Evaluate Renal Artery Denervation In Addition to Catheter Ablation To Eliminate Atrial Fibrillation (ERADICATE-AF) Trial

Protocol
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Study Sponsor:
None
1. OBJECTIVES

Purpose of the Study

The objective of this trial is to determine the role of renal sympathetic denervation in the prevention of atrial fibrillation (AF) recurrence in patients with hypertension for whom a catheter-based AF ablation procedure is planned. Patients will be randomized to either AF catheter ablation (usual therapy) or AF catheter ablation plus renal sympathetic denervation.

1.1 Primary Hypothesis

In hypertensive patients undergoing catheter ablation for AF, there will be a difference at 12 months between the two treatment arms in AAD-free freedom from recurrent AF after a 3-month blanking period following an AF ablation procedure. The null hypothesis is that there will be no difference at 12 months between the two treatment arms in single-procedure freedom from AF off of all AADs after a 3 month blanking period in patients randomized to AF ablation with additional renal sympathetic denervation procedure compared to patients randomized to AF ablation alone.

1.2 Secondary Aims

1. Compare freedom from AF recurrence at 12 months without antiarrhythmic drug (AAD) use (excluding the 3 month blanking period)

2. Examine blood pressure control between the two groups as compared to baseline at 3, 6 and 12 months

3. Examine differences between treatment groups in measures of LV hypertrophy (LV wall thickness) and LA size by TTE at baseline and at 12 months for each patient

5. Procedure-related adverse events

6. Major Adverse Cardiac Events (MACE)

7. Serious Adverse Events

2. BACKGROUND

Current Practices

Activation of the sympathetic nervous system has been described in the development and progression of systemic hypertension. The degree of sympathetic nervous system activation correlates with the severity of blood pressure elevation and is more pronounced in the presence of comorbidities such as diabetes, obesity and metabolic syndrome. Sympathetic overdrive is also associated with target-organ damage related to chronic
hypertension and has been detected in patients with heart failure, chronic kidney disease, and end-stage renal disease. Many of these comorbidities or consequences of hypertension can predispose patients to a treatment-resistant disease state. Preliminary data indicate that by specifically targeting efferent sympathetic and afferent sensory renal nerve signalling, selective renal sympathetic nerve ablation reduces central sympathetic drive and thus improves blood pressure control.

Hypertension is also a risk factor for developing atrial fibrillation (AF); the incidence of AF also increases with left ventricular hypertrophy (LVH), coronary heart disease and heart failure, all consequences of poorly controlled hypertension. Effective treatment of hypertension might also decrease AF burden in patients with paroxysmal (P) AF or persistent (Pers) AF. It has recently been shown that renin-angiotensin system blockers appear to protect against AF recurrences after PVI in patients with low-burden paroxysmal AF and hypertension and meta-analyses suggest decreased AF incidence in patients with hypertension treated with ACEI or ARBs.

**Pilot Study**

We conducted a prospective, single-center, randomized study (www.clinicaltrials.gov Identifier NCT01117025) to assess the impact of renal artery denervation in patients with a history of refractory AF and drug-resistant hypertension who were referred for pulmonary vein isolation (PVI). Patients with a history of symptomatic PAF or PersAF refractory to ≥ 2 antiarrhythmic drugs and drug-resistant hypertension (systolic BP > 160 mm Hg despite triple drug therapy) were eligible for enrolment. Consenting patients were randomized to PVI only or PVI with renal artery denervation. All patients were followed ≥ 1 year to assess maintenance of sinus rhythm and to monitor changes in blood pressure.

Real-time 3D aorta-renal artery maps were reconstructed with the use of a navigation system and ablation catheter used for PVI via femoral artery access. Both mapping and ablation were performed under modified sedation using propofol infusion. RF ablations of 8-10 watts were applied discretely from the first distal main renal artery bifurcation all the way back to the ostium. The duration of each RF delivery was 2 mins, and up to six lesions (separated by > 5 mm) were performed both longitudinally and rotationally within each renal artery. To confirm renal denervation, we used high-frequency stimulation (HFS) before the initial and after each RF delivery within the renal artery. Rectangular electrical stimuli were delivered at the ostium of the targeted renal artery at a frequency of 20 Hz, with an amplitude 15 V and pulse duration of 10 ms (Stimulator B-53, Biotok Inc, Russia) for 10 secs. Renal sympathetic denervation was considered to have been achieved when the sudden increase of blood pressure (> 15 mm Hg from invasive arterial monitoring) was eliminated in the presence of HFS. HFS was performed one minute apart for 5 consecutive mins before onset of and at the conclusion of RF delivery in each renal artery.

Twenty-seven patients were enrolled, and 14 were randomized to PVI only and 13 to PVI with renal artery denervation. During follow-up, significant reductions in systolic (25 ± 5 mm Hg) and diastolic blood pressure (10 ± 2 mm Hg) were observed at 12 months in
patients treated with PVI with renal denervation (p<0.001) without significant change in the PVI only group. Nine (69%) of the 13 patients treated with PVI with renal denervation were AF-free at the 12-month post-ablation follow-up examination versus 4 (29%) of the 14 patients in the PVI-only group (p=0.033). There were no serious complications related to renal artery denervation. The study concluded that renal artery denervation had a positive impact on AF suppression in hypertensive patients with AF who underwent PVI.

**Study Rationale**

Pilot data strongly but not definitively, suggest an important role for renal artery denervation as an antiarrhythmic intervention in hypertensive patients with AF. The mechanism(s) mediating this benefit is not certain but may include better BP control in poorly controlled hypertensives or a direct effect via a decrease in central sympathetic output that contributes to AF development. AF is common in patients with hypertension and contributes importantly to outcome including stroke risk, heart failure and quality of life. Catheter ablation is used is an option in the many patients who have unsatisfactory results with pharmacologic treatment of AF. Although superior to drug therapy, ablation is nonetheless an imperfect intervention with a failure rate of 20-40%, a high rate of repeat procedures of 15-30%, and a disturbing long-term failure incidence even after initial success. The latter may be related to the presence of hypertension. Renal artery denervation has been demonstrated to control BP in difficult to treat patients with sustained effect and minimal risk. These results and the sympatholytic effects make it a potentially very useful adjunct to standard ablation techniques to treat AF.

3. SPECIFIC AIMS

3.1 Primary Endpoint

**Efficacy**

The primary endpoint of this study is AAD-free freedom from AF/flutter/tachycardia ≥30 seconds at 12 months (not including a 3 month blanking period).

3.2 Secondary Endpoints

a. Freedom from AF recurrence at 12 months (not-including the pre-defined 3 month blanking period) despite taking AADs
b. Blood pressure control between the two groups as compared to baseline at 6 and 12 months
c. Differences in measures of LV hypertrophy (LV wall thickness) and LA size
e. Procedure adverse events
f. Major adverse cardiac events (defined as a composite of: death, stroke, CHF hospitalization, clinically diagnosed thromboembolic events other than stroke and hemorrhage requiring transfusion within 12 months of randomization)
g. Serious adverse events throughout follow-up
4. STUDY DESIGN

This is a prospective, multi-center, single-blinded, randomized trial. The trial will be conducted in clinical sites in Europe.

5. RANDOMIZATION

All patients who have given informed consent for the study will undergo catheter ablation for AF, the standard care they would receive regardless of enrollment in the study. During the pre-procedure work-up, a renal MRA will be performed to assess the accessibility of the renal vasculature, and its appropriateness for catheter-based renal sympathetic denervation. If the renal anatomy meets the protocol-defined dimensions, the patient will be eligible for randomization.

Patients will be randomized to one of two treatment groups in a 1:1 fashion:
Group 1: catheter ablation of atrial fibrillation plus renal sympathetic denervation
Group 2: catheter ablation of atrial fibrillation (control group)

5. MASKING

The operating physician will be aware of the randomization assignment, but the patient will not. The blinding of the patient is maintained by the renal denervation being performed with the same sedation as used for the ablation procedure. This is typically either deep sedation or under general anesthesia (per the usual protocol of the EP laboratory); this amount of anesthesia used for the AF ablation procedure is sufficient for the discomfort felt during the renal denervation procedure. This approach has been selected to minimize study bias and placebo effect. The randomization schema will be blocked by size for each site.

6. STUDY POPULATION

Characterization of Patient Population
The patient population for this trial consists of patients with AF and a history of hypertension. All patients should be referred for a catheter ablation procedure for atrial fibrillation.

Inclusion Criteria
1. Age ≥ 18 years of age

2. History of PAF and plans for a guideline-supported catheter ablation procedure. Paroxysmal AF is defined as AF with duration of 30 secs to 7 days.

3. History of significant hypertension (defined as SBP ≥130 mm Hg and/or DBP ≥80 mmHg) and receiving treatment with at least one anti-hypertensive medication

4. Renal vasculature accessible as determined by pre-procedural renal MRA
5. Willingness to comply with all post-procedural follow-up requirements and to sign informed consent

**Exclusion Criteria**
1. Inability to undergo AF catheter ablation (e.g., presence of a left atrial thrombus, contraindication to all anticoagulation)
2. Prior left atrial ablation for an atrial arrhythmia
3. NYHA class IV congestive heart failure or LVEF < 255
4. Persistent or longstanding Persistent AF (duration > 7 days)
5. Renal artery anatomy that is ineligible for treatment including:
   a. Inability to access renal vasculature
   b. Main renal arteries < 4 mm in diameter or < 20 mm in length.
   c. Hemodynamically or anatomically significant renal artery abnormality or stenosis in either renal artery
   d. A history of prior renal artery intervention including balloon angioplasty or stenting that precludes a possibility of ablation treatment
   e. Multiple main renal arteries to either kidney
5. An estimated glomerular filtration rate (eGFR) < 45mL/min/1.73m², using the MDRD calculation
6. Life expectancy <1 year for any medical condition

**7. TREATMENT INTERVENTIONS**

**Catheter Ablation for Atrial Fibrillation**
- Patient anesthesia will be administered according to standard EP lab protocol
- Arterial and venous access will be achieved through cannulation of the right and/or left femoral arteries and veins as per the usual practice of the EP lab
- Full systemic anticoagulation will be instituted as per standard hospital procedures to a target ACT of approximately 350 seconds or greater
- Intravascular ultrasound may be used to assist in the positioning of study catheters during the procedure.
- The AF ablation procedure will be performed using a cryoballoon ablation catheter.
- Complete pulmonary vein isolation will be the goal of the ablation procedure and
PV isolation must be confirmed by a multielectrode mapping catheter within each PV. Pulmonary vein isolation is the only intervention.

- A cavo-tricuspid isthmus line may be placed in patients with either a history of ECG-determined typical flutter or induced typical flutter during the procedure.

Renal Sympathetic Denervation

- Right or left femoral artery access
- Real-time 3D aorta-renal artery maps constructed with the use of a navigation system and ablation catheter
- Mapping and ablation performed after PVI and under identical sedation protocol used for AF ablation
- RF delivery of 8-12 watts to be applied discretely from the first distal main renal artery bifurcation all the way back to the ostium; RF duration of each delivery 2.0 mins; lesions delivered at multiple sites based on multipolar catheter position within renal artery. Use of specifically designed RF delivery system for renal artery denervation is permitted.

Anticoagulation

- As per the ACC/AHA/HRS Guidelines on AF ablation, systemic anticoagulation should be administered to the patient for a minimum of 1 month after the procedure. Options include warfarin with a target INR 2-3 or alternative oral anticoagulant such as dabigatran or rivaroxaban. LMWH may be used to bridge warfarin therapy or the ablation may be performed during continuous therapeutic warfarin.
- As per the ACC/AHA/HRS Guidelines on AF ablation, long-term management of anticoagulation should be according to the baseline risk status for embolic stroke.

Blanking Period and Repeat Ablation Procedures

- The duration of the blanking period for all patients is 3 months during which time AF endpoints are not counted.
- All class I and III antiarrhythmic drugs must be stopped no later than 1 – 3 months after ablation.
- A repeat ablation procedures may not be performed during the blanking period or at anytime for any patient experiencing clinical arrhythmia recurrences.

8. DEFINITIONS AND MEASUREMENT OF ENDPOINTS

8.1 Primary Endpoint

Efficacy

The primary endpoint of this study is AAD-free freedom from AF recurrence at 12 months (not including the pre-defined 3 month blanking period). This will be defined by absence of any electrocardiographically documented AF, clinically documented AF or AF determined by ECG monitoring. AF duration must be > 30 secs. Patient death is
considered a treatment failure.

8.2 Specific Secondary Endpoints

**Blood pressure control between the two groups as compared to baseline at 6 and 12 months**

Determined by office visit blood pressure measurements as the mean of 3 consecutive readings

**Differences in measures of LV hypertrophy**

LV wall thickness and LA dimension/volume from 2D TTE at baseline and at 12 months for each patient

8.3 Safety

**Adverse Events**

The incidence of serious adverse events over the course of the trial will be compared between the two treatment groups.

9. CLINICAL CENTERS

The study will be conducted in up to 4-6 sites in Europe. Each clinical center will be required to obtain IRB approval for the protocol and consent (and their revisions) in a timely fashion, to recruit patients, to collect data and enter it accurately in the case report forms.

10. POST-RANDOMIZATION DATA COLLECTION

**Ablation Procedures**

Includes information regarding specific primary procedure, operative variables, device used for ablation, lesion sets created, additional procedures performed at time of initial operation, intra-operative pharmacological agents.

**Follow-up Visits**

1, 3, 6, 9 and 12 months

Follow-up visits will be conducted by investigative site personnel to document that the patient is alive and to assess the following:

- **7-day Holter Monitoring (3, 6, 9, 12 months only)**
  The Holter device provided to patients prior to discharge or at outpatient visits will be used for this assessment.

- **Medications**
  All cardiovascular, inotropic, antiplatelet agents and anticoagulants will be recorded. Medications (including AADs) will be recorded at each follow-up, and also as indicated at the time of associated adverse events.

- **Adverse Events, Antiarrhythmic Interventions, and Hospitalizations**
  Patients will be asked to recall any adverse events (including stroke and bleeding) and the number of hospitalizations that occurred out of network since the previous contact. Patients will also be asked if they had a permanent pacemaker insertion, cardioversion or
subsequent ablation since the last contact.

- **Transthoracic Doppler Echocardiogram (12 months only)**
  All patients will undergo follow-up transthoracic Doppler echocardiography at the investigative center.

11. DATA MANAGEMENT

**Sample Size**
This trial will randomize a total of 300 patients in equal proportions to AF ablation with renal sympathetic denervation to AF ablation alone. The randomization will be stratified by clinical center and use a random permuted block design, with blocks of size 4 or 8 chosen at random. This sample size provides 80% power to detect a relative 40% decrease in the one-year incidence of AF (from 40% to 24%) in patients treated with AF ablation with renal sympathetic denervation compared to AF ablation alone based on a two-tailed 0.05 level chi-square test.

**Statistical Analysis**
Continuous variables will be presented as mean values with standard deviations and categorical variables will be expressed as rates. Pearson Chi-square and Student's t-test were used for univariate analyses; multivariate analysis of freedom from AF and time to event will be analyzed using Cox Proportional Regression Hazards models. Statistical significance was determined using a p-value of < 0.05).

12. REFERENCES

ERADICATE-AF Trial: Statistical Analysis Plan (Original)

1. Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>PVI</td>
<td>Pulmonary vein isolation</td>
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<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
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<tr>
<td>RDN</td>
<td>Renal artery denervation</td>
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<tr>
<td>AAD</td>
<td>Antiarrhythmic drug</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>BNP</td>
<td>Brain natriuretic peptide</td>
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<tr>
<td>LV</td>
<td>Left ventricle</td>
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<tr>
<td>LA</td>
<td>Left atrium</td>
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<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
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2. Introduction

Catheter ablation via pulmonary vein isolation (PVI) is used as an option in the many patients who have unsatisfactory results with pharmacologic therapy of atrial fibrillation (AF). Renal artery denervation (RDN) can produce significant sympatholysis that may result in an antiarrhythmic effect AF.

3. Study design and hypothesis

3.1. Study design

The study will be a multicenter, single-blind, longitudinal randomized clinical trial.

3.2. Study hypothesis

RDN in addition to PVI enhances long-term antiarrhythmic efficacy in comparison to PVI alone for patients with AF and hypertension.

4. Study endpoints

4.1. Primary outcome measure

Freedom from AF recurrence at 12 months off antiarrhythmic drug (AAD) (not including the pre-defined 3 month blanking period following the ablation procedure). This end point was defined by AF duration of ≥ 30 seconds captured by ECG monitoring, or any clinical presentation with AF. The definition of “AF” also included any observed atrial flutter or tachycardia. The protocol specified 7-day Holter recordings at 3, 6, 9 and 12 months. Follow-up visits were scheduled at 1, 3, 6, 9 and 12 months.

4.2. Secondary outcome measures

- Freedom from AF recurrence (not-including the pre-defined 3 month blanking period) despite taking AADs (Time Frame: 12 months)
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- Blood pressure control between the two groups as compared to baseline (Time Frame: 6 months)
- Blood pressure control between the two groups as compared to baseline (Time Frame: 12 months)
- Differences in plasma norepinephrine and brain natriuretic peptide (BNP) measurements (Time Frame: 6 months)
- Differences in plasma norepinephrine and BNP measurements (Time Frame: 12 months)
- Differences in measures of LV hypertrophy/compliance (LV wall thickness, mitral inflow parameters) and LA size (Time Frame: 12 months)
- Procedure adverse events (Time Frame: 12 months)
- Major adverse cardiac events (defined as a composite of: death, stroke, CHF hospitalization, clinically diagnosed thromboembolic events other than stroke and hemorrhage requiring transfusion) (Time Frame: 12 months)
- Serious adverse events throughout follow-up (Time Frame: 12 months)
- Quality of life (Time Frame: 12 months).

5. Sample size estimation
The sample size provided 80% power to detect a relative 40% decrease in the one-year incidence of recurrent AF (from 40% to 24%) in patients treated with AF ablation with RDN compared to AF ablation alone based on a two-tailed 0.05 level chi-square test.

6. Analyses population
For all the analyses, the intention-to-treat approach will be adopted.

7. Handling of missing data
Missing data will not be imputed. Whenever the percentage of missing data will be of concern (e.g. >10%), the respective variable will be dropped from the analysis.

8. Statistical methods

8.1. Demographics and baseline clinical characteristics
Details of patients screened, those who meet the study inclusion criteria, those who are eligible and randomized, those who are eligible but not randomized, those who withdraw from the study after randomization, as well as those who are lost to follow-up will be summarized in the CONSORT flow diagram.

8.2. Demographics
- Age, years
- Gender: male/female

8.3. Baseline clinical characteristics
- Diabetes: yes/no
8.4. Concomitant medications
Data on antiarrhythmic and antihypertensive medications taken before randomization and until the end of the study will be collected.

8.5. Echocardiographic data
The following data will be obtained at baseline, 6 months and 12 months post-randomization: LV ejection fraction (%), LA diameter (mm), interventricular septum (mm).

8.6. Biochemical data
Blood samples for BNP and norepinephrine will be drawn at baseline and at 12 months post-randomization.

8.7. Procedural data
Type of catheter used for renal denervation, application of high frequency stimulation (yes/no), response to high frequency stimulation (yes/no), fluoroscopic time (min), number of RDN applications to each renal artery as well as complications will be recorded.

8.8. Follow-up
Information on adverse events, echocardiographic data, systolic and diastolic office blood pressure, recurrence of AF and repeat PVI procedures will be collected during the 12 months follow-up period.

9. Efficacy analyses

9.1. Primary outcome
9.1.1. Freedom from AF recurrence at 12 months off AADs (not including the pre-defined 3 month blanking period following the ablation procedure)

The response to treatment will be assessed by calculating cumulative probability for AF using a Kaplan-Meier estimator (time to event analysis). Periods at risk of AF will be defined in months for each participant, such that each period between the end of the blanking period and the first AF event or between the end of the blanking period and censoring date, will constitute a separate observation. An observation not resulting in an event may end in death, loss to follow-up or end of the study period (i.e. 12 months). The survival curves will be constructed, and the log-rank test will be used to explore differences of survival probabilities between the two
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groups. Additionally, a univariable Cox regression model will be used to quantify the excess risk associated with each treatment by calculating hazard ratios and associated 95% confidence intervals. The constant relative hazard assumption will be investigated by correlating scaled Schoenfeld residuals with a suitable transformation of time, along with a global test for the model as a whole. The assumption of linearity between log-hazard ratio and the covariate will be assessed graphically by plotting Martingale residuals against the covariate.

9.2. Secondary outcomes

9.2.1. Freedom from AF recurrence (not-including the pre-defined 3 month blanking period) despite taking AADs (Time Frame: 12 months).
This analysis on the subset of patients receiving AADs at 12 months will repeat the primary outcome analysis.

9.2.2. Blood pressure control between the two groups as compared to baseline (Time Frame: 6 months).
Linear mixed-effects models with treatment and time as fixed effects and subject as random effect to account for within-subject correlation will be used. The P values reported by mixed-effects models will be corrected for multiplicity using the Tukey’s single-step method.
Additionally, a univariable Cox regression model will be used to estimate hazard ratios and associated 95% confidence intervals for changes of blood pressure for various cut-offs (e.g. 10 mm Hg, 20 mm Hg)

9.2.3. Differences in plasma norepinephrine and BNP measurements (Time Frame: 6 months).
Unpaired t-test or Mann-Witney test will be used for between-group comparisons.

9.2.4. Differences in plasma norepinephrine and BNP measurements (Time Frame: 12 months).
Unpaired t-test or Mann-Witney test will be used for between-group comparisons.

9.2.5. Differences in measures of LV hypertrophy/compliance (LV wall thickness, mitral inflow parameters) and LA size (Time Frame: 12 months).
For within-group comparisons, mean change and associated 95% confidence intervals will be calculated. Additionally, a univariable Cox regression model will be used to estimate hazard ratios and associated 95% confidence intervals for changes of echocardiographic measurements at various cut-offs. Respective Kaplan-Meier 12-month event rates and between-group differences of event rates will be estimated.

9.2.6. Procedure adverse events (Time Frame: 12 months).
Kaplan-Meier 12-month event rates and between-group differences of event rates will be estimated as well as hazard ratios and associated 95% confidence intervals.
9.2.7. Major adverse cardiac events (defined as a composite of: death, stroke, CHF hospitalization, clinically diagnosed thromboembolic events other than stroke and hemorrhage requiring transfusion) (Time Frame: 12 months).

Kaplan-Meier 12-month event rates and between-group differences of event rates will be estimated as well as hazard ratios and associated 95% confidence intervals.

9.2.8. Serious adverse events throughout follow-up (Time Frame: 12 months).

Kaplan-Meier 12-month event rates and between-group differences of event rates will be estimated as well as hazard ratios and associated 95% confidence intervals.

9.2.9. Total number of anti-hypertensive medications at study end, compared between the two treatment arms (Time Frame: 12 months).

Fisher’s exact test will be used for between-group comparisons.

9.2.10. Quality of life (Time Frame: 12 months).

Mann-Whitney test will be used for between-group comparisons of ordinal data.