A randomized sham-controlled study of pulmonary vein isolation in symptomatic atrial fibrillation (The SHAM-PVI study)

Rajdip Dulai MBBS[1,2,3],Neil Sulke MD[4], Stephen S Furniss MD[†], Nick Freemantle PhD[5], Pier D Lambiase MD PhD[2], David Farwell MD[3], Neil T Srinivasan PhD[3], Stuart Tan MD[3], Nikhil Patel MBBS[1], Adam Graham PhD[6], Rick A Veasey MD[1,2]

1. Cardiology Research Department, Eastbourne District General Hospital, East Sussex Hospitals NHS Trust, UK.

2. Institute of Cardiovascular Science, University College London, London, UK.

3. Mid and South Essex NHS Foundation Trust, The Essex Cardiothoracic Centre, Basildon, Essex, United Kingdom.

4. CVS Healthcare Ltd, Eastbourne UK.

5. Institute for Clinical Trials and Methodology, University College London, London WC1V 6LJ, UK.

6. Nottingham University Hospital NHS Trust, Hucknall Road, Nottingham, NG5 1PB.

† Deceased 14/05/2022

Word Count : 3234

Corresponding authors

Dr. Rick Veasey can be contacted at rick.veasey@nhs.net or at the Cardiology Research Department, East Sussex Hospitals NHS Trust, Eastbourne District General Hospital, Kings Drive, Eastbourne, UK. Dr Rajdip Dulai can be contacted at rajdip.dulai.21@ucl.ac.uk

Key points

Question: Does pulmonary vein isolation (PVI) have a placebo effect?

Findings: In this double blind randomized trial of 126 patients with symptomatic atrial fibrillation PVI resulted in a significant and clinically important decrease in AF burden with substantial improvements in symptoms and quality of life when compared to a sham procedure.

Meaning: PVI significantly reduced AF burden compared to a sham procedure. The benefit of PVI in symptomatic atrial fibrillation is largely not because of a placebo effect.

Abstract

Importance

There are concerns that pulmonary vein isolation (PVI) for atrial fibrillation (AF) may have a profound placebo effect. Prior to SHAM-PVI no double-blind randomized controlled studies have been conducted.

Objective

To determine whether PVI is more effective than a sham procedure for improving outcomes in AF.

Design and Setting

The SHAM-PVI study is an investigator-initiated double blind randomized controlled trial conducted at two tertiary centres in the United Kingdom. Study dates were January 2020–March 2024.

Participants

Patients with symptomatic paroxysmal or persistent AF were included. Major exclusion criteria included long-term persistent AF, prior left atrium ablation, patients with other arrhythmias requiring ablative therapy, LA ≥ 5.5 cm, and ejection fraction less than 35%.

Intervention

Pulmonary vein isolation with cryoablation (n = 64) or sham intervention with phrenic nerve pacing (n = 62).

Main Outcomes and Measures

The primary end point was AF burden at 6-months, excluding a 3-month blanking period. Secondary outcomes included quality of life indices, time to events and safety. AF burden was measured by an implantable loop recorder (Medtronic Reveal LINQ™)

Results

A total of 126 participants were randomized (mean age, 66.8 [8.62] years; 89 [70.63%] male; 20.63% with paroxysmal AF)**.** The absolute mean AF burden change from baseline to 6 months was 60.31% in the ablation group and 35.0% in the sham intervention group (geometric mean difference, 0.252; 95% confidence interval [CI], 0.150 to 0.422; P<0.0001). The estimated difference in the overall Atrial Fibrillation Effect on Quality of Life (AFEQT) score at 6 months, favoring catheter ablation, was 18.39 points (95% CI, 11.48-25.30). The SF-36 General Health score also improved substantially more with ablation with an estimated difference of 9.27 points at 6 months (95% CI, 3.78 – 14.76).

Conclusions and Relevance

PVI results in a significant and clinically important decrease in AF burden with substantial improvements in symptoms and quality of life when compared to a sham procedure.

Trial Registration

ClinicalTrials.gov number, NCT04272762

Introduction

Pulmonary vein isolation (PVI) is the standard ablation technique used to treat atrial fibrillation (AF) and currently has a class 1 recommendation for the treatment of symptomatic AF where patients have failed or are intolerant to antiarrhythmic medication. (1) Despite evidence led indications and previous studies showing that ablation reduces the occurrence of AF, improves quality of life and symptoms there have been no randomized controlled trials comparing PVI with a sham procedure. (2,3)

Previous studies of catheter ablation for AF have not shown consistent benefits in endpoints such as death, stroke, and cardiac arrest.(4) Given these results there is a concern that PVI exhibits a substantial placebo effect which has not been evaluated.(5,6) Thus a sham controlled trial is warranted to provide conclusive evidence for the efficacy of PVI.

Additionally, previous clinical studies involving a sham procedure have been shown to be safe and feasible and have shown placebo effects of therapy e.g. coronary angioplasty and renal denervation. (7,8) This study compared the effects of PVI versus a sham procedure on AF burden, quality of life and symptoms.

Methods

Trial design

We conducted a dual centre randomized double-blind controlled study to evaluate PVI (via cryoballoon ablation) compared with a sham procedure in patients with symptomatic paroxysmal or persistent AF. The trial protocol has been previously published.(9) The trial was designed and overseen by a steering committee, sponsored by East Sussex Healthcare NHS Trust and was conducted in accordance with the Declaration of Helsinki. The trial was approved by the West Midlands—South Birmingham Ethics Committee. An independent data safety monitoring committee advised the sponsor on safety of participants. A blinded

adjudication committee assessed the ILR recordings. Written informed consent was obtained from all patients who participated in the study. The results are owned by the sponsor.

Trial participants

Adults with symptomatic paroxysmal or persistent AF despite at least one anti-arrhythmic drug (AAD Type I or III, including β-blocker and AAD intolerance) and who had been referred for catheter ablation were enrolled in the study. The major exclusion criteria included long-term persistent AF (any continuous AF episode lasting more than 1 year), prior left atrium (LA) catheter or surgical AF ablation, patients with other arrhythmias requiring ablative therapy, LA $\geq$ 5.5 cm, and ejection fraction (LVEF) less than 35%.

Implantable loop recorder insertion

At enrollment, all patients had a Medtronic Reveal LINQ™ inserted, if this had not been inserted previously as per the manufacturer's guidelines. The device settings were optimized to record all AF episodes longer than 2 minutes and any tachycardia episode lasting more than 16 beats (eTable 1). All patients had the ILR inserted at least 2 weeks before the main procedure day (eTable 1 note).

Preprocedural medication management

Antiarrhythmic medication was discontinued 5 half-lives (up to 5 days) before the procedure, except for Amiodarone, which was discontinued 8 weeks before the procedure day. All procedures were performed using uninterrupted anticoagulation, and all patients remained on anticoagulation during the study.

Randomization

Participants were randomly assigned in a 1:1 ratio to undergo either catheter ablation ± direct current cardioversion (DCCV) if in AF or a sham procedure ± DCCV if in AF. A computerized central blocked randomization design was generated and stratified according to the type of AF (paroxysmal/persistent). Randomization was conducted using a concealed central process. (9)

Sedation and blinding

During each procedure, patients were given over-the-ear headphones to play music to prevent hearing of communication between the catheter lab staff. The patients were then sedated during the procedure using opiates and benzodiazepines and had eye coverings if necessary. After the procedure, all nursing staff, physicians, and other healthcare professionals performing the procedure had no further contact with the patient during follow-up. Healthcare professionals and research staff involved in patient care post-procedure and during follow-up were blinded to the treatment strategy. All patients were discharged with standardized discharge documentation that did not reveal treatment allocation. Participant and staff blinding was assessed at discharge and at 3 and 6 months follow-up.

Cryoablation procedure

At the beginning of the procedure, two femoral venous access was achieved using ultrasound guidance. If the patient was in AF, DCCV was performed to cardiovert to sinus rhythm. Transeptal puncture was performed and PVI was achieved using a Medtronic 28mm cryoballoon catheter as previously described with phrenic nerve pacing when ablating the right PV's.(9) At the end of the procedure, once the sheaths were removed, all patients underwent a three-way stopcock suture to achieve hemostasis.(10)

Sham procedure

After x2 venous access has been achieved using ultrasound guidance, DCCV was performed if the patient was in AF. A 5-Fr pacing catheter was then placed in the right subclavian vein to pace the phrenic nerves as described previously.(9) The phrenic nerve were paced for 4 minutes on four occasions during the procedure. At the end of the procedure once sheaths had been removed all patients had a three-way stopcock suture to achieve haemostasis.(10)

Follow-up

AF episodes were managed medically as per the European Society of Cardiology (ESC) guidelines during the follow-up phase.(11) Only one DCCV was permitted for each participant during the follow-up phase. Anti-arrhythmic medications were allowed to be restarted depending on the recurrence of AF and symptoms. Antiarrhythmic medications were stopped 5 half-lives before follow-up at 3 months. The use of Amiodarone was discouraged. If patients had an alternative indication for beta blocker medications (e.g. Hypertension or heart failure) then this was continued where clinically indicated. Patients underwent scheduled follow-up at 3 and 6 months.

End points

The primary outcome AF burden was measured using continuous monitoring between the end of month 3 and end of month 6 post-randomization between the ablation group and sham intervention group. The first 3 months of follow-up were defined as the blanking period, and AF burden and arrhythmia-based outcomes in this period were censored. Baseline AF burden was derived from the ILR monitor from time of insertion to the main procedure day.

Prespecified secondary endpoints included AF symptoms, which were assessed using the Atrial Fibrillation Effect on Quality-of-Life (AFEQT), Mayo AF-Specific Symptom Inventory (MAFSI), and European Heart Rhythm Association (EHRA) score with scores compared

between baseline, 3 months and 6 months. The overall quality of life was compared using the 36-Item Short Form Health Survey (SF-36). Healthcare use and medication usage were also compared between the two groups. Secondary arrhythmia-based endpoints included time to any atrial tachyarrhythmia stratified by the length of episode (more than 30 s and more than 7 days), time to symptomatic atrial tachyarrhythmia and number of atrial tachyarrhythmia episodes (symptomatic and asymptomatic) in the follow-up period. Other endpoints included serious adverse events and procedural characteristics.

Statistical Analysis

In the calculations of sample size, we estimated the AF burden in the intervention group to be 25% at the 6-month follow-up and in the sham intervention group to be 50% based on previously published data and clinical investigators' experience.(12) We assumed a standard deviation of 48%. Based on these data and assumptions with 80% power and two-sided 0.05 α 118 patients were required in total to be recruited. We recruited 140 patients to take into account unexpected methodological challenges and withdrawals which were minimized by design.

All analysis was based on the intention to treat population using available data. Missing data were not inputted as part of the principal analyses. Data is summarized and presented as mean with standard deviation (sd) or medians with interquartile range (IQR) for continuous variables and absolute number and percentages for categorical data.

The primary efficacy end point was evaluated using a generalised mixed repeated measures model, including baseline and post intervention observations for each subject and parameterized to identify the period (baseline or post randomization) and the randomized condition in the post treatment period. The stratification factor (Persistent versus PAF) was included in this and all other statistical models for prespecified outcomes. Observations within a patient were linked with a random intercept term and the denominator degrees of freedom for

the principal analysis were derived from the number of patients rather than the number of observations.(13) It is our expectation from previous experience that the distribution of data followed a log(e) linear distribution, and so the generalised mixed model included the log(e) AF burden. The log(e) AF burden was back transformed and presented as a geometric mean.

The widths of the 95% confidence intervals were not adjusted for multiple comparisons and should not be used to infer definitive effects of the intervention, and instead inference should be through the primary analysis.

Frequency distribution of patients and staff perception of treatment allocation post procedure, at three months and six months follow-up is provided. We utilised the BANG Index (BI) to describe the extent to which blinding appears intact.(14)

All analyses were conducted with, R V4.3.1 and SAS V9.4 (SAS Institute, Cary NC). (Additional details regarding the statistical analyses are provided in the supplementary materials.)

Results

Trial participants

One hundred and forty patients were enrolled between January 2020 and August 2023. The study was suspended and paused between March 2020 and July 2021 due to COVID-19 restrictions. 13 patients recruited between January 2020 and March 2020 were removed from the study due to COVID-19 measures. The primary endpoint analysis intention-to-treat population consisted of 123 patients- 62 randomized to ablation and 61 randomized to the sham procedure (Figure 1). Demographic and clinical characteristics were generally well balanced between the groups (Table 1). Procedural characteristics are shown in Table 2.

AF burden

Results for the primary end point of AF burden are summarized in figure 2, eTable 2 and 3. The absolute change in AF burden from baseline in the ablation group was 60.31% and 35.0% in the sham intervention group (geometric mean difference, 0.252; 95% confidence interval [CI], 0.150 to 0.422; P < 0.001). In the persistent AF patients, there was a absolute reduction of 71.39% in the ablation group and 44.85% in the sham intervention group (geometric mean difference, 0.255; 95% confidence interval [CI], 0.141 to 0.461). In the paroxysmal AF patients, there was a absolute reduction of 16.13% in the ablation group and a absolute increase of 2.81% in the sham intervention group (geometric mean difference, 0.226; 95% CI, 0.095 to 0.539). Time to event hazard ratios and Kaplan–Meier curves are presented in eTable 4 and eFigure 1,2 and 3 in the supplementary appendix.

Quality of life and symptoms

The mean AFEQT summary score (range, 0-100; a higher score indicates a lower level of AF-related disability) at baseline was 53.3 (16.3) points in the ablation group and 51.3 (18.1) points in the sham intervention group (eTable 5 and eTable 6). At 6 months, the mean scores were 77.4 (20.4) points in the catheter ablation group and 58.3 (25.2) points in the sham intervention group. The estimated difference at 6 months, favoring catheter ablation, was 18.39 points (95% CI, 11.48-25.30). All subdomains of the AFEQT were substantially in favour of ablation at six months (Figure 3A) and 3 months (eFigure 4).

The mean MAFSI frequency and severity score at baseline was 15.5 (5.80) and 11.3 (4.77) points in the ablation group and in the sham intervention group was 16.1 (6.16) and 11.3 (4.59) points. At 6 months, the mean frequency and severity scores in the catheter ablation group was 7.21 (6.54) and 5.24 (4.77) and in the sham intervention group was 13.9 (7.34) and 10.2 (5.37) points. The estimated difference in frequency score at 6 months, favoring catheter ablation, was

-6.36 points (95% CI, -8.46 - -4.26) and the estimated difference in severity score at 6 months, favoring catheter ablation, was -4.84 points (95% CI, -6.43 - -3.26) (Figure 3B). All subdomain results of the MAFSI frequency and severity scoring are presented in eTable 7, eTable 8, eFigure 5 and 6.

The SF-36 General Health score improved more in the ablation group than in the sham intervention group (eTable 9). At baseline, the scores were 54.2 (20.1) in the ablation group and 51.4 (18.6) in the sham intervention group. At 6 months, the scores improved to 58.3 (20.3) in the ablation group and decreased to 47.2 (20.7) in the sham intervention group. The estimated difference at 6 months, favoring catheter ablation, was 9.27 points (95% CI, 3.78 – 14.76). All seven remaining SF-36 subscales showed substantial improvements with catheter ablation vs. the sham intervention group as shown Figure 3C.

During follow-up, the number of AF episodes and symptomatic AF episodes was lower in the ablation group than in the sham intervention group (eTable 10). EHRA classification scores are provided in eTable 11, eTable 12 and eTable 13.

Healthcare and medication use during follow-up

There were no differences in the number of repeat cardioversions between the groups during follow-up (eTable 14). During the blanking period, 25 (39.7%) and 30 (48.4%) patients underwent repeat DCCV in the ablation and sham intervention groups, respectively. Between three and six months 33 of 61 patients (54.1%) of patients in the sham intervention group had restarted a class 1 or 3 anti-arrhythmic versus 20 of 62 patients (32.3%) in the ablation group.

Blinding assessment

The BI on discharge on the procedure day for patients was 0.016 (-0.053 – 0.084) in the ablation group and -0.032 (95% CI -0.095 - 0.030) in the sham intervention group, indicating near perfect blinding (eTable 15). At the 6-month follow-up, 24 of 62 patients in the ablation group

correctly guessed their treatment allocation, and 8 of 62 patients believed they had a sham procedure (95% CI 0.258 (0.091 - 0.425)). In the sham intervention group, 18 of 61 patients correctly guessed their treatment allocation and 11 of 61 patients believed they had undergone an ablation procedure. (95% CI 0.115 (- 0.056 – 0.285)).

Procedural Complications and Serious Adverse Events

There was one serious adverse event in the sham intervention group. One patient randomized to sham intervention died of an intracranial hemorrhage 2 months after their procedure, which was deemed unrelated to the study procedures by the IDMC. In the ablation group, one patient had pericarditis post procedure, one patient had an aortic pressure tracing on transeptal puncture without further adverse consequence, and one patient had transient leg weakness/numbness due to lidocaine.

Discussion

In this double-blind randomized sham controlled trial of PVI with cryoballoon ablation, there was a significant decrease in AF burden, the primary objective, compared with that in the sham intervention group. In addition, the reduction in AF burden was accompanied by robust and clinically important improvements in symptoms and quality of life.

To date, there have been multiple clinical trials reporting the beneficial effects of PVI using several end points, including AF burden, time to AF, and symptoms. The CIRCA-DOSE study reported significant reductions in AF burden in paroxysmal AF using cryoballoon and radiofrequency technologies, although no arm was treated with medical therapy alone.(15) In addition the CAPTAF trial also reported significant improvements in quality of life indices when comparing AF ablation with medical therapy and also the CABANA trial reported significant improvements in AF specific symptoms.(2,16) However, to date all previous trials have not included an arm with a sham intervention raising the possibility of a placebo effect.

This trial is the first to compare PVI with a sham procedure. Our findings confirm previous trial results and show that PVI exhibits no clinically relevant placebo effect.

This study shows and confirms a clear direct relationship between AF burden reduction and symptom improvement. This is similar to previous studies, notably CIRCA-DOSE which indirectly demonstrated an inverse association between AF burden and quality of life although these studies did not include a sham intervention limb.(17) Changes in AFEQT score of + or -5 points has been shown to be associated with clinically important changes in patients' health status. In this study we report a robust and clinically important change of 14.32.(19) AF burden was pragmatically chosen as the primary outcome in this study as it is closely related to symptom improvement and due to the difficulty in estimating the placebo effect with a quality of life measure.

Previous studies examining PVI have had high crossover rates, which affect the interpretation of results for example, in the CABANA trial 9% of patients in the ablation group did not undergo ablation and 22.3% of the patients in the medical therapy group underwent ablation.(4) In the CAPTAF trial comparing ablation and antiarrhythmic medications 8 of 72 (10.5%) randomized to antiarrhythmic therapy crossed over to having an ablation.(16) In this study there were no crossovers, increasing that the validity of the study and highlighting the improvements seen are solely due to PVI. At end follow-up 58 of 61 patients in the sham intervention group proceeded to ablation treatment.

The SHAM PVI study reports similar outcomes to that of the APPROVAL study with significant reductions in recurrence rates in patients randomised to PVI versus those patients who did not receive PVI. The major strength of this study compared to the APPROVAL study is the inclusion of continuous monitoring to assess outcomes and AF specific quality of life indices which were all in favour of PVI. The APPROVAL study also included a different patient

cohort including patients with CTI dependent atrial flutter whereas these patients were excluded in this study.

In this study, a substantial number of patients underwent repeat cardioversion (25 in the ablation group and 30 in the sham intervention group) during the blanking period because patients were treated without bias with rhythm control intent throughout the study. Despite this, PVI resulted in reductions in AF burden with improvements in quality of life compared with the sham intervention group. Furthermore, there was a numerical increase in the use of class 1 or 3 anti-arrhythmic's in the sham intervention group when compared to patients randomized to PVI. Reintroduction of antiarrhythmic medications was guided by the ESC guidelines and it was not mandated to use previous ineffective anti-arrhythmic's.

We assessed patient and staff blinding before discharge on the day of the procedure, which showed near perfect blinding in each group. During follow-up, there was a loss of blinding in both patient groups although half of all patients were still unable to guess to their treatment allocation. The loss of blinding appeared to be attributable to the clinical effect of the treatment or lack thereof.

Limitations

Our study has several limitations. First, the study was limited to six months. This is shorter than previous clinical trials assessing AF ablation, which typically have a follow-up of at least one year; however, the study aim was not to elucidate the long-term effect of AF ablation but rather the placebo effect, if any. There may be reversion to the mean with a longer follow-up, but this would not be due to a placebo effect but rather treatment failure due to disease progression or nondurable PVI. Finally, the study was limited to pulmonary vein isolation only. This is unlikely to affect the results given that additional ablation, including complex fractionated electrogram and linear ablation, has not been shown to be superior to PVI alone in

large randomized controlled trials.(20) Despite advances in technology PVI remains the cornerstone ablation strategy for treatment of symptomatic AF. It would not be expected that PVI with radiofrequency or pulsed field ablation would have a differing result than that of cryoablation. Finally the study was only conducted in two centres.

Conclusion

In conclusion, PVI results in a clinically important decrease in AF burden with substantial improvements in symptoms and quality of life compared with a sham procedure. At 6 months follow-up this study has demonstrated no clinically relevant placebo effect with PVI.

Author Contributions

Dr Dulai and Dr Veasey had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Dulai, Furniss, Veasey

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Dulai

Critical review of the manuscript for important intellectual content: Dulai, Sulke, Freemantle, Lambiase, Farwell, Srinivasan, Tan, Patel, Graham, Veasey

Statistical analysis: Dulai, Freemantle

Obtained funding: Dulai, Veasey

Administrative, technical, or material support: All authors

Supervision: Lambiase, Veasey

Additional contribution and Acknowledgments

We thank all the dedicated staff at East Sussex Healthcare NHS Trust and the Mid and South Essex NHS Foundation Trust. We thank Dr Stanislav Hadjivassilev for his assistance in the preparation of the randomisation sequences.

Conflicts of Interest

Dr Neil Sulke is a trustee of Eastbourne Cardiology Research Charity Fund. Prof Pier Lambiase receives research grants from Medtronic, Abbott, and Boston Scientific. Prof Nick Freemantle receives consulting fees from ALK, Sanofi Aventis, Gedeon Richter, Abbott, Galderma, AstraZeneka, Ipsen, Vertex, Thea, Novo Nordisk, Aimmune and sits on a DSMB for Orion. Dr Neil Srinivasan receives research grants from Abbott. Dr Rick Veasey receives research grants from Medtronic. The remaining authors declare no conflict of interest.

Funding/Support:

The study was supported by an unrestricted research grant from Eastbourne Cardiology Research Charity Fund. Unrestricted in-kind support (implantable loop recorder devices) was provided by Medtronic.

Role of the Funder/Sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in

collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. European Heart Journal. 2021 Feb 1;42(5):373–498.

2. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, et al. Effect of Catheter Ablation vs Medical Therapy on Quality of Life among Patients with Atrial Fibrillation: The CABANA Randomized Clinical Trial. In: JAMA - Journal of the American Medical Association. 2019. p. 1275–85.

3. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: First results of the North American arctic front (STOP AF) pivotal trial. Journal of the American College of Cardiology. 2013;61(16):1713–23.

4. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. JAMA. 2019 Apr 2;321(13):1261–74.

5. Ozeke O, Cay S, Ozcan F, Topaloglu S, Aras D. The placebo effect in atrial fibrillation ablation: Placebo or pseudo-placebo effect? Vol. 41, PACE - Pacing and Clinical Electrophysiology. 2018. p. 872–3.

6. Ozeke O, Cay S, Ozcan F, Baser K, Topaloglu S, Aras D. Similarities between the renal artery and pulmonary vein denervation trials: Do we have to use sham procedures for atrial fibrillation catheter ablation trials? International Journal of Cardiology. 2016;211:55–7.

7. Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. The Lancet. 2018;

8. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. New England Journal of Medicine. 2014;

9. Dulai R, Furniss SS, Sulke N, Freemantle N, Lambiase PD, Farwell D, et al. A randomized sham-controlled study of pulmonary vein isolation in symptomatic atrial fibrillation (The SHAM-PVI study): Study design and rationale. Clinical Cardiology. 2023;46(8):973–80.

10. Payne J, Aznaurov S, Gautam S. Three-way stopcock suture technique for hemostasis after ablation for atrial fibrillation. Journal of Cardiovascular Electrophysiology. 2018;29(12):1724–7.

11. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Vol. 37, European Heart Journal. 2016.

12. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter ablation for atrial fibrillation with heart failure. New England Journal of Medicine. 2018;378(5):417–27.

13. Lu K. On Efficiency of Constrained Longitudinal Data Analysis Versus Longitudinal Analysis of Covariance. Biometrics. 2010 Sep 1;66(3):891–6.

14. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. Controlled Clinical Trials. 2004 Apr 1;25(2):143–56.

15. Andrade JG, Champagne J, Dubuc M, Deyell MW, Verma A, Macle L, et al. Cryoballoon or Radiofrequency Ablation for Atrial Fibrillation Assessed by Continuous Monitoring: A Randomized Clinical Trial. Circulation. 2019;140:1779–88.

16. Blomström-Lundqvist C, Gizurarson S, Schwieler J, Jensen SM, Bergfeldt L, Kennebäck G, et al. Effect of Catheter Ablation vs Antiarrhythmic Medication on Quality of Life in Patients with Atrial Fibrillation: The CAPTAF Randomized Clinical Trial. JAMA - Journal of the American Medical Association. 2019;321(11):1059–68.

17. Noujaim C, Assaf A, Lim C, Feng H, Younes H, Mekhael M, et al. Comprehensive atrial fibrillation burden and symptom reduction post-ablation: insights from DECAAF II. EP Europace. 2024 May 1;26(5):euae104.

18. Samuel M, Khairy P, Champagne J, Deyell MW, Macle L, Leong-Sit P, et al. Association of Atrial Fibrillation Burden With Health-Related Quality of Life After Atrial Fibrillation Ablation: Substudy of the Cryoballoon vs Contact-Force Atrial Fibrillation Ablation (CIRCA-DOSE) Randomized Clinical Trial. JAMA Cardiology. 2021 Nov 1;6(11):1324–8.

19. Holmes DN, Piccini JP, Allen LA, Fonarow GC, Gersh BJ, Kowey PR, et al. Defining Clinically Important Difference in the Atrial Fibrillation Effect on Quality-of-Life Score. Circulation: Cardiovascular Quality and Outcomes [Internet]. 2019 May [cited 2024 May 26]; Available from: https://www.ahajournals.org/doi/abs/10.1161/CIRCOUTCOMES.118.005358

20. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. New England Journal of Medicine. 2015;372(19):1812–22.

Figure legends

Figure 1: Randomization and follow-up of patients

Figure 2: Changes in mean atrial fibrillation burden in all patients (2A), persistent AF patients (2B), paroxysmal AF patients (2C) and geometric mean from baseline to 6 months (2D). Error bars in 2A to 2C represent 95% confidence interval.

Figure 3: Estimated difference of AFEQT scores at six months (3A), MAFSI scores at three and six months (3B) and SF-36 scores at 6 months (3C). AFEQT, MAFSI and SF-36 are

secondary outcomes. Additional AFEQT and MAFST estimates at 3 months is presented in the supplementary material

Table 1 : Baseline characteristics of the patients

Characteristic	Ablation (N =64)	Sham (N =62)
Mean age (sd)	66.1 (8.9)	67.5 (8.3)
Male sex— N (%)	47 (73.4)	42 (67.7)
Female sex – N (%)	17 (26.6)	20 (32.26)
Type of atrial fibrillation		
Paroxysmal atrial fibrillation N (%)	13 (20.3)	13 (21.0)
Persistent atrial fibrillation N (%)	51 (79.7)	49 (79.0)
Co-morbidities N (%)		
Hypertension	30 (46.9)	30 (48.4)

Coronary artery disease	16 (25.0)	14 (22.6)
Myocardial infarction	6 (9.4)	4 (6.5)
Type 2 diabetes	6 (9.4)	5 (8.1)
Heart failure	6 (9.4)	7 (11.3)
Thyroid disease	2 (3.1)	2 (3.2)
CVA/TIA	2 (3.1)	0 (0)
COPD/Asthma	2 (3.1)	9 (14.5)
New York Heart Association Class (%)[A]		
1	61 (95.3)	59 (95.2)
2	3 (4.7)	3 (4.8)
Previous AF medication history N (%)		
Beta blocker	58 (90.6)	59 (95.2)
Sotalol	17 (26.6)	8 (12.9)
Amiodarone	14 (21.9)	17 (27.4)
Flecainide	11 (17.2)	13 (21.0)
Dronedarone	7 (10.9)	3 (4.8)
Calcium channel blocker	5 (7.8)	2 (3.2)
Digoxin	4 (6.3)	6 (9.7)
Propafenone	1 (1.6)	1 (1.6)
Any prior Class I/III AAD use (%)	39 (60.9)	35(56.5)
Anticoagulation N (%)		
Vitamin K antagonist	1 (1.6)	0 (0)
Direct oral anticoagulant	63 (98.4)	62 (100)
Mean body mass index (sd)	29.1 (4.0)	29.6 (6.9)
Blood pressure (mm Hg)		
Mean systolic blood pressure (sd)	134 (17.6)	133 (18.8)
Mean diastolic blood pressure (sd)	82.4 (13.9)	81.1 (12.0)

Mean monthly time since the first diagnosis of AF (sd)	44.6 (45.3)	38.8 (52.5)
Mean number of cardioversions (sd)	2.0 (1.8)	1.5 (0.7)
Previous hospitalization for AF N (%)	22 (34.4)	21 (33.9)
Mean left atrial diameter in millimetre (sd)	42.4 (4.2)	40.4 (5.2)
Mean left ventricular ejection fraction percentage (sd)	55.3 (4.8)	54.2 (5.6)
Mean CHA2DS2-VASc score (sd)[B]	2.0 (1.4)	2.1 (1.4)
Mean average alcohol intake per week in units (sd)[C]	7.1 (10.0)	5.9 (7.5)
Mean pre-procedure ILR monitoring days (sd)	45.6 (96.0)	36.6 (35.1)
Smoking history		
Ex-smoker	33 (51.6)	23 (37.1)
Never	28 (43.8)	38 (61.3)
Current	3 (4.7)	1 (1.6)

A The CHA2DS2-VASc risk score estimated the one year stroke risk in patients with atrial fibrillation; score range 0 to 9, The higher the score the higher risk of stroke.

B New York Heart Association Class is a measure of functional class in patients with heart failure; score range 0-4, class 1 No limitation of physical activity, class 2 Slight limitation of physical activity

C One unit equals 10ml or 8g of pure alcohol

Table 2 : Procedural characteristics

	Ablation (N =64)	Sham (N =62)
Mean procedure time in minutes (sd)	64.55 (7.36)	62.84 (7.36)
Mean fluoroscopy time in minutes (sd)	9.26 (4.12)	1.13 (1.32)
Mean radiation dose in cGycm^2 (sd)	819.11 (1128.23)	55.63 (106.91)
Direct Current Cardioversion N (%)	50 (78.13)	48 (77.42)
focal cryotherapy catheter	0 (0)	0 (0)