

BMJ Open Surgical ablation of atrial fibrillation: a protocol for a systematic review and meta-analysis of randomised controlled trials

Graham R McClure,¹ Emilie P Belley-Cote,^{2,3,4,5} Rohit K Singal,^{6,7} Iqbal H Jaffer,^{8,9} Nazari Dvirnik,^{2,4,9} Kevin R An,¹ Gabriel Fortin,⁵ Jessica Spence,^{2,10} Richard P Whitlock^{2,4,9}

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For numbered affiliations see end of article.

Correspondence to

Dr Richard P Whitlock;
Richard.Whitlock@phri.ca

ABSTRACT

Introduction: Atrial fibrillation (AF) affects 10% of patients undergoing cardiac surgery and is an independent risk factor for all-cause mortality, ischaemic stroke and heart failure. Surgical AF ablation has been shown to significantly improve maintenance of sinus rhythm, however, small to medium size trials conducted to date lack the power required to assess patient-important outcomes such as mortality, stroke, heart failure and health-related quality of life. Moreover, a recent randomised trial (RCT) suggested harm by surgical AF ablation with an almost threefold increase in the requirement for permanent pacemaker postablation. We aim to perform a systematic review and meta-analysis to evaluate efficacy and safety of surgical AF ablation compared to no surgical ablation.

Methods and analysis: We will search Cochrane CENTRAL, MEDLINE and EMBASE for RCTs evaluating the use of surgical AF ablation, including any lesion set, versus no surgical AF ablation in adults with AF undergoing any type of cardiac surgery. Outcomes of interest include mortality, embolic events, quality of life, rehospitalisation, freedom from AF and adverse events, including need for pacemaker and worsening heart failure. Independently and in duplicate, reviewers will screen references, assess eligibility of potentially relevant studies using predefined eligibility criteria and collect data using prepiloted forms. We will pool data using a random effects model and present results as relative risk with 95% CIs for dichotomous outcomes and as mean difference with 95% CI for continuous outcomes. We will assess risk of bias using the Cochrane Collaboration tool, and quality of evidence with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Ethics and dissemination: Our results will help guide clinical practice by providing the most comprehensive analysis of risks and benefits associated with the procedure. Our results will be disseminated through publication in peer-reviewed journals and conference presentations.

Trial registration number: CRD42015025988.

Strengths and limitations of this study

- Most up-to-date review of literature on surgical atrial fibrillation ablation, including largest randomised controlled trial on the topic from *NEJM* 2015.
- Rigorous search strategy including grey literature and non-indexed trials.
- Quality of evidence assessment using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.
- Previous systematic reviews on the topic demonstrated small expected sample size in published literature.
- Broad range of lesion sets and energies reflecting heterogeneity in clinical practice.

DESCRIPTION OF THE PROBLEM

Atrial fibrillation (AF) is the most prevalent tachyarrhythmia worldwide, affecting 2.8% of the population in the Western world.¹ The pathophysiology of AF is multifactorial, hence, it is viewed as a common phenotype for a range of disease pathways.²⁻⁴ Broadly, AF results either from (1) structural change to the atria including dilation, fibrosis, ischaemia and hypertrophy, or (2) from pathological changes to atrial electrical activity including changes to conduction, cellular automaticity or from autonomic nervous system dysregulation.²⁻⁴

AF requires a trigger to be initiated and then appropriate conditions to be propagated. The trigger is classically thought to originate from ectopic focal activations in the atria outside of the sinoatrial node. Propagation then results either from recurrent ectopic foci or, alternatively, by re-entrant circuits of atrial activation.²⁻⁴

AF is an independent risk factor for ischaemic stroke, heart failure and mortality.^{5 6} Additional haemodynamic consequences and symptoms of AF vary from patient to patient but include fatigue, dyspnoea and palpitations. Consequently, maintenance of sinus rhythm in the setting of AF is thought to be associated with decreased mortality, stroke and heart failure,⁷ in addition to symptom reduction and improved quality of life.⁸

The rates of hospitalisation in Canada related to AF are increasing.^{5 9} This issue is compounded by the fact that AF is a high cost-impact condition with an average annual per-patient reported cost of \$5450±3624 (CAD), contributed mostly from acute care services.¹⁰

DESCRIPTION OF THE INTERVENTION

Surgical AF ablation aims to inhibit the generation and propagation of macro-reentry circuits in the atria, using surgical lesions to block electrical conduction with the goal of eliminating AF and maintaining atrial contraction.^{11 12} Performed concomitantly with another indicated cardiac surgery, the technique has been shown to reduce the burden of AF on follow-up.^{12–15} The lesions used for this procedure are categorised into three groups: pulmonary vein isolation, left atrial lesion sets and biatrial lesion sets. These lesions are commonly generated by one of three main methods: radio frequency ablation, cryoablation or cut-and-sew. The literature directly comparing the efficacy of the different lesion sets and lesion energies is limited.¹²

HOW THE INTERVENTION MIGHT WORK

AF requires a trigger to be initiated and an appropriate substrate to propagate the arrhythmia. Based on this model, interventions that mechanically inhibit re-entrant circuits have been developed (eg, Maze procedure), where surgical lesions are placed to physically inhibit re-entrant circuit propagation.^{11 12 16} The literature suggests that electrically isolating one or both atria during cardiac surgery prevents AF recurrence.^{12 16}

WHY IS IT IMPORTANT TO DO THIS REVIEW?

Both the Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/European Cardiac Arrhythmia Society (ECAS) consensus statement and the American College of Cardiology (ACC) guidelines currently consider surgical AF ablation concomitant to cardiac surgery a reasonable treatment for patients with persistent or permanent AF.^{2 15} However, supporting evidence is based on the maintenance of sinus rhythm at 6 and 12 months, and further investigation is required to establish impact on long-term, patient-important outcomes, including stroke, heart failure, health-related quality of life and mortality.^{2 14 15} The small to medium size trials conducted lack the power required to assess these outcomes.^{2 14 15} Of further concern, a recent randomised trial suggested harm from surgical ablation,

with an almost threefold increase in the requirement for permanent pacemaker postprocedure.¹³

We intend to evaluate the impact of this widely performed procedure on patient-important, long-term outcomes by conducting a systematic review of randomised trials that assesses the relative benefits and risks associated with surgical AF ablation in patients undergoing cardiac surgery.

RESEARCH QUESTION

In patients with a history of AF undergoing cardiac surgery, what is the impact of concomitant surgical AF ablation, using any lesion set or energy, compared to no surgical AF ablation? We will assess this question based on the following outcomes:

- ▶ Freedom from AF
- ▶ Mortality
- ▶ Myocardial infarction (MI)
- ▶ Stroke
- ▶ Ischaemic stroke (including transient ischaemic attacks (TIA))
- ▶ Pulmonary embolism
- ▶ Worsening heart failure
- ▶ Rehospitalisation
- ▶ Readmission for cardiovascular causes
- ▶ Postoperative emergency room visits
- ▶ Intensive care unit (ICU) mortality
- ▶ Hospital mortality
- ▶ Permanent pacemaker requirement (at hospital discharge and latest follow-up)
- ▶ Atrioesophageal perforation
- ▶ Deep sternal wound infection
- ▶ Hospital and ICU length of stay (LOS)
- ▶ Postoperative bleeding
- ▶ Health-related quality of life (HrQoL).

METHODS

Eligibility criteria

Types of studies

Only randomised trials will be included in this systematic review. Quasi-randomised and observational studies will be excluded. No language constraints will be placed.

Types of participants

The population of interest includes all adult patients (18 years of age and older) undergoing any type of cardiac surgery with a documented history of paroxysmal, persistent or permanent AF. We will exclude animal studies.

Types of interventions

The intervention of interest is the use of any surgical AF ablation during cardiac surgery, regardless of lesion set. We will exclude studies where catheter ablation was performed after cardiac surgery.

Types of outcome

Primary outcomes include freedom from AF at 6 and 12 months, HrQoL as reported by any standardised and validated instrument, mortality, ischaemic stroke (including TIA with positive imaging) and pacemaker insertion at latest follow-up.

Secondary outcomes include (at latest follow-up unless otherwise specified) TIA, pulmonary embolism, rehospitalisation, cardiovascular rehospitalisation, emergency room visits, LOS during index hospitalisation, MI, worsening heart failure (defined as an increase in one or more classes in New York Heart Association (NYHA) classification, pacemaker implantation, atrio-oesophageal perforation, postoperative bleeding and deep sternal wound infection).

Search strategy

Databases

We will search CENTRAL, MEDLINE and EMBASE from inception to May 2016, using pretested SIGN filters (<http://www.sign.ac.uk>) to select for randomised controlled trials. Online supplementary appendices 1 and 2 for complete MEDLINE and EMBASE search strategies.

Other sources (grey literature)

We will review Clinicaltrials.gov, ISRCTN Register and WHO ICTRP for relevant unpublished studies. We will also review the references of included studies and prior systematic reviews on the topic for other potentially relevant studies. We will review conference proceedings for American Heart Association (AHA), American College of Cardiology (ACC), American Association for Thoracic Surgery (AATS) and European Society of Cardiology (ESC) meetings in the last 2 years. Finally, we will contact experts in the field to see if they are aware of other relevant studies.

Study selection process

After initial search results are obtained, two independent reviewers will assess eligibility of each study to be included in the review using specific eligibility criteria. The kappa statistic¹⁷ will be used to measure agreement between reviewers. Titles and abstracts of each reference will be reviewed in duplicate to assess relevance to the review. Any reference deemed relevant by either reviewer will be retrieved in full text for full article review. Full article review will be performed independently by two reviewers. Studies will be included in the review if they meet all eligibility criteria.

Studies excluded after full text review will have the most relevant justification for exclusion recorded. Any disagreement will be resolved through discussion between reviewers and consensus decision as to eligibility. If consensus cannot be reached, a third party will be involved in decision-making. In the event that information regarding one eligibility criterion is not provided but all other criteria are met, the authors of the paper in question will be contacted for further information.

The article will be listed as 'unclear eligibility' until the information is available.

Data collection

After identification of all eligible studies, data extraction will be carried out independently and in duplicate using prepiloted forms (see online supplementary appendix 3). Data collected will include study characteristics, population characteristics, details of procedures performed (including lesion sets and energy), follow-up assessment method for the verification of freedom from AF, as well as all relevant primary and secondary outcomes outlined previously. Data disagreement will be resolved through discussion or deferral to an outside third party for final decision. In the event that outcome data are not available in the study report, additional information will be requested from the corresponding author. If no response is received after two contact attempts over a 2-week period, the data will be deemed unavailable.

Assessment of risk of bias

Using the Cochrane Collaboration tool,¹⁸ two reviewers will independently assess the risk of bias for each included study. The reviewers will evaluate risk of bias as 'low', 'high' or 'unclear' for six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting and other sources of bias. Overall risk of bias for each paper will be considered 'low' if all risk of bias domains are ranked 'low', 'unclear' if at least one domain is ranked 'unclear' without any domains ranked as 'high', and 'high' if one or more domain is ranked as 'high' risk of bias. The standards for adequacy in each domain are as follows.

Random sequence generation (selection bias)

Sequence generation will be considered adequately randomised if it is generated from a computer randomisation generator or a published table of random values. Coin tosses or dice rolls will also be considered adequate methods of sequence randomisation.

Allocation concealment

We will deem allocation concealment adequate if consistent measures have been taken to ensure that a participant's allocation is not known until they are assigned to a trial arm.

Blinding of participants and personnel

If it is explicitly stated that specific measures were taken to ensure patients were unaware of their trial arm assignment and personnel who may practically be blinded have been, the patient and personnel blinding will be considered adequate. Risk of bias due to blinding will be assessed for each outcome in each study.

Blinding of outcome assessment

Blinding of outcome assessors will be considered adequate if all assessors and outcome adjudicators who may practically be blinded have measures taken to ensure that they are.

Incomplete outcome assessment

Whenever data regarding the number of patients assessed at different stages of the trial is available, we will assess for significant patient loss to follow-up not explainable by random chance for each reported outcome.

Selective reporting

Each included study with a published protocol will be assessed for incomplete outcome reporting. Reporting will be considered adequate if all prespecified outcomes are included and reported in full. Studies without published protocols available for review will be graded as 'unclear'.

Other sources of bias

Any other apparent sources of bias identified such as source of funding and authors' conflict of interest will be assessed and recorded by each independent reviewer.

Data analyses and assessment of heterogeneity

A random effects model will be used to pool the relevant studies to summarise the evidence using the DerSimonian and Laird method.¹⁹ The results will be presented as relative risk (RR) with 95% CIs for dichotomous outcomes and as mean difference (MD) with 95% CI for continuous outcomes. For dichotomous outcomes, we will assess variance and adjust for outcomes with zero observations using the Mantel-Haenszel method,²⁰ and in continuous outcomes we will assess by inverse variance. The pooled results for HrQoL scales will be presented as standardised mean differences (SMD) with 95% CI. Before pooling any outcome, we will evaluate whether or not it is appropriate based on clinical and methodological heterogeneity, including population characteristics and used assessment tools. Should they be inappropriate for combination we will present the results of each study independently. Further, if we assess that statistics are appropriate to be pooled, we will assess for heterogeneity using the χ^2 test for homogeneity and the I^2 statistic. We will conduct subgroup analyses to assess clinical and methodological sources of heterogeneity in intervention effect if the I^2 is >50%, consistent with substantial heterogeneity. We will look for publication bias in each outcome using funnel plots. These analyses will be performed using Revman 5.3 (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). If visual inspection of the funnel plot suggests potential publication bias, we will perform the Egger test for continuous outcomes or the arcsine test for dichotomous outcomes using Stata

V.12 (StataCorp. 2011. Stata Statistical Software: Release V.12. College Station, Texas: StataCorp LP). Finally, we will conduct a plausible worst-case scenario analysis of each outcome to account for missing potentially non-zero study data.²¹

A priori hypotheses to explain clinical heterogeneity

Sources of clinical heterogeneity are expected to arise from surgical lesion set, concomitant surgical procedure, study population AF type and potential study risk of bias. To assess for significant heterogeneity, we will perform the following subgroup analyses: (1) paroxysmal and persistent versus permanent and long-standing persistent AF, hypothesising that patients with paroxysmal and persistent AF will derive more benefit; (2) biatrial AF ablation versus left sided ablation only, hypothesising that patients undergoing biatrial AF ablation only will derive more benefit; (3) studies at low risk of bias versus at moderate or high risk of bias, hypothesising that studies at high risk of bias will suggest more benefit;²² (4) stand-alone procedure versus concomitant procedure, hypothesising that patients undergoing a stand-alone AF ablation procedure will derive more benefit; And (5) concomitant left atrial appendage (LAA) occlusion versus no concomitant LAA occlusion, hypothesising that patients undergoing concomitant LAA occlusion will derive more benefit.

Assessment of pooled effect estimates

Confidence in the pooled effects estimates will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.²³ According to GRADE, data from randomised controlled trials are considered high quality evidence but can be rated down according to risk of bias, imprecision, inconsistency, indirectness or publication bias.

DISCUSSION

Surgical AF ablation is a technique that is widely used in cardiac surgery despite evidence limitations that include small study size, inconsistent secondary outcomes and varying lengths of follow-up. This review will summarise evidence derived from RCTs regarding the safety and efficacy of surgical AF ablation. By pooling available data, our review will have more power to evaluate patient-important outcomes. New trials have been published since the last systematic reviews of surgical AF ablation including the largest RCT conducted to date on the topic. Compared to previously published reviews,^{24 25} this protocol uses the GRADE framework to summarise confidence in estimates of effect, uses a more rigorous search strategy and will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see online supplementary appendix 4).

Author affiliations

- ¹Michael G. DeGroot School of Medicine, McMaster University, Hamilton, Ontario, Canada
- ²Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada
- ³Department of Medicine, McMaster University, Hamilton, Ontario, Canada
- ⁴Population Health Research Institute, Hamilton, Ontario, Canada
- ⁵Department of Medicine, Université de Sherbrooke, Sherbrooke, Quebec, Canada
- ⁶Department of Surgery, University of Manitoba, Manitoba, Ontario, Canada
- ⁷I.H. Asper Clinical Research Institute, Winnipeg, Manitoba, Canada
- ⁸Thrombosis & Atherosclerosis Research Institute (TaARI), McMaster University, Hamilton, Ontario, Canada
- ⁹Division of Cardiac Surgery, McMaster University, Hamilton, Ontario, Canada
- ¹⁰Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada

Contributors RPW, EPB-C and GRM developed the initial concept and search strategy for this work. GRM, EPB-C, RKS, IHJ, ND, KRA, GF, JS and RPW participated in the protocol design process with subject matter expertise provided. RPW, RKS, IHJ and ND contributed to cardiovascular surgery. JS contributed to statistical analysis. EBC and RW contributed to clinical epidemiology. Data abstraction forms were designed by EPB-C, GRM, RPW, IHJ, ND, KRA and GF. GRM, EPB-C, RKS, IHJ, ND, KRA, GF, JS and RPW contributed directly to the drafting of the final protocol and have reviewed and approved the final work prior to submission.

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REFERENCES

- Ball J, Carrington MJ, McMurray JJV, *et al.* Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. *Int J Cardiol* 2013;167:1807–24.
- January CT, Wann LS, Alpert JS, *et al.* 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;130:2071–104.
- Nattel S. New ideas about atrial fibrillation 50 years on. *Nature* 2002;415:219–26.
- Schotten U, Verheule S, Kirchhof P, *et al.* Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiol Rev* 2011;91:265–325.
- Benjamin EJ, Wolf PA, D'Agostino RB, *et al.* Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98:946–52.
- Stewart S, Hart CL, Hole DJ, *et al.* A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;113:359–64.
- Friberg L, Tabrizi F, Englund A. Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: data from Swedish health registries. *Eur Heart J* 2016;37:2478–87.
- Van Gelder IC, Hagens VE, Bosker HA, *et al.* A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;347:1834–40.
- Humphries KH, Jackevicius C, Gong Y, *et al.* Population rates of hospitalization for atrial fibrillation/flutter in Canada. *Can J Cardiol* 2004;20:869–76.
- Wodchis WP, Bhatia RS, Leblanc K, *et al.* A review of the cost of atrial fibrillation. *Value Health* 2012;15:240–8.
- Cox JL, Schuessler RB, D'Agostino HJ, *et al.* The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. *J Thorac Cardiovasc Surg* 1991;101:569–83.
- Toeg HD, Al-Atassi T, Lam BK. Atrial fibrillation therapies: lest we forget surgery. *Can J Cardiol* 2014;30:590–7.
- Gillinov AM, Gelijns AC, Parides MK, *et al.* Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med* 2015;372:1399–409.
- Ad N, Cheng DCH, Martin J, *et al.* Surgical ablation for atrial fibrillation in cardiac surgery: a Consensus Statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2009. *Innovations (Phila)* 2010;5:74–83.
- Calkins H, Kuck KH, Cappato R, *et al.* 2012 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;14:528–606.
- Cox JL, Boineau JP, Schuessler RB, *et al.* Five-year experience with the maze procedure for atrial fibrillation. *Ann Thorac Surg* 1993;56:814–23; discussion 823–4.
- Cohen J. A Coefficient of agreement for nominal scales. *Educ Psychol Meas* 1960;20:37–46.
- Higgins JPT, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
- 16.9.2 Studies with zero-cell counts. http://handbook.cochrane.org/chapter_16/16_9_2_studies_with_zero_cell_counts.htm (accessed 7 Aug 2016).
- Akl EA, Briel M, You JJ, *et al.* Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): systematic review. *BMJ* 2012;344:e2809.
- Moher D, Pham B, Jones A, *et al.* Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;352:609–13.
- Guyatt GH, Oxman AD, Schünemann HJ, *et al.* GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol* 2011;64:380–2.
- Phan K, Xie A, Tian DH, *et al.* Systematic review and meta-analysis of surgical ablation for atrial fibrillation during mitral valve surgery. *Ann Cardiothorac Surg* 2014;3:3–14.
- Phan K, Xie A, La Meir M, *et al.* Surgical ablation for treatment of atrial fibrillation in cardiac surgery: a cumulative meta-analysis of randomised controlled trials. *Heart* 2014;100:722–30.