Study Protocol and Statistical Analysis Plan

Cryoballoon Ablation Versus Medical Therapy in Patients with Atrial Fibrillation and Heart Failure with Different Ejection Fraction Categories

1. Study objective

This study is to assess the effectiveness and safety of cryoballoon ablation comparing with medical therapy in patients with atrial fibrillation and heart failure with different ejection fraction categories

2. Study Design

Study Type	Interventional (Clinical Trial)
Estimated Enrollment:	200 participants
Allocation:	No-Randomized
Intervention Model:	Parallel Assignment
Primary Purpose:	Treatment
Estimated Study Start Date:	May 1,2022
Estimated Primary Completion Date:	December 31, 2023
Estimated Study Completion Date:	June 1, 2024

3. Study subjects

Subjects with atrial fibrillation and heart failure with different ejection fraction categories are divided to either an anti-arrhythmic drug or cryoballoon catheter pulmonary vein isolation.

(1) Medical treatment group： receive class I or class III AAD to restore or maintain sinus rhythm; Antiarrhythmic drug including Propafenone, Sotalol, Dronedarone and

Amiodarone;

(2) Experimental: cryoballoon ablation group receive cryoballoon ablation to restore sinus rhythm; Pulmonary vein isolation by cryoballoon ablation using Medtronic Arctic Front Advance™ Cardiac CryoAblation Catheters (23mm and 28mm);

4. Eligibility Criteria

➢ Inclusion Criteria:

(1) Diagnosed with symptomatic paroxysmal or persistent atrial fibrillation： defined as at least two symptomatic episodes in the last six months prior to enrollment.

(2) At least 18 years old and not older than 80 years old.

(3) Able and willing to give informed consent.

➢ Exclusion Criteria:

(1) History of AF treatment with class I or III AAD, including sotalol, with the intention to prevent an AF recurrence. However, patients pretreated with above AAD for less than 7 days with the intention to convert an AF episode are allowed;

(2) Previous left atrial ablation;

(3) Previous cardiac surgery including prosthetic valves;

(4) Permanent pacemaker or defibrillator implant;

(5) Second degree type II or third-degree AV-block or a pattern of left/right bundle branch block;

(6) History of previous myocardial infarction or percutaneous intervention during the last 3 months;

(7) Any history of previous transient ischemic attack, prolonged reversible ischemic neurological deficit, and/or stroke;

(8) Known intracardiac thrombus formation;

(9) Pulmonary vein stent;

(10) Known cryoglobulinaemia;

(11) Active systemic infection;

(12) Hypertrophic cardiomyopathy;

(13) Life expectancy is ≤1 year;

(14) Reversible cause of atrial fibrillation (eg, hyperthyroidism or alcoholism);

(15) Abnormal long or short QT intervals, signs of Brugada syndrome, known family history of inherited ion channel disease, and/or arrhythmogenic right ventricular dysplasia;

(16) Chronic obstructive pulmonary disease with detected pulmonary hypertension and/or any other evidence of significant lung disease;

(17) Contraindication for oral anticoagulation;

(18) Pregnant women or woman of childbearing potential with inadequate birth control;

(19) Women who are breastfeeding;

(20) Any significant congenital heart defect corrected or not corrected; however, patent foramen ovale is allowed;

(21) Thrombocytosis (platelet count＞600,000 /μL) or thrombocytopenia (platelet count＜100,000 /μL);

(22) Untreated or uncontrolled hyperthyroidism or hypothyroidism;

(23) Renal dysfunction with glomerular filtration rate ＜60 mL/min;

(24) Unstable angina pectoris;

(25) Symptomatic carotid stenosis;

(26) Myxoma based on laboratory abnormalities;

(27) Sarcoidosis;

(28) Unwilling to unable to comply with the study procedure and follow-up schedule due to any disease condition;

(29) Legal incapacity or evidence that the patient cannot understand the purpose and risks of the study, including inability to comply fully with study procedures and follow-up;

(30) Employed by Medtronic, or the department of an investigator, or close-familial relative of an investigator;

(31) Enrolled or planning to participate in a potentially confounding drug or device trial during this study.

5. Study Process

5.1 Medical treatment group

Patients admitted to the medical treatment group after screening could receive electrocardiography and receive class I or class III AAD to restore or maintain sinus rhythm. The survey included variables that concern the baseline characteristics of patients, including risk factors, clinical history, cardiac diagnosis, electrocardiogram, echocardiography, laboratory blood tests, and treatments. All patients were symptomatic (functional NYHA class II–IV) and were treated according to contemporary clinical guidelines.

5.2 Cryoballoon ablation group

- **Pre-procedure**

In addition to survey contents for medical treatment group, the Transesophageal echocardiography (TEE) was performed in all patients prior to the procedure. The echocardiographic parameters include left ventricular ejection fraction (LVEF), peak early trans-mitral inflow velocity/peak late mitral inflow velocity ratio (E/A), left atrial diameter (LAD), LV end-diastolic diameter (LVEDD), and LV mass. All recordings were performed and analyzed by the same investigator. In patients on vitamin K antagonists, anticoagulation was continued throughout the procedure, aiming at an international normalized ratio (INR) of 2-3. In patients treated with novel oral anticoagulants (NOACs), the drug was discontinued 12-24 hour prior to the procedure and re-initiated 6-hour post-ablation at half the regular dose, and then at full dose on the following day.

- **Procedure**

All procedures were performed under deep sedation using midazolam, fentanyl, and propofol. A single trans-septal puncture was performed via the right femoral vein under fluoroscopic guidance. Heparin was administered after trans-septal puncture to maintain an activated clotting time ranging from 250 - 350s. In order to identify all PV ostia, selective PV angiography was performed. The second-generation 28-mm CB was advanced into the LA via the 12Fr steerable sheath and a spiral mapping catheter (20-mm diameter; Achieve, Medtronic, Inc.) was advanced into the target PV to record electrical activity. In patients demonstrating AF at the time of the procedure, electrical cardioversion was performed after the final freeze-cycle and PVI was reconfirmed in SR. Phrenic nerve capture was monitored by intermittent fluoroscopy and by tactile feedback of diaphragmatic contraction by the operator’s hand positioned on the patient’s abdomen. The procedure-related complications such as bleeding, phrenic nerve palsy (PNP), cerebral embolism, pericardial effusion/ tamponade or atrioesophageal fistula were evaluated.

- **Post-procedure**

Following ablation, low-molecular-weight heparin was administered to patients on vitamin K antagonists and an INR <2.0 until a therapeutic INR of 2–3 was achieved. NOACs were re-initiated 6 h post-ablation. Anticoagulation was recommended for at least 3 months and thereafter according to the individual CHA2DS2-VASc scores. Previously ineffective antiarrhythmic drugs were continued for 3 months post-ablation. All patients were treated with proton-pump inhibitors for 6 weeks. All patients were treated with optimal medical treatment according to the latest guidelines.

Post-ablation, all patients had in-office Follow-up visit at discharge. A subset of patients reconsented for 1, 3, 6, and 12-month follow-up visits. On follow-up visits physical examination was performed, a 12-lead electrocardio gram (ECG) and 24-h Holter monitor were recorded, and medication changes were documented. In addition, regular telephone interviews were performed. Additional outpatient clinic visits were immediately initiated in cases of symptoms suggestive of recurrent arrhythmia. Repeat ablation was offered to the patient in cases of symptomatic AF/AT recurrence after the blanking period or symptomatic drug-refractory recurrent AF/AT within the blanking period that could not be managed without intervention. Furthermore, LVEF and the NYHA score were systematically evaluated at follow-up on TTE.

6. Outcome Measures

- **Primary Outcome Measures:**

(1) Treatment success at one year

Treatment success at 12 months after antiarrhythmic drug (AAD) initiation or ablation utilizing cryoballoon catheter measured by freedom from AF recurrence following a 3-month period after the index ablation or AAD initiation.

The primary outcome was time to first documented recurrence of symptomatic or asymptomatic atrial tachyarrhythmia (AF, atrial flutter, or atrial tachycardia)

(2) Rate of serious adverse events

Rate of complications and adverse events occurred during cryoballoon ablation and postoperative follow-up, including procedure-related complications such as bleeding, phrenic nerve palsy (PNP), cerebral embolism, pericardial effusion/ tamponade, atrioesophageal fistula, and all-cause mortality, re- hospitalization for HF, and the composite event of all-cause mortality or HF hospitalization.

- **Secondary Outcome Measures**

(1) Quality of life changes at 12 months measured by AF Quality of Life Survey (AFEQT)

The improvement in quality of life between baseline and 12 months after the index ablation procedure or AAD measured by AFEQT is evaluated.

(2) Quality of life changes at 12 months measured by 12-Item Short Form Survey (SF-12)

The improvement in quality of life between baseline and 12 months after the index ablation procedure or AAD measured by SF-12 is evaluated.

(3) Arrhythmia recurrence during blanking period (Time Frame: 3 months)

Atrial tachycardia recurrence rate during the blanking period is evaluated.

7. Statistical analysis

(1) All statistical analyses were performed using SPSS version 22.0 software (SPSS, Chicago, IL, USA).

(2) All continuous variables were recorded as mean ± standard deviation (SD). Categorical variables were presented as numbers or percentages. Between-group comparisons were performed using t-test, Mann–Whitney test, or Chi-square test. Fisher's exact test was used when the observed value in any of the 2×2 contingency table cells was <5. Continuous variables were compared among groups using one-way analysis of variance or Kruskal–Wallis test.

(3) The effect of variables on the EF value was analyzed by univariate and multivariate logistic regression analyses. Baseline clinical features, medical history, and clinical and

laboratory parameters on admission were considered as candidate variables in the multivariate analysis.

(4) The association between the EF group and the outcomes was assessed using univariable and multivariable Cox analyses. Variables of relevant clinical interest considered as covariates were included in the multivariable model to identify the predictors for adverse outcomes according to EF category.

(5)A 2-sided p value less than 0.05 was considered as statistically significant.