BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064861
Article Type:	Protocol
Date Submitted by the Author:	17-May-2022
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Keywords:	Adult cardiology < CARDIOLOGY, Valvular heart disease < CARDIOLOGY, SURGERY

Title: Bi-atrial versus left atrial ablation for patients with rheumatic mitral valve disease and non-paroxysmal atrial fibrillation (ABLATION): Rationale, design and study protocol for a multicenter randomized controlled trial

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Key words: Atrial fibrillation, surgical ablation, bi-atrial ablation, rheumatic mitral valve disease, mitral operations

Word count: 5868; Figures: 1 Tables: 2

Strengths and limitations of this study

- The trial is the first multicenter randomized controlled trial with large sample size to evaluate the efficacy of bi-atrial ablation for patients with rheumatic mitral valve disease (RMVD) and non-paroxysmal atrial fibrillation (AF).
- In order to clarify the topic that whether the additional right atrial ablation to left atrial ablation increases the risk of permanent pacemaker implantation, we also evaluate the incidence of permanent pacemaker implantation in ABALTION trial as the key secondary endpoint.
- In order to reduce the missed diagnosis rate of recurrent paroxysmal AF, we assess the primary endpoint of the survival rate without any recurrence of atrial tachyarrhythmias by means of 3-day continuous Holter monitoring at 6-month and 12-month follow-up after surgery.
- All surgeons are required to watch the video of standard Cox-Maze Ⅳ procedure and their surgical ablation procedures will be recorded before the trial, and incorrect or irregular manipulation will be reported back to surgeons, which is initiated to eliminate the impact of different tools and lesions on the results.

ABSTRACT

Introduction: Atrial fibrillation (AF) is common in patients with rheumatic mitral valve disease (RMVD) and increase the risk of stroke and death. Bi-atrial or left atrial ablation remains controversial for treatment of AF during mitral valve surgery. The study aims to compare the effectiveness and safety of bi-atrial ablation with those of left atrial ablation among patients with RMVD and persistent or longstanding persistent AF.

Methods and analysis: The ABALTION trial (Bi-atrial versus Left Atrial Ablation for Patients with RMVD and Non-paroxysmal AF) is a prospective, multicenter, randomized controlled study. The trial will randomly assign 320 patients with RMVD and persistent or long-standing persistent AF to bi-atrial ablation procedure or left atrial ablation procedure in a 1:1 randomization. The primary end point is freedom from documented AF, atrial flutter, or atrial tachycardia of more than 30 seconds at 12 months after surgery off antiarrhythmic drugs. Key secondary endpoint is the survival rate without permanent pacemaker implantation at 12 months after surgery. Secondary outcomes include the survival rate without any recurrence of atrial tachyarrhythmias with antiarrhythmic drugs, AF burden, incidence of adverse events and cardiac function documented by echocardiography at 12 months after operation.

Ethics and dissemination: The central ethics committee at Fuwai Hospital approved the ABLATION trial. The results of this study will be disseminated through publications in peer-reviewed journals and conference presentations.

Trial registration number: ClinicalTrials.gov, identifier NCT05021601.

INTRODUCTION

Rheumatic heart disease (RHD) remains endemic among vulnerable groups in many low- and middle-income countries, and resource-limited regions of high-income countries[1 2]. About one-third of patients with RHD have atrial fibrillation (AF), with an incidence of AF almost triples every five years after diagnosis of RHD, and prevalence of AF is higher in severe mitral valve disease comparing with severe aortic disease[3]. In patients with RHD, AF is associated with increased prevalence of heart failure, stroke, peripheral embolism and death[4-7]. Especially, about 80% of the strokes in patients with RHD occur in patients with mitral stenosis and AF[8].

Guidelines recommended that surgical ablation for AF could be performed without additional risk of operative mortality or major morbidity, and was recommended at the time of concomitant mitral valve (MV) operations to restore sinus rhythm (Class I, Level A)[9]. A. Marc Gillinov et al reported the addition of surgical ablation to MV surgery significantly increased the rate of freedom from AF at 1 year among patients with persistent or long-standing persistent AF in a multicenter randomized controlled trial (RCT)[10]. Similarly, some studies concluded that the additional surgical ablation also decreased the risk of stroke or death and increased early and long-term sinus rhythm maintenance in patients with AF and RMVD[11-13].

However, there has been debate on the standard surgical ablation strategy during MV operations. Generally, bi-atrial (BA) lesion set could be created during surgical ablation because the open left atrium facilitates a BA ablation procedure, nevertheless, others believed that adding right atrial ablation had no influence on freedom from AF and conversely increased the risk of permanent pacemaker implantation. The discrepancy on the efficacy and

safety between BA and left atrial (LA) ablation was also reported in the past years, whether in patients with MV disease or in patients with RMVD[14].

Patients with RMVD usually have a long history and relatively severe LA remodeling, progressive pulmonary hypertension, secondary tricuspid valve regurgitation or rheumatic tricuspid valve abnormalities, which can also contribute to severe right atrial remodeling[15 16]. The rationality of BA ablation is stronger in patients with RMVD and AF, however, the increased risk of permanent pacemaker implantation should not be neglected due to right atrial remodeling and fibrosis. To our knowledge, the only RCT reported a confused results that BA ablation was not superior to LA ablation in patients with RMVD and AF (P=0.09) and no conclusion on the permanent pacemaker implantation due to the limited sample[14]. It might also be noted that all lesions were create by mono-polar radiofrequency pen which is replaced by bipolar radiofrequency clamp in majority of lesions now.

To sum up, there is no sufficient evidence to determine the safety and potential benefits of BA ablation procedure when comparing with those of LA ablation procedure in patients with RMVD and non-paroxysmal AF. We designed this multi-center prospective RCT to compare the effectiveness and safety of BA ablation with LA ablation strategies in patients with RMVD and non-paroxysmal AF.

METHODS AND ANALYSIS

Study objective

The ABALTION trial is designed to examine the hypothesis that for patients with RMVD and non-paroxysmal AF, BA ablation is superior to LA ablation in the survival rate without any recurrence of atrial tachyarrhythmias in the absence of antiarrhythmic drugs, and non-inferior to LA ablation in the survival rate without permanent pacemaker implantation.

Study design

ABALTION is a multicenter, open-label, two-arm, single-blind, parallel RCT designed to compare the effectiveness and safety of BA ablation with those of LA ablation among patients with RMVD and non-paroxysmal AF.

The study will recruit patients from 11 large academic cardiac centers all over Chinese mainland. Patients aged ≥ 18 years, with RMVD and non-paroxysmal AF who underwent MV surgery concomitant surgical ablation will be eligible for enrollment. RMVD is determined by history of acute rheumatic fever, valve morphology, echocardiographic findings and pathological diagnosis. Echocardiographic and intraoperative findings of leaflet thickening and retraction, commissural fusion or/and chordal fusion and shortening are considered as RMVD[17].

Exclusion criteria include paroxysmal AF, degenerative or ischemic MV disease, previous catheter ablation or surgical ablation for AF, surgical management of hypertrophic obstructive cardiomyopathy, absolute contraindications for anticoagulation therapy, LA thrombosis, chronic obstructive pulmonary disease, uncontrolled hypo- or hyperthyroidism, LA diameter>70mm, right ventricular dysfunction or moderate to severe tricuspid regurgitation or pulmonary artery pressure >60mmHg, coronary artery bypass grafting required for participants with coronary heart disease. See **Table 1** for details.

Table 1. The inclusion and exclusion criteria for the study

Inclusion criteria
1) Age ≥ 18 years
2) Persistent or long-standing persistent AF documented by medical history or direct electrocardiographic
3) Concomitant cardiac surgery involves at least mitral valve surgery
4) Agree to perform ablation procedure
Exclusion criteria
1) Paroxysmal AF
2) Degenerative or ischemic mitral valve disease
3) Evidence of active infection
4) Previous percutaneous catheter ablation or surgical ablation for AF

5) Surgical management of hypertrophic obstructive cardiomyopathy
6) Absolute contraindications for anticoagulation therapy
7) Left atrial thrombosis (not including left atrial appendage thrombosis alone)
8) Chronic obstructive pulmonary disease (Forced expiratory volume in 1 second (FEV1) <30% anticipated value)
9) Uncontrolled hypo- or hyperthyroidism
10) Mental impairment or other conditions that may not allow participants to understand the nature, significance, and scope of study
11) Left atrial diameter>70mm
12) Right ventricular dysfunction (TAPSE<16) or moderate to severe tricuspid regurgitation or pulmonary artery pressure (estimated by echocardiography) >60mmHg
13) Coronary artery bypass grafting is required for participants with coronary heart disease
14) Previous cardiac surgery
15) Refuse to participate in this study

AF, atrial fibrillation; FEV1: Forced expiratory volume in 1 second; TAPSE, Tricuspid annular plane systolic excursion

Information about trial objective, design, interventions and potential risks and benefits will be introduced thoroughly to all potential participants. They are encouraged to ask questions to study personnel and discuss the trial with family or friends prior to decision to participate. A written consent is mandatory prior to randomization. The study is approved by ethics committees in Fuwai Hospital and has been registered at ClinicalTrials.gov, identifier NCT05021601. All participating sites accepted the central ethics approval or obtained approval by the local ethics committee. The ABLATION trial began recruitment in May 2022 and is expected to complete recruitment by the end of April 2023.

Randomization

Eligible patients were randomized (1:1) to BA ablation group or LA ablation group. An Interactive Web-based Response system will be used to preserve allocation concealment. Randomization is stratified according to center and balanced using randomly permuted blocks (4 or 6 patients per block). Surgeons are aware of randomization results, however, participants, research staff and members of the data monitoring committee (DMC) are all blinded to the randomization schemes.

Treatment arms

The operation will be performed under cardiopulmonary bypass under general anesthesia, and preoperative transesophageal echocardiography will be used to exclude intracardiac thrombi. Except for MV operations, participants randomly assigned to BA ablation group will receive BA ablation, and who randomly assigned to LA ablation group will receive LA ablation. Unified ablation tools and lesion sets are applied during surgical ablation, and the principles of using ablation tools are strictly followed.

BA group

In this arm, Cox-Maze IV lesion sets are created. The detailed lesions were reported by Damiano et al[18]. After the initiation of cardiopulmonary bypass, a vertical right atriotomy is made extending from the intra-atrial septum up towards the atrioventricular groove near the free margin of the heart. And then, from the inferior aspect of the incision, the radiofrequency bipolar clamp is used to create ablation lines up to the superior vena cava and down towards the inferior vena cava. An ablation lesion perpendicular to the right incision is created along the free wall of the right atrium by clamping the right atrial appendage using radiofrequency ablation clamp (at least 2 cm from the vertical right incision)[18]. The transpolar or irrigated radiofrequency pen is used to create an endocardial ablation line from the superior aspect of this vertical right incision down onto the tricuspid annulus at the 2 o'clock position and an endocardial ablation line down to the tricuspid annulus at the 10 o'clock position (**Figure 1A**). In order to ensure transmurality, overlap epicardial ablation can be created by radiofrequency pen at endocardial ablation line when right atrium wall is thickened significantly.

At left atrium, right pulmonary veins can be isolated by radiofrequency bipolar clamp firstly, and other LA lesions are performed on the arrested heart after aortic cross-clamping. After the ligament of Marshall division, left pulmonary veins (PVs) are isolated by radiofrequency

bipolar clamp. After left atrial appendage (LAA) is amputated, LA roof and floor ablation lines are created to connect with bilateral pulmonary vein isolation (PVI) loops by radiofrequency bipolar clamp. In addition, ablation lines are created to connect right PVI loop to the posterior mitral annulus, as well as left superior PV to the LAA by radiofrequency bipolar clamp. Finally, a radiofrequency pen is used to complete the endocardial mitral isthmus lesion, and to perform an epicardial radiofrequency ablation across the coronary sinus in line with the endocardial mitral isthmus lesion created by radiofrequency pen (**Figure 1B**).

LA group

As mentioned above, in this arm, participants are performed LA ablation alone on the arrested heart after aortic cross-clamping (**Figure 1B**).

Each site is effectively ablated at least 3 times with radiofrequency clamp. When using dry radiofrequency clamp, the ablation peak value of conductance curve no less than15 and the time of each ablation to the transmural impedance value no longer than 10 seconds is determined as effective ablation. The first time to reach the transmural impedance value must be no less than 3 seconds using irrigated radiofrequency bipolar clamp. Endocardial ablation by radiofrequency pen is performed twice at each 1cm long distance for no less than 15 seconds. MV surgery and other surgery (such as aortic valve surgery) are performed after ablation.

Study endpoints

The primary endpoint is the survival rate without any recurrence of atrial tachyarrhythmias at 12 months after operation documented by 3-day Holter monitoring. Atrial tachyarrhythmia recurrence will be considered when any episode of AF, atrial flutter or atrial tachycardia is sustained equal to or longer than 30 s on electrocardiogram monitoring after the blanking period[19]. The first 3 months after operation is considered as blanking period.

The key secondary endpoint is the survival rate without permanent pacemaker implantation at 12 months after operation, that is, the percentage of participants who do not have a new implanted permanent pacemaker.

The secondary endpoints are the survival rate without any recurrence of atrial tachyarrhythmias with antiarrhythmic drugs, AF burden, incidence of adverse events (including cardiac death, stroke, hospitalization for heart failure, hospitalization for embolism events or major bleeding events), and cardiac function documented by echocardiography at 12 months after operation. All endpoints are listed in **Table 2**.

Table 2. Endpoints in this trial

Primary endpoint
• Survival rate without any recurrence of atrial tachyarrhythmias without AADs at 12 months after operation
Key secondary endpoint
• Survival rate without permanent pacemaker implantation at 12 months after operation
Secondary endpoints
• Survival rate without any recurrence of atrial tachyarrhythmias with AADs at 12 months after operation
• Burden of AF (Evaluating with 3-day Holter monitoring at 12 months after operation)
• Incidence of adverse events (including cardiac death, stroke, hospitalization for heart failure, hospitalization for embolism events or bleeding events)
• Cardiac function documented by echocardiography at 12 months after operation

AF: Atrial fibrillation; AADs: Antiarrhythmic drugs

Hospital and surgeon selection

This is a multicenter study, and there are strict requirements for collaborative hospitals and surgeons. The annual volume of surgical ablation concomitant MV operations of hospital should be > 100 cases; surgeons should be proficient in the standard use of radiofrequency bipolar clamps and pens, and the total volume of surgical ablation should be > 20 cases.

Post-ablation management

After the operation, anticoagulation with warfarin is routinely initiated in all participants in the early postoperative period for 3 months, and participants with cardiac mechanical prosthetic valve need lifetime anticoagulation therapy. However, antiarrhythmic drugs are prescribed for 2 months only if AF or atrial flutter occurs during perioperative period.

Data collection and follow-up

A web-based data entry system has been established on the Chinese Cardiac Surgery Registry (CCSR) website (http://ccsr.cvs-china.com)[20]. This web-based CCSR data collection platform uses a high-level secure socket layer. The ABLATION trial uses this paperless data submission system for data collection, follow-up and management. All 11 hospitals participating in the study are authorized to access the data submission system. The dataset for this study includes the following four modules: subject screening, informed consent and randomization, baseline in-hospital information, 3- month, 6-month and 12-month follow-up data.

For baseline data, participating sites may directly import the in-hospital data into the CCSR database, including patient characteristics, comorbidities, oral medications, preoperative examination (24-hour Holter monitoring, echocardiography, thyroid function and etc.), surgical information, postoperative complications and discharge data. Baseline data should be completed within 14 days after discharge.

All the follow-ups are completed by a professional team blinded to the group allocation. The 3-month and 6-month follow-ups are completed via a remote video interview using social media. All video interviews are recorded. 24-hour Holter monitoring information and questionnaire are collected at 3-month follow-up, and 3-day Holter monitoring information and questionnaire are collected at 6-month follow-up. For the 12-month follow-up, a face-to-face visit is conducted in hospital or via a remote video interview. The study participants will be contacted in advance to confirm the type of 12-month follow-up. Three-

day Holter monitoring information, questionnaire and echocardiography are collected at 12-month follow-up. The 3-day Holter monitoring devices are mailed to participants for wearing at 6-month and 12-month follow-up. After wearing, they are sent back to the project team for data analysis. All the follow-up information will be uploaded to the web-based CCSR data collection platform. In addition, we request participants to have electrocardiogram tests at each follow-up and at any time after surgery if they have cardiac symptoms.

Data monitoring and clinical event committee

Data quality and safety are monitored by an independent DMC. The DMC has no competing interests in the ABLATION trial and monitors the study implementation and adverse event occurrence which is blinded to the group allocation. All serious adverse events are reported to the DMC for urgent review. DMC monitors the quality of study implementation by reviewing the study data, including monitoring protocol compliance, recruitment status, shedding rate of subjects, and the integrity of study data, and etc. If serious quality problems are found during study execution, DMC shall advise sponsors to improve the quality of study.

An independent clinical events committee (CEC) will adjudicate all clinical outcomes in accordance with the study's prespecified adverse event definitions and in accordance with the CEC charter, which comprises experienced experts in the field blinded to the randomization schemes.

Statistical analysis plan

Sample size calculation

The calculation of the sample size is based on the primary endpoint and the key secondary endpoint according to previously published data and our own clinical experience. The primary endpoint of the study is the survival rate without any recurrence of atrial tachyarrhythmias at 12 months after operation. It is estimated that the probability of freedom from atrial tachyarrhythmias at 12 months in the LA group is 70%[10 17 21] and that in the BA group is 85%[10]

[17 22]. Therefore, a sample size of 131 patients (per group) is needed to provide 90% power based on a one-sided Z test with pooled variance and a significance level of 0.05 (one-sided).

The key secondary endpoint of this study is the survival rate without permanent pacemaker implantation at 12 months. It is estimated that the probability of freedom from permanent pacemaker implantation at 12 months in the LA group is 97%[14 23]. Considering the feasibility of clinical studies, the non-inferiority margin is determined as -5%[24-26]. Therefore, a sample size of 144 patients (per group) is needed to provide 80% power based on a one-sided Z test with pooled variance and a significance level of 0.05 (one-sided).

As mentioned above, both primary and key secondary endpoints should be considered. Therefore, 144 patients per group are required. When considering a withdrawal rate of 10%, 320 patients are required to be randomly assigned into two groups in a 1:1 allocation.

Statistical analysis

A hierarchical testing procedure is applied to the primary and key secondary endpoints to preserve the overall type I error of 5%. The key secondary endpoint would only be tested (at significance level 5%) if the test for the primary endpoint is statistically significant (significance level 5%). Non-inferiority will be concluded if the lower limit of the 95% CI for the difference in proportion of participants achieving freedom from atrial tachyarrhythmias is greater than the –5% non-inferiority margin.

We will use frequencies with percentages to describe categorical variables, and means with standard deviations or medians with interquartile ranges to describe continuous variables. We will compare baseline participant characteristics and endpoints between the LA and BA groups using chi-square tests for categorical variables and student's t-tests for continuous variables. The Kaplan-Meier estimator will be applied to evaluate the survival rate without any recurrence of atrial tachyarrhythmias, and the log-rank test will be used for the evaluation

of between-group variance. The primary and key secondary endpoints are determined on the basis of the intention-to-treat principle. In addition, a per-protocol analysis is also performed, which includes participants who complete their assigned treatments as scheduled. All statistical tests are one-tailed with a significance level of 0.05.

Patient and Public Involvement

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. Patients and/or the public are not involved in the design, or conduct, or reporting, or dissemination plans of this research.

ETHICS AND DISSEMINATION

Ethics and governance approvals were obtained by the central ethics committee at Fuwai Hospital. Written informed consent will be obtained from all study participants prior any study-specific assessments. The results of this study will be disseminated through publications in peer-reviewed journals and conference presentations.

DISCUSSION

There has been a long-time debate about BA ablation or LA ablation alone for concomitant surgical ablation during MV surgery and relevant guidelines have not given explicit recommendations about it[9 19 27]. After a period of relative neglect, there has been a resurging interest in RHD worldwide over the past decade[2]. Comparing degenerative MV disease, RMVD often has a chronic condition with immune and inflammatory cells attack, which tends to affect the right atrium apart from left atrium, including pulmonary hypertension or tricuspid regurgitation[28]. Previous studies showed that structural and electrical remodeling uniformly distributed across both atria in RMVD[15 16]. Which lesion set should be preferred to be created during surgical ablation in patients with RMVD and AF? The current literature provides insufficient evidence to address this important clinical issue. Few studies with limited sample size have reported different results of surgical ablation with diverse lesion sets

in patients with RMVD and non-paroxysmal AF[11 14 29-33]. Therefore, to the best of our knowledge, ABLATION trial is the first multicenter RCT with large sample size to evaluate the efficacy of BA ablation for patients with RMVD and non-paroxysmal AF.

Whether the additional right atrial ablation to LA ablation increases the risk of permanent pacemaker implantation has been an important controversial topic. Right atrial structural remodelling including atrial fibrosis may influence sinoatrial node function or contribute to sinoatrial block[34]. This condition might be even worse with right atrial lesions are created. However, James L Cox and Niv Ad believe that there are many reasons for permanent pacemaker implantation after surgery, but standardized right atrial ablation set do not increase the risk of permanent pacemaker implantation[35 36]. Other studies displayed LA fibrosis or dilation was associated with sinus node dysfunction requiring pacemaker implant[37 38]. Nevertheless, previous meta-analyses showed that the additional right atrial ablation increased the risk of permanent pacemaker implantation[23]. In order to clarify this topic, we also evaluate the incidence of permanent pacemaker implantation in ABALTION trial. We regard the survival rate without permanent pacemaker implantation at 12 months after operation as the key secondary endpoint. A hierarchical testing procedure is applied to the primary and key secondary endpoints to preserve the overall type I error of 5%, which were widely used by previous studies[39 40]. If the hypothesis with endpoint on permanent pacemaker implantation is supported by the result of the ABALTION trial, it's believed that this conclusion can be applied in other MV diseases which have less right atrial remodelling.

In order to reduce the missed diagnosis rate of recurrent paroxysmal AF, we assess the primary endpoint of the survival rate without any recurrence of atrial tachyarrhythmias by means of 3-day continuous Holter monitoring at 6-month and 12-month follow-up after surgery, which was used by previous study[10]. In addition, 24-hour Holter monitoring will be performed at 3-month follow-up, and 12-lead electrocardiograms will be performed at each follow-up, and for participants who have AF episode or other suspicious cardiac symptoms,

all electrocardiograms will be analyzed at any time point after surgery.

It's common that every surgeon has the surgical option based on their understanding on AF[41]. According to the guideline[42], all participated surgeons in ABALTION trial are experienced and undergo the training and education to improve their understanding of AF, complete lesion set and every reliable lesion. All surgeons are required to watch the video of standard Cox-Maze Ⅳ procedure and their surgical ablation procedures will be recorded before the trial is initiated. Incorrect or irregular manipulation will be reported back to surgeons. Compared to previous study[43], unified ablation tools and matched lesion set in every group will be emphasized and implemented in order to eliminate the impact of different tools and lesions on the results. In addition, it's possible that the severe right atrial remodeling exists when right ventricular dysfunction or moderate to severe tricuspid regurgitation or severe pulmonary hypertension, which may contribute to the substrate of AF. In these patients, LA ablation alone is unethical, thus, these patients are not enrolled in ABALTION trial.

In conclusion, the ABLATION trial is designed to examine the effectiveness and safety of BA ablation procedure versus LA ablation procedure with unified ablation tools and matched lesion set in patients with RMVD and non-paroxysmal AF. The findings from this trial may help determine an optimal ablation lesion set to further improve the prognosis of patients with RMVD and non-paroxysmal AF.

Authors' contributions: CY, HL, YW, SC, YZ, ZZ: study concept and design; CY, HL, ZZ: drafting the initial manuscript and critical revision of the paper. All authors read and approved the final manuscript.

Funding statement: This work was supported by the CAMS Innovation Fund for Medical Sciences (CIFMS, 2021-I2M-1-063).

Disclosures: None

Conflicts of interests: The authors declare no conflicts of interests

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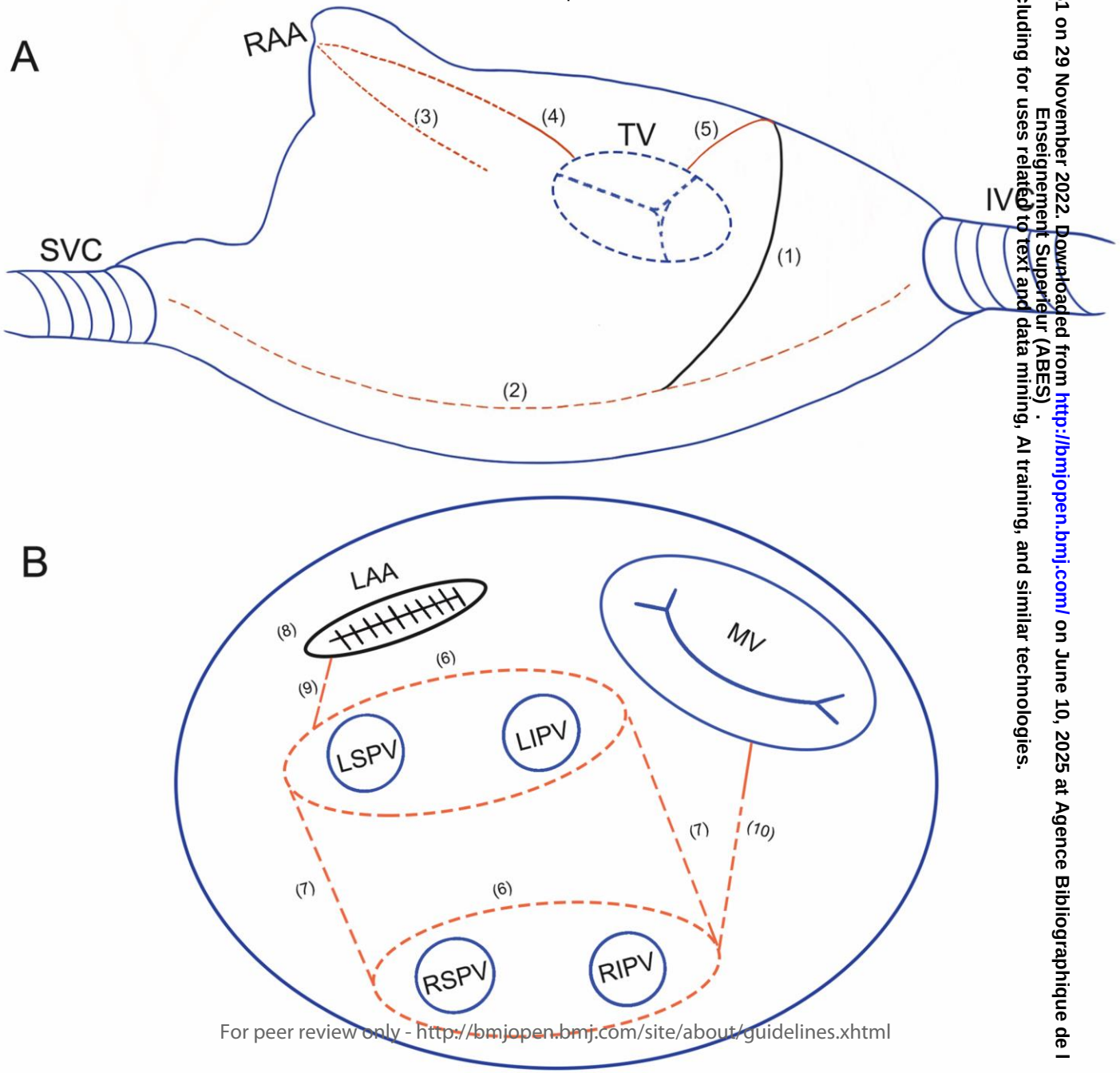
FIGURE LEGENDS

Figure 1. Schematic surgical lesion sets. A, right atrial lesions. B, left atrial lesions. The solid black lines indicate the surgical incision, and the dotted red lines indicate the ablation lines by radiofrequency bipolar clamp, and the solid red lines indicate the ablation lines by radiofrequency pen. (1) a vertical right atriotomy extending from the intra-atrial septum up towards the atrioventricular groove; (2) line from SVC to IVC; (3) an ablation lesion perpendicular to the right incision along the free wall of the right atrium by clamping the RAA; (4) an endocardial ablation line down to the tricuspid annulus at the 10 o'clock position; (5) an endocardial ablation line from the superior aspect of the vertical right incision down onto the tricuspid annulus at the 2 o'clock position; (6) PVI; (7) isolation of the posterior left atrium; (8) management of the LAA; (9) left superior PV to the LAA; (10) mitral isthmus line. IVC, inferior vena cava; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; MV, mitral valve; PVI, pulmonary veins isolation; RAA, right atrial appendage; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SVC, superior vena cava; TV, tricuspid valve.



BMJ Open

Bi-atrial versus left atrial ablation for patients with rheumatic mitral valve disease and non-paroxysmal atrial fibrillation (ABLATION): Rationale, design and study protocol for a multicenter randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064861.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Nov-2022
Complete List of Authors:	Yu, Chunyu; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital Li, Haojie; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital Yang, Wang; Fuwai Hospital State Key Laboratory of Cardiovascular Disease Chen, Sipeng; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital Zhao, Yan; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital Zheng, Zhe; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital, Department of Cardiovascular Surgery
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Surgery
Keywords:	Adult cardiology < CARDIOLOGY, Valvular heart disease < CARDIOLOGY, Clinical trials < THERAPEUTICS, Cardiac surgery < SURGERY

Title: Bi-atrial versus left atrial ablation for patients with rheumatic mitral valve disease and non-paroxysmal atrial fibrillation (ABLATION): Rationale, design and study protocol for a multicenter randomized controlled trial

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Key words: Atrial fibrillation, surgical ablation, bi-atrial ablation, rheumatic mitral valve disease, mitral operations

Word count: 6057; Figures: 2 Tables: 2

ABSTRACT

Introduction: Atrial fibrillation (AF) is common in patients with rheumatic mitral valve disease (RMVD) and increase the risk of stroke and death. Bi-atrial or left atrial ablation remains controversial for treatment of AF during mitral valve surgery. The study aims to compare the efficacy and safety of bi-atrial ablation with those of left atrial ablation among patients with RMVD and persistent or longstanding persistent AF.

Methods and analysis: The ABLATION trial (Bi-atrial versus Left Atrial Ablation for Patients with RMVD and Non-paroxysmal AF) is a prospective, multicenter, randomized controlled study. The trial will randomly assign 320 patients with RMVD and persistent or long-standing persistent AF to bi-atrial ablation procedure or left atrial ablation procedure in a 1:1 randomization. The primary endpoint is freedom from documented AF, atrial flutter, or atrial tachycardia of more than 30 seconds at 12 months after surgery off antiarrhythmic drugs. Key secondary endpoint is the probability of freedom from permanent pacemaker implantation at 12 months after surgery. Secondary outcomes include the probability of freedom from any recurrence of atrial tachyarrhythmias with antiarrhythmic drugs, AF burden, incidence of adverse events and cardiac function documented by echocardiography at 12 months after operation.

Ethics and dissemination: The central ethics committee at Fuwai Hospital approved the ABLATION trial. The results of this study will be disseminated through publications in peer-reviewed journals and conference presentations.

Trial registration number: ClinicalTrials.gov, identifier NCT05021601.

Strengths and limitations of this study

1. The trial is the first multicenter randomized controlled trial with large sample size to evaluate the efficacy of bi-atrial ablation for patients with rheumatic mitral valve disease and non-paroxysmal atrial fibrillation.
2. Randomization is stratified according to center and balanced using randomly permuted blocks (4 or 6 patients per block), and an Interactive Web-based Response system will be used to preserve allocation concealment.
3. The key secondary endpoint is the probability of freedom from permanent pacemaker implantation at 12 months after operation, which has been an important controversial topic.
4. All surgeons in this study are required to watch the video of standard Cox-Maze Ⅳ procedure and their surgical ablation procedures will be recorded before the trial, and incorrect or irregular manipulation will be reported back to surgeons, which is initiated to eliminate the impact of different tools and lesions on the results.

INTRODUCTION

Rheumatic heart disease (RHD) remains endemic among vulnerable groups in many low- and middle-income countries, and resource-limited regions of high-income countries[1 2]. About one-third of patients with RHD have atrial fibrillation (AF), with an incidence of AF almost triples every five years after diagnosis of RHD, and prevalence of AF is higher in severe mitral valve disease comparing with severe aortic disease[3]. In patients with RHD, AF is associated with increased prevalence of heart failure, stroke, peripheral embolism and death[4-7]. Especially, about 80% of the strokes in patients with RHD occur in patients with mitral stenosis and AF[8].

Guidelines recommended that surgical ablation for AF could be performed without additional risk of operative mortality or major morbidity, and was recommended at the time of concomitant mitral valve (MV) operations to restore sinus rhythm (Class I, Level A)[9]. A. Marc Gillinov et al reported the addition of surgical ablation to MV surgery significantly increased the rate of freedom from AF at 1 year among patients with persistent or long-standing persistent AF in a multicenter randomized controlled trial (RCT)[10]. Similarly, some studies concluded that the additional surgical ablation also decreased the risk of stroke or death and increased early and long-term sinus rhythm maintenance in patients with AF and RMVD[11-13].

However, there has been debate on the standard surgical ablation strategy during MV operations. Generally, bi-atrial (BA) lesion set could be created during surgical ablation because the open left atrium facilitates a BA ablation procedure, nevertheless, others believed that adding right atrial ablation had no influence on freedom from AF and conversely increased the risk of permanent pacemaker implantation. The discrepancy on the efficacy and

safety between BA and left atrial (LA) ablation was also reported in the past years, whether in patients with MV disease or in patients with RMVD[14].

Patients with RMVD usually have a long history and relatively severe LA remodeling, progressive pulmonary hypertension, secondary tricuspid valve regurgitation or rheumatic tricuspid valve abnormalities, which can also contribute to severe right atrial remodeling[15 16]. The rationality of BA ablation is stronger in patients with RMVD and AF, however, the increased risk of permanent pacemaker implantation should not be neglected due to right atrial remodeling and fibrosis. To our knowledge, the only RCT reported a confused results that BA ablation was not superior to LA ablation in patients with RMVD and AF (P=0.09) and no conclusion on the permanent pacemaker implantation due to the limited sample[14]. It might also be noted that all lesions were create by mono-polar radiofrequency pen which is replaced by bipolar radiofrequency clamp in majority of lesions now.

To sum up, there is no sufficient evidence to determine the safety and potential benefits of BA ablation procedure when comparing with those of LA ablation procedure in patients with RMVD and non-paroxysmal AF. We designed this multi-center prospective RCT to compare the efficacy and safety of BA ablation with LA ablation strategies in patients with RMVD and non-paroxysmal AF.

METHODS AND ANALYSIS

Study objective

The ABLATION trial is designed to examine the hypothesis that for patients with RMVD and non-paroxysmal AF, BA ablation is superior to LA ablation in the probability of freedom from any recurrence of atrial tachyarrhythmias in the absence of antiarrhythmic drugs, and non-inferior to LA ablation in the probability of freedom from permanent pacemaker implantation.

Study design

ABLATION is a multicenter, open-label, two-arm, single-blind, parallel RCT designed to compare the efficacy and safety of BA ablation with those of LA ablation among patients with RMVD and non-paroxysmal AF.

The study plans to recruit patients from 19 large academic cardiac centers all over Chinese mainland. Patients aged ≥ 18 years, with RMVD and non-paroxysmal AF who underwent MV surgery concomitant surgical ablation will be eligible for enrollment. RMVD is determined by history of acute rheumatic fever, valve morphology, echocardiographic findings and pathological diagnosis. Echocardiographic and intraoperative findings of leaflet thickening and retraction, commissural fusion or/and chordal fusion and shortening are considered as RMVD[17].

Exclusion criteria include paroxysmal AF, degenerative or ischemic MV disease, previous catheter ablation or surgical ablation for AF, surgical management of hypertrophic obstructive cardiomyopathy, absolute contraindications for anticoagulation therapy, LA thrombosis, chronic obstructive pulmonary disease, uncontrolled hypo- or hyperthyroidism, LA diameter>70mm, right ventricular dysfunction or moderate to severe tricuspid regurgitation or pulmonary artery systolic pressure >60mmHg, coronary artery bypass grafting required for participants with coronary heart disease. See **Table 1** for details.

Table 1. The inclusion and exclusion criteria for the study

Inclusion criteria
1) Age ≥ 18 years
2) Persistent or long-standing persistent AF documented by medical history or direct electrocardiographic
3) Concomitant cardiac surgery involves at least mitral valve surgery
4) Agree to perform ablation procedure
Exclusion criteria
1) Paroxysmal AF
2) Degenerative or ischemic mitral valve disease

3) Evidence of active infection
4) Previous percutaneous catheter ablation or surgical ablation for AF
5) Surgical management of hypertrophic obstructive cardiomyopathy
6) Absolute contraindications for anticoagulation therapy
7) Left atrial thrombosis (not including left atrial appendage thrombosis alone)
8) Chronic obstructive pulmonary disease (Forced expiratory volume in 1 second (FEV1) <30% anticipated value)
9) Uncontrolled hypo- or hyperthyroidism
10) Mental impairment or other conditions that may not allow participants to understand the nature, significance, and scope of study
11) Left atrial diameter>70mm
12) Right ventricular dysfunction (TAPSE<16) or moderate to severe tricuspid regurgitation or pulmonary artery systolic pressure (estimated by echocardiography) >60mmHg
13) Coronary artery bypass grafting is required for participants with coronary heart disease
14) Previous cardiac surgery
15) Refuse to participate in this study

AF, atrial fibrillation; FEV1: Forced expiratory volume in 1 second; TAPSE, Tricuspid annular plane systolic excursion

Information about trial objective, design, interventions and potential risks and benefits will be introduced thoroughly to all potential participants. They are encouraged to ask questions to study personnel and discuss the trial with family or friends prior to decision to participate. A written consent is mandatory prior to randomization. The study is approved by ethics committees in Fuwai Hospital and has been registered at ClinicalTrials.gov, identifier NCT05021601. All participating sites accepted the central ethics approval or obtained approval by the local ethics committee. The ABLATION trial began recruitment in May 2022 and is expected to complete recruitment by the end of April 2024 and follow-up will be completed by the end of April 2025 (**Figure 1**).

Randomization

Eligible patients were randomized (1:1) to BA ablation group or LA ablation group. An Interactive Web-based Response system will be used to preserve allocation concealment. Randomization is stratified according to center and balanced using randomly permuted blocks

(4 or 6 patients per block). Surgeons are aware of randomization results, however, participants and research staff are all blinded to the randomization schemes.

Treatment arms

The operation will be performed under cardiopulmonary bypass under general anesthesia, and preoperative transesophageal echocardiography will be used to exclude intracardiac thrombi. Except for MV operations, participants randomly assigned to BA ablation group will receive BA ablation, and who randomly assigned to LA ablation group will receive LA ablation. Unified ablation tools and lesion sets are applied during surgical ablation, and the principles of using ablation tools are strictly followed.

BA group

In this arm, Cox-Maze IV lesion sets are created. The detailed lesions were reported by Damiano and James L Cox[18 19]. After the initiation of cardiopulmonary bypass, a vertical right atriotomy is made extending from the intra-atrial septum up towards the atrioventricular groove near the free margin of the heart. And then, from the inferior aspect of the incision, the radiofrequency bipolar clamp is used to create ablation lines up to the superior vena cava and down towards the inferior vena cava. Then the right atrium appendage is clamped by bipolar clamp from the side of the right atrial vertical incision near the atrioventricular groove toward the tip of the right atrium appendage[19]. The transpolar or irrigated radiofrequency pen is used to create an endocardial ablation line from the superior aspect of this vertical right incision down onto the tricuspid annulus at the 2 o'clock position (**Figure 2A**). In order to ensure transmurality, overlap epicardial ablation can be created by radiofrequency pen in line with endocardial ablation line when right atrium wall is thickened significantly.

At left atrium, right pulmonary veins can be isolated by radiofrequency bipolar clamp firstly, and other LA lesions are performed on the arrested heart after aortic cross-clamping. After the ligament of Marshall division, left pulmonary veins (PVs) are isolated by radiofrequency

bipolar clamp. After left atrial appendage (LAA) is amputated, LA roof and floor ablation lines are created to connect with bilateral pulmonary vein isolation (PVI) loops by radiofrequency bipolar clamp. In addition, ablation lines are created to connect right PVI loop towards to the posterior mitral annulus, as well as left superior PV to the LAA by radiofrequency bipolar clamp. Finally, a radiofrequency pen is used to complete the endocardial mitral isthmus lesion, and to perform an epicardial radiofrequency ablation across the coronary sinus in line with the endocardial mitral isthmus lesion created by radiofrequency pen (**Figure 2B**).

LA group

As mentioned above, in this arm, participants are performed LA ablation alone on the arrested heart after aortic cross-clamping (**Figure 2B**).

Each site is effectively ablated at least 3 times with radiofrequency clamp without releasing the radiofrequency clamp. When using dry radiofrequency clamp, the ablation peak value of conductance curve no less than15 and the time of each ablation to the transmural impedance value no longer than 10 seconds is determined as effective ablation. The first time to reach the transmural impedance value must be no less than 3 seconds using irrigated radiofrequency bipolar clamp. Endocardial ablation by radiofrequency pen is performed twice at each 1cm long distance for no less than 15 seconds. MV surgery and other surgery (such as aortic valve surgery) are performed after ablation. All surgeons in this study are required to watch the video of standard Cox-Maze Ⅳ procedure and their surgical ablation procedures will be recorded before the trial, and incorrect or irregular manipulation will be reported back to surgeons, which is initiated to eliminate the impact of different tools and lesions on the results.

Study endpoints

The primary endpoint is the probability of freedom from any recurrence of atrial tachyarrhythmias off antiarrhythmic drugs at 12 months after operation documented by 3-day Holter monitoring. Atrial tachyarrhythmia recurrence will be considered when any episode of AF, atrial flutter or atrial tachycardia is sustained equal to or longer than 30 s on electrocardiogram monitoring after the blanking period[20]. The first 3 months after operation is considered as blanking period.

The key secondary endpoint is the probability of freedom from permanent pacemaker implantation at 12 months after operation, that is, the percentage of participants who do not have a new implanted permanent pacemaker.

The secondary endpoints are the probability of freedom from any recurrence of atrial tachyarrhythmias with antiarrhythmic drugs, AF burden, incidence of adverse events (including cardiac death, stroke, hospitalization for heart failure, hospitalization for embolism events or major bleeding events), and cardiac function documented by echocardiography at 12 months after operation. All endpoints are listed in **Table 2**.

Table 2. Endpoints in this trial

Primary endpoint
• The probability of freedom from any recurrence of atrial tachyarrhythmias without AADs at 12 months after operation
Key secondary endpoint
• The probability of freedom from permanent pacemaker implantation at 12 months after operation
Secondary endpoints
• The probability of freedom from any recurrence of atrial tachyarrhythmias with AADs at 12 months after operation • Burden of AF (Evaluating with 3-day Holter monitoring at 12 months after operation) • Incidence of adverse events (including cardiac death, stroke, hospitalization for heart failure, hospitalization for embolism events or bleeding events) • Cardiac function documented by echocardiography at 12 months after operation

AF: Atrial fibrillation; AADs: Antiarrhythmic drugs

Hospital and surgeon selection

This is a multicenter study, and there are strict requirements for collaborative hospitals and surgeons. The annual volume of surgical ablation concomitant MV operations of hospital should be > 100 cases; surgeons should be proficient in the standard use of radiofrequency bipolar clamps and pens, and the total volume of surgical ablation should be > 20 cases.

Post-ablation management

After the operation, anticoagulation with warfarin is routinely initiated in all participants in the early postoperative period for 3 months, and participants with cardiac mechanical prosthetic valve need lifetime anticoagulation therapy. However, antiarrhythmic drugs are prescribed for 2 months only if AF or atrial flutter occurs during perioperative period.

Data collection and follow-up

A web-based data entry system has been established on the Chinese Cardiac Surgery Registry (CCSR) website (http://ccsr.cvs-china.com)[21]. This web-based CCSR data collection platform uses a high-level secure socket layer. The ABLATION trial uses this paperless data submission system for data collection, follow-up and management. All enrolled hospitals participating in the study are authorized to access the data submission system. The dataset for this study includes the following four modules: subject screening, informed consent and randomization, baseline in-hospital information, 3- month, 6-month and 12-month follow-up data.

For baseline data, participating sites may directly import the in-hospital data into the CCSR database, including patient characteristics, comorbidities, oral medications, preoperative examination (24-hour Holter monitoring, echocardiography, thyroid function and etc.), surgical information, postoperative complications and discharge data. Baseline data should be completed within 14 days after discharge.

All the follow-ups are completed by a professional team blinded to the group allocation. The 3-month and 6-month follow-ups are completed via a remote video interview using social media. All video interviews are recorded. 24-hour Holter monitoring information and questionnaire are collected at 3-month follow-up, and 3-day Holter monitoring information and questionnaire are collected at 6-month follow-up. For the 12-month follow-up, a face-to-face visit is conducted in hospital or via a remote video interview. The study participants will be contacted in advance to confirm the type of 12-month follow-up. Three-day Holter monitoring information, questionnaire and echocardiography are collected at 12-month follow-up. The questionnaire includes questions on subject survival status, cardiac function classification, stroke, peripheral thromboembolic events, hospitalization for heart failure, bleeding events, medication use, and permanent pacemaker implantation. The 3-day Holter monitoring devices are mailed to participants for wearing at 6-month and 12-month follow-up. After wearing, they are sent back to the project team for data analysis. If permanent pacemaker is implanted in a participant during follow-up, we will record the date and reason that the participant's pacemaker is implanted by questionnaire. During participant enrollment, we inform participants that if they have a subsequent readmission for treatment, they need to save and submit their case information to us during follow-up. In addition, we will record and analyze the time taken by the pacing rhythm by 3-day Holter monitoring at 6-month and 12-month follow-up. All the follow-up information will be uploaded to the web-based CCSR data collection platform. In addition, we request participants to have electrocardiogram tests at each follow-up and at any time after surgery if they have cardiac symptoms. The 3-day Holter monitoring, 12-lead electrocardiograms and echocardiograms will be analyzed by a core lab blinded to the group allocation.

Statistical analysis plan

Sample size calculation

The calculation of the sample size is based on the primary endpoint and the key secondary endpoint according to previously published data and our own clinical experience. The primary

endpoint of the study is the probability of freedom from any recurrence of atrial tachyarrhythmias at 12 months after operation. It is estimated that the probability of freedom from atrial tachyarrhythmias at 12 months in the LA group is 70%[10 17 22] and that in the BA group is 85%[10 17 23]. Therefore, a sample size of 131 patients (per group) is needed to provide 90% power based on a one-sided Z test with pooled variance and a significance level of 0.05 (one-sided).

The key secondary endpoint of this study is the probability of freedom from permanent pacemaker implantation at 12 months. It is estimated that the probability of freedom from permanent pacemaker implantation at 12 months in the LA group is 97%[14 24]. Considering the feasibility of clinical studies, the non-inferiority margin is determined as -5%[25-27]. Therefore, a sample size of 144 patients (per group) is needed to provide 80% power based on a one-sided Z test with pooled variance and a significance level of 0.05 (one-sided).

As mentioned above, both primary and key secondary endpoints should be considered. Therefore, 144 patients per group are required. When considering a withdrawal rate of 10%, 320 patients are required to be randomly assigned into two groups in a 1:1 allocation.

Statistical analysis

A hierarchical testing procedure is applied to the primary and key secondary endpoints to preserve the overall type I error of 5%. The key secondary endpoint would only be tested (at significance level 5%) if the test for the primary endpoint is statistically significant (significance level 5%). Non-inferiority will be concluded if the lower limit of the 95% CI for the difference in proportion of participants achieving freedom from atrial tachyarrhythmias is greater than the –5% non-inferiority margin.

We will use frequencies with percentages to describe categorical variables, and means with standard deviations or medians with interquartile ranges to describe continuous variables. We

will compare baseline participant characteristics and endpoints between the LA and BA groups using chi-square tests for categorical variables and student's t-tests for continuous variables. The Kaplan-Meier estimator will be applied to evaluate the probability of freedom from any recurrence of atrial tachyarrhythmias, and the log-rank test will be used for the evaluation of between-group variance. The primary and key secondary endpoints are determined on the basis of the intention-to-treat principle. In addition, a per-protocol analysis is also performed, which includes participants who complete their assigned treatments as scheduled. All statistical tests are one-tailed with a significance level of 0.05.

Patient and Public Involvement

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. Patients and/or the public are not involved in the design, or conduct, or reporting, or dissemination plans of this research.

ETHICS AND DISSEMINATION

Ethics and governance approvals were obtained by the central ethics committee at Fuwai Hospital. Written informed consent will be obtained from all study participants prior any study-specific assessments. The results of this study will be disseminated through publications in peer-reviewed journals and conference presentations.

DISCUSSION

There has been a long-time debate about BA ablation or LA ablation alone for concomitant surgical ablation during MV surgery and relevant guidelines have not given explicit recommendations about it[9 20 28]. After a period of relative neglect, there has been a resurging interest in RHD worldwide over the past decade[2]. Comparing degenerative MV disease, RMVD often has a chronic condition with immune and inflammatory cells attack, which tends to affect the right atrium apart from left atrium, including pulmonary hypertension or tricuspid regurgitation[29]. Previous studies showed that structural and electrical remodeling

uniformly distributed across both atria in RMVD[15 16]. Which lesion set should be preferred to be created during surgical ablation in patients with RMVD and AF? The current literature provides insufficient evidence to address this important clinical issue. Few studies with limited sample size have reported different results of surgical ablation with diverse lesion sets in patients with RMVD and non-paroxysmal AF[11 14 30-34]. Therefore, to the best of our knowledge, ABLATION trial is the first multicenter RCT with large sample size to evaluate the efficacy of BA ablation for patients with RMVD and non-paroxysmal AF.

Whether the additional right atrial ablation to LA ablation increases the risk of permanent pacemaker implantation has been an important controversial topic. Right atrial structural remodelling including atrial fibrosis may influence sinoatrial node function or contribute to sinoatrial block[35]. This condition might be even worse with right atrial lesions are created. However, James L Cox and Niv Ad believe that there are many reasons for permanent pacemaker implantation after surgery, but standardized right atrial ablation set do not increase the risk of permanent pacemaker implantation[36 37]. Other studies displayed LA fibrosis or dilation was associated with sinus node dysfunction requiring pacemaker implant[38 39]. Nevertheless, previous meta-analyses showed that the additional right atrial ablation increased the risk of permanent pacemaker implantation[24]. In order to clarify this topic, we also evaluate the incidence of permanent pacemaker implantation in ABLATION trial. We regard the probability of freedom from permanent pacemaker implantation at 12 months after operation as the key secondary endpoint. A hierarchical testing procedure is applied to the primary and key secondary endpoints to preserve the overall type I error of 5%, which were widely used by previous studies[40 41]. If the hypothesis with endpoint on permanent pacemaker implantation is supported by the result of the ABLATION trial, it's believed that this conclusion can be applied in other MV diseases which have less right atrial remodelling.

This is an investigator-initiated study, and false positive can be controlled less strictly because the issue of false negative is equally important. From the overall study design, a hierarchical

testing procedure is applied to the primary and key secondary endpoints, the hypothesis test of the key secondary endpoint can be carried out only if the primary endpoint reached positive. Therefore, it is very important to obtain the positive result of the primary endpoint with greater power, and then to carry out the sequential test of the key secondary endpoint. Once the hypothesis test of primary endpoint fails, there is no need for hypothesis test of key secondary endpoint. In order to take into account this goal, we tend to choose a greater power (90%). Therefore, we chose a significance level of one-side 0.05 and 90% power.

In order to reduce the missed diagnosis rate of recurrent paroxysmal AF, we assess the primary endpoint of the probability of freedom from any recurrence of atrial tachyarrhythmias by means of 3-day continuous Holter monitoring at 6-month and 12-month follow-up after surgery, which was used by previous study[10]. In addition, 24-hour Holter monitoring will be performed at 3-month follow-up, and 12-lead electrocardiograms will be performed at each follow-up, and for participants who have AF episode or other suspicious cardiac symptoms, all electrocardiograms will be analyzed at any time point after surgery.

It's common that every surgeon has the surgical option based on their understanding on AF[42].According to the guideline[43], all participated surgeons in ABLATION trial are experienced and undergo the training and education to improve their understanding of AF, complete lesion set and every reliable lesion. All surgeons are required to watch the video of standard Cox-Maze Ⅳ procedure and their surgical ablation procedures will be recorded before the trial is initiated. Incorrect or irregular manipulation will be reported back to surgeons. Compared to previous study[44], unified ablation tools and matched lesion set in every group will be emphasized and implemented in order to eliminate the impact of different tools and lesions on the results. In addition, it's possible that the severe right atrial remodeling exists when right ventricular dysfunction or moderate to severe tricuspid regurgitation or severe pulmonary hypertension, which may contribute to the substrate of AF. In these patients, LA ablation alone is unethical, thus, these patients are not enrolled in ABLATION

trial.

In conclusion, the ABLATION trial is designed to examine the efficacy and safety of BA ablation procedure versus LA ablation procedure with unified ablation tools and matched lesion set in patients with RMVD and non-paroxysmal AF. The findings from this trial may help determine an optimal ablation lesion set to further improve the prognosis of patients with RMVD and non-paroxysmal AF.

Authors' contributions: CY, HL, YW, SC, YZ, ZZ: study concept and design; CY, HL, ZZ: drafting the initial manuscript and critical revision of the paper. All authors read and approved the final manuscript.

Funding statement: This work was supported by the CAMS Innovation Fund for Medical Sciences (CIFMS, 2021-I2M-1-063).

Disclosures: None

Conflicts of interests: The authors declare no conflicts of interests

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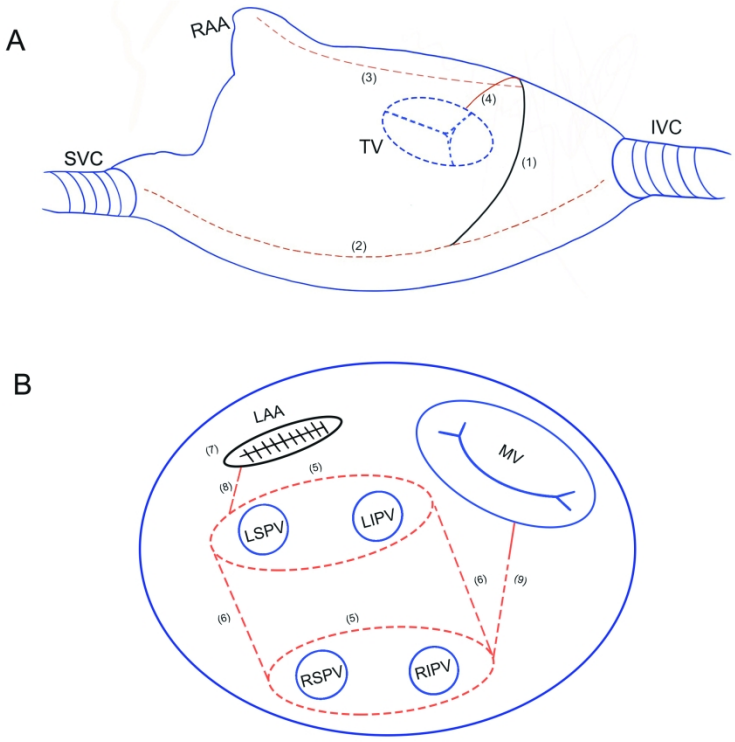
FIGURE LEGENDS

Figure 1. A Gantt plot showing the progress of this study.

Figure 2. Schematic surgical lesion sets. A, right atrial lesions. B, left atrial lesions. The solid black lines indicate the surgical incision, and the dotted red lines indicate the ablation lines by radiofrequency bipolar clamp, and the solid red lines indicate the ablation lines by radiofrequency pen. (1) a vertical right atriotomy extending from the intra-atrial septum up towards the atrioventricular groove; (2) line from SVC to IVC; (3) the RAA is clamped by bipolar clamp from the side of the right atrial vertical incision near the atrioventricular groove toward the tip of the RAA; (4) an endocardial ablation line from the superior aspect of the vertical right incision down onto the tricuspid annulus at the 2 o'clock position; (5) PVI; (6) isolation of the posterior left atrium; (7) management of the LAA; (8) left superior PV to the LAA; (9) mitral isthmus line. IVC, inferior vena cava; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; MV, mitral valve; PVI, pulmonary veins isolation; RAA, right atrial appendage; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SVC, superior vena cava; TV, tricuspid valve.

A Gantt plot showing the progress of this study.

338x190mm (96 x 96 DPI)



Schematic surgical lesion sets. A, right atrial lesions. B, left atrial lesions. The solid black lines indicate the surgical incision, and the dotted red lines indicate the ablation lines by radiofrequency bipolar clamp, and the solid red lines indicate the ablation lines by radiofrequency pen. (1) a vertical right atriotomy extending from the intra-atrial septum up towards the atrioventricular groove; (2) line from SVC to IVC; (3) the RAA is clamped by bipolar clamp from the side of the right atrial vertical incision near the atrioventricular groove toward the tip of the RAA; (4) an endocardial ablation line from the superior aspect of the vertical right incision down onto the tricuspid annulus at the 2 o'clock position; (5) PVI; (6) isolation of the posterior left atrium; (7) management of the LAA; (8) left superior PV to the LAA; (9) mitral isthmus line. IVC, inferior vena cava; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; MV, mitral valve; PVI, pulmonary veins isolation; RAA, right atrial appendage; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SVC, superior vena cava; TV, tricuspid valve.

1119x874mm (72 x 72 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	See clinicaltrials.gov
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2, 18
	5b	Name and contact information for the trial sponsor	See clinicaltrials.gov
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12-13
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14-15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14-15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	See Informed Consent Form
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	See Informed Consent Form
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	See Informed Consent Form
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See Supplemental file

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Bi-atrial versus left atrial ablation for patients with rheumatic mitral valve disease and non-paroxysmal atrial fibrillation (ABLATION): Rationale, design and study protocol for a multicenter randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064861.R2
Article Type:	Protocol
Date Submitted by the Author:	15-Nov-2022
Complete List of Authors:	Yu, Chunyu; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital Li, Haojie; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital Yang, Wang; National Center for Cardiovascular Diseases Chen, Sipeng; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital Zhao, Yan; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital Zheng, Zhe; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital, Department of Cardiovascular Surgery
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Surgery
Keywords:	Adult cardiology < CARDIOLOGY, Valvular heart disease < CARDIOLOGY, Clinical trials < THERAPEUTICS, Cardiac surgery < SURGERY

Title: Bi-atrial versus left atrial ablation for patients with rheumatic mitral valve disease and non-paroxysmal atrial fibrillation (ABLATION): Rationale, design and study protocol for a multicenter randomized controlled trial

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Key words: Atrial fibrillation, surgical ablation, bi-atrial ablation, rheumatic mitral valve disease, mitral operations

Word count: 6061; Figures: 2 Tables: 2

ABSTRACT

Introduction: Atrial fibrillation (AF) is common in patients with rheumatic mitral valve disease (RMVD) and increase the risk of stroke and death. Bi-atrial or left atrial ablation remains controversial for treatment of AF during mitral valve surgery. The study aims to compare the efficacy and safety of bi-atrial ablation with those of left atrial ablation among patients with RMVD and persistent or longstanding persistent AF.

Methods and analysis: The ABLATION trial (Bi-atrial versus Left Atrial Ablation for Patients with RMVD and Non-paroxysmal AF) is a prospective, multicenter, randomized controlled study. The trial will randomly assign 320 patients with RMVD and persistent or long-standing persistent AF to bi-atrial ablation procedure or left atrial ablation procedure in a 1:1 randomization. The primary endpoint is freedom from documented AF, atrial flutter, or atrial tachycardia of more than 30 seconds at 12 months after surgery off antiarrhythmic drugs. Key secondary endpoint is the probability of freedom from permanent pacemaker implantation at 12 months after surgery. Secondary outcomes include the probability of freedom from any recurrence of atrial tachyarrhythmias with antiarrhythmic drugs, AF burden, incidence of adverse events and cardiac function documented by echocardiography at 12 months after operation.

Ethics and dissemination: The central ethics committee at Fuwai Hospital approved the ABLATION trial. The results of this study will be disseminated through publications in peer-reviewed journals and conference presentations.

Trial registration number: ClinicalTrials.gov, identifier NCT05021601.

Strengths and limitations of this study

1. The trial is the first multicenter randomized controlled trial with large sample size to evaluate the efficacy of bi-atrial ablation for patients with rheumatic mitral valve disease and non-paroxysmal atrial fibrillation.
2. Randomization is stratified according to center and balanced using randomly permuted blocks (4 or 6 patients per block), and an Interactive Web-based Response system will be used to preserve allocation concealment.
3. The key secondary endpoint is the probability of freedom from permanent pacemaker implantation at 12 months after operation, which has been an important controversial topic.
4. All surgeons in this study are required to watch the video of standard Cox-Maze Ⅳ procedure and their surgical ablation procedures will be recorded before the trial, and incorrect or irregular manipulation will be reported back to surgeons, which is initiated to eliminate the impact of different tools and lesions on the results.

INTRODUCTION

Rheumatic heart disease (RHD) remains endemic among vulnerable groups in many low- and middle-income countries, and resource-limited regions of high-income countries[1 2]. About one-third of patients with RHD have atrial fibrillation (AF), with an incidence of AF almost triples every five years after diagnosis of RHD, and prevalence of AF is higher in severe mitral valve disease comparing with severe aortic disease[3]. In patients with RHD, AF is associated with increased prevalence of heart failure, stroke, peripheral embolism and death[4-7]. Especially, about 80% of the strokes in patients with RHD occur in patients with mitral stenosis and AF[8].

Guidelines recommended that surgical ablation for AF could be performed without additional risk of operative mortality or major morbidity, and was recommended at the time of concomitant mitral valve (MV) operations to restore sinus rhythm (Class I, Level A)[9]. A. Marc Gillinov et al reported the addition of surgical ablation to MV surgery significantly increased the rate of freedom from AF at 1 year among patients with persistent or long-standing persistent AF in a multicenter randomized controlled trial (RCT)[10]. Similarly, some studies concluded that the additional surgical ablation also decreased the risk of stroke or death and increased early and long-term sinus rhythm maintenance in patients with AF and RMVD[11-13].

However, there has been debate on the standard surgical ablation strategy during MV operations. Generally, bi-atrial (BA) lesion set could be created during surgical ablation because the open left atrium facilitates a BA ablation procedure, nevertheless, others believed that adding right atrial ablation had no influence on freedom from AF and conversely increased the risk of permanent pacemaker implantation. The discrepancy on the efficacy and

safety between BA and left atrial (LA) ablation was also reported in the past years, whether in patients with MV disease or in patients with RMVD[14].

Patients with RMVD usually have a long history and relatively severe LA remodeling, progressive pulmonary hypertension, secondary tricuspid valve regurgitation or rheumatic tricuspid valve abnormalities, which can also contribute to severe right atrial remodeling[15 16]. The rationality of BA ablation is stronger in patients with RMVD and AF, however, the increased risk of permanent pacemaker implantation should not be neglected due to right atrial remodeling and fibrosis. To our knowledge, the only RCT reported a confused results that BA ablation was not superior to LA ablation in patients with RMVD and AF (P=0.09) and no conclusion on the permanent pacemaker implantation due to the limited sample[14]. It might also be noted that all lesions were create by mono-polar radiofrequency pen which is replaced by bipolar radiofrequency clamp in majority of lesions now.

To sum up, there is no sufficient evidence to determine the safety and potential benefits of BA ablation procedure when comparing with those of LA ablation procedure in patients with RMVD and non-paroxysmal AF. We designed this multi-center prospective RCT to compare the efficacy and safety of BA ablation with LA ablation strategies in patients with RMVD and non-paroxysmal AF.

METHODS AND ANALYSIS

Study objective

The ABLATION trial is designed to examine the hypothesis that for patients with RMVD and non-paroxysmal AF, BA ablation is superior to LA ablation in the probability of freedom from any recurrence of atrial tachyarrhythmias in the absence of antiarrhythmic drugs, and non-inferior to LA ablation in the probability of freedom from permanent pacemaker implantation.

Study design

ABLATION is a multicenter, open-label, two-arm, single-blind, parallel RCT designed to compare the efficacy and safety of BA ablation with those of LA ablation among patients with RMVD and non-paroxysmal AF.

The study plans to recruit patients from 19 large academic cardiac centers all over Chinese mainland. Patients aged ≥ 18 years, with RMVD and non-paroxysmal AF who underwent MV surgery concomitant surgical ablation will be eligible for enrollment. RMVD is determined by history of acute rheumatic fever, valve morphology, echocardiographic findings and pathological diagnosis. Echocardiographic and intraoperative findings of leaflet thickening and retraction, commissural fusion or/and chordal fusion and shortening are considered as RMVD[17].

Exclusion criteria include paroxysmal AF, degenerative or ischemic MV disease, previous catheter ablation or surgical ablation for AF, surgical management of hypertrophic obstructive cardiomyopathy, absolute contraindications for anticoagulation therapy, LA thrombosis, chronic obstructive pulmonary disease, uncontrolled hypo- or hyperthyroidism, LA diameter>70mm, right ventricular dysfunction or moderate to severe tricuspid regurgitation or pulmonary artery systolic pressure >60mmHg, coronary artery bypass grafting required for participants with coronary heart disease. See **Table 1** for details.

Table 1. The inclusion and exclusion criteria for the study

Inclusion criteria
1) Age ≥ 18 years
2) Persistent or long-standing persistent AF documented by medical history or direct electrocardiographic
3) Concomitant cardiac surgery involves at least mitral valve surgery
4) Agree to perform ablation procedure
Exclusion criteria
1) Paroxysmal AF
2) Degenerative or ischemic mitral valve disease

3) Evidence of active infection
4) Previous percutaneous catheter ablation or surgical ablation for AF
5) Surgical management of hypertrophic obstructive cardiomyopathy
6) Absolute contraindications for anticoagulation therapy
7) Left atrial thrombosis (not including left atrial appendage thrombosis alone)
8) Chronic obstructive pulmonary disease (Forced expiratory volume in 1 second (FEV1) <30% anticipated value)
9) Uncontrolled hypo- or hyperthyroidism
10) Mental impairment or other conditions that may not allow participants to understand the nature, significance, and scope of study
11) Left atrial diameter>70mm
12) Right ventricular dysfunction (TAPSE<16) or moderate to severe tricuspid regurgitation or pulmonary artery systolic pressure (estimated by echocardiography) >60mmHg
13) Coronary artery bypass grafting is required for participants with coronary heart disease
14) Previous cardiac surgery
15) Refuse to participate in this study

AF, atrial fibrillation; FEV1: Forced expiratory volume in 1 second; TAPSE, Tricuspid annular plane systolic excursion

Information about trial objective, design, interventions and potential risks and benefits will be introduced thoroughly to all potential participants. They are encouraged to ask questions to study personnel and discuss the trial with family or friends prior to decision to participate. A written consent is mandatory prior to randomization. The study is approved by ethics committees in Fuwai Hospital and has been registered at ClinicalTrials.gov, identifier NCT05021601. All participating sites accepted the central ethics approval or obtained approval by the local ethics committee. The ABLATION trial began recruitment in May 2022 and is expected to complete recruitment by the end of April 2024 and follow-up will be completed by the end of April 2025 (**Figure 1**).

Randomization

Eligible patients were randomized (1:1) to BA ablation group or LA ablation group. An Interactive Web-based Response system will be used to preserve allocation concealment. Randomization is stratified according to center and balanced using randomly permuted blocks

(4 or 6 patients per block). Surgeons are aware of randomization results, however, participants and research staff are all blinded to the randomization schemes.

Treatment arms

The operation will be performed under cardiopulmonary bypass under general anesthesia, and preoperative transesophageal echocardiography will be used to exclude intracardiac thrombi. Except for MV operations, participants randomly assigned to BA ablation group will receive BA ablation, and who randomly assigned to LA ablation group will receive LA ablation. Unified ablation tools and lesion sets are applied during surgical ablation, and the principles of using ablation tools are strictly followed.

BA group

In this arm, Cox-Maze IV lesion sets are created. The detailed lesions were reported by Damiano and James L Cox[18 19]. After the initiation of cardiopulmonary bypass, a vertical right atriotomy is made extending from the intra-atrial septum up towards the atrioventricular groove near the free margin of the heart. And then, from the inferior aspect of the incision, the radiofrequency bipolar clamp is used to create ablation lines up to the superior vena cava and down towards the inferior vena cava. Then the right atrium appendage is clamped by bipolar clamp from the side of the right atrial vertical incision near the atrioventricular groove toward the tip of the right atrium appendage[19]. The transpolar or irrigated radiofrequency pen is used to create an endocardial ablation line from the superior aspect of this vertical right incision down onto the tricuspid annulus at the 2 o'clock position (**Figure 2A**). In order to ensure transmurality, overlap epicardial ablation can be created by radiofrequency pen in line with endocardial ablation line when right atrium wall is thickened significantly.

At left atrium, right pulmonary veins can be isolated by radiofrequency bipolar clamp firstly, and other LA lesions are performed on the arrested heart after aortic cross-clamping. After the ligament of Marshall division, left pulmonary veins (PVs) are isolated by radiofrequency

bipolar clamp. After left atrial appendage (LAA) is amputated, LA roof and floor ablation lines are created to connect with bilateral pulmonary vein isolation (PVI) loops by radiofrequency bipolar clamp. In addition, ablation lines are created to connect right PVI loop towards to the posterior mitral annulus, as well as left superior PV to the LAA by radiofrequency bipolar clamp. Finally, a radiofrequency pen is used to complete the endocardial mitral isthmus lesion, and to perform an epicardial radiofrequency ablation across the coronary sinus in line with the endocardial mitral isthmus lesion created by radiofrequency pen (**Figure 2B**).

LA group

As mentioned above, in this arm, participants are performed LA ablation alone on the arrested heart after aortic cross-clamping (**Figure 2B**).

Each site is effectively ablated at least 3 times with radiofrequency clamp without releasing the radiofrequency clamp. When using dry radiofrequency clamp, the ablation peak value of conductance curve no less than15 and the time of each ablation to the transmural impedance value no longer than 10 seconds is determined as effective ablation. The first time to reach the transmural impedance value must be no less than 3 seconds using irrigated radiofrequency bipolar clamp. Endocardial ablation by radiofrequency pen is performed twice at each 1cm long distance for no less than 15 seconds. MV surgery and other surgery (such as aortic valve surgery) are performed after ablation. All surgeons in this study are required to watch the video of standard Cox-Maze Ⅳ procedure and their surgical ablation procedures will be recorded before the trial, and incorrect or irregular manipulation will be reported back to surgeons, which is initiated to eliminate the impact of different tools and lesions on the results.

Study endpoints

The primary endpoint is the probability of freedom from any recurrence of atrial tachyarrhythmias off antiarrhythmic drugs at 12 months after operation documented by 3-day Holter monitoring. Atrial tachyarrhythmia recurrence will be considered when any episode of AF, atrial flutter or atrial tachycardia is sustained equal to or longer than 30 s on electrocardiogram monitoring after the blanking period[20]. The first 3 months after operation is considered as blanking period.

The key secondary endpoint is the probability of freedom from permanent pacemaker implantation at 12 months after operation, that is, the percentage of participants who do not have a new implanted permanent pacemaker.

The secondary endpoints are the probability of freedom from any recurrence of atrial tachyarrhythmias with antiarrhythmic drugs, AF burden, incidence of adverse events (including cardiac death, stroke, hospitalization for heart failure, hospitalization for embolism events or major bleeding events), and cardiac function documented by echocardiography at 12 months after operation. All endpoints are listed in **Table 2**.

Table 2. Endpoints in this trial

Primary endpoint
• The probability of freedom from any recurrence of atrial tachyarrhythmias without AADs at 12 months after operation
Key secondary endpoint
• The probability of freedom from permanent pacemaker implantation at 12 months after operation
Secondary endpoints
• The probability of freedom from any recurrence of atrial tachyarrhythmias with AADs at 12 months after operation • Burden of AF (Evaluating with 3-day Holter monitoring at 12 months after operation) • Incidence of adverse events (including cardiac death, stroke, hospitalization for heart failure, hospitalization for embolism events or bleeding events) • Cardiac function documented by echocardiography at 12 months after operation

AF: Atrial fibrillation; AADs: Antiarrhythmic drugs

Hospital and surgeon selection

This is a multicenter study, and there are strict requirements for collaborative hospitals and surgeons. The annual volume of surgical ablation concomitant MV operations of hospital should be > 100 cases; surgeons should be proficient in the standard use of radiofrequency bipolar clamps and pens, and the total volume of surgical ablation should be > 20 cases.

Post-ablation management

After the operation, anticoagulation with warfarin is routinely initiated in all participants in the early postoperative period for 3 months, and participants with cardiac mechanical prosthetic valve need lifetime anticoagulation therapy. However, antiarrhythmic drugs are prescribed for 2 months only if AF or atrial flutter occurs during perioperative period.

Data collection and follow-up

A web-based data entry system has been established on the Chinese Cardiac Surgery Registry (CCSR) website (http://ccsr.cvs-china.com)[21]. This web-based CCSR data collection platform uses a high-level secure socket layer. The ABLATION trial uses this paperless data submission system for data collection, follow-up and management. All enrolled hospitals participating in the study are authorized to access the data submission system. The dataset for this study includes the following four modules: subject screening, informed consent and randomization, baseline in-hospital information, 3- month, 6-month and 12-month follow-up data.

For baseline data, participating sites may directly import the in-hospital data into the CCSR database, including patient characteristics, comorbidities, oral medications, preoperative examination (24-hour Holter monitoring, echocardiography, thyroid function and etc.), surgical information, postoperative complications and discharge data. Baseline data should be completed within 14 days after discharge.

All the follow-ups are completed by a professional team blinded to the group allocation. The 3-month and 6-month follow-ups are completed via a remote video interview using social media. All video interviews are recorded. 24-hour Holter monitoring information and questionnaire are collected at 3-month follow-up, and 3-day Holter monitoring information and questionnaire are collected at 6-month follow-up. For the 12-month follow-up, a face-to-face visit is conducted in hospital or via a remote video interview. The study participants will be contacted in advance to confirm the type of 12-month follow-up. Three-day Holter monitoring information, questionnaire and echocardiography are collected at 12-month follow-up. The questionnaire includes questions on subject survival status, cardiac function classification, stroke, peripheral thromboembolic events, hospitalization for heart failure, bleeding events, medication use, and permanent pacemaker implantation. The 3-day Holter monitoring devices are mailed to participants for wearing at 6-month and 12-month follow-up. After wearing, they are sent back to the project team for data analysis. If permanent pacemaker is implanted in a participant during follow-up, we will record the date and reason that the participant's pacemaker is implanted by questionnaire. During participant enrollment, we inform participants that if they have a subsequent readmission for treatment, they need to save and submit their case information to us during follow-up. In addition, we will record and analyze the time taken by the pacing rhythm by 3-day Holter monitoring at 6-month and 12-month follow-up. All the follow-up information will be uploaded to the web-based CCSR data collection platform. In addition, we request participants to have electrocardiogram tests at each follow-up and at any time after surgery if they have cardiac symptoms. The 3-day Holter monitoring, 12-lead electrocardiograms and echocardiograms will be analyzed by a core lab blinded to the group allocation.

Statistical analysis plan

Sample size calculation

The calculation of the sample size is based on the primary endpoint and the key secondary endpoint according to previously published data and our own clinical experience. The primary

endpoint of the study is the probability of freedom from any recurrence of atrial tachyarrhythmias at 12 months after operation. It is estimated that the probability of freedom from atrial tachyarrhythmias at 12 months in the LA group is 70%[10 17 22] and that in the BA group is 85%[10 17 23]. Therefore, a sample size of 131 patients (per group) is needed to provide 90% power based on a one-sided Z test with pooled variance and a significance level of 0.05 (one-sided).

The key secondary endpoint of this study is the probability of freedom from permanent pacemaker implantation at 12 months. It is estimated that the probability of freedom from permanent pacemaker implantation at 12 months in the LA group is 97%[14 24]. Considering the feasibility of clinical studies, the non-inferiority margin is determined as -5%[25-27]. Therefore, a sample size of 144 patients (per group) is needed to provide 80% power based on a one-sided Z test with pooled variance and a significance level of 0.05 (one-sided).

As mentioned above, both primary and key secondary endpoints should be considered. Therefore, 144 patients per group are required. When considering a withdrawal rate of 10%, 320 patients are required to be randomly assigned into two groups in a 1:1 allocation.

Statistical analysis

A hierarchical testing procedure is applied to the primary and key secondary endpoints to preserve the overall type I error of 5%. The key secondary endpoint would only be tested (at significance level 5%) if the test for the primary endpoint is statistically significant (significance level 5%). Non-inferiority will be concluded if the lower limit of the 95% CI for the difference in proportion of participants achieving freedom from atrial tachyarrhythmias is greater than the –5% non-inferiority margin.

We will use frequencies with percentages to describe categorical variables, and means with standard deviations or medians with interquartile ranges to describe continuous variables. We

will compare baseline participant characteristics and endpoints between the LA and BA groups using chi-square tests for categorical variables and student's t-tests for continuous variables. The Kaplan-Meier estimator will be applied to evaluate the probability of freedom from any recurrence of atrial tachyarrhythmias, and the log-rank test will be used for the evaluation of between-group variance. The primary and key secondary endpoints are determined on the basis of the intention-to-treat principle. In addition, a per-protocol analysis is also performed, which includes participants who complete their assigned treatments as scheduled. All statistical tests are one-tailed with a significance level of 0.05.

Patient and Public Involvement

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. Patients and/or the public are not involved in the design, or conduct, or reporting, or dissemination plans of this research.

ETHICS AND DISSEMINATION

Ethics and governance approvals were obtained by the central ethics committee at Fuwai Hospital. Written informed consent will be obtained from all study participants prior any study-specific assessments. The results of this study will be disseminated through publications in peer-reviewed journals and conference presentations.

DISCUSSION

There has been a long-time debate about BA ablation or LA ablation alone for concomitant surgical ablation during MV surgery and relevant guidelines have not given explicit recommendations about it[9 20 28]. After a period of relative neglect, there has been a resurging interest in RHD worldwide over the past decade[2]. Comparing degenerative MV disease, RMVD often has a chronic condition with immune and inflammatory cells attack, which tends to affect the right atrium apart from left atrium, including pulmonary hypertension or tricuspid regurgitation[29]. Previous studies showed that structural and electrical remodeling

uniformly distributed across both atria in RMVD[15 16]. Which lesion set should be preferred to be created during surgical ablation in patients with RMVD and AF? The current literature provides insufficient evidence to address this important clinical issue. Few studies with limited sample size have reported different results of surgical ablation with diverse lesion sets in patients with RMVD and non-paroxysmal AF[11 14 30-34]. Therefore, to the best of our knowledge, ABLATION trial is the first multicenter RCT with large sample size to evaluate the efficacy of BA ablation for patients with RMVD and non-paroxysmal AF.

Whether the additional right atrial ablation to LA ablation increases the risk of permanent pacemaker implantation has been an important controversial topic. Right atrial structural remodelling including atrial fibrosis may influence sinoatrial node function or contribute to sinoatrial block[35]. This condition might be even worse with right atrial lesions are created. However, James L Cox and Niv Ad believe that there are many reasons for permanent pacemaker implantation after surgery, but standardized right atrial ablation set do not increase the risk of permanent pacemaker implantation[36 37]. Other studies displayed LA fibrosis or dilation was associated with sinus node dysfunction requiring pacemaker implant[38 39]. Nevertheless, previous meta-analyses showed that the additional right atrial ablation increased the risk of permanent pacemaker implantation[24]. In order to clarify this topic, we also evaluate the incidence of permanent pacemaker implantation in ABLATION trial. We regard the probability of freedom from permanent pacemaker implantation at 12 months after operation as the key secondary endpoint. A hierarchical testing procedure is applied to the primary and key secondary endpoints to preserve the overall type I error of 5%, which were widely used by previous studies[40 41]. If the hypothesis with endpoint on permanent pacemaker implantation is supported by the result of the ABLATION trial, it's believed that this conclusion can be applied in other MV diseases which have less right atrial remodelling.

This is an investigator-initiated study, and false positive can be controlled less strictly because the issue of false negative is equally important. From the overall study design, a hierarchical

testing procedure is applied to the primary and key secondary endpoints, the hypothesis test of the key secondary endpoint can be carried out only if the primary endpoint reached positive. Therefore, it is very important to obtain the positive result of the primary endpoint with greater power, and then to carry out the sequential test of the key secondary endpoint. Once the hypothesis test of primary endpoint fails, there is no need for hypothesis test of key secondary endpoint. In order to take into account this goal, we tend to choose a greater power (90%). Therefore, we chose a significance level of one-side 0.05 and 90% power.

In order to reduce the missed diagnosis rate of recurrent paroxysmal AF, we assess the primary endpoint of the probability of freedom from any recurrence of atrial tachyarrhythmias by means of 3-day continuous Holter monitoring at 6-month and 12-month follow-up after surgery, which was used by previous study[10]. In addition, 24-hour Holter monitoring will be performed at 3-month follow-up, and 12-lead electrocardiograms will be performed at each follow-up, and for participants who have AF episode or other suspicious cardiac symptoms, all electrocardiograms will be analyzed at any time point after surgery.

It's common that every surgeon has the surgical option based on their understanding on AF[42].According to the guideline[43], all participated surgeons in ABLATION trial are experienced and undergo the training and education to improve their understanding of AF, complete lesion set and every reliable lesion. All surgeons are required to watch the video of standard Cox-Maze Ⅳ procedure and their surgical ablation procedures will be recorded before the trial is initiated. Incorrect or irregular manipulation will be reported back to surgeons. Compared to previous study[44], unified ablation tools and matched lesion set in every group will be emphasized and implemented in order to eliminate the impact of different tools and lesions on the results. In addition, it's possible that the severe right atrial remodeling exists when right ventricular dysfunction or moderate to severe tricuspid regurgitation or severe pulmonary hypertension, which may contribute to the substrate of AF. In these patients, LA ablation alone is unethical, thus, these patients are not enrolled in ABLATION

trial.

In conclusion, the ABLATION trial is designed to examine the efficacy and safety of BA ablation procedure versus LA ablation procedure with unified ablation tools and matched lesion set in patients with RMVD and non-paroxysmal AF. The findings from this trial may help determine an optimal ablation lesion set to further improve the prognosis of patients with RMVD and non-paroxysmal AF.

Authors' contributions: CY, HL, WY, SC, YZ, ZZ: study concept and design; CY, HL, ZZ: drafting the initial manuscript and critical revision of the paper. All authors read and approved the final manuscript.

Funding statement: This work was supported by the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS, 2021-I2M-1-063).

Disclosures: None

Conflicts of interests: The authors declare no conflicts of interests

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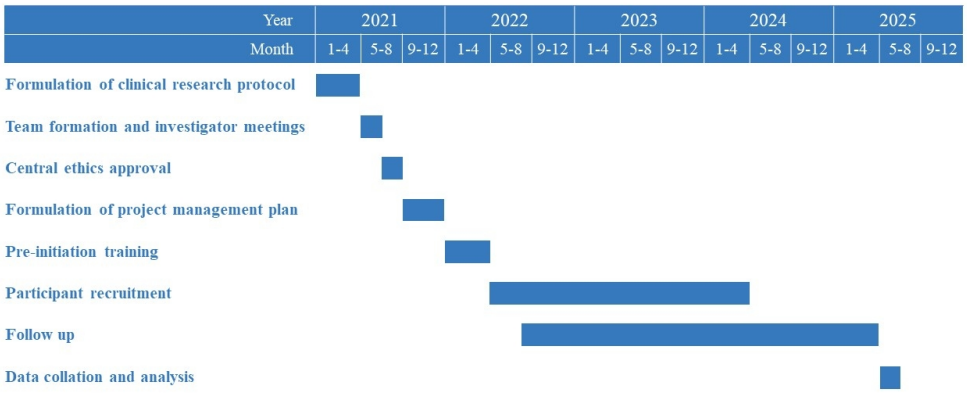
FIGURE LEGENDS

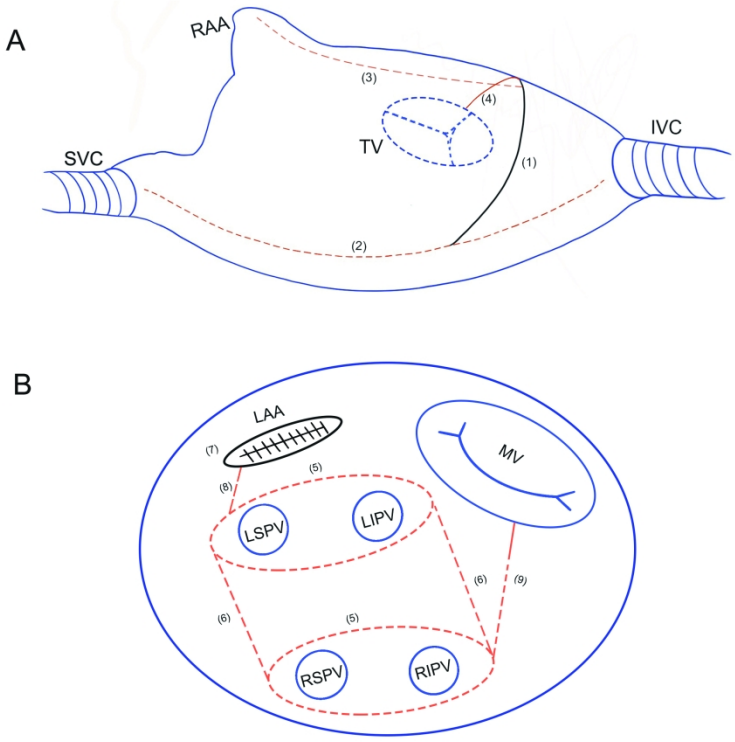
Figure 1. A Gantt plot showing the progress of this study.

Figure 2. Schematic surgical lesion sets. A, right atrial lesions. B, left atrial lesions. The solid black lines indicate the surgical incision, and the dotted red lines indicate the ablation lines by radiofrequency bipolar clamp, and the solid red lines indicate the ablation lines by radiofrequency pen. (1) a vertical right atriotomy extending from the intra-atrial septum up towards the atrioventricular groove; (2) line from SVC to IVC; (3) the RAA is clamped by bipolar clamp from the side of the right atrial vertical incision near the atrioventricular groove toward the tip of the RAA; (4) an endocardial ablation line from the superior aspect of the vertical right incision down onto the tricuspid annulus at the 2 o'clock position; (5) PVI; (6) isolation of the posterior left atrium; (7) management of the LAA; (8) left superior PV to the LAA; (9) mitral isthmus line. IVC, inferior vena cava; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; MV, mitral valve; PVI, pulmonary veins isolation; RAA, right atrial appendage; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SVC, superior vena cava; TV, tricuspid valve.



A Gantt plot showing the progress of this study.

338x190mm (96 x 96 DPI)



Schematic surgical lesion sets. A, right atrial lesions. B, left atrial lesions. The solid black lines indicate the surgical incision, and the dotted red lines indicate the ablation lines by radiofrequency bipolar clamp, and the solid red lines indicate the ablation lines by radiofrequency pen. (1) a vertical right atriotomy extending from the intra-atrial septum up towards the atrioventricular groove; (2) line from SVC to IVC; (3) the RAA is clamped by bipolar clamp from the side of the right atrial vertical incision near the atrioventricular groove toward the tip of the RAA; (4) an endocardial ablation line from the superior aspect of the vertical right incision down onto the tricuspid annulus at the 2 o'clock position; (5) PVI; (6) isolation of the posterior left atrium; (7) management of the LAA; (8) left superior PV to the LAA; (9) mitral isthmus line. IVC, inferior vena cava; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; MV, mitral valve; PVI, pulmonary veins isolation; RAA, right atrial appendage; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SVC, superior vena cava; TV, tricuspid valve.

1119x874mm (72 x 72 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	See clinicaltrials.gov
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2, 18
	5b	Name and contact information for the trial sponsor	See clinicaltrials.gov
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12-13
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14-15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14-15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	See Informed Consent Form
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	See Informed Consent Form
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	See Informed Consent Form
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See Supplemental file

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.