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[Intervention Protocol]

Catheter ablation for atrial fibrillation

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To determine the efficacy and safety of any catheter ablation in people with first diagnosed, paroxysmal, persistent, and long-standing persistent atrial fibrillation versus any medical therapy.

BACKGROUND

Description of the condition

Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting 37.5 million people worldwide in 2017 (James 2018). Every year, 3 million people are diagnosed with AF. Because of an aging population, as many as 12 million people in the USA, and 18 million in Europe are expected to be affected in the next 30 to 40 years (Chugh 2014;James 2018;Miyasaka 2006). AF is a serious condition, which is associated with high morbidity and mortality, and presents a large burden on health systems. A diagnosis of AF increases the future risk of stroke five-fold, doubles the risk of heart failure, and leads to increased mortality (Calkins 2012; Kirchhof 2017). It is estimated that worldwide, 287,000 deaths were linked to AF in 2017; around 3 million years of life were lost, and another 3 million years of life were spent in disability (Haro Abad 2018; James 2018).

There are five types of AF, based on the presentation, duration, and spontaneous termination of AF episodes: first diagnosed; paroxysmal (self-terminating, lasts for up to seven days); persistent (terminated by cardioversion, lasts longer than seven days); long-standing persistent (lasts for more than one year); and permanent (accepted by the person and their clinician (Hindricks 2021;Kirchhof 2017)). Advances in the management of AF have led to improvements in quality of life and exercise capacity, and have substantially reduced the global burden of stroke (Johnson 2019; Singh 2006). Asymptomatic people, especially those with persistent or permanent AF, are usually treated with rate control, and if needed, anticoagulation; while people with symptoms may require therapy to restore normal sinus rhythm, such as electrical cardioversion (by sending electric signals to the heart through electrodes placed on the chest), antiarrhythmic drugs, ablation procedures, or anticoagulation.

Description of the intervention

Historically, AF was thought to be secondary to spiral depolarisation waves originating in the atria (Link 2016). Early ablative procedures focused on interrupting these atrial fibrillatory waves, initially with surgical methods (Link 2016), and later on with transvenous catheters (Swartz 1994). Catheter ablation of AF has since become one of the most widely conducted electrophysiology procedures (Eckardt 2018).

This is a procedure that interrupts the abnormal circuits by getting rid of small amounts of tissue. This is done through plastic tubes, which are inserted into the veins in the legs. The procedure usually takes two to three hours (www.nhs.uk/conditions/atrial-fibrillation/treatment/).

Various technologies for AF ablation are currently available; the most common uses radiofrequency and cryo energy, both of which induce scarring in the atrial tissues that transmit electrical impulses (Mujović 2017).

In 1998, the ablation focus shifted towards the areas between the pulmonary veins and atrium as a possible trigger for AF (Haïssaguerre 1998). Since then, pulmonary vein isolation has become the cornerstone of AF ablation. Typically, the pulmonary (lung) veins (from which most electrical triggers come) are electrically isolated, preventing them from reaching the atrium and causing atrial fibrillation. Additional triggers originating from non-pulmonary vein areas, such as the left atrium (one of the two smaller chambers of the heart); superior vena cava (a large vein that brings blood back to the heart); coronary sinus (a collection of veins from the heart that join to form a large vessel); right atrium, including the crista terminalis (a crescent-shaped part of the heart muscle that is at the start of the atrial appendage, which is a part of the left atrium); interatrial septum (the wall between the two atria); and the ligament of Marshall (an area between the atrial appendage and the pulmonary veins) can also initiate AF. Ablation of these sites has been proposed, especially in people with non-paroxysmal AF (Haïssaguerre 1998; Link 2016).

Choosing people with more favourable profiles increases the likelihood of procedural success, which can vary from 50% to 80%. Ideal candidates are people with symptomatic paroxysmal AF, with no significant structural heart disease or left atrial enlargement (Link 2016).

AF ablation is considered a low risk procedure, however rarely, it can lead to serious complications, such as vascular access injury**,** cardiac tamponade, stroke, atrio-oesophageal fistula, and pulmonary vein stenosis (Cappato 2010). In most cases, these safety considerations have kept AF ablation as a second-line treatment option to antiarrhythmic drugs, despite the fact it is superior in improving symptoms and overall quality of life (Mujović 2017). AF-ablation and medical therapy also have comparable efficacy in reducing mortality and thromboembolic events (Dagres 2009). AF ablation may also decrease the risk of death in people with atrial fibrillation and heart failure. Therefore, AF ablation is recommended as a first-line treatment in people with heart failure (Hindricks 2021).

How the intervention might work

Ablation for AF is primarily based on the electrical isolation of the pulmonary venous ostium or venous antrum (Haïssaguerre 1998). The isolation of AF triggers by pulmonary vein isolation (PVI) using radiofrequency or cryotherapy is the mainstay of therapy in people with paroxysmal AF. In non-paroxysmal AF, additional AF substrate modification may be needed to improve the procedural success rate (Nyong 2016).

Why it is important to do this review

Current guidelines recommend using AF ablation to restore and maintain sinus rhythm in people with symptomatic paroxysmal, persistent, and probably long-standing persistent AF (Hindricks 2021; January 2019; Kirchhof 2017). Guidelines further recommend AF ablation after the failure of, or intolerance to, antiarrhythmic drug therapy. However, there remains a degree of uncertainty about the optimal rhythm management strategy for people with AF. Recently, the European Heart Rhythm Association (EHRA) and the European Society of Cardiology (ESC) AF guidelines identified some major knowledge gaps on the impact of AF catheter ablation on clinical outcomes, including death, stroke, AF recurrence, and quality of life (Goette 2019; Hindricks 2021). Recent data suggest a prognostic benefit of AF ablation in people with heart failure with reduced ejection fraction. However, there are no conclusive data available on the role of catheter ablation for people with asymptomatic AF, or AF and heart failure with preserved ejection fraction.

While antiarrhythmic medications have been the cornerstone of AF treatment for several years, their success in preventing

recurrences is low to moderate, and they are associated with serious side effects, including increased mortality (e.g. sotalol), ventricular arrhythmias, lung disease, and thyroid and liver dysfunction (Valembois 2019). The evaluation of the optimal treatment strategies, by assessing the efficacy and safety of catheter ablation versus antiarrhythmic drugs, is an ongoing need in AF management. Several recent systematic reviews have mainly concentrated on paroxysmal AF (Cheng 2014; Khan 2014; Nault 2010; Turagam 2021). Reviews of non-paroxysmal AF have included non-randomised and observational studies, and had inconclusive results (Calkins 2009; Saglietto 2020). This Cochrane Review will combine both paroxysmal and non-paroxysmal AF, using Cochrane methodology to assess the best available evidence that evaluates AF ablation treatment strategies.

OBJECTIVES

To determine the efficacy and safety of any catheter ablation in people with first diagnosed, paroxysmal, persistent, and long-standing persistent atrial fibrillation versus any medical therapy.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), randomised at the level of the participant or as a cluster-randomised design. We will include studies reported as full-text, those published as an abstract only, and unpublished data. We will include cross-over trials, but due to the long effects of some alpha 1-antitrypsins (AATs, e.g. amiodarone), we will only include the first period before the cross over.

Types of participants

We will include adults at least 18 years of age, with first diagnosed; paroxysmal (self-terminating, lasts for up to seven days); persistent (terminated by cardioversion, lasts longer than seven days); long-standing persistent (lasts for more than one year), regardless of any concomitant, underlying heart disease. We used definitions from the European Society of Cardiology (ESC) Guidelines for the Management of Patients with atrial fibrillation (AF (Hindricks 2021)).

In trials with mixed populations, that is, trials in which some participants meet the inclusion criteria and others do not, we will attempt to include only the eligible participants, if this information is reported separately, or we are able to obtain it from trial authors. Otherwise, we will include studies with a mixed population if the majority (> 80%) of the participants meet the eligibility criteria.

Types of interventions

We plan one comparison: catheter ablation versus medical rhythm control. We will include pulmonary vein electrical isolation (PVI), with or without other catheter ablation techniques, including superior vena cava isolation, left atrium appendage and posterior wall ablation, crista terminalis ablation, coronary sinus ostium ablation, interatrial septum ablation, and ligament of Marshall ablation.

The comparators will be class I and class III antiarrhythmic drugs approved by the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for treating atrial fibrillation, which include any of the following: flecainide, propafenone, quinidine, amiodarone, sotalol, dofetilide, or dronedarone. Any co-medications, if given equally to all participants, are eligible.

We will exclude studies in which the comparator is rate control, or the intervention is concomitant surgical ablation (that is, surgical atrial fibrillation ablation done during open-heart surgery for another indication or condition).

Types of outcome measures

Reporting one or more of the outcomes of interest is not an inclusion criterion. When a published report does not appear to report one of these outcomes, we will access the trial protocol and contact the trial authors to ascertain whether the outcomes were measured but not reported. We will include relevant trials that measured these outcomes but did not report the data, or did not report them in a usable format, as part of the narrative.

We will consider time-to-first event for participants with multiple events of a given type, e.g. multiple strokes, multiple hospitalisations. We will count the first event for each specific type of event in a participant, and we will assess the outcomes at the longest available follow-up.

Primary outcomes

1. Recurrence of AF
2. All-cause mortality
3. All-cause hospitalisation

For trial purposes, an episode of AF is most commonly defined as a 30-second episode of irregular atrial rhythm. Surveillance for AF is usually accomplished with intermittent electrocardiogram (ECG) recordings at predefined time points, or instigated by self-reporting of symptoms. Many trials conduct surveillance with ambulatory ECG recording, ranging between 24 hours to 7 days, and more recently, with continuous cardiac monitoring, using implantable loop recorders. For people undergoing catheter or surgical ablation, recurrent AF episodes are included if they fall outside the blanking period, which is more than three months after the ablation procedure. Episodes of AF occurring within three months of the ablation procedure do not contribute to the recurrence data, as ablation scar maturation is posited to occur during the first three months, and therefore, is excluded in the assessment of ablation treatment efficacy (Calkins 2012).

Secondary outcomes

1. All-cause mortality or all-cause hospitalisation
2. Death from a cardiovascular or thromboembolic event
3. Cardiac hospitalisation
4. Ischaemic stroke
5. Venous thromboembolic event (deep vein thrombosis or pulmonary embolism)
6. Need for cardioversion
7. Quality of life, measured with, for example with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)

Adverse effects

1. Significant bradycardia

2. Need for a pacemaker
3. Periprocedural complications, such as
   a. cardiac tamponade
   b. transient ischaemic attack (TIA)
   c. atrio-oesophageal fistula
   d. vascular access complications
   e. pulmonary vein stenosis

We will treat the each periprocedural complication as an individual outcome.

Search methods for identification of studies

Electronic searches

We will identify trials by systematically searching the following bibliographic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
- MEDLINE Ovid (from 1946 onwards; see Appendix 1)
- Embase Ovid (from 1980 onwards)
- Conference Proceedings Citation Index – Science (CPCI-S) on Web of Science (Clarivate Analytics, from 1990 onwards)

We will adapt the preliminary search strategy for MEDLINE Ovid to use in the other databases. We will apply the Cochrane sensitivity and precision-maximising RCT filter to MEDLINE Ovid and the adaptations to the other databases, except CENTRAL (Lefebvre 2019).

We will also search the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/) for ongoing or unpublished trials.

We will search all databases from their inception to the present, and impose no restrictions on language of publication or publication status. If we identify papers in a language unknown to the review team, we will seek assistance, which we will acknowledge in the published review.

We will not conduct a separate search for adverse effects of interventions used for the treatment of AF. We will only consider adverse effects described in the included studies.

Searching other resources

We will check reference lists of all included studies and any relevant systematic reviews identified during the literature search for additional references to trials. We will also examine any relevant retraction statements and errata for included studies.

Data collection and analysis

Selection of studies

Two review authors (SAS, SJ) will independently screen titles and abstracts for all the potential studies we identify as a result of the search, and code them as retrieve (eligible, potentially eligible, or unclear) or do not retrieve. If there are any disagreements, we will ask a third review author to arbitrate (SA). We will retrieve the full-text study reports or publications, and two review authors (SAS, SJ) will independently screen the full-text report to identify studies for inclusion, and identify and record reasons for excluding the ineligible studies. We will resolve any disagreement through discussion, or if required, we will consult a third person (SA). We will identify and exclude duplicates, and collate multiple reports of the same study, so that each study, rather than each report, is the unit of interest. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table (Liberati 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one included study. We will extract the following study characteristics.

- Methods: study design, total duration of study, details of any run-in period, number of study centres and location, study setting, and date of study
- Participants: N randomised, N lost to follow-up or withdrawn, N analysed, mean age, age range, gender, paroxysmal or persistant AF, diagnostic criteria for atrial fibrillation, diabetes mellitus, hypertension, previous history of ischaemic heart disease, previous history of heart failure, left atrial size (mean and standard deviation (SD)), CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age 65 to 74, and sex category (female)) score, duration of atrial fibrillation, inclusion criteria, and exclusion criteria
- Interventions: type of ablation and technique used, comparisons, concomitant medications, and excluded medications
- Outcomes: primary and secondary outcomes specified and collected, and time points reported
- Notes: funding for trial, and notable conflicts of interest of trial authors

Two review authors (SAS, SJ) will independently extract outcome data from included studies. We will resolve disagreements by consensus, or by involving a third person (SA). One review author (SAS) will transfer the data into the Review Manager 5 file (Review Manager 2020). A second review author (SA) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (SAS, SJ) will independently assess the risk of bias for each study using version one of the Cochrane risk of bias (RoB 1) tool, which assesses the criteria outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We will resolve any disagreements by discussion, or by involving another author (SA). We will assess the risk of bias for 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

In addition to the above, we will also assess the following biases for cluster-randomised trials (Higgins 2017).

1. Recruitment bias
2. Baseline imbalance
3. Loss of clusters
4. Incorrect analysis
5. Comparability with individually randomised trials

We will assess the risk of bias in all included studies. We will grade each potential source of bias as high, low, or unclear. We will also provide a quote from the study report, together with justification for the judgement, in the risk of bias table. We will summarise the risk of bias judgements across the studies for each of the domains listed for each outcome. The overall risk of bias for the result is the least favourable assessment across the domains of bias.

If information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the risk of bias table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RR) with 95% confidence intervals (CI), and continuous data as mean difference (MD), or standardised mean difference with 95% CI. We will enter data presented as a scale with a consistent direction of effect. We will narratively describe skewed data reported as medians and interquartile ranges.

We will analyse continuous data as MD with 95% CIs provided the studies all used the same tool to measure the outcome. If studies used different tools to measure an outcome, we will use the SMD with 95% CIs instead. For SMD, we will use Hedges' (adjusted) g, which uses a pooled SD in the denominator – an estimate of the SD using outcome data from intervention groups, based on the assumption that the SDs in the two groups are similar (Higgins 2020). We will use the one-half standard deviation benchmark of an outcome measure, which suggests that an improvement of more than one-half of the outcome score's standard deviation is a minimal clinically important difference (Farivar 2020). For continuous data provided as a mean difference or change from baseline, we will try to extract data for both, however our preference is change from baseline data, as these results can be combined with MD or SMD).

For quality of life outcomes, we will use the SF-36, and will transform SMDs from other dyspnoea scales to the SF-36. We will present the results as SMDs.

Unit of analysis issues

We will include parallel design and cluster-randomised trials. If we find cluster-randomised trials, we will ensure that we use appropriate analysis to account for the cluster design, according to MECIR PR30 and C70, and sections 6.2, 23.1, and 23.2 in the *Cochrane Handbook* (Higgins 2021). If the trial authors do not report the appropriate analysis, we will calculate the correct estimates using the intracluster correlation coefficient. If we include both individual- and cluster-randomised clinical trials, we will analyse the results separately.

If we have trials that could contribute multiple, correlated, comparisons with multiple treatment arms, we will combine groups to create a single pair-wise comparison for analysis. For continuous outcomes, we will carry out multiple pair-wise comparisons, for which we will split the control group accordingly, to avoid double-counting. If there are studies that have measured an outcome more than once, with more than one scale, then we will establish a hierarchy of measures, using the SF-36 as our first preference.

For multiple observations on participants, we will select the longest follow-up from each study.

For cross-over trials, we will analyse data from the first period only, due to issues with carry-over effects.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data (e.g. when a study is identified as abstract only). When possible, we will use the RevMan 5 calculator to calculate missing SD, using other data from the trial, such as CIs, based on the methods outlined in the *Cochrane Handbook (*Higgins 2019b*).* When this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results with a sensitivity analysis.

Assessment of heterogeneity

We will inspect forest plots visually to consider the direction and magnitude of effects and the degree of overlap between CIs. We will use the I^2 statistic to measure heterogeneity among the trials in each analysis, but acknowledge that there is substantial uncertainty in the value of I^2 when there are only a small number of studies, We will also consider the P value from the Chi^2 test. If we identify substantial heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis. We will follow the recommendations for threshold outlined in Section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017; Higgins 2019a)).

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

We will ultimately consider not conducting an overall meta-analysis, if the subgroup analyses show different effects and the overall meta-analysis shows substantial or considerable statistical heterogeneity (assessed by visual inspection of forest plots and I^2 statistic (Higgins 2019a)).

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study biases for the primary outcomes.

Data synthesis

We will undertake meta-analyses only when this is meaningful, i.e. if the treatments, participants, and the underlying clinical questions are similar enough for pooling to make sense. All studies will be included in the primary analysis; we will assess the potential effects

of studies at high risk or unclear risk with sensitivity analyses. (Boutron 2020).

We will use a random-effects model, due to the high probability of heterogeneity among the RCTs that will be included in this review. We will also run tests for heterogeneity, but as these tests are known to have low power (and also a non-significance test does not prove the null hypothesis of homogeneity), we will not rely solely on these tests to choose between fixed-effect or random-effects models. We think that it is more appropriate to provide the results from both approaches, and from the heterogeneity statistics and tests. If both models coincide there should be no problem in reaching a conclusion, but if they do not then we will discuss the discrepancies in the light of the evidence. Each model implies strong assumptions and has to be interpreted with caution.

If a meta-analysis is not possible, we will present our data narratively, using the nine-point checklist in the new SWiM (synthesis without meta-analysis) reporting guideline. We will group studies by intervention; use vote counting based on the direction of effect; and present characteristics, such as study design, sample sizes, and risk of bias. We will describe synthesis findings, clarifying which studies contribute to each synthesis, and also explain the limitations of the synthesis (Campbell 2020).

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce heterogeneity into the results of the review, and plan to carry out subgroup analyses for them with an investigation of interactions on all outcomes (Review Manager 2020):

1. Paroxysmal versus persistent atrial fibrillation
2. Left atrial size: normal (≤ 28 mL/m^2) or increased (mild: 29 mL/m^2 to 33 mL/m^2; moderate: 34 mL/m^2 to 39 mL/m^2; or severe: ≥ 40 mL/m^2)
3. Intervention with antiarrhythmic drugs (during + post-ablation) versus without anti-arrhythmic drugs
4. Left ventricular function (50% to 70% ejection fraction) versus moderate (30% to 50% ejection fraction) versus severe (< 30% ejection fraction (Patel 2011))
5. By CHA2DS2-VASc score (0 to 1 and > 1; C: congestive heart failure, H: hypertension, A2: age ≥75 years, D: diabetes, S: stroke, V: vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque), A: Age 65 years to 74 years, Sc:**s**ex category (i.e. female) (Hindricks 2021))
6. flecainide, propafenone, quinidine, amiodarone, sotalol, dofetilide, or dronedarone individually versus ablation
7. Class I (sodium channel blockers) versus Class III (potassium channel blockers) antiarrhythmic agents individually versus ablation.

For each of these variables, we will carry out a meta-analysis in each category and measure the variability between them. For each variable that is summarised with a mean and an SD in each study (e.g. left atrial size or left ventricular function), we will carry out a meta-regression of the study effect on the variable means. For each variable that is summarised in each study with a proportion (e.g. proportion of catheter versus surgical ablation), we will carry out a meta-regression of the study effect on that proportion.

Sensitivity analysis

We plan to carry out the following sensitivity analyses, to test whether key methodological factors or decisions have affected the main result.

1. exclude randomised studies with an overall high and unclear risk of bias
2. explore the impact of missing data. If we identify studies with missing data that we are unable to obtain, we will repeat the analyses excluding them, to find their impact on the primary analyses.
3. use a fixed-effects model

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table and include the following outcomes:

1. Recurrence of AF
2. All-cause mortality
3. All-cause hospitalisation
4. All-cause mortality or hospitalisation
5. Death from a cardiovascular or thromboembolic event
6. Cardiac hospitalisation
7. Ischaemic stroke

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019), using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of the evidence using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

Two review authors (SAS, SJ*)* will independently make judgements about the quality of the evidence quality, with disagreements resolved by discussion, or involving a third author (SA). We will justify, document, and incorporated the judgements into our reporting of results for each outcome.

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APPENDICES

Appendix 1. Preliminary MEDLINE Ovid search strategy

1 Atrial Fibrillation/ (56340)

2 (atrial adj3 fibrillat*).tw. (71644)

3 (auricular* adj3 fibrillat*).tw. (977)

4 (atrium adj3 fibrillat*).tw. (186)

5 atrial arrhythmi*.tw. (3462)

6 AF.tw. (40876)

7 1 or 2 or 3 or 4 or 5 or 6 (99228)

8 Catheter Ablation/ (32528)

9 (catheter and (ablat* or isolate*)).tw. (20888)

10 ((cardiac or AF) and ablat*).tw. (14434)

11 (transcatheter and (ablat* or isolate*)).tw. (1826)

12 8 or 9 or 10 or 11 (48752)

13 7 and 12 (15099)

14 randomized controlled trial.pt. (515641)

15 controlled clinical trial.pt. (93896)

16 randomized.ab. (496133)

17 placebo.ab. (211852)

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18 clinical trials as topic.sh. (193405)

19 randomly.ab. (343068)

20 trial.ti. (227164)

21 14 or 15 or 16 or 17 or 18 or 19 or 20 (1320514)

22 exp animals/ not humans.sh. (4747614)

23 21 not 22 (1215725)

24 13 and 23 (1651)

CONTRIBUTIONS OF AUTHORS

S Al Said, M Ahmad, and S Alabed conceived, designed, co-ordinated, and drafted the protocol.

P Garg, M Qintar, A Kyriacou, S Jenkins, M Ahmad, N Verma, R Providencia, and J Camm provided clinical expertise and general advice and revised the protocol.

All authors approved the final version of the protocol, and will do the same with the final manuscript.

DECLARATIONS OF INTEREST

S Al Said: none known

P Garg: none known

M Qintar: none known

A Kyriacou: none known

S Jenkins: none known

M Ahmad: none known

N Verma: personal fees from Medtronic and Biotronik (educational presentations); Abbott (travel); institutional payments from Attune Medical (research grant)

R Providencia: none known

J Camm: personal fees from Biotronic (DSMB Chair for CASTLE-AF); Daiichi Sankyo (trial steering committee, anticoagulation peri-ablation); Abbott (events committee, ablation techniques for atrial fibrillation, leadless pacemaker); Boehringer Ingelheim, Boston Scientific and Sanofi (board membership); Bayer, BMS/Pfizer, and Daiichi Sankyo (consultancy); Medtronic, Bayer, and Abbott (lectures); Wiley and Oxford University Press (royalties), Daiichi Sankyo (educational presentations); Acesion, Omeicos, and Milestone Incarda (new antiarrhythmic drug developments); institutional payments from Boehringer Ingelheim, Bayer, and Daiichi Sankyo (research grants). Author of a recent publication in New England Journal of Medicine (EAST-AFNET 4 trial), which demonstrated that early rhythm control was preferable to guidelines mandated rate control; ablation was used for a minority of patients for rhythm control.

S Alabed: none known

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