RE-ABLATION OF PERSISTENT ATRIAL FIBRILLATION: A RANDOMIZED STUDY, EVALUATING VEIN OF MARSHALL ETHANOL ABLATION IN COMBINATION WITH BLOCK OF MITRAL AND TRICUSPID ISTHMUSES AND DOME LINE

An investigator initiated, randomized, patient-assessor blinded multi-center trial

Sponsor: Aarhus University Hospital

Participating centres:

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List of abbreviations

AF Atrial fibrillation

AFEQT: Atrial Fibrillation Effect on Quality of Life

AAD: Antiarrhythmic drugs

CFAE: Complex Fractionated Atrial Electrograms

CTI: Cavotricuspid Isthmus

DC: Direct Current

ECG: Electrocardiogram

LA: Left atrium

PAF: Paroxysmal atrial fibrillation

PsAF: Persistent atrial fibrillation

PV: Pulmonary Vein

PVI: Pulmonary Vein Isolation

QoL: Quality of Life

VOM: Vein of Marshall

Protocol overview	
Title	RE-ABLATION OF PERSISTENT ATRIAL FIBRILLATION: A RANDOMIZED STUDY, EVALUATING VEIN OF MARSHALL ETHANOL ABLATION IN COMBINATION WITH BLOCK OF MITRAL AND TRICUSPID ISTHMUSES AND DOME LINE
Acronym	Re-AF study
Study design	**An investigator initiated, randomized, patient-assessor blinded multi-center trial**
Participating centers	Department of Cardiology, Aarhus University Hospital Department of Cardiology, Karolinska University Hospital, Stockholm Department of Cardiology, Leiden University Medical Center
Hypotheses	Addition of Vein of Marshall ethanol ablation in combination with block of mitral and tricuspid isthmuses and dome line to standard pulmonary vein re-isolation improves quality of life and reduces recurrence of atrial arrhythmias as compared to standard pulmonary vein re-isolation alone in patients undergoing re-ablation for persistent atrial fibrillation.
Eligibility criteria	Inclusion criteria: • Previous pulmonary vein isolation for atrial fibrillation • Indication for catheter ablation with at least two episodes of symptomatic PsAF during the last 12 months • Age ≥ 18 years • Expected survival ≥ 12 months • Able to provide informed consent Exclusion criteria: • Previous extrapulmonary atrial ablation other than cavotricuspid isthmus line, roof- or dome line or posterior wall isolation/ablation • Atypical atrial flutter in addition to atrial fibrillation • Atrial fibrillation secondary to a transient abnormality • Uncontrolled hypertension • Acute coronary syndrome, cardiac surgery, or TIA/stroke within the last 3 months • Planned cardiac surgery within 1 year • Dialysis or severe renal failure • Active substance or alcohol abuse (>14 units/week)

Randomization and conduct of the study	In a patient-assessor blinded, randomized multi-center study, consecutive patients undergoing re-ablation for persistent atrial fibrillation are randomized (1:1) to: 1) standard therapy including re-isolation of pulmonary veins (control group) or 2) re-isolation of pulmonary veins and vein of Marshall ethanol ablation in combination with block of mitral and tricuspid isthmuses and dome line (intervention group). Patients are followed with standard ECG at 3 months, with standard ECG, 5-days' ECG monitoring and quality of life assessment after 12 months, with standard ECG and quality of life assessment after 24 months, through patient files at 60 months after the ablation.
Primary endpoint	Change in AFEQT score between baseline and 12 months.
Safety endpoints	Peri- or postprocedural complications (vascular complication needing intervention, conduction disturbances requiring a pacemaker, gastroesophageal fistula, phrenic nerve damage, stroke or systemic embolism, pulmonary vein stenosis, cardiac tamponade, anaphylactic reaction, pericarditis and death).
Secondary endpoints	• Freedom from documented atrial arrhythmia at a whole standard ECG recording (regardless of the estimated duration) or Holter/CIED (≥24 hours) at 12 and 24 months and 5 years (after 3 months blanking period), on or off antiarrhythmic drugs (AAD). • Freedom from documented persistent atrial arrhythmia at 12 and 24 months and 5 years (after 3 months blanking period), on or off AAD. • Freedom from DC cardioverted atrial arrhythmia at 12 and 24 months and 5 years (after 3 months blanking period), on or off AAD. • Number of DC-cardioversions (after 3 months blanking period) and sustained atrial arrhythmia episodes at 12 and 24 months and 5 years. • Freedom from accepted chronic atrial fibrillation at 12 and 24 months and 5 years. • Freedom from re-ablation procedure at 12 and 24 months and 5 years. • Change in AFEQT score between baseline and 24 months and between baseline and 5 years.
Number of patients	180
Follow up time	12 months (primary endpoint) and 24 months and 60 months

1.0 Background

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults with a lifetime risk of approximately 30%. AF significantly increases the risk of stroke, is associated with increased overall mortality and may impair quality of life.[1] Treatments to effectively eliminate AF and maintain sinus rhythm may not only improve quality of life, but may even reduce mortality.[2,3]

In patients with paroxysmal AF (PAF), AF has been found to be triggered by frequent ectopic atrial activity emerging from the pulmonary veins (PVs). Pulmonary vein isolation (PVI) has been developed to isolate the ectopic activity from initiating AF. PVI has proven efficient in patients with PAF with 1-year success rates up to 90%.

In patients with persistent AF (PsAF), data on a PV trigger-based initiation is not so clear, and the 1-year efficacy of pulmonary vein isolation only in this population is reported between 50-70% and significant lower as compared with patients with PAF. Furthermore, in patients having recurrence after PVI, a large proportion of patients with PsAF have isolated pulmonary veins at re-ablation. This indicates that patients with PsAF that have recurrence after PVI might benefit from ablation outside the pulmonary veins.

For some time, it has been assumed that in patients with PsAF there may be additive effect to PVI, by targeting the atrial substrate responsible for AF maintenance.[4] However, the best method to characterize and target this so-called “substrate” remains elusive. The most commonly employed techniques for targeting the substrate used in the past were the creation of linear lesions across critical structures of the left atrium (LA), ablation of complex fractionated electrograms (CFAE), and targeting areas of low voltage detected by multipolar electroanatomical mapping.

The STAR AF II study showed that addition of either linear ablation or ablation of CFAE to PVI for PsAF did not offer any additional benefit over PVI alone.[5] There was no significant difference in the results of the three strategies in terms of freedom from AF or any atrial arrhythmia. In fact, there seemed to be a weak trend towards better outcome with PVI alone. However, the STAR- AF II study included only de-novo procedures and in patients returning for re-do procedures, only 20% had isolated veins, indicating that durable block across the lines was achieved in a minority of this cohort.[5]

With updated approaches and technologies, including introduction of pulsed-field ablation, the efficiency of creating durable isolation of PVs has significantly increased over the last years. While PVI alone still remains the standard for the first ablation in patients with PsAF, the PVs are found to be isolated in a higher proportion of patients referred for re-do ablation. This shows that in these patients, PVI alone is not sufficient and revive the relevance of investigating the significance of targeting substrate outside PVs.

The VENUS study demonstrated the benefit of vein of Marshall (VOM) ethanol ablation in de novo ablation of PsAF.[6] Furthermore, preliminary results of the Marshall plan study suggest the benefit of VOM ethanol ablation in combination with block of mitral and tricuspid isthmus and dome line, also in de novo ablation of PsAF. Whether this strategy improves outcome in patients with PsAF undergoing re-ablation where the need for extrapulmonary ablation might be higher has not been tested in a randomized study We aim to investigate,

if the addition of VOM ethanol ablation in combination with block of mitral and tricuspid isthmuses and dome line to PV re-isolation will improve the results of re-ablation of PsAF.

2.0 Aim

The aim of this study is to investigate whether the addition of VOM ethanol ablation in combination with block of mitral and tricuspid isthmuses and dome line to standard PV re-isolation improves quality of life as compared to PV re-isolation alone, in patients who undergo re-ablation for PsAF.

2.1 Hypothesis

Addition of VOM ethanol ablation in combination with block of mitral and tricuspid isthmuses and dome line to standard PV re-isolation improves quality of life and reduces recurrence of atrial arrhythmias as compared to standard PV re-isolation alone in patients undergoing re-ablation for PsAF.

3.0 Methods

3.1 Study conduct

This is an investigator-initiated and investigator-sponsored multi-center trial at the Department of Cardiology Aarhus University Hospital, Department of Cardiology, Karolinska University Hospital, Stockholm and Department of Cardiology, Leiden University Medical Center. The study is conducted in accordance with the protocol, applicable regulatory requirements and the ethical principles of the Declaration of Helsinki.

3.2 Study design

This study is a prospective, patient and assessor blinded, 1:1 randomized superiority trial. Consecutive patients referred for re-ablation of symptomatic PsAF after previous PVI will be included. All preoperative procedures will be conducted according to the department's standard operational procedures for AF ablation. In all patients, an electro anatomical map (CARTO™, Biosense Webster, Diamond Bar, CA, or EnSite X™, Abbott Laboratories, Abbott Park, IL) of the LA with a multipolar mapping catheter (PENTARAY™ or OCTARAY™, Biosense Webster, Diamond Bar, CA, or Advisor™ HD Grid, Abbott Laboratories, Abbott Park, IL) will be constructed and reconnection of PVs will be assessed in sinus rhythm. If reconnection is present, re-PVI will be performed and confirmed with the multipolar mapping catheter. Patients in atrial fibrillation will undergo cardioversion to sinus rhythm prior to mapping. After mapping and confirming isolation of the PVs, patients will be randomized using the Redcap Database software to intervention or control. The intervention group will undergo VOM ethanol ablation including supplementary LA and coronary sinus ablation, if needed to achieve mitral isthmus block plus creation of dome line and cavotricuspid isthmus (CTI) block according to section 3.7. VOM ablation, mitral and CTI ablation and dome line will not be performed in control group and patients in control group will undergo no further ablation. The energy source used will be radiofrequency ablation or pulsed field ablation, at the discretion of the physician. However, radiofrequency should be preferred near coronary arteries. For dome line, focal PFA is preferred. All post-procedural work-up and follow-up will be the same for both randomization groups and assessment of outcomes will be performed by personnel blinded to randomization.

3.3 Definition of persistent atrial fibrillation

A standard 12-lead ECG recording or a single-lead ECG tracing of ≥30 s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF.[1] A high-rate episode detected by implanted device or wearable monitor, may be diagnostic of AF after inspection of the stored electrogram.

An episode of AF, continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after ≥7 days, is regarded as PsAF.

3.4 Eligibility criteria

Consecutive patients are included on the following criteria:

3.4.1 Inclusion criteria:

- Previous pulmonary vein isolation for atrial fibrillation
- Indication for catheter ablation with at least two episodes of symptomatic PsAF during the last 12 months during
- Previous PVI for atrial fibrillation
- Age ≥ 18 years
- Expected survival ≥ 12 months
- Able to provide informed consent

3.4.2 Exclusion criteria:

- Previous extrapulmonary atrial ablation other than cavotricuspid isthmus line, roof- or dome-line or posterior wall isolation/ablation
- Atypical atrial flutter in addition to atrial fibrillation
- Atrial fibrillation secondary to a transient abnormality
- Uncontrolled hypertension
- Acute coronary syndrome, cardiac surgery, or TIA/stroke within the last 3 months
- Planned cardiac surgery within 1 year
- Dialysis or severe renal failure
- Active substance or alcohol abuse (>14 units/week)

3.4 Power calculation

Assuming a 10-point difference in the change in AFEQT score between the intervention and control group with 90% power and a 5% significance level, assuming a standard deviation of 20 points (typical standard deviation for QoL in studies using the AFEQT questionnaire), a sample size of 168 patients will be required. With expected dropout during follow-up, 180 patients will be randomized in the study. The study will also be powered for the secondary endpoint (90% power and a 5% significance level, assuming 75% freedom of persistent atrial arrhythmia in the intervention group and 50% in the control group, a sample size of 148 patients is required).

3.5 Study endpoints

Primary endpoint:

- Change in AFEQT score between baseline and 12 months.

Secondary endpoints:

- Freedom from documented atrial arrhythmia at a whole standard ECG recording (regardless of the estimated duration) or Holter/CIED (≥24 hours) at 12 and 24 months and 5 years (after 3 months blanking period), on or off antiarrhythmic drugs (AAD).
- Freedom from documented persistent atrial arrhythmia at 12 and 24 months and 5 years (after 3 months blanking period), on or off AAD.
- Freedom from DC cardioverted atrial arrhythmia at 12 and 24 months and 5 years (after 3 months blanking period), on or off AAD.
- Number of DC-cardioversions (after 3 months blanking period) and sustained atrial arrhythmia episodes at 12 and 24 months and 5 years.
- Freedom from accepted chronic atrial fibrillation at 12 and 24 months and 5 years.
- Freedom from re-ablation procedure at 12 and 24 months and 5 years.
- Change in AFEQT score between baseline and 24 months and between baseline and 5 years.

Primary safety endpoints:

- Peri- or postprocedural complications (vascular complication needing intervention, conduction disturbances requiring a pacemaker, gastroesophageal fistula, phrenic nerve damage, stroke or systemic embolism, PV stenosis, cardiac tamponade, anaphylactic reaction, pericarditis and death).

3.6 Supplementary study parameters

The following baseline parameters will be collected from patients in the study: age, sex, body mass index, CHA2DS2-VASc score, AF history and duration, details of previous ablation procedures, history of heart disease and previos treatment of heart disease and other related conditions as diabetes, hypertension, thyroid dysfunction, cardiovascular risk factors, failed and current anti-arrhythmic drugs, left ventricular ejection fraction, LA dimensions and volume index, mitral insufficiency grade (0-4), mitral stenosis grade (0-4), any other structural heart disease, INR values at the day of ablation, ACT levels during ablation, total amount of units of heparin infused, total cholesterol, HDL- and LDL-cholesterol, triglycerides, TSH.

Procedural parameters as procedure duration, fluoroscopy time and dose will be collected as well.

In addition, the result from standard follow-up at 12 months after the procedure including recurrence of atrial fibrillation, ECG, medication and symptoms as well as EHRA score and quality of life assessment (AFEQT) will be analyzed to compare long term outcome.

3.7 Strategy for the procedure

According to standard clinical protocol and in accordance with international recommendations, after obtaining venous vascular access, a 10-polar catheter is placed in the coronary sinus and one transseptal puncture is performed. After the placement of a steerable sheath (Agilis™, Abbott, Abbott Park, IL), a multipolar mapping catheter PENTARAY™ or OCTARAY™ (Biosense Webster, Diamond Bar, CA, US) or Advisor™ HD Grid (Abbott, Abbott Park, IL) will be deployed in the LA.

The procedure will subsequently consist of two phases:

1: Mapping and randomization in the study

- A voltage map of the LA during atrial pacing will be created. Patients in AF will be cardioverted first. Reconnected PVs will be re-isolated.
- Then pts will be randomized.

2: Intervention

Control group:

- Programmed atrial stimulation (4 extra stimuli (ES) at 350 ms baseline cycle length (CL), with simultaneous decrement of all four ES down to refractory period). If AFL or AF will not be induced with programmed atrial stimulation, then burst pacing (5 s bursts with 10 ms decrement between bursts, starting from CL 300 ms down to 180 ms), will be performed. Mean CL of AF will be measured in left and right appendage. If AFL is induced, this is mapped using a combination of activation and entrainment mapping, but will not be ablated. Patients will be cardioverted to sinus rhythm and no additional ablation will be performed.

Intervention group:

- CTI block and VOM ethanol injection will be performed. Mitral isthmus block will be completed with endocardial and, if necessary, epicardial ablation in coronary sinus followed by dome line. Order of the ablation lines will be performed at the discretion of the physician. Programmed atrial stimulation will be performed as described above, and if AFL or AF will not be induced, then burst pacing will be performed as described above. In case of AF, mean CL will be measured in left and right appendage. No additional mapping or ablation of AF will be performed and the patient will be cardioverted. If AFL is induced, this is mapped and ablated using a combination of activation and entrainment mapping. Afterwards, induction will be performed again until AFL is not inducible anymore. If AF will be induced two times in a row, AF will be cardioverted and the procedure ended. The procedure is ended earlier on the discretion of the operator or if induced AFL is judged non-clinical. All the lines will be checked at the end of procedure for bidirectional block according to the respective institution's standard and a waiting time after the last ablation at a line will be 30 minutes.

3.10 Follow up

After 3 months, a clinical follow-up is performed including ECG. If persistent AF or AFL is present, the patient will be cardioverted. AAD (class I and III) will be discontinued at 3 months of follow-up if the patient is in sinus rhythm and discouraged during follow-up. In case of recurrences during follow-up, AAD will be initiated at the discretion of the physician.

In the case of recurrent symptomatic atrial arrhythmia, the patient will be offered a new procedure. However, repeat procedures during the first twelve months will be avoided. In case that a re-procedure cannot be avoided, QOL measurements will be taken immediately before the procedure.

After 12 months, a 5 days Holter recording in addition to an ECG and quality of life assessment (AFEQT) is included. The medical history is reviewed to identify documented AF or AFL as indication of recurrence.

After 24 months and 5 years, an ECG and quality of life assessment (AFEQT) is included.

All follow-up will be performed by personnel blinded for the randomization.

3.11 Statistics and data analysis plan

All analysis will be conducted according to the intention-to-treat (ITT) principle (as a superiority analysis) and difference in the primary endpoint AFECT score from baseline to 12 months follow-up will be analysed using student t-test and presented with mean difference and 95% CI.

For secondary endpoints, continuous variables will be evaluated by independent sample student's t-test, discrete variables will be evaluated by Chi-square statistics (or fisher's exact test if applicable), time dependent endpoints will be displayed with Kaplan-Maier curves and compared using a two-sided log-rank test.

Demographic and baseline data will be compared between the two groups. Variables will be expressed as mean ± SD, and percentage. If differences exist between groups in baseline data, these variables will be used in final comparison between the two treatment groups as potential confounders.

Procedure related parameters (fluoroscopy-, procedure- and ablation times) will be compared between the two groups and expressed as mean ± SD, and percentage.

3.12 Randomization

The patients will be randomly assigned in a 1:1 ratio to intervention or control group after the initial mapping and PVI using the Redcap web-based database system. Apart from the investigator, all health care professionals and the patient will be blinded to the allocation.

4.0 RECRUITMENT OF PARTICIPANTS

4.1 Consent to participate

As normal clinical praxis, all patients scheduled for AF ablation are seen in the out-patient-clinic 4-6 weeks before the procedure where the medical history is clarified, CT scanning is done and the patients receive information about the procedure. Patients referred to redo procedures for AF (approximately 200 patients) are screened to identify candidates that comply to the inclusion and exclusion criteria. Following information in patient record is used for this screening: age, frequency, symptomatology and duration of AF episodes during the last year, previous ablation procedures and concomitant diseases. This information will be found in the medical record from the last year. This information will be passed-on to the project. Potential candidates will be approached by a study dedicated nurse and under un-disturbed conditions, she will provide oral and written information about the study. Written consent form may be signed at this time, later during the day or on the day of the procedure. This ensures that the patient has sufficient time (at least >48 hours) to consider participation and to discuss this with relatives if desired. Another meeting with participation of relatives can be arranged. At any time, participants may withdraw their consent without having to give a reason for this. Patients who decide not to join the study will receive treatment according to current best clinical practice.

Normally, inclusion of 180 patients in the three participating centers will last less than a year.

4.2 Insurance

Participants are covered by, at the participating center, standard insurance in case they experience serious adverse events. The options to complain and apply for compensation will be explained in the written information about the study.

5.0 ETHICAL ASPECTS

5.1 Risks and inconvenience

The duration of the procedure is expected to be approximately 60 minutes longer in the intervention group compared to the control group. However, the majority of complications related to AF ablation, are related to the transseptal puncture, which will be performed in both groups.

In the intervention group, more widespread ablation will take place, potentially increasing the risk of severe complications such as tamponade, stroke, coronary artery lesion, esoph-ageal fistula, phrenic nerve palsy, and conduction disturbances requiring a pacemaker. These complications are rare and reported after less than <0.1% of procedures, including procedures with extensive ablation for PsAF.[7] VOM ethanol ablation carries an increase in the risk of pericarditis and a very small risk (0.4%) of anaphylactic reaction.

5.2 Beneficial effects

On an individual level, the participants will be followed more closely than after a standard procedure, accordingly reaction to adverse events and recurrence may be prompt. As hypothesized, the participants in the intervention group may have lower risk of arrhythmias after the procedure compared to standard treatment.

On a population basis, future patients undergoing redo ablation for PsAF, may benefit from results of this study.

6.0 BIO BANK

No biological material will be removed from the patient and nothing will be stored for further research during this study.

7.0 Data collection, processing, and storage

7.1 Monitoring

The investigator will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

7.2 Data Collection

Electronic Case Report Forms (eCRFs) will be developed to capture the information outlined in this protocol. Data from these eCRFs will be used in the analysis of study results. Modification of the eCRFs will only be made if deemed necessary by the primary investigators.

All data related to the study will be stored in a REDCAP database administered by Aarhus University in accordance with local regulations including “Databeskyttelsesforordningen” and “Databeskyttelsesloven” and only after approval by local data storage authorities. The data are stored in Denmark and are thereby subjected to Danish legislation. Only the main investigator and one study nurse will have access to the data. Data will be kept until 10 years after completion of the study.

7.3 Data reporting

The study nurse and primary investigator are responsible for recording all data from the study on the eCRFs based on source-documented hospital chart reviews.

7.4 Source Documentation

Data entered on to the eCRFs will be taken from source documentation, such as hospital procedure reports, admission and discharge summaries, and other hospital or physician office/clinic documents. For some information unique to this study, no standard hospital or office document exists. Therefore, a worksheet will be developed for this purpose, signed by the primary investigator and serve as the source document for those data parameters. These source documents will be used for monitoring the eCRFs. Electronic patient records

will be considered as source documents in general. All eCRFs will undergo manual inspection for omitted data, gross data inconsistencies, and timelines of reporting.

7.5 Data update

Regulations require that physicians maintain information in the subject's medical records, which corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained.

Medical history/physical condition of the study subject before inclusion in the study sufficient to verify inclusion criteria (if not already present). Adverse events reported and their resolution, including supporting documents such as discharge summaries, EP lab reports, ECGs, lab results. Study subject's condition upon completion of or withdrawal from the study.

7.5 Access to patient related information

Only after patient have signed consent to participate in the study, information as described in section 3.5 and 3.6 (Study parameters/endpoints) will be acquired from the medical record. This means that the main investigator will directly access the medical record to obtain the information needed to complete the study as described.

7.6 Final Data Analyses

All exported datasets for analyses will undergo a final data verification procedure. Once all critical data are monitored and locked, the final analyses of study data will be performed blinded to the treatment allocation.

8.0 QUALITY ASSURANCE

Periodic monitoring of the study will be performed to ensure that all subjects have signed Informed Consent Form, that randomization procedures are being followed, and that source document verification is conducted.

The physician should not deviate from the protocol without the prior notification and approval from the Principal Investigator, except when unavoidable due to a medical emergency.

Periodic analyses of eCRFs will be performed in order to examine the expected distributions of data, and to identify outliers for possible data mistakes.

9.0 ECONOMICS

This is an investigator-initiated study and funding will be applied for in public and private funds to cover expenses of extra monitoring and study personnel including nurses and study coordinators. No companies or other external funders are involved in the conduction of the study or will be granted access to any of the stored information in the study. Patients and investigators will not receive any compensation for participating in the study. Study nurse

will participate in patient inclusion and follow-up. The investigators do not have any economical association with subjects interested in the results of this study.

10.0 ADDITIONAL STUDY INFORMATION

The study is initiated by Dept. of Cardiology, Aarhus University Hospital and electrophysiologists at Department of Cardiology, Karolinska University Hospital, Stockholm and Department of Cardiology, Leiden University Medical Center will be involved in the study. Patients are covered by hospital liability insurance.

11.0 PUBLICATION POLICY

Before start, the study will be registered at ClinicalTrials.gov. After finalization of the project, a publication in an international peer-reviewed journal is intended regardless of whether the results are positive, negative or inconclusive.

12.0 LITERATURE

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