Supplement Protocol

Additional low-voltage area ablation in older patients with paroxysmal atrial fibrillation: a randomized controlled trial

This supplement contains the following items：

1. Original protocol.
2. Protocol amendment

Additional low-voltage area ablation in older patients with paroxysmal atrial fibrillation: a randomized controlled trial

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CONTENTS

1 BACKGROUND

Current Status of Catheter Ablation of Paroxysmal Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac rhythm disorder, which affects patients' morbidity and mortality. In 1998, Haissaguerre reported that the pulmonary veins are an important source of ectopic beats, initiating frequent paroxysms of paroxysmal atrial fibrillation (PAF). [1] These foci respond well to the treatment with radiofrequency ablation. Pappone applied circumferential pulmonary vein ablation under the guidance of the electroanatomical mapping system to treat paroxysmal and chronic atrial fibrillation. [2] Then, doctors in Hamburg further emphasized the isolation endpoint of this circumferential ablation confirmed by the double-lasso technique. [3] Currently, the most commonly employed strategy for trigger ablation is the isolation of the pulmonary venous antra from the rest of the left atrium (LA), which has become the cornerstone of all AF ablation. [4]

Pulmonary Vein Isolation alone is not enough

When circumferential wide-antral pulmonary vein isolation (CPVI) was undertaken, the short-term of single-procedure success rate could reach 90%.[3] However, the long-term outcome was quite different. Data from the Hamburg center reported, sinus rhythm (SR) was present in only 46.6% of patients after the single-procedure during a long-term follow-up of 5 years. [5] Recently, CPVI was achieved by using the contact-force sensing catheter and algorithm-based lesion quality control, the single-procedure success rate for PAF was as high as 72.5-75.9% over 1-year follow-up. [6-7] However, the overall success rate for PAF is still unsatisfactory, especially in senior patients, with larger LA size or more comorbidities. [8-9]

Additional Linear Ablation and CFE Ablation without Additional Benefit

In our previous study, we randomized 118 patients with drug-refractory PAF to receive CPVI ablation (n = 60) or complex fragmental electrograms (CFE) ablation (n = 58). Patients who received CFE ablation alone had significantly lower overall success rate (38% vs 77%, P = 0.002) and higher recurrence rate of atrial tachycardia (AT) (34.5% vs 11.9%, P = 0.004) compared with patients who received CPVI alone. Further analysis demonstrated that CPVI plus CFE ablation did not improve the overall success rate (CPVI vs CPVI plus CFE, 77% vs 69%).[10]
In the STAR-AF II trial, 589 patients with persistent atrial fibrillation (PeAF) were enrolled in a 1:4:4 ratio to ablation with pulmonary-vein isolation alone (67 patients), pulmonary-vein isolation plus ablation of electrograms showing complex fractionated activity (263 patients), or pulmonary-vein isolation plus additional linear ablation across the left atrial roof and mitral valve isthmus (259 patients). It demonstrated no reduction in the rate of recurrent AF when either linear ablation or ablation of CFEs was performed in addition to pulmonary-vein isolation in PeAF patients. [11] Similarly, our single-center study found that even with a combination of all these strategies (additional linear ablation or ablation of CFEs), the 15-month success rate was only 50%.[12] It appears that additional linear ablation and CFEs ablation do not dramatically improve the overall success of PeAF ablation. This unsatisfactory result might be due to the high occurrence of post-procedural AT and suggested that extensive CFEs and/or line ablation might be proarrhythmic and more selective areas might be needed to characterize an individualized arrhythmogenic substrate.

Scar Homogenization as the Ablation Strategy for AF

Since the atrial fibrotic areas correlate strongly with AF, catheter ablation targeting these areas as substrate modification beyond CPVI is a new strategy. In the study of Rolf et al, 178 patients with paroxysmal or persistent AF were included. The confined lower voltage area (LVA) was targeted for regional ablation, which aimed to homogenize the diseased LA tissue by radiofrequency ablation during SR. [13] The end point for areal ablation was reached with a significant reduction in local electrograms, defragmentation, and loss of capture while

stimulating the ablation catheter with high output (10 mA; 2 ms) during SR. Strategic linear lesions were performed whenever ablative substrate homogenization could not be completed because of potential collateral damage (e.g, septal near the AV-node or posterior close to the esophagus) or when extensive regional ablation might have created critical isthmus sites for potential macro-reentrant tachycardias (e.g, near the roof or anterior LA to prevent roof-dependent or peri-mitral AT). These strategic linear lesions either connected non-conducting tissues with other anatomic electrical barrier structures traversing target LVA or encircled large LVA to electrically isolate the diseased tissue from the rest of the healthy atrium. The end-point for strategic lesion creation was reached with the confirmation of a complete block (e.g, peri-mitral conduction) as indicated by (1) reduction of local electrogram amplitude, (2) loss of local capture, (3) confirmation of double potentials on the line and analysis of activation sequence, while stimulating near the linear lesion line. After CPVI with or without substrate modification, burst pacing (10V; 2ms) from the proximal coronary sinus was conducted (10-s periods, decreasing cycle lengths from 300ms until refractoriness in 20-ms steps). Inducible regular AT were targeted for radiofrequency ablation with AT termination and non-inducibility as the clinical end-point. The success rate at 12 months was 70% in patients with LVA, and 62% in patients without LVA. Success rate did not differ significantly in paroxysmal patients versus patients with PeAF (69% vs 61%; P = 0.28). In the same way, Kottkamp H et al. applied box isolation of fibrotic areas in both paroxysmal and non-paroxysmal AF patients and achieved favorable results. [14-15]

Voltage-guided ablation of the posterior wall beyond CPVI may also improve arrhythmia-free survival. [16] After CPVI was achieved, posterior wall voltage mapping was performed using a 3-D electro-anatomical mapping system during SR. The presence of a scar was defined as a region that reproducibly demonstrated an area of > 0.25 cm^2 on the posterior wall with a voltage less than 0.5mV. Posterior wall ablation, if the low voltage was found, was preferably performed using a posterior roof line and a floor line completing a posterior wall “box”. Importantly, the borders of the box were intended to encompass the area of low voltage. The low voltage to be targeted without completion of the “box” was allowed if clinically indicated, such as esophageal temperature concerns. Voltage-guided ablation increased 1-year AF/AT free survival in patients compared to standard ablation (80% vs 57%; P = 0.005). However, another study compared the long-term outcome in patients with PAF and severe LA scarring identified by 3-D mapping, in which CPVI only, CPVI plus the scar homogenization, or CPVI plus a strategy of the non-PV triggers were applied. [17] In this selective population, the long-term outcome of CPVI plus scar homogenization was only slightly improved.

We noticed the correlation between AF and atrial fibrosis and hypothesized that the LA fibrotic areas might be the AF-maintaining substrate. Based on this proposition, we performed LA high-density substrate mapping during SR in different AF populations (paroxysmal, non-paroxysmal, and longstanding persistent AF), with 20 normal subjects as controls. Our study showed that with AF progression, the average voltage of LA decreased and the area of the low voltage zone increased; the activation time of the entire LA got longer, while more complex electrograms during SR were found in LA. Importantly, we defined the LVA (voltage range: 0.1-0.4 mV) and the transitional zone (TZ, voltage range: 0.4-1.3 mV) in which 95% of sampling points were located during SR. [18] After this study, a novel ablation strategy was developed (CPVI plus, STABLE-SR), which modified the LA substrate during SR. Our sequential ablation protocol includes 5 steps. First, CPVI should be completed followed by cavotricuspid isthmus ablation. Then, if AF is maintained, direct current cardioversion was performed. High-density mapping of LA substrate would be done during SR to identify the LVA and TZ. Homogenization of the low voltage zones and elimination of the complex electrograms from the TZs would be performed. If possible, linear ablation would be designed according to the mapping results. Finally, bidirectional conduction block should be demonstrated for all the linear lesions, and all the PVs would be double checked for isolation. [19] The most important revolution of our novel approach was the individualized LVA ablation based on electrophysiological mapping results to

avoid empirical linear ablation and subjective CFE ablation.

STABLE-SR Pilot Study

In our single-center pilot study regarding this new ablation strategy for non-paroxysmal AF patients, the promising results were shown. A total of 78 matched patients who had a traditional stepwise ablation strategy were used as the control group. During a follow-up period of >30 months, the Kaplan-Meier estimated probability to maintain SR was 69.8% vs 51.3%. After a single procedure, 3.5% developed post procedural AT in the study group compared with 30% in the control group (P = 0.0003). [19] This strategy proposed a more comprehensive substrate modification approach not only targeting the profound LVA but also addressing the TZs. It is analogous to what has been used in conventional pathologic ventricular tachycardia ablation and is supposed to be the combination of both curative (AF) and preventative (AT) strategies. The other reproducible study was from Dr. Yamaguchi's work. [20]

A Randomised Controlled Multicenter Trial (STABLE-SR)

A large-scale randomized controlled clinical trial was designed and conducted by our center to prove the effectiveness and the reproducibility of this new approach compared to the STEPWISE strategy. In this multicenter, randomized clinical trial, 229 symptomatic non-paroxysmal AF patients were 1:1 randomized to the STABLE-SR group (n=114) or the conventional STEPWISE (n=115) group. At 18 months, 74.0% of the patients in the STABLE-SR group and 71.5% in the STEPWISE group (HR: 0.78, 95% CI: 0.47-1.29, P = 0.325) achieved success according to intention-to-treat analysis. However, less procedure time (186.8±52.7 min vs 210.5±48.0 min, P < 0.001), reduced post-CPVI fluoroscopic time (11.0±7.8 min vs 13.7±8.9 min, P = 0.006), and shorter energy delivery time (60.1±25.1min vs 75.0±24.3 min, P < 0.001) were observed in the STABLE-SR group compared to the STEPWISE group. Over 50% of non-paroxysmal AF patients do not need further ablation beyond CPVI and therefore can avoid excessive ablation. [21]

Why We Start STABLE-SR III Trial?

Currently, effective ablation strategies including CPVI at the PV antrum level, drug provocation, targeting non-PV triggers, and LVA modification have been performed in PAF patients to further improve the success rate. [6-7,13,22] Among these, the benefit of durable CPVI and non-PV triggers ablation has been reported and sufficiently proved. However, the long-term outcome of CPVI is worse in older PAF individuals than that in younger patients; [23-25] moreover, data on LVA ablation in PAF patients is limited and which population benefits the most remains unknown. This poor result might be attributed to the development of different extents of atrial fibrosis which has been supported by various studies of histopathology, [26-27] magnetic resonance imaging, [28]and voltage map. [29] It has been demonstrated that left atrial fibrosis increased with age in both men and women with AF. Our previous studies demonstrated that atrial fibrosis was the proarrhythmic substrate which could be translated into electric signal abnormalities and depicted on 3-D voltage map, [12,19,21] and targeting LVA beyond CPVI was a simplified and personalised adjunctive strategy for persistent AF. [19,21] We hypothesize that senior PAF patients who might have more LA substrate could also benefit from LVA ablation beyond CPVI for further improving the single ablation success rate. Moreover, no study has investigated the prevalence of LVA in senior PAF patients and no randomized clinical trial has been conducted to prove the efficacy and safety of LVA ablation in older patients with PAF. Therefore, we design this multicenter randomized single-blind trial to compare the efficacy of CPVI plus LVA ablation vs CPVI alone in older PAF individuals.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of this investigation is to compare the efficacy of two different AF ablation strategies in older patients with PAF.

The definition of the groups:

Study Group (CPVI plus group): CPVI plus LVA ablation in the left atrium during SR;

Control Group (CPVI alone group): only CPVI.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this investigation are to evaluate and compare:

2.2.1 The safety of:

"CPVI plus" versus "CPVI alone"

2.2.2 The total procedural time of:

"CPVI plus" versus "CPVI alone"

2.2.3 The total fluoroscopic time of:

"CPVI plus" versus "CPVI alone"

2.2.4 The total radiofrequency delivery time of:

"CPVI plus" versus "CPVI alone"

2.3 SUBGROUPS OBJECTIVES

2.3.1 According to the presence or absence of LVA and different ablation strategies, all enrolled patients will be divided into 3 subgroups to evaluate the primary and secondary end-points:
The definition of the subgroup:
Subgroup A: patients with LVA who received "CPVI plus"
Subgroup B: patients with LVA who received "CPVI alone"
Subgroup C: all the enrolled patients without LVA of both groups

2.3.2 Six prespecified subgroups were used for pairwise subgroup analyses: age, sex, body mass index (BMI); AF history; left atrial diameter (LAD); CHA_2DS_2-VASc.

3 ENDPOINTS

3.1 PRIMARY ENDPOINT

The primary endpoint of the study is freedom from atrial tachyarrhythmia (ATA) lasting longer than 30 seconds occurring after a single-ablation procedure. ATA occurrence in the first 3 months after the index ablation (post-blanking period) is not counted. The episodes of ATA are confirmed through blinded review by two senior electrophysiologists. In case of disagreement, a third senior electrophysiologist will be invited for further consultation.

3.2 SECONDARY ENDPOINT

The secondary endpoints of this investigation between two groups are:

3.2.1 Incidence of peri-procedural complications, including stroke, PV stenosis, cardiac perforation, esophageal injury, and death;

3.2.2 Total procedure time;

3.2.3 Total fluoroscopic time;

3.2.4 Total radiofrequency delivery time.

4 PATIENT SELECTION CRITERIA

4.1 PATIENT ENROLMENT

A patient who meets all the inclusion criteria and does not meet any of the exclusion criteria is eligible to participate in the investigation. A patient is enrolled in the investigation only when she/he has provided written informed consent. Once enrolled, the patient is expected to comply with the scheduled visits and required activities according to the protocol.

4.2 INCLUSION CRITERIA

4.2.1 Patient's age is 65-80 years;

4.2.2 Patients with paroxysmal AF; paroxysmal AF will be defined as a sustained episode lasting ≤ 7 days;

4.2.3 Patients can sign the written informed consent for the study;

4.3 EXCLUSION CRITERIA

4.3.1 Patients with previous radiofrequency ablation;

4.3.2 Patients with platelet count less than 80×10^9/L, or with contraindications to systemic anticoagulation with heparin or coumadin or a direct thrombin inhibitor;

4.3.3 Patients with LA size ≥ 55 mm (2D echocardiography, parasternal long-axis view);

4.3.4 Patients with thromboemboli in LA (transesophageal echocardiogram or computed tomographic angiography);

4.3.5 Patients with severe structural cardiac disease (medium or severe mitral regurgitation, dilated cardiomyopathy, hypertrophic cardiomyopathy, or other severe valvular heart diseases);

4.3.6 Patients with abnormal thyroid function;

4.3.7 Patients with severe liver or renal dysfunction (AST or ALT ≥ 3-fold of upper limit value; the Scr > 3.5 mg/dl or Ccr < 30 ml/min);

4.3.8 Previous cardiac surgery history in last 3 months;

4.3.9 Patients with life expectancy < 12 months.

5 INVESTIGATION DESIGN

5.1 TYPE

This investigation is a randomized, prospective, parallel, single-blind multicenter design.

5.2 DURATION

5.2.1 The first enrollment will be in Q1 of April 1, 2018.

5.2.2 The enrolment period will last approximately 24 months.

5.2.3 Patients will participate in this investigation for at least 12 months from enrolment to the last follow-up.

5.2.4 Patients may withdraw from the investigation at any time, for any reason. In this case, the procedures for reporting should be followed as mentioned in section 8.4 Early Conclusion to Patient Participation.

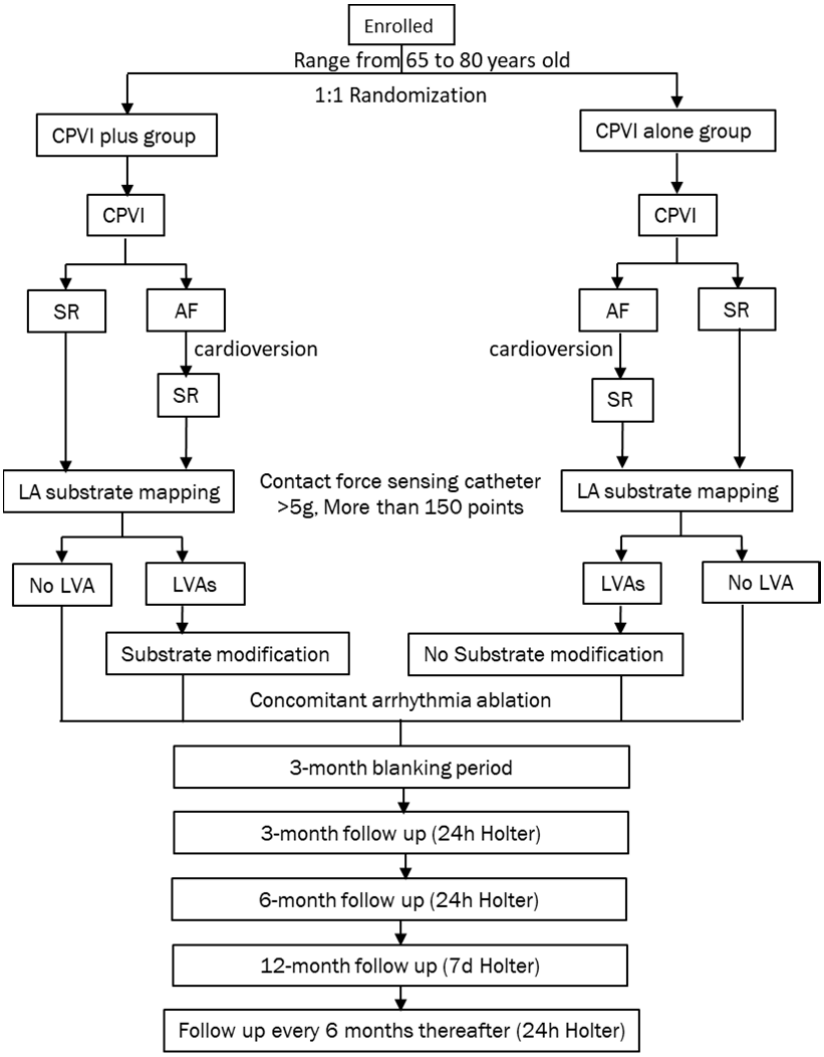
5.3 ENROLMENT TARGET

The enrolment target for this investigation is 434 patients. For more information, refer to section 7.1 Sample Size Justification.

5.4 RANDOMISATION

5.4.1 Simple computerized randomization is used.
5.4.2 Patients are randomized in a 1:1 fashion into the investigation arm or the control arm.
5.4.3 Because of the nature of the ablation procedures, physicians cannot be blinded to the randomization. Patients will be blinded to their ablation strategy (single-blind design).

5.5 DESIGN



CPVI plus group: CPVI plus LVA ablation in the LA during SR;
CPVI alone group: only CPVI.
AF/AT/AFL recurrence during the blanking period will not be considered. If AF/AT/AFL recurrence is detected after the blanking period, the patient would be advised to receive a redo procedure according to the operator.

6 PRODUCT

6.1 MAPPING PLATFORM

CARTO® 3 Mapping system.

6.2 OTHER PRODUCTS

Thermocool smart-touch contact force sensing ablation catheter
Vistag™, ablation index, CARTO® 3

7 SCIENTIFIC SOUNDNESS

7.1 SAMPLE SIZE JUSTIFICATION

7.1.1 The sample size calculation is based on the hypothesis and study design. It is expected that the survival proportion (freedom from AF and/or AT) in the "CPVI plus" group is 85%, while the survival proportion (freedom from AF and/or AT) in the CPVI group is 75% at 12 months follow-up. To test whether the "CPVI plus" strategy is superior to the CPVI strategy using the log-rank test, a total of 369 patients is needed to maintain an overall power of 90% at a significance level of 5%; with a randomization ratio of 1:1, 185 patients are needed in each group. The sample size was calculated based on the Log-rank statistic test (enrolment duration of 24 months, follow-up duration of at least 12 months, PASS 13).

7.1.2 Expecting a dropout rate of 15%, a total of 434 patients (217 in each group) will be recruited.

7.2 HYPOTHESIS

The "CPVI plus" approach will be superior to the "CPVI alone" approach in terms of freedom from AF and/or AT at 12 months after one ablation procedure.
H0: S "CPVI plus" ≤ S"CPVI alone" vs *H1: S"CPVI plus" > S"CPVI alone"*

7.3 PRIMARY ENDPOINT ANALYSIS

7.3.1 The primary endpoint analyses will be based on the modified intention-to-treat (mITT) principle comparing treatment randomized, and all protocol deviators will be included. mITT is defined as patient undergoing ablation and completing at least one follow-up visit. In addition, per-protocol (PPS) analyses will compare patient data based on the actual treatment received and will exclude protocol deviators.

7.3.2 The primary outcome will be analyzed to compare the two groups using survival analyses, in which Kaplan-Meier curves are generated, and log-rank tests are performed. Cox proportion hazards regression is used to estimate HR and 95% confidence intervals (CI). Proportional hazard assumption will be tested by including both the interaction term "treatment*time" and the binary treatment variable into one model. If the proportional hazard assumption is violated, milestone analysis will be used to estimate the treatment effect at the time of 24 months and 36 months. The interactions by age, sex, BMI, AF history, left atrial diameter, and CHA2DS2-VASc score were examined.

7.3.3 Any baseline demographic factor found to be significantly different between the treatments will be assessed for its impact on the primary endpoint analysis. For this purpose, a Cox regression model with treatment and above baseline factor will be used.

7.4 SECONDARY ENDPOINT ANALYSIS

7.4.1 The continuous variables will be summarized using descriptive statistics (mean ± standard deviation) if data are normal distribution or median (IQR) if data are non-normal distribution). Comparisons between the randomization groups will be performed using ANOVA; an equivalent nonparametric method, the Kruskal-Wallis test, will be used in case the assumption for ANOVA is violated. Normality of data will be assessed with the aid of box plots, normal quartile plots, and normality tests. The results will be expressed

in terms of p-values.

7.4.2 All categorical data will be presented using frequencies and percentages, and the comparisons between the randomization groups will be performed using chi-square tests if each cell in the contingency table has an expected frequency of five or more. If this is violated, Fisher's exact test will be used instead. The results will be expressed in terms of p-values.

8 PROTOCOL DESCRIPTION

8.1 PROCEDURES OVERVIEW

Table 1 Procedure Overview

	When	Window	Activities
Enrolment	Within 14 days before or during Baseline Visit	Not Applicable	• Patient Eligibility • Patient Informed Consent
Baseline Visit	Within 30 days before Ablation Procedure	Not Applicable	• Patient Demographics & Physical Examination • Patient Cardiovascular History • Patient Current Cardiac Medications • Patient Medical History • Patient AF History • 12-Lead ECG • UCG (Size of LA, LVEDD, LVEF) • INR (2-3), if warfarin was prescribed • Exclusion of LAA emboli
Ablation Procedure	Within 30 days after Baseline Visit	Not Applicable	• Randomisation • Ablation Procedure Data Collection • Adverse Events (*)
1st protocol follow-up	91 days after first Ablation Procedure (3 Months)	± 14 days	• AF/AT Recurrence Assessment • Patient Current Cardiac Medications • 24-Hour Holter • Adverse Events (*)
2nd protocol follow-up	183 days after first Ablation Procedure (6 Months)	± 14 days	• AF/AT Recurrence Assessment • Patient Current Cardiac Medications • 24-Hour Holter • Adverse Events (*)
3rd protocol follow-up	364 days after first Ablation Procedure (12 Months)	± 14 days	• AF/AT Recurrence Assessment • Patient Current Cardiac Medications • 12-Lead ECG • 7-Day Holter • UCG (Size of LA, LVEDD, LVEF) • Adverse Events (*)
Follow-up every 6 months thereafter	Follow-up every 6 months after 12 Months	± 14 days	• AF/AT Recurrence Assessment • Patient Current Cardiac Medications • 12-Lead ECG • 24-Hour Holter

			• Adverse Events (*)

(*) This is only to be performed when applicable.

8.2 ADVERSE EVENTS

Definition of adverse event, adverse device effect, serious adverse event, and serious adverse device effect according to ISO 14155:

8.2.1 Adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation patient.

8.2.2 Serious adverse event (SAE) is defined as an adverse event that led to a serious deterioration in the health of a patient that resulted in death, a life-threatening illness or injury, permanent impairment of a body structure or a body function, in-patient hospitalization or prolongation of existing hospitalization; and medical or surgical intervention to prevent permanent impairment to a body structure or a body function.

Table 2-Possible Adverse Events

Cardiac Events	Non-cardiac Events
Myocardial infarction	Air embolism
Coronary artery injury	Anesthesia reaction
Pericardial effusion/cardiac tamponade	Cerebrovascular accident
Pulmonary vein stenosis	High creatinine phosphokinase (CPK)
Heart failure	Infections
Component damage to ICD or implantable pacemaker	Local hematomas/ecchymosis
Death	Phrenic nerve damage
Endocarditis	Pneumonia
Hypotension	Pneumothorax
Inadvertent AV block (complete heart block)	Pulmonary edema
Vessel wall/valvular damage or insufficiency	Pulmonary embolism
Pericarditis	Pleural effusion
Pulmonary vein stenosis	Pseudoaneurysm
Ventricular arrhythmia requiring defibrillation	Respiratory depression
	Skin burns
	Syncope
	Transient ischemic attack
	Vasovagal reactions
	cancer

8.2.3 Procedure for Recording and Reporting Adverse Events

8.2.3.1 Safety surveillance and reporting will be done for all patients enrolled in the investigation, regardless of the randomization group.

8.2.3.2 All serious adverse events and all adverse device effects are to be documented and reported to the sponsor immediately.

8.2.3.3 Non-serious adverse events documentation and reporting are limited to cardiovascular and neurovascular events. Within cardiovascular, all arrhythmias that require a medical assessment and/or intervention should be documented as an adverse event.

8.2.3.4 Should an AE occur, record AE information in the hospital records, document the information into the adverse event case report form (CRF) as soon as possible. By completing the CRF, the sponsor will be notified.

8.2.3.4.1 Refer to appendices "Data Collection" and "Data Collection Method."

8.2.3.4.2 Access the eCRF application.

8.2.3.4.3 Select the visit the AE is related to or indicate it as an unscheduled visit.

8.2.3.4.4 Enter adverse event information into the AE Notification section of the CRF.

- ✓ Date the AE occurred;
- ✓ Date the center investigator or delegate became aware of the AE;
- ✓ Main complaints/symptoms of the AE;
- ✓ Initial diagnosis of the AE;
- ✓ Potential cause of the AE;
- ✓ Pre-existing medical conditions related to the AE;
- ✓ The seriousness of the AE;
- ✓ Device relationship to AE; and
- ✓ Status of the AE.

8.2.3.5 When the AE occurs, investigators should report to the Ethic Committee.

NOTE: If an adverse event is documented at the patient's last follow-up visit (12 months), both the notification and follow-up information on the AE CRF is to be provided to the sponsor. Pre-existing cardiac conditions that require planned hospitalization are not to be considered as AE.

8.3 PATIENT DEATH

8.3.1 Procedure for Recording and Reporting Patient Death

Safety surveillance and reporting will be done for all patients enrolled in the investigation, regardless of the randomization group. All Patient Deaths are to be documented and reported to the sponsor immediately. Refer to appendices "Data Collection" and "Data Collection Method";

8.3.1.1 Access the eCRF application;

8.3.1.2 Select the visit the patient death is related to or indicate it as an unscheduled visit.

8.3.1.3 Enter patient death information into the Patient Death CRF:

- ✓ Date the death occurred;
- ✓ Date the center investigator or delegate became aware of the death;
- ✓ Place where the death occurred (e.g., hospital, nursing home, patient's home);
- ✓ If death was witnessed;
- ✓ If an autopsy was performed;
- ✓ Temporal cause of death
- ✓ The primary cause of death;
- ✓ Details regarding death; and
- ✓ If details of a serious adverse event associated with death are known by the center/investigator/delegate.

8.3.1.4 Submit the CRF. When the CRF is submitted, an alert is generated notifying the sponsor.

8.3.1.5 The CRF must be authorized by the principal investigator or delegated co-investigator.

8.3.1.6 Patient death is an early conclusion to the patient's participation in the investigation. Complete Termination CRF.

8.3.1.7 The investigator must notify the EC or IRB, if appropriate, in accordance with national and local laws and regulations.

8.4 EARLY CONCLUSION TO PATIENT PARTICIPATION

All reasonable efforts should be made to retain the patient in the clinical investigation until completion of the clinical investigation.

8.4.1 A patient/family member may request to withdraw from the investigation at any time; she/he may do so without having to justify it and without affecting her/his relationship with the investigator.

8.4.2 A patient dies. Refer to section 8.3, "Patient Death";

8.4.3 An investigator may withdraw a patient from the investigation at any time if she/he thinks it is in the patient's best interest;

8.4.4 An investigator may withdraw a patient if the patient does not attend their scheduled visits and/or is not compliant with the protocol regimen. A patient will be considered "lost to follow-up" when 3 attempts to contact the patient were unsuccessful.

8.4.5 Should a patient withdraw and conclude participation in the investigation, document the information in the termination case report form (CRF) as soon as possible. By completing the CRF, the sponsor will be notified.

8.4.5.1 Refer to appendices "Data Collection" and "Data Collection Method."

8.4.5.2 Access the eCRF application.

8.4.5.3 Enter patient early conclusion information into the Termination CRF.

- ✓ Date the early conclusion occurred;
- ✓ Reason for the early conclusion;

8.5 DEVIATIONS

A deviation is defined as a situation in which there is a non-compliance with the protocol.

8.5.1 Patient informed consent is not approved by Ethics Committee;

8.5.2 Patient informed consent is not signed and/or dated by the patient and/or investigator;

8.5.3 Study-specific procedure was performed before the Patient Informed Consent was signed and dated by the patient;

8.5.4 Investigational required visit not performed;

8.5.5 Investigational required visit performed outside the window;

8.5.6 24-hour or 7-day Holter not performed/data corrupted and not available;

8.5.7 ECG not performed/data corrupted and not available;

8.5.8 Should a deviation occur, document the information in the deviation case report form (CRF). By completing the CRF, the sponsor will be notified.

NOTE: When a deviation occurs after enrolment for patient consent, record the information in the hospital record, immediately document the information in the deviation and termination case report form (CRF). By completing the CRF, the sponsor will be notified.

8.6 ENROLMENT

Enrolment activities are performed after patients are screened and may occur prior to or at the same time as the baseline visit. A patient who meets the inclusion criteria and does not meet the exclusion criteria is eligible to participate in the investigation.

8.6.1 Inform the eligible patient about the investigation and provide written consent to the patient. The process of obtaining written consent from an eligible patient needs to comply with the Declaration of Helsinki, International Standards Organization (ISO) 14155-1, and applicable local laws and regulations.

8.6.2 File the second original appropriately in the Investigator Study Binder (ISB).

8.7 BASELINE VISIT

All baseline activities are performed after the patient is enrolled in the investigation and no more than

30 days prior to undergoing the catheter ablation procedure. The following information will be collected at the baseline visit either from hospital records or through patient interaction:

8.7.1 Patient Demographics & Physical Examination:

8.7.1.1 Record the age;

8.7.1.2 Record the gender;

8.7.1.3 Provide the most recent value (within the last month) of the patient's height;

8.7.1.4 Provide the most recent value (within the last month) of the patient's weight; and

8.7.1.5 Record the blood pressure.

8.7.2 Patient Cardiovascular History

8.7.2.1 Provide the most recent value (within the last month) of the New York Heart Association (NYHA) classification;

8.7.2.2 Provide the most recent value (within the last month) of the left ventricular ejection fraction (LVEF) derived from echocardiography and;

8.7.2.3 Provide the most recent value of the left atrial size derived from echocardiography.

8.7.3 Patient Cardiac Medication

8.7.3.1 Identify the drug category of the cardiac medications the patient is taking currently; and

8.7.3.2 Document the type of antiarrhythmic the patient was taking in the past to manage AF.

8.7.4 Patient Medical History

8.7.4.1 Indicate the pre-existing cardiac conditions and cardiac procedures; and

8.7.4.2 Indicate the non-cardiac medical conditions.

8.7.5 Patient AF History

8.7.5.1 Record the date (year) the patient first experienced AF;

8.7.5.2 Record the number of previous cardioversions for ATAs.

8.7.5.3 Indicate if the patient experienced any arrhythmias other than AF.

8.7.5.4 Calculate CHA_2DS_2-VASc Score

8.7.6 ECG Information: provide the information of the most recent ECG performed (heart rate, rhythm on ECG, QT information, general findings).

8.7.7 Record baseline visit information in hospital records, complete the Baseline Case Report Forms. Every effort would be made to notify the sponsor within 14 days of the visit. The CRF must be authorized by the principal investigator or delegate.

8.8 ABLATION PROCEDURE

8.8.1 All patients will undergo catheter ablation using radiofrequency energy in the cardiac electrophysiology lab as per site practice. Patients may undergo pre-ablation transesophageal echocardiography or LA CTA scan as per site practice. If such imaging is performed, and a LA thrombus is detected, the ablation procedure should be deferred until the thrombus is resolved.

8.8.2 Randomisation: prior to the ablation procedure, randomize the patient. For the randomization instructions, refer to "Appendix Randomisation Instructions."

8.8.3 Ablation Procedure

8.8.3.1 A decapolar diagnostic catheter will be placed in the coronary sinus (CS).

8.8.3.2 All procedures will be performed via transseptal access to the LA.

8.8.3.3 After transseptal access, patients should be anticoagulated with intravenous heparin to maintain an ACT of 250-350 seconds.

8.8.3.4 Pulmonary venography should be performed before ablation. PV stenosis should be documented in CRF.

8.8.3.5 A mapping catheter (Pentaray, Lasso Sensor or Lasso) should be used for both anatomical mapping and confirmation of pulmonary vein isolation.

8.8.3.6 Ablation will be performed using a market-approved open irrigated tip ablation catheter (smart-touch contact force sensing ablation catheter). In Table 3, the maximum authorized power and irrigation settings are shown.

Table 3-Irrigated ablation catheter maximum authorized settings

Power	30-40 W
Flow Rate	17-30 ml/min
Contact force	5-30 g

8.8.3.7 Continuous impedance monitoring should be employed and RF should be discontinued if a ≥10 ohm impedance rise or drop is observed.

8.8.3.8 All procedures will be guided using a cardiac mapping system-CARTO3 System, Biosense Webster Inc. The mapping system will be used to construct a 3-D reconstruction (shell) of the LA, the PV, the CS, and RA if required. LA anatomy was created with a multipolar mapping catheter (Lasso sensor or Pentaray, Biosense Webster) or smart touch contact force sensing ablation catheter. If AF did not convert to SR after CPVI, SR was restored by electrical cardioversion. The number of collected surface points should be at least 150 for LA voltage mapping using smart touch contact force sensing catheter with over 5 g per point. If the AF transforms to atrial flutter or tachycardia during ablation, LA voltage mapping will be conducted until SR was achieved by ablation.

8.8.3.9 After the geometry is completed, the ablation catheter is used to accurately mark the orifices of PVs on the model. After the substrate map, the region and size of LVA and the average voltage will be calculated.

8.8.4 Ablation Strategies

8.8.4.1 A description of the specific catheter ablation strategies is detailed in the following sections: see 8.8.5. and 8.8.6.

"CPVI plus" group: CPVI plus LVA ablation if LVA existed; See 8.8.6.
Control group: CPVI alone regardless of LVA (see 8.8.5).

8.8.5 Wide Circumferential Pulmonary Vein Antrum Isolation

8.8.5.1 Through transseptal accesses, the mapping and ablation catheters will be advanced into the LA, followed by reconstruction of the LA and PV anatomy using the CARTO3 system.

8.8.5.2 The ostia and the antra of the PVs will be defined by pulmonary venography, 3D electroanatomical shell, and local potentials.

8.8.5.3 The mapping catheter will then be placed sequentially within each of the PV antra to record PV potentials. Circumferential RF lesions will then be placed at least 1-2 cm outside of the PV ostia to encircle and electrically isolate each of the PV antra in order to avoid PV stenosis.

8.8.5.4 As each antrum is encircled, the mapping catheter should be used to confirm electrical isolation. Isolation of the PV antrum will be considered complete when all PV potentials within each antrum are abolished, as recorded by the Pentaray, Lasso Sensor or Lasso mapping catheter.

8.8.5.5 No intravenous antiarrhythmics should be used during ablation to change AF cycle length or to help regularize/terminate AF if AF is sustainable after CPVI.

8.8.5.6 If AF terminates or converts to AT before isolation, ablation should not be discontinued until PVs are isolated.

8.8.5.7 Ablation lesion tags should be added to the model surface using the Vistag^{TM}. The settings of Vistag^{TM} were as follows：

Table 4-Settings for Vistag™

Respiration Adjustment	2.5 mm
Stability Min. Time	3 ms
Contact force	5-30 g

8.8.5.8 The target ablation index (AI) was 500 for anterior, 450 for roof, and 400 for inferior and posterior segments.

8.8.6 CPVI Plus LVA Ablation in the LA during SR

8.8.6.1 Patients randomized to the study group will first undergo wide CPVI as described in Section 8.8.5. The endpoint will be complete isolation of all four PV antra as detailed above.

8.8.6.2 After sedation, Cardioversion with direct current (biphased 200 J or monophased 360 J) should be applied if AF is present following CPVI.

8.8.6.2.1 If the rhythm is converted to SR, the times and energy should be recorded;

8.8.6.3 If organized AT with consistent cycle length occurs during ablation, electrophysiologic mapping and ablation should be performed until conversion to SR.

8.8.6.4 Electrophysiologic voltage substrate mapping under SR with smart-touch contact force with over 5 g per point.

8.8.6.4.1 At least 150 surface points should be mapped;

8.8.6.4.2 Bipolar recordings are to be filtered at 30-300 Hz.

8.8.6.5 LA Substrate Ablation

8.8.6.5.1 After voltage mapping with the setting of Color bar 0.1-0.5 mV, the area with voltage less than 0.1 mV is identified as a dense scar. LVA was defined as areas with amplitude less than 0.5 mV in more than 3 adjacent low-voltage points with space difference of 0.5 cm. LVA burden was defined as the proportion of LVA over entire LA surface.

8.8.6.5.1.1 The endpoint of ablation: all the electrograms in LVA should be ablated down to 0.1 mV to create a dense scar or box isolation surrounding LVA.

8.8.6.5.1.2 If the distance between two LVA or LVA to electrical barriers is less than 1 cm, the ablation lines will be designed to close the "channel".

8.8.6.6 Ablation catheter will be withdrawn into the right atrium. CTI ablation will proceed if typical atrial flutter was recorded before the procedure or present during the ablation procedure.

8.8.6.7 All ablation lines should be assessed with bidirectional conduction block if linear ablation was applied. Box isolation should be assessed by dissociated electric activities with high output pacing inside the box area (10 mA, 2 ms). Homogenized areas should be checked with the non-capture property also by high output pacing. All assessment segments should be recorded.

8.8.6.7.1 **To assess the block of CTI**: the CS catheter is always set as position reference and the proximal electrodes are placed at the ostium of CS. Activation mapping is recommended for assessment:

8.8.6.7.1.1 ABLd will be placed at the lateral side of the CTI line as possible as close to the lower RA:

8.8.6.7.1.1.1 Pacing from ABLd (S1S1 500 ms), segments should be recorded after consistent capture. The interval between stimulation spike and CSp will be measured as "LRA-S1."

8.8.6.7.1.1.2 Pacing from CSp (S1S1 500 ms), segments should be recorded after consistent capture. The interval between stimulation spike and ABLd will be measured as "CSp-S1."

8.8.6.7.1.2 The ABLd will be moved more laterally away from the CTI line (approximately 1 cm):

8.8.6.7.1.2.1 Pacing from ABLd (S1S1 500 ms), segments should be

recorded after consistent capture. The interval between stimulation spike and CSp will be measured as "LRA-S2."

8.8.6.7.1.2.2 Pacing from CSp (S1S1 500 ms), segments should be recorded after consistent capture. The interval between stimulation spike and ABLd will be measured as "CSp-S2."

8.8.6.7.1.3 The criteria for bidirectional block:

8.8.6.7.1.3.1 Counterclockwise conduction block: LRA-S1 > LRA-S2.

8.8.6.7.1.3.2 Clockwise conduction block: CSp-S1 > CSp-S2.

8.8.6.7.2 **To assess the block of roof line**: the mapping catheter will be placed into LAA. The electrode pair near the roof is chosen as LAA recording electrodes:

8.8.6.7.2.1 ABLd will be positioned on the posterior wall at the middle of two PV ablation circles nearby the roof line (PS):

8.8.6.7.2.1.1 Pacing from LAA (S1S1 500 ms), segments should be recorded after consistent capture. The interval between stimulation spike and ABLd will be measured as "LAA-PS."

8.8.6.7.2.1.2 Pacing from ABLd (S1S1 500 ms), segments should be recorded after consistent capture. The interval between stimulation spike and LAA will be measured as "PS-LAA."

8.8.6.7.2.2 The ABLd will be moved more inferiorly away from the roof line (approximately 1 cm):

8.8.6.7.2.2.1 Pacing from LAA (S1S1 500 ms), segments should be recorded after consistent capture. The interval between stimulation spike and ABLd will be measured as "LAA-PI."

8.8.6.7.2.2.2 Pacing from ABLd (S1S1 500 ms), segments should be recorded after consistent capture. The interval between stimulation spike and LAA will be measured as "PI-LAA"

8.8.6.7.2.3 The criteria for bidirectional block:

8.8.6.7.2.3.1 Conduction from anterior to posterior has been blocked: LAA-PS > LAA-PI.

8.8.6.7.2.3.2 Conduction from posterior to anterior has been blocked: PS-LAA > PI-LAA.

8.8.6.7.2.3.3 If the posterior wall cannot be captured because of isolation, it can be accepted as blocked.

8.8.6.7.2.4 The criteria for box isolation

8.8.6.7.2.4.1 The endpoint of Box isolation non-capture by high output pacing within box area.

8.8.6.7.3 **To assess the block of anterior or lateral mitral line:**

The mapping catheter will be placed into LAA. A quick activation map should be performed to check the bidirectional conduction block by pacing on both sides at 500 ms.

8.8.6.8 If the assessment of the conduction block does not meet the criteria, the next steps are as follows:

8.8.6.8.1 Continue linear ablation along with the previous lesion until blocked;

8.8.6.8.2 If a complete linear block cannot ever be achieved in 30 min, despite the investigator's best efforts, then this should be documented in the Ablation Case Report Form. This, however, would not be considered a protocol deviation.

8.8.6.9 **Non-PV triggers or concomitant arrhythmia ablation:**

8.8.6.9.1 Further ablation should be performed, if non-PV triggers, atrial tachycardias, or supraventricular tachycardias were present after CPVI and LVA ablation procedure.

8.8.7 All cases will be recorded and uploaded to the core lab. Patient with the information

including study site number, patient number, patient name, and study group and date.

8.8.8 Post Ablation Activities

8.8.8.1 If sustained ATAs occur during the blank period, cardioversion should be undertaken within 48 hours.

8.8.8.2 Anticoagulation therapy: all patients will remain anticoagulated with warfarin to maintain an INR of 2-3 or a NOAC for a minimum of 3 months post-ablation.

8.8.8.3 Antiarrhythmic medications: antiarrhythmic medications may be continued for the first 3 months following the first ablation to avoid early recurrences. At 3 months, antiarrhythmics must be stopped to assess for clinical recurrence. The decision to use antiarrhythmics after three months, and the choice of AAD, will be left to the discretion of the investigators.

8.9 REQUIRED FOLLOW-UP

8.9.1 Scheduled visits will occur at 3, 6, 12 months after the first ablation procedure (± 14 days for each time point for follow-up). The follow-up will be performed in the outpatient department clinic of each participating institution.

8.9.2 The Follow-Up schedule is summarized in Table 1.

8.9.3 The following information will be collected at the follow-up visit either from hospital records or through patient interaction:

8.9.3.1 Physical Examination

Collect the blood pressure;

8.9.3.2 Recurrence of ATAs

List the ATA episodes the patient experienced since the last visit;

Provide the duration of the episodes;

8.9.3.3 Patient Cardiac Current Medication

Document a change in cardiac medication therapy since the last visit.

8.9.3.4 ECG Information

Provide the information from ECG performed during the visit (heart rate, rhythm, QT information, and other findings).

8.9.3.5 24-hour Holter

List the ATA episodes collected by the 24-hour Holter;

Provide the duration of episodes.

8.9.4 At the follow-up of 12 months, it is recommended that patients have a final standard transthoracic echocardiogram to assess left atrial size, valvular heart disease, and ejection fraction. 7-day Holter will also be performed.

8.10 REPEAT ABLATION PROCEDURES

8.10.1 Blanking Period after the first ablation procedure:

A 3-month blanking period will be employed after the first procedure as per the HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation. During this blanking period, recurrences of ATAs will not be counted and repeat procedures should not be performed in the first 3 months after the first ablation.

8.10.2 Repeat ablation procedure in both groups:

8.10.2.1 During the second procedure in both arms, identification of conduction gaps between the PVs and LA should be identified. Gaps should be targeted for ablation to re-isolate the PV antra.

8.10.2.2 Repeat ablation in both arms will be performed as STABLE-SR-III 8.8.6.

9 RISK DESCRIPTION AND MINIMIZATION

There are no data suggesting that the risks as reported in section 8.2 Adverse Events are any higher with one strategy over the other. In fact, as shown in our STABLE-SR pilot study, this novel approach was not associated with any increased risk over CPVI alone. Even fluoroscopic exposure time and procedural time were not significantly different between the two arms.

10 INVESTIGATION ORGANIZATION

10.1 INVESTIGATION MANAGEMENT

The organization that takes responsibility for the initiation and/or implementation and coordination of the investigation is The First Affiliated Hospital of Nanjing Medical University, located at:

300 Guangzhou Road
Nanjing, Jiangsu Province
P.R. China
Tel: +86 25 68303117

10.1.1 Sponsor's responsibilities are in accordance with applicable ISO 14155 guidelines;
10.1.2 This includes but is not limited to the following activities:
10.1.2.1 Select the clinical investigators;
10.1.2.2 Activate the study centers after receipt of the required documentation;
10.1.2.3 Develop the study database, and perform the analysis;
10.1.2.4 Sign off the clinical investigational plan before the start of the investigation or after modifications to the protocol;
10.1.2.5 Reviewing collected data and investigation documentation for completeness and accuracy;
10.1.2.6 Ensure that all adverse events and adverse device effects are reported and reviewed by the clinical investigator(s) and where appropriate that all serious adverse events and serious adverse device effects are reported to the relevant authorities and Ethics Committee(s) and or safety monitoring committee(s).

10.2 CLINICAL COORDINATING INVESTIGATOR

The clinical coordinating investigator of the STABLE-SR III investigation is:
Minglong Chen, M.D.
Department of Cardiology
300 Guangzhou Road
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Tel: +86 13809000791
E-mail: chenminglong@njmu.edu.cn

10.3 INVESTIGATOR

An investigator is defined as an individual and/or institution responsible for the conduct of a clinical investigation who and/or which takes the clinical responsibility for the well-being of the subjects involved.

10.3.1 Investigator Responsibilities

By agreeing to this protocol, the investigators and their institutions accept to allow monitoring, audits, Ethics Committee and IRB review, and regulatory inspections that are related to the investigation. They also agree to provide authorized individuals with direct access to source data and documentation and the right to copy records, provided that such activities do not violate patient consent and patient data confidentiality:

10.3.1.1 Providing signed Investigator/Co-Investigator(s) Agreement.
10.3.1.2 Providing appropriate Ethics Committees Approved Informed Consent.
10.3.1.3 Collection and archiving of data obtained after implant and at follow-up examinations and after the investigation has been completed.
10.3.1.4 Screening and selecting appropriate patients.

10.3.1.5 Supporting the monitor and auditor, if applicable, in their activities to verify compliance with the CIP, to perform source data verification and to correct the case report forms where inconsistencies or missing values are identified.

10.3.2 Investigator study binder

The investigator will be provided with an Investigator Study Binder (ISB) at the start of the investigation. This file contains all relevant documents necessary for the conduct of the investigation.

10.4 ETHICAL BASIS

This investigation will be performed in accordance with the World Medical Association Declaration of Helsinki (Appendix C), ISO 14155, and all local legal and regulatory requirements.

Prior to the start of the investigation, the clinical investigational plan will be submitted together with its associated documents (patient information sheets, patient informed consent forms in the local language) to the relevant Ethics Committee (EC)/Institutional Review Board (IRB) for review. Any amendments to the protocol should be submitted to the relevant EC/IRB. EC/IRB will be informed about SAEs and UADEs in accordance with local and national requirements.

10.5 MONITORING

It is the responsibility of the CRO to ensure proper monitoring of the investigation and ensure that the investigation is conducted, recorded, and reported in accordance with the Clinical Investigational Plan, the signed Clinical Study Agreement, and the applicable laws and regulations. Monitoring will be conducted at the centers participating in the investigation according to the standard operating procedures and work instructions. An overview of the monitoring activities is shown in Table 5.

Table 5-Monitoring Activities

Visit Type	Prompted By	Scope of Visit	
Initiation	● Receipt of essential documents for center ● Ethics Committee (EC) approval of Protocol ● EC approved Patient Informed Consent (PIC) ● Agreement plus exhibits completed, signed and dated by the center	No patient data	● Train staff participating in the investigation

Periodic	• Enrolment of minimum, 1 patient at the center • Enrolment of greater than 10 patients at the center • Verification of critical data before database freeze and analysis • Patient data quality issues identified at the center • Regulatory issues identified • Safety issues identified	• Review patient's consent, and review patient data compared to the source document • Generate DCFs for missing and/or inaccurate patient data recorded in the CRFs • Review adherence to the protocol	• Resolve outstanding issues from previous monitoring visits • Meet with delegated center staff to review and resolve issues and DCFs in a report • Retrain staff (center) conducting the investigation when necessary
Close Out	• All patients enrolled at the center completed participation in the protocol	• Review patient's consent, and review patient data compared to the source document • Generate DCFs for missing and/or inaccurate patient data recorded in the CRFs • Review adherence to the protocol	• Resolve outstanding issues from previous monitoring visits • Meet with delegated center staff to review and resolve issues and DCFs in a report • Retrain staff (center) conducting the investigation when necessary

10.6 STUDY REPORT AND PUBLICATION POLICY

After the conclusion of the investigation, an integrated clinical and statistical report shall be written by the clinical coordinating investigator. The first publication will contain all data from all sites.

11 APPENDIX A: ABBREVIATIONS

Abbreviation	Description
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AT	Atrial Tachycardia
CRF	Case Report Form
EC	Ethics Committee
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EGM	Intracardiac Electrograms
FU	Follow-Up
INR	International Normalized Ratio
LA	Left Atrium
MA	Mitral Annulus
MRI	Magnetic Resonance Imaging
CPVI	Circumferential Pulmonary Vein Isolation
RA	Right Atrium
SAE	Serious Adverse Event

12 APPENDIX B: DATA COLLECTION

Assessments	Baseline/ Pre-Ablation	Pre-Discharge	3 M [Days 76-104]	6 M [Days 166-210]	12 M [Days 330-420]	every 6 months thereafter
Clinic visit	X	/	X	X	X	X
Informed Consent	X					
Demographics	X					
Medical history	X					
AF status	X					
Past and current Cardiac medication	X	X	X	X	X	X
Current anticoagulation regime	X	X	X	X	X	X
ECG	X				X	X
24h Holter	X		X	X		X
7days Holter					X	
UCG	X				X	
TEE or CT	X					
TTE	X					X
AF/AT/AFL recurrence		X	X	X	X	X
Repeat ablation		X	X	X	X	X
Adverse events	X	X	X	X	X	X
Major clinical events as defined in the protocol	X	X	X	X	X	X

13 APPENDIX C: RANDOMISATION INSTRUCTIONS

Central randomization is used in this investigation. You must log in the Automated Randomisation System via the internet. Each patient will be given a random number.

APPENDIX D: REFERENCES

1. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10):659-666.
2. Pappone C, Rosanio S, Oreto G, et al. Circumferential radiofrequency ablation of pulmonary vein ostia: A new anatomic approach for curing atrial fibrillation. Circulation. 2000;102(21):2619-2628.
3. Ouyang F, Bänsch D, Ernst S, et al. Complete isolation of left atrium surrounding the pulmonary veins: new insights from the double-Lasso technique in paroxysmal atrial fibrillation. Circulation. 2004;110(15):2090-2096.
4. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31(19):2369-2429.
5. Ouyang F, Tilz R, Chun J, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation. 2010;122(23):2368-2377.
6. Reddy VY, Dukkipati SR, Neuzil P, et al. Randomized, Controlled Trial of the Safety and Effectiveness of a Contact Force-Sensing Irrigated Catheter for Ablation of Paroxysmal Atrial Fibrillation: Results of the TactiCath Contact Force Ablation Catheter Study for Atrial Fibrillation (TOCCASTAR) Study. Circulation. 2015;132(10):907-915.
7. Natale A, Reddy VY, Monir G, et al. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. J Am Coll Cardiol. 2014;64(7):647-656.
8. Berruezo A, Tamborero D, Mont L, et al. Pre-procedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation. Eur Heart J. 2007;28(7):836-841.
9. Kornej J, Hindricks G, Shoemaker MB, et al. The APPLE score: a novel and simple score for the prediction of rhythm outcomes after catheter ablation of atrial fibrillation. Clin Res Cardiol. 2015;104(10):871-876.
10. Chen M, Yang B, Chen H, et al. Randomized comparison between pulmonary vein antral isolation versus complex fractionated electrogram ablation for paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2011;22(9):973-981.
11. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015;372(19):1812-1822.
12. Lin Y, Ju W, Yang B, et al. Does linear ablation and defragmentation really improve the success rate of persistent AF? Follow-up results and electrophysiological findings from 169 consecutive patients. Int J Cardiol. 2013;168(1):452-457.
13. Rolf S, Kircher S, Arya A, et al. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol. 2014;7(5):825-833.
14. Kottkamp H, Bender R, Berg J. Catheter ablation of atrial fibrillation: how to modify the substrate. J Am Coll Cardiol. 2015;65(2):196-206.
15. Kottkamp H, Berg J, Bender R, Rieger A, Schreiber D. Box Isolation of Fibrotic Areas (BIFA): A Patient-Tailored Substrate Modification Approach for Ablation of Atrial Fibrillation. J Cardiovasc Electrophysiol. 2016;27(1):22-30.
16. Cutler MJ, Johnson J, Abozguia K, et al. Impact of Voltage Mapping to Guide Whether to Perform Ablation of the Posterior Wall in Patients With Persistent Atrial Fibrillation. J Cardiovasc Electrophysiol. 2016;27(1):13-21.
17. Mohanty S, Mohanty P, Di Biase L, et al. Long-term follow-up of patients with paroxysmal atrial fibrillation and severe left atrial scarring: comparison between pulmonary vein antrum isolation only or pulmonary vein isolation combined with either scar homogenization or trigger ablation. Europace. 2017;19(11):1790-1797.
18. Lin Y, Yang B, Garcia FC, et al. Comparison of left atrial electrophysiologic abnormalities during sinus rhythm in patients with different type of atrial fibrillation. J Interv Card Electrophysiol. 2014;39(1):57-67.
19. Yang G, Yang B, Wei Y, et al. Catheter Ablation of Nonparoxysmal Atrial Fibrillation Using Electrophysiologically Guided Substrate Modification During Sinus Rhythm After Pulmonary Vein Isolation. Circ Arrhythm Electrophysiol. 2016;9(2):e003382.
20. Yamaguchi T, Tsuchiya T, Nakahara S, et al. Efficacy of Left Atrial Voltage-Based Catheter Ablation of Persistent Atrial Fibrillation. J Cardiovasc Electrophysiol. 2016;27(9):1055-1063.
21. Yang B, Jiang C, Lin Y, et al. STABLE-SR (Electrophysiological Substrate Ablation in the Left Atrium During Sinus Rhythm) for the Treatment of Nonparoxysmal Atrial Fibrillation: A Prospective, Multicenter Randomized Clinical Trial. Circ Arrhythm Electrophysiol. 2017;10(11).
22. Lin WS, Tai CT, Hsieh MH, et al. Catheter ablation of paroxysmal atrial fibrillation initiated by

non-pulmonary vein ectopy. Circulation. 2003;107(25):3176-3183.
23. Bulava A, Hanis J, Dusek L. Clinical outcomes of radiofrequency catheter ablation of atrial fibrillation in octogenarians-10-year experience of a one high-volume center. J Geriatr Cardiol. 2017;14(9):575-581.
24. Metzner I, Wissner E, Tilz RR, et al. Ablation of atrial fibrillation in patients ≥75 years: long-term clinical outcome and safety. Europace. 2016;18(4):543-549.
25. Bunch TJ, May HT, Bair TL, et al. The Impact of Age on 5-Year Outcomes After Atrial Fibrillation Catheter Ablation. J Cardiovasc Electrophysiol. 2016;27(2):141-146.
26. Gramley F, Lorenzen J, Knackstedt C, et al. Age-related atrial fibrosis. Age (Dordr). 2009;31(1):27-38.
27. Goette A, Juenemann G, Peters B, et al. Determinants and consequences of atrial fibrosis in patients undergoing open heart surgery. Cardiovasc Res. 2002;54(2):390-396.
28. Oakes RS, Badger TJ, Kholmovski EG, et al. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. Circulation. 2009;119(13):1758-1767.
29. Tuan TC, Chang SL, Tsao HM, et al. The impact of age on the electroanatomical characteristics and outcome of catheter ablation in patients with atrial fibrillation. J Cardiovasc Electrophysiol. 2010;21(9):966-972.

Supplement Protocol amendment

This supplementary appendix has been provided by the investigators to give readers additional materials about their work.

Supplement to: Additional low voltage area ablation in older patients with paroxysmal atrial fibrillation: a randomized controlled trial (STABLE-SR-III)

Protocol amendment

Ten centers in mainland China initially participated in this randomized trial in March 2018 as following:

1. The First Affiliated Hospital of Nanjing Medical University
2. The First Affiliated Hospital of Wannan Medical College
3. The Affiliated Hospital of Xuzhou Medical University
4. The Second Affiliated Hospital of Nantong University
5. The Second Hospital of Hebei Medical University
6. ZhongDa Hospital, Southeast University
7. The First Affiliated Hospital of Soochow University
8. Air Force Military Medical University
9. the Affiliated Xuzhou Hospital of Medical College of Southeast University
10. The Third Affiliated Hospital of Soochow University

Due to the COVID-19 pandemic and the slow enrollment than expected in some centers, we invited the following four more centers to participate the multicenter randomized control trial in June 2019. Hence, fourteen centers participated in this randomized trial.

1. The First Affiliated Hospital of Wenzhou Medical University
2. Tianjin Chest Hospital
3. The First Affiliated Hospital of Southern Medical University
4. Sir Run Run Shaw Hospital, affiliated with the Zhejiang University School of Medicine