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CLINICAL TRIAL STUDY DESIGN

Pulmonary vein isolation Alone or in Combination with substrate modulation after electrical Cardioversion failure in patients with persistent atrial fibrillation: The PACIFIC trial: Study design

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Short Title: The PACIFIC study design

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Conflict of interest disclosure: The authors have no conflicts of interest to declare.


Ethics approval statement: The study has been approved by the local ethics committees (CPPs).

Patient consent statement: All patients will give their written informed consent before taking part in the study. Each patient taking part in the study will also provide their written consent for access to their individual data for quality control purposes and the use of their data for the study analysis.

Clinical trial registration: ClinicalTrials.gov: NCT05264831 / ID RCB: 2021-A02291-40

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ABSTRACT

Introduction: Pulmonary vein isolation (PVI) is effective at treating 50% of unselected patients with persistent atrial fibrillation (AF). Alternatively, PVI combined with a new ablation strategy entitled the Marshall-PLAN ensures a 78% 1-year sinus rhythm (SR) maintenance rate in the same population. However, a substantial subset of patients could undergo the Marshall-PLAN unnecessarily. It is therefore essential to identify those patients who can be treated with PVI alone versus those who may truly benefit from the Marshall-PLAN before ablation is performed. In this context, we hypothesised that electrical cardioversion (EC) could help to select the most appropriate strategy for each patient.

Methods: In this multicentre, prospective, randomised study, patients with AF recurrence within 4 weeks after EC will be randomised 1:1 to PVI alone or the Marshall-PLAN. Conversely, patients in whom SR is maintained for ≥ 4 weeks after EC will be treated with PVI only and included in a prospective registry. The primary endpoint will be the 1-year SR maintenance rate after a single ablation procedure.

Results and Conclusion: The Marshall-PLAN might be necessary in patients with an advanced degree of persistent AF (i.e., where SR is not maintained for ≥ 4 uninterrupted weeks after EC). Conversely, in patients with mild or moderate persistent AF (i.e., where SR is maintained for ≥ 4 weeks after EC), PVI alone might be a sufficient ablation strategy. The PACIFIC trial is the first study designed to

assess whether rhythm monitoring after EC could help to identify patients who should undergo adjunctive ablation strategies beyond PVI.

Keywords: Atrial fibrillation; Electrical cardioversion; Comparative study; Pulmonary vein isolation; Randomised study; Marshall-PLAN

INTRODUCTION

Pulmonary vein isolation (PVI) alone ensures only a 50% 1-year sinus rhythm (SR) maintenance rate in unselected patients with persistent atrial fibrillation (AF).^{1,2} Considerable efforts have therefore been invested in adjunctive ablation strategies beyond PVI, among which only a recent randomised study proved to be successful while the others have all failed to demonstrate any significant benefit.³⁻⁶

A recent lesion set entitled the Marshall-PLAN (Marshall bundle elimination, Pulmonary vein isolation and Line completion for ANatomical ablation of persistent atrial fibrillation: Marshall-PLAN) has yielded encouraging results. This combination of ablation steps could effectively treat $\approx 78\%$ of unselected patients with persistent AF.^{7,8} However, a substantial number of patients who are potential candidates for the Marshall-PLAN may still be successfully managed with PVI alone. It can be therefore postulated that only a subset of unselected patients with persistent AF might really require the Marshall-PLAN lesion set while the others might be successfully managed with PVI alone. This is of particular importance since the Marshall-PLAN compared to PVI alone entails a longer and more complex procedure with an increased risk of complications.

Several parameters have been proposed to select patients who truly require an ablation strategy beyond PVI.⁹⁻¹³ Unfortunately, none of these parameters have successfully identified these patients so far.

Restoration of SR by electrical cardioversion (EC) before catheter ablation has been shown to decrease the amount of ablation required while retaining the same clinical efficacy in patients with persistent AF.¹⁴ In addition, it was recently shown that pharmacological SR restoration before ablation made it possible to identify, within a population of patients with persistent AF, those in whom PVI alone might provide good results.¹⁵

We hypothesised that when SR can be restored by EC and maintained for at least 1 full month before ablation, PVI alone might be the most adequate ablation strategy in patients with persistent AF. Conversely, if SR is not maintained for at least 1 month after EC, the Marshall-PLAN might be indicated.

The main objective of this multicentre, prospective, randomised, parallel group, open-label study is to determine the most appropriate ablation strategy for patients with persistent AF based on their response to EC cardioversion prior to ablation.

MATERIALS AND METHODS

1. Study design

The PACIFIC trial is a multicentre, prospective, randomised, parallel group, open-label, interventional study. The study will be carried out in seven cardiology centres across France (Lille, Lyon, Nîmes, Paris, Perpignan, Toulouse, and Rennes). Patients with recurrence of AF within 4 weeks after EC will be randomised to PVI alone

versus the Marshall-PLAN. Patients who maintained SR for at least 4 weeks will undergo PVI alone and will be included in a prospective registry.

The study has been approved by the local ethics committees (CPPs) and will comply with ICH E6 guidelines on Good Clinical Practice and with the principles of the Declaration of Helsinki (<http://www.wma.net>). The study protocol was developed according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist guidelines and is registered at ClinTrials.gov (NCT05264831 (<https://clinicaltrials.gov/>)) and under registration number ID-RCB: 2021-A02291-40.

The start date of the study is November 1st, 2022 (first patient recruitment) and the expected end of the study will be May 1st, 2026. The duration of study participation for each patient will be up to 14 months, starting up to 6 weeks before the ablation procedure and continuing for 12 months after it. The total duration of the study will be 42 months. The study is not yet recruiting.

2. Patient population

Patients with persistent AF and for whom an ablation procedure is required will be seen in an outpatient clinic by a study investigator. Participation in the study will be proposed and explained to the patient during this consultation and the patient will be given a written information document and a consent form. Patients agreeing to participate in the study will return their signed informed consent form on the day they present for EC. Following EC, maintenance of SR will be observed for 4 weeks. Any patient failing to maintain SR within 4 weeks will be reviewed on the day of ablation, included in the study, and randomised to undergo either a PVI only strategy or the

Marshall-PLAN (Figure 1). All patients will then be followed for 1 year after the ablation procedure.

Inclusion criteria for the study: (i) persistent AF (continuous for at least 7 days without interruption according to information transmitted by the cardiologist and the patient), symptomatic and resistant to anti-arrhythmic drug treatment, including amiodarone; (ii) life-expectancy of >5 years; (iii) age between 18- and 80-years; (iv) affiliation with a health insurance system; and (v) patient informed of the study and giving their written informed consent. The additional inclusion criterion for the randomised arms of this study includes failure to maintain SR for at least 4 weeks after EC, as seen on the day of ablation. The remaining patients who maintain SR for at least 4 uninterrupted weeks will be included in the prospective study.

The exclusion criteria to be applied before performing EC are: (i) current hyperthyroidism; (ii) pregnancy or breastfeeding; (iii) body mass index >35; (iv) severe chronic obstructive pulmonary disease; (v) hypertrophic heart disease; (vi) mechanical or biological mitral prosthesis; (vii) contraindications to anticoagulants; (viii) transient ischaemic attack/stroke in the previous 6 months; (ix) psychiatric illness affecting follow-up; (x) active cancer; (xi) left ventricular ejection fraction <40%; (xii) uncontrolled ischaemic heart disease (angina, myocardial ischemia); (xiii) patient under legal protection; (xiv) uncontrolled inflammatory condition (rheumatoid arthritis, acute or chronic periodontitis, Crohn's disease, ulcerative colitis); (xv) previous atrial fibrillation ablation; (xvi) pulmonary embolism or phlebitis <6 months previously; (xvi) previous left atrial surgery. Additional exclusion criteria on the day of ablation include: (i) patients in normal SR \geq 4 weeks after EC: these patients will be included in the prospective registry (Figure 1); (ii) patients with complete absence

of SR (<10 sec) after three EC attempts: these patients will be withdrawn from the study.

3. Intervention

The aim of the study is to assess whether early AF recurrence after EC can help discriminate patients who require further atrial ablation beyond PVI. EC will be performed in all patients up to 6 weeks before the ablation procedure (Figure 1). The pathophysiological hypothesis is that being able to interrupt persistent AF for at least 4 weeks by EC reflects mild to moderate electrical remodelling, which is likely to be effectively treated with PVI alone. In contrast, AF that recurs within 4 weeks after EC possibly reflects more advanced electrical remodelling, with a less favourable response to PVI alone. The 4-week time-period is justified by the fact that reverse electrical remodelling in tachycardia-related cardiomyopathy and in experimental models of chronic AF requires at least 4 weeks to take place.^{14,16,17}

3.1. Electrical cardioversion

In this study, a maximum of three attempts (biphasic wave 200 J) will be made to restore SR, to reflect clinical practice. In addition, if SR is not restored at all or lasts for <10 sec, the patient will be withdrawn from the study and will be treated according to Standard of Care (SoC) and ESC recommendations.¹⁸

Medications, including antiarrhythmic drugs, will be maintained during and after EC throughout the entire period before the ablation procedure.

3.2. Catheter ablation

If the patient presents in SR on the day of the ablation procedure (i.e., successful EC, estimated 70% of patients), she/he will be treated with PVI only in accordance with ESC recommendations.¹⁸ These patients will be included in a prospective registry.

If the patient presents in AF (i.e., failure of EC, estimated 30% of patients), she/he will be randomised (1:1) into one of two groups: (i) Group 1: PVI alone, in accordance with ESC recommendations; (ii) Group 2: the Marshall-PLAN ablation approach (Figure 1).

Prior to catheter ablation, the presence, location, and extent of diseased left atrial (LA) myocardium will be quantified using a voltage threshold of 0.5 mV (Figure 2).¹⁹⁻²² Appreciation of the LA voltage will be done in SR using a multipolar catheter (Pentaray, Biosense Webster). In the case of AF at the beginning of the ablation procedure, up to three attempts at EC will be performed to restore SR. If the three EC attempts fail, PVI will be done and up to three additional EC attempts will be subsequently carried out.

The ablation strategy will not be guided by the presence or magnitude of low voltage areas. In addition, low voltage areas will not be considered ablation targets *per se*. After catheter ablation, antiarrhythmic drugs will be discontinued in all patients.

3.2.1. Lone PVI procedures: All PVI procedures will be carried out under general anaesthesia and electro-anatomical navigation system guidance (CARTO; Biosense Webster, Diamond Bar, CA, USA). PVI procedures will correspond to wide antral circumferential ablation (≥ 9 cm of perimeter) of ipsilateral pairs of pulmonary veins (PVs). Radiofrequency (RF) applications will be carried out following a point-by-point strategy. All RF applications will be ablation index-guided (≥ 350 to the posterior left atrium wall and ≥ 450 elsewhere) and will be made in a power-controlled mode with the aid of a SmartTouch SF catheter (Biosense Webster) and the SmartAblate generator (Biosense Webster). The ablation settings will be as follows: 45 W, $\leq 40^\circ\text{C}$, saline irrigation rate of 8–15 mL/min. The VisiTag settings will be: (i)

catheter stability range of motion ≤ 3 mm over 3 sec; (ii) minimum contact force (CF) ≥ 10 g over time of 70%; (iii) 3 mm (radius) tag size; and (iv) maximal inter-tag distance < 6 mm. In all patients, a linear probe will provide oesophageal temperature monitoring and will prompt cessation of RF applications as soon as the recorded temperature exceeds 38°C . PVI will be validated by the absence of any activity recorded inside the PV encirclement by a multipolar catheter (Pentaray) (entrance block) and by non-capture of the left atrium despite pacing manoeuvres from inside the encirclement (exit block). The bidirectional block will be validated again after a 10 min waiting period. No adenosine challenge will be done.

3.2.2. Marshall-PLAN procedures: This strategy corresponds to PVI (as described above) combined with transection of the three atrial anatomic isthmuses: **(a)** Mitral isthmus transection. This step has three parts: (i) injection of OH (10 ml) into the Marshall vein as described by Pambrun et al.⁷ and Valderrabano et al.^{23,24}; (ii) RF applications (45 W AI-guided 500) at the endocardial level; and (iii) RF applications inside the great cardiac vein (25 W AI-guided 250). Conduction block will be validated by activation mapping as described previously.²⁵ **(b)** Dome isthmus transection. A roof line is created in first intention by RF applications (45 W AI-guided 500) between superior PVs. Conduction block will be validated by activation mapping.²⁶ In the case of epicardial gaps across the roof line supported by the septopulmonary bundle, an alternative floor line will be deployed between the inferior PVs (45 W AI-guided 350). Conduction block will be validated by assessing coronary sinus activation modification.²⁶ **(c)** Cavotricuspid isthmus transection. RF application (40 W AI-guided 450) will be performed from the tricuspid annulus to the inferior vena cava. Conduction block will be validated by differential pacing.²⁷

3.3 Post-trial care

Patients with AF recurrence will receive an immediate appointment with their cardiologist. The 3-month period following the ablation procedure is called the “blinking” period. Recurrence during this time-period will not be considered for the outcome analysis. If AT (atrial tachycardia)/AF recurs during these 3 months, transient amiodarone administration and/or EC are recommended while a repeat ablation procedure is not recommended. After the blanking period, in the case of AF/AT recurrence, a new ablation procedure is recommended and data from such redo procedure will be collected.

4. Data collection and management

4.1.Data collection

The measurement time-points for each assessed parameter are shown in Figure 3. Descriptive data for the study population will be collected prior to the ablation procedure. These data will be presented using descriptive statistics according to the EC result and according to the adopted ablation strategy.

The following data will be collected during and after the ablation procedure: procedure duration, fluoroscopy duration, blood pressure, 24-h Holter monitoring and ECG.

4.2.Data management

An electronic Case Report Form (eCRF) will be set up to collect data in this study. eCRFs will be completed through the Electronic Data Capture (EDC) system. Designated, trained staff at each study site will be responsible for data entry into the eCRF and the correction of such data when necessary. In the event of any discrepant data, the study sponsor will request data clarification from the sites. The eCRFs will

be reviewed and electronically signed and dated by the investigator or a designee. At the end of the study, the investigator will receive subject data for his/her site in a readable format on a compact disc or any other appropriate format that must be kept with the study records. Missing data will not be replaced.

Data recorded during the study will be processed in compliance with Regulation (EU) 2016/679 of the European Parliament on the protection of personal data (General Data Protection Regulations) and France's 1978 act on data privacy.

5. Outcomes

5.1. Primary outcome

The primary outcome will be the 1-year SR maintenance rate (yes/no) after a single ablation procedure in the two groups. The diagnosis of AT/AF recurrence (failure of the ablation procedure) will be made by ECG and/or Holter monitoring. AT/AF recurrence during the blanking period will not be considered as a failure of the primary endpoint. A procedure will be considered as successful if, after the blanking period, the patient maintains SR for up to 1 year after ablation.

5.2. Secondary outcomes

The secondary outcomes will be: (i) the rate of patients in SR 1 year after a single ablation procedure (randomised patients); (ii) the rate of patients in SR 1 year after a single ablation procedure (registry patients); (iii) the rate of patients in SR 1 year after a single PVI procedure (randomised and registry patients); (iv) the duration (in min) of the ablation procedure; (v) the duration (in min) of radiofrequency applications; (vi) the duration (in min) of fluoroscopy; (vii) the duration (in days) of hospital stay; (viii) the complication rate directly related to the ablation strategy including tamponade, transient ischaemic attack/stroke, vascular access injury, atrio-oesophageal fistula, pericardial reaction, and non cavotricuspid isthmus-dependent

atrial flutter; (vi) the number of patients using drug treatment and/or who undergo EC during the blanking period; (vii) PVI as well as other linear lesions block assessment during redo procedures; (viii) the relationship between the presence or absence of LA low voltage areas and the response to EC prior to catheter ablation; (ix) the relationship between the extent of LA low voltage areas and the response to EC prior to catheter ablation; (x) the relationship between the location of LA low voltage areas and the response to EC prior to catheter ablation; (xi) the relationship between the presence or absence of LA low voltage areas and the success of the ablation procedure; (xii) the relationship between the extent of LA low voltage areas and the success of the ablation procedure; (xiii) the relationship between the location of LA low voltage areas and the success of the ablation procedure.

6. Sample size and statistical considerations

6.1. Sample size estimation

Considering an (α) risk of 5% (two-sided) and 90% power, a minimum of 60 patients/group is required to show that the Marshall-PLAN is superior to PVI alone in patients with persistent AF in whom SR is not maintained for ≥ 4 uninterrupted weeks after EC. To account for a possible 10% rate of patients lost to follow-up or missing data, a total of 134 patients will be randomised (67 patients/group). Patients who fail EC correspond to approximately 30% of all-comers. Thus, a total of 450 patients will be recruited to the study.

The efficacy of PVI alone in unselected patients with persistent AF is accepted to be around 50%,¹⁻³ and will be the reference rate both in the registry and the randomised study. Likewise, the efficacy of the Marshall-PLAN in unselected patients with persistent AF has been reported to be $\approx 78\%$.^{7,8} To demonstrate the interest of EC

as a discriminating factor between the two ablation strategies in the case of EC failure, the difference observed between the two randomised groups (PVI alone or the Marshall-PLAN) should be >25%.

6.2. Statistical analysis

Statistical analyses will be performed after all patients have completed the study and after the database has been frozen. Binary and multinomial descriptive variables will be described as number and percentage for each analysis population. Continuous and ordinal variables will be described as the number of observations, mean, standard deviation, median, interquartiles (Q1 and Q3) and range (min–max). For each primary and secondary endpoint, the reference value (baseline) will be defined as the last non-missing value collected before ablation.

The primary outcome, rate of patients in SR during the first year after a single ablation procedure, will be compared between the two groups: PVI alone versus the Marshall-PLAN, using the Chi² test or Fisher's exact test for qualitative variables. Withdrawn patients will not be replaced. Missing data will not be replaced or considered in the final analysis.

Quantitative procedure variables relating to secondary outcomes (duration of ablation, duration of hospital stay, etc.) will be compared using the Student's t test or Mann-Whitney test. The discriminative power of EC as a decision factor to perform PVI alone will be determined by analysis of specificity, sensitivity, and receiver-operating characteristic (ROC) curves.

All statistical tests will be two-sided with a significance level of 5%. Confidence intervals will be presented as two-sided with a confidence level of 95%. A p-value <0.05 will be considered as statistically significant.

All statistical analyses will be performed using SAS[®] or equivalent software.

6.3. Analysis data sets

The following analysis sets will be defined: (i) ***included patients***: all patients that meet the eligibility criteria and undergo EC and the ablation procedure; (ii) ***randomisation set (RS)***: all randomised patients; (iii) ***safety set (SS)***: all patients who undergo EC. Patients in this set will be analysed according to their actual group; (iv) ***full analysis set (FAS)***: all randomised patients who undergo an ablation procedure with post-procedure efficacy data. (v) ***per protocol set (PPS)***: a subset of patients included in the FAS without any major deviation from the study protocol.

The primary and secondary endpoint analyses will be performed on the FAS population. The primary endpoint analysis will also be performed on the PPS population if the FAS and PPS populations are at least 10% different. This analysis will be considered as a confirmatory analysis.

DISCUSSION

Multiple clinical trials have shown that PVI is superior to anti-arrhythmic drug therapy at maintaining SR in both paroxysmal and persistent AF.²⁸⁻³¹ Accordingly, PVI is recommended by the European Society of Cardiology (ESC), the American Heart Association and the American College of Cardiology as the first-line treatment strategy for persistent AF (ESC Class IA).¹⁷

PVI alone, however, is effective at treating only 50% of unselected patients with persistent AF.¹⁻³ An alternative strategy is to combine PVI with so-called substrate modulation. However, to date, only one randomised study has shown that additional ablation beyond PVI is superior to PVI alone while all others have failed to show any difference between the two ablation strategies.³⁻⁶ This explains why

substrate modulation as an adjunct to PVI is still an ESC Class IIb recommendation only.¹⁸ In this respect, the Marshall-PLAN set has yielded promising results. This relatively new ablation approach has the potential to effectively treat $\approx 78\%$ of unselected patients with persistent AF.^{7,8}

This being the case, it is also possible that unnecessary substrate ablation will be performed in a substantial subset of patients when the Marshall-PLAN is carried out. This is of utmost importance since the Marshall-PLAN will *de facto* be associated with a longer procedural duration and may be associated with an increased risk of complications compared to PVI alone. Thus, it is important to identify which patients should be treated by PVI alone and which should really require the Marshall-PLAN set before ablation is performed.

The aim of the proposed multicentre, prospective, randomised study as well as the registry, carried out in parallel, is to assess whether EC can help better select patients with persistent AF who can be treated with PVI alone and those in whom the Marshall-PLAN is really required. The answer to this question will likely: (i) streamline the ablation management of patients with persistent AF; (ii) allow patients to be treated according to the degree of progression of their arrhythmic disorder; and (iii) increase the cost-effectiveness of hospitalisations, since patients undergoing PVI alone could potentially be treated on an ambulatory basis.

Abbreviations

AF: atrial fibrillation

EC: electric cardioversion

EKG: electrocardiogram

LA: left atrial

PV: pulmonary vein

PVI: pulmonary vein isolation

SoC: standard of care

SR: sinus rhythm

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Figure 1. Study Scheme

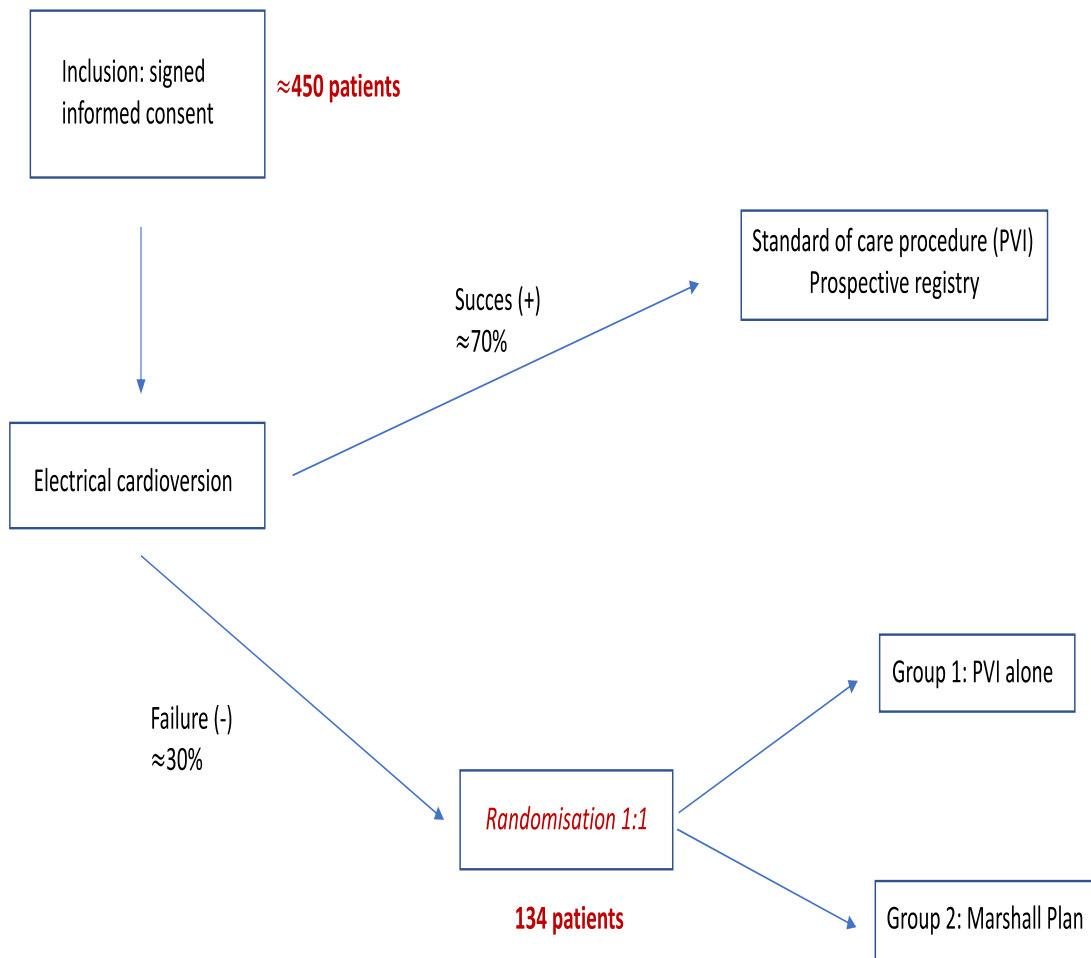


Figure 2. Segmentation of the left atrium to rationalise the distribution of any low voltage areas

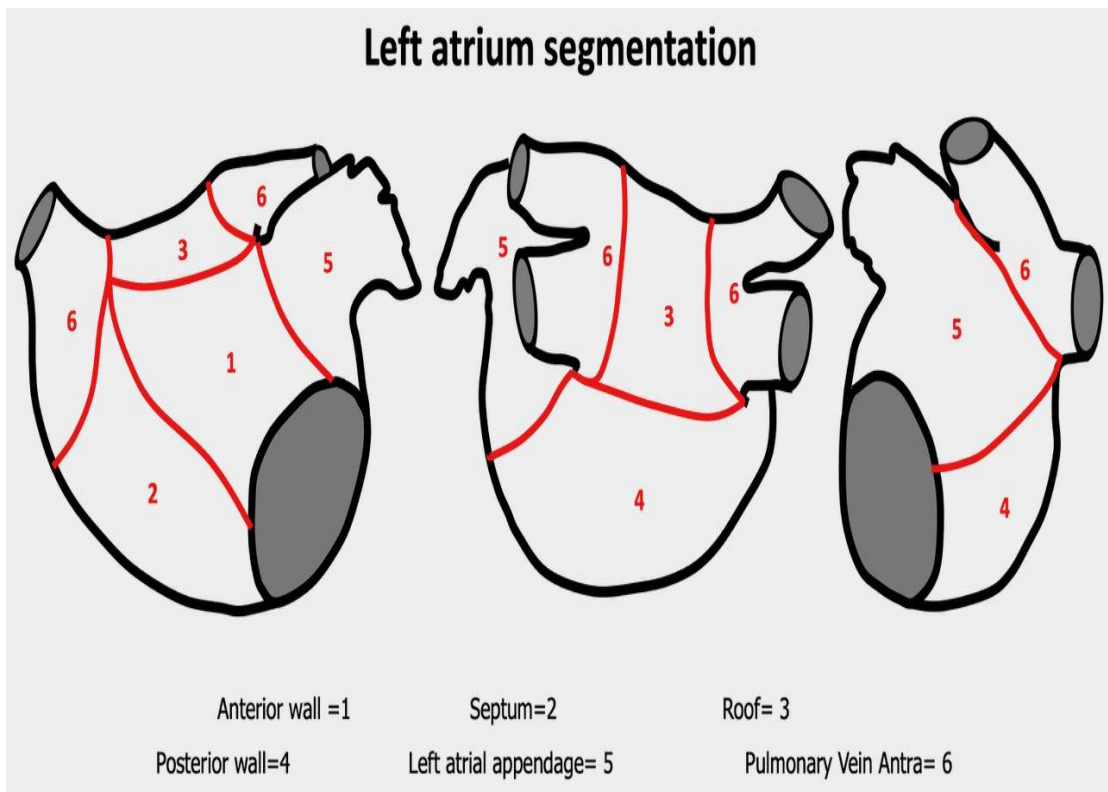


Figure 3. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist providing information about the recruitment of patients and the variables evaluated at each time period according to SPIRIT recommendations.

Screening and enrolment			Intervention and evaluation				
Visit 1	Visit 2	Visit 3	Visit	Visit	Visit	Visit	Visit

TIMEPOINT	Up to 6 weeks before ablation	D0: ablation	Hospital discharge	4 M1 (30 days ± 3 days)	5 M3 (91 days ± 3 days)	6 M6 (182 days ± 1 week)	7 M9 (272 days ± 1 week)	8 M12 (365 days ± 1 week)
Study visits for	✓	✓	✓	✓	✓	✓	✓	✓
Study visits for	✓	✓	✓	As per Standard of Care				
Enrolment:								
Collection of	✓							
Demographics	✓							
Medical history	✓	✓						
Vital signs ¹	✓							
Medical history ²	✓							
Interventions:								
EC	✓							
PVI (ablation)		✓						
Assessments and								
<i>EC assessment</i>		✓						
<i>Randomisation</i>		✓						
<i>Heart assessment</i>		✓						
<i>LA low voltage</i>		✓						
<i>LA low voltage</i>		✓						
<i>LA low voltage</i>		✓						
<i>LA low voltage</i>		✓						
<i>LA low voltage</i>		✓						
<i>LA low voltage</i>		✓						
<i>LA low voltage</i>		✓						
<i>LA low voltage</i>		✓						
<i>Ablative</i>		✓						
<i>Scopy duration</i>		✓						
<i>Procedure total</i>		✓						
<i>Vascular</i>			✓ ↔ ✓					
<i>Minor</i>			✓ ↔ ✓	✓	✓	✓	✓	✓
<i>Major</i>			✓ ↔ ✓					
<i>Major</i>			✓ ↔ ✓	✓				
<i>Hospitalisation</i>			✓ ↔ ✓					
<i>24-h Holter</i>		✓			✓	✓		✓

AF: atrial fibrillation; EC: electric cardioversion; SR: sinus rhythm; PVI: pulmonary vein isolation; LAA: left atrial appendage.

¹ Weight, height, body mass index, blood pressure, heart rate

² Hypertension, diabetes, vascular disorder, cardiomyopathy

³ Left atrial volume (ml), left atrial posterior wall, mitral isthmus (endocardial line, sinus rhythm (SR, ethanolisation of Marshall's vein, left atrial voltage in normal SR)

⁴ False aneurysm or fistulas at the puncture sites, pericarditis reaction

⁵ Tamponade, stroke

⁶ Atrio-oesophageal fistula