 0.1 mV
Purerfellner <i>et al.</i> , 2006 ⁹²	PV segmental ostial ablation	Segmental PV isolation	Celsius Thermocool 7Fr	Lasso catheter	Electrical entrance block from the LA to the PV
Ren <i>et al.</i> , 2004 ⁹⁴	PV ostial ablation	Segmental PV isolation	NAVI-STAR ablation catheter	Circular mapping catheter (Lasso) guided by intracardiac echocardiography	Electrical isolation of PV from LA
Saad <i>et al.</i> , 2003 ⁹⁸	Ostial isolation guided by intracardiac echocardiography	Segmental PV isolation	Unclear	Circular mapping catheter guided by intracardiac echocardiography	NR
	Ostial isolation guided by PV angiography	Segmental PV isolation	4-mm tip catheter in temperature-controlled mode	Selective PV angiography	NR
	Distal isolation guided by circular mapping	Other PV isolation	Unclear	Decapolar circular mapping catheter (Lasso)	NR
	Electroanatomic mapping	CPVA	4-mm tip catheter in temperature-controlled mode	Electroanatomic mapping (CARTO)	NR

PVs ablated, mean (SD)	Other details	Were AADs discontinued before RFCA?	Return to AADs as part of treatment?	Anti-coagulant	Length on anticoagulant
	LS, LI, RS PVs targeted in all 188 patients, RI PV also targeted in 41% (n = 77)	Unclear	Unclear	Heparin	1–3 months (on warfarin)
	Three PVs isolated in all patients; right inferior PV ablated at operator's discretion	Unclear	Unclear	Heparin	1–3 months (on warfarin)
	Circumferential lines > 5 mm from the PV ostia. In most cases, each individual PV was encircled, although occasionally ipsilateral pairs of veins were encircled	Unclear	No	Warfarin	3 months
	Each PV was encircled individually	Yes	No	Warfarin	3–4 months
	Encircling lines were created by contiguous RF lesions > 15 mm from the PV ostia	Yes	No	Heparin	NR (on warfarin)
	As CPVA but with additional ablation lines in the posterior left atrium connecting contralateral superior and inferior PVs and along the mitral isthmus between inferior aspect of left-sided encircling ablation line and mitral annulus	Yes	No	Heparin	NR (on warfarin)
3.5	Three PVs were targeted for ablation in the first 45% of patients, all four were targeted in the remaining 55%	Unclear	Unclear		NR
3.1		Unclear	Unclear	Heparin	NR
	In some patients, delivery of radiofrequency energy was controlled by progressively increasing power until microbubbles were visualised	Unclear	Unclear		NR
		Unclear	Unclear		NR
		Unclear	Unclear		NR
		Unclear	Unclear		NR

continued

Appendix 3.3: Intervention details: atrial fibrillation case series

Study	Intervention	Ablation technique	Catheter size	Mapping technique	How was end point of procedure defined?
Saad <i>et al.</i> , 2003 ⁹⁶	Circumferential mapping and PV isolation	Segmental PV isolation	4-mm, 8-mm and cooled-tip ablation catheters	Circular mapping catheter (Lasso)	Electrical isolation of all PVs from the left atrium
	Electroanatomic mapping and PV isolation	CPVA	4-mm, 8-mm and cooled-tip ablation catheters	Electroanatomic mapping system (CARTO)	PV isolation, elimination of ectopic activity or both
Shah <i>et al.</i> , 2001 ¹⁰⁰	Curative RFCA	Segmental PV isolation	4-mm tip catheter or irrigated-tip catheter	7Fr multipolar mapping catheter(s) facilitated by selective angiography	Elimination of arrhythmias and/or elimination of distal PV activity in the ablated veins
Shah <i>et al.</i> , 2003 ¹⁰²	PV ablation	Segmental PV isolation	4-mm tip quadripolar ablation catheter	Circular decapolar catheter guided by selective PV angiography	Elimination of PV potentials distal to the ablation site
Trevisi <i>et al.</i> , 2003 ¹⁰⁴	Ostial PV disconnection		NR	NR	Disconnection of PVs
Verma <i>et al.</i> , 2005 ⁶⁵	PV antrum isolation	Segmental PV isolation	8-mm tip	Decapolar mapping catheter (Lasso) guided by intracardiac echocardiography	Complete electrical disconnection of the PV antrum from the left atrium
Wazni <i>et al.</i> , 2005 ¹⁰⁷	Ostial isolation guided by intracardiac echocardiography	Segmental PV isolation	4-mm or cooled-tip catheter	Intracardiac echocardiography	NR
	Ostial isolation guided by PV angiography	Segmental PV isolation	4-mm tip catheter in temperature-controlled mode	Selective PV angiography	NR
	Ultrasound balloon system (CUVA)	Other PV isolation	0.035-inch luminal catheter	Custom-made mapping catheter	NR
	Electroanatomical mapping	CPVA	4-mm tip catheter in temperature-controlled mode	Electroanatomical mapping (CARTO)	
	Distal isolation guided by circular mapping	Other PV isolation	4-mm tip catheter in temperature-controlled mode	Decapolar circular mapping catheter (Lasso)	NR
Weerasooriya <i>et al.</i> , 2003 ¹⁰⁹	Radio frequency ablation	Segmental PV isolation	4-mm tip electrode catheter	Multielectrode catheters (Lasso or basket) guided by selective venous angiography	Complete disconnection of PV (abolition or dissociation of the distal PV potential)
Weerasooriya <i>et al.</i> , 2003 ¹¹¹	RFCA	Segmental PV isolation	NR	Circumferential mapping catheter	NR

PVs ablated, mean (SD)	Other details	Were AADs discontinued before RFCA?	Return to AADs as part of treatment?	Anti-coagulant	Length on anticoagulant
	Used in 264 patients	Yes	Yes		
	Only superior PVs were targeted unless firing from other veins was noted	Yes	Yes		
2	Different mapping strategies used in different patient groups were described in the paper	Unclear	Unclear	Heparin	At least 3 months
3.4	Non-PV foci triggering AF were also ablated	Unclear	Unclear	Heparin	Until appropriate INR levels achieved
		Unclear	Yes		2 months
	No ablation lines were drawn between the mitral annulus and PVs	Unclear	Yes	Heparin	At least 3 months (on warfarin)
	In some patients, power titration was directed by formation of microbubbles with a cooled- or 8-mm tip catheter	Yes	Unclear	Heparin	4–6 months (coumadin)
		Yes	Unclear	Heparin	4–6 months (coumadin)
		Yes	Unclear	Heparin	4–6 months (coumadin)
		Yes	Unclear	Heparin	4–6 months (coumadin)
		Yes	Unclear	Heparin	4–6 months (coumadin)
2.5	In first 102 patients, only suspected arrhythmogenic PVs were targeted; in the remaining 50, three or four PVs were disconnected without attempts to identify arrhythmogenicity	Unclear	Unclear	Heparin	NR
		Unclear	Unclear		NR

continued

Appendix 3.3: Intervention details: atrial fibrillation case series

Study	Intervention	Ablation technique	Catheter size	Mapping technique	How was end point of procedure defined?
Yamada <i>et al.</i> , 2006 ¹¹³	Segmental ostial catheter ablation (SOCA)	Segmental PV isolation	4-mm or 8-mm tip	Multielectrode basket catheter with computerised 3D mapping system	Abolition or dissociation of distal PV potentials
Yamane <i>et al.</i> , 2002 ¹¹⁵	PV ablation	Segmental PV isolation	Quadripolar ablation catheter or irrigated-tip catheter	Decapolar circular mapping catheter (Lasso)	Elimination of PV conduction (abolition or dissociation of PV potentials distal to ablation site)
Yu <i>et al.</i> , 2001 ¹¹⁷	RFCA	Other PV isolation	4-mm tip electrode	6Fr decapolar catheters guided by selective PV angiography	Success is absence of ectopic beats and inability to reinitiate AF using pre-RFCA protocol

CFAE, complex fractionated atrial electrograms; CTI, cavotricuspid isthmus; CPVA, circumferential pulmonary vein ablation; ICE, intracardiac electrocardiography; INR, international normalised ratio; LA, left atrium; LI, left inferior pulmonary vein; LS, left superior pulmonary vein; NR, not reported; PV, pulmonary vein; PVI, pulmonary vein isolation; RA, right atrium; RI, right inferior pulmonary vein; RS, right superior pulmonary vein; SPVA, segmental pulmonary vein ablation; SR, sinus rhythm; SVC, superior vena cava; TOE, transoesophageal echocardiography.

PVs ablated, mean (SD)	Other details	Were AADs discontinued before RFCA?	Return to AADs as part of treatment?	Anti-coagulant	Length on anticoagulant
3.6	RF max 30W (4-mm catheter) or 40W (8-mm catheter); additional RF deliveries in 8-mm group to edge of original electrical connections and between RF lesions on the continuous broad electrical connections identified by PV potential maps	Yes	No	Heparin	NR
2.6		Unclear	Unclear	Heparin	NR
	Presumed ablation site chosen at earliest bipolar activity and/or local unipolar QS pattern of ectopic beats preceding AF from the PVs	Unclear	Unclear	Heparin	2 months (warfarin)

Appendix 3.4: Freedom from arrhythmia at mean follow-up: atrial fibrillation case series

Study	Number ablated	Mean follow-up (months)	Overall freedom	Overall freedom (assuming AF)	Freedom without AADs	Freedom with AADs	Freedom from paroxysmal AF	Freedom from chronic AF	Includes repeat ablation	Occurrence of AFI or other arrhythmia	Freedom from any arrhythmia (calculated)	Repeat ablation	Freedom after repeat ablation
Bertaglia et al., 2005 ⁷³	143	18.7	102/143 (71.3%)	102/143 (71.3%)	38/143 (26.6%)	64/143 (44.8%)						NR	
Beukema et al., 2005 ⁷⁵	105	14.6	71/105 (67.6%)	71/105 (67.6%)	46/105 (43.8%)	25/105 (23.8%)	39/52 (75%)	32/53 (60.4%)	No			23/105	15/23
Bhargava et al., 2004 ⁷⁷	323	14.8	269/323 (83.3%)	269/323 (83.3%)			152/174 (87.4%)	117/149 (78.5%)				NR	
Cha et al., 2005 ⁸⁰	395	17.4	313/395 (79.2%)	313/395 (79.2%)	260/395 (65.8%)	54/395 (13.7%)	190/239 (79.5%)	123/156 (78.8%)				NR	
Chen et al., 2004 ⁸²	377	14.7	316/377 (83.8%)	316/377 (83.8%)	296/377 (78.5%)	20/377 (5.3%)			No	AFI 5/377	311/377 (82.5%)	40/377	40/40
Daoud et al., 2006 ⁸⁷	112	14								AFI 28/112	84/112 (75%)		
Della Bella et al., 2005 ⁸⁸	234	13	189/263 ^a (71.9%)				155/204 (76%)	34/59 (57.6%)				NR	
Dong et al., 2005 ⁸⁷	151	10.2	106/151 (70.2%)	106/151 (70.2%)	106/151 (70.2%)							NR	
Ernst et al., 2003 ⁸⁹	196	17	121/196 (69.9%)	121/196 (69.9%)					Yes			38/196	38/38
Herweg et al., 2005 ⁹⁵	170	18	136/170 (80.0%)	136/170 (80.0%)			110/139 (79.1%)	25/31 (80.6%)	Yes			27/170	27/27
Hsieh et al., 2003 ⁹⁹	227	30	137/207 (66.2%)	137/227 (60.4%)								NR	
Hsu et al., 2004 ¹⁰¹	116	12	94/116 (81.0%)	94/116 (81.0%)	81/116 (69.8%)	13/116 (11.2%)			Yes			56/116	Unclear
Kilicasian et al., 2005 ¹⁰⁶	1125	18.2	911/1125 (81%)	911/1125 (81%)						AFI within 2 months 230/1125; AFI after 2 months 64/1125	617/1125 (54.8%)	NR	

Study	Number ablated	Mean follow-up (months)	Overall freedom	Overall freedom (assuming dropouts AF)	Freedom without AADs	Freedom with AADs	Freedom from paroxysmal AF	Freedom from chronic AF	Includes repeat ablation	Occurrence of AFI or other arrhythmia	Freedom from any arrhythmia (calculated)	Repeat ablation	Freedom after repeat ablation
Kobza et al., 2004 ¹¹⁰	150	14.4								28/150 (18.7%)	122/150 (81.3%)	24/207	15/24
Lee et al., 2004 ¹¹⁶	207	30	137/207 (66.2%)	137/207 (66.2%)					No				
Ma et al., 2006 ⁷²	200	6	161/200 (80.5%)	161/200 (80.5%)								NR	
Macle et al., 2002 ⁷⁴	136	8.8	110/136 (80.9%)	110/136 (80.9%)	90/136 (66.2%)	20/136 (14.7%)			Yes			67/136	Unclear
Marrouche et al., 2002 ⁷⁸	211	6.4	187/211 (88.6%)	187/211 (88.6%)	176/190 (92.6%)	11/190 (5.8%)						NR	
Nademanee et al., 2002 ⁷⁹	214	14	163/214 (76.2%)	163/214 (76.2%)			84/103 (81.6%)	79/111 (71.2%)				NR	
Oral et al., 2004 ⁸³	176									Left AFI 2/176			
Pappone et al., 2001 ⁸⁶	127	14.7	106/127 (83.5%)	106/127 (83.5%)	75/127 (59.1%)	31/127 (24.4%)	84/98 (85.7%)	22/29 (75.9%)				NR	
Pappone et al., 2001 ⁸⁸	251	10.4	201/251 (80.1%)	201/251 (80.1%)	188/251 (74.9%)	13/251 (5.2%)	152/179 (84.9%)	49/72 (68.1%)				NR	
Purerfellner et al., 2006 ⁹²	117	21	24/39 (61.5%)	24/117 (20.5%)	16/39 (41%)	8/39 (20.5%)			Yes			63/117	Unclear
Shah et al., 2001 ¹⁰⁰	200	16	148/200 (74%)	148/200 (74%)	148/200 (74%)				Yes			108/200	Unclear
Shah et al., 2003 ¹⁰²	160	8	108/160 (67.5%)	108/160 (67.5%)	108/160 (67.5%)				Yes			76/160	Unclear
Trevisi et al., 2003 ¹⁰⁴	158	5.53	113/158 (71.5%)	113/158 (71.5%)								NR	
Weerasooriya et al., 2003 ¹¹¹	118	8	85/118 (72.0%)	85/118 (72.0%)					Yes			Unclear	
Weerasooriya et al., 2003 ¹⁰⁹	152	9	79/152 (52.0%)	79/152 (52.0%)	79/152 (52%)							NR	
Yamane et al., 2002 ¹¹⁵	157	9	116/157 (73.9%)	116/157 (73.9%)	116/157 (73.9%)							60/157	Unclear

AFI, atrial flutter; NR, not reported. a 263 refers to procedures rather than patients.

Appendix 3.5: Immediate complications: atrial fibrillation case series

Study	Number ablated	Stroke/ CVA	Cerebroembolic complications	Ischaemia	Tamponade	Pericardial effusion	Haemo-pericardium	PV stenosis
Beukema <i>et al.</i> , 2005 ⁷⁵	105							
Chen <i>et al.</i> , 2004 ⁸²	377	5/377 (1.3%)			2/377 (0.5%)			
Della Bella <i>et al.</i> , 2005 ⁶⁸	234	1/234 (0.4%)			3/234 (1.3%)			
Fassini <i>et al.</i> , 2005 ⁹³	187			1/187 (0.5%)	1/187 (0.5%)			
Hsu <i>et al.</i> , 2004 ¹⁰¹	116	1/116 (0.9%)			2/116 (1.7%)			
Jais <i>et al.</i> , 2004 ¹⁰³	200				4/200 (2%)			
Kilicaslan <i>et al.</i> , 2005 ¹⁰⁸	202		4/202 (2%)					
Kottkamp <i>et al.</i> , 2004 ^{112a}	100	0/100 (0%)			0/100 (0%)			0/100 (0%)
Liu <i>et al.</i> , 2005 ¹¹⁸	130	1/130 (0.8%)			1/130 (0.8%)			
Macle <i>et al.</i> , 2002 ⁷⁴	136							1/136 (0.7%)
Marchlinski <i>et al.</i> , 2003 ⁷⁶	107				1/107 (0.9%)			
Marrouche <i>et al.</i> , 2002 ⁷⁸	211	2/211 (0.9%)			2/211 (0.9%)			5/211 (2.4%)
Nademanee <i>et al.</i> , 2002 ⁷⁹	214	1/214 (0.5%)					5/214 (2.3%)	
Nademanee <i>et al.</i> , 2004 ⁸¹	121	1/121 (0.8%)			2/121 (1.7%)			
Nilsson <i>et al.</i> , 2006 ⁶⁴	100	2/100 (2%)		2/100 (2%)				
Pappone <i>et al.</i> , 2001 ⁸⁶	127					5/127 (3.9%)	2/127 (1.6%)	
Pappone <i>et al.</i> , 2001 ⁸⁸	251				2/251 (0.8%)	2/251 (0.8%)		
Pappone <i>et al.</i> , 2004 ⁹⁰	560				4/560 (0.7%)			
Ren <i>et al.</i> , 2004 ^{94b}	232	0/232 (0%)			0/232 (0%)			0/232 (0%)
Saad <i>et al.</i> , 2003 ⁹⁸	608	4/608 (0.7%)			3/608 (0.5%)			
Wazni <i>et al.</i> , 2005 ¹⁰⁷	785		12/785 (1.5%)		2/785 (0.3%)	2/785 (0.3%)		
Yamane <i>et al.</i> , 2002 ¹¹⁵	157							2/157 (1.3%)

AV, atrioventricular; CVA, cardiovascular accident; PV, pulmonary vein.

a This study reported no procedure-related complications.

b This study reported no clinical complications other than thrombus.

Respiratory symptoms	AV block	Pulmonary oedema	Haematoma	Fistula	Vascular complications	Thrombosis/thrombus	Coronary spasm	Charring
							1/105 (1%)	
		1/377 (0.3%)		8/234 (3.4%)		2/234 (0.9%)		
					6/214 (2.8%)			
5/100 (5%)	1/121 (0.8%)	1/121 (0.8%)		1/121 (0.8%)				
	1/127 (0.8%)							
	30/251 (12%)							
			5/560 (0.9%)					
						24/232 (10.3%)		
			3/608 (0.5%)					
			5/785 (0.6%)			5/785 (0.6%)		95/785 (12.1%)

Appendix 3.6: Complications at 12 months: atrial fibrillation case series

Study	Number ablated	Stroke/CVA	Tamponade	Pericardial effusion	PV stenosis	Other
Berkowitsch <i>et al.</i> , 2005 ⁷¹	104				18/104 (17%)	
Beukema <i>et al.</i> , 2005 ⁷⁵	105					
Deisenhofer <i>et al.</i> , 2004 ⁸⁴	115					
Della Bella <i>et al.</i> , 2005 ⁶⁸	234					
Essebag <i>et al.</i> , 2005 ⁹¹	102					
Fassini <i>et al.</i> , 2005 ⁹³	187					
Hindricks <i>et al.</i> , 2005 ⁹⁷	114					
Jais <i>et al.</i> , 2004 ¹⁰³	200					
Kottkamp <i>et al.</i> , 2004 ¹¹²	100					
Kumagai <i>et al.</i> , 2005 ¹¹⁴	100			1/100 (1%)	18/100 (18%)	Unilateral quadrantopsia 1/100 (1%)
Marchlinski <i>et al.</i> , 2003 ⁷⁶	107					
Marrouche <i>et al.</i> , 2002 ⁷⁸	211					
Nademanee <i>et al.</i> , 2004 ^{81a}	121	0/121 (0%)	0/121 (0%)	0/121 (0%)	0/121 (0%)	0/121 (0%)
Nilsson <i>et al.</i> , 2006 ⁶⁴	100					
Oral <i>et al.</i> , 2004 ⁸⁵	188					
Oral <i>et al.</i> , 2004 ⁸³	176					
Pappone <i>et al.</i> , 2004 ⁹⁰	560					
Saad <i>et al.</i> , 2003 ⁹⁶	335				18/335 (5.4%)	

CVA, cardiovascular accident; PV, pulmonary vein.
a This study reported no late complications.

Appendix 3.7: Complications at mean follow-up: atrial fibrillation case series

Study	Number ablated	Mean follow-up (months)	Stroke/ CVA	Cerebroembolic complications	TIA	Tamponade	Pericardial effusion	Haemo-pericardium
Bertaglia <i>et al.</i> , 2005 ⁷³	143	18.7			1/143 (0.7%)	2/143 (1.4%)		
Bhargava <i>et al.</i> , 2004 ⁷⁷	323	14.8	3/323 (0.9%)		2/323 (0.6%)	3/323 (0.9%)		
Della Bella <i>et al.</i> , 2005 ⁶⁸	234	13						
Ernst <i>et al.</i> , 2003 ⁸⁹	196	17	1/196 (0.5%)		2/196 (1%)			
Herweg <i>et al.</i> , 2005 ⁹⁵	170	18						
Kilicaslan <i>et al.</i> , 2005 ¹⁰⁶	1125	18.2		7/1125 (0.6%)			2/1125 (0.2%)	
Oral <i>et al.</i> , 2004 ⁸³	176	15				1/176 (0.6%)		
Purerfellner <i>et al.</i> , 2006 ⁹²	117	21	2/117 (1.7%)			2/117 (1.7%)	2/117 (1.7%)	
Shah <i>et al.</i> , 2001 ¹⁰⁰	200	16			2/200 (1%)			2/200 (1%)
Shah <i>et al.</i> , 2003 ¹⁰²	160	8					2/160 (1.2%)	
Weerasooriya <i>et al.</i> , 2003 ^{111c}	118	8	0/118 (0%)			0/118 (0%)		
Yu <i>et al.</i> , 2001 ¹¹⁷	102	7						

AV, atrioventricular; CVA, cardiovascular accident; PV, pulmonary vein; TIA, transient ischaemic attack.

a Ventilation perfusion defect.

b Retinal artery embolism.

c Study reported no significant complications.

Pericarditis	PV stenosis	AV block	Haematoma	Coronary spasm	Pneumo-haemothorax	Phrenic nerve paralysis	Pseudo-aneurysm	Other
		1/143 (0.7%)				1/143 (0.7%)	1/143 (0.7%)	
	6/323 (1.9%)							
	3/234 (1.3%)							
	2/196 (1%)							
	4/1125 (0.4%)							1/170 (0.6%) ^a
	5/176 (2.8%)							1/176 (0.6%) ^b
1/117 (0.9%)	9/117 (7.7%)		2/117 (1.7%)		2/117 (1.7%)			
	2/200 (1%)							
	3/160 (1.9%)			1/160 (0.6%)				
	0/118 (0%)							
	34/102 (33.3%)							

Appendix 3.8: Complications at 3 and 6 months: atrial fibrillation case series

Study	Number ablated	Stroke/CVA	Tamponade	Pericardial effusion	PV stenosis	Heart block	Haematoma	Coronary spasm	Embolism	Bleeding/haemorrhage	Other
3 months											
Chen et al., 2004 ⁸²	377				6/377 (1.6%)						
Saad et al., 2003 ⁹⁸	608				Mild 47/608 (8%); moderate 27/608 (4%); severe 21/608 (3.5%); all 95/608 (16%)						
6 months											
Bourke et al., 2005 ⁶⁶	100		6/100 (6%)		0/100 (0%)	1/100 (1%)	2/100 (2%)	2/100 (2%)	2/100 (2%)	1/100 (1%)	Sedation-related hypotension 1/100 (1%)
Essebag et al., 2005 ⁹¹	102	1/102 (1%)	1/102 (1%)	2/102 (2%)						4/102 (3.9%)	
Karch et al., 2005 ¹⁰⁵	100				9/100 (9%)				4/100 (4%)		
Yamada et al., 2006 ^{113a}	108	0/108 (0%)	0/108 (0%)		0/108 (0%)						No serious adverse events
CVA, cardiovascular accident; PV, pulmonary vein. a Study reported no serious adverse events.											

Appendix 3.9: Intervention details: atrial flutter case series

Study	Intervention	Ablation technique	Catheter size	Mapping technique	How was end point of procedure defined?
Andronache <i>et al.</i> , 2003 ¹²⁵	RF ablation	Anterior CTI ablation	8-mm or 10-mm tip electrodes	24-pole mapping catheter and quadripolar CTI mapping/ablation catheter	Bidirectional conduction block lasting > 30 minutes
Bertaglia <i>et al.</i> , 2004 ¹¹⁹	RFCA	Posterior CTI ablation	4-mm distal tip, 8-mm distal tip, 10-mm distal tip or 4-mm distal irrigated tip	Multipolar mapping catheters	Complete conduction block between tricuspid valve and inferior vena cava (posterior isthmus)
Calkins <i>et al.</i> , 2004 ¹²⁶	RFCA	CTI ablation	8-mm tip 7Fr quadripolar catheter	Not reported	Bidirectional isthmus block lasting > 30 minutes
Chen <i>et al.</i> , 2002 ¹²⁷	RF ablation	CTI ablation	Deflectable quadripolar catheters, 4-, 8- or 10-mm tips	24-pole mapping catheter in the right atrium	Bidirectional conduction for at least 30 minutes
Da Costa <i>et al.</i> , 2002 ¹²⁸	RF ablation of atrial flutter	CTI ablation	8-mm tip	Not stated	Bidirectional block
Da Costa <i>et al.</i> , 2003 ¹²²	RFCA	CTI ablation	8-mm tip catheter	Quadripolar and dodecapolar mapping catheters	Complete bidirectional isthmus block
Da Costa <i>et al.</i> , 2004 ¹²⁹	RFCA	CTI ablation	8-mm tip or cooled-tip catheter	Quadripolar and dodecapolar mapping catheters with right atrial angiography	Complete bidirectional isthmus block
Da Costa <i>et al.</i> , 2005 ¹²³	RFCA	CTI ablation	Not stated	Not stated	Complete bidirectional isthmus block
Feld <i>et al.</i> , 2004 ¹²⁰	RFCA	CTI ablation	8-mm or 10-mm tip investigational catheter	Standard multielectrode catheters; three-dimensional contact or non-contact mapping was allowed	Bidirectional isthmus block
Gilligan <i>et al.</i> , 2003 ¹³⁰	Typical atrial flutter ablation	CTI ablation	4-mm, 5-mm or 8-mm tip	Quadripolar recording catheter or 20-pole Halo catheter (Cordis-Webster)	Termination of arrhythmia and bidirectional block (non-inducibility of flutter in first 16 patients)
Heidbuchel <i>et al.</i> , 2006 ¹³¹	Flutter ablation	CTI ablation	4-mm or 6-mm tip or irrigated-tip electrodes	Mapping catheters guided by RA angiography	Bidirectional conductance block

Other details	Were AADs discontinued before RFCA?	Return to AADs as part of treatment?	Anticoagulant	Length on anticoagulant
	Unclear	No	Heparin	Not reported
If first attempt was unsuccessful a line was drawn between the septal portion of the tricuspid valve, the ostium of the coronary sinus and the inferior vena cava (septal isthmus)	Unclear	Unclear	Heparin	At least 4 weeks
	Yes	Unclear	Warfarin	3 weeks
Ablation was performed from the ventricular side progressively to the inferior vena cava under fluoroscopic control. Conduction was monitored continuously during RF energy delivery	Yes	No		Not reported
	Unclear	Unclear		Not stated
	Unclear	Unclear	Heparin	7 days
	Yes	Unclear	Heparin	7 days on heparin then oral anticoagulant or aspirin
Inferior vena cava–tricuspid isthmus ablation	Unclear	Unclear		Not stated
8-mm and 10-mm tip catheters were used in approximately equal numbers in a non-randomised fashion. 100 W RF generator used	Unclear	Unclear		1–6 months
	Yes	Unclear	Warfarin	4 weeks
	No	Yes		Not reported

continued

Appendix 3.9: Intervention details: atrial flutter case series

Study	Intervention	Ablation technique	Catheter size	Mapping technique	How was end point of procedure defined?
Hsieh <i>et al.</i> , 2002 ¹³²	RFCA	CTI ablation	4-mm or 8-mm tip	Decapolar catheter in coronary sinus, two quadripolar catheters in low right atrium, plus deflectable 20-electrode Halo catheter	Bidirectional isthmus conduction block and no induction of typical AFI
Jais <i>et al.</i> , 2001 ¹³³	Common flutter ablation	CTI ablation	Irrigated-tip catheter		Flutter termination with bidirectional isthmus block and complete line of block
Loutrianakis <i>et al.</i> , 2002 ¹³⁴	RFCA	Anterior CTI ablation	4-mm tip catheter	Multisite activation mapping	Bidirectional isthmus block with termination of AFI and non-inducibility of spontaneous AFI
Mantovan <i>et al.</i> , 2002 ¹³⁵	RF ablation of atrial flutter	CTI ablation	4-mm, 8-mm, 4+4-mm or irrigated tip	Not stated	Bidirectional isthmus block
Marrouche <i>et al.</i> , 2003 ¹³⁶	Ablation of isthmus-dependent atrial flutter	CTI ablation	Standard 4-mm, high-power 8-mm or 10-mm, or cooled tip	Mapping catheter or CARTO	Bidirectional block across the ablation line
Ozaydin <i>et al.</i> , 2003 ¹³⁷	CTI ablation	CTI ablation	4-mm tip catheter	Duodecapolar Halo catheter plus quadripolar mapping/ablation catheter under fluoroscopic guidance	Complete bidirectional conduction block across the CTI
Paydak <i>et al.</i> , 1998 ³⁰	Atrial flutter ablation	CTI ablation	4-, 5- or 8-mm standard	Quadripolar catheter or 20-electrode Halo catheter	Termination and non-inducibility of flutter, with/without bidirectional block
Schmieder <i>et al.</i> , 2003 ¹³⁸	RF ablation (anatomical approach)	CTI ablation	8-mm tip, cooled tip or 4-mm tip ablation catheter	20-polar catheter in tricuspid annulus and 8-polar mapping catheter in coronary sinus	Bidirectional isthmus block and arrhythmia no longer inducible
Schreieck <i>et al.</i> , 2002 ¹²⁴	Ablation of typical atrial flutter	CTI ablation	8-mm standard or 4-mm cooled tip	Halo mapping catheter	Flutter termination and bidirectional isthmus block
Stovicek <i>et al.</i> , 2006 ¹³⁹	RFCA	CTI ablation	8-mm tip or 4-mm cooled-tip catheters	Duodecapolar Halo catheter and decapolar catheter in coronary sinus	Bidirectional CTI conduction block

Other details	Were AADs discontinued before RFCA?	Return to AADs as part of treatment?	Anticoagulant	Length on anticoagulant
RF energy was applied during pullback of the ablation catheter from the tricuspid annulus towards the inferior vena cava	Yes	Unclear		Not reported
Ablation was not performed in the septal isthmus or inside the ostium of the coronary sinus	Unclear	Unclear	Heparin	Not reported
A long, linear ablation line was produced if possible. If conduction persisted more lesions were created along the same line and/or a second linear lesion was created	Unclear	Unclear	Heparin	Not reported
Inferior isthmus ablation (between tricuspid annulus and inferior vena cava) and/or septal isthmus ablation (between tricuspid annulus and coronary sinus ostium)	Unclear	Unclear		Not stated
RF energy applied between the tricuspid annulus and the Eustachian ridge	Yes	Unclear		
If complete block could not be achieved after three passes, a new ablation line was created at a different site in the CTI	Unclear	Unclear		Not reported
Line of conduction block between the tricuspid annulus and Eustachian ridge/inferior vena cava	Yes	No	Heparin	Unclear
	Yes	Unclear		At least 2 months
Ablation line was not drawn near the septal aspect of the isthmus	Unclear	Unclear		3 months
Patients were observed for at least 30 minutes after CTI block and further RF was delivered if conduction recurred	Unclear	Unclear		Not reported

continued

Appendix 3.9: Intervention details: atrial flutter case series

Study	Intervention	Ablation technique	Catheter size	Mapping technique	How was end point of procedure defined?
Ventura et al., 2003 ¹⁴⁰	RFCA	CTI ablation	4-mm or 8-mm tip ablation catheter	20-pole electrode mapping catheter	Bidirectional isthmus block
Ventura et al., 2004 ¹⁴¹	RF current ablation	CTI ablation	Open cooled-tip or solid 8-mm tip catheters	Decapolar mapping catheter	Bidirectional isthmus block

AFI, atrial flutter; CTI, cavotricuspid isthmus; RA, right atrium.

Other details	Were AADs discontinued before RFCA?	Return to AADs as part of treatment?	Anticoagulant	Length on anticoagulant
Additional RF pulses were applied to fill gaps in ablation line. An additional short ablation line was drawn parallel to the first if necessary	Unclear	Unclear		
Additional RF pulses were applied to fill gaps in ablation line. An additional line was drawn parallel to the original line in cases of failure	No	Unclear		Not reported

Appendix 3.10: Freedom from arrhythmia at mean follow-up: atrial flutter case series

Study	Mean follow-up (months)	Number ablated	Overall freedom from AFI as reported	Overall freedom from AFI (assuming dropouts AFI)	Result without repeat ablation?	Occurrence of AF or other arrhythmia ^a	Freedom from any arrhythmia (calculated)	Repeat ablation	Freedom from AFI after repeat ablation
Andronache et al., 2003 ¹²⁵	33	100	95/100 (95%)	95/100 (95.0%)	No	NR		7	7/7
Bertaglia et al., 2004 ¹¹⁹	20.5	383	326/383 (85.1%)	326/383 (85.1%)	No	AF: 174/383 (41.5%)	152/383 (39.7%)	41?	27/41?
Chen et al., 2002 ¹²⁷	21	124	118/124 (95.2%)	118/124 (95.2%)	No	NR		6/124	6/6
Da Costa et al., 2002 ¹²⁸	15	161	152/161 (94.4%)	152/161 (94.4%)	NR	AF: 14/161 (8.7%)	138/161 (85.7%)		
Da Costa et al., 2003 ¹²²	12.4	248	236/248 (95.2%)	236/248 (95.2%)	No	AF or AT: 65/248 (26.2%)	171/248 (69.0%)	12/248?	7/12?
Da Costa et al., 2004 ¹²⁹	9.5	185	181/185 (97.8%)	181/185 (97.8%)	No	AF: 24/185 (13%)	157/185 (84.9%)	4/185?	4/4?
Da Costa et al., 2005 ¹²³	23.4	176	159/170 (93.5%)	159/176 (90.34%)	NR	AF or AT: 39/176 (22.1%)	120/170 (70.6%)		
Gilligan et al., 2003 ¹³⁰	17	126	86/126 (68.3%)	86/126 (68.3%)	NR	AF or atypical AFI: 46/126 (36.5%)	40/126 (31.7%)		
Heidbuechel et al., 2006 ¹³¹	30	154	131/137 (95.6%)	131/154 (85.1%)	No	AF: 82/154 (53.2%)	49/137 (35.8%)	6/154	4/6
Hsieh et al., 2002 ¹³²	29	333	304/333 (91.3%)	304/333 (91.3%)	No	AF: 102/333 (30.6%)	202/333 (60.7%)	10/333	9/10
Jais et al., 2001 ¹³³	12	221	214/221 (96.8%)	214/221 (96.8%)	No	NR		7/221	7/7
Loutrianakis et al., 2002 ¹³⁴	28	104	91/104 (87.5%)	91/104 (87.5%)	No	AF: 28/104 (26.9%)	63/104 (60.6%)	13/104	13/13
Mantovan et al., 2002 ¹³⁵	19	417	326/417 (78.2%)	326/417 (78.2%)	NR	NR			

Study	Mean follow-up (months)	Number ablated	Overall freedom from AFI as reported	Overall freedom from AFI (assuming dropouts AFI)	Result without repeat ablation?	Occurrence of AF or other arrhythmia ^a	Freedom from any arrhythmia (calculated)	Repeat ablation	Freedom from AFI after repeat ablation
Marrouche <i>et al.</i> , 2003 ¹³⁶	20.1	102	91/102 (89.2%)	91/102 (89.2%)	NR	NR			
Ozaydin <i>et al.</i> , 2003 ¹³⁷	6	100	86/90 (95.5%)	86/100 (86.0%)	NR	NR			
Paydak <i>et al.</i> , 1998 ³⁰	20.1	110	105/110 (95.5%)	105/110 (95.5%)	NR	AF: 28/110 (25.4%)	87/110 (79.1%)		
Schmieder <i>et al.</i> , 2003 ¹³⁸	16.3	363	310/363 (85.4%)	310/363 (85.4%)	No	AF: 132/363 (36.4%)	178/363 (49.0%)		
Schreieck <i>et al.</i> , 2002 ¹²⁶	8.3	100	96/100 (96%) ^c	76/100 (76%)	Yes	Atypical flutter: 2/100 (2%)		20/100	20/20 ^d
Stovicek <i>et al.</i> , 2006 ¹³⁹		108	99/100 (99%)	99/108 (91.7%)	No	NR		9/108	NR
Ventura <i>et al.</i> , 2003 ¹⁴⁰	15	174	158/174 (90.8%)	158/174 (90.8%)	No	NR		16/174	7/16
Ventura <i>et al.</i> , 2004 ¹⁴¹	14	130	127/130 (97.7%)	127/130 (97.7%)	No	AF: 14/130 (10.8%)	113/130 (86.9%)	3/130	3/3

AF: atrial fibrillation; AFI, atrial flutter; AT: atrial tachycardia; NR, not reported.
 a Calculated as 'worst case' intention to treat. Where more than one type of arrhythmia reported assumed to represent one patient per arrhythmia.
 b Result: includes 20 patients who had received repeat ablations.

Appendix 3.11: Complications at mean follow-up: atrial flutter case series

Author	Number ablated	Mean follow-up (months)	AV block	Haematoma	Mortality	Other complications
Bertaglia <i>et al.</i> , 2004 ¹¹⁹	383	20.5	2/383 (0.5%)		3/383 (0.8%)	Four unspecified 'complications'
Da Costa <i>et al.</i> , 2002 ¹²⁸	161	15			NR	No complications
Da Costa <i>et al.</i> , 2005 ¹²³	176	23.4		1/176 (0.6%)	NR	
Hsieh <i>et al.</i> , 2002 ¹³²	333	29			31/333 (9.3%)	
Loutrianakis <i>et al.</i> , 2002 ¹³⁴	104	28			13/104 (12.5%)	
Schmieder <i>et al.</i> , 2003 ¹³⁸	363	16.3			6/363 (1.7%)	

AV, atrioventricular; NR, not reported.

Appendix 3.12: Immediate complications: atrial flutter case series

Author	Number ablated	AV block	Ventricular tachycardia/fibrillation	Hypotension	Haematoma	False femoral aneurysm
Andronache <i>et al.</i> , 2003 ¹²⁵	100					
Bertaglia <i>et al.</i> , 2004 ¹¹⁹	383	2/383 (0.5%)	1/383 (0.3%)		2/383 (0.5%)	
Calkins <i>et al.</i> , 2004 ¹²⁶	150		1/150 (0.7%)	1/150 (0.7%)	1/150 (0.7%)	
Chen <i>et al.</i> , 2002 ¹²⁷	124					
Da Costa <i>et al.</i> , 2003 ¹²²	248					
Da Costa <i>et al.</i> , 2004 ¹²⁹	185					2/185 (1%)
Feld <i>et al.</i> , 2004 ¹²⁰	169					
Jais <i>et al.</i> , 2001 ¹³³	221				5/221 (2.3%)	2/221 (0.9%)
Loutrianakis <i>et al.</i> , 2002 ¹³⁴	104					
Mantovan <i>et al.</i> , 2002 ¹³⁵	417	2/417 (0.5%)	1/417 (0.2%)			
Schmieder <i>et al.</i> , 2003 ¹³⁸	363	3/363 (0.8%)				
Schreieck <i>et al.</i> , 2002 ¹²⁴	100	1/100 (1%)				
Ventura <i>et al.</i> , 2003 ¹⁴⁰	174					

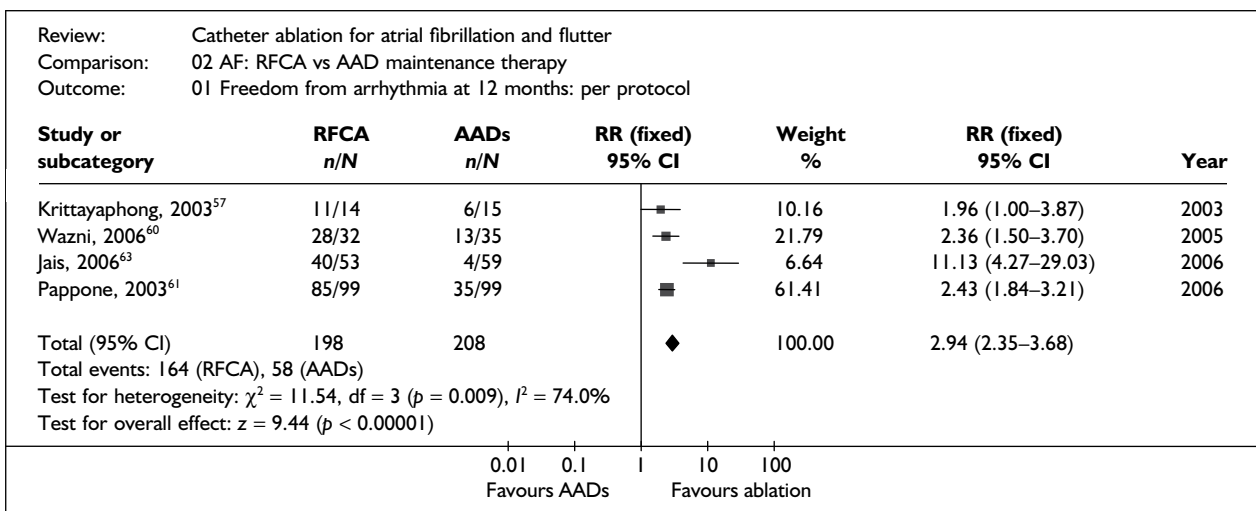
AV, atrioventricular.
a One clearly not procedure related.

Fistulas	Thrombosis	Vascular complications	Pericardial effusion	Pleural effusion	Other
	1/383 (0.3%)			1/150 (0.7%)	No significant complications
					No significant complications
					No significant complications
		4/417 (1%)			Eight ^a major adverse events in six patients
4/363 (1.1%)			2/363 (0.6%)		No significant complications
			2/100 (2%)		
					No significant complications

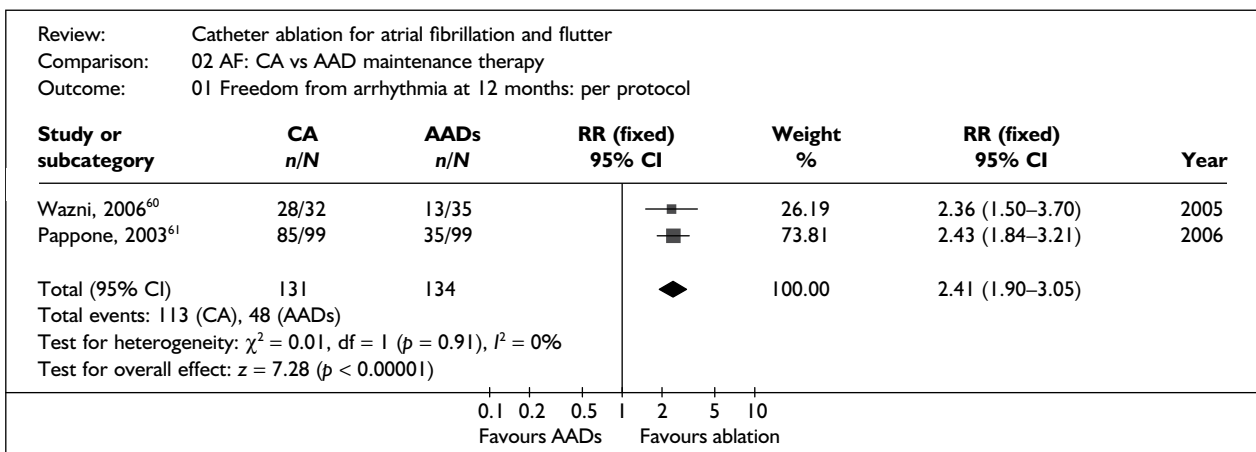
Appendix 4

Clinical evaluation of RFCA in atrial fibrillation: additional analyses

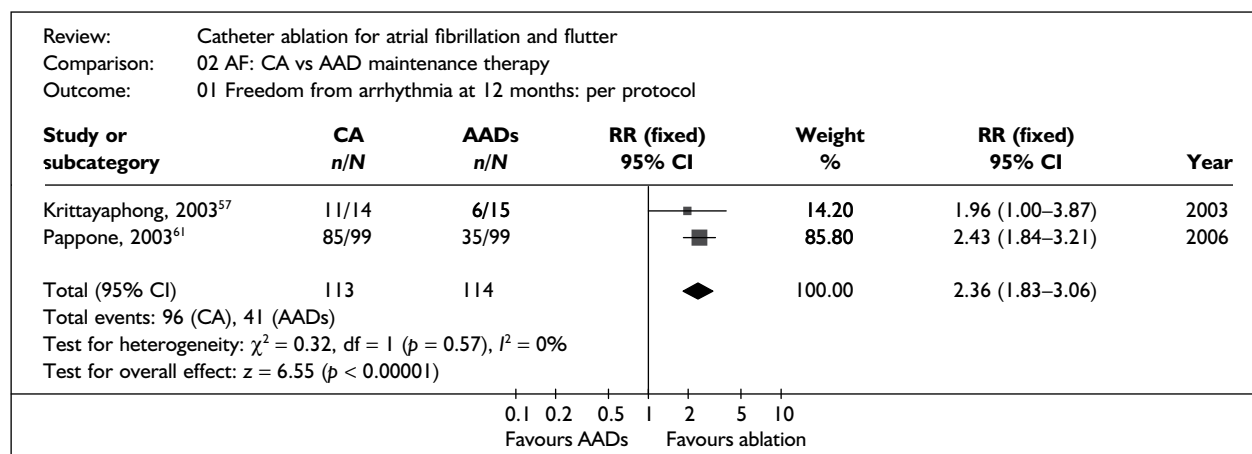
Meta-analysis of all RCTs evaluating RFCA against AADs in paroxysmal atrial fibrillation: freedom from arrhythmia at 12 months (per protocol)



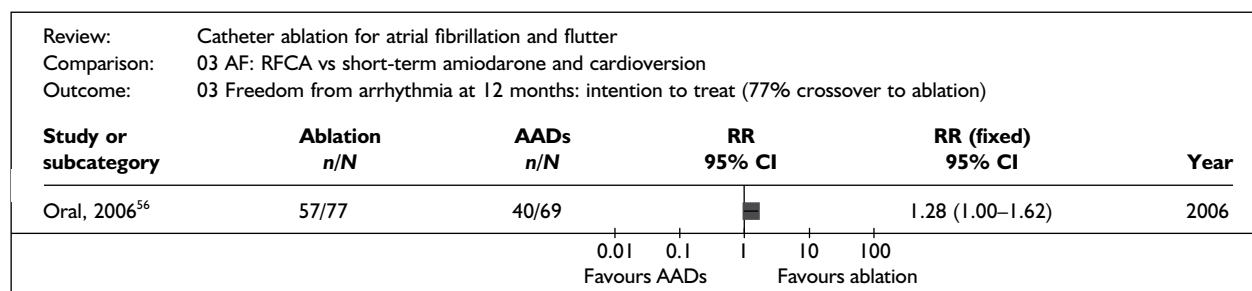
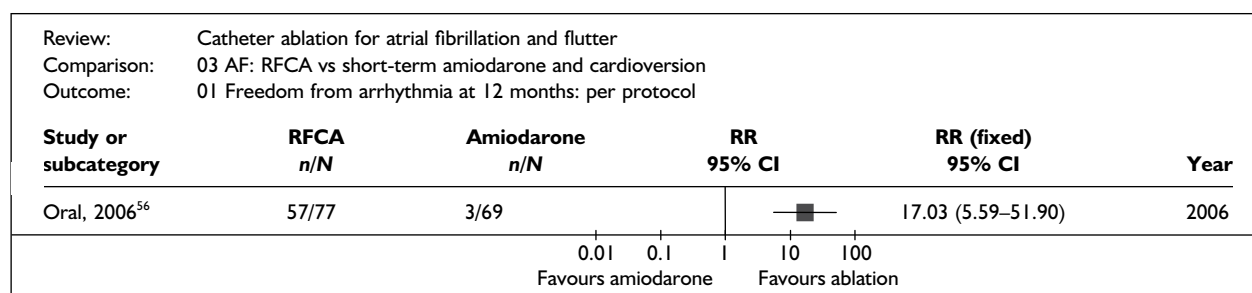
RFCA versus long-term AAD therapy in studies with 100% paroxysmal atrial fibrillation patients: freedom from arrhythmia at 12 months



RFCA versus long-term AAD therapy in studies with 100% drug-refractory atrial fibrillation patients: freedom from arrhythmia at 12 months



RFCA versus cardioversion/short-term amiodarone in persistent atrial fibrillation: freedom from arrhythmia at 12 months (per protocol and intention to treat analyses)



RFCA plus AAD therapy versus AAD therapy alone in paroxysmal/persistent atrial fibrillation: freedom from arrhythmia at 12 months (per protocol, intention to treat, and 'worst case' analyses)

Review:	Catheter ablation for atrial fibrillation and flutter				
Comparison:	06 AF: RFCA plus AAD therapy versus AAD maintenance therapy alone				
Outcome:	01 Freedom from arrhythmia at 12 months: per protocol				
Study or subcategory	RFCA + AADs n/N	AAD therapy alone n/N	RR 95% CI	RR (fixed) 95% CI	Year
Stabile, 2006 ⁵⁹	36/66	4/67		9.14 (3.44-24.23)	2006
			0.01 0.1 10 100		
			Favours AADs alone	Favours RFCA + AADs	

Review:	Catheter ablation for atrial fibrillation and flutter				
Comparison:	06 AF: RFCA plus AAD therapy versus AAD maintenance therapy alone				
Outcome:	02 Freedom from arrhythmia at 12 months: 'worst case'				
Study or subcategory	RFCA + AADs n/N	AAD therapy alone n/N	RR 95% CI	RR (fixed) 95% CI	Year
Stabile, 2006 ⁵⁹	36/68	6/69		6.09 (2.74-13.51)	2006
			0.01 0.1 10 100		
			Favours AADs alone	Favours RFCA + AADs	

Review:	Catheter ablation for atrial fibrillation and flutter				
Comparison:	06 AF: RFCA plus AAD therapy versus AAD maintenance therapy alone				
Outcome:	03 Freedom from arrhythmia at 12 months: intention to treat				
Study or subcategory	RFCA + AADs n/N	AAD therapy alone n/N	RR 95% CI	RR (fixed) 95% CI	Year
Stabile, 2006 ⁵⁹	38/68	6/69		6.43 (2.91-14.21)	2006
			0.01 0.1 10 100		
			Favours AADs alone	Favours RFCA + AADs	

Appendix 5

Excluded studies

Studies excluded because of lack of outcome data are listed below. A complete list of excluded studies is available from the authors on request.

Ahmed *et al.*, 2006¹⁸⁴

Bernstein *et al.*, 2004¹⁸⁶

Da Costa *et al.*, 2006¹⁸⁸

Ekinci *et al.*, 2003¹⁹⁰

Gerstenfeld *et al.*, 2003¹⁹²

Gronefeld *et al.*, 2002¹⁹⁴

Hsu *et al.*, 2005¹⁹⁶

Kluge *et al.*, 2004¹⁹⁸

Lee *et al.*, 2005²⁰⁰

Mansour *et al.*, 2004²⁰²

Marrouche *et al.*, 2003¹⁸⁵

Piorkowski *et al.*, 2006¹⁸⁷

Ren *et al.*, 2005¹⁸⁹

Rotter *et al.*, 2005¹⁹¹

Sacher *et al.*, 2006¹⁹³

Scharf *et al.*, 2004¹⁹⁵

Scharf *et al.*, 2004¹⁹⁷

Schmidt *et al.*, 2001¹⁹⁹

Takahashi *et al.*, 2003²⁰¹

Wieczorek *et al.*, 2005²⁰³

Appendix 6

Ongoing and not yet published studies

These studies initially appeared relevant to the review but results were not yet available.

Title of study	Country	Study details	Expected completion date
RFCA as first-line therapy for typical atrial flutter: a multicentre randomised study of cost-effectiveness	France	Multicentre trial in which patients with a first symptomatic episode of typical atrial flutter are randomised to undergo ablation or to receive antiarrhythmic drugs after electrical cardioversion. The primary end point is the absence of recurrence of typical atrial flutter at 6 and 12 months of follow-up. Secondary end points are cost and cost-effectiveness ratio	N/A
NAVI-STAR® THERMOCOOL® catheter for the radiofrequency ablation of symptomatic paroxysmal atrial fibrillation	USA	Prospective, randomised, unblinded, multicentre pivotal clinical investigation involving up to 230 participants using a 2:1 randomised scheme for the test (ablation procedure) and control (medical therapy) groups respectively. Participants with symptomatic paroxysmal atrial fibrillation are eligible	June 2010
Linear anatomically versus focal electrophysiologically guided substrate ablation in patients with persistent atrial fibrillation	Germany	Randomised study comparing two different approaches to RFCA of persistent atrial fibrillation	November 2008
A multicentre randomised controlled trial comprising RFCA against direct current cardioversion for the treatment of coarse atrial fibrillation (AF)	UK	Randomised comparison of TA-IVC isthmus ablation and conventional therapy (direct-current cardioversion) in patients with chronic atrial fibrillation (> 72 hours) with a coarse fibrillation waveform on their 12-lead electrocardiogram	Published June 2007, as this monograph was in production. Evaluates a hybrid of the two RFCA interventions reviewed, using a conventional flutter ablation technique in atrial fibrillation, showing no significant impact on arrhythmia relative to cardioversion

N/A, not available; TA-IVC, tricuspid annulus-inferior vena cava.

Appendix 7

Economic evaluation

Appendix 7.1: Details of quality assessment for economic studies

All items will be graded as ✓ (yes, item adequately addressed), ✗ (no, item not adequately addressed), ? unclear or not enough information), NA (not applicable) or NS (not stated).

Chan <i>et al.</i> , 2006 ¹⁴⁴		
Study question	Grade	Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	✓	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	Further details are given in an accompanying technical appendix
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✗	Effectiveness data derived from case series. Results reported to be consistent with their review of RCTs
11. Potential biases identified (especially if data not from RCTs)	✗	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	No formal synthesis undertaken

Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✗	
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	✓	2004, US\$
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation is clearly stated	✓	
20. Methods to value health states and other benefits are stated	✗	No health states were valued
21. Details of the individuals from whom valuations were obtained are given	NA	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	Costs and life expectancy were discounted at 3% per year
26. Do discount rates accord with NHS guidance?	✗	NHS guidance recommends 3.5% per year for costs and benefits
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	NA	
28. Uncertainty around cost-effectiveness expressed [e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves]	NA	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	

Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✓	Only in a sensitivity analysis
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	✗	No distributions are given. The sampling was conducted across the ranges of parameter estimates
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis, etc.)	✓	One-way and multivariate sensitivity analysis
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✗	US based and unclear how generalisable these results are to a UK setting

Appendix 7.2: WinBUGS code

Below is the WinBUGS code used to synthesise the RCT evidence and the non-RCT data.

```
#A random baseline, fixed-effect model is adopted as the basis for the meta-analysis.
#The model estimates the baseline for RFCA and the relative treatment effect for AADs.
```

```
model{

  #prior on random treatment effect variance
  baseMean ~ dnorm(0,1.0E-5)
  baseSd ~ dunif(0,10)
  baseTau <- 1/pow(baseSd,2)

  beta[1]<-0

  #prior on treatment effect mean
  for (q in 2:nTx)
  {
    beta[q]~dnorm(0,1.0E-4)
  }

  #Random baseline effect
  for(s in 1:nStudies)
  {
    alpha[s] ~ dnorm(baseMean,baseTau)
  }

  #fit data
  for(i in 1:nObs)
  {
    logOdds[i] <- alpha[study[i]] + beta[tx[i]]

    #logit link for probability of response
    logit(p[i]) <- logOdds[i]

    #binomial link between number of responses and
    probability of response #from treatment arm
    r[i] ~ dbin(p[i], n[i])
  }

  #Probability of freedom from AF at 12 months: baseline
  (RFCA) and p2 (AADs)
  logit(baseline) <- baseMean
  logit(p2) <- baseMean + beta[2]
  #Odds ratio: relative treatment effect
  OR <- exp(beta[2])
}

#Sample data: RCT evidence
list(tx=c(1,2,1,2,1,2), r=c(11,6,28,13,85,35),
     n=c(14,15,32,35,99,99), study=c(1,1,2,2,3,3),nStudies=3,nObs
     =6,nTx=2)

#Initial values
list(beta=c(NA,0),alpha=c(0,0,0))
```

Appendix 7.3: Input parameters for model Parameter estimates applied in the model

Parameter	Mean (95% CI)	Distribution	Description	Source
Baseline patient characteristics				
Age (years)	52	Fixed	Average age of patients at start of treatment	Bourke et al., 2005 ⁶⁶
Gender	80% male	Fixed	Proportion of patients that are male	Bourke et al., 2005 ⁶⁶
Baseline event rates and relative treatment effect				
Analysis 1: RCT evidence				
Probability of freedom from AF at 12 months			WinBUGS evidence synthesis	
RFCA	0.8405 (0.5579–0.9631) ^a	Posterior	Baseline for RFCA from RCT evidence	
AADs	0.3682 (0.1060–0.7083) ^a	Posterior	Baseline for AADs from RCT evidence	
Odds ratio	0.0968 (0.0520–0.1641) ^a	Posterior	Relative treatment effect from RCT evidence	
Analysis 2: RCT and case series evidence				
Probability of freedom from AF at 12 months			WinBUGS evidence synthesis	
RFCA	0.7404 (0.6478–0.8213) ^a	Posterior	Baseline for RFCA from RCTs and case series	
AADs	0.2428 (0.1380–0.3705) ^a	Posterior	Baseline for AADs from RCTs and case series	
Odds ratio	0.1122 (0.0621–0.1835) ^a	Posterior	Relative treatment effect from RCTs and case series	
Analysis 3: RCT and Cappato et al., 2005 ²⁵ evidence				
Probability of freedom from AF at 12 months			WinBUGS evidence synthesis	
RFCA	0.7867 (0.5318–0.9467) ^a	Posterior	Baseline for RFCA from RCTs and Cappato et al., 2005 ²⁵	
AADs	0.3116 (0.0946–0.6229) ^a	Posterior	Baseline for AADs from RCTs and Cappato et al., 2005 ²⁵	
Odds ratio	0.1079 (0.0561–0.1850) ^a	Posterior	Relative treatment effect from RCTs and Cappato et al., 2005 ²⁵	
Long-term reversion rates (NSR to AF)				
Probability of recurrent AF				
RFCA	0.0335 (0.0220–0.0451)	Beta	Annual rate of reversion to AF for RFCA	Pappone et al., 2003 ⁶¹
AADs	0.2883 (0.2323–0.3456)	Beta	Annual rate of reversion to AF for AADs	Roy et al., 2000 ¹⁵⁶

continued

Parameter estimates applied in the model

Parameter	Mean (95% CI)	Distribution	Description	Source
Stroke risk for AF (%)				
CHADS ₂ score = 0	1.9 (1.2–3.0)	Beta	The CHADS ₂ index combines the stroke risk classification schemes of the SPAF trial investigators ¹⁵⁸ and the AF investigators ¹⁵⁹	Gage <i>et al.</i> , 2001 ¹⁵⁷
CHADS ₂ score = 1	2.8 (2.0–3.8)	Beta		
CHADS ₂ score = 2	4.0 (3.1–5.1)	Beta		
CHADS ₂ score = 3	5.9 (4.6–7.3)	Beta		
Stroke risk for NSR				
Hazard ratio for AF relative to NSR	1.60 (1.11–2.30)	Log normal	The reciprocal of the hazard gives the stroke risk reduction for NSR	Sherman <i>et al.</i> , 2005 ²⁰⁴
Anticoagulant (OAC) use (%)				
Warfarin	64.0	Dirichlet	Proportion of patients receiving warfarin	Nieuwlaat <i>et al.</i> , 2006 ¹⁶¹
Aspirin	27.3	Dirichlet	Proportion of patients receiving aspirin	Nieuwlaat <i>et al.</i> , 2006 ¹⁶¹
None	8.7	Dirichlet	Proportion of patients receiving no OACs	Nieuwlaat <i>et al.</i> , 2006 ¹⁶¹
Stroke risk reduction with OAC use (RR)				
Warfarin vs placebo	0.33 (0.24–0.45)	Log normal	Relative risk for warfarin vs no treatment	Lip and Edwards, 2006 ¹⁶⁰
Warfarin vs aspirin	0.59 (0.40–0.86)	Log normal	Relative risk for warfarin vs aspirin	Lip and Edwards, 2006 ¹⁶⁰
Mortality risk from stroke (RR)				
In year 1	7.40 (6.50–8.50)	Log normal	Relative risk of dying compared with the general population in the first year of stroke and subsequent years	Dennis <i>et al.</i> , 1993 ¹⁶²
In subsequent years	2.30 (2.00–2.70)	Log normal		
Side effects (AADs)				
General toxicity (%)				
In year 1	12.50 (10.00–15.00) ^b	Betapert	Probability of general toxicity during the first year and subsequent years	Owens <i>et al.</i> , 1997 ¹⁵⁵
In subsequent years	6.25 (5.00–7.50) ^b	Betapert		
Withdrawal because of toxicity (%)				
In year 1	10.00 (6.25–12.50) ^b	Betapert	Probability of withdrawal because of toxicity during the first year and subsequent years	Owens <i>et al.</i> , 1997 ¹⁵⁵
In subsequent years	5.00 (3.13–6.25) ^b	Betapert		

Parameter	Mean (95% CI)	Distribution	Description	Source
Pulmonary toxicity (%)				
Pulmonary complication	15.19 (1.00–30.00) ^b	Betapert	Probability of pulmonary complication given withdrawal	Owens <i>et al.</i> , 1997 ¹⁵⁵
Irreversible pulmonary complication	25.00 (0.00–30.00) ^b	Betapert	Probability of irreversible pulmonary toxicity given withdrawal for pulmonary complication	
Mortality risk (%)				
Irreversible pulmonary toxicity	20.00 (5.00–25.00) ^b	Betapert	Probability of death given irreversible pulmonary toxicity	Owens <i>et al.</i> , 1997 ¹⁵⁵
Adverse bleeding from OAC use (%)				
Major bleed on warfarin	2.40 (1.70–8.10) ^b	Betapert	Annual probability of a major bleed on warfarin	NICE, 2006 ¹⁶⁷
Minor bleed on warfarin	15.80 (15.00–16.60) ^b	Betapert	Annual probability of a minor bleed on warfarin	
Bleeding risk reduction on aspirin (RR)				
Major bleed	0.58 (0.35–0.97)	Log normal	Relative risk for major and minor bleeds comparing warfarin with aspirin	Lip and Edwards, 2006 ¹⁶⁰
Minor bleed	0.45 (0.32–0.64)	Log normal		Lip and Edwards, 2006 ¹⁶⁰
Bleeding risk reduction on no OACs (RR)				
Major bleed	0.45 (0.25–0.82)	Log normal	Relative risk for major and minor bleeds comparing warfarin with no OACs	Lip and Edwards, 2006 ¹⁶⁰
Minor bleed	0.46 (0.36–0.59)	Log normal		Lip and Edwards, 2006 ¹⁶⁰
Complications (RFCA) (%)				
Operative death	0.05 (0.00–0.09)	Beta	Probability of procedural death	Cappato <i>et al.</i> , 2005 ²⁵
Cardiac tamponade	1.22 (0.99–1.45)	Beta	Probability of cardiac tamponade during procedure	
Stroke	0.28 (0.16–0.40)	Beta	Probability of stroke during procedure	
PV stenosis	0.74 (0.54–0.94)	Beta	Probability of PV stenosis during procedure	
RFCA procedures				
Mean number of procedures	1.304 (1.293–1.315)	Normal	Mean number of procedures per patient per year	Cappato <i>et al.</i> , 2005 ²⁵
Annual discount rate (%)				
On costs	3.5	Fixed	Cost discount rate	
On QALYs	3.5	Fixed	Outcome discount rate	NICE ¹⁵⁰

CI, confidence interval; NSR, normal sinus rhythm; OAC, oral anticoagulant; PV, pulmonary vein; QALY, quality-adjusted life-year; RCT, randomised controlled trial; RR, relative risk.
a 95% credibility interval.
b Range.

Utilities for the health states used in the model

Health state	Mean (standard error)	Distribution	Description	Source
Main health states: NSR and AF				
Utility decrement for NSR			Decrement for NSR applied to UK age-specific utilities conditional on RFCA or AAD treatment	Berkowitsch <i>et al.</i> , 2003 ²⁰⁵
RFCA	0.0000 (–)			
AADs	0.0199 (0.0100)	Gamma		
Utility decrement for AF			Decrement for AF applied to UK age-specific utilities conditional on RFCA or AAD treatment	Rienstra <i>et al.</i> , 2006 ²⁰⁶
RFCA	0.0034 (0.0017)	Gamma		
AADs	0.0925 (0.0361)	Gamma		
Stroke			Utilities for stroke	Jones <i>et al.</i> , 2004 ¹⁶⁸
Non-disabled stroke (year 1 and post year 1)	0.74 (0.026)	Beta		
Disabled stroke (year 1 and post year 1)	0.38 (0.046)	Beta		
Combined stroke (assuming 30.9% disabled)	0.63			
Toxicity			Decrement for pulmonary and non-pulmonary toxicity applied to UK age-specific utilities	Sullivan and Ghushchyan, 2006 ¹⁷²
Decrement for pulmonary toxicity	0.0329 (0.0030)	Gamma		
Decrement for non-pulmonary toxicity (days of perfect health lost)	1 (0–30) ^b	Betapert		
Bleeding event			Decrement for bleeding event applied to UK age-specific utilities	Owens <i>et al.</i> , 1997 ¹⁵⁵
Decrement for bleeding event ^a (days of perfect health lost)	1 (0–30) ^b	Betapert		
NSR, normal sinus rhythm.				
a Assumed the same as a non-pulmonary toxic event.				
b Range.				

Unit costs used in the analysis (costs uprated to 2006)

Unit cost	Unit	Base-case value	Source
Catheter ablation			
Consumables ^a	Item	£5687	Personal communication
Ward	Item	£182	
Laboratory	Item	£1979	
Total accumulated cost (includes administrative overheads and VAT)	Procedure	£9810	
Procedural complications			
Cardiac tamponade	Item	£815	Department of Health, 2005 ¹⁶⁴
PV stenosis	Item	£3217	Department of Health, 2005 ¹⁶⁴
Amiodarone			
Inpatient initiation	Visit	£3360	Department of Health, 2005 ¹⁶⁴
Outpatient initiation	Visit	£154	Department of Health, 2005 ¹⁶⁴
Amiodarone	200 mg daily	£32 per annum	Department of Health, 2005 ¹⁶⁴
Anticoagulants			
Warfarin	5 mg daily	£19 per annum	BMA and RPS, 2007 ¹⁶⁶
Aspirin	75 mg daily	£20 per annum	BMA and RPS, 2007 ¹⁶⁶
Stroke			
In year 1	Per annum	£9431	Jones <i>et al.</i> , 2004 ¹⁶⁸
In subsequent years	Per annum	£2488	
Toxicity			
Toxic event	Item	£1497	Buxton <i>et al.</i> , 2006 ¹⁶⁵
Reversible toxicity	Per day	£0.43	BMA and RPS, 2007 ¹⁶⁶
Irreversible toxicity	50 mg daily	£158	BMA and RPS, 2007 ¹⁶⁶
Bleeding event			
Major bleed	Per annum	£1573	NICE, 2006 ¹⁶⁷
Minor bleed	Per annum	£87	NICE, 2006 ¹⁶⁷
AF health states			
NSR	Per annum	£646	Stewart <i>et al.</i> , 2004 ¹⁷
AF	Per annum	£646	Stewart <i>et al.</i> , 2004 ¹⁷
<p>NSR, normal sinus rhythm; PV, pulmonary vein. a Four catheters (£2180), one Seldinger needle (£4), four sheaths (£36), two TSP/sheaths (£220), two sterile packs (£100), one ESI/CARTO system (£2000), one computed tomography/magnetic resonance imaging scan (£300). Total costs = £4840 + VAT @ 17.5%.</p>			

Appendix 7.4: Review of quality of life evidence for decision model

Methods

For the assessment of QoL a separate systematic search of relevant databases was undertaken. A total of 134 potential references were identified. Two reviewers (SVH and CM) independently screened the titles and abstracts of the studies identified from all searches and sources. A full paper copy of any study judged to be relevant by either reviewer was obtained when possible. A total of 48 studies were then selected as being potentially relevant to the decision problem being addressed.

The review focused on three specific aspects related to QoL:

1. Studies evaluating the QoL of patients with AF (regardless of the intervention).
2. Studies evaluating the impact of RFCA on the QoL of patients with AF.
3. Studies evaluating the impact of NSR on the QoL of patients with AF.

The review focused on studies reporting utility data in relation to these aspects. However, given the lack of published utility data in relation to the second and third areas, consideration was also given to studies reporting other generic measures of health (e.g. SF-36) that could potentially be converted into a utility score for the model.

Studies evaluating the quality of life of patients with atrial fibrillation (regardless of the intervention)

Based on a review of the abstracts, 22 papers were identified and paper copies obtained. Six were subsequently rejected as not relevant. For half of these studies the health utilities reported were derived from a combination of author assumptions and previously published data. The review identified a significant degree of cross-referencing between studies with most of the health state utilities cited in the literature sourced to only three original papers (Naglie and Detsky,²⁰⁷ Gage *et al.*¹⁴⁷ and Gage *et al.*²⁰⁸). Although the studies by Gage *et al.* generated health state utilities using a time trade-off (TTO) method, the utilities reported by Naglie and Detsky were based on the consensus of three experts.

Most of the utilities reported refer to health-related QoL (HRQoL) associated with stroke, bleeding

events and oral anticoagulation use, reflecting the emphasis of studies in this area primarily on stroke prevention. None of the studies reported utility data directly relevant to the economic model. For example, none of the studies reported a utility estimate for AF, with the exception of a few previous decision-analytic models that assumed a value of 1 (i.e. equivalent to full health) for this state. Furthermore, no study reported utility values following catheter ablation, or estimates for patients restored to normal sinus rhythm. As a result, utility estimates for the model could not be informed from this review and an extensive evaluation of other sources identified in the initial literature search was required.

Studies evaluating the impact of RFCA on the quality of life of patients with atrial fibrillation

Although no utility estimates were reported in relation to the use of catheter ablation, the search revealed a number of studies reporting QoL data using the Short Form 36 (SF-36) instrument.¹⁶⁹ The SF-36 is a generic health profile instrument that measures health on eight dimensions (BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality). Scores on each dimension are standardised on a 0–100 scale in which a higher score reflects better health. SF-36 data can also be represented in the form of two summary scores: a physical components summary score (PCS) and a mental components summary score (MCS). In the absence of a single index or utility score, SF-36 data cannot be used directly in a cost-effectiveness study. However, a number of algorithms have been proposed that can be used to convert SF-36 data into a utility score. Although most of these methods require access to individual patient level data, Kind *et al.*²⁰⁹ have recently produced an algorithm that allows for the transformation of SF-36 summary data into an EQ-5D weighted index score. Hence, this approach provides a potential basis for estimating utility values based on the aggregate individual domain scores from SF-36.

Studies were therefore considered for inclusion in the review (and hence to provide a potential source of data for the model) if they reported individual domain scores at 12 months, consistent with the time horizon of the short-term model. Of the 15 papers identified in the literature search, eight were excluded as they did not present the individual domain scores for the SF-36 instrument. Of the remaining seven papers reporting tabulated

mean scores for each of the domains, two reported data at a follow-up of 12 months.^{205,210} A brief overview of each study follows.

Berkowitsch *et al.*, 2003²⁰⁵

Origin: Germany.

Objectives: To evaluate the clinical relevance of SF-36 and an arrhythmia-related symptom severity checklist (SSCL) to post-procedure AF recurrences in patients with paroxysmal AF undergoing pulmonary vein isolation (PVI).

Methods: 60 patients with AF (mean age 58 years) refractory to drug therapy underwent PVI and

discontinued using arrhythmia drugs after the procedure. Patients completed SF-36 at baseline and then at 3, 6, 9 and 12 months after the procedure.

Results: 21 out of 60 patients experienced recurrence of AF during follow-up. Three months after ablation, patients without AF recurrence showed improvements on all SF-36 dimensions compared with baseline, and these improvements were generally maintained at 12 months. In contrast, patients with AF recurrence showed significant improvements only on the mental health dimension at 3 months, and the improvement in general was less significant at 12 months.

Effect of RFCA on quality of life as measured by the SF-36 instrument in patients with no recurrence of atrial fibrillation post ablation (n = 39)

Dimension	Baseline	3 months	6 months	9 months	12 months
PF	61.99 (23.43)	80.89 (18.62)	77.50 (21.47)	73.33 (24.66)	83.93 (15.83)
RP	29.79 (35.99)	68.75 (39.88)	56.82 (43.26)	68.06 (37.32)	67.86 (39.73)
BP	64.71 (29.43)	83.86 (20.05)	84.73 (26.33)	76.44 (21.71)	71.71 (27.49)
RE	47.49 (45.13)	68.45 (39.93)	69.70 (40.09)	71.30 (39.21)	80.95 (32.65)
MH	54.66 (19.06)	72.07 (17.26)	70.73 (18.70)	65.67 (19.85)	67.71 (21.60)
SF	57.62 (26.09)	83.93 (20.82)	81.82 (25.76)	75.69 (22.23)	80.36 (32.98)
VT	41.13 (18.16)	55.45 (16.26)	57.84 (18.62)	57.78 (19.47)	56.61 (17.87)
GH	49.36 (18.06)	63.50 (13.47)	62.50 (18.87)	57.83 (18.67)	66.07 (15.42)

BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.
Figures are presented as mean score (SD) for each dimension.

Effect of RFCA on quality of life as measured by the SF-36 instrument in patients with recurrence of atrial fibrillation post ablation (n = 21)

Dimension	Baseline	3 months	6 months	9 months	12 months
PF	61.99 (23.43)	68.80 (21.27)	72.05 (18.86)	70.56 (14.76)	70.45 (17.90)
RP	29.79 (35.99)	39.00 (40.07)	36.36 (42.46)	36.11 (40.33)	36.36 (28.93)
BP	64.71 (29.43)	56.24 (28.45)	73.41 (22.07)	60.35 (29.73)	72.00 (23.25)
RE	47.49 (45.13)	64.00 (43.12)	53.03 (43.41)	44.44 (41.41)	72.73 (34.28)
MH	54.66 (19.06)	62.56 (19.33)	68.18 (15.47)	70.00 (11.13)	64.73 (12.86)
SF	57.62 (26.09)	67.50 (28.06)	77.84 (18.82)	70.83 (19.23)	70.45 (17.05)
VT	41.13 (18.16)	44.60 (19.69)	48.86 (18.40)	46.11 (17.58)	44.09 (14.11)
GH	49.36 (18.06)	51.84 (18.74)	56.14 (17.41)	53.83 (13.97)	51.55 (15.91)

BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.
Figures are presented as mean score (SD) for each dimension.

Weerasooriya et al., 2005²¹⁰

Origin: Australia.

Objectives: To determine the effect of RFCA on QoL of patients with symptomatic, drug-refractory paroxysmal AF.

Methods: 63 patients (mean age 56 years) were referred for RFCA. Patients completed the SF-36 questionnaire at baseline and at 3 and 12 months' follow-up after ablation.

Results: 54 patients (86%) were free of recurrence of AF without AADs at the 12-month follow-up. Successful ablation resulted in improvements on all eight dimensions of the SF-36 at the 3-month follow up and this was maintained at 12 months.

The biggest improvements were observed on the role physical (RP) and bodily pain (BP) dimensions.

Studies evaluating the impact of normal sinus rhythm on the quality of life of patients with atrial fibrillation

The literature search identified five studies that reported SF-36 data for patients in AF and those in NSR. Of these, two reported SF-36 domain scores at 12 months' follow-up.^{206,211} A brief overview of these studies follows.

Rienstra et al., 2006²⁰⁶

Origin: Netherlands.

Objectives: To compare outcome of AF patients treated with effective rhythm control with patients treated with rate control.

Effect of RFCA on quality of life as measured by the SF-36 instrument

Dimension	Baseline (n = 63)	3 months (n = 63)	12 months (n = 59)
PF	68.1 (22.4)	79.5 (27.2)	82.1 (22.3)
RP	43.7 (42.3)	67.5 (41.6)	79.9 (32.5)
BP	55.6 (42.7)	73.0 (40.5)	86.1 (40.0)
RE	47.9 (24.5)	66.3 (22.5)	68.0 (21.7)
MH	59.0 (22.8)	74.9 (17.9)	75.1 (17.2)
SF	64.9 (29.2)	82.1 (19.2)	86.9 (18.3)
VT	68.1 (28.9)	81.9 (21.5)	81.7 (32.5)
GH	52.9 (23.0)	67.1 (18.9)	68.7 (23.7)

BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.
Figures are presented as mean score (SD) for each dimension.

SF-36 scores according to rhythm status

Dimension	Normal sinus rhythm (n = 49)			Atrial fibrillation (n = 178)		
	Baseline	12 months	Study end	Baseline	12 months	Study end
PF	59 (24)	63 (22)	60 (27)	63 (25)	62 (23)	59 (24)
RP	38 (42)	53 (40)	43 (47)	48 (46)	62 (42)	54 (44)
BP	77 (20)	77 (19)	78 (23)	81 (21)	81 (22)	80 (22)
RE	71 (40)	71 (37)	61 (44)	71 (41)	78 (37)	74 (38)
MH	73 (17)	80 (16)	77 (15)	75 (18)	77 (18)	76 (17)
SF	78 (20)	81 (21)	79 (20)	78 (23)	83 (21)	80 (22)
VT	55 (20)	63 (20)	63 (20)	62 (21)	59 (20)	59 (21)
GH	54 (15)	58 (18)	55 (19)	56 (19)	59 (18)	56 (18)

BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.
Figures are presented as mean score (SD) for each dimension.

Methods: 49 out of 266 AF patients randomised to rhythm control in the RACE study achieved long-term sinus rhythm ($\geq 75\%$ of the follow-up time with a maximum of one cardioversion per year) and were continuously treated with oral anticoagulation. Quality of life in these patients was compared with that in 178 patients out of 256 of the rate control group who were in AF and using oral anticoagulation continuously. Patients completed SF-36 at baseline, at 1 year and at the end of the study (30 or 36 months).

Results: At baseline and follow-up, no significant differences in QoL were observed between those in sinus rhythm and those in AF on any of the SF-36 dimensions.

Singh *et al.*, 2006²¹¹

Origin: USA.

Objectives: To determine QoL and exercise performance in patients with persistent AF converted to sinus rhythm compared with those remaining in or reverting to AF.

Methods: Patients with persistent AF (mean age 67 years) were randomised to amiodarone, sotalol or placebo. Those not achieving sinus rhythm by day 28 were cardioverted and classified into sinus rhythm or AF groups at 8 weeks ($n = 624$) and 1 year ($n = 556$). At both follow-ups, patients completed the SF-36 instrument.

Results: Out of the 556 patients followed to 1 year, SF-36 data were available for 496 patients (176 in the AF group and 320 in the NSR group). At the 1-year follow-up, sinus rhythm patients showed significant improvements on the general health (GH) and social functioning (SF) dimensions compared with AF patients. At 1 year, SF-36 scores for AF patients decreased on six out of the eight dimensions.

Converting SF-36 domain scores into a utility value (EQ-5D)

SF-36 scores were transformed into a utility-weighted EQ-5D index score, suitable for calculating QALYs, using a recently developed algorithm that uses data from the 1996 Health Survey for England.²⁰⁹ The Health Survey contains both SF-36 and EQ-5D scores from the general population. The algorithm attempts to match the aggregate profile of the SF-36 domain scores to the 20 closest matches from the general population. The EQ-5D scores from these 20 closest matches are then averaged to estimate a mean utility score.

The resulting EQ-5D scores for each study [mean (range)] are summarised below. The results from Singh *et al.*²¹¹ are not presented because the matching algorithm did not appear to generate sufficiently reliable results.

Mean change in SF-36 scores from baseline to 1 year according to rhythm status

Dimension	Normal sinus rhythm ($n = 320$)		Atrial fibrillation ($n = 176$)	
	Baseline	Change from baseline to 1 year	Baseline	Change from baseline to 1 year
PF	58.6 (28.6)	+2.1 (23.7)	57.4 (25.7)	-1.3 (21.5)
RP	47.5 (42.8)	+4.1 (40.9)	44.9 (42.9)	+1.5 (43.1)
BP	68.9 (26.2)	-2.5 (25.3)	68.6 (28.5)	-2.7 (28.0)
RE	62.9 (42.9)	+0.5 (49.6)	65.1 (42.6)	-3.2 (49.5)
MH	75.3 (19.2)	-1.7 (16.3)	76.0 (17.9)	-2.1 (18.6)
SF	75.8 (26.1)	+1.4 (25.0)	78.2 (25.6)	-4.2 (24.6)
VT	50.1 (24.9)	+3.6 (20.1)	49.0 (22.3)	+0.8 (19.5)
GH	59.8 (21.3)	+0.1 (17.3)	61.3 (20.3)	-4.7 (18.5)

BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.
Figures are presented as mean score (SD) for each dimension.

Berkowitsch et al., 2003²⁰⁵**No recurrence of AF post ablation**

Baseline EQ-5D index = 0.7704 (1–0.516)

12-month EQ-5D index = 0.8629 (1–0.656)

Recurrence of AF post ablation

Baseline EQ-5D index = 0.7704 (1–0.516)

12-month EQ-5D index = 0.8595 (1–0.19)

This gives a corresponding improvement in QoL: no recurrence of AF = 0.09219; recurrence of AF = 0.0891.

Weerasooriya et al., 2005²¹⁰

Baseline EQ-5D index = 0.8527 (1–0.62)

12-month EQ-5D index = 0.9314 (1–0.725)

This gives a corresponding improvement in QoL post ablation = 0.0787.

Rienstra et al., 2006²⁰⁶**AF group**

Baseline EQ-5D index = 0.8807 (1–0.19)

12-month EQ-5D index = 0.8887 (1–0.691)

Sinus rhythm group

Baseline EQ-5D index = 0.822 (1–0.193)

12-month EQ-5D index = 0.8946 (1–0.689)

This gives a corresponding improvement in QoL for the main health states: AF = 0.008; NSR = 0.0726.

Summary

The results of the two catheter ablation studies were remarkably similar. Both studies estimated improvements in utility of between 0.0787 and 0.09219. For the model it was decided that the study by Berkowitsch *et al.*²⁰⁵ more closely reflected the decision problem addressed within the model by presenting QoL according to whether patients were free of symptoms at follow-up or not. The study by Weerasooriya *et al.*²¹⁰ presented the average QoL estimate post ablation and hence includes patients with and without recurrent AF and also those who continue to receive AAD therapy. Hence, the utility improvements associated with 'no recurrence' (0.09219) and 'recurrence' (0.0891) were used as the basis for the NSR and AF states following RFCA.

From the review of QoL studies reporting the impact of NSR, only two studies were identified that presented data in a suitable format for the conversion algorithm. Only the study by Rienstra *et al.*²⁰⁶ generated utility data that appeared sufficiently robust for the purposes of the modelling. Patients achieving NSR were estimated to have an improvement in utility equivalent to 0.0726 – marginally lower than the utility values estimated for either of the RFCA states. The baseline and 12-month utility scores for patients with recurrent AF were virtually identical, suggesting no real change in QoL over this period. Hence, the utility improvements associated with the NSR state and AF state for AADs were derived from these estimates. A utility improvement of 0.0726 was assigned to the NSR state and no change in utility was assumed for the AF state.

Appendix 7.5: Detailed sensitivity analysis results

Scenario 1: Source of data used to estimate baseline event rates (catheter ablation) and relative treatment effects

Lifetime analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
(a) Treatment effect from Cappato et al., 2005²⁵ + RCTs							
RFCA	£26,064	12.13	£7814	0.721	0.990	1.000	1.00
AADs	£15,351	10.76		0.279	0.010	0.000	0.000
(b) Treatment effect from case series + RCTs							
RFCA	£26,119	12.11	£7834	0.709	0.983	0.998	1.000
AADs	£15,365	10.74		0.291	0.017	0.002	0.000

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, willingness to pay.

5-Year analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
(a) Treatment effect from Cappato et al., 2005²⁵ + RCTs							
RFCA	£26,043	11.18	£25,623	0.000	0.154	0.701	0.913
AADs	£15,331	10.77		1.000	0.846	0.299	0.087
(b) Treatment effect from case series + RCTs							
RFCA	£26,108	11.16	£25,302	0.000	0.189	0.682	0.913
AADs	£15,353	10.74		1.000	0.811	0.318	0.087

Scenario 2: Duration of quality of life benefit with catheter ablation

Lifetime/5-year not applicable

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
(a) QoL duration = 10 years							
RFCA	£26,018	11.49	£14,771	0.072	0.794	0.973	0.994
AADs	£15,355	10.77		0.928	0.206	0.027	0.006
(b) QoL duration = 15 years							
RFCA	£26,026	11.73	£11,237	0.307	0.923	0.993	0.998
AADs	£15,361	10.78		0.693	0.077	0.007	0.002
(c) QoL duration = 20 years							
RFCA	£26,028	11.90	£9,492	0.499	0.972	0.997	1.000
AADs	£15,366	10.78		0.501	0.028	0.003	0.000

Scenario 3: Additional mortality risk for atrial fibrillation compared with general population

Lifetime analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
Multiplier = 1.5							
RFCA	£24,825	11.19	£8,577	0.615	0.965	0.999	1.000
AADs	£14,141	9.95		0.385	0.035	0.001	0.000
Multiplier = 2.0							
RFCA	£23,881	10.46	£9,415	0.463	0.939	0.992	0.999
AADs	£13,171	9.33		0.537	0.061	0.008	0.001
Multiplier = 2.5							
RFCA	£23,119	9.86	£9,990	0.444	0.931	0.992	0.995
AADs	£12,383	8.79		0.556	0.069	0.008	0.005

5-Year analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
Multiplier = 1.5							
RFCA	£24,814	10.33	£27,362	0.000	0.098	0.607	0.884
AADs	£14,127	9.94		1.000	0.902	0.393	0.116
Multiplier = 2.0							
RFCA	£23,886	9.68	£28,794	0.000	0.091	0.501	0.814
AADs	£13,176	9.31		1.000	0.909	0.499	0.186
Multiplier = 2.5							
RFCA	£23,128	9.15	£29,908	0.000	0.064	0.435	0.772
AADs	£10,736	8.79		1.000	0.936	0.565	0.228

Scenario 4: Prognostic impact of normal sinus rhythm**Lifetime analysis**

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
Risk of stroke the same for NSR and AF							
RFCA	£26,779	11.94	£9327	0.506	0.948	0.996	1.000
AADs	£15,541	10.74		0.494	0.052	0.004	0.000

5-Year analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
Risk of stroke the same for NSR and AF							
RFCA	£26,797	11.02	£37,997	0.000	0.015	0.204	0.469
AADs	£15,558	10.72		1.000	0.985	0.796	0.531

Scenario 5: Quality of life (utilities)

Lifetime analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
(a) $NSR(RFCA) > AF(RFCA) = NSR(AADs) > AF(AADs)$							
RFCA	£26,023	12.14	£7872	0.714	0.978	0.999	1.000
AADs	£15,363	10.79		0.286	0.022	0.001	0.000
(b) $NSR(RFCA) > NSR(AADs) > AF(RFCA) > AF(AADs)$							
RFCA	£26,020	12.05	£8463	0.616	0.954	0.991	0.997
AADs	£15,362	10.79		0.384	0.046	0.009	0.003
(c) $NSR(RFCA) = NSR(AADs) > AF(RFCA) = AF(AADs)$							
RFCA	£26,021	11.63	£12,840	0.197	0.839	0.963	0.987
AADs	£15,356	10.80		0.803	0.161	0.037	0.013

5-Year analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
(a) $NSR(RFCA) > AF(RFCA) = NSR(AADs) > AF(AADs)$							
RFCA	£26,022	11.19	£26,298	0.000	0.145	0.659	0.912
AADs	£15,364	10.78		1.000	0.855	0.341	0.088
(b) $NSR(RFCA) > NSR(AADs) > AF(RFCA) > AF(AADs)$							
RFCA	£26,029	11.17	£27,216	0.000	0.132	0.599	0.851
AADs	£15,368	10.77		1.000	0.868	0.401	0.149
(c) $NSR(RFCA) = NSR(AADs) > AF(RFCA) = AF(AADs)$							
RFCA	£26,025	11.10	£32,524	0.000	0.035	0.399	0.756
AADs	£15,366	10.78		1.000	0.965	0.601	0.244

Scenario 6: Population**Lifetime analysis**

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
(a) All male							
RFCA	£25,728	11.85	£7921	0.722	0.977	0.997	1.000
AADs	£15,044	10.50		0.278	0.023	0.003	0.000
(b) All female							
RFCA	£27,377	13.00	£7322	0.729	0.983	0.999	1.000
AADs	£16,814	11.56		0.271	0.017	0.001	0.000

5-Year analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
(a) All male							
RFCA	£25,738	10.90	£25,527	0.000	0.150	0.690	0.909
AADs	£15,057	10.48		1.000	0.850	0.310	0.091
(b) All female							
RFCA	£27,394	11.96	£25,450	0.000	0.169	0.685	0.910
AADs	£16,832	11.54		1.000	0.831	0.315	0.090

Lifetime analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
(c) Age = 50 years							
RFCA	£26,777	12.74	£7549	0.772	0.989	1.000	1.000
AADs	£16,163	11.33		0.228	0.011	0.000	0.000
(d) Age = 55 years							
RFCA	£25,191	11.26	£8300	0.673	0.979	0.997	1.000
AADs	£14,516	9.97		0.327	0.021	0.003	0.000
(e) Age = 60 years							
RFCA	£22,969	9.80	£9443	0.524	0.965	0.994	1.000
AADs	£12,120	8.65		0.476	0.035	0.006	0.000
(f) Age = 65 years							
RFCA	£21,098	8.27	£11,223	0.320	0.899	0.990	0.997
AADs	£10,154	7.29		0.680	0.101	0.010	0.003

5-Year analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
(c) Age = 50 years							
RFCA	£26,774	11.73	£25,152	0.000	0.200	0.720	0.919
AADs	£16,160	11.31		1.000	0.800	0.280	0.081
(d) Age = 55 years							
RFCA	£24,885	10.38	£26,234	0.000	0.121	0.627	0.886
AADs	£14,150	9.97		1.000	0.879	0.373	0.114
(e) Age = 60 years							
RFCA	£22,976	9.04	£27,531	0.000	0.102	0.569	0.865
AADs	£12,130	8.64		1.000	0.898	0.431	0.135
(f) Age = 65 years							
RFCA	£21,098	7.65	£29,394	0.000	0.074	0.492	0.796
AADs	£10,152	7.28		1.000	0.926	0.508	0.204

Scenario 7: Discount rate**Lifetime analysis**

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
6% costs, 1.5% outcomes							
RFCA	£22,508	15.52	£5984	0.889	0.998	1.000	1.000
AADs	£11,712	13.72		0.111	0.002	0.000	0.000

5-Year analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
6% costs, 1.5% outcomes							
RFCA	£22,502	14.20	£21,452	0.000	0.375	0.858	0.966
AADs	£11,708	13.70		1.000	0.625	0.142	0.034

Scenario 8: Administration of amiodarone**Lifetime analysis**

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
Proportion of inpatients = 42.5%, proportion of outpatients = 57.5%							
RFCA	£26,021	12.14	£6822	0.813	0.996	1.000	1.000
AADs	£16,725	10.78		0.187	0.004	0.000	0.000

5-Year analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
Proportion of inpatients = 42.5%, proportion of outpatients = 57.5%							
RFCA	£26,019	11.18	£22,155	0.000	0.358	0.853	0.965
AADs	£16,721	10.76		1.000	0.642	0.147	0.035

Scenario 9: Cost of normal sinus rhythm and atrial fibrillation states

Lifetime analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
<i>Difference in cost of NSR and AF states: AF = £646, NSR = £331</i>							
RFCA	£23,285	12.15	£5978	0.881	0.994	0.998	0.999
AADs	£15,073	10.77		0.119	0.006	0.002	0.001

5-Year analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
<i>Difference in cost of NSR and AF states: AF = £646, NSR = £331</i>							
RFCA	£23,284	11.18	£19,673	0.004	0.488	0.899	0.974
AADs	£15,067	10.77		0.996	0.512	0.101	0.026

Scenario 10: Transition probabilities – reversion back to atrial fibrillation for patients receiving RFCA

Lifetime analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
5%							
RFCA	£26,077	12.12	£7999	0.691	0.983	0.999	1.000
AADs	£15,343	10.78		0.309	0.017	0.001	0.000
10%							
RFCA	£26,230	12.07	£8401	0.655	0.970	0.998	1.000
AADs	£15,346	10.77		0.345	0.030	0.002	0.000
15%							
RFCA	£26,335	12.03	£8703	0.578	0.944	0.992	0.997
AADs	£15,360	10.77		0.422	0.056	0.008	0.003

5-Year analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
5%							
RFCA	£26,087	11.17	£26,969	0.000	0.123	0.618	0.882
AADs	£15,352	10.77		1.000	0.877	0.382	0.118
10%							
RFCA	£26,238	11.13	£29,910	0.000	0.072	0.441	0.766
AADs	£15,355	10.76		1.000	0.928	0.559	0.234
15%							
RFCA	£26,342	11.10	£32,035	0.000	0.060	0.374	0.690
AADs	£15,366	10.76		1.000	0.940	0.626	0.310

Scenario 11: Costs of catheter ablation**Lifetime analysis**

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
Consumables reduced by £500							
RFCA	£25,237	12.14	£7213	0.794	0.991	1.000	1.000
AADs	£15,351	10.77		0.206	0.009	0.000	0.000
Consumables increased by £500							
RFCA	£26,782	12.15	£8347	0.651	0.987	0.998	1.000
AADs	£15,347	10.78		0.349	0.013	0.002	0.000
Consumables increased by £1000							
RFCA	£27,574	12.14	£8894	0.571	0.971	0.997	0.999
AADs	£15,361	10.77		0.429	0.029	0.003	0.001

5-Year analysis

Treatment	Cost	QALY	ICER	Probability cost-effective for maximum WTP			
				£10,000	£20,000	£30,000	£40,000
Consumables reduced by £500							
RFCA	£25,236	11.18	£23,638	0.000	0.243	0.773	0.941
AADs	£15,350	10.76		1.000	0.757	0.227	0.059
Consumables increased by £500							
RFCA	£26,787	11.18	£27,377	0.000	0.091	0.610	0.877
AADs	£15,345	10.76		1.000	0.909	0.390	0.123
Consumables increased by £1000							
RFCA	£27,578	11.19	£29,283	0.000	0.053	0.517	0.823
AADs	£15,363	10.77		1.000	0.947	0.483	0.177

Health Technology Assessment reports published to date

Volume 1, 1997

No. 1

Home parenteral nutrition: a systematic review.

By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

No. 2

Diagnosis, management and screening of early localised prostate cancer.

A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

No. 3

The diagnosis, management, treatment and costs of prostate cancer in England and Wales.

A review by Chamberlain J, Melia J, Moss S, Brown J.

No. 4

Screening for fragile X syndrome.

A review by Murray J, Cuckle H, Taylor G, Hewison J.

No. 5

A review of near patient testing in primary care.

By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, *et al.*

No. 6

Systematic review of outpatient services for chronic pain control.

By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

No. 7

Neonatal screening for inborn errors of metabolism: cost, yield and outcome.

A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, *et al.*

No. 8

Preschool vision screening.

A review by Snowdon SK, Stewart-Brown SL.

No. 9

Implications of socio-cultural contexts for the ethics of clinical trials.

A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

No. 10

A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.

By Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S.

No. 11

Newborn screening for inborn errors of metabolism: a systematic review.

By Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, *et al.*

No. 12

Routine preoperative testing: a systematic review of the evidence.

By Munro J, Booth A, Nicholl J.

No. 13

Systematic review of the effectiveness of laxatives in the elderly.

By Petticrew M, Watt I, Sheldon T.

No. 14

When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.

A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

Volume 2, 1998

No. 1

Antenatal screening for Down's syndrome.

A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

No. 2

Screening for ovarian cancer: a systematic review.

By Bell R, Petticrew M, Luengo S, Sheldon TA.

No. 3

Consensus development methods, and their use in clinical guideline development.

A review by Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, Askham J, *et al.*

No. 4

A cost-utility analysis of interferon beta for multiple sclerosis.

By Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D.

No. 5

Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.

By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, *et al.*

No. 6

Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.

By Faulkner A, Kennedy LG, Baxter K, Donovan J, Wilkinson M, Bevan G.

No. 7

Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.

By Song F, Glenny AM.

No. 8

Bone marrow and peripheral blood stem cell transplantation for malignancy.

A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

No. 9

Screening for speech and language delay: a systematic review of the literature.

By Law J, Boyle J, Harris F, Harkness A, Nye C.

No. 10

Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions.

By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

No. 11

Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.

By Ebrahim S.

No. 12

Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.

By McQuay HJ, Moore RA.

No. 13

Choosing between randomised and nonrandomised studies: a systematic review.

By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

No. 14

Evaluating patient-based outcome measures for use in clinical trials.

A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

No. 15

Ethical issues in the design and conduct of randomised controlled trials.

A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

No. 16

Qualitative research methods in health technology assessment: a review of the literature.

By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

No. 17

The costs and benefits of paramedic skills in pre-hospital trauma care.

By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

No. 18

Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.

By Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, *et al.*

No. 19

Systematic reviews of trials and other studies.

By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

No. 20

Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.

A review by Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, *et al.*

Volume 3, 1999

No. 1

Informed decision making: an annotated bibliography and systematic review.

By Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, *et al.*

No. 2

Handling uncertainty when performing economic evaluation of healthcare interventions.

A review by Briggs AH, Gray AM.

No. 3

The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.

By Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H.

No. 4

A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.

By Simpson WM, Johnstone FD, Boyd FM, Goldberg DJ, Hart GJ, Gormley SM, *et al.*

No. 5

Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.

By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

No. 6

Assessing the costs of healthcare technologies in clinical trials.

A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

No. 7

Cooperatives and their primary care emergency centres: organisation and impact.

By Hallam L, Henthorne K.

No. 8

Screening for cystic fibrosis.

A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

No. 9

A review of the use of health status measures in economic evaluation.

By Brazier J, Deverill M, Green C, Harper R, Booth A.

No. 10

Methods for the analysis of quality-of-life and survival data in health technology assessment.

A review by Billingham LJ, Abrams KR, Jones DR.

No. 11

Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.

By Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

No. 12

Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.

A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al.*

No. 13

'Early warning systems' for identifying new healthcare technologies.

By Robert G, Stevens A, Gabbay J.

No. 14

A systematic review of the role of human papillomavirus testing within a cervical screening programme.

By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al.*

No. 15

Near patient testing in diabetes clinics: appraising the costs and outcomes.

By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

No. 16

Positron emission tomography: establishing priorities for health technology assessment.

A review by Robert G, Milne R.

No. 17 (Pt 1)

The debridement of chronic wounds: a systematic review.

By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2)

Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.

By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

No. 18

A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.

By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, *et al.*

No. 19

What role for statins? A review and economic model.

By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al.*

No. 20

Factors that limit the quality, number and progress of randomised controlled trials.

A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, *et al.*

No. 21

Antimicrobial prophylaxis in total hip replacement: a systematic review.

By Glenny AM, Song F.

No. 22

Health promoting schools and health promotion in schools: two systematic reviews.

By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23

Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.

A review by Lord J, Victor C, Littlejohns P, Ross FM, Axford JS.

Volume 4, 2000**No. 1**

The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.

A review by Cairns JA, van der Pol MM.

No. 2

Geriatric rehabilitation following fractures in older people: a systematic review.

By Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, *et al.*

No. 3

Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.

By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

No. 4

Community provision of hearing aids and related audiology services.

A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

No. 5

False-negative results in screening programmes: systematic review of impact and implications.

By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

No. 6

Costs and benefits of community postnatal support workers: a randomised controlled trial.

By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

No. 7

Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.

By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, *et al.*

No. 8

An introduction to statistical methods for health technology assessment.

A review by White SJ, Ashby D, Brown PJ.

No. 9

Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.

By Clegg A, Bryant J, Milne R.

No. 10

Publication and related biases.

A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

No. 11

Cost and outcome implications of the organisation of vascular services.

By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

No. 12

Monitoring blood glucose control in diabetes mellitus: a systematic review.

By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

No. 13

The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.

By Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M, *et al.*

No. 14

The determinants of screening uptake and interventions for increasing uptake: a systematic review.

By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

No. 15

The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.

A rapid review by Song F, O'Meara S, Wilson P, Golder S, Kleijnen J.

No. 16

Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views.

By Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, *et al.*

No. 17

A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.

By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

No. 18

Liquid-based cytology in cervical screening: a rapid and systematic review.

By Payne N, Chilcott J, McGoogan E.

No. 19

Randomised controlled trial of non-directive counselling, cognitive-behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.

By King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, *et al.*

No. 20

Routine referral for radiography of patients presenting with low back pain: is patients' outcome influenced by GPs' referral for plain radiography?

By Kerry S, Hilton S, Patel S, Dundas D, Rink E, Lord J.

No. 21

Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration.

By O'Meara S, Cullum N, Majid M, Sheldon T.

No. 22

Using routine data to complement and enhance the results of randomised controlled trials.

By Lewsey JD, Leyland AH, Murray GD, Boddy FA.

No. 23

Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review.

By Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C.

No. 24

Outcome measures for adult critical care: a systematic review.

By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Daly K, *et al.*

No. 25

A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding.

By Fairbank L, O'Meara S, Renfrew MJ, Woolridge M, Sowden AJ, Lister-Sharp D.

No. 26

Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review.

By Parkes J, Bryant J, Milne R.

No. 27

Treatments for fatigue in multiple sclerosis: a rapid and systematic review.

By Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C.

No. 28

Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial.

By Baxter-Jones ADG, Helms PJ, Russell G, Grant A, Ross S, Cairns JA, *et al.*

No. 29

Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.

By Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW.

No. 30

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina.

By McDonagh MS, Bachmann LM, Golder S, Kleijnen J, ter Riet G.

No. 31

A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.

By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

No. 32

Intrathecal pumps for giving opioids in chronic pain: a systematic review.

By Williams JE, Louw G, Towler G.

No. 33

Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.

By Shepherd J, Waugh N, Hewitson P.

No. 34

A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.

By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

No. 35

Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.

By Berry E, Kelly S, Hutton J, Lindsay HSJ, Blaxill JM, Evans JA, *et al.*

No. 36

A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.

By Simpson S, Corney R, Fitzgerald P, Beecham J.

No. 37

Systematic review of treatments for atopic eczema.

By Hoare C, Li Wan Po A, Williams H.

No. 38

Bayesian methods in health technology assessment: a review.

By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

No. 39

The management of dyspepsia: a systematic review.

By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al.*

No. 40

A systematic review of treatments for severe psoriasis.

By Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC.

Volume 5, 2001

No. 1

Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.

By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al.*

No. 2

The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.

By Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al.*

No. 3

Equity and the economic evaluation of healthcare.

By Sassi F, Archard L, Le Grand J.

No. 4

Quality-of-life measures in chronic diseases of childhood.

By Eiser C, Morse R.

No. 5

Eliciting public preferences for healthcare: a systematic review of techniques.

By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, *et al.*

No. 6

General health status measures for people with cognitive impairment: learning disability and acquired brain injury.

By Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

No. 7

An assessment of screening strategies for fragile X syndrome in the UK.

By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

No. 8

Issues in methodological research: perspectives from researchers and commissioners.

By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, *et al.*

No. 9

Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.

By Cullum N, Nelson EA, Flemming K, Sheldon T.

No. 10

Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.

By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, *et al.*

No. 11

Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.

By Jobanputra P, Parry D, Fry-Smith A, Burls A.

No. 12

Statistical assessment of the learning curves of health technologies.

By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

No. 13

The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.

By Dinnes J, Cave C, Huang S, Major K, Milne R.

No. 14

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.

By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

No. 15

Home treatment for mental health problems: a systematic review.

By Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, *et al.*

No. 16

How to develop cost-conscious guidelines.

By Eccles M, Mason J.

No. 17

The role of specialist nurses in multiple sclerosis: a rapid and systematic review.

By De Broe S, Christopher F, Waugh N.

No. 18

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.

By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 19

The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.

By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 20

Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in preoperative assessment in elective general surgery.

By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, *et al.*

No. 21

Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.

By Marshall M, Crowther R, Almaraz-Serrano A, Creed F, Sledge W, Kluiter H, *et al.*

No. 22

The measurement and monitoring of surgical adverse events.

By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23

Action research: a systematic review and guidance for assessment.

By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.

By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al.*

No. 25

A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.

By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26

Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.

By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al.*

No. 27

The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.

By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, *et al.*

No. 28

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.

By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29

Superseded by a report published in a later volume.

No. 30

The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.

By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

No. 31

Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.

By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, *et al.*

No. 32

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.

By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33

Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.

By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34

Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.

By David AS, Adams C.

No. 35

A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.

By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al.*

No. 36

Cost analysis of child health surveillance.

By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002**No. 1**

A study of the methods used to select review criteria for clinical audit.

By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2

Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.

By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al.*

No. 3

Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.

By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al.*

No. 4

A systematic review of discharge arrangements for older people.

By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al.*

No. 5

The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.

By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6

The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.

By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7

The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.

By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al.*

No. 8

Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.

By Carroll B, Ali N, Azam N.

No. 9

Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.

By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al.*

No. 10

A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.

By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11

Screening for gestational diabetes: a systematic review and economic evaluation.

By Scott DA, Loveman E, McIntyre L, Waugh N.

No. 12

The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.

By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

No. 13

The clinical effectiveness of trastuzumab for breast cancer: a systematic review.

By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al.*

No. 14

The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.

By Lewis R, Bagnall A-M, King S, Woolacott N, Forbes C, Shirran L, *et al.*

No. 15

A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.

By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

No. 16

The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.

By Woolcott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al.*

No. 17

A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.

By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18

Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.

By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al.*

No. 19

Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.

By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al.*

No. 20

Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.

By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freemantle N, Vail A.

No. 21

The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.

By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22

A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.

By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23

A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.

By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

No. 24

A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.

By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al.*

No. 25

A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.

By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, *et al.*

No. 26

A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.

By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al.*

No. 27

A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.

By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, *et al.*

No. 28

Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.

By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29

Treatment of established osteoporosis: a systematic review and cost-utility analysis.

By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30

Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.

By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, *et al.*

No. 31

Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.

By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al.*

No. 32

The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.

By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, *et al.*

No. 33

The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.

By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34

A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.

By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, *et al.*

No. 35

A systematic review of the costs and effectiveness of different models of paediatric home care.

By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, *et al.*

Volume 7, 2003

No. 1

How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.

By Egger M, Jüni P, Bartlett C, Hohenstein F, Sterne J.

No. 2

Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.

By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al.*

No. 3

Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.

By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4

A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.

By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al.*

No. 5

Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.

By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al.*

No. 6

The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.

By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al.*

No. 7

The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.

By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al.*

No. 8

A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.

By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al.*

No. 9

Clinical effectiveness and cost-utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.

By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10

Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.

By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al.*

No. 11

First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).

By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12

The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.

By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13

A systematic review of atypical antipsychotics in schizophrenia.

By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al.*

No. 14

Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.

By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al.*

No. 15

Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.

By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al.*

No. 16

Screening for fragile X syndrome: a literature review and modelling.

By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17

Systematic review of endoscopic sinus surgery for nasal polyps.

By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18

Towards efficient guidelines: how to monitor guideline use in primary care.

By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19

Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.

By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20

Prioritisation of health technology assessment. The PATHS model: methods and case studies.

By Townsend J, Buxton M, Harper G.

No. 21

Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.

By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al.*

No. 22

The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.

By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23

The role of modelling in prioritising and planning clinical trials.

By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24

Cost-benefit evaluation of routine influenza immunisation in people 65-74 years of age.

By Allsup S, Gosney M, Haycox A, Regan M.

No. 25

The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.

By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26

Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.

By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27

Evaluating non-randomised intervention studies.

By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakaravitch C, Song F, *et al.*

No. 28

A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.

By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, *et al.*

No. 29

The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.

By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30

The value of digital imaging in diabetic retinopathy.

By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, *et al.*

No. 31

Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.

By Law M, Wald N, Morris J.

No. 32

Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.

By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33

Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.

By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34

Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.

By Royle P, Waugh N.

No. 35

Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.

By Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K.

No. 36

A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.

By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37

Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.

By MacArthur C, Winter HR, Bick DE, Lilford RJ, Lancashire RJ, Knowles H, *et al.*

No. 38

Estimating implied rates of discount in healthcare decision-making.

By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

No. 39

Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling.

By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, *et al.*

No. 40

Treatments for spasticity and pain in multiple sclerosis: a systematic review.

By Beard S, Hunn A, Wight J.

No. 41

The inclusion of reports of randomised trials published in languages other than English in systematic reviews.

By Moher D, Pham B, Lawson ML, Klassen TP.

No. 42

The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.

By Bankhead CR, Brett J, Bukach C, Webster P, Stewart-Brown S, Munafo M, *et al.*

Volume 8, 2004

No. 1

What is the best imaging strategy for acute stroke?

By Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, *et al.*

No. 2

Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.

By Mant J, McManus RJ, Oakes RAL, Delaney BC, Barton PM, Deeks JJ, *et al.*

No. 3

The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.

By Garside R, Stein K, Wyatt K, Round A, Price A.

No. 4

A systematic review of the role of bisphosphonates in metastatic disease.

By Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, *et al.*

No. 5

Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.

By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

No. 6

Effectiveness and efficiency of guideline dissemination and implementation strategies.

By Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, *et al.*

No. 7

Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.

By Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P.

No. 8

Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.

By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9

Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.

By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10

A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.

By Kaltenthaler E, Bravo Vergel Y, Chilcott J, Thomas S, Blakeborough T, Walters SJ, *et al.*

No. 11

The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.

By Barton P, Jobanputra P, Wilson J, Bryan S, Burls A.

No. 12

Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review.

By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

No. 13

Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation.

By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J.

No. 14

Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.

By Townsend J, Wolke D, Hayes J, Davé S, Rogers C, Bloomfield L, *et al.*

No. 15

Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.

By Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, *et al.*

No. 16

A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.

By Reeves BC, Angelini GD, Bryan AJ, Taylor FC, Cripps T, Spyt TJ, *et al.*

No. 17

Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.

By Gilbert FJ, Grant AM, Gillan MGC, Vale L, Scott NW, Campbell MK, *et al.*

No. 18

The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.

By Clark W, Jobanputra P, Barton P, Burls A.

No. 19

A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.

By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al.*

No. 20

Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.

By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

No. 21

Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.

By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, *et al.*

No. 22

Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.

By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23

Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.

By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24

Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.

By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, *et al.*

No. 25

Development and validation of methods for assessing the quality of diagnostic accuracy studies.

By Whiting P, Rutjes AWS, Dimnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26

EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.

By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, *et al.*

No. 27

Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon- β and glatiramer acetate for multiple sclerosis.

By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28

Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.

By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29

VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.

By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, on behalf of the VenUS Team.

No. 30

Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.

By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, *et al.*

No. 31

A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.

By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32

The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.

By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, *et al.*

No. 33

Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.

By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34

Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.

By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

No. 35

Coronary artery stents: a rapid systematic review and economic evaluation.

By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, *et al.*

No. 36

Review of guidelines for good practice in decision-analytic modelling in health technology assessment.

By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al.*

No. 37

Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.

By Knight C, Hind D, Brewer N, Abbott V.

No. 38

Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.

By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al.*

No. 39

Pegylated interferon α -2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.

By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40

Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.

By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al.*

No. 41

Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.

By Beswick AD, Rees K, Griebisch I, Taylor FC, Burke M, West RR, *et al.*

No. 42

Involving South Asian patients in clinical trials.

By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43

Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.

By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44

Identification and assessment of ongoing trials in health technology assessment reviews.

By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al.*

No. 45

Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine

By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

No. 46

Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.

By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al.*

No. 47

Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.

By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48

Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.

By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al.*

No. 49

Generalisability in economic evaluation studies in healthcare: a review and case studies.

By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al.*

No. 50

Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.

By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al.*

Volume 9, 2005

No. 1

Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.

By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al.*

No. 2

Do the findings of case series studies vary significantly according to methodological characteristics?

By Dalziel K, Round A, Stein K, Garside R, Castelnovo E, Payne L.

No. 3

Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.

By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, *et al.*

No. 4

Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.

By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5

A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.

By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6

Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.

By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7

Issues in data monitoring and interim analysis of trials.

By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al.*

No. 8

Lay public's understanding of equipoise and randomisation in randomised controlled trials.

By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, *et al.*

No. 9

Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.

By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10

Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.

By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, *et al.*

No. 11

Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.

By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, *et al.*

No. 12

A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.

By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13

Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.

By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

No. 14

Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.

By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, *et al.*

No. 15

Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.

By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, *et al.*

No. 16

A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.

By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, *et al.*

No. 17

Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.

By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, *et al.*

No. 18

A randomised controlled comparison of alternative strategies in stroke care.

By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

No. 19

The investigation and analysis of critical incidents and adverse events in healthcare.

By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20

Potential use of routine databases in health technology assessment.

By Raftery J, Roderick P, Stevens A.

No. 21

Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.

By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al.*

No. 22

A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.

By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

No. 23

A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.

By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al.*

No. 24

An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.

By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al.*

No. 25

Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.

By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al.*

No. 26

Indirect comparisons of competing interventions.

By Glenny AM, Altman DG, Song F, Sakarovich C, Deeks JJ, D'Amico R, *et al.*

No. 27

Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.

By Robinson M, Palmer S, Sculpher M, Phillips Z, Ginnelly L, Bowens A, *et al.*

No. 28

Outcomes of electrically stimulated gracilis neosphincter surgery.

By Tillin T, Chambers M, Feldman R.

No. 29

The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.

By Garside R, Stein K, Castelnovo E, Pitt M, Ashcroft D, Dimmock P, *et al.*

No. 30

Systematic review on urine albumin testing for early detection of diabetic complications.

By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al.*

No. 31

Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.

By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32

Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.

By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al.*

No. 33

Cost-effectiveness and safety of epidural steroids in the management of sciatica.

By Price C, Arden N, Cogan L, Rogers P.

No. 34

The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.

By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35

Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.

By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al.*

No. 36

The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.

By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37

A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.

By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al.*

No. 38

The causes and effects of socio-demographic exclusions from clinical trials.

By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al.*

No. 39

Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.

By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al.*

No. 40

A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.

By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al.*

No. 41

Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.

By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42

Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.

By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al.*

No. 43

The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.

By Castelnovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44

Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.

By Knowles R, Griebisch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45

The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.

By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al.*

No. 46

The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.

By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47

Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.

By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al.*

No. 48

Systematic review of effectiveness of different treatments for childhood retinoblastoma.

By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49

Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.

By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al.*

No. 50

The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.

By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al.*

Volume 10, 2006

No. 1

The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.

By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al.*

No. 2

FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.

By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3

The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.

By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al.*

No. 4

A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.

By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al.*

No. 5

Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.

By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6

Systematic review and evaluation of methods of assessing urinary incontinence.

By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al.*

No. 7

The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.

By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al.*

No. 8

Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.

By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9

Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.

By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al.*

No. 10

Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.

By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11

Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.

By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al.*

No. 12

A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.

By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al.*

No. 13

Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).

By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al.*

No. 14

The cost-effectiveness of screening for oral cancer in primary care.

By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, *et al.*

No. 15

Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.

By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al.*

No. 16

Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.

By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al.*

No. 17

Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.

By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al.*

No. 18

Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.

By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al.*

No. 19

Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.

By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al.*

No. 20

A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.

By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al.*

No. 21

Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.

By Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22

Pressure relieving support surfaces: a randomised evaluation.

By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al.*

No. 23

A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.

By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al.*

No. 24

The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.

By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al.*

No. 25

Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.

By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al.*

No. 26

A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.

By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al.*

No. 27

A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost-utility for these groups in a UK context.

By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al.*

No. 28

Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.

By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29

An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.

By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al.*

No. 30

Accurate, practical and cost-effective assessment of carotid stenosis in the UK.

By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al.*

No. 31

Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.

By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al.*

No. 32

The cost-effectiveness of testing for hepatitis C in former injecting drug users.

By Castelnovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al.*

No. 33

Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.

By Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, *et al.*

No. 34

Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.

By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al.*

No. 35

Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.

By Brazier J, Tumur I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al.*

No. 36

Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.

By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al.*

No. 37

Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.

By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38

A comparison of the cost-effectiveness of five strategies for the prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.

By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, *et al.*

No. 39

The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.

By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40

What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).

By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, *et al.*

No. 41

The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.

By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42

A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.

By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al.*

No. 43

Telemedicine in dermatology: a randomised controlled trial.

By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

No. 44

Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.

By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

No. 45

Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.

By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al.*

No. 46

Etanercept and efalizumab for the treatment of psoriasis: a systematic review.

By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al.*

No. 47

Systematic reviews of clinical decision tools for acute abdominal pain.

By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al.*

No. 48

Evaluation of the ventricular assist device programme in the UK.

By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al.*

No. 49

A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.

By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al.*

No. 50

Amniocentesis results: investigation of anxiety. The ARIA trial.

By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, *et al.*

Volume 11, 2007

No. 1

Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.

By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, *et al.*

No. 2

A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.

By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al.*

No. 3

A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.

By Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al.*

No. 4

The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.

By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5

A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.

By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, *et al.*

No. 6

Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.

By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, *et al.*

No. 7

Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis.

By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8

Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.

By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al.*

No. 9

Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.

By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al.*

No. 10

Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.

By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, *et al.*

No. 11

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.

By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12

Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.

By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13

A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.

By Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al.*

No. 14

A systematic review and economic evaluation of statins for the prevention of coronary events.

By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al.*

No. 15

A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.

By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, *et al.*

No. 16

Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.

By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17

Screening for type 2 diabetes: literature review and economic modelling.

By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, *et al.*

No. 18

The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.

By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, *et al.*

No. 19

The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.

By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20

A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.

By Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, *et al.*

No. 21

The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.

By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22

A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.

By Fayer D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, *et al.*

No. 23

Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.

By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, *et al.*

No. 24

The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.

By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al.*

No. 25

A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.

By Boyle J, McCartney E, Forbes J, O'Hare A.

No. 26

Hormonal therapies for early breast cancer: systematic review and economic evaluation.

By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27

Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.

By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28

Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.

By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al.*

No. 29

Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.

By Colbourn T, Asseburg C, Bojke L, Phillips Z, Claxton K, Ades AE, *et al.*

No. 30

Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.

By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al.*

No. 31

A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.

By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al.*

No. 32

Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.

By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, *et al.*

No. 33

The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.

By Black C, Cummins E, Royle P, Philip S, Waugh N.

No. 34

Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.

By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al.*

No. 35

The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Homebased compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.

By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, *et al.*

No. 36

A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.

By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, *et al.*

No. 37

A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.

By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al.*

No. 38

Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anti-coagulation therapy: a systematic review and economic modelling.

By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, *et al.*

No. 39

A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.

By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, *et al.*

No. 40

Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.

By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41

The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.

By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al.*

No. 42

Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.

By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43

Contamination in trials of educational interventions.

By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, *et al.*

No. 44

Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.

By Facey K, Bradbury I, Laking G, Payne E.

No. 45

The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.

By Garside R, Pitt M, Anderson R, Rogers G, Dyer M, Mealing S, *et al.*

No. 46

Drug-eluting stents: a systematic review and economic evaluation.

By Hill RA, Boland A, Dickson R, Dünder Y, Haycox A, McLeod C, *et al.*

No. 47

The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.

By Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, *et al.*

No. 48

Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.

By Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, *et al.*

No. 49

Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial.

By Sharples L, Hughes V, Crean A, Dyer M, Buxton M, Goldsmith K, *et al.*

No. 50

Evaluation of diagnostic tests when there is no gold standard. A review of methods.

By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

No. 51

Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.

By Leontiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW, *et al.*

No. 52

A review and critique of modelling in prioritising and designing screening programmes.

By Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, *et al.*

No. 53

An assessment of the impact of the NHS Health Technology Assessment Programme.

By Hanney S, Buxton M, Green C, Coulson D, Raftery J.

Volume 12, 2008

No. 1

A systematic review and economic model of switching from nonglycopeptide to glycopeptide antibiotic prophylaxis for surgery.

By Cranny G, Elliott R, Weatherly H, Chambers D, Hawkins N, Myers L, *et al.*

No. 2

'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.

By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

No. 3

A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.

By Thornton J, Ashcroft D, O'Neill T, Elliott R, Adams J, Roberts C, *et al.*

No. 4

Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial.

By Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F.

No. 5

A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.

By Hirst A, Dutton S, Wu O, Briggs A, Edwards C, Waldenmaier L, *et al.*

No. 6

Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.

By Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, *et al.*

No. 7

The use of economic evaluations in NHS decision-making: a review and empirical investigation.

By Williams I, McIver S, Moore D, Bryan S.

No. 8

Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.

By Burch J, Epstein D, Baba-Akbari A, Weatherly H, Fox D, Golder S, *et al.*

No. 9

The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.

By Loveman E, Frampton GK, Clegg AJ.

No. 10

Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.

By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

No. 11

Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.

By Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, *et al.*

No. 12

The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation.

By Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y, *et al.*

No. 13

Stepped treatment of older adults on laxatives. The STOOL trial.

By Mihaylov S, Stark C, McColl E, Steen N, Vanoli A, Rubin G, *et al.*

No. 14

A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial.

By Goodyer IM, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, *et al.*

No. 15

The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.

By Hind D, Tappenden P, Tumor I, Eggington E, Sutcliffe P, Ryan A.

No. 16

Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.

By Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A.

No. 17

Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.

By Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, *et al.*

No. 18

Structural neuroimaging in psychosis: a systematic review and economic evaluation.

By Albon E, Tsourapas A, Frew E, Davenport C, Oyebo F, Bayliss S, *et al.*

No. 19

Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta₂ agonists for the treatment of chronic asthma in adults and children aged 12 years and over.

By Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, *et al.*

No. 20

Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta₂ agonists for the treatment of chronic asthma in children under the age of 12 years.

By Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, *et al.*

No. 21

Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.

By Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, *et al.*

No. 22

Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study.

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