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Efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation (Review)

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[Intervention Review]

Efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation

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ABSTRACT

Background

The optimal rhythm management strategy for people with non-paroxysmal (persistent or long-standing persistent) atrial fibrilation is currently not well defined. Antiarrhythmic drugs have been the mainstay of therapy. But recently, in people who have not responded to antiarrhythmic drugs, the use of ablation (catheter and surgical) has emerged as an alternative to maintain sinus rhythm to avoid long-term atrial fibrillation complications. However, evidence from randomised trials about the efficacy and safety of ablation in non-paroxysmal atrial fibrillation is limited.

Objectives

To determine the efficacy and safety of ablation (catheter and surgical) in people with non-paroxysmal (persistent or long-standing persistent) atrial fibrillation compared to antiarrhythmic drugs.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Ovid, Embase Ovid, conference abstracts, clinical trial registries, and Health Technology Assessment Database. We searched these databases from their inception to 1 April 2016. We used no language restrictions.

Selection criteria

We included randomised trials evaluating the effect of radiofrequency catheter ablation (RFCA) or surgical ablation compared with antiarrhythmic drugs in adults with non-paroxysmal atrial fibrillation, regardless of any concomitant underlying heart disease, with at least 12 months of follow-up.

Data collection and analysis

Two review authors independently selected studies and extracted data. We evaluated risk of bias using the Cochrane 'Risk of bias' tool. We calculated risk ratios (RRs) for dichotomous data with 95% confidence intervals (CIs) a using fixed-effect model when heterogeneity was

low (I^2 <= 40%) and a random-effects model when heterogeneity was moderate or substantial (I^2 > 40%). Using the GRADE approach, we evaluated the quality of the evidence and used the GRADE profiler (GRADEpro) to import data from Review Manager 5 to create 'Summary of findings' tables.

Main results

We included three randomised trials with 261 participants (mean age: 60 years) comparing RFCA (159 participants) to antiarrhythmic drugs (102) for non-paroxysmal atrial fibrillation. We generally assessed the included studies as having low or unclear risk of bias across multiple domains, with reported outcomes generally lacking precision due to low event rates. Evidence showed that RFCA was superior to antiarrhythmic drugs in achieving freedom from atrial arrhythmias (RR 1.84, 95% CI 1.17 to 2.88; 3 studies, 261 participants; low-quality evidence), reducing the need for cardioversion (RR 0.62, 95% CI 0.47 to 0.82; 3 studies, 261 participants; moderate-quality evidence), and reducing cardiac-related hospitalisation (RR 0.27, 95% CI 0.10 to 0.72; 2 studies, 216 participants; low-quality evidence) at 12 months follow-up. There was substantial uncertainty surrounding the effect of RFCA regarding significant bradycardia (or need for a pacemaker) (RR 0.20, 95% CI 0.02 to 1.63; 3 studies, 261 participants; low-quality evidence), periprocedural complications, and other safety outcomes (RR 0.94, 95% CI 0.16 to 5.68; 3 studies, 261 participants; very low-quality evidence).

Authors' conclusions

In people with non-paroxysmal atrial fibrillation, evidence suggests a superiority of RFCA to antiarrhythmic drugs in achieving freedom from atrial arrhythmias, reducing the need for cardioversion, and reducing cardiac-related hospitalisations. There was uncertainty surrounding the effect of RFCA with significant bradycardia (or need for a pacemaker), periprocedural complications, and other safety outcomes. Evidence should be interpreted with caution, as event rates were low and quality of evidence ranged from moderate to very low.

PLAIN LANGUAGE SUMMARY

Benefits and harms of ablation for people with non-paroxysmal atrial fibrillation

Background

Atrial fibrillation is a heart condition that causes an irregular and often abnormally fast heart rate (tachycardia). A normal heart rate should be regular and between 60 and 100 beats a minute when resting. In atrial fibrillation, the heart rate is irregular and can sometimes be very fast. In some cases, it can be considerably higher than 100 beats a minute. This can cause symptoms such as dizziness, shortness of breath, and tiredness that affect quality of life, but more importantly, atrial fibrillation increases the risk of suffering a stroke.

In the majority of people, atrial fibrillation is recurrent and progresses from self-terminating short episodes (paroxysmal), to longer episodes (persistent) with the need for cardioversion into normal heart rhythm, or it can progress into permanent forms. Management of atrial fibrillation includes control of symptoms, and reducing the risk of stroke. One strategy to achieve this is to restore the normal heart rhythm by using medications. However, not all people respond well to heart rhythm drugs and therefore a new medical procedure, called ablation, using either a catheter or through surgery, has been developed to overcome this problem. The number of randomised trials comparing heart rhythm drugs versus ablation is limited.

The aim of this systematic review is to compare the benefits and harms of ablation (using either catheter or surgery) to heart rhythm drugs in people with persistent or long-standing persistent (non-paroxysmal) atrial fibrillation.

Study characteristics

We searched scientific databases from their inception to 1 April 2016 and found three studies where people are randomly allocated into one of two or more treatment groups (known as randomised trials). The three trials included 261 adults (mean age: 60 years) comparing catheter ablation (159 participants) to heart rhythm drugs (102) for non-paroxysmal atrial fibrillation at 12 months follow-up.

Key results

When compared to participants receiving heart rhythm drugs, those participants receiving catheter ablation were more likely to be free from atrial fibrillation, had reduced risk of being hospitalised due to cardiac causes, and had a reduced risk of needing cardioversion after 12 months. There was uncertainty surrounding the effect of catheter ablation with significant bradycardia (or need for a pacemaker), periprocedural complications, and other safety outcomes.

Quality of evidence

Evidence should be interpreted with caution as evidence quality ranged from moderate to very low across the different outcomes due to the limitations of the original studies. It is likely that further high-quality and adequately powered trials may affect the confidence in reported results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Ablation compared to antiarrhythmic drug for participants with non-paroxysmal atrial fibrillation

Ablation compared to antiarrhythmic drugs for participants with non-paroxysmal atrial fibrillation

Population: people with non-paroxysmal atrial fibrillation
Settings: hospital
Intervention: ablation
Comparison: antiarrhythmic drugs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Antiarrhythmic drugs	Ablation			
Freedom from atrial arrhythmia Follow-up: 12 months	**Study population**		**RR 1.84** (1.17 to 2.88)	261 (3 studies)	⊕⊕⊖⊖ **low** [1,2]
	353 per 1000	**649 per 1000** (413 to 1000)			
	Moderate population				
	429 per 1000	**789 per 1000** (502 to 1000)			
Participants needing cardioversion Follow-up: 12 months	**Study population**		**RR 0.62** (0.47 to 0.82)	261 (3 studies)	⊕⊕⊕⊖ **moderate** [2]
	422 per 1000	**261 per 1000** (198 to 346)			
	Moderate population				
	500 per 1000	**310 per 1000** (235 to 410)			
Cardiac hospitalisation Hospitalisations directly related to ablation or antiarrhythmic drugs Follow-up: 12 months	**Study population**		**RR 0.27** (0.10 to 0.72)	216 (2 studies)	⊕⊕⊖⊖ **low** [3]
	181 per 1000	**49 per 1000** (18 to 130)			
	Moderate population				

	203 per 1000	**55 per 1000** (20 to 146)			
Significant bradycardia or need for a pacemaker Follow-up: 12 months	**Study population**		**RR 0.20** (0.02 to 1.63)	261 (3 studies)	⊕⊕⊖⊖ **low** [4]
	49 per 1000	**10 per 1000** (1 to 80)			
	Moderate population				
	0 per 1000	**0 per 1000** (0 to 0)			
Periprocedural complications and other safety outcomes Follow-up: 12 months	**Study population**		**RR 0.94** (0.16 to 5.68)	261 (3 studies)	⊕⊖⊖⊖ **very low** [1,4]
	78 per 1000	**74 per 1000** (13 to 445)			
	Moderate population				
	42 per 1000	**39 per 1000** (7 to 239)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High-quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate-quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-quality: We are very uncertain about the estimate.

[1] Unexplained heterogeneity; downgraded one level of evidence.
[2] Serious imprecision due to low event rates compared to total participants; downgraded one level of evidence.
[3] Very serious imprecision due to very low event rates compared to total participants; downgraded two levels of evidence.
[4] Very serious imprecision due to very low event rates compared to total participants, with confidence interval crossing line of no effect; downgraded two levels of evidence.

BACKGROUND

Description of the condition

Atrial fibrillation is currently the most common serious arrhythmia, with a prevalence of 1% to 2% in the general population, and the incidence increasing with age (Rahman 2014). In the majority of people, the disease is recurrent and progresses from being paroxysmal (self-terminating short episodes) to a persistent (longer episodes, need for cardioversion into normal sinus rhythm), or permanent form (Kerr 2005). People with atrial fibrillation have poorer outcomes and significantly poorer quality of life compared with healthy controls, people with coronary heart disease (Dorian 2000), or the general population (Thrall 2006). Management of atrial fibrillation includes reduction of stroke risk, control of symptoms, and prevention of tachycardia-induced cardiomyopathy. To achieve the latter two, controlling the heart rate can be the preferred way to manage atrial fibrillation in some people (Wyse 2002), while others may require therapy to maintain normal sinus rhythm and prevent atrial fibrillation recurrence in order to control their symptoms. Furthermore, restoration of sinus rhythm improves both quality of life and exercise capacity (Singh 2006). Therapy to maintain sinus rhythm includes antiarrhythmic drugs or ablation procedures.

Description of the intervention

The use of catheter ablation for treatment of atrial fibrillation based on electrical isolation of triggers from the pulmonary veins has grown rapidly over the last decade (Jaïs 2008). Evidence from randomised trials (mainly in people where antiarrhythmic drugs have failed) indicates clear benefit for paroxysmal atrial fibrillation (Hakalahti 2015; Khan 2014; Morillo 2014; Nair 2009). However, ablation success is reduced in people with persistent or long-standing persistent (from now on referred to as 'non-paroxysmal') atrial fibrillation, where it is associated with longer procedure duration and lower long-term success rates compared to paroxysmal atrial fibrillation (Calkins 2012). Although guidelines have suggested that operators should consider more aggressive ablation strategies (including linear lesions and targeting of complex fractionated electrocardiograms) for non-paroxysmal atrial fibrillation (Andrade 2012; Pokushalov 2013), recent evidence from the STAR AF II trial has challenged this view (Verma 2015).

Current reported success rates for persistent atrial fibrillation vary significantly between studies and the evidence is primarily derived from non-randomised studies. Single-centre cohort studies have reported a single procedure one-year atrial fibrilation-free survival rate of less than 30% (Brooks 2010). Randomised trials comparing different ablation techniques have shown that pulmonary vein isolation as a single procedure has a one-year atrial fibrilation-free survival rate of around 40% (Elayi 2008; Oral 2005). Adding linear ablation or targeting people with complex fractionated atrial electrocardiograms (CFAEs) (or both) might increase the reported success rate. However, the evidence for the efficacy and safety of catheter ablation in non-paroxysmal atrial fibrillation comes primarily from analysis of case series. The largest and longest case series (80 participants) reported a single procedure success rate of around 50% using an aggressive ablation protocol (Rivard 2012). The recent European Survey on Methodology and Results of Catheter Ablation for Atrial Fibrillation, conducted in 72 medium- to high-volume centres (i.e. 50 or more atrial fibrillation ablations per year) from 10 European countries, reported a 29.5% overall success rate of ablation at one year for persistent atrial fibrillation (Arbelo 2014).

Endocardial catheter-based techniques for atrial fibrillation ablation initially used radiofrequency energy sources. Newer energy sources have now evolved, which include cryoenergy, laser, and high frequency ultrasound (Cappato 2010). Surgical techniques, such as the epicardial approach, as well as hybrid surgical and endocardial techniques previously involved the Cox maze procedure but now increasingly utilise radiofrequency energy or cryoablation, either intraoperatively during open surgery or via an epicardial approach. Some of these techniques have been assessed in either observational studies or randomised trials (Calkins 2012).

How the intervention might work

Ablation to prevent atrial fibrillation is primarily based on electrical isolation of triggers, mainly premature atrial beats and atrial tachycardia arising from the pulmonary veins at the venous ostium or around the antral area of the veins (Haïssaguerre 1998). Pulmonary vein isolation is therefore the mainstay of therapy. While pulmonary vein isolation is effective in people with paroxysmal atrial fibrillation, it is less effective in people with non-paroxysmal atrial fibrillation, and therefore a variety of complementary ablation targets have been investigated including lines, CFAE mapping, and rotors to increase the success of catheter ablation of atrial fibrillation (Andrade 2012; Narayan 2012). These ablation strategies are thought to either compartmentalise the atria or reduce the critical mass of tissue required for maintenance of atrial fibrillation (lines), or they are thought to represent sites of atrial fibrillation rotors (CFAE). However, there is no robust evidence that adding other targets to pulmonary vein isolation is beneficial. Recently there have been developments in signals processing and mapping techniques to target rotors thought to be the extra-pulmonary vein sources of atrial fibrillation maintenance (Narayan 2012). Other approaches have been reported in a few trials, including targeting of the cardiac autonomic system (ganglionated plexi ablation) and ablation of the ganglionic plexi alone or in conjunction with pulmonary vein isolation (Kottkamp 2015).

Why it is important to do this review

The best rhythm management strategy for people with non-paroxysmal atrial fibrillation is currently not well defined. Antiarrhythmic drugs have been the mainstay of therapy, however a meta-analysis of non-randomised and randomised studies of all antiarrhythmic drugs showed an average success rate for prevention of atrial fibrillation recurrence of 52% over one year (Calkins 2009). In addition, antiarrhythmic drugs have serious side effects including ventricular arrhythmias and lung disease (Singh 2005). Non-pharmacological interventions (catheter and surgical ablation techniques) have been developed as alternatives to maintain sinus rhythm in people with atrial fibrillation. Several international society practice guidelines recommend both antiarrhythmic drugs as well as radiofrequency catheter ablation (RFCA) as acceptable options for rhythm control in people with atrial fibrillation (Calkins 2012; Camm 2012). However, there has been a tremendous upsurge in the use of RFCA, driven by the idea that it is a better therapy and that it might change the natural history of the disease. This has the potential to have a significant impact on health systems worldwide (Kneeland 2009; Kumar 2013).

Antiarrythmic drugs are perceived to be a less acceptable therapeutic option, despite being more readily available and cheaper, and possibly being more effective in particular groups of people with atrial fibrillation (Kumar 2013). With the diversification of atrial fibrillation ablation techniques, an analysis of efficacy outcomes and safety is critical to inform the field and help identify optimal treatment strategies. Several systematic reviews have been conducted over recent years, but these have concentrated mainly on paroxysmal atrial fibrillation (Cheng 2014; Khan 2014; Nault 2010). When non-paroxysmal atrial fibrillation has been the focus of attention, reviews have included non-randomised studies and case series, with largely inconclusive results (Calkins 2009). In addition, none of the previous reviews have used state-of-the-art systematic review methods, such as those implemented by Cochrane. Therefore, there is a need for a de novo systematic review using Cochrane recommended methods to evaluate the efficacy and safety of ablation (catheter and surgical) versus antiarrhythmic drugs in non-paroxysmal atrial fibrillation. This will help to inform the adoption of an optimal treatment strategy.

OBJECTIVES

To determine the efficacy and safety of ablation (catheter and surgical) in people with non-paroxysmal (persistent or long-standing persistent) atrial fibrillation compared to antiarrhythmic drugs.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised trials of parallel-group design with the individual as the unit of randomisation. All studies had at least 12 months of follow-up.

Types of participants

We included three studies with adults aged 18 years and over with persistent atrial fibrillation (defined as lasting more than seven days or requiring termination by cardioversion either with drugs or by direct current cardioversion) or long-standing persistent atrial fibrillation (defined as lasting more than one year when it is decided to adopt a rhythm control intervention), regardless of any concomitant underlying heart disease. Where studies had a mixed population, at least 50% of participants should have had either persistent or long-standing persistent atrial fibrillation (Forleo 2009). If studies had 50% or more participants with paroxysmal atrial fibrillation, we contacted the authors to obtain information on the participants with only non-paroxysmal atrial fibrillation (Stabile 2006).

Types of interventions

We included trials using the radiofrequency catheter ablation (RFCA) technique. The comparison was approved antiarrhythmic drugs, which includes any of the following: flecainide, propafenone, quinidine, amiodarone, sotalol, dofetilide, or dronedarone.

We excluded all studies where the comparator was rate control and excluded concomitant surgical ablation studies (that is, surgical atrial fibrillation ablation done during open heart surgery for another indication or condition).

Types of outcome measures

We defined outcome measures according to a recent consensus statement regarding randomised trials in atrial fibrillation. Where atrial fibrillation was defined as a common supraventricular arrhythmia that is characterised by chaotic contraction of the atrium, needing an electrocardiogram (ECG) recording for its diagnosis (Calkins 2012). We evaluated the following outcomes at 12 months and for the longest term available.

Primary outcomes

1. Freedom from atrial arrhythmias (i.e. atrial fibrillation, atrial flutter, or atrial tachycardia) or recurrence of any atrial arrhythmias
2. Participants needing cardioversion
3. Cardiac hospitalisation

Secondary outcomes

1. All-cause mortality
2. Fatal or non-fatal stroke
3. Any embolic complication
4. Combined endpoint of any major adverse cardiac event (MACE)
5. Significant bradycardia or need for a pacemaker
6. Health-related quality of life measured by a validated scale
7. Cost
8. Periprocedural complications and other safety outcomes

Periprocedural complications and other safety outcomes here refers to adverse events and/or complications arising from ablation e.g. pericarditis, pericardial effusion, minor vascular access complications.

Search methods for identification of studies

Electronic searches

We searched the following sources from their inception. Which also includes the year the first ablation procedure was performed to the specified date, and placed no restrictions on language of publication.

- CENTRAL; Issue 2 of 12, March 2016 (the Cochrane Library)
- MEDLINE (OVID 1946 to February week 4 2016)
- EMBASE (OVID, 1980 to 2016 week 09)
- Health Technology Assessment Database; Issue 1 of 4, January 2016
- Conference Proceedings Citation Index-Science (CPCI-S); 1990 to present (Web of Science)
- ClinicalTrials.gov (clinicaltrials.gov; searched 1 April 2016)
- World Health Organization International Clinical Trials Registry Platform (who.int/ictrp/en; searched 3 March 2016)

We adapted the preliminary search strategy for MEDLINE (Ovid) for use in the other databases. We applied the Cochrane sensitivity-maximising RCT filter to MEDLINE (Ovid) and adapted it to the other databases (Lefebvre 2011), except CENTRAL. For details of terms used in search strategies please see Appendix 1.

Searching other resources

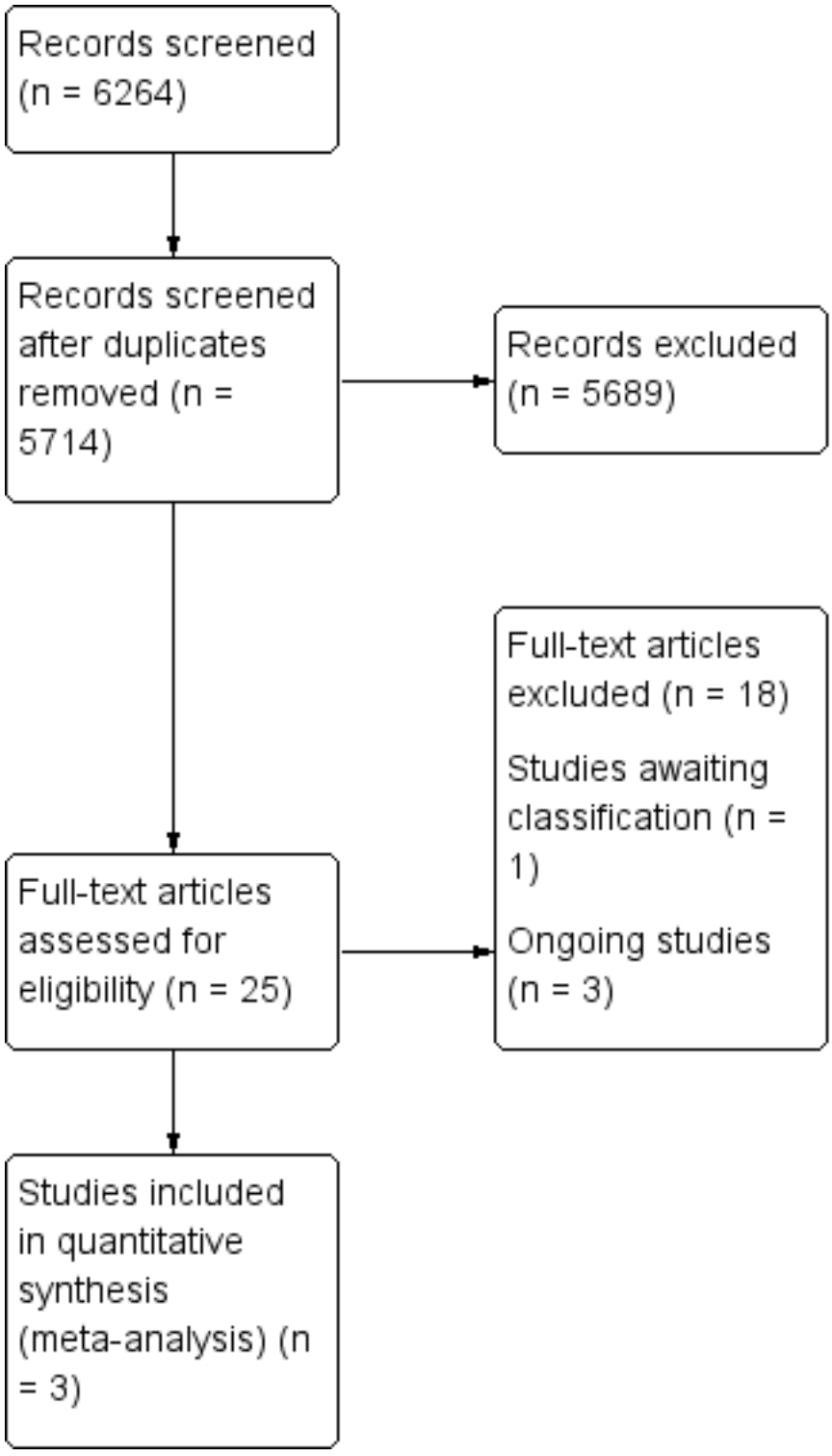
We identified other potentially eligible trials or ancillary publications by handsearching the reference lists of retrieved included trials, systematic reviews, meta-analyses, and health technology assessment reports. We also contacted study authors of included or registered trials to identify any further studies we may have missed.

Data collection and analysis

Selection of studies

Two review authors (JN, OO) independently screened titles and abstracts for inclusion of all the potential studies. We retrieved the full-text study reports/publication and three authors (JN, OO and AJA) independently screened the full-text and identified studies for inclusion; any disagreement was resolved with consultation between the other review authors (GA, CAM and JPC). We have presented a PRISMA flow diagram showing the process of study selection (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

We extracted the following study characteristics.

1. Methods: study design, study duration, length of follow-up, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: number, mean age, age range and standard deviation (SD), gender, severity of condition, diagnostic criteria, smoking history, underlying heart disease conditions, left atrial size (mean and SD) proportion of normal/abnormal, duration of atrial fibrillation (mean and SD), inclusion criteria, and exclusion criteria.

3. Interventions: type of ablation and technique used, comparisons, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported. We extracted both numbers of events and means as well as estimated effect sizes and 95% confidence intervals (CIs).
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

For studies that met our inclusion criteria, two review authors (JN, OO) independently extracted data from the trials and transferred the data into a pro forma with any disagreements resolved by discussion, by consultation with a third review author (GA), or, when required, by contacting authors of included studies. We tried to find the protocol of each included study and report primary, secondary, and other outcomes in comparison with data in publications.

Assessment of risk of bias in included studies

Two review authors (JN, OO) independently assessed risk of bias for each included study. We resolved disagreements by consultation with a third review author (GA or JPC) or by general consensus. We applied the Cochrane 'Risk of bias' tool to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias (e.g. industry funding).

We judged each potential source of bias as 'high', 'low' or 'unclear' and provided quote(s) from the study report together with justification(s) for our judgement in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. When considering the treatment effects, we took into account the risk of bias for the studies that contributed to that outcome. We considered the implications of missing outcome data from individual participants per outcome, such as high dropout rates (for example, above 15%) or disparate attrition rates (for example, a difference of 10% or more between study arms).

Measures of treatment effect

We expressed dichotomous outcome data as risk ratios (RRs) with 95% CIs. We analysed all included studies using intention-to-treat analyses.

Unit of analysis issues

All included trials were randomised at the individual participant level.

Dealing with missing data

We contacted authors of included studies to obtain missing numerical outcome data and to verify key study characteristics, where possible. Where this was not possible, and the missing data were thought to introduce serious bias, we considered exploring the impact of including such studies in the overall assessment of results by conducting sensitivity analyses. We also obtained information from trial registries. For trials where more than 50% of participants had paroxysmal atrial fibrillation, we contacted the trial authors to obtain data on non-paroxysmal participants. We then included the data obtained in our analyses.

Assessment of heterogeneity

We identified heterogeneity through visual inspection of the forest plots and by using a standard Chi^2 test with a significance level of $\alpha = 0.1$. We also use the I^2 statistic to quantify the heterogeneity across trials. We attempted to determine possible reasons for heterogeneity by examining individual studies and subgroup characteristics.

Assessment of reporting biases

We were unable to assess small-study bias as the number of included studies was not sufficient for an informative funnel plot (Higgins 2011).

Data synthesis

We undertook meta-analyses if the participants, interventions, and the comparisons were similar enough for pooling to be appropriate (Wood 2008). If I^2 is less than or equal to 40%, we used a fixed-effect model, whereas if the I^2 statistic was greater than 40%, we used both the fixed-effect and random-effects model (Higgins 2011), but reported results from the random-effects model.

The quality of evidence was evaluated using the GRADE approach (Higgins 2011) and the GRADE profiler (GRADEPRO) 3.6 (GRADEpro GDT) was employed to import data from Review Manager 5.3 (RevMan 2014) to create 'Summary of findings' table (Summary of findings for the main comparison). Outcomes reported in the summary of findings table include:

- Freedom from atrial arrhythmia
- Participants needing cardioversion
- Cardiac hospitalisation
- significant bradycardia or need for a pacemaker
- Periprocedural complications and other safety outcomes

Subgroup analysis and investigation of heterogeneity

We planned on conducting a subgroup analysis, however due to the small number of included studies we were unable to do so.

Sensitivity analysis

We planned on conducting a sensitivity analysis, however due to the small number of included studies we were unable to do so.

RESULTS

Description of studies

Results of the search

Appendix 1 outlines the search strategies, and Figure 1 includes the PRISMA flow chart depicting numbers of included and excluded studies. After de-duplication, the search resulted in 5714 results, of which we excluded 5689 records as they were not relevant to our review question. We assessed 25 full-text articles for eligibility. Five out of these 25 studies had a mix of atrial fibrillation participants, with more than 50% having paroxysmal atrial fibrillation. We

contacted authors for data on non-paroxysmal atrial fibrillation cases. We only received information from the Stabile 2006 trial. We excluded 18 studies and reasons for full-text exclusion are shown in Characteristics of excluded studies.

We also identified one study awaiting classification (NCT00821353), and three ongoing studies (NCT00196209; NCT00911508; NCT01420393). The study awaiting classification compares radiofrequency catheter ablation with rhythm control in participants with hypertrophic cardiomyopathy and paroxymal or chronic atrial fibrillation (NCT00821353). This trial was yet to be published when this review was developed, with no study result posted. Details are outlined in the Characteristics of studies awaiting classification section. Although we identified three ongoing studies, the comparison arm used in NCT00196209 and NCT01420393 was not antiarrhythmic drugs. NCT01420393 compared ablation versus rate control, while NCT00196209 compared catheter ablation versus external electric cardioversion. NCT00911508 compared rate control or rhythm control drug therapy for atrial fibrillation to catheter ablation. Details are outlined in the Characteristics of ongoing studies section.

A total of three studies were suitable for inclusion.

Included studies

A summary description of studies included is reported in Characteristics of included studies. Studies were published between 2006 and 2014. Of the three randomised trials included (Forleo 2009; Mont 2014; Stabile 2006), one was conducted in Spain (Mont 2014), and two in Italy (Stabile 2006; Forleo 2009). With the exception of Forleo 2009, all studies were prospectively registered (ClinicalTrials.gov identifier: NCT00227344 and NCT00863213). The total number of participants included was 261 (mean age: 60 years) comparing radiofrequency catheter ablation (RFCA) (159 participants) with antiarrhythmic drugs (102). Though we set out to include trials with outcomes evaluated at 12 months or for the longest term available, most trials reported a follow-up of 12 months, except Stabile 2006 that reported a median of 18 months of follow-up. The majority of participants recruited were male, with the percentage of women ranging from 11.6% to 40.9%. All trials included participants that have not responded to antiarrhythmic drug therapy. Further details of included studies and the characteristics of participants included in the studies are described in Table 1 and Table 2, respectively.

In all three trials, ablation was through radiofrequency to isolate the pulmonary veins and details of the specific technique used in the three trials are described in Table 1. The need for a second ablation (due to recurrent atrial fibrillation or flutter within the blanking period) was reported in 8.2% of the participants in Mont 2014. In all trials, the ablation group also received antiarrhythmic drugs mainly during the blanking period (range: 1 to 3 months after ablation) with the exception of Stabile 2006, where the antiarrhythmic drugs were used throughout the duration of the study (Personal communication from Study authors Bertaglia 2015 [pers comm]). In the antiarrhythmic drug arm (comparison), the decision on the specific antiarrhythmic drug was based on recommended guidelines or physician preference with amiodarone (Stabile 2006: 66%; Forleo 2009: 63%; and Mont 2014: 46%) being the most commonly used antiarrhythmic drug. Full details of interventions can be found in Table 1.

Excluded studies

We excluded 18 studies on second pass and 5711 studies in total (Figure 1). Reasons for exclusion were mainly due to studies not addressing prespecified population, intervention, and comparison characteristics. Excluded studies were either on paroxysmal atrial fibrillation, rate control, or on concomitant surgical ablation studies. For studies with a mixed population of atrial fibrillation, with more than 50% having paroxysmal atrial fibrillation, we contacted authors for data on only non-paroxysmal atrial fibrillation cases. If data were not provided as requested, we excluded these studies. Full details of 18 studies excluded on second pass can be found in Characteristics of excluded studies.

Risk of bias in included studies

Figure 2 and Figure 3 demonstrate the overall and trial specific information on risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

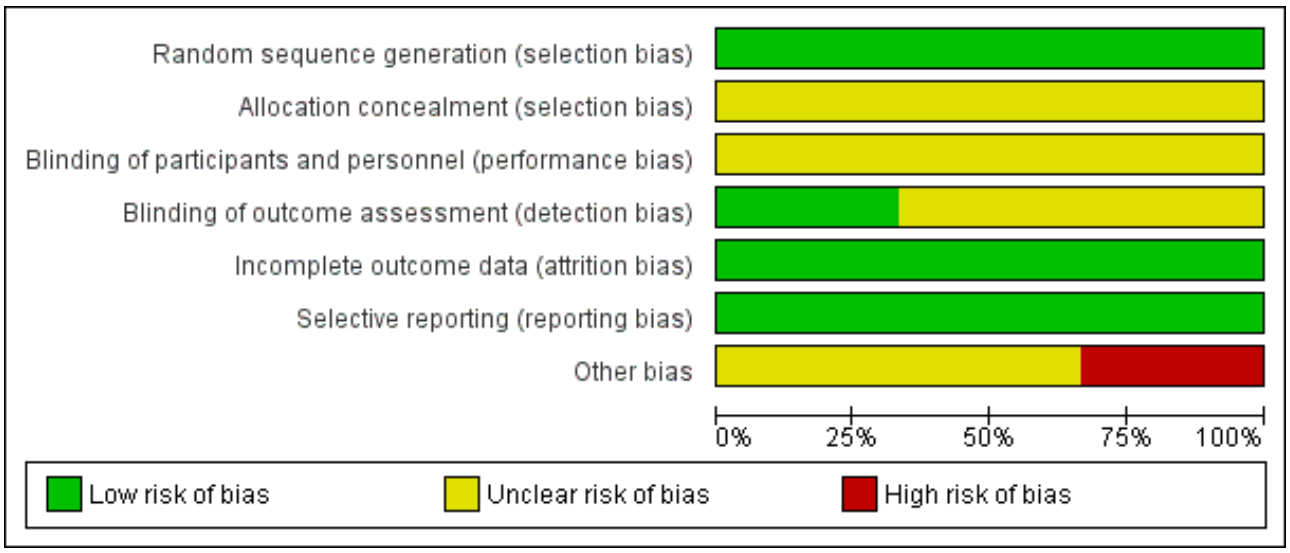


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

The risk of bias was low for sequence generation, and unclear for allocation concealment in all studies. We judged allocation to be unclear because information from study authors was not available to clarify the allocation.

Blinding

Given the nature of the intervention, blinding of participants and personnel was not possible. This makes it difficult to judge the direction of effect due to blinding. Therefore, we considered the risk of performance bias to be unclear. However, blinding of outcome assessment was unclear for two of the included studies (Forleo 2009 and Stabile 2006) and low for Mont 2014.

Incomplete outcome data

Regarding, Intention-to-treat used, attrition bias, and losses to follow-up, we judged all trials to be at low risk.

Selective reporting

We judged all three trials to be at low risk of outcome reporting bias for our primary outcomes. We judged two studies at low risk for all secondary outcomes (Mont 2014; Stabile 2006).

Other potential sources of bias

Regarding other potential biases, Mont 2014 was terminated before reaching the planned sample size due to a lower than expected recruitment rate, resulting in a loss of statistical power. However, the study authors claim that the difference between groups in the primary endpoint was higher than assumed in the sample size calculation, which likely compensated for the loss of statistical power in the sample size. Apart from the Mont 2014 trial, no other study was sponsored by industry (Medtronic and Biosense Webster). One of the investigators from Forleo 2009 reported to have received lecture fees from Industry.

Effects of interventions

See: **Summary of findings for the main comparison** Ablation compared to antiarrhythmic drug for participants with non-paroxysmal atrial fibrillation

The main result findings are reported in Summary of findings for the main comparison. Analysis 1.1, Analysis 1.2, Analysis 1.3, Analysis 1.4, Analysis 1.5, Analysis 1.6, and Analysis 1.7 describe the forest plots for the efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation for various outcomes.

Primary outcomes

Freedom from atrial arrhythmias or recurrence of any atrial arrhythmias

All three trials reported information on this outcome. All studies included a blanking period and any atrial fibrillation or flutter detected during this period was not included in the analysis. The definition of atrial arrhythmias, mode of ascertainment, and frequency of evaluation to detect an atrial arrhythmia varied considerably by study (details are reported in Table 3). After pooling data, radiofrequency catheter ablation (RFCA) increased freedom from atrial arrhythmias at 12 months compared with antiarrhythmic drugs (risk ratio (RR) 1.84, 95% confidence interval (CI) 1.17 to 2.88; 3 studies, 261 participants; low-quality evidence) (Analysis 1.1). We judged the quality of evidence as low as a result of unexplained heterogeneity and imprecision due to small event rates compared to total participants (Summary of findings for the main comparison).

Participants needing cardioversion

All three studies reported information on this outcome. However, Forleo 2009 reported zero participants needing cardioversion after the blanking period in both arms. Only the event data from Mont 2014 and Stabile 2006 contributed to the meta-analysis. After pooling data from these studies, participants randomised to RFCA had a reduced risk of needing cardioversion (RR 0.62, 95% CI 0.47 to 0.82); I^2 = 20%, 3 studies, 261 participants; moderate-quality evidence) (Analysis 1.3). As a result of imprecision due to small event rates compared to total participants, we judged the quality of evidence to be of moderate-quality (Summary of findings for the main comparison) .

Cardiac hospitalisation

Forleo 2009 and Mont 2014 provided the event data for cardiac hospitalisation and result findings showed evidence of catheter ablation reducing the risk of cardiac hospitalisation (RR 0.27, 95% CI 0.10 to 0.72; I^2 = 0%, 2 studies, 216 participants; low-quality evidence) (Analysis 1.4). However, Mont 2014 only reported on atrial fibrilation-related hospitalisations. Stabile 2006, when contacted (Bertaglia 2015 [pers comm]), reported no data specifically on cardiac hospitalisations, but only data on all hospitalisations as follows: ablation median of 1 (interquartile range (IQR): 1, 2) and antiarrhythmic drug arm median of 2 (IQR: 1, 2), this includes the hospitalisations required for ablation. Thus, we judged data from Stabile 2006 not suitable for meta-analysis. As a result of significant imprecision due to small event rates compared to total participants, we judged the quality of evidence to be low (Summary of findings for the main comparison).

Secondary outcomes

Significant bradycardia or need for a pacemaker

All three studies reported on this outcome. However studies by Mont 2014 and Stabile 2006 reported zero events in either arm. Only the event data from Forleo 2009 contributed to the meta-analysis. Result findings showed substantial uncertainty surrounding the summary estimate (RR 0.20, 95% CI 0.02 to 1.63; 3 studies, 261 participants; low-quality evidence) (Analysis 1.5). As a result of imprecision with confidence intervals crossing the 'no effect' line, we judged the quality of evidence to be low (Summary of findings for the main comparison).

Periprocedural complications and other safety outcomes

All three studies reported event data on this outcome. Periprocedural complications and other safety outcomes reported were adverse events and/or complications arising from ablation, e.g. pericarditis, pericardial effusion, and minor vascular access complications. Result findings showed that RFCA showed no effect with periprocedural complications and other safety outcomes compared with antiarrhythmic drugs (RR 0.94, 95% CI 0.16 to 5.68; 3 studies, 261 participants; very low-quality evidence) (Analysis 1.6). As a result of imprecision due to small event rates with confidence intervals crossing the 'no effect' line, and unexplained heterogeneity, we judged the quality of evidence to be very low (Summary of findings for the main comparison).

All-cause mortality

Two trials reported all-cause mortality. In the Mont 2014 study, authors reported that no death was observed in either arm after 12 months of follow-up, while the cause of death in Stabile 2006 was gastrointestinal haemorrhage (information provided by the authors). Given the extremely low number of events (N = 1 for Stabile 2006) and the absence of events in the comparison arm, we decided not to pool the results for this outcome.

Fatal or non-fatal stroke

Information on stroke was reported in two studies (Mont 2014; Stabile 2006), and they both reported zero stroke events in either arm.

Any embolic complication

All three included studies reported zero embolic complications in either arm (Forleo 2009; Mont 2014; Stabile 2006).

Combined endpoint of any major adverse cardiac event (MACE)

None of the included studies reported on the combined endpoint of MACE.

Health-related quality of life

All studies, except Stabile 2006 reported this outcome, but used different tools. In Forleo 2009, the information reported was not suitable for meta-analysis and not available from the study authors. Forleo 2009 used the Medical Outcomes Study 36-item short-form health survey (SF-36) to evaluate quality of life and reported improvements in the mean change in quality of life scores in the ablation arm compared with the mean change in quality of life scores in the antiarrhythmic drug arm for five out of eight SF-36 subscales. However, this was only reported as "P < 0.05, PVI versus ADT group" which is insufficient for meta-analysis. Mont 2014

used an atrial fibrillation-quality of life questionnaire and authors reported no difference in the global score of quality of life between the two arms at six months (5.5, 95% CI -2.3 to 13.4) or 12 months (3.8, 95% CI -5.2 to 12.8). Likewise, no differences were observed for the physical, psychological, and sexual domains.

Cost

None of the three included trials reported on cost. However, screening identified one cost-effectiveness study from the perspective of the UK National Health Service (NHS) (McKenna 2008). This study examined the cost-effectiveness of RFCA compared with antiarrhythmic drugs in adults with paroxysmal atrial fibrillation predominantly refractory to at least one previous antiarrhythmic drug. The antiarrhythmic drug considered was amiodarone. The efficacy of the intervention included in the cost-effectiveness models was derived from trials where the majority of the participants had paroxysmal atrial fibrillation, therefore the findings from this analysis are not applicable to people with non-paroxysmal atrial fibrillation.

DISCUSSION

Summary of main results

The main findings of this systematic review and meta-analysis in people with non-paroxysmal atrial fibrillation who have not responded to antiarrhythmic drug therapy suggest that radiofrequency catheter ablation (RFCA) is superior to antiarrhythmic drugs in achieving freedom from atrial arrhythmias, reducing the need for cardioversion, and reducing cardiac hospitalisation at 12 months. There was substantial uncertainty surrounding the effect of RFCA on significant bradycardia (or need for a pacemaker) and no effect on total mortality, stroke, embolic complications, or any major adverse cardiac event. Result findings should be interpreted with caution, as the quality of the evidence was at the very best moderate, mainly due to extremely low numbers of outcomes in the pooled analysis together with substantial heterogeneity within included studies (Summary of findings for the main comparison).

Overall completeness and applicability of evidence

Despite the widespread use of RFCA as treatment for non-paroxysmal atrial fibrillation, only three trials with 261 participants that fulfilled the inclusion criteria were eligible. Most of the studies were performed before the definition of 'long-standing persistent' was introduced. The Mont 2014 study excluded participants with long-standing persistent atrial fibrillation, while the other two included studies had a mixed population of persistent and long-standing persistent atrial fibrillation (Forleo 2009; Stabile 2006), without the ability to differentiate the two. All studies were conducted in high-income countries, and due to strict selection criteria of participants included in these studies, the applicability of this evidence to certain groups is limited. These groups are women, elderly (> 70 years), people with comorbidities, and people naive to antiarrhythmic drugs. Likewise, it is important to note that (with the exception of Mont 2014) included studies were designed and started recruitment more than 10 years ago, and all use a single source of energy, namely RFCA. Not a single surgical ablation trial was eligible, and therefore, although aiming to broaden the evidence, this systematic review and meta-analysis only compared RFCA with antiarrhythmic drugs. Furthermore, novel technologies such as contact force catheters were not included. Evidence should be interpreted with caution, as event rates were low across reported outcomes with the quality of evidence ranging from moderate to very low.

Quality of the evidence

The quality of evidence, using the GRADE approach and GRADEpro (GRADEpro GDT), for efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation versus antiarrhythmic drugs is reported in Summary of findings for the main comparison. The quality ranged from moderate to very low across the different outcomes. This was mainly due to moderate to substantial heterogeneity and imprecise results due to extremely low numbers of events for outcomes analysed.

It is important to highlight certain limitations in terms of design of the included trials. The definitions of their primary outcome (freedom from atrial arrhythmias) including the frequencies and monitoring strategies to detect atrial fibrillation or flutter varied for the three included trials (Table 3). Two of the included trials (Forleo 2009; Stabile 2006), predated the current monitoring and atrial fibrillation recurrence recommendations suggested when conducting randomised trials evaluating the efficacy of RFCA (Calkins 2012). This could have led to under-reporting of arrhythmia recurrence, though unlikely to introduce systematic bias (due to randomised design) this might have reduced statistical power in included studies. Moreover, there was no information on the recurrence of atrial fibrillation according to whether or not these were symptomatic. These issues highlight the need for adherence to internationally agreed definitions of atrial fibrillation ablation success. A further limitation of these studies is that efficacy of persistent ablation remains suboptimal for a single procedure, averaging about 50% maintenance of sinus rhythm. This limits the ability of many studies to fully establish the procedures' efficacy due to the fact that at least 30% require a repeat intervention to maintain sinus rhythm, with the cumulative risk of complications and additional hospitalisations, plus the lag in ensuing follow-up. Most studies have only objectively evaluated the participants in the one-year window postprocedure, when further intervention means that very often they may be in the first three- to six-month follow-up phase of the second procedure. This makes evaluating the full balanced comparisons of outcomes challenging.

Potential biases in the review process

We followed the methods as outlined in the published Cochrane protocol (Amit 2016). The methodological and search strategies were rigorous and comprehensive and we consider it unlikely that we missed substantial trials. In order to minimise the consequences of reporting bias, we contacted study authors, asking for necessary information when this was, either, not available or inadequately reported. By applying this strategy we obtained unpublished data from the Stabile 2006 study relevant only to non-paroxsymal atrial fibrillation participants for both primary and secondary outcomes. With the exception of the outcomes not reported in the Summary of findings for the main comparison, all analysed primary and secondary outcomes in this review were adequately reported by all identified trials.

Agreements and disagreements with other studies or reviews

Current practice guidelines vary on their recommendations for RFCA in people with non-paroxsymal atrial fibrillation; the

European Society of Cardiology (ESC) guideline recommendation class for persistent symptomatic atrial fibrillation that is refractory to antiarrhythmic drugs is IIa; this was not updated in the 2012 ESC guidelines for the management of atrial fibrillation (Camm 2012). The recent Wynn 2014 systematic review and meta-analysis that included both randomised and non-randomised trials, reported a benefit for RFCA of reducing atrial fibrillation recurrence (odds ratio (OR) 0.32, 95% confidence interval (CI) 0.20 to 0.53). Our findings are in agreement with previous reviews, although reporting a more modest effect in favour of RFCA regarding atrial fibrillation recurrence. In contrast to the Wynn 2014 review, we expanded the coverage of clinical outcomes and observed a significant reduction in the need for cardioversion and hospitalisation, which may be relevant in terms of reducing health resource utilisation. However, the importance of these findings is weakened by the overall quality of the evidence; moderate-quality for participants needing cardioversion and low-quality for hospitalisation. Additional outcomes included in this review, not covered by previous systematic reviews, were total mortality, stroke, embolic complications, and any major adverse cardiac event (MACE). Unfortunately the number of events in included trials was too low to preclude any reliable conclusion on the effects that RFCA may have on these outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence suggests that radiofrequency catheter ablation (RFCA) is effective in restoring and maintaining sinus rhythm as well as reducing both cardioversion and cardiac hospital admissions in younger people (mean age 60 years) with primarily non-paroxysmal atrial fibrillation who have not responded to antiarrhythmic drug therapy with 12 months follow-up. However, quality of the evidence was moderate at the very best. Current practice suggests that RFCA is being recommended in this younger population, despite lack of strong evidence (Cappato 2010). Personal choice, benefit and risk, supported by an atrial fibrillation heart team should be considered, also bearing in mind the stated limitations with included studies and the quality of reported outcomes. Further high-quality research is needed to improve the selection of people that will benefit the most from RFCA.

Implications for research

Based on the quality of the evidence reported, moderate-quality at the very best, it is very likely that further adequately powered and high-quality randomised trials will have an impact on our confidence in the current estimates of effect that RFCA has on people with non-paroxysmal atrial fibrillation. Key characteristics of these high-quality randomised trials should include standardised methods for monitoring rhythm, longer follow-up, broader selection of participants (in particular at high risk of hard endpoints), larger sample size, use of stricter endpoints in terms of success of ablation, and use of validated quality of life instruments more suited to participants with atrial fibrillation. The impact of RFCA on health resource utilisation (cost-effectiveness) also needs to be consistently captured in future randomised trials; we expect the ongoing CABANA trial to provide some information in this regard (NCT00911508).

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REFERENCES

References to studies included in this review

Forleo 2009 *{published data only}*

Forleo G, Mantica M, De Luca L, Leo R, Santini L, Panigada S, et al. Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. *Journal of Cardiovacsular Electrophysiology* 2009;**20**(1):22-8.

Mont 2014 *{published data only}*

Mont L, Bisbal F, Hernández-Madrid A, Pérez-Castellano N, Viñolas X, Arenal A, et al: SARA Investigators. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *European Heart Journal* 2014;**35**(8):501-7.

Stabile 2006 *{published data only}*

Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, et al. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation for the Cure of Atrial Fibrillation Study). *European Heart Journal* 2006;**27**(2):216-21.

References to studies excluded from this review

Andrade 2014 *{published data only}*

Andrade JG, Khairy P, Macle L, Packer DL, Lehmann JW, Holcomb RG, et al. Incidence and significance of early recurrences of atrial fibrillation after cryoballoon ablation: insights from the multicenter Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) Trial. *Circulation. Arrhythmia and Electrophysiology* 2014;**7**(1):69-75.

Bladino 2013 *{published data only}*

Blandino A, Toso E, Scaglione M, Anselmino M, Ferraris F, Sardi D, et al. Long-term efficacy and safety of two different rhythm control strategies in elderly patients with symptomatic persistent atrial fibrillation. *Journal of Cardiovascular Electrophysiology* 2013;**24** (7) : 731-8 .

Cosedis 2012 *{published data only}*

Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *New England Journal of Medicine* 2012;**367**(17):1587-95.

Gaita 2008 *{published data only}*

Gaita F, Caponi D, Scaglione M, Montefusco A, Corleto A, Di Monte F, et al. Long-term clinical results of 2 different ablation strategies in patients with paroxysmal and persistent atrial fibrillation. *Circulation. Arrhythmia and Electrophysiology* 2008;**1**(4):269-75.

Hunter 2014 *{published data only}*

Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circulation. Arrhythmia and Electrophysiology* 2014;**7**(1):31-8.

Jais 2008 *{published data only}*

Jaïs P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* 2008;**118**(24):2498-505.

Jones 2013 *{published data only}*

Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *Journal of the American College of Cardiology* 2013;**61**(18):1894-903.

Krittayaphong 2003 *{published data only}*

Krittayaphong R, Raungrattanaamporn O, Bhuripanyo K, Sriratanasathavorn C, Pooranawattanakul S, Punlee K, et al. A randomized clinical trial of the efficacy of radiofrequency catheter ablation and amiodarone in the treatment of symptomatic atrial fibrillation. *Journal of the Medical Association of Thailand* 2003;**86 Suppl 1**:S8-16.

MacDonald 2011 *{published data only}*

MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart* 2011;**97**(9):740-7.

Morillo 2014 *{published data only}*

Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, et al. RAAFT-2 Investigators. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA* 2014;**311**(7):692-700.

Oral 2006 *{published data only}*

Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F Jr, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *New England Journal of Medicine* 2006;**9**(354):934-41.

Packer 2013 *{published data only}*

Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic (Front STOP-AF) pivotal trial. *Journal of the American College of Cardiology* 2013;**61**(16):1713-23.

Pappone 2006 *{published data only}*

Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. *Journal of the American College of Cardiology* 2006;**48**(11):2340-7.

Raatikainen 2015 *{published data only}*

Raatikainen MJ, Hakalahti A, Uusimaa P, Nielsen JC, Johannessen A, Hindricks G, et al. MANTRA-PAF investigators. Radiofrequency catheter ablation maintains its efficacy better than antiarrhythmic medication in patients with paroxysmal atrial fibrillation: On-treatment analysis of the randomized controlled MANTRA-PAF trial. *International Journal of Cardiology* 2015;**198**:108-114.

Schneider 2015 *{published data only}*

Schneider R, Lauschke J, Tischer T, Schneider C, Voss W, Moehlenkamp F, et al. Pulmonary vein triggers play an important role in the initiation of atrial flutter: Initial results from the prospective randomized Atrial Fibrillation Ablation in Atrial Flutter (Triple A) trial. *Heart Rhythm* 2015;**12**(5):865-71.

Tang 2006 *{published data only}*

Tang RB, Dong JZ, Liu XP, Fang DP, Long de Y, Liu XH, et al. Safety and efficacy of catheter ablation of atrial fibrillation in patients with diabetes mellitus - single center experience. *Journal of International Cardiac Electrophysiology* 2006;**17**(1):41-6.

Wazni 2005 *{published data only}*

Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA* 2005;**293**(21):2634-40.

Wilber 2010 *{published data only}*

Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, et al. ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010;**303**(4):333-40.

References to studies awaiting assessment

NCT00821353 *{published data only}*

NCT00821353. Sinus rhythm maintenance in patients with hypertrophic cardiomyopathy and atrial fibrillation - randomized comparison of antiarrhythmic therapy vs. radiofrequency catheter ablation (SHAARC). clinicaltrials.gov/ct2/show/NCT00821353.

References to ongoing studies

NCT00196209 *{published data only}*

NCT00196209. Randomized study comparing cardioversion vs. catheter ablation in patients with persistent atrial fibrillation. clinicaltrials.gov/ct2/show/NCT00196209.

NCT00911508 *{published data only}*

NCT00911508. Catheter ablation vs anti-arrhythmic drug therapy for atrial fibrillation trial (CABANA). clinicaltrials.gov/ct2/show/NCT00911508.

NCT01420393 *{published data only}*

NCT01420393. A randomized ablation-based atrial fibrillation rhythm control versus rate control trial in patients with heart failure and high burden atrial fibrillation. clinicaltrials.gov/ct2/show/NCT01420393.

Additional references

Andrade 2012

Andrade JG, Macle L, Khairy P, Khaykin Y, Mantovan R, De Martino G, et al. Incidence and significance of early recurrences associated with different ablation strategies for AF: a STAR-AF substudy. *Journal of Cardiovascular Electrophysiology* 2012;**23**(12):1295-301.

Arbelo 2014

Arbelo E, Brugada J, Hindricks G, Maggioni AP, Tavazzi L, Vardas P, et al. The atrial fibrillation ablation pilot study: a European Survey on Methodology and results of catheter ablation for atrial fibrillation conducted by the European Heart Rhythm Association. *European Heart Journal* 2014;**35**(22):1466-78.

Bertaglia 2015 [pers comm]

Bertaglia E. Request for information about study for systematic review-Catheter ablation for the cure of Atrial Fibrillation. Email to: Drs Stabile, Bertaglia and Senatore 09 July 2015.

Brooks 2010

Brooks AG, Stiles MK, Laborderie J, Lau DH, Kuklik P, Shipp NJ, et al. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. *Heart Rhythm* 2010;**7**(6):835-46.

Calkins 2009

Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circulation. Arrhythmia and Electrophysiology* 2009;**2**(4):349-61.

Calkins 2012

Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace* 2012;**14**(4):528-606.

Camm 2012

Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *European Heart Journal* 2012;**33**(21):2719-47.

Cappato 2010

Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circulation. Arrhythmia and Electrophysiology* 2010;**3**:32-8.

Cheng 2014

Cheng X, Li X, He Y, Liu X, Wang G, Cheng L, et al. Catheter ablation versus anti-arrhythmic drug therapy for the management of a trial fibrillation: a meta-analysis. *Journal of Interventional Cardiac Electrophysiology* 2014;**41**(3):267-72.

Dorian 2000

Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *Journal of the American College of Cardiology* 2000;**36**(4):1303-9.

Elayi 2008

Elayi CS, Verma A, Di Biase L, Ching CK, Patel D, Barrett C, et al. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. *Heart Rhythm* 2008;**5**(12):1658-64.

GRADEpro GDT [Computer program]

Schünemann H, Brożek J, Guyatt G, Oxman A. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) profile (pro) and Guideline development tool (GDT). Version 3.6. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Hakalahti 2015

Hakalahti A, Biancari F, Nielsen JC, Raatikainen MJP. Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. *Europace* 2015;**17**(3):370-8.

Haïssaguerre 1998

Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *New England Journal of Medicine* 1998;**339**(10):659-66.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. Wiley-Blackwell.

Jaïs 2008

Jaïs P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* 2008;**118**(24):2498-505.

Kerr 2005

Kerr CR, Humphries KH, Talajic M, Klein GJ, Connolly SJ, Green M, et al. Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: results from the Canadian Registry of Atrial Fibrillation. *American Heart Journal* 2005;**149**(3):489-96.

Khan 2014

Khan AR, Khan S, Sheik MA, Khuder S, Grubb B, Moukarbel GV. Catheter ablation and antiarrhythmic drug therapy as first- or second-line therapy in the management of atrial fibrillation: systematic review and meta-analysis. *Circulation. Arrhythmia and Electrophysiology* 2014;**7**(5):853-60.

Kneeland 2009

Kneeland PP, Fang MC. Trends in catheter ablation for atrial fibrillation in the United States. *Hospital Medicine* 2009;**4**:E1-5.

Kottkamp 2015

Kottkamp H, Bender R, Berg J. Catheter ablation of atrial fibrillation: how to modify the substrate?. *Journal of the American College of Cardiology* 2015;**65**(2):196-201.

Kumar 2013

Kumar S, Walters TE, Halloran K, Morton JB, Hepworth G, Wong CX, et al. Ten-year trends in the use of catheter ablation for treatment of atrial fibrillation vs. the use of coronary intervention for the treatment of ischaemic heart disease in Australia. *Europace* 2013;**15**:1702-9.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

McKenna 2008

C McKenna, S Palmer, M Rodgers, D Chambers, N Hawkins, S Golder, S Van Hout, C Pepper, D Todd, N Woolacott. Cost-effectiveness of radiofrequency catheter ablation for the treatment of atrial fibrillation in the United Kingdom. *Heart* 2008;**95**:542–549.

Nair 2009

Nair GM, Nery PB, Diwakaramenon S, Healey JS, Connolly SJ, Morillo CA. A systematic review of randomized trials comparing radiofrequency ablation with antiarrhythmic medications in patients with atrial fibrillation. *Journal of Cardiovascular Electrophysiology* 2009;**20**:138-44.

Narayan 2012

Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. CONFIRM (conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation) trial. *Journal of the American College of Cardiology* 2012;**60**(7):628-36.

Nault 2010

Nault I, Miyazaki S, Forclaz A, Wright M, Jadidi M, Jaïs P, et al. Drugs vs. ablation for the treatment of atrial fibrillation: the evidence supporting catheter ablation. *European Heart Journal* 2010;**31**(9):1046-54.

Oral 2005

Oral H, Chugh A, Good E, Igic P, Elmouchi D, Tschopp DR, et al. Randomized comparison of encircling and nonencircling left atrial ablation for chronic atrial fibrillation. *Heart Rhythm* 2005;**2**(11):1165-72.

Pokushalov 2013

Pokushalov E, Romanov A, Katritsis DG, Artyomenko S, Shirokova N, Karaskov A, et al. Ganglionated plexus ablation vs

linear ablation in patients undergoing pulmonary vein isolation for persistent/long-standing persistent atrial fibrillation: a randomized comparison. *Heart Rhythm* 2013;**10**(9):1280-6.

Rahman 2014

Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nature Reviews. Cardiology* 2014;**11**(11):639-54.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rivard 2012

Rivard L, Hocini M, Rostock T, Cauchemez B, Forclaz A, Jadidi AS, et al. Improved outcome following restoration of sinus rhythm prior to catheter ablation of persistent atrial fibrillation: a comparative multicenter study. *Heart Rhythm* 2012;**9**(7):1025-30.

Singh 2005

Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, et al. Amiodarone versus sotalol for atrial fibrillation. *New England Journal of Medicine* 2005;**352**:1861-72.

Singh 2006

Singh SN, Tang XC, Singh BN, Dorian P, Reda DJ, Harris CL, et al. Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation: a veterans affairs cooperative studies program substudy. *Journal of the American College of Cardiology* 2006;**48**(4):721-30.

Thrall 2006

Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. *American Journal of Medicine* 2006;**119**(5):448.e1-19.

Verma 2015

Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. *New England Journal of Medicine* 2015;**372**(19):1812-22.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;**336**(7644):601-5.

Wynn 2014

Wynn GJ, Das M, Bonnett LJ, Panikker S, Wong T, Gupta D. Efficacy of catheter ablation for persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized and nonrandomized controlled trials. *Circulation. Arrhythmia and Electrophysiology* 2014;**7**(5):841-52.

Wyse 2002

Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *New England Journal of Medicine* 2002;**347**(23):1825-33.

References to other published versions of this review

Amit 2016

Amit G, Adler AJ, Owolabi OO, Nyong J, Casas JP, Prieto-Merino D, et al. Efficacy and safety of ablation for patients with non-paroxysmal atrial fibrillation. *Cochrane Database of Systematic Reviews* 2016, Issue 2. [DOI: 10.1002/14651858.CD012088]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Forleo 2009

Methods	RCT
Participants	**Country:** Italy **Inclusion criteria:** Diabetes mellitus 2 participants with symptomatic paroxysmal or persistent AF for ≥ 6 months refractory to ≥ 1 class 1-3 antiarrhythmic drugs. **Exclusion criteria:** • Age < 18 or > 75 years • Ejection fraction < 30%, left atrial size > 55 mm • Absence of informed participant consent. • Any condition that would make survival for 1 year unlikely. • Participants with prior cardiac surgery as well participants with history of previous ablation for AF. **Randomised:** Control: 35, Intervention: 35 **Age (mean in years):** Control: 64.8, Intervention: 63.2

Forleo 2009 *(Continued)*

	% Male gender: Control: 23, Intervention: 20
Interventions	**Control:** New ADT. In participants with persistent AF, cardioversion was performed under a new ADT to maintain the sinus rhythm. 5-week blanking period. **Intervention:** Pulmonary vein isolation. Participants were discharged on antiarrhythmic drugs.
Outcomes	Analysis was by intention-to-treat. **Primary outcomes** **1. Freedom from atrial arrhythmias** Control: 15/35, Intervention: 28/35 **2. % Needing cardioversion after blanking period** Control: 0/35, Intervention: 0/35
Notes	Persistent AF was not self-terminating within 7 days and permanent AF if cardioversion had failed or had not been attempted. Pilot study and not adequately powered.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible participants were randomised to receive either pulmonary vein isolation or a new ADT according to a computer-generated study list.
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment not specified by authors.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open RCT. Not possible to blind participants receiving ablation due to the nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	At each visit, participants were asked whether medical events or symptoms suggestive of cardiac arrhythmias occurred and an ECG Holter Monitoring was performed to detect the presence of asymptomatic arrhythmias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Pre-specified outcomes reported
Other bias	Unclear risk	Pilot study and not adequately powered.

Mont 2014

Methods	RCT
Participants	**Country:** Spain

Mont 2014 *(Continued)*

	Inclusion criteria: Participants with symptomatic persistent atrial fibrillation (> 7 or < 7 days requiring electrical or pharmacological cardioversion) refractory to at least one class I or class III antiarrhythmic drug. **Exclusion criteria:** • Age < 18 or > 70 years • Long-standing persistent AF (> 1 year of continuous AF) • First episode of AF • Hyper- or hypothyroidism • Hypertrophic cardiomyopathy • Implanted pacemaker or defibrillator • Moderate or severe mitral disease or mitral prosthesis • Left ventricular ejection fraction < 30% • Left atrial diameter > 50 mm • Prior ablation procedure • Contraindication for oral anticoagulation • Left atrial thrombus • Active infection or sepsis • Pregnancy • Unstable angina • Acute myocardial infarction during previous 3 months • Life expectation < 12 months • Current participation in another clinical trial • Mental disease or inability to give informed consent • Disease contraindicating ablation or ADT **Randomised:** Control: 48, Intervention: 98 **Age (mean in years):** Control: 55, Intervention: 55 **% Male gender:** Control: 77, Intervention: 77.5
Interventions	**Control:** Participants were treated depending on physician's choice and according to current guidelines. Discontinuation of the antiarrhythmic treatment was not required before inclusion in the ADT group. There was no predefined protocol on the use of ADT during the blanking period. **Intervention:** Pulmonary vein ablation. Antiarrhythmic drugs were discontinued ≥ 5 half-life periods (or ≥ 1 week for amiodarone) before ablation; antiarrhythmics were reinitiated immediately after CA for the blanking period. 3-month blanking period.
Outcomes	Analysis was by intention-to-treat **Primary outcomes** **1. Freedom from atrial arrhythmias** Control: 43.7%, Intervention: 70.4% **2. % Needing cardioversion after blanking period** Control: 50, Intervention: 34.7
Notes	Possible loss of statistical power as study was terminated before reaching planned sample size due to lower than expected recruitment rate. The study was supported by an unrestricted grant from Medtronic and Biosense Webster. FB was supported by a grant from Hospital Clinic (premi de Fi de Residencia Emili Letang). No other potential conflict of interest relevant to this study was reported.

Mont 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Recruited participants were randomly assigned to either ablation (CA group) or medical therapy (ADT group) according to a 2:1 blocked randomisation list stratified by centre.
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment not specified by authors.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open RCT. Not possible to blind participants receiving ablation due to the nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded. The primary endpoint was assessed by an independent endpoint committee, which evaluated the episodes based on the information received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	83 participants (84%) in intervention group provided outcome data compared to all of the control group.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Pre-specified outcomes were reported
Other bias	High risk	Loss of statistical power. Study was terminated before reaching the planned sample size due to a lower than expected recruitment rate (study limitations) though authors claim that "the difference between groups in the primary endpoint was higher than assumed in the sample size calculation, which likely compensated for the loss of statistical power."

Stabile 2006

Methods	RCT
Participants	**Country:** Italy **Inclusion criteria:** Participants with paroxysmal or persistent AF who were intolerant of antiarrhythmic drugs or in whom two or more antiarrhythmic drug regimens had failed. **Exclusion criteria:** • Age < 18 or > 80 years • Permanent AF (AF was the sole rhythm for the last 12 months) • AF secondary to a transient or correctable abnormality, including electrolyte imbalance, trauma, recent surgery, infection, toxic ingestion, and endocrinopathy • Persistence of AF episodes triggered by another uniform arrhythmia (i.e. atrial flutter or atrial tachycardia) despite previous supraventricular tachycardia ablation • Intra-atrial thrombus, tumour, or other abnormality precluding catheter insertion • Wolff-Parkinson-White syndrome • Heart failure with New York Heart Association (NYHA) class III or IV or ejection fraction ≤ 35% • Unstable angina or acute myocardial infarction within 3 months • Cardiac revascularisation or other cardiac surgery within 6 months or with prior atrial surgery

Stabile 2006 *(Continued)*

	• Renal failure requiring dialysis, or hepatic failure • An implanted device (pacemaker or cardioverter-defibrillator) • Left atrial diameter > 60 mm **Randomised:** Control: 19, Intervention: 26 **Age (mean in years):** Control: 62.3, Intervention: 62.2 **%Male gender:** Control: 64, Intervention: 54
Interventions	**Control:** The antiarrhythmic drug preferentially administered was amiodarone. In participants with history of intolerance to amiodarone, a class IC antiarrhythmic was administered. The final decision was left to the physician. **Intervention:** Pulmonary vein isolation, circumferential ablation, plus left atrial linear lesion ± cavo-tricuspid isthmus.
Outcomes	Analysis was by intention-to-treat **Primary outcomes** **1. Absence of any recurrence of atrial arrhythmias** Control: 6/69, Intervention: 38/68 **2. % Needing cardioversion after blanking period** Control: 0/69, Intervention: 0/77
Notes	Only participants that had persistent AF were included in the analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment not specified by authors.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not possible to blind participants receiving ablation due to the nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Pre-specified outcomes were reported
Other bias	Unclear risk	Our analysis is restricted to the subsample of participants with persistent AF.

ADT: antiarrhythmic drug treatment

AF: atrial fibrillation
CA: cardiac ablation
ECG: electrocardiogram
RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Andrade 2014	Mixed population with > 75% paroxysmal atrial fibrillation.
Bladino 2013	Not RCT.
Cosedis 2012	Not addressing prespecified population; participants with paroxysmal atrial fibrillation.
Gaita 2008	Not addressing prespecified intervention; study comparing two different ablation strategies.
Hunter 2014	Not addressing prespecified comparison; ablation compared to rate control and follow-up not up to 12 months.
Jais 2008	Not addressing prespecified population; participants with paroxysmal atrial fibrillation.
Jones 2013	Not addressing prespecified comparison; study on rate control.
Krittayaphong 2003	Mixed population with > 90% paroxysmal atrial fibrillation.
MacDonald 2011	Not addressing prespecified comparison; study on rate control.
Morillo 2014	Not addressing prespecified intervention; on participants with paroxysmal atrial fibrillation.
Oral 2006	Study did not directly compare antiarrhythmic drug therapy to circumferential pulmonary vein ablation. Also, 77% of the participants in the AAD group crossed over to undergo circumferential pulmonary vein ablation in addition to antiarrhythmic drug therapy.
Packer 2013	Mixed population with > 75% paroxysmal atrial fibrillation.
Pappone 2006	Not addressing prespecified population; participants with paroxysmal atrial fibrillation.
Raatikainen 2015	Not addressing prespecified population; participants with paroxysmal atrial fibrillation.
Schneider 2015	Not addressing prespecified population; participants with atrial flutter.
Tang 2006	Not RCT.
Wazni 2005	Mixed population with > 90% paroxysmal atrial fibrillation.
Wilber 2010	Not addressing prespecified population; participants with paroxysmal atrial fibrillation.

AAD: antiarrhythmic drug
RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00821353

Methods	RCT

NCT00821353 *(Continued)*

Participants	**Country:** Poland **Eligibility:** • Ages eligible for study: 18 years to 70 years (adult, senior) • Genders eligible for study: both • Accepts healthy volunteers: no **Inclusion criteria:** Participants with hypertrophic cardiomyopathy and paroxysmal or chronic atrial fibrillation **Exclusion criteria:** • Severe heart failure (NYHA IV) • Left ventricular ejection fraction < 0.30 • Left atrial diameter > 65 mm • Age > 70 years • Contraindication to anticoagulation with warfarin • Presence of a mechanical prosthetic valve • Presence of left atrial thrombus on TEE or CT • Woman currently pregnant • Renal failure (GFR < 30 ml/min) • Hepatic failure • Untreated hypothyroidism or hyperthyroidism • LVOT gradient > 50 mmHg **Estimated enrolment:** 90 **Follow-up:** 12 months
Interventions	**Control:** Antiarrhythmic drugs (preferably amiodarone) and cardioversion in cases of chronic AF **Intervention:** Radiofrequency catheter ablation
Outcomes	**Primary Outcome** 1. Freedom from atrial fibrillation and atrial flutter (> 1 min) on or off antiarrhythmic medications **Secondary outcomes** 1. Changes in total symptomatic and asymptomatic AF burden 2. Incidence of complications 3. Changes in left atrial diameter and left ventricular function 4. Changes in level of Nt-pro-BNP 5. Changes in symptom severity and quality of life 6. Changes in exercise capacity assessed by cardiopulmonary exercise testing
Notes	Please refer to this study by its ClinicalTrials.gov identifier: NCT00821353. Phase three completed but not published as of when this review was developed.

AF: atrial fibrillation
RCT: randomised controlled trial
CT: computerized tomography
GFR: glomular filtration rate
LVOT: left ventricular outflow tract

Nt-pro-BNP: N-terminal pro-brain natriuretic peptide
NYHA: New York Heart Association
RCT: randomised controlled trial
TEE: transesophageal echocardiography

Characteristics of ongoing studies *[ordered by study ID]*

NCT00196209

Trial name or title	Randomized study comparing cardioversion vs. catheter ablation in patients with persistent atrial fibrillation
Methods	RCT
Participants	**Country:** Germany **Eligibility:** • Ages eligible for study: 20 years to 75 years (adult, senior). • Genders eligible for study: both. • Accepts healthy volunteers: no. **Inclusion criteria:** • Age > 20 years and < 75 years. • Documented persistent atrial fibrillation for at least 3 months (documented in at least 2 ECGs or Holter-ECGs during the previous 3 months before inclusion and persistent atrial fibrillation in a 7-day-Holter). • Documented sufficient anticoagulation for at least 4 weeks before inclusion. **Exclusion criteria:** • Paroxysmal atrial fibrillation. • NYHA IV (if recompensation is not possible). • Contraindication for warfarin. • Disturbance of blood coagulation. • Myocardial infarction, PTCA/stenting, bypass operation, stroke, intracranial bleeding less than 3 months before. • Reversible causes of atrial fibrillation (i.e. hyperthyroidism). • Pregnancy. • LA diameter > 55 mm. • LV function < 30% EF. • Aortic or mitral stenosis or regurgitation III°-IV°. • Prosthetic valves. **Estimated enrolment:** 130 **Follow-up:** 6 months
Interventions	**Control:** Cardioversion and drug prophylaxis to treat persistent atrial fibrillation. **Intervention:** Catheter ablation to treat persistent atrial fibrillation.
Outcomes	**Primary outcome:** Event-free survival after 6 months (i.e. freedom of atrial tachyarrhythmias - as evaluated in a 7-day-Holter, stroke, pulmonary vein stenosis - as evaluated in a CT-/MRT scan 6 months after the initial procedure - and death). **Secondary outcomes:** • Success-rate immediately after intervention.

NCT00196209 *(Continued)*

- Need for reintervention between 2 and 3 months after initial procedure if not stable sinus rhythm at the two-month follow-up (further ablation/cardioversion).
- Burden of atrial fibrillation in a 7-day-Holter after 6 months.
- Significant improvement in exercise capacity (measured by spiroergometry).
- Decrease in NT-pro-BNP levels in the blood after 6 months compared to the level before initial intervention.
- Improvement of quality of life (combined questionnaire including the SF-36 form) before initial intervention and at the 6-months follow-up.

Starting date	August 2005
Contact information	Heidi L Estner, MD; 0049 89 1218 2020; estner@dhm.mhn.de
Notes	Please refer to this study by its ClinicalTrials.gov identifier: NCT00196209. The recruitment status of this study is unknown.

NCT00911508

Trial name or title	Catheter ablation vs anti-arrhythmic drug therapy for atrial fibrillation trial
Methods	RCT

Participants	**Country:** USA
	
	Eligibility:
	
	• Ages eligible for study: 18 years to 90 years (adult, senior).
	• Genders eligible for study: both.
	• Accepts healthy volunteers: no.
	
	Inclusion criteria:
	
	Over the preceding 6 months have:
	
	• ≥ 2 paroxysmal (electrocardiographic documentation of at least 1) AF episodes lasting ≥ 1 hour in duration: (that terminate spontaneously within 7 days or cardioversion is performed within 48 hours of AF onset): or
	• electrocardiographic documentation of 1 persistent AF episode: (sustained for ≥ 7 days or cardioversion is performed more than 48 hours after AF onset): or
	• electrocardiographic documentation of 1 longstanding persistent AF episode: (continuous AF of duration > 1 year).
	• Warrant active therapy (within the past 3 months) beyond simple ongoing observation.
	• Be eligible for catheter ablation and ≥ 2 sequential rhythm control and/or ≥ 2 rate control drugs.
	• Be ≥ 65 yrs of age, or < 65 yrs with one or more of the following risk factors for stroke:
	  ○ hypertension (treated and/or defined as a blood pressure > 140/90 mmHg)
	  ○ diabetes (treated and/or defined as a fasting glucose ≥ 126 mg/dl)
	  ○ congestive heart failure (including systolic or diastolic heart failure)
	  ○ prior stroke, TIA or systemic emboli
	  ○ atherosclerotic vascular disease (previous MI, peripheral arterial disease or aortic plaque), LA size > 5.0 cm (or volume index ≥ 40 cc/m2), or EF ≤ 35.
	• Have the capacity to understand and sign an informed consent form.
	• Be ≥18 years of age.
	• Participants < 65 yrs of age whose only risk factor is hypertension must have a second risk factor or LV hypertrophy to qualify. Participants receiving new drug therapy initiated within the previous 3

NCT00911508 *(Continued)*

months may continue that therapy if randomised to the drug therapy arm. Participants may have documented atrial flutter in addition to atrial fibrillation and remain eligible for enrolment.

Exclusion criteria:

- Lone AF in the absence of risk factors for stroke in participants < 65 years of age.
- Participants who in the opinion of the managing clinician should not yet receive any therapy for AF.
- Participants who have not responded to > 2 membrane active AADs at a therapeutic dose due to inefficacy or side effects (Table 5.2.2).
- An efficacy failure of full dose amiodarone treatment > 8 weeks duration at any time.
- Reversible causes of AF including thyroid disorders, acute alcohol intoxication, recent major surgical procedures, or trauma.
- Recent cardiac events including MI, PCI, or valve or bypass surgery in the preceding 3 months.
- Hypertrophic obstructive cardiomyopathy (outflow track).
- Class IV angina or Class IV CHF (including past or planned heart transplantation).
- Other arrhythmias mandating AAD therapy (i.e. ventricular tachycardia, ventricular fibrillation).
- Heritable arrhythmias or increased risk for torsade de pointes with class I or III drugs.
- Prior LA catheter ablation with the intention of treating AF.
- Prior surgical interventions for AF such as the MAZE procedure.
- Prior AV nodal ablation.
- Participants with other arrhythmias requiring ablative therapy.
- Contraindication to appropriate anticoagulation therapy.
- Renal failure requiring dialysis.
- Medical conditions limiting expected survival to < 1 year.
- Women of childbearing potential (unless postmenopausal or surgically sterile).
- Participation in any other clinical mortality trial (participation in other non-mortality trials should be reviewed with the clinical trial management centre).
- Unable to give informed consent.

Estimated enrolment: 2204

Follow-up: until date of event

Interventions	**Control:** Current state-of-the-art drug therapy for atrial fibrillation (rate control or rhythm control). Treating physicians will be encouraged to follow the American College of Cardiology/American Heart Association/European Society of Cardiology Atrial Fibrillation Guidelines with regard to drug therapy for atrial fibrillation. **Intervention:** Pulmonary vein isolation using a circumferential ablative approach in the left atrium. Ablation may be performed using circular mapping catheter-guided ablation, antral isolation using a circular guided approach, or wide area circumferential ablation.
Outcomes	**Primary outcome:** LA catheter ablation is superior to rate or rhythm control drug therapy for decreasing the incidence of the composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest in participants warranting therapy for AF. **Secondary outcomes:** LA catheter ablation is superior to rate or rhythm control drug therapy for reducing total mortality. • Total mortality or cardiovascular hospitalisation. • Cardiovascular death. • Cardiovascular death or disabling stroke. • Arrhythmic death or cardiac arrest. • Heart failure death. • Freedom from recurrent AF. • Cardiovascular hospitalisation.

NCT00911508 *(Continued)*

	• Medical costs, resource utilisation, and cost-effectiveness. • Quality of life. • Composite adverse events. • Left atrial size, morphology and function and its relationship to morbidity and mortality.
Starting date	August 2009
Contact information	Douglas L Packer, MD, Mayo Clinic
Notes	Please refer to this study by its ClinicalTrials.gov identifier: NCT00911508. This study is ongoing, but not recruiting participants.

NCT01420393

Trial name or title	A randomized ablation-based atrial fibrillation rhythm control versus rate control trial in patients with heart failure and high burden atrial fibrillation
Methods	RCT
Participants	Country: Canada **Eligibility:** • Ages eligible for study: 18 years and older (adult, senior). • Genders eligible for study: both. • Accepts healthy volunteers: no. **Inclusion criteria:** Participants with one of the following AF categories and at least one ECG documentation of AF. • High burden paroxysmal defined as ≥ 4 episodes of AF in the last 6 months, and at least one episode > 6 hours (and no episode requiring cardioversion and no episode > 7 days). • Persistent AF (1) defined as ≥ 4 episodes of AF in the last 6 months, and at least one episode > 6 hours, and at least one AF episode less than 7 days but requires cardioversion. No AF episodes are > 7 days. • Persistent AF (2) as defined by at least one episode of AF > 7 days but not > 1 year. • Long-term persistent AF defined as an AF episode, at least one year in length and no episodes > 3 years. • Optimal therapy for heart failure of at least 6 weeks (according to 2009 ACCF/AHA class 1 recommendations). • HF with NYHA class II or III symptoms with either impaired LV function (LVEF ≤ 45%) as determined by EF assessment within the previous 12 months or preserved LV function (LVEF > 45%) determined by EF assessment within the previous 12 months. • NT-pro BNP measures: A) participant has been hospitalised for heart failure (heart failure admission is defined as admission to hospital > 24 hours and received treatment for heart failure) in the past 9 months, has been discharged and: i) is presently in normal sinus rhythm and NT-pro BNP is ≥ 400 pg/mL; ii) is presently in atrial fibrillation and NT-pro BNP is ≥ 600 pg/mL or B) participant has had no hospitalisation for heart failure in the past 9 months and: i) has had paroxysmal atrial fibrillation, is presently in normal sinus rhythm and NT-proBNP is ≥ 600 pg/mL; ii) is presently in atrial fibrillation and NT-proBNP is ≥ 900 pg/mL. • Suitable candidate for catheter ablation or rate control therapy for the treatment of AF. • Age ≥ 18. **Exclusion criteria**: • Have an LA dimension > 55 mm as determined by echocardiography within the previous year.

NCT01420393 *(Continued)*

	• Had an acute coronary syndrome or coronary artery bypass surgery within 12 weeks. • Have rheumatic heart disease, severe aortic or mitral valvular heart disease using the AHA/ACC guidelines. • Have congenital heart disease including previous ASD repair, persistent left superior vena cava. • Had prior surgical or percutaneous AF ablation procedure or atrioventricular nodal (AVN) ablation. • Have a medical condition likely to limit survival to < 1 year. • Have New York Heart Association (NYHA) class IV heart failure symptoms. • Have contraindication to systematic anticoagulation. • Have renal failure requiring dialysis. • AF due to reversible cause, e.g. hyperthyroid state. • Are pregnant. • Are included in other clinical trials that will affect the objectives of this study. • Have a history of non-compliance to medical therapy. • Are unable or unwilling to provide informed consent. **Estimated enrolment:** 600 **Follow-up:** 5 years
Interventions	**Control:** Participants in the rate control group will receive optimal heart failure therapy and rate control measures to achieve a resting HR < 80 beats per minute (bpm) and 6-minute walk HR < 110 bpm **Intervention:** Participants randomised to catheter ablation-based AF rhythm control group will receive optimal heart failure therapy and one or more aggressive catheter ablation, which include PV antral ablation and LA substrate ablation with or without adjunctive antiarrhythmic drug.
Outcomes	**Primary outcome**: Composite of all-cause mortality and hospitalisation for heart failure defined as an admission to a health care facility for > 24 hours. **Secondary outcomes**: • All-cause mortality. • Cardiovascular mortality. • All-cause hospitalisation. • Heart failure hospitalisation. • Cardiovascular hospitalisation. • Health-related quality of life (MLWHF, EQ5D, AFEQT, Specific Activity scale). • Health economics. • 6-minute walk (6MW) distance. • CCS-SAF scale.
Starting date	September 2011
Contact information	Anthony Tang, MD; anthonysltang@gmail.com
Notes	Please refer to this study by its ClinicalTrials.gov identifier: NCT01420393. This study is currently recruiting participants.

AFEQT: atrial fibrillation effect on quality-of-life
ASD: atrial septal defect
AV: Atrioventricular
CCS-SAF: Canadian cardiovascular society severity of atrial fibrillation
CHF: congestive heart failure
EF: ejection fraction
EQ5D: EuroQol five dimensions

HR: heart rate
HF: heart failure
LA: left atrial
LV: left ventricular
LVEF: left ventricular ejection fraction
MI: myocardial infarction
MLWHF: Minnesota living with heart failure
MRT: magnetic resonance tomography
Nt-pro-BNP: N-terminal pro-brain natriuretic peptide
PCI: percutaneous coronary intervention
PTCA: percutaneous transluminal coronary angioplasty
PV: pulmonary vein
TIA: transient Ischaemic attack

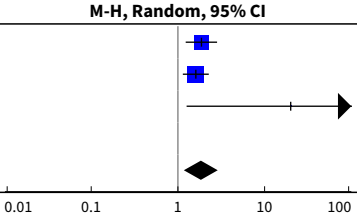
DATA AND ANALYSES

Comparison 1. Ablation versus antiarrhythmic drugs for non-paroxysmal atrial fibrillation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Freedom from atrial arrhythmia at 12 months follow-up (random-effects model)	3	261	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.17, 2.88]
2 Freedom from atrial arrhythmia at 12 months follow-up (fixed-effect model)	3	261	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.48, 2.55]
3 Participants needing cardioversion	3	261	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.47, 0.82]
4 Cardiac hospitalisation	2	216	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.10, 0.72]
5 Significant bradycardia or need for a pacemaker	3	261	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.02, 1.63]
6 Periprocedural complications and other safety outcomes (random-effects model)	3	261	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.16, 5.68]
7 Periprocedural complications and other safety outcomes (fixed-effect model)	3	261	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.33, 2.21]

Analysis 1.1. Comparison 1 Ablation versus antiarrhythmic drugs for non-paroxysmal atrial fibrillation, Outcome 1 Freedom from atrial arrhythmia at 12 months follow-up (random-effects model).

Study or subgroup	Ablation n/N	AADs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Forleo 2009	28/35	15/35		45.54%	1.87[1.23,2.83]
Mont 2014	69/98	21/48		51.91%	1.61[1.14,2.27]
Stabile 2006	13/26	0/19		2.55%	20[1.26,316.89]
Total (95% CI)	**159**	**102**		**100%**	**1.84[1.17,2.88]**



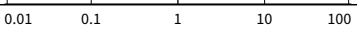
Study or subgroup	Ablation n/N	AADs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 110 (Ablation), 36 (AADs)					
Heterogeneity: Tau²=0.07; Chi²=3.89, df=2(P=0.14); I²=48.58%					
Test for overall effect: Z=2.65(P=0.01)					

Analysis 1.2. Comparison 1 Ablation versus antiarrhythmic drugs for non-paroxysmal atrial fibrillation, Outcome 2 Freedom from atrial arrhythmia at 12 months follow-up (fixed-effect model).

Study or subgroup	Ablation n/N	AADs n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Forleo 2009	28/35	15/35		34.27%	1.87[1.23,2.83]
Mont 2014	69/98	21/48		64.41%	1.61[1.14,2.27]
Stabile 2006	13/26	0/19		1.31%	20[1.26,316.89]
Total (95% CI)	**159**	**102**		**100%**	**1.94[1.48,2.55]**
Total events: 110 (Ablation), 36 (AADs)					
Heterogeneity: Tau²=0; Chi²=3.89, df=2(P=0.14); I²=48.58%					
Test for overall effect: Z=4.76(P<0.0001)					

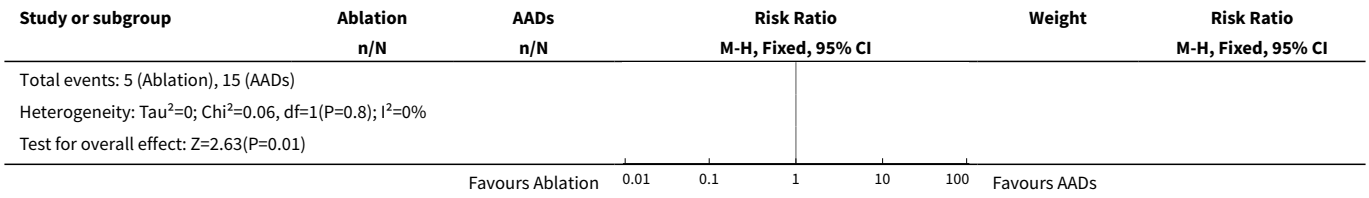
Analysis 1.3. Comparison 1 Ablation versus antiarrhythmic drugs for non-paroxysmal atrial fibrillation, Outcome 3 Participants needing cardioversion.

Study or subgroup	Ablation n/N	AADs n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Forleo 2009	0/35	0/35			Not estimable
Mont 2014	34/98	24/48		58.98%	0.69[0.47,1.03]
Stabile 2006	13/26	19/19		41.02%	0.51[0.35,0.75]
Total (95% CI)	**159**	**102**		**100%**	**0.62[0.47,0.82]**
Total events: 47 (Ablation), 43 (AADs)					
Heterogeneity: Tau²=0; Chi²=1.25, df=1(P=0.26); I²=20.25%					
Test for overall effect: Z=3.31(P=0)					

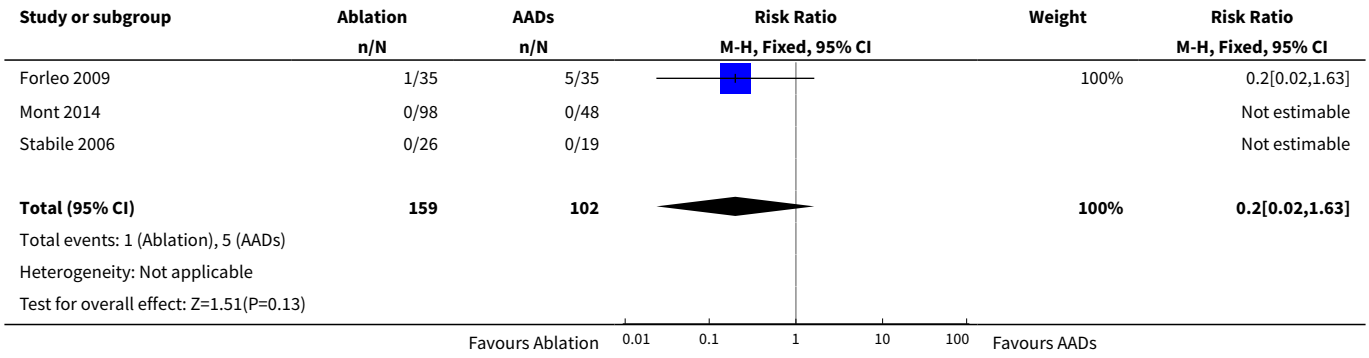


Analysis 1.4. Comparison 1 Ablation versus antiarrhythmic drugs for non-paroxysmal atrial fibrillation, Outcome 4 Cardiac hospitalisation.

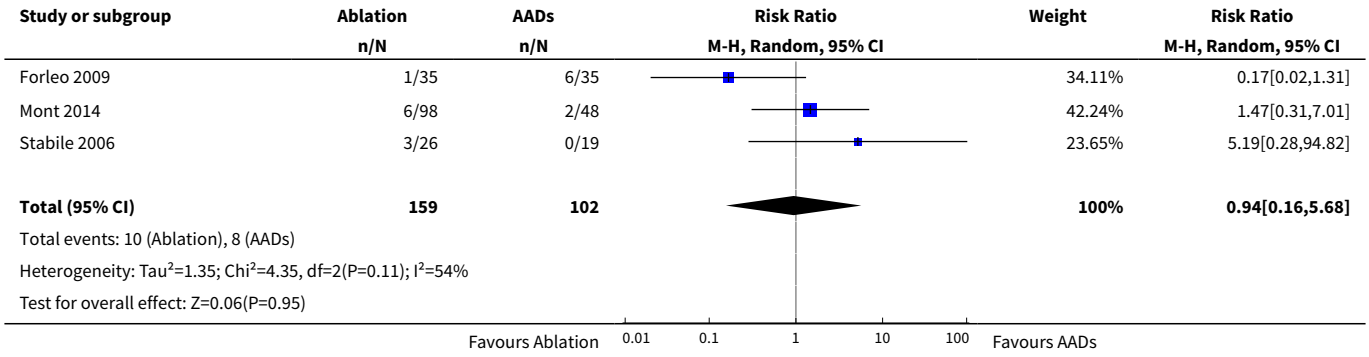
Study or subgroup	Ablation n/N	AADs n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Forleo 2009	3/35	12/35		74.87%	0.25[0.08,0.81]
Mont 2014	2/98	3/48		25.13%	0.33[0.06,1.89]
Total (95% CI)	**133**	**83**		**100%**	**0.27[0.1,0.72]**



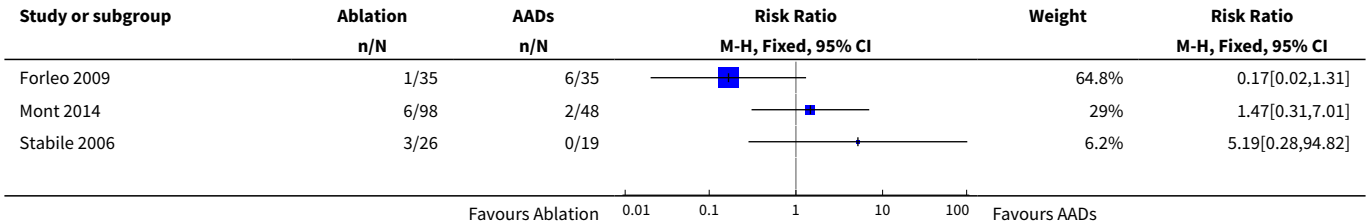
Analysis 1.5. Comparison 1 Ablation versus antiarrhythmic drugs for non-paroxysmal atrial fibrillation, Outcome 5 Significant bradycardia or need for a pacemaker.

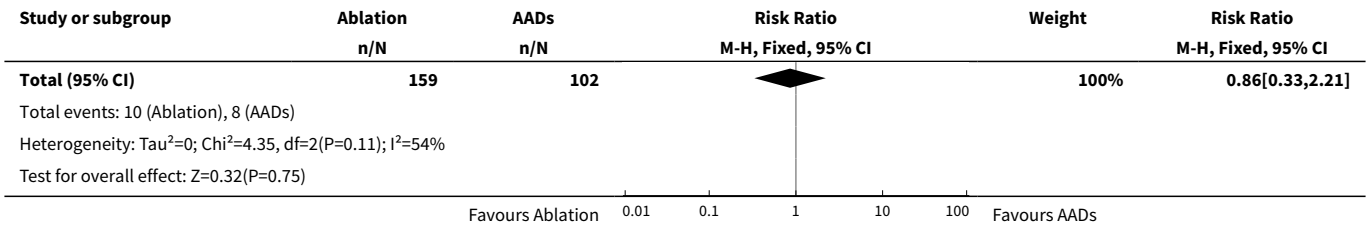


Analysis 1.6. Comparison 1 Ablation versus antiarrhythmic drugs for non-paroxysmal atrial fibrillation, Outcome 6 Periprocedural complications and other safety outcomes (random-effects model).



Analysis 1.7. Comparison 1 Ablation versus antiarrhythmic drugs for non-paroxysmal atrial fibrillation, Outcome 7 Periprocedural complications and other safety outcomes (fixed-effect model).





ADDITIONAL TABLES

Table 1. Further details of included studies

Study Name	Forleo 2009	Mont 2014	Stabile 2006[1]
Study period	January 2005-September 2006	May 2009-November 2011	February 2002-June 2003
No. participants per arm (Intervention/comparator)	35 / 35	98 / 48	26 / 19
Average follow-up (months)	12	12	18
No. participants lost-to-follow up (intervention/comparator)	0 / 0	3 / 0	This information was not available for the sub-group with persistent AF.
% participants with paroxysmal atrial fibrillation (intervention/comparator)	37 / 46	0 / 0	0 / 0 Though the original trial included paroxysmal atrial fibrillation, this reported only analysed persistent atrial fibrillation
Interventions post-trandomisation and before Ablation	AADs were not suspended before the ablation.	AAD were discontinued ≥5 half-life periods (or ≥1 week for amiodarone) before ablation.	Not described.
Type of ablation (Surgical vs radiofrequency catheter)	Radiofrequency Catheter	Radiofrequency Catheter	Radiofrequency Catheter
Ablation technique	Pulmonary vein isolation, segmental ostial + left atrial linear lesion (roof line, mitral isthmus) + CFAE ablation.	Pulmonary vein isolation, circumferential ablation ± cavo-tricuspid isthmus ± left atrial	Pulmonary vein isolation, circumferential ablation, plus left atrial linear lesion ± cavo-tricuspid isthmus.

Table 1. Further details of included studies *(Continued)*

		linear lesion ± CFAE ablation	
Use of AADs posterior to ablation	Participants were discharged on AAD. Discontinuation of AADs was complete within 1 month in participants without structural heart disease and up to 3 months in the remaining participants.	AADs for 3 months (blanking period)	AADs were given for the whole duration of the study. Participants were preferentially on amiodarone. In participants with history of intolerance to amiodarone, a class IC antiarrhythmic was administered. The final decision was left to the physician.
Comparator arm	ADT at maximum tolerable dose either as single or combination. The recommended regimen was: oral flecainide 100 mg e/12 hours, oral propafenone (150–300 mg) 3 times daily, oral sotalol at an initial dose of 80 mg three times daily, and oral amiodarone 600 mg/day for 2 weeks, 400 mg/day for the next 2 weeks, and 200 mg daily thereafter. In participants with persistent atrial fibrillation, cardioversion was performed under a new ADT to maintain the sinus rhythm.	Discontinuation of the AADs was not required before inclusion in the ADT group. Participants were treated depending on physician's choice and according to current guidelines. There was not predefined protocol on the use of ADT during the blanking period.	The antiarrhythmic drug preferentially administered was amiodarone. In participants with history of intolerance to amiodarone, a class IC antiarrhythmic was administered. The final decision was left to the physician.

AAD: antiarrhythmic drugs; ADT: antiarrhythmic drug therapy; CFAE: complex fractionated atrial electrograms
[1] Stabile 2006: only participants with persistent atrial fibrillation were included in the analysis.

Table 2. Characteristics of participants included in the studies

Study Name	Forleo 2009	Mont 2014	Stabile 2006
Mean Age (years) **(intervention/comparison)**	63.2 / 64.8	55 / 55	62.2 / 62.3
% of women	38.6	22.6	40.9
Selection criteria atrial fibrilation-related	Symptomatic paroxysmal or persistent atrial fibrillation for ≥6 months	Symptomatic persistent atrial fibrillation: >7 or <7 days requiring electrical or pharmacological cardioversion. Participants with long-standing persistent atrial fibrillation were excluded.	Persistent atrial fibrillation: occurrence in the previous 12 months of ≥2 episodes of atrial fibrillation, each lasting > 7 days before being terminated, or lasting less than 7 days but necessitating early cardioversion. In all participants, the first diagnosis of atrial fibrillation had been made at least 6 months before enrolment
History of AADs	Participants had to be refractory to ≥1 class 1–3 AADs.	Participants had to be refractory to at least one class I or class III AADs.	Participants had to be intolerant to AADs or in whom two or more AADs regimens had failed.
Atrial fibrillation History (years)	3.4 / 3	N.R	5.1 / 7.1

Table 2. Characteristics of participants included in the studies *(Continued)*

(intervention/comparison)			
Mean LA size (mm)	44.3 / 45.2	41.3 / 42.7	46 / 45.4
(intervention/comparison)			
Mean LVEF (%)	54.6 / 52.6	61.1 / 60.8	59.1 / 57.9
(intervention/comparison)			
% any CV co-morbidity[1]	45.7 / 54.3	10 / 8	63.2 / 62.3
(intervention/comparison)			

% CV co-morbidities: Oral refers to Nonischemic cardiomyopathy, coronary artery disease, valvular heart disease and congenital heart disease. Forleo refers to structural heart disease (CHD, dilated cardiomyopathy, valve disease and previous embolic episodes). Mont refers to TIA, Stroke, peripheral embolism and ischaemic cardiomyopathy. Stabile refers to heart disease. NR, not reported

Table 3. Study characteristics regarding the ascertainment of their primary outcome - freedom from atrial arrhythmias

Study name	Forleo 2009	Mont 2014	Stabile 2006
Outcome definition	Time to the first atrial fibrillation (or atypical flutter) recurrence after 5 weeks and within 12 months after randomisation.	Any episode of atrial fibrillation or flutter lasting > 24 hours or requiring cardioversion after a 3-month blanking period.	Absence of any recurrence of atrial arrhythmias (atrial fibrillation or flutter) lasting > 30 seconds in the 1-year follow-up, after the 1-month blanking period.
Censoring	Participants were censored after first atrial fibrillation recurrence.	Participants were censored after first atrial fibrillation recurrence.	Participants were censored after first occurrence of atrial arrhythmias (atrial fibrillation or flutter).
Definition of atrial arrhythmias (primary outcome)	Electrocardiographically-confirmed episode of atrial fibrillation or atypical flutter had to last "> 30 seconds".	Atrial fibrillation or flutter lasting > 24 hours or requiring cardioversion. In cases where the Holter recorded atrial fibrillation < 24 hours, symptoms were taken into consideration.	Atrial arrhythmias lasting > 30 seconds.
Blanking period	5 weeks.	3 months.	1 month.
Mode of ascertainment	Pulse evaluation confirmed by ECG when any arrhythmia was suspected and Holter monitoring.	A 24-hour Holter monitor.	Transtelephonic ECG recording (Life watch monitor) and Holter monitoring.
Frequency of ascertainment	Pulse: regularly. Holter: during visits a 1, 3, 6, 9 and 12 months.	Holter: 6 and 12 months.	Transtelephonic ECG: daily for 3 months and whenever they had palpitations. Holter: 1, 4, 7, 10, and 13 months.

ECG: electrocardiogram

APPENDICES

Appendix 1. Search strategies

CENTRAL

#1 MeSH descriptor: [Atrial Fibrillation] this term only
#2 (atrial near/3 fibrillat*):ti,ab,kw (Word variations have been searched)
#3 (auricular* near/3 fibrillat*):ti,ab,kw (Word variations have been searched)
#4 (atrium near/3 fibrillat*):ti,ab,kw (Word variations have been searched)
#5 atrial arrhythmi*:ti,ab,kw (Word variations have been searched)
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Catheter Ablation] this term only
#8 (catheter near/6 (ablat* or isolat*)):ti,ab,kw (Word variations have been searched)
#9 (transcatheter and (ablat* or isolat*)):ti,ab,kw (Word variations have been searched)
#10 ((surgical near/3 ablat*) or MAZE procedure):ti,ab,kw (Word variations have been searched)
#11 #7 or #8 or #9 or #10
#12 #6 and #11

MEDLINE OVID

1. Atrial Fibrillation/
2. (atrial adj3 fibrillat*).tw.
3. (auricular* adj3 fibrillat*).tw.
4. (atrium adj3 fibrillat*).tw.
5. atrial arrhythmi*.tw.
6. or/1-5
7. Catheter Ablation/
8. (catheter adj6 (ablat$ or isolat$)).tw.
9. (transcatheter and (ablat$ or isolat$)).tw.
10. ((surgical adj3 ablat$) or MAZE procedure).tw.
11. or/7-10
12. 6 and 11
13. adverse effects.fs.
14. contraindications.fs.
15. poisoning.fs.
16. toxicity.fs.
17. drug effects.fs.
18. (toxi* adj2 (effect or effects or reaction* or event or events or outcome*)).tw.
19. (adverse* adj2 (effect or effects or reaction* or event or events or outcome*)).tw.
20. (side adj3 (effect or effects)).tw.
21. (adr or adrs).tw.
22. or/13-21
23. exp animals/ not humans.sh.
24. 22 not 23
25. 12 and 24
26. randomized controlled trial.pt.
27. controlled clinical trial.pt.
28. randomized.ab.
29. placebo.ab.
30. drug therapy.fs.
31. randomly.ab.
32. trial.ab.
33. groups.ab.
34. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. exp animals/ not humans.sh.
36. 34 not 35
37. 12 and 36

EMBASE OVID

1. heart atrium fibrillation/

2. (atrial adj3 fibrillat*).tw.
3. (auricular* adj3 fibrillat*).tw.
4. (atrium adj3 fibrillat*).tw.
5. atrial arrhythmi*.tw.
6. or/1-5
7. Catheter Ablation/
8. (catheter adj6 (ablat$ or isolat$)).tw.
9. (transcatheter and (ablat$ or isolat$)).tw.
10. ((surgical adj3 ablat$) or MAZE procedure).tw.
11. or/7-10
12. ae.fs.
13. to.fs.
14. co.fs.
15. si.fs.
16. (toxi* adj2 (effect or effects or reaction* or event or events or outcome*)).tw.
17. (adverse* adj2 (effect or effects or reaction* or event or events or outcome*)).tw.
18. (side adj3 (effect or effects)).tw.
19. (adr or adrs).tw.
20. adverse drug reaction/
21. or/12-20
22. (animal/ or nonhuman/) not human/
23. 21 not 22
24. 6 and 11 and 23
25. random$.tw.
26. factorial$.tw.
27. crossover$.tw.
28. cross over$.tw.
29. cross-over$.tw.
30. placebo$.tw.
31. (doubl$ adj blind$).tw.
32. (singl$ adj blind$).tw.
33. assign$.tw.
34. allocat$.tw.
35. volunteer$.tw.
36. crossover procedure/
37. double blind procedure/
38. randomized controlled trial/
39. single blind procedure/
40. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. (animal/ or nonhuman/) not human/
42. 40 not 41
43. 6 and 11 and 42
44. 24 or 43

CONTRIBUTIONS OF AUTHORS

- Jonathan Nyong: screening, statistical advice, and writing.
- Guy Amit: design of study and expert advice on atrial fibrillation.
- Alma J Adler: design of study, screening, and writing.
- Onikepe O Owolabi: screening and writing.
- David Prieto-Merino: statistical advice.
- Pablo Perel: design of study and writing.
- Pier Lambiase: design of study and expert advice on atrial fibrillation.
- Juan Pablo Casas: design of study and writing.
- Carlos A Morillo: design of study, expert advice on atrial fibrillation, and writing.

DECLARATIONS OF INTEREST

- Jonathan Nyong: none known.
- Guy Amit: receives funding from Johnson & Johnson for consultation for work unrelated to the content of this Cochrane review.

- Alma J Adler: none known.
- Onikepe O Owolabi: none known.
- David Prieto-Merino: none known.
- Pablo Perel: none known.
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Internal sources

- No sources of support supplied

External sources

- European Society of Cardiology, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol of the Review, we planned to address the 'percentage of participants needing cardioversion' as a primary outcome but addressed 'participants needing cardioversion' instead; participants needing cardioversion is easier to analyse and interpret.

We planned on searching relevant manufacturers' websites for trial information but did not do this because we searched other relevant websites, more suited to our Review questions instead.

We used a random-effects model to incorporate unexplained moderate heterogeneity where the I^2 statistic was greater than 40%, as opposed to the I^2 statistic greater than 50%, as a more accurate conclusion would be drawn by investigating and using a random-effects model to incorporate an I^2 statistic greater than 40%.

In the protocol of the Review our objective was to determine the effect of ablation to maintin sinus rhythm in patients with persistent or long-standing persistent atrial fibrillation compared to anti-arrhythmic drugs. In our Review we have modified to objective to determine the efficacy and safety of ablation (catheter and surgical) in people with non-paroxysmal (persistent or long-standing persistent) atrial fibrillation compared to antiarrhythmic drugs.

In the protocol of the Review we planned to include only randomised controlled trials (RCTs) of parallel-group design with the individual or cluster as the unit of randomisation. In our Review we included only randomised trials of parallel-group design with the individual as the unit of randomisation.

INDEX TERMS

Medical Subject Headings (MeSH)

*Catheter Ablation [adverse effects]; Anti-Arrhythmia Agents [*therapeutic use]; Atrial Fibrillation [*drug therapy] [*surgery]; Bradycardia [therapy]; Electric Countershock [statistics & numerical data]; Hospitalization [statistics & numerical data]; Pacemaker, Artificial [statistics & numerical data]; Randomized Controlled Trials as Topic; Safety; Treatment Outcome

MeSH check words

Humans; Middle Aged