A Sham-Controlled Evaluation of Pulmonary Vein Isolation in Atrial Fibrillation

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Declaration of originality

I, Dr Rajdip Singh Dulai confirm that the work presented in my thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

This thesis presents the results of the first randomised, sham-controlled trial of pulmonary vein isolation for the treatment of symptomatic atrial fibrillation (AF). Despite catheter ablation being widely used and endorsed by international guidelines, there are concerns that pulmonary vein isolation may have a profound placebo effect. Its efficacy has not previously been tested against a placebo procedure.

In a dual centre, double-blind design, patients with symptomatic paroxysmal or persistent AF were randomised to undergo either cryoablation or a sham procedure. The study assessed changes in AF burden using continuous rhythm monitoring, symptoms and quality of life. The results showed a significant reduction in AF burden with improvements seen in symptoms and quality of life metrics providing strong evidence that pulmonary vein isolation delivers genuine symptomatic improvement with no placebo effect.

The thesis also explores the relationship between AF burden and quality of life, showing a strong association between symptom improvement and AF burden reduction. These findings highlight the value of combining objective and patient-reported outcomes in future research.

In summary, pulmonary vein isolation resulted in a statistically significant and clinically important decrease in AF burden with substantial improvements in symptoms and quality of life when compared to a sham procedure.

Impact statement

The studies presented in this thesis will have a significant impact on the clinical practice of patients with atrial fibrillation. The SHAM-PVI trial, the main focus of this thesis, was published in the Journal of the American Medical Association and was presented as a late-breaking clinical trial at the European Society of Cardiology Congress 2024. The findings were widely disseminated on platforms such as X, featured on multiple cardiology podcasts, and was covered extensively in the medical press.

The SHAM-PVI trial is the first sham-controlled study of pulmonary vein isolation and addressed a longstanding question regarding its true clinical benefit. The study confirmed that pulmonary vein isolation provides significant improvements in atrial fibrillation burden, quality of life and symptoms. These findings have already influenced clinical guidelines and directly impact the care of patients with atrial fibrillation.

The thesis contributes to a deeper understanding of both the short and long-term effectiveness of atrial fibrillation ablation. The thesis also serves as a model for incorporating rigorous methodology including sham controls into atrial fibrillation ablation research. The broader impact of this thesis lies not only in its contribution to evidence-based practice, but also in its potential to impact the lives of patients living with atrial fibrillation.

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I am deeply grateful to Dr Rick Veasey for his unwavering support and guidance throughout this journey. His shared enthusiasm for the SHAM-PVI trial and contributions were instrumental in its completion.

I thank Professor Pier Lambiase for his support and guidance in completing this PhD, and to Professor Nick Freemantle for his invaluable input on the statistical analysis. I learned a great deal about statistics through his mentorship. I would also like to thank Dr Neil Sulke for his consistent encouragement and support.

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Author contributions

For this thesis, I designed and conducted the SHAM-PVI trial. I developed the research questions and hypotheses and authored the trial protocol. I secured all grant funding for the study and obtained all necessary approvals, including sponsorship, ethical, and R&D approval at each site. Additionally, I coordinated all assessments, procedures, and contracting for each location.

I completed the ethics application and attended the ethics meeting. I registered the trial with ClinicalTrials.gov and implemented all subsequent amendments. I applied for and secured the adoption of the trial into the National Institute of Health and Research portfolio.

I coordinated and led the trial throughout its duration. I was responsible for recruiting all patients enrolled in the trial and organised all baseline and follow-up assessments at all sites. The procedures were performed by consultant electrophysiologists at Eastbourne District General Hospital and the Essex Cardiothoracic Centre. I presented all adverse events at the Data Safety Monitoring Board meetings and provided clinical trial updates to the trial steering committee. Professor Nick Freemantle conducted the primary statistical analysis, and I performed additional statistical analysis under his supervision. Subsequently, I compiled all data and authored the full paper for publication as the lead author. I managed the submission process and addressed all subsequent revisions. The SHAM PVI study was published in the Journal of the American Medical Association. Furthermore, I presented the trial during the HOT LINE session at the European Society of Cardiology Congress 2024.

For the sub-study of the SHAM-PVI trial, I developed the research hypothesis and design. Professor Nick Freemantle conducted the primary statistical analysis, and I performed additional statistical analysis under his supervision. Subsequently, I authored the full paper for publication as the lead author which has been published in JACC: Clinical Electrophysiology.

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1 Introduction

1.1 General Introduction

Atrial fibrillation (AF) is reported to be the most common cardiac arrhythmia, with a 7.1% prevalence in women and 8.5% prevalence over the age of 55 years.(1) It is estimated that there are 8.8 million adults with AF in the European Union.(1) The prevalence of AF is increasing year on year and it is associated with significant morbidity and mortality.(2,3)

In the UK alone, treatment and expenditure related to AF is currently estimated to cost the National Health Service (NHS) between £1435 million and £2548 million which is between 0.9% and 1.6% of the current yearly NHS expenditure.(4) Over the next two decades expenditure is forcasted to increase to 1.35%–4.27% of NHS expenditure.(4) The prevalence and incidence of AF is anticipated to rise over the next decades and with this the number of AF-related stroke events and hospitalisations is also anticipated to increase with an estimated additional 0.5–4 million hospitalisations for AF, 280–340,000 new ischaemic strokes and 100–220 million outpatient visits.(2,5)

There are various treatment options for patients with symptomatic AF, ranging from conservative treatment, medical therapy with antiarrhythmics, electrical cardioversion, or catheter ablation.(3) Over the past two decades catheter ablation via pulmonary vein isolation for symptomatic AF has emerged as the preferred treatment choice with significant improvements in symptoms and overall quality of life when compared to medical therapy alone.(6,7) The absolute number of catheter ablations per million inhabitants has more than doubled from 156 per million inhabitants in 2007 to 378 per million inhabitants in 2016 in Europe, although there are regional variances with a higher number of ablations occurring in developed western countries.(3,8)

To date, there have been no sham controlled studies evaluating the effectiveness of pulmonary vein isolation. Randomised controlled trials have proven the efficacy of AF ablation over

medical treatment; however, even in these studies, many patients have recurrences after their procedure and require re-do procedures. In 2018, Ozeke et al. postulated that AF ablation exhibits a placebo effect.(9) Many patients in previous clinical studies reported relief of symptoms even in cases where the arrhythmia persisted despite undergoing an AF ablation procedure suggesting a placebo effect.(9–11) More recently, the CAPTAF study reported significant improvements in quality of life after AF ablation when compared with medical treatment; however, this study was not placebo controlled raising the possibility of bias and placebo effect.(6)

The call for a sham-controlled study of AF ablation has been proposed internationally, including by the American Heart Association, especially since sham-controlled trials have been successfully conducted in other medical specialties, not just cardiology, and have shown a lack of effectiveness of invasive procedures, including renal denervation and percutaneous coronary intervention.(12,13)

A sham controlled study is further needed as an analysis of previous clinical trials has shown that the use of blinding was limited to only, 4% of proceduralists, 16% of patients, and 44% of event ascertainers, thus potentially confounding the results of many studies further justifying the need for a sham controlled study.Furthermore, the relationship between AF burden and quality of life metrics has not previously been studied in the context of a placebo-controlled trial.

Pulmonary vein isolation for symptomatic AF can be achieved using various techniques, including radiofrequency energy using 3D navigation systems, balloon cryoablation, and pulsed field ablation.

Second-generation cryoablation has been to shown to be an effective and safe treatment for AF improving arrhythmia recurrence rates in patients with paroxysmal and persistent AF.(14–16)

The STOP AF trial, using the first-generation cryoballoon, reported a freedom from arrhythmia rate of 69.9%. (15) Additionly, the STOP Persistent AF trial reported a 12-month freedom from arrhythmia rate of 54.8%.(16)

Furthermore, the majority of studies rely on intermittent monitoring such as three to six monthly Holters to objectively determine outcomes, which significantly overestimates the true success rate of catheter ablation.(14,17) Implantable devices such as pacemakers, implantable cardiac defibrillators and loop recorders are able to overcome these limitations and reflect the actual arrhythmia success rate of catheter ablation.(18)

This thesis has two main core themes and hypotheses, which are novel:

1. Does a procedure intended to isolate the pulmonary veins exert a placebo effect?
2. What is the relationship between AF burden and quality of life?

2 Literature Review

2.1 History of Atrial Fibrillation

The description of AF has evolved over the years and has been described by many physicians using various techniques. Descriptions of the pulse can be traced back to the Ancient Egyptians. Phrases in the Ebers Papyrus, such as 'trembling of the heart' and 'forgotten beats,' have been interpreted as early observations of irregular heart rhythms.(19) In approximately 1187, the Andalusian philosopher Moses Maimonides was the first to write aphorisms related to the human pulse. In his writings, he observed an irregular pulse and was partially correct in his findings when he wrote "The pulse which is very abnormal and totally irregular demonstrates that the cause for its abnormal condition migrates".(20)

Sir William Harvey (1578-1657) in 1628 published his findings in the book Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus (Latin for "An anatomical exercise on the movement of the heart and blood in living beings").(21) Sir William Harvey reported direct observations of the heart in humans and other mammals.(21) Harvey wrote "But I . .. have noticed, that after the heart proper, and even the right auricle were ceasing to beat and appeared on the point of death, an obscure movement, undulation/palpitation had clearly continued in the right auricular blood itself for as long as the blood was perceptibly imbued with warmth and spirit".(21)

Sir William Harvey is credited with the first direct observation of AF.(21) Similar to Sir William Harvey, Jean-Baptiste de Senac (1693-1770) a physician to Louis XV also reported his observations of AF in the dying heart.(21) In the earliest observation of AF, De Senac confirmed the atrial origin of the heart beat as described by Sir William Harvey and also confirmed observations of the rippling heart in death hinting that the irregularity may be due to an ectopic origin commenting "the causes of palpitation are not the causes of the natural heart-beat".(21) Both Sir Willam Harvey and De Senac were well ahead of their time, and their

advanced understanding of AF was based only on their direct observations and critical thought.(21)

In 1883, James Mackenzie helped devise an ink-writing polygraph to measure serial venous and arterial pulse recordings which he would use for a clinical study and correlate with clinical presentations.(22) Mackenzie was able to discern the 3 major jugular venous waves, which he lettered “A, C, and V waves” which he correlated with auricular contraction, the carotid impulse, and overfilling of the right auricle and/or regurgitation from the right ventricle.(22)

Between 1880 to 1897, Mackenzie meticulously followed up a patient who had mitral stenosis. Serial recordings had always shown a regular rhythm in this patient and a presystolic jugular A wave. However, in 1897, the patient developed a rapid irregular rhythm associated with the loss of the jugular A wave on his recordings.(23) Mackenzie postulated that this phenomenon was due “paralysis of the auricle”.(23)

In 1908, Mackenzie met Thomas Lewis, whose work had induced auricular fibrillation in dogs. Lewis demonstrated that the arterial pulse was irregular and the venous pulse was similar to the findings of Mackenzie.(24,25)

In 1901, Willem Einthoven in Utrecht published his work on the “string galvanometer” which would later become the electrocardiogram.(26) In 1906, Einthoven, using the galvanometer, was the first to publish a tracing (Figure 1) termed “pulsus inaequalis et irregularis”; however, Einthoven did not recognise its significance.(27)

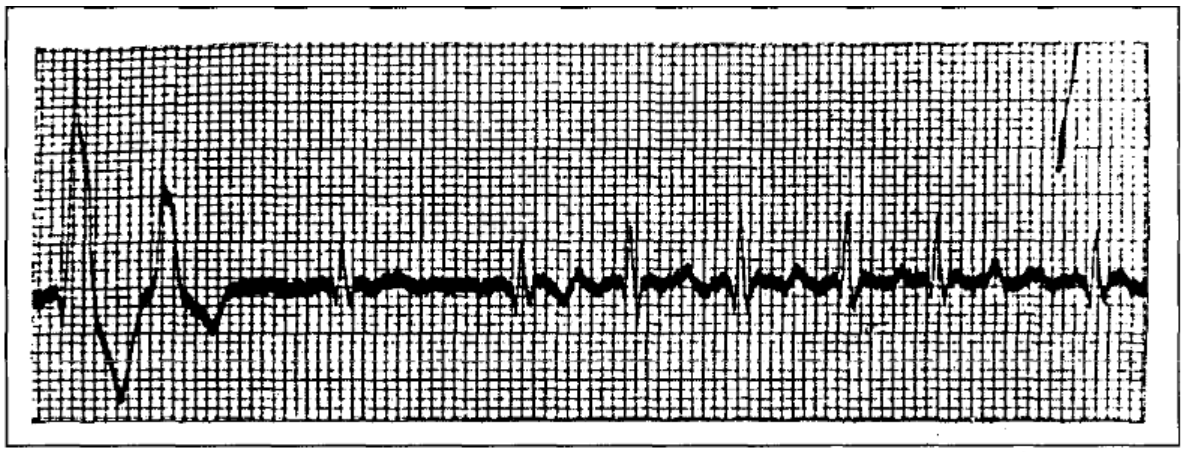

Figure 1: Electrocardiogram showing “pulsus inaequalis et irregularis” From Einthoven*(28)*

When Mackenzie met Lewis in 1908, he directed him to visit Einthoven and to use the string galvanometer to analyse arrhythmias.(27,29) In subsequent years, Lewis applied the string galvanometer to his patients with pulsus irregularis perpetuus demonstrating irregular waves (Figure 2) corresponding to his previous experiments. (25,30)

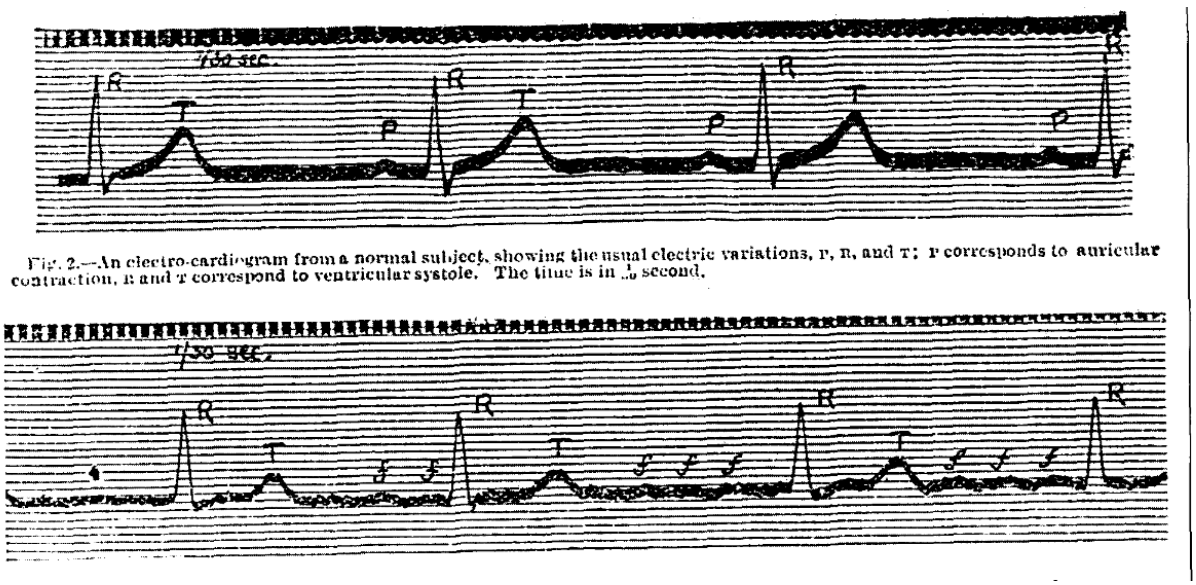

Fig. 2.—An electro-cardiogram from a normal subject, showing the usual electric variations, P, R, and T; P corresponds to auricular contraction, R and T correspond to ventricular systole. The time is in $\frac{1}{50}$ second.

Figure 2:Electrogram recorded by Dr Lewis showing sinus rhythm above and auricular fibrillation below. From Thomas Lewis*(25)*

At the time Lewis commented “Fibrillation of the auricle yields curves which are identical in every respect. . . Further, the waves on the experimental electrocardiograms can be shown to

correspond to the fibrillary movements in the auricle. . .The facts point clearly to the conclusion that the irregularity in question is the result of auricular fibrillation".(27,30)

On studying and listening to Thomas Lewis' theory, Mackenzie concurred with his ideas commenting "The facts point clearly to the conclusion that the irregularity in question is the result of auricular fibrillation".(30) Thus the mystery of the irregular pulse and its origins was solved and the irregular pulse was indeed due to auricular fibrillation.(27) The works of Lewis and Mackenzie were further confirmed by Rothberger and Winterberg in 1909.(27,31)

In 1924, the Nobel Prize was awarded to Einthoven. At the time, he acknowledged that "But for the work of Thomas Lewis I would not have the honour of standing here today".(32) Auricular fibrillation would later be termed atrial fibrillation. However, although Einthoven, Lewis, and Mackenzie had diagnosed AF, its mechanism of action was still not completely understood, and its treatment remained problematic.(27)

It was not until the early 1900s that our understanding of AF improved exponentially with the advent of the electrocardiogram, which improved our understanding of the mechanisms of AF.

2.2 Mechanism of AF

Since the introduction of the electrocardiogram by Einthoven in the 20th century, our understanding of the mechanisms underlying AF and its clinical importance has greatly improved.(33)

AF is characterised by high frequency and highly irregular excitation of the atrium, which results in irregular and fast excitation of the ventricular myocardium. Over the last few decades, research has shown that AF is associated with other comorbid conditions that may cause electrical and structural changes to the atrium, resulting in an atrial cardiomyopathy or atrial substrate.(33,34)

2.3 Pulmonary vein ectopic firing

The dominant and most widely accepted theory concerning the origin of AF postulates that AF onset is precipitated by rapid ectopic firing that then propagates re-entrant waves through an atrial substrate that is already susceptible to AF.(33) As the substrate implicated in AF evolves and the disease progresses, the significance of the initial ectopic firing wanes, and the condition of AF then tends to stabilize and progress from paroxysmal AF to persistent AF and then finally to permanent AF.(33,34)

Research to date has shown that the pulmonary veins possess distinctive electrophysiological characteristics and an intricate myocyte fibre structure, which facilitate re-entrant circuits and ectopic firing that can trigger AF.(33,35) Perez-Lugones et al. reported in their study of post-mortem examinations the existence of pacemaker cells, transitional cells, and Purkinje-like fibres within the pulmonary veins that can initiate ectopic firing.(33,36)

The mechanism of pulmonary vein ectopic triggers has largely been ascribed to aberrant handling of calcium ions (Ca2+).(33) The leakage of Ca2+ during the diastolic phase from the sarcoplasmic reticulum instigates an inward sodium (Na+) current through the Na+/Ca2+ exchanger, leading to the spontaneous depolarisation of myocytes (manifesting as early or delayed afterdepolarizations).(33) Hyperactivation of key proteins and enzymes such as ryanodine receptor type 2, phospholamban, protein kinase A and calmodulin kinase II, is closely associated with the sarcoplasmic reticulum Ca2+ surplus and results in diastolic membrane instability initiating ectopic firing.(33,37,38) Alternatively, a re-entrant paradigm for pulmonary vein ectopic triggers has been proposed. Heterogeneity and variable repolarization within the pulmonary veins provide the conditions for localised re-entrant activity and may act as a focal precursor for AF.(33)

2.4 Re-entrant mechanism of AF

Although, as described, triggers are essential for the onset of AF, a predisposed atrial substrate is of equal importance in maintaining and perpetuating AF.(39) Structural and electrophysiological abnormalities in the atrium facilitate the continuation of AF by re-entrant pathways.(39)

The exact mechanism underlying re-entry in AF is debated, with two prevailing theories: either re-entrant rotors or multiple independent wavelets.(33,40–42) Technological advancements in electroanatomic mapping and ablation have increasingly corroborated the rotor hypothesis.(33,43,44) In addition, the double layer hypothesis postulates that electrical dissociation between the endocardial and epicardial layer of the atrium may further enable re-entry.(45)

The maintenance of functional reentry necessitates that the transmission of the electrical wavefront is timed such that the atrial tissue within the reentrant circuit regains excitability (evidenced by the effective refractory period, ERP).(33) Hence, conditions with slow conduction velocity or shortened ERP are conducive to reentry. (46) These factors contribute to a decrease in the wavelength, increasing the probability of concurrent re-entrant circuits and the sustained presence of AF.(33)

Atrial substrates conducive to re-entry are often distinguished by irregularities in atrial myocytes, fibrotic transformation, and modifications in the interstitial matrix, predominantly characterised by non-collagenous deposits.(33,34) Such molecular histopathological alterations due to fibrosis or diminished cellular connectivity can lead to reduced atrial ERP.(33) For example, hereditary forms of AF are associated with mutations that enhance K+ channel activity, thereby curtailing the ERP in atrial myocytes.(33) Conversely, in the context of heart failure, there is a synergy between atrial fibrosis and myocyte functional changes,

resulting in reduced conduction velocity and a shortened ERP.(33) Therefore, the identification and characterisation of atrial substrate susceptible to AF is inherently tied to specific risk factors for AF.(33)

2.5 Non modifiable risk factors for AF

2.5.1 Genetics

Population-based studies to date have shown that a familial history of AF is linked with a 40% increased risk of first-degree relatives developing AF, giving credence to the existence of specific gene loci responsible for AF.(33,47,48) To date, there have been at least fifteen identified AF-causing mutations in K^+ channel genes and six variations in Na^+ channel genes associated with AF.(33)

2.5.2 Gender

It has been shown that males have a higher incidence of AF than females; however, this is most likely due to a taller structure and higher number of risk factors, such as coronary artery disease, although other risk factors, such as hypertension, are higher in females.(49,50) Adjusting for risk factors shows that male gender is not an independent risk factor for the development of AF.(51)

2.5.3 Age

Advancing age has been found to be the most prevalent risk factor for the development of AF, and indeed, patients with AF less than 65 years of age have been shown to be healthier and have a different risk factor profile to older patients which affects treatment and management decisions. (52,53)

2.6 Modifiable risk factors

2.6.1 Hypertension

Multiple studies, including the Framingham heart study and the CHARGE-AF study have shown that hypertension is associated with the development of AF and that both systolic and diastolic blood pressure elevation is predictive of developing AF.(51,54,55) Hypertension increases the risk of AF in multiple ways including left ventricular hypertrophy, increasing atrial size and diastolic dysfunction.(54,56) All result in an elevated left ventricular end diastolic pressure which increases left atrial volume and pressure resulting in remodelling and slowing of atrial conduction and an increase in pulmonary vein ectopy.(33)

2.6.2 Diabetes

The Framingham heart study showed that there was a 40% and 60% increased risk of AF in males and females with diabetes, respectively.(33,57) Studies have found this association to be due to glucose intolerance and insulin resistance which mediate atrial substrate formation.(58) In patients undergoing AF ablation abnormal glucose metabolism is associated with reduced bipolar voltages and the formation of atrial scar and fibrosis.(59)

2.6.3 Obesity

Obesity increases the risk of multiple conditions that predispose patients to AF, including hypertension, diabetes, myocardial infarction, diastolic dysfunction, left ventricular hypertrophy and increased atrial size. (33) When controlling for these risk factors, obesity increases the risk of developing AF. (33,60) The elevated risk of AF in obese patients has been shown to be due to increased left atrial size and left ventricular mass which in turn increases

left atrial volume and pressure and deposition of pericardial fat.(33,61,62) These changes result in decreased conduction velocity in the atria and the development of AF.(63)

2.6.4 Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) has been shown to be highly prevalent in patients with AF and often coexists with other risk factors, including diabetes, obesity and hypertension. (64,65) The Sleep Heart Health Study found that OSA was associated with a 4-fold increase in the prevalence of AF and that one-third of participants had arrhythmias during sleep.(66) Studies have found that in patients with OSA, there is an increased atrial size and low voltages indicating atrial fibrosis and loss of atrial myocardium.(67,68) Several mechanisms have been proposed for how OSA causes atrial substrate, including hypoxia during apnoeic episodes causing increased blood pressure, apnoea causing fluctuation in intrathoracic pressure thus increasing left atrial pressure and volume, increasing atrial remodelling via increased oxidative stress and hypercapnia causing slowing of atrial conduction.(33,69–72)

2.7 Management of AF

The goal of AF management is to restore atrial synchrony and atrial contraction.(73) The 2020 ESC guidelines on the management of AF proposes characterising patients with AF using the 4S-AF scheme calculating patients stroke risk via the CHA_2DS_2VASc score, calculating symptom severity using the EHRA score, defining the type of AF (paroxysmal, persistent or permanent) and finally assessing atrial substrate severity by assessing comorbidities.(73,74) The guideline advises an holistic approach using the Atrial fibrillation Better Care (ABC) holistic pathway. A standing for avoiding stroke with anticoagulation.(74)

AF is associated with an increase in the risk of stroke by at least five times, and the risk increase is dependent on the presence of various risk factors.(73,75) The most commonly used and most predictive score to assess stroke risk is the CHA_2DS_2VASc score.(76) The guidelines advise anticoagulation in all patients unless they are at low risk, defined as those patients with a CHA_2DS_2VASc score of 0 in men or 1 in women and a stroke event rate <1% per year.(73,74,76)

Further management of AF beyond stroke risk reduction is based on better control and relief of symptoms associated with AF via a rhythm or rate control strategy.(71) Antiarrhythmic medications such as Amiodarone, Sotalol, Flecainide, Dronedarone and Propafenone aim to restore and maintain sinus rhythm in patients with AF, whereas rate control medications such as Bisoprolol, Diltiazem and Digoxin aim to regulate the ventricular rate during AF to alleviate symptoms.(77)

Previous studies comparing rhythm and rate control strategies include

- AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management).(78)
- AF-CHF (Atrial Fibrillation and Congestive Heart Failure).(79)
- Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation.(78)
- PIAF (Pharmacological Intervention in Atrial Fibrillation).(80)

In general, there have been no significant differences in either approach regarding mortality, stroke, and bleeding, although studies have found that the degree of AF burden is associated with a reduction in quality of life and restoration of sinus rhythm can improve symptoms and quality of life.(81) Current guidelines thus advocate a rhythm control strategy primarily to improve symptoms.

2.7.1 Rhythm control medications

Pharmacological therapy for AF has evolved exponentially over the past years and has been the initial guideline directed therapy for AF.(77) Although many of the randomised controlled trials involving antiarrhythmic medications have not shown improvements in mortality and cardiovascular events, many of the studies were completed in the 1980s and 1990s with small sample sizes, included patients with long-term persistent AF and were performed when medications were still relatively novel with unbalanced therapies for stroke reduction confounding results.(77) Furthermore, the use of antiarrhythmic medications was dampened following the results of the Cardiac Arrhythmia Suppression Trial showing an increased mortality rate in patients with impaired left ventricular function and prior myocardial infarction taking Flecainide.(82) Additionally, pulmonary vein isolation has been shown to be more effective than antiarrhythmic medications in maintaining sinus rhythm.(83,84)

2.7.2 Catheter ablation for AF

In a seminal paper published in 1998, Haissaguerre et al. were pivotal in discovering that paroxysmal AF often originates from the myocardial sleeves of the pulmonary veins, where ectopic discharges occur.(85) Subsequent ablation of these ectopic sources substantiated their integral role in the onset of AF.(85) There have been many iterations, techniques and novel catheter ablation technologies aimed at treating AF.

Initial investigations into ablation techniques demonstrated superiority in restoring sinus rhythm over pharmacological medications, however these studies often only included patients with symptomatic AF who had not responded to antiarrhythmic drug therapy thus, potentially introducing bias.

In contrast, the RAAFT and RAAFT-2 trials focussed on patients who had not failed antiarrhythmic treatment.(17,86) Both of these studies showed a significantly lower incidence of AF recurrence in the ablation group than in the antiarrhythmic group. In the RAAFT trial 63% of patients who received antiarrhythmic drugs had at least one recurrence of symptomatic AF compared with 13% of patients who were randomised to pulmonary vein isolation at one year follow-up (P<.001).(86) Similarly in RAAFT-2 72.1% of patients in the antiarrhythmic group experienced a recurrence of arrhythmia compared to 54.5% in the ablation group at two years follow-up (P = .02).(17)

In contrast to the RAAFT and RAAFT-2 trials, the MANTRA-PAF study, encompassing symptomatic paroxysmal AF patients without prior antiarrhythmic therapy, did not show a significant difference in cumulative AF burden over 24 months between radiofrequency ablation and antiarrhythmic therapy (90th percentile of arrhythmia burden, 13% and 19%, respectively; P=0.10).(86) Although, the authors also reported that significantly more patients in the ablation group than in the medical therapy group were free from symptomatic AF (93% vs. 84%, P=0.01) and any atrial fibrillation (85% vs. 71%, P=0.004) at 24 months.(87)

Subsequent trials such as CAPTAF, CABANA, AATAC, and CASTLE-AF have consistently demonstrated that ablation markedly reduces AF burden and recurrence compared with pharmacological rhythm control treatment.(6,88–90) The CABANA trial, however, did not find a significant difference in the primary composite end points of death, disabling stroke, serious bleeding, or cardiac arrest at 5 years between patients randomised to ablation treatment and those randomised to drug therapy (8% vs. 9.2% (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.65-1.15, p = 0.3). (88) Although, the study did show a reduction in persistent or long-standing AF in the ablation group.(88) This trial highlighted the necessity of repeated ablation procedures, underscoring that in some patients repeat catheter ablation is required.(88)

In patients with heart failure, early ablation studies not only showed efficacy in sinus rhythm restoration but also in improving left ventricular ejection fraction, outperforming antiarrhythmic therapy.(77,91,92) The multicenter AATAC study corroborated these findings, with catheter ablation proving superior to amiodarone therapy in various outcomes, including freedom from AF and improvement in left ventricular function.(89) Similarly, the CASTLE-AF trial found catheter ablation to be more effective than pharmacological rate-control therapy in patients with coexisting AF and heart failure, although the trial faced methodological criticism. (90)

Further reinforcing the efficacy of ablation, the EARLY-AF, STOP-AF and CRYO-First trials, along with meta-analyses of multiple studies, have consistently shown ablation to be as safe as antiarrhythmic therapy and more effective in maintaining sinus rhythm in patients with symptomatic AF.(15,93,94) These studies also revealed significant reductions in mortality, stroke, and heart failure related hospitalisations, thereby confirming ablation as a potent therapeutic option in the management of AF.(77)

2.7.3 Catheter ablation and quality of life

Catheter ablation for AF is currently indicated to improve symptoms and quality of life. Assessment of quality of life in previous trials has ranged from using general health questionnaires including the Short Form Health Survey (SF-36) and the EuroQol Five Dimensions Questionnaire (EQ5D) questionnaires which have a low specificity for assessing symptoms related to AF. AF-specific questionnaires include the “AF effect on Quality of Life Survey” (AFEQT), “Mayo AF Specific Symptom Inventory” (MAFSI), “Quality of Life Questionnaire for Patients with AF” (AFQoL), the “European Heart Rhythm Association” (EHRA) score and the “Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale”

(CCS-SAF).(7,95,96) Various trials have examined the effects of medical therapy via antiarrhythmic medication versus pulmonary vein isolation on quality of life.

The multicenter RAAFT study published in 2005 randomised 70 symptomatic AF patients to either catheter ablation or antiarrhythmics as first-line therapy, primarily including patients with paroxysmal and some with persistent AF.(86) The study revealed a marked superiority in arrhythmia control and quality of life enhancement with ablation treatment at 6-month follow-up with improvements in 5 domains of the Short-Form 36 health survey. (86,95)

The A4 study later compared catheter ablation with various antiarrhythmics in a multicenter randomised controlled trial as a second-line therapy for paroxysmal AF.(97) Over 12 months, both groups exhibited a reduced AF burden, with a median within-subject reduction at 365 days of 10.0 minutes (range: 0.0 and 588.0 minutes) in the ablation group versus a reduction of 3.2 minutes (range: 0.0 and 154.6 minutes) in patients assigned to antiarrhythmic therapy.(97) In patients randomized to ablation there was a median within-subject reduction in AF burden at 365 days of 10.0 minutes (range: 0.0 and 588.0 minutes) versus patients in assigned to antiarrhythmic therapy where there was a reduction of 3.2 minutes (range : 0.0 and 154.6 minutes). Quality of life improvements were significantly better with pulmonary vein isolation, as assessed by the SF-36 questionnaire in several domains and in symptom severity, although symptom frequency did not differ significantly.(97)

The ThermoCool AF trial compared pulmonary vein isolation post-antiarrhythmic failure, with ongoing antiarrhythmic therapy in a 2:1 ratio.(98) This study reported greater improvements in the SF-36 physical and mental summary scores following catheter ablation at three months, which was maintained throughout the study duration.(98,99) Unlike the A4 study, the ThermoCool AF trial also observed a reduction in symptom frequency after ablation.(98) This

trial underscored the benefits of early catheter ablation after antiarrhythmic failure for effective symptom control and quality of life enhancement.(98,99)

The RAAFT-2 trial later examined catheter ablation as a first-line therapy using the EQ5D score.(17) While no significant quality of life difference was observed between the groups, the ablation cohort exhibited a lower atrial arrhythmia recurrence rate.(17)

In the MANTRA PAF trial comparing RF ablation and antiarrhythmics as first-line therapies, significant quality of life improvements were noted in both groups using the SF-36 questionnaire after 24 months.(87) The ablation group demonstrated slightly better quality of life improvement, particularly in physical scales.(87)

More recently, The CAPTAF trial, enrolled 155 patients post-antiarrhythmic treatment failure and using implantable cardiac monitors for arrhythmia assessment, showed significant quality of life improvements with catheter ablation.(6) In the ablation group, the General Health score increased from 61.8 to 73.9 points vs 62.7 to 65.4 points in the medical therapy group (between-group difference, 8.9 points; 95% CI, 3.1-14.7; $P = .003$).(6)

The CABANA trial, the largest clinical trial comparing antiarrhythmic therapy with catheter ablation in patients with symptomatic AF, included 2204 participants. It demonstrated significant quality of life improvements with catheter ablation, persisting even after 60 months.(7) At the 12-month mark, the catheter ablation cohort demonstrated a more significantly higher mean AFEQT summary score compared to the drug therapy group (86.4 vs 80.9 points), with an adjusted difference of 5.3 points (95% CI, 3.7-6.9; $P < .001$).(7) Additionally, the mean MAFSI frequency score was significantly better in the intervention group than in the medical therapy group at the same time point (6.4 vs 8.1 points), with an adjusted difference of -1.7 points (95% CI, -2.3 to -1.2; $P < .001$).(7) Similarly, the mean

MAFSI severity score was significantly higher in the intervention group compared to the medical therapy group at 12 months (5.0 points vs 6.5 points), with an adjusted difference of -1.5 points (95% CI, -2.0 to -1.1; P < .001).(7)

More recently, the CIRCA-DOSE study, which involved 346 patients with drug-refractory paroxysmal AF, reported significant improvements in quality of life and a significant reduction in health care use in the year following AF ablation.(100) The study authors used stringent monitoring with all patients having an implantable loop recorder. Disease-specific (AFEQT) and generic (EQ-5D) scores significantly improved following catheter ablation, and this was maintained until the 12-month follow-up.(100)

2.8 The need for a sham controlled study

Despite studies showing the superiority of catheter ablation over medical therapy, there has been scepticism relating to whether the improvement seen with catheter ablation is due to a placebo effect. To date, there has been no study that has had a placebo-controlled design. The placebo response is complex, and it is likely that there are multifactorial effects at play, including a real physiological response combined with natural fluctuation in the disease state, spontaneous remission, observer enthusiasm and expectations, patients' own beliefs and expectations, regression to the mean, and random variability.(101)

Following the negative results of the SYMPLICITY HTN-3 trial, which was a randomised controlled trial with a sham intervention examining the effects of renal denervation on hypertension, Ozeke et al. were the first to postulate whether pulmonary vein isolation has a placebo effect in 2016.(10) While the evidence for the role of the pulmonary veins initiating AF is not disputed, success rates of AF ablation in the real world are less than those reported in clinical trials which is similar to what is seen in renal denervation.(10) Furthermore, some

patients have been reported to be AF-free post-ablation despite reconnected pulmonary veins, suggesting potential substrate modification or placebo effects.(10) Ozeke et al. report that although sham surgeries or interventions pose ethical dilemmas due to potential harm and patient deception, the need to benchmark safety and efficacy against placebo-controlled trials in AF treatment remains, considering the risks associated with monetarily-driven, unproven treatments.(10)

Furthermore, in a study of 54 patients who completed the 24-month follow-up, Björkenheim et al. reported that patient-reported outcomes and physician assessments proved beneficial in evaluating symptom relief after AF ablation.(102) A notable divergence was observed between patient-reported outcomes and physician assessments following ablation.(102) Whilst the absence of AF and a minimal AF burden typically led to symptom reduction, symptom alleviation was also reported in cases with minimal impact on the arrhythmia.(102)

In a prospective, multicenter Study, Verma et al. published the results of the DISCERN-AF study which examined the predictors and incidence of asymptomatic AF before and after catheter ablation.(103) 50 patients were followed up for 18 months after ablation. The total AF burden was reduced by 86% after ablation ($P < .001$); however, 56.0% of all episodes were asymptomatic.(103) The ratio of asymptomatic to symptomatic AF episodes increased after ablation from 1.1 to 3.7 ($P = .002$).(103) Based on this data the authors postulated the possibility of a placebo effect after ablation.(103)

Furthermore, studies have reported that the improvement in quality of life after ablation may be independent of procedural success. Wokhlu et al. reported that AF ablation produces sustained quality of life improvement at 2 years in patients with and without AF recurrence.(104) Post-ablation there were improvements seen across different ablation outcomes, including recurrent AF with there being no significant differences in quality of life

improvement between the 3 different efficacy outcomes.(104) Additionally, Fichtner et al. reported significant improvements in quality of life as measured by seven different questionnaires three months after ablation in all patients (regardless of ablation success or AF type). These improvements in quality of life persisted after a median follow-up of 4.3±0.5 years.(105)

In a report from the National Heart, Lung, and Blood Institute Virtual Workshop published in 2019, the authors highlighted the need for sham ablation trial.(106) Despite several challenges relating to sham controlled trials, including patient acceptance, potential enrolment bias, funding and endpoint assessment the authors note that such such trials may be beneficial in definitively examining hard outcomes of AF ablation.(106)

3 Research Aims and Hypotheses

3.1 General Research Aims & Hypotheses

Our understanding of AF, its triggers, and the role of the pulmonary veins in the pathophysiology of AF is well established. However, there are several unresolved questions regarding the management of AF and the actual success rates of ablation treatments, which have become widespread and routine. The clinical benefits observed from pulmonary vein isolation maybe attributable to both a genuine physical effect and a placebo component. The placebo component of pulmonary vein isolation has never been elucidated. In this thesis I report the effectiveness of pulmonary vein isolation on AF burden, symptoms and quality of life from the SHAM-PVI trial

The objective of this thesis is to investigate the effectiveness of pulmonary vein isolation against a sham procedure. Additionally, it aims to examine the relationship between AF burden, symptoms, and quality of life.

This thesis will address the following hypotheses, which are novel:

1. Does a procedure intended to isolate the pulmonary veins exert a placebo effect?
2. How do AF burden, quality of life, and symptoms relate?

The effectiveness of pulmonary vein isolation was investigated through a double-blind, randomised controlled study comparing pulmonary vein isolation using the cryoballoon technique with a sham procedure (The SHAM-PVI trial). A sub-analysis of the SHAM-PVI trial examined the relationship between AF burden, quality of life, and symptoms.

4 Methodology

4.1 Rationale

AF is the most common cardiac arrhythmia with an 8.5% prevalence in men and 7.1% prevalence in women over the age of 55.(107) It is estimated there are 8.8 million adults with AF in the European Union. (107)

Catheter ablation has been shown to reduce the occurrence of AF and improve quality of life and symptoms in patients with symptomatic AF when compared to medical therapy, for example the CABANA study showed significant improvements in quality of life and symptoms.(7,83) However previous trials involving catheter ablation have not been blinded raising the possibility of a placebo effect accounting for the differences in outcomes.

The ORBITA trial (Percutaneous intervention vs placebo in angina patients) and SYMPLICITY HTN-3 (renal denervation vs sham procedure in resistant hypertension) trials have shown that placebo controlled trials for device therapy are safe and feasible.(12,13) Indeed both trials provided evidence for a placebo effect in device therapy, which had not been accounted for previously.(12,13)

This study was an investigator led randomised double blind trial comparing catheter ablation to sham therapy in patients with symptomatic paroxysmal or persistent AF.

4.2 Methods

We conducted a dual centre randomised double-blind controlled study to evaluate pulmonary vein isolation (via cryoballoon ablation) compared with a sham procedure in patients with symptomatic paroxysmal or persistent AF. The trial protocol has been previously

published.(108) 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.

The objective of this study was to evaluate the effectiveness of pulmonary vein isolation vs a sham procedure in patients with symptomatic paroxysmal or persistent AF. The null hypothesis predicted that pulmonary vein isolation had no effect on AF burden compared to a sham procedure.

Paroxysmal AF (PAF), also termed intermittent AF, is defined as any episode of AF that terminates spontaneously or with intervention in less than seven days.(109) Persistent AF is defined as any continuous AF episode that is sustained beyond seven days.(109) Long-term persistent AF is defined as any continuous AF episode lasting more than 12 months in duration and patients in permanent AF are defined as such when the clinician and patient make a joint decision to stop further attempts at maintaining sinus rhythm.(109)

The major inclusion criteria for the study comprised patients with symptomatic paroxysmal or persistent AF despite at least one antiarrhythmic drug (AAD Type I or III, including β-blocker and AAD intolerance). The major exclusion criteria included long-term persistent AF (any continuous AF episode lasting more than one year), prior left atrium catheter or surgical AF ablation, patients with other arrhythmias requiring ablative therapy, left atrium (LA) ≥5.5cm

and ejection fraction (LVEF) less than 35% (Table 1). Patients who had undergone a previous catheter ablation were excluded as they would require a different procedure, typically involving radiofrequency ablation to identify and treat pulmonary vein reconnections. Patients with long-term persistent AF and a left atrial diameter >5.5 cm were excluded because previous studies have shown that these patients often require more extensive ablation strategies beyond pulmonary vein isolation alone. Finally, patients with a left ventricular ejection fraction <35% were excluded as trials such as CASTLE-AF have demonstrated a mortality benefit from AF ablation in this group, and therefore withholding or delaying ablation for the purposes of a sham-controlled study may be viewed as unethical.(90) Any patient enrolled in the study who withdrew their consent was removed from the study, but at enrolment their consent was sought to use the data already recorded. For participants who were lost to or did not attend follow-up, data was obtained from hospital medical records and/or primary care records where possible.

Table 1: Inclusion and exclusion criteria

Inclusion criteria
Age greater than or equal to 18 years
Symptomatic paroxysmal or persistent atrial fibrillation despite at least one antiarrhythmic drug (AAD Type I or III, including β-blocker and AAD intolerance)
Referred for catheter ablation
Exclusion criteria
Long term persistent AF (any continuous AF episode lasting more than one year)
Prior left atrium catheter or surgical atrial fibrillation ablation
Patients with other arrhythmias requiring ablative therapy
Left atrium (LA) ≥5.5 cm
Left ventricular ejection fraction (LVEF) less than 35%
Any cardiac surgery or percutaneous coronary intervention (PCI) within three months prior to enrolment.
Awaiting cardiac surgery or PCI
Myocardial infarction within three months prior to enrolment
Stroke or transient ischemic attack (TIA) within three months prior to enrolment
Unstable angina
Any significant congenital heart defect corrected or not (including atrial septal defects or PV abnormalities) but not including patent foramen ovale
Any condition contraindicating chronic anticoagulation
Any untreated or uncontrolled hyperthyroidism or hypothyroidism
Severe chronic kidney disease (stage V, requiring or almost requiring dialysis, glomerular filtration rate (GFR) < 15 ml / min)
Patients with prosthetic valves
Pregnant or breastfeeding women
Medical conditions limiting expected survival to <1 year
History of claustrophobia or panic attacks

Outcome measures were evaluated at 3 months post randomisation and 6 months post randomisation (Table 2). The first three months post randomisation constituted the blanking period.

The primary outcome AF burden was measured using continuous monitoring between the end of month 3 and end of month 6 post-randomisation 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 AFEQT, MAFSI, and EHRA score with scores compared between baseline, 3 months and 6 months. Overall quality of life was compared using the SF-36 score. 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.(Table 3).

Table 2: Schedule of interventions and assessments

	Enrolment	Day 0 / Procedure day	3 MONTHS	6 MONTHS
Consent	X			
AF symptom review	X		X	X
Clinical examination	X		X	X
Medication review	X		X	X
Adverse event review		X	X	X
Echo (if not performed in last 12 months)	X			
ECG	X	X	X	X
Questionnaires		X	X	X
ILR implantation (if not already implanted)	X			
ILR interrogation		X	X	X
Procedure (ablation/ sham)		X		
Blinding assessment		X	X	X

Table 3: Secondary outcomes of the SHAM-PVI trial

Time to any atrial tachyarrhythmia stratified by length of episode (more than 30 seconds / more than 7 days)
Time to symptomatic atrial tachyarrhythmia
Number of atrial tachyarrhythmia episodes (symptomatic and asymptomatic) in the follow up period in each group stratified by length of episode (more than 30 seconds / more than 7 days)
Comparison of medical treatment in each group in the follow up period
Comparison of health related quality of life in each group (SF-36)
Comparison of AF specific quality of life score between each group; Atrial Fibrillation Effect on Quality-of-Life (AFEQT) Questionnaire, Mayo AF Symptom Inventory (MAFSI) and EHRA class
Comparison of unscheduled use of health care services during follow up
Procedure related complications / adverse events between each group

4.3 Procedures

This was a double blind, randomised sham controlled study commenced in December 2019 (Figure 3). Patients meeting the inclusion and exclusion criteria were recruited from hospitals within East Sussex Healthcare NHS Trust and Mid and South Essex NHS Foundation Trust. 140 patients meeting the inclusion and exclusion criteria were recruited. Ethical approval was obtained from the West Midlands – South Birmingham Committee (19/WM/0361).

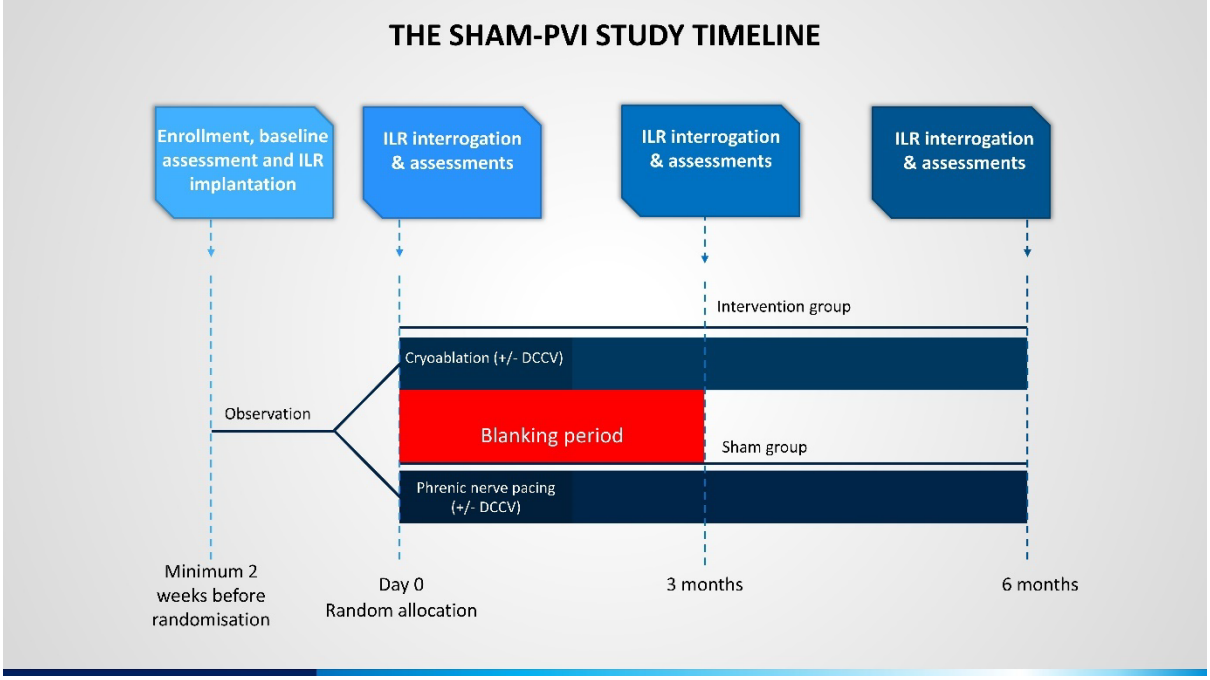

Figure 3: The SHAM PVI study timeline.

Following recruitment and baseline measurements, all patients underwent an implantable loop recorder implantation (Reveal LINQ, Medtronic Inc., Minneapolis, USA) if this was not inserted previously. It was recommended the implantable loop recorder be inserted at least two weeks prior to the main procedure day or on the main procedure day dependent on covid-19 restrictions.

4.3.1 Implantable loop recorder insertion

A Medtronic Reveal LINQ loop recorder was inserted as per manufacturer guidelines at study enrolment. The device settings were optimised to record all AF episodes longer than 2 minutes (Table 4). The device is able to wirelessly transmit all ECG recordings and activated episodes on a daily basis. The AF algorithm has a reported sensitivity of 97.4% and positive predictive value of 73% however all recordings were manually reviewed by a 3-person adjudication

committee blinded to patient group.(110,111) All patients had the ILR inserted at least 2 weeks before the main procedure day.

Table 4: Implantable loop recorder programming settings

Parameter	**Setting**
AF detection threshold	Balanced Sensitivity
Ectopy rejection	Nominal
Episode storage threshold	All
Tachycardia detection	Interval = 400 ms duration 16 beats

4.4 Pre procedure medication management

Antiarrhythmic drugs were discontinued five half-lives (up to 5 days) before the procedure, except for Amiodarone, which was discontinued eight weeks prior to procedure day. Procedures were performed on uninterrupted anticoagulation. Patients remained on anticoagulation for the duration of the study.

4.5 Randomisation

Participants were randomly assigned in a 1:1 ratio to undergo either catheter ablation +/- DCCV (if in AF) or a sham procedure +/- DCCV (if in AF). A computerised central blocked randomisation design was generated and stratified according to type of atrial fibrillation (paroxysmal / persistent). Randomisation blocks were performed with “ralloc”, Stata’s randomisation process v.16.0. The block sizes were not disclosed to study investigators, to ensure concealment.

The randomisation sequence and study-group assignments were prepared and placed in sequential numbered sealed, opaque envelopes by a fellow with no involvement in the execution of the trial. The envelopes were kept securely by a sponsor administrator not involved in the conduct of the study.

The allocation remained concealed until after sedation had been achieved at the time of the procedure.

4.6 Sedation and blinding

During each procedure patients were given over-the-ear headphones playing music to prevent hearing of communication between cath-lab staff. 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 health care professionals performing the procedure had no further contact with the patient during follow-up. Healthcare professionals or research staff involved in the patient care post procedure and during follow-up were blinded to the treatment strategy (Figure 4).

NHS
East Sussex Healthcare
NHS Trust

Eastbourne District General Hospital
Kings Drive
Eastbourne
East Sussex
BN21 2UD

Tel: 01323 417400
Website: www.esht.nhs.uk

[DATE]

[GP Address]

Dear Dr

RE: Catheter ablation in symptomatic atrial fibrillation: a double blind randomised controlled trial

Re: [Patient Name]: [Patient DOB]
Trust Hospital ID:
NHS No:

[Patient Name] presented today for their procedure as part of the "Catheter ablation in symptomatic atrial fibrillation: a double blind randomised controlled trial"

The procedure was completed as per protocol.

We shall organise follow up in 3 months.

Please contact me if you have any concerns relating to the study.

Yours Sincerely

Figure 4: Example discharge summary given to all patients

Participant blinding was assessed at the time of discharge, 3 months and at 6 months follow-up. Participants were asked to guess one of the following: (1) ablation, (2) placebo, (3) Don't know. Participants were asked to state the certainty of their answers on a grade scale of 1-5 with 5 being most sure.

Staff members were also asked at discharge, 3 months and at 6 months follow-up to guess the patient treatment allocation.

4.7 Cryoablation procedure

At the beginning of the procedure 2x femoral venous access was achieved using ultrasound guidance. If the patient was in AF then DCCV was undertaken to cardiovert to sinus rhythm.

A multipolar catheter was placed in the coronary sinus(CS). The left atrium (LA) was then accessed via trans-septal (TS) puncture or patent foramen ovale. Following left atrial access, IV heparin was administered as sequential boluses maintaining an > ACT 300 sec. Thereafter the TS sheath was exchanged with a steerable 15 Fr sheath (Flexcath, Medtronic). A 28 mm cryoballoon catheter (Arctic Front Advance, Medtronic) was advanced through the steerable sheath into the LA with a guide wire or the Achieve mapping catheter in the central lumen.

The cryoballoon was positioned in the ostium of each pulmonary vein using fluoroscopic guidance and contrast injection with minimal or no dye leak on injection after inflation.

Prior to ablation of the right pulmonary veins, the multipolar catheter was placed in the right subclavian vein to pace the right phrenic nerve (10–20 mA at 1.0–2.0 msec pulse width at a cycle length of 1000 msec). Ablation was immediately terminated upon any perceived reduction in the strength of diaphragmatic contraction.

Cryoablation in each PV was applied for a minimum duration of 180 seconds and maximum duration of 240 seconds. If the temperature had not reached -40 degrees by 60 seconds then this was deemed to be an ineffectual ablation and the ablation was stopped and the balloon

repositioned. A further 2 attempts at ablation was allowed. Entrance and exit block was confirmed and if the operator fails to isolate the PV (excluding common ostia) after a minimum of 3 attempted cryoballoon applications then focal ablation with the 8 mm cryocatheter (Freezor Max) targeted to sites of LA-PV breakthrough was permitted at operator discretion.

At the end of the procedure once sheaths have been removed all patients had a three-way stopcock suture in order to achieve haemostasis.

4.8 Sham procedure

After 2x venous access had been achieved using ultrasound guidance, DCCV was undertaken if the patient was in AF. A 5-Fr pacing catheter was then placed at the right subclavian vein to pace the phrenic nerve (10–20 mA at 1.0–2.0 msec pulse width at a cycle length of 1000 msec). The phrenic nerves were paced for 4 minutes on four occasions during the procedure. Operators were advised to keep the patient in the catheter lab for a minimum of one hour.

At the end of the procedure once sheaths have been removed all patients had a three-way stopcock suture in order to achieve haemostasis.

4.9 Follow-up

AF episodes were managed medically as per the European Society of Cardiology (ESC) guidelines during the follow-up phase.(112) Only one DCCV was permitted for each participant during the follow-up phase. Antiarrhythmic 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.

4.10 Sample Size Calculation

The study was powered to address the primary hypothesis that pulmonary vein isolation reduced the total AF burden compared to patients undergoing a sham procedure at 6 months post randomisation. The CASTLE AF trial reported AF burden using continuous monitoring at 3 months in the ablation group to be 27% and 51% in the pharmacological group. At 6 months the AF burden in the ablation group was reported to be 23% vs 51% in the pharmacological group. (113) Based on previous published data and the clinical investigators experience we estimated the AF burden in the intervention group to be 25% at 6 months follow-up and in the control group to be 50%. We assume a standard deviation of 48%. Based on these data and assumptions with 80% power and two-sided 0.05 alpha 118 patients were required in total to be recruited. We recruited 140 patients to take into account unexpected methodological challenges and withdrawals which were minimised by design.

4.11 Statistical Analysis

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 summarised 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

parameterised to identify the period (baseline or post randomisation) and the randomised 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.(114) 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.(115)

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 appendix.)

A generalised mixed-effects model was used because it appropriately handles repeated measures within individuals, adjusts for baseline values directly, and allows for non-normally distributed outcomes through suitable link functions. This provides a more efficient and robust estimate of treatment effect than change-score analyses.

4.12 Screening and Recruitment

A total of 140 participants were recruited into this trial. Those screened but not recruited were not disadvantaged in their usual care. An anonymised record of those patients screened, as well

as their reasons for not participating in the trial (but no other information) were kept in the screening log.

4.13 Data Monitoring and Safety Committee (DMSC)

An independent data monitoring and safety committee (DMSC) was convened containing 3 members which met to provide independent advice on study conduct and safety issues. Meetings were held approximately annually or as required throughout the duration of the trial. Safety data was studied after 70 patients had received treatment and completed the study, or one year after the first patient was randomised, whichever occured sooner. Meetings were also held as necessary should any urgent issues occurred.

4.14 Funding

The study was supported by an unrestricted research grant from The Eastbourne Cardiology Research Charity Fund. The implantable loop recorders were provided via a general research grant from Medtronic LTD. Medtronic LTD had no role in the design of the study or data collection, and had no role in the analysis, interpretation of data, or in the writing of the report and decision to submit results for publication.

4.15 Discussion

To date there has not been a double-blind randomised controlled trial comparing pulmonary vein isolation to a sham procedure. Given this, physicians have advocated for a sham-controlled study in patients with AF to fully evaluate the efficacy of pulmonary vein isolation to account for any placebo effect.(116–118) The study is one of two ongoing full scale clinical trials examining the placebo effect of pulmonary vein isolation.(119,120)

In this study, healthcare professionals and physicians post procedure were blinded to treatment strategy. Although previous studies examining catheter ablation for pulmonary vein isolation have included end point blinded adjudication committees, the lack of blinding of physicians treating patients may confound results. As physicians post procedure are blinded to the treatment received in this study, all patients will be treated equally on the same pathway, thus minimising bias.

The first three months post procedure constitute the blanking period as recommended by the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation.(15) Although outcomes are measured at three months, arrhythmia-based outcomes and burden in the blanking period were censored.

The study is powered to address the primary hypothesis that AF ablation results in a significant AF burden reduction compared to a sham procedure. Quality of life and AF symptoms were assessed as secondary outcomes. The sample size calculation and standard deviations are based on CASTLE-AF data and the clinical investigators own experience, specifically continuous monitoring data from The Eastbourne District General Hospital AF Ablation Registry.(113) An independent DMSC was convened to primarily monitor study conduct and safety issues. There were no stopping rules for overwhelming superiority.

The study is limited to six months follow-up. Previous studies examining pulmonary vein isolation with a longer follow-up have had high crossover rates, which affects the interpretation of results e.g. 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.(7) Given

the shorter duration of follow-up in this study, crossovers were not expected however the sample size was increased to 140 to take in-to account a potentially high number of withdrawals. Additionally, as follow-up is limited to six months, the use of amiodarone was discouraged given its extremely long plasma half-life.(121)

A challenge of the study was the recruitment of patients during the COVID-19 pandemic which delayed study recruitment. Recruitment was paused in March 2020 and restarted in July 2021 to limit any potential effect of the COVID-19 pandemic. Protocol changes were made to facilitate follow-up during the COVID-19 pandemic. The ILR insertion timing recommendation was reduced to a minimum of two weeks before the ablation/sham procedure date. During 2021, there was uncertainty regarding further surges in COVID-19 and the impact this would have on the study. Thus the ILR insertion was also allowed to be performed at the time of the ablation/sham procedure. This would have reduced the requirement for patients to isolate before entering hospital sites. However, this was not required and all patients had their ILR inserted before the ablation/sham procedure allowing a pre procedure AF burden in all patients.

4.16 Conclusion

The SHAM-PVI study is a double-blind randomised controlled study comparing pulmonary vein isolation and a sham procedure. The study evaluated AF burden and patient-reported outcomes. The study also provides evidence on the placebo effect, if any, of pulmonary vein isolation.

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

5.1 Abstract

5.1.1 Importance

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

5.1.2 Objective

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

5.1.3 Design, setting and participants

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

5.1.4 Intervention

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

5.1.5 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™).

5.1.6 Results

140 patients were recruited. 13 patients were withdrawn before randomization due to COVID-19 and 1 patient withdrew consent. A total of 126 participants were randomised (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, 0.25; 95% confidence interval [CI], 0.15 to 0.42; 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).

5.1.7 Conclusions and Relevance

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

5.2 Key points

5.2.1 Question

Does pulmonary vein isolation have a placebo effect?

5.2.2 Findings

In this double blind randomised trial of 126 patients with symptomatic AF pulmonary vein isolation 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.

5.2.3 Meaning

Pulmonary vein isolation significantly reduced AF burden compared to a sham control, providing evidence that the benefit of pulmonary vein isolation in symptomatic atrial fibrillation is not because of a placebo effect.

5.3 Introduction

Pulmonary vein isolation is the standard ablation technique used to treat AF and currently has a class 1 recommendation for the treatment of symptomatic AF where patients have failed or are intolerant to antiarrhythmic medication.(122) 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 randomised controlled trials comparing pulmonary vein isolation with a sham procedure. (7,123)

Previous studies of catheter ablation for AF have not shown consistent benefits in endpoints such as death, stroke, and cardiac arrest.(88) Given these results there is a concern that pulmonary vein isolation exhibits a substantial placebo effect which has not been evaluated.(116,117) 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. (124,125) This study compared the effects of pulmonary vein isolation versus a sham procedure on AF burden, quality of life and symptoms.

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5.4 Results

5.4.1 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. No patients crossed from sham intervention to ablation during the trial and 59/62 randomised to ablation received this treatment. The primary endpoint analysis intention-to-treat population consisted of 123 patients- 62 randomised to ablation and 61 randomised to the sham procedure (Figure 5). Demographic and clinical characteristics were generally well balanced between the groups (Table 5). Procedural characteristics are shown in Table 6.

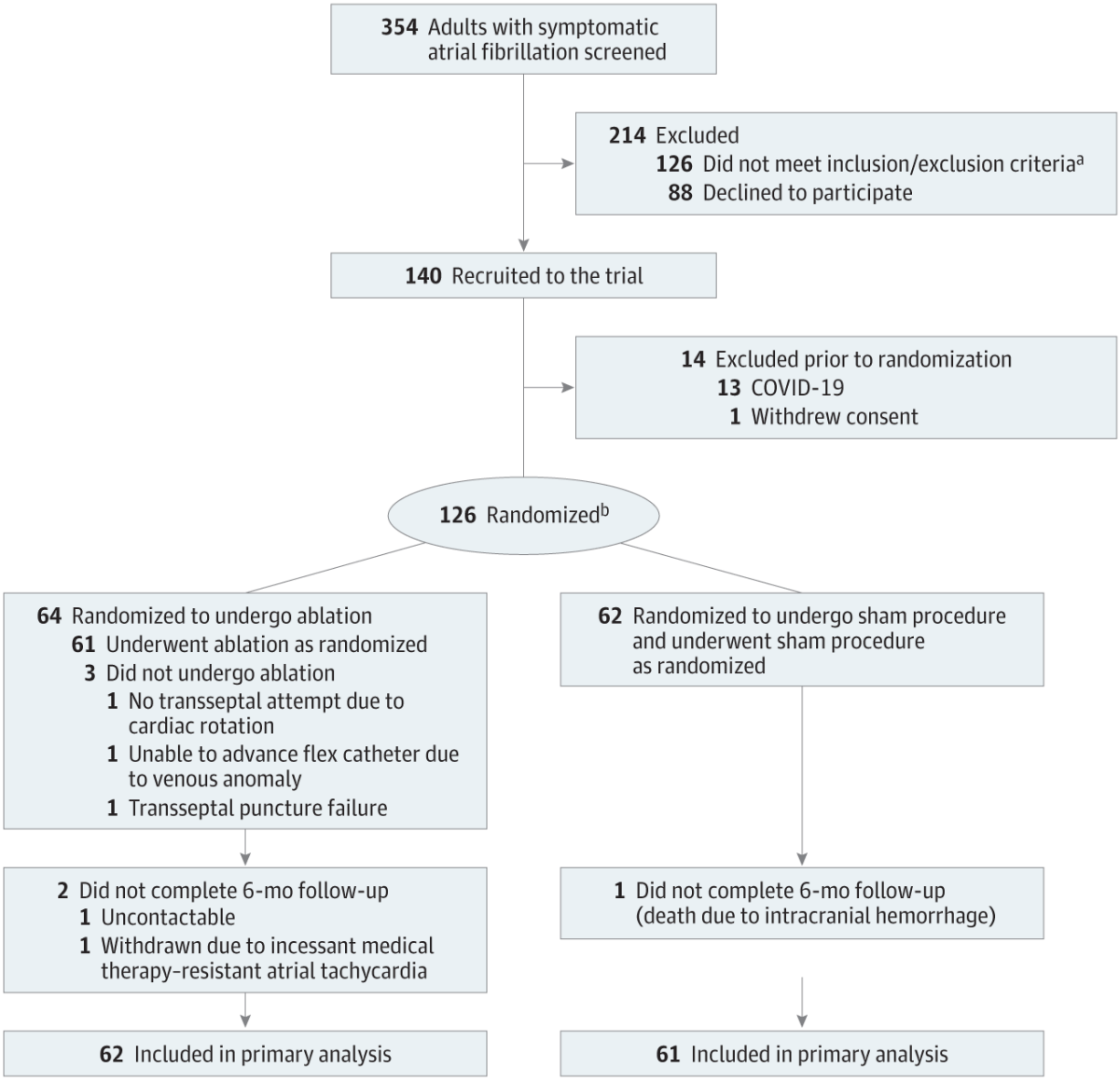

Figure 5: Participant Flow Through the SHAM-PVI Trial

a Each excluded patient was recorded as having a single reason on screening logs (eg, "met exclusion criteria"). b Randomization was stratified according to type of atrial fibrillation (paroxysmal or persistent).

Table 5: Baseline characteristics of the patients

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)	28.9 (4.1)
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)
Median monthly time since the first diagnosis of AF (q1,q3)	25.0 (12.0,60.0)	24.0 (12.0,48.0)
Median number of cardioversions (q1,q3)	2.0 (1.0,2.0)	1.0 (1.0,2.0)
Previous hospitalization for AF N (%)	22 (34.4)	21 (33.9)
Median left atrial diameter in millimetre (q1,q3)[B]	42.5 (40.0, 45.0)	41.0 (38.0,43.0)
Median left ventricular ejection fraction percentage (q1,q3)[B]	55.0 (55.0,60.0)	55.0 (55.0,60.0)
Median CHA2DS2-VASc score (q1,q3)[C]	2.0 (1.0,3.0)	2.0 (1.0,3.0)
Median alcohol intake per week in units (q1,q3)[D]	4.0 (0.0, 10.75)	2.0 (0.0,10.0)
Median pre-procedure ILR monitoring days (q1,q3)	28.0 (25.75, 35.5)	28.0 (25.0, 35.0)
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 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

B Echocardiogram performed on enrolment or data collected from chart review if performed recently prior to enrolment. All patients had echocardiogram within one year of enrolment.

C 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.

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

Table 6: Procedural characteristics

Median procedure time in minutes (q1,q3)	62.5 (60.0,70.0)	60.0 (60.0,65.0)
Median fluoroscopy time in minutes (q1,q3)	8.1 (6.9, 10.3)	0.7 (0.3,1.1)
Mean radiation dose in cGycm^2 (q1,q3)	565.5 (282.5,880.0)	15.0 (9.0, 39.3)
Direct Current Cardioversion N (%)	50 (78.1)	48 (77.4)

5.4.2 AF burden

Results for the primary end point of AF burden are summarised in Figure 6. 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, 0.25; 95% confidence interval [CI], 0.15 to 0.42; $P < 0.0001$). Thus PVI resulted in a 75% reduction in AF burden.

In the persistent AF patients, there was an absolute reduction of 71.39% in the ablation group and 44.85% in the sham intervention group (geometric mean difference, 0.26; 95% confidence interval [CI], 0.14 to 0.46). 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, 0.23; 95% CI, 0.10 to 0.54). The P value for the interaction between ablation and PAF (vs Persistent) is 0.04. Time to event hazard ratios and Kaplan–Meier curves are presented in Table 7 and Figure 7,8 and 9.

	AF burden, mean (SD), %				
	Ablation group		Sham procedure group		Geometric mean difference at 6 mo (95% CI)[a]
Patients	Baseline	6 Months	Baseline	6 Months	
All patients	78.52 (37.68) [n=64]	18.21 (36.31) [n=62]	78.19 (39.54) [n=62]	43.19 (44.75) [n=61]	0.25 (0.15-0.42)
Patients with persistent AF	94.21 (20.69) [n=51]	22.82 (39.63) [n=49]	97.10 (15.29) [n=49]	52.25 (46.20) [n=48]	0.26 (0.14-0.46)
Patients with paroxysmal AF	16.93 (22.71) [n=13]	0.80 (2.12) [n=13]	6.91 (6.83) [n=13]	9.72 (10.62) [n=13]	0.23 (0.10-0.54)

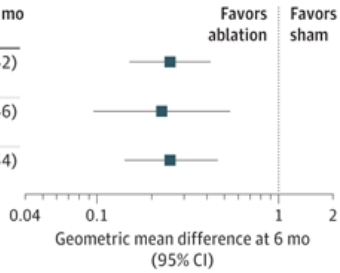

Figure 6: Primary Outcome: Mean and Geometric Mean AF Burden in All Patients, Patients With Persistent AF, and Patients With Paroxysmal AF

AF indicates atrial fibrillation.

[a]Mixed models with repeated measures. The geometric mean is on a ratio scale and describes the relative reduction in mean AF at the end point for participants in the ablation group compared with participants in the sham group, accounting for their baseline values. $P < .001$ for geometric mean difference at 6 months.

Table 7: Hazard ratios and 95% confidence intervals for time to event outcomes

Event	Hazard ratio	Lower 95% CI	Upper 95% CI
Time to any AF (>30 seconds)	0.439	0.286	0.674
Time to persistent AF (> 7 days)	0.392	0.202	0.759
Time to symptomatic AF	0.468	0.230	0.952

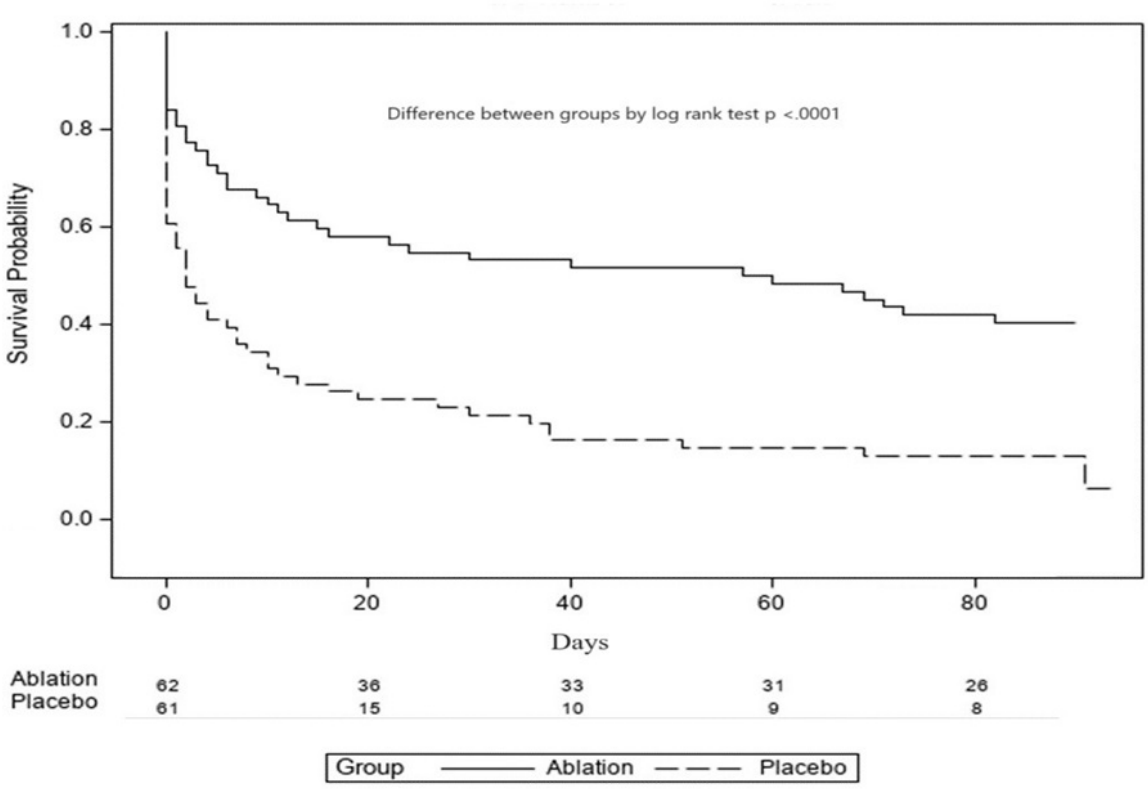

Figure 7: Time to any atrial tachyarrhythmia (lasting more than 30 seconds)

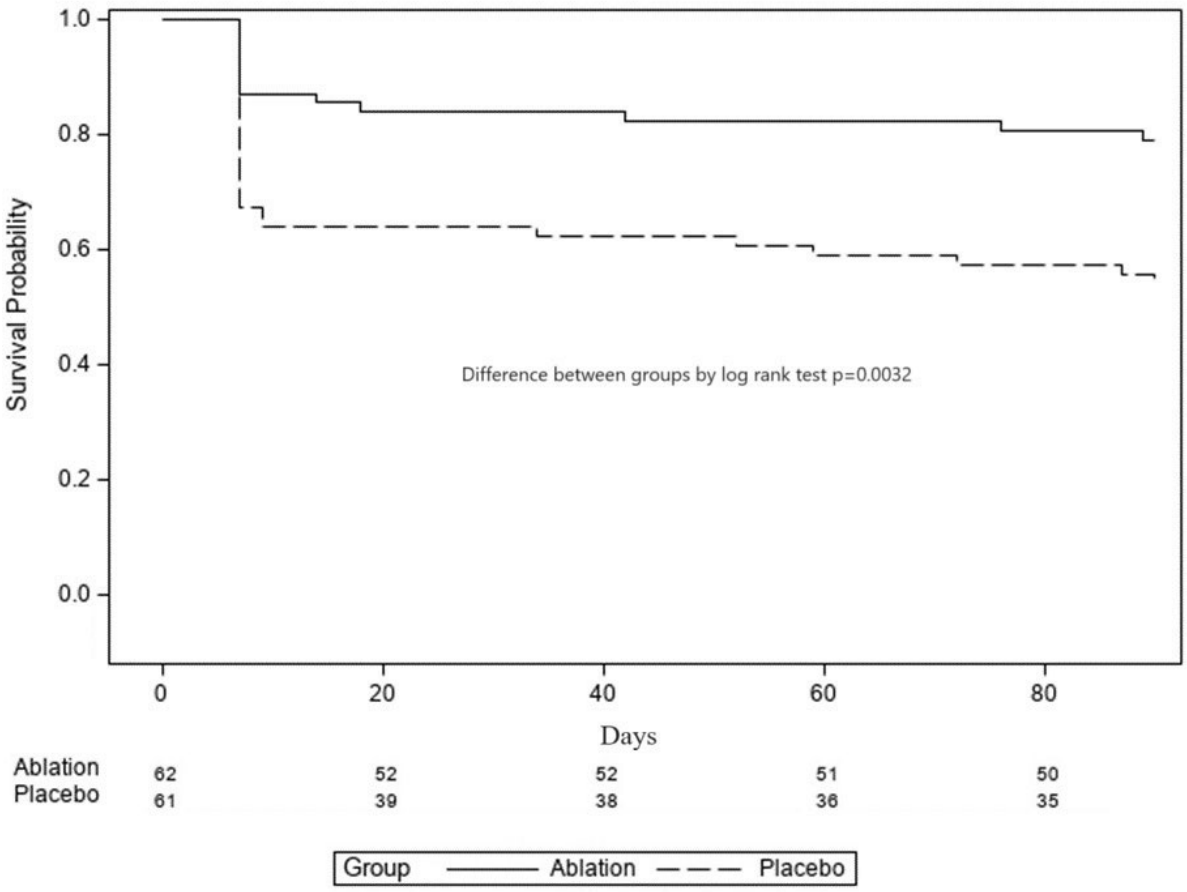

Figure 8: Time to any atrial tachyarrhythmia (lasting more than 7 days)

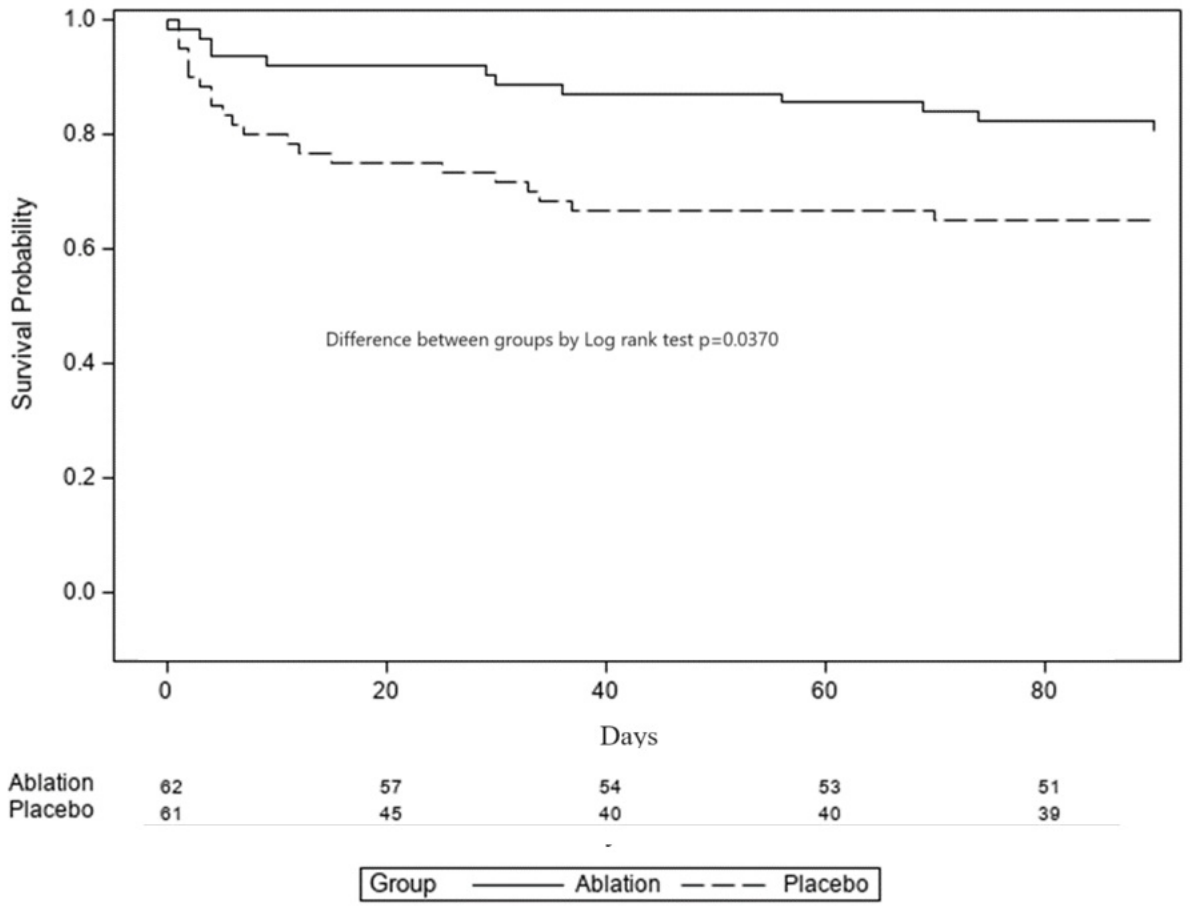

Figure 9: Time to any symptomatic atrial tachyarrhythmia (determined by ILR activation only)

5.4.3 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 (Table 8 and Table 9). 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, favouring 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 10A) and at 3 months (Figure 11).

Table 8: AFEQT Overall, Symptoms, Daily Activities, and Treatment Concern Scores in the SHAM-PVI Trial

	Ablation	**Sham intervention**
Mean overall score (sd)		
Baseline	53.3 (16.3)	51.3 (18.1)
3 months	73.3 (22.4)	58.3 (24.4)
6 months	77.4 (20.4)	58.3 (25.2)
Mean symptoms score (sd)		
Baseline	62.0 (21.8)	58.5 (22.2)
3 months	82.5 (22.4)	66.7 (26.4)
6 months	81.2 (23.0)	66.6 (25.7)
Mean daily activities score (sd)		
Baseline	44.5 (23.6)	41.0 (23.4)
3 months	69.5 (30.4)	52.6 (29.9)
6 months	74.9 (27.7)	50.1 (32.3)
Mean treatment concern score (sd)		
Baseline	59.0 (18.0)	55.1 (21.6)
3 months	71.5 (21.3)	61.1 (24.3)
6 months	74.9 (21.5)	62.9 (23.9)
Mean how well current treatment controls AF score (sd)		
Baseline	48.7 (24.7)	53.5 (20.3)
3 months	73.2 (29.2)	62.0 (25.1)
6 months	74.5 (24.3)	57.7 (28.3)
Mean extent to which treatment has relieved symptoms score (sd)		
Baseline	47.7 (23.5)	51.9 (23.0)
3 months	74.1 (28.7)	61.5 (27.8)
6 months	75.3 (26.1)	57.9 (28.5)

The AFEQT overall or subscale scores range from 0-100.

A score of 0 corresponds to complete disability (or responding “extremely” limited, difficult or bothersome to all questions answered), while a score of 100 corresponds to no disability (or responding “not at all” limited, difficult or bothersome to all questions answered).

Table 9: Estimated difference in AFEQT treatment satisfaction scores at 3 months and 6 months

Outcome	Time	Estimated difference	Lower CI	Upper CI
How well your current treatment controls your atrial fibrillation?	3 months	12.46	3.88	21.04
How well your current treatment controls your atrial fibrillation?	6 months	17.56	8.94	26.18
The extent to which treatment has relieved your symptoms of atrial fibrillation?	3 months	13.38	4.34	22.42
The extent to which treatment has relieved your symptoms of atrial fibrillation?	6 months	17.93	9.00	26.87

Note the last two questions of the AFEQT relate to treatment satisfaction and are not included as part of the overall score.

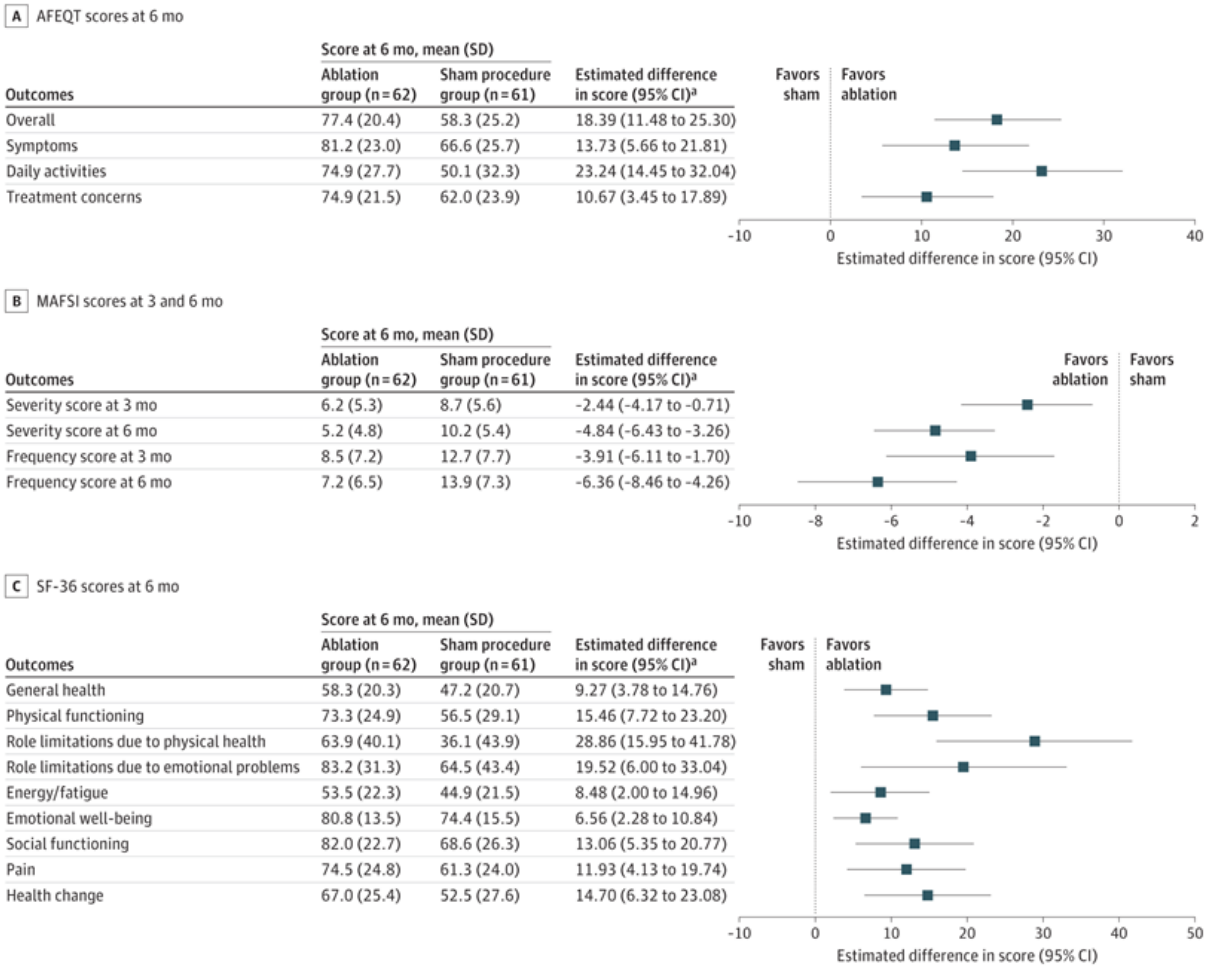

Figure 10: Estimated Differences in Secondary Outcomes: A)AFEQT Scores at 6 Months, B) MAFSI Scores at 3 and 6 Months, and C) SF-36 Scores at 6 Months

AFEQT indicates Atrial Fibrillation Effect on Quality of Life questionnaire; MAFSI, Mayo AF-Specific Symptom Inventory; SF-36, 36-Item Short Form Health Survey.. AFEQT overall and subscale scores range from 0 to 100. A score of 0 corresponds to complete disability (responding "extremely" limited, difficult, or bothersome to all questions answered), while a score of 100 corresponds to no disability (responding "not at all" limited, difficult, or bothersome to all questions answered). A change of 5 points or greater is considered to be a clinically important difference. MAFSI frequency scores were measured via 5-item Likert scale ranging from 0 (never) to 4 (always) and summed to generate a summary score with a theoretical range from 0 (no atrial fibrillation [AF] symptoms) to 40 (all symptoms constant).

MAFSI severity scores were measured via 4-item Likert scale ranging from 0 (never) to 3 (severe) and summed to generate a summary score with a theoretical range from 0 (no AF symptoms) to 30 (all 10 symptoms at the most severe level). Scores for each SF-36 domain range from 0 to 100, with higher scores defining a more favorable health state.

[a]Mixed models with repeated measures.

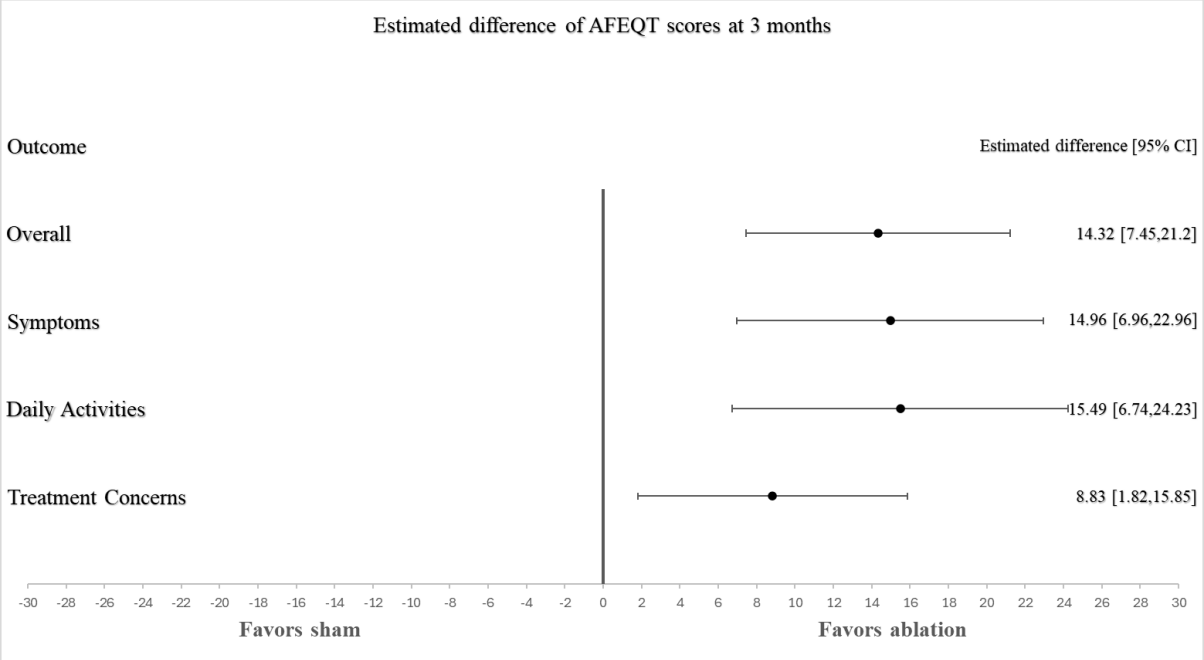

Figure 11:Estimated difference of AFEQT scores at 3 months

The mean MAFSI frequency and severity score at baseline was 15.5 (5.8) and 11.3 (4.8) points in the ablation group and in the sham intervention group was 16.1 (6.2) and 11.3 (4.6) points. At 6 months, the mean frequency and severity scores in the catheter ablation group was 7.2 (6.5) and 5.2 (4.8) and in the sham intervention group was 13.9 (7.3) and 10.2 (5.4) points. The estimated difference in frequency score at 6 months, favouring catheter ablation, was -6.36 points (95% CI, -8.46 - -4.26) and the estimated difference in severity score at 6 months,

favouring catheter ablation, was -4.84 points (95% CI, -6.43 - -3.26) (Figure 10B). All subdomain results of the MAFSI frequency and severity scoring are presented in Table 10, Table 11, Figure 12 and 13.

Table 10: Individual and total MAFSI frequency scores in the SHAM-PVI Trial

	Ablation	Sham intervention
Mean palpitations score (sd)		
Baseline	2.2 (1.0)	2.0 (1.2)
3 months	1.0 (1.0)	1.6 (1.3)
6 months	1.1 (1.1)	1.6 (1.2)
Mean slow heart rate score (sd)		
Baseline	1.1 (1.0)	1.1 (1.1)
3 months	0.6 (1.0)	1.1 (1.3)
6 months	0.5 (0.8)	1.0 (1.2)
Mean fainting score (sd)		
Baseline	0.1 (0.4)	0.1 (0.3)
3 months	0.0 (0.2)	0.0 (0.2)
6 months	0.0 (0.2)	0.1 (0.5)
Mean dizziness score (sd)		
Baseline	1.4 (0.9)	1.7 (1.0)
3 months	0.9 (1.1)	1.4(1.0)
6 months	0.7 (0.9)	1.6 (1.1)
Mean chest pain score (sd)		
Baseline	0.9 (0.9)	0.9 (1.0)
3 months	0.4 (0.9)	0.7 (0.9)
6 months	0.4 (0.7)	0.8 (1.0)
Mean shortness of breath score (sd)		
Baseline	2.1 (1.1)	2.4 (1.1)
3 months	1.3(1.2)	1.9 (1.4)
6 months	1.0 (1.1)	2.2 (1.3)
Mean unable to exercise score (sd)		
Baseline	1.8 (1.3)	2.1 (1.3)
3 months	0.9 (1.3)	1.5 (1.4)
6 months	0.7 (1.1)	1.7 (1.5)
Mean tiredness score (sd)		
Baseline	2.4 (1.1)	2.6 (1.1)
3 months	1.7 (1.2)	2.1(1.2)
6 months	1.3 (1.3)	2.3(1.2)
Mean weakness score (sd)		
Baseline	1.8 (1.2)	2.0 (1.2)
3 months	0.9 (1.2)	1.6 (1.3)
6 months	0.7 (1.0)	1.6(1.3)
Mean flushed score (sd)		
Baseline	1.6 (1.2)	1.3 (1.1)
3 months	0.7 (1.0)	0.9 (1.2)
6 months	0.7 (1.0	1.0 (1.2)
Mean total frequency score (sd)		
Baseline	15.5 (5.8)	16.1(6.2)
3 months	8.5 (7.2)	12.7 (7.7)
6 months	7.2 (6.5)	13.9 (7.3)

The MAFSI frequency scores were collected with a 5-item Likert scale ranging from 0 (never) to 4 (always) and summed to generate a summary frequency score that has a theoretical range from 0 (no AF symptoms) to 40 (all 10 symptoms constant).

Table 11:Individual and total MAFSI severity scores in the SHAM-PVI Trial

	Ablation	Sham intervention
Mean palpitations score (sd)		
Baseline	1.6 (0.8)	1.4 (0.9)
3 months	0.8 (0.9)	1.1 (1.0)
6 months	0.8 (0.9)	1.2 (0.9)
Mean slow heart rate score (sd)		
Baseline	0.7 (0.8)	0.7 (0.8)
3 months	0.3 (0.6)	0.7 (0.8)
6 months	0.3 (0.6)	0.6 (0.8)
Mean fainting score (sd)		
Baseline	0.1 (0.4)	0.1 (0.3)
3 months	0.1(0.2)	0.0 (0.1)
6 months	0.0 (0.2)	0.1 (0.5)
Mean dizziness score (sd)		
Baseline	1.1 (0.8)	1.2 (0.8)
3 months	0.6 (0.8)	0.9 (0.8)
6 months	0.5 (0.6)	1.1 (0.8)
Mean chest pain score (sd)		
Baseline	0.6 (0.7)	0.7 (0.8)
3 months	0.4 (0.7)	0.5 (0.7)
6 months	0.4 (0.7)	0.7 (0.8)
Mean shortness of breath score (sd)		
Baseline	1.6 (0.9)	1.8 (0.9)
3 months	0.9 (0.9)	1.3 (1.1)
6 months	1.0 (1.2)	2.2 (1.3)
Mean unable to exercise score (sd)		
Baseline	1.3 (1.0)	1.5 (1.0)
3 months	0.7 (1.0)	1.1 (1.1)
6 months	0.6 (0.9)	1.4 (1.1)
Mean tiredness score (sd)		
Baseline	1.8 (0.8)	1.9 (0.7)
3 months	1.1 (0.9)	1.4 (0.9)
6 months	0.9 (0.9)	1.7 (0.8)
Mean weakness score (sd)		
Baseline	1.3 (0.8)	1.3 (0.9)
3 months	0.7 (0.8)	1.0 (0.9)
6 months	0.6 (0.7)	1.2 (0.9)
Mean flushed score (sd)		
Baseline	1.0 (0.9)	0.9 (0.8)
3 months	0.5 (0.8)	0.7 (0.9)
6 months	0.4 (0.6)	0.8 (0.9)
Mean total severity score (sd)		
Baseline	11.3 (4.8)	11.3 (4.6)
3 months	6.2 (5.3)	8.7 (5.6)
6 months	5.2 (4.8)	10.2 (5.4)

The MAFSI severity score was collected with a 4-item Likert scale from 0 (never) to 3 (severe) and summed to generate a summary score with a theoretical range from 0 (no AF symptoms) to 30 (all 10 symptoms at the most severe level).

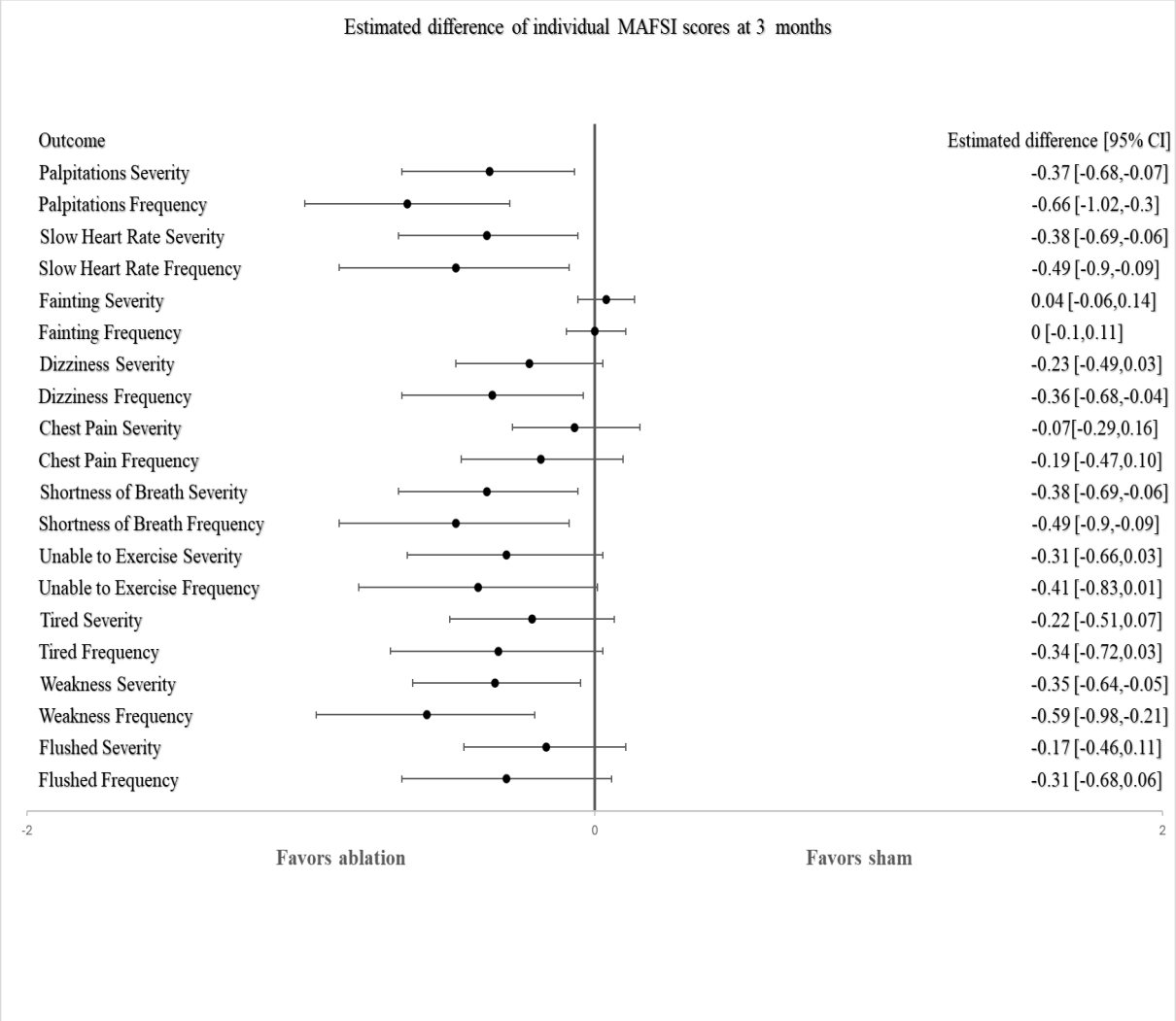

Figure 12: Estimated difference of individual MAFSI scores at 3 months

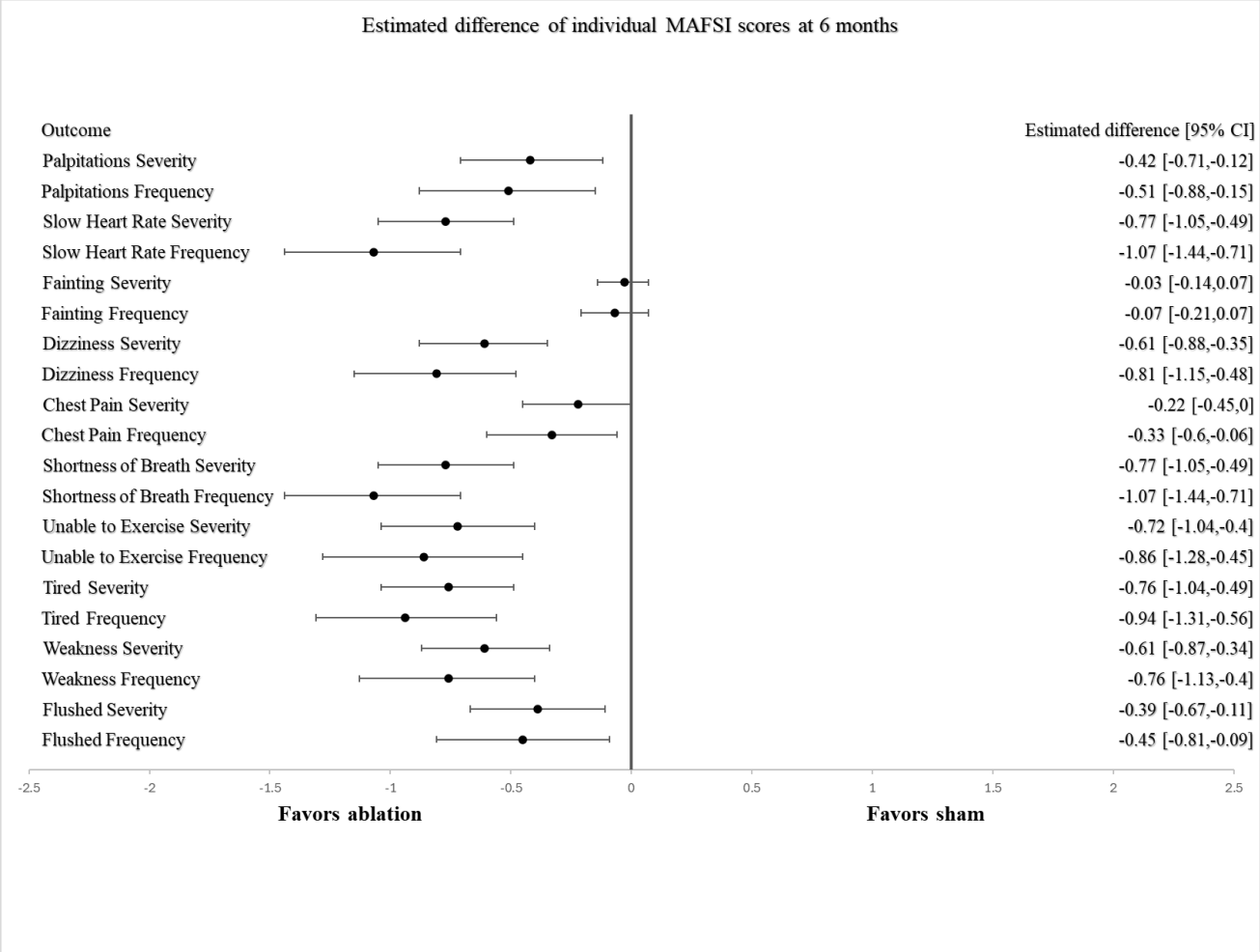

Figure 13:Estimated difference of individual MAFSI scores at 6 months

The SF-36 General Health score improved more in the ablation group than in the sham intervention group (Table 12, Figure 10C and Figure 14). 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 in Figure 10C.

Table 12:36-Item Short Form Survey (SF-36) Scoring in the SHAM-PVI study

	Ablation	**Sham intervention**
Mean physical functioning score (sd)		
Baseline	56.0 (22.6)	53.3(24.7)
3 months	71.2 (25.6)	55.4 (28.9)
6 months	73.3 (24.9)	56.5 (29.1)
Mean role limitations due to physical health score (sd)		
Baseline	31.7 (38.1)	33.1 (37.8)
3 months	56.0 (45.5)	45.5 (41.2)
6 months	63.9 (40.1)	36.1 (43.9)
Mean role limitations due to emotional problems score (sd)		
Baseline	61.0 (41.8)	62.4 (41.2)
3 months	79.9 (33.7)	68.8 (41.3)
6 months	83.2 (31.3)	64.5 (43.4)
Mean energy / fatigue score (sd)		

Baseline	40.2 (20.6)	40.4 (16.8)
3 months	51.9 (22.4)	44.6 (20.0)
6 months	53.5 (22.3)	44.9 (21.5)
Mean emotional well-being score (sd)		
Baseline	72.2 (15.9)	72.6 (16.1)
3 months	78.2 (16.3)	73.8 (15.8)
6 months	80.8 (13.5)	74.4 (15.5)
Mean Social functioning score (sd)		
Baseline	64.2 (24.4)	62.6 (24.6)
3 months	76.1 (28.1)	69.4 (25.2)
6 months	82.0 (22.7)	68.6 (26.3)
Mean pain score (sd)		
Baseline	73.0 (24.0)	71.1 (27.0)
3 months	72.9 (27.1)	66.2 (25.4)
6 months	74.5 (24.8)	61.3 (24.0)
Mean general health score (sd)		
Baseline	54.2 (20.1)	51.4 (18.6)
3 months	55.2 (20.5)	48.9 (20.5)
6 months	58.3 (20.3)	47.2 (20.7)
Mean health change score (sd)		
Baseline	34.4 (20.2)	36.2 (21.1)
3 months	61.9 (28.0)	52.0 (27.1)
6 months	67.0 (25.4)	52.5 (27.6)

Scores for each SF-36 domain range from 0 to 100, with a higher score defining a more favorable health state.

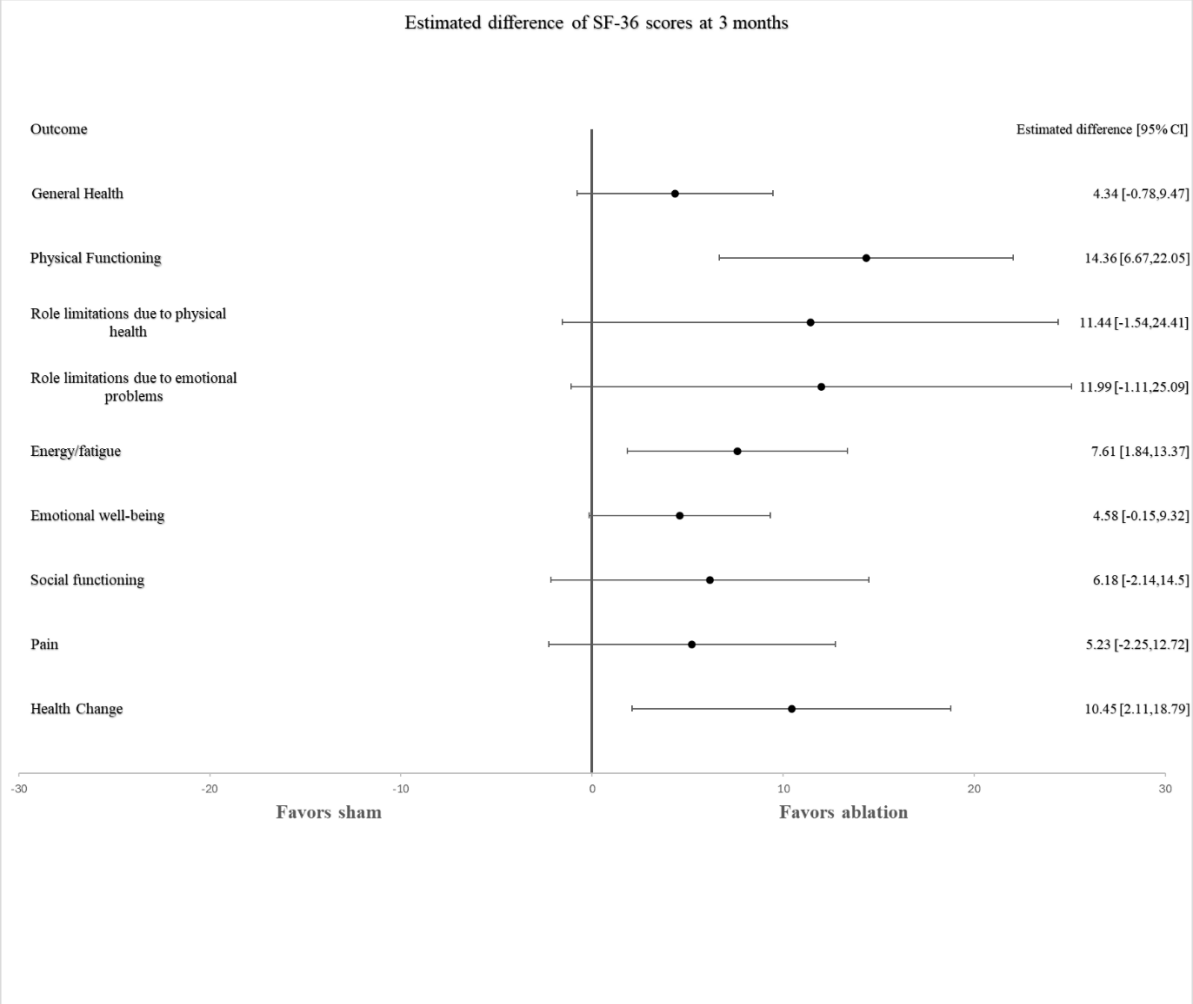

Figure 14: Estimated difference of SF-36 scores at 3 months

During follow-up, the number of AF episodes and symptomatic AF episodes was lower in the ablation group than in the sham intervention group (Table 13). EHRA classification scores are provided in Table 14, Table 15 and Table 16.

Table 13:Number of activations and AF episodes during follow up

Count	Time	Geometric Mean	Lower 95% CI	Upper 95% CI
AF activations	3 months	0.758	0.637	0.902
AF activations	6 months	0.454	0.359	0.574
AT activations	3 months	Not estimable		
AT activations	6 months	Not estimable		
SR / ST activations	3 months	0.257	0.167	0.394
SR / ST activations	6 months	0.214	0.133	0.344
Ectopy activations	3 months	0.737	0.447	1.213
Ectopy activations	6 months	1.300	0.700	2.417
AF episodes	3 months	0.780	0.648	0.939
AF episodes	6 months	0.755	0.622	0.916
PAF episodes	3 months	0.839	0.685	1.029
PAF episodes	6 months	0.914	0.740	1.130
Persistent AF episodes	3 months	0.587	0.371	0.928
Persistent AF episodes	6 months	0.416	0.214	0.808

Note for inference; estimate is like a relative risk e.g. if = 0.5 then it implies the halving of the number of events. Accounting for different observation times pre procedure using $\log_e$(days) as offset variable.

Table 14: EHRA scores at baseline

	EHRA score				
Group	**1**	**2**	**3**	**4**	**Total**
Ablation (%)	1 (1.56)	34 (53.13)	25 (39.06)	4 (6.25)	64
Sham intervention (%)	0 (0.00)	27 (43.55)	30 (48.39)	5 (8.06)	62
Total	1 (0.79)	61 (48.41)	55 (43.65)	9 (7.14)	126

Table 15: EHRA scores at 3 months

	EHRA score				
Group	**1**	**2**	**3**	**4**	**Total**
Ablation (%)	20 (31.75)	34 (53.97)	7 (11.11)	2 (3.17)	63
Sham intervention (%)	6 (9.84)	24 (39.34)	28 (45.90)	3 (4.92)	61
Total	26 (20.97)	58 (46.77)	35 (28.23)	5 (4.03)	124

Table 16: EHRA scores at 6 months

	EHRA score				
Group	**1**	**2**	**3**	**4**	**Total**
Ablation (%)	27 (43.55)	26 (41.94)	8 (12.90)	1 (1.61)	62
Sham intervention (%)	9 (14.75)	28 (45.90)	21 (34.43)	3 (4.92)	61
Total	36 (29.27)	54 (43.90)	29 (23.58)	4 (3.25)	123

5.4.4 Healthcare and medication use during follow-up

There were no differences in the number of repeat cardioversions between the groups during follow-up (Table 17). 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 antiarrhythmic versus 20 of 62 patients (32.3%) in the ablation group.

Table 17: Healthcare utilisation and medication use in follow-up

Outcome	Ablation (%)	Placebo (%)
DCCV 0-3 months	25 (39.7%)	30 (48.4%)
ED Attendance 0-3 months	1 (1.6%)	1 (1.6%)
DCCV 3-6 months	4 (6.5%)	6 (9.8%)
ED Attendance 3-6 months	1 (1.6%)	1 (1.6%)
Bisoprolol 0-3 months	26 (41.3%)	25 (41.0%)
Sotalol 0-3 months	19 (30.2%)	21 (34.4%)
Flecainide 0-3 months	13 (20.6%)	16 (26.2%)
Dronedarone 0-3 months	2 (3.2%)	1 (1.6%)
Amiodarone 0-3 months	2 (3.2%)	0 (0%)
Diltiazem 0-3 months	0 (0%)	2 (3.3%)
Digoxin 0-3 months	0 (0%)	1 (1.6%)
Bisoprolol 3-6 months	19 (30.7%)	23 (37.7%)
Sotalol 3-6 months	9 (14.5%)	18 (29.5%)
Flecainide 3-6 months	7 (11.3%)	13 (21.3%)
Dronedarone 3-6 months	1 (1.6%)	3 (4.9%)
Amiodarone 3-6 months	3 (4.8%)	2 (3.3%)
Diltiazem 3-6 months	2 (3.2%)	1 (1.6%)
Digoxin 3-6 months	0 (0%)	0 (0%)

5.4.5 Blinding assessment

The Bang Index 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 (Table 18). 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)).

Table 18: Blinding assessment frequency scores and Bang index

	Ablation	Sham	Don't know	Total	Bang index
Patients post procedure					
Ablation	3	2	59	64	0.016 (-0.053 - 0.084)
Sham	3	1	58	62	-0.032 (-0.095 - 0.030)
Patients at 3 month follow up					
Ablation	25	8	30	63	0.270 (0.104 - 0.436)
Sham	8	18	35	61	0.164 (0.005 - 0.323)
Patients at 6 month follow up					
Ablation	24	8	30	62	0.258 (0.091 - 0.425)
Sham	11	18	32	61	0.115 (-0.056 - 0.285)
Medical staff post procedure					
Ablation	1	0	63	64	0.016 (- 0.015 - 0.046)
Sham	0	0	62	62	N/A
Medical staff at 3 month follow up					
Ablation	1	1	61	63	0 (-0.044 - 0.044)
Sham	1	1	59	61	0 (-0.045 - 0.045)
Medical staff at 6 month follow up					
Ablation	2	1	59	62	0.016 (-0.038 - 0.071)
Sham	1	2	58	61	0.016 (-0.039 - 0.072)

The Bang index was used to assess blinding in patients and staff. The blinding index is scaled to an interval of -1 to 1, 1 being complete lack of blinding, 0 indicating perfect blinding and -1 indicating opposite guessing which may be related to unblinding. A bang index greater than 0.20 indicated unblinding. At 3 and 6 months medical staff were asked to guess assignment before speaking to patients.

5.4.6 Procedural Complications and Serious Adverse Events

There was one serious adverse event in the sham intervention group. One patient randomised to sham intervention died of an intracranial haemorrhage 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.

5.5 Discussion

In this double-blind randomised sham controlled trial of pulmonary vein isolation with cryoballoon ablation, there was a statistically 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 clinically important improvements in symptoms and quality of life.

To date, there have been multiple clinical trials reporting the beneficial effects of pulmonary vein isolation 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.(126) 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.(6,7) 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 pulmonary vein isolation with a sham

procedure. Our findings show that the clinically relevant beneficial effects of pulmonary vein isolation are not explained by a placebo effect of the intervention.

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 CIRCA-DOSE 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.(128) AF burden was chosen as the primary outcome in this study as it is directly related to symptom improvement and due to the difficulty in estimating the placebo effect with a quality of life measure.

Previous studies examining pulmonary vein isolation 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.(88) In the CAPTAF trial comparing ablation and antiarrhythmic medications 8 of 72 (10.5%) randomised to antiarrhythmic therapy crossed over to having an ablation.(6) In this study there were no crossovers, increasing that the validity of the study and highlighting the improvements seen are solely due to pulmonary vein isolation. 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 pulmonary vein isolation versus those patients who did not receive pulmonary vein isolation.(129) 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 pulmonary

vein isolation.(129) The APPROVAL study also included a different patient cohort including patients with cavo-tricuspid isthmus dependent atrial flutter whereas these patients were excluded in this study.(129)

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, pulmonary vein isolation 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 antiarrhythmics in the sham intervention group when compared to patients randomised to pulmonary vein isolation. Reintroduction of antiarrhythmic medications was guided by the ESC guidelines and it was not mandated to use previous ineffective antiarrhythmics.

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.

5.6 Limitations

Our study has several limitations. One of the limitations of this study is that follow-up was only six months. This is shorter than previous clinical trials of AF ablation, which have a minimum follow-up of at least 1 year, although all previous studies have been unblinded.(6,130,131).However, the study aim was not to elucidate the long-term effect of AF ablation but rather the placebo effect, if any.

A six month follow-up was selected as this is the shortest period of time required to see the treatment effect of pulmonary vein isolation. In addition, we considered patient feedback when designing the study. The majority of patients reported that they would unlikely consent for a study involving a sham procedure that lasted one year as opposed to six months. Extending follow-up to one year may have caused a selection bias as patients who are mildly symptomatic or have very infrequent episodes of AF would be the patients who accept being in the study as opposed to patients who are more symptomatic.

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 pulmonary vein isolation. 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 pulmonary vein isolation alone in large randomised controlled trials.(132) Despite advances in technology pulmonary vein isolation remains the cornerstone ablation strategy for the treatment of symptomatic AF. It would not be expected that pulmonary vein isolation with radiofrequency or pulsed field ablation would have a differing result than that of cryoablation. Finally the study was only conducted in two centres.

5.7 Conclusion

In conclusion, pulmonary vein isolation 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 pulmonary vein isolation.

6 The Association Between Atrial Fibrillation Burden and Quality of Life: A Secondary analysis of the SHAM-PVI Trial

6.1 Abstract

6.1.1 Background

The SHAM-PVI trial demonstrated that pulmonary vein isolation reduces AF burden and enhances quality of life (QoL). However, the relationship between QoL improvements and actual reductions in AF burden remains insufficiently studied, particularly with regard to the potential influence of the placebo effect.

6.1.2 Objectives

To investigate the relationship between AF burden and patient-reported quality of life outcomes in the context of a sham-controlled, double-blind trial comparing pulmonary vein isolation to a sham procedure.

6.1.3 Methods

This is a secondary analysis of the SHAM-PVI trial involving 126 patients with symptomatic paroxysmal or persistent AF. Participants were randomised to cryoballoon pulmonary vein isolation or a sham procedure, with AF burden measured continuously via an implantable loop recorder (ILR). QoL was assessed using AFEQT, MAFSI, and SF-36 instruments. Associations between AF burden and QoL were analysed using regression models, including interaction terms for treatment group.

6.1.4 Results

Reduction in geometric mean AF burden was statistically significantly associated with improvements in overall AFEQT score (Estimate 0.971, 95% CI, 0.962 to 0.981 ; P<.0001), MAFSI

symptom severity and frequency, and multiple SF-36 subdomains. The relationship between the geometric mean AF burden and QoL outcomes were constant between the two groups. Symptom-specific analysis highlighted stronger associations between AF burden and palpitations, dizziness, shortness of breath, tiredness, unable to exercise and weakness.

6.1.5 Conclusions

In this secondary analysis of the SHAM-PVI trial there was a statistically significant relationship between AF burden reduction and QoL improvements. The study provides robust evidence for the use of AF burden as a marker of success and further reinforces that pulmonary vein isolation exhibits no placebo effect.

6.2 Introduction

AF is the most common cardiac arrhythmia and is associated with a significant impairment in quality of life through increased symptoms and psychological distress. (133,134) Interventions such as pulmonary vein isolation improves AF burden in patients with symptomatic AF.(135,136)

Pulmonary vein isolation has been shown to reduce AF recurrence and burden in multiple randomised controlled trials. However, many patients have reported improvements in physical and mental health after AF ablation even if they have experienced an AF recurrence. (104,105,137,138) Improvements in quality of life post AF ablation has been shown to be related to a reduction in AF burden rather than the complete elimination of AF.(81,139) To date, the relationship between AF burden and quality of life has not been ascertained when considering the placebo effect of pulmonary vein isolation.

The purpose of the previously published SHAM-PVI study was to compare pulmonary vein isolation with a sham procedure in patients with symptomatic paroxysmal and persistent AF. (136) The trial found a clear benefit of pulmonary vein isolation with a statistically significant reduction in the primary outcome of AF burden.(136) Quality of life metrics were also measured, and improvements were noted. This trial is the first to compare pulmonary vein isolation to a sham procedure and thus provides a unique opportunity to study quality of life and its association with AF burden.

6.3 Methods

6.3.1 Study design

The SHAM-PVI trial was a double-blind sham controlled randomised clinical trial conducted at two centres in the United Kingdom. Details of the protocol have been reported previously.(108,136) In brief, the study randomised 126 symptomatic paroxysmal or persistent AF patients aged >18 years to pulmonary vein isolation via cryoballoon ablation or to a sham procedure. 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.

All patients underwent insertion of an implantable loop recorder (Medtronic Reveal LINQ™) at enrolment. All patients had the implantable loop recorder inserted at least 2 weeks before the main procedure day. The implantable loop recorder was used for the determination of AF burden and arrhythmia recurrence. Patients underwent scheduled follow-up at 3 and 6 months after their procedure.

The primary outcome of the study was AF burden which was measured using continuous monitoring between the end of month 3 and end of month 6 post-randomisation 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 implantable loop recorder 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. Overall quality of life was compared using the 36-Item Short Form Health Survey (SF-36). Arrhythmia recurrence endpoints included time to any atrial tachyarrhythmia stratified by the length of episode (more than 30 s and more than 7 days) and time to symptomatic atrial tachyarrhythmia in the follow-up period. Quality of life questionnaires were measured at baseline, 3 months and 6 months post randomisation.

6.3.2 Statistical analysis

All analyses was based on the intention to treat population using available data. Missing data were not inputted as part of the principal analyses. Data is summarised 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 principal aim of this sub study was to assesses the relationship of AF burden reduction with quality of life and symptoms. The secondary analyses assessed the relationship of AF burden with quality of life and symptom difference in the ablation group versus the sham intervention group.

The relationship between AF burden and Quality of life was estimated in a model including time period and randomised group. A linear regression model was used with log-transformed AF burden as the dependent variable. The main predictors were time period, randomised group, and their interaction. MAFSI scores were used as predictors rather than outcomes; although derived from ordinal items, the aggregated symptom scores are commonly treated as approximately continuous. The interaction between randomised group and quality of life was assessed and model fit was assessed by comparing the Akaike Information Criterion from nested models. Where the model fit deteriorates this is indicated as ‘Model Worse’ and no

interaction term is reported. Where the model is improved a p value for interaction is reported. Where interaction is P≤0.1 the interaction term, 95% CI and p value are reported. A significant interaction indicates that the effect of AF burden on QoL differs between the ablation and sham groups. In all cases the model is assessed on the geometric mean (exponentiated output from $\log_e$ AF as response variable) meaning the result provides the ratio of scores thus for 1 point improvement in SF36 General Health the AF burden of 100% would be correspondingly improved to 98.7% (97.6% to 99.8%). The results shown are agnostic to the direction of causality and provides the relationship between the geometric AF burden and quality of life metrics. There are multiple statistical analyses described in this paper, with the consequential risk of false positives. It is appropriate to consider the overall pattern of results rather than focus on specific p values. All analyses were conducted with, R V4.3.1 and SAS V9.4 (SAS Institute, Cary NC).

6.4 Results

The intention-to-treat population consisted of 123 patients- 62 randomised to ablation and 61 randomised to the sham procedure. Demographic and clinical characteristics were well balanced between the groups and has been previously reported.(136)

AFEQT

There was a statistically significant relationship observed between the change in the geometric mean AF burden and the overall AFEQT score (Estimate 0.971, 95% CI, 0.962 to 0.981 ; P<.0001) i.e if the geometric mean AF burden decreased from 100% to 97.1% this is associated with a one point improvement in the overall AFEQT score (Figure 15 and Table 21). There was also a statistically significant relationship observed between each subscale of the AFEQT and the geometric mean AF burden.

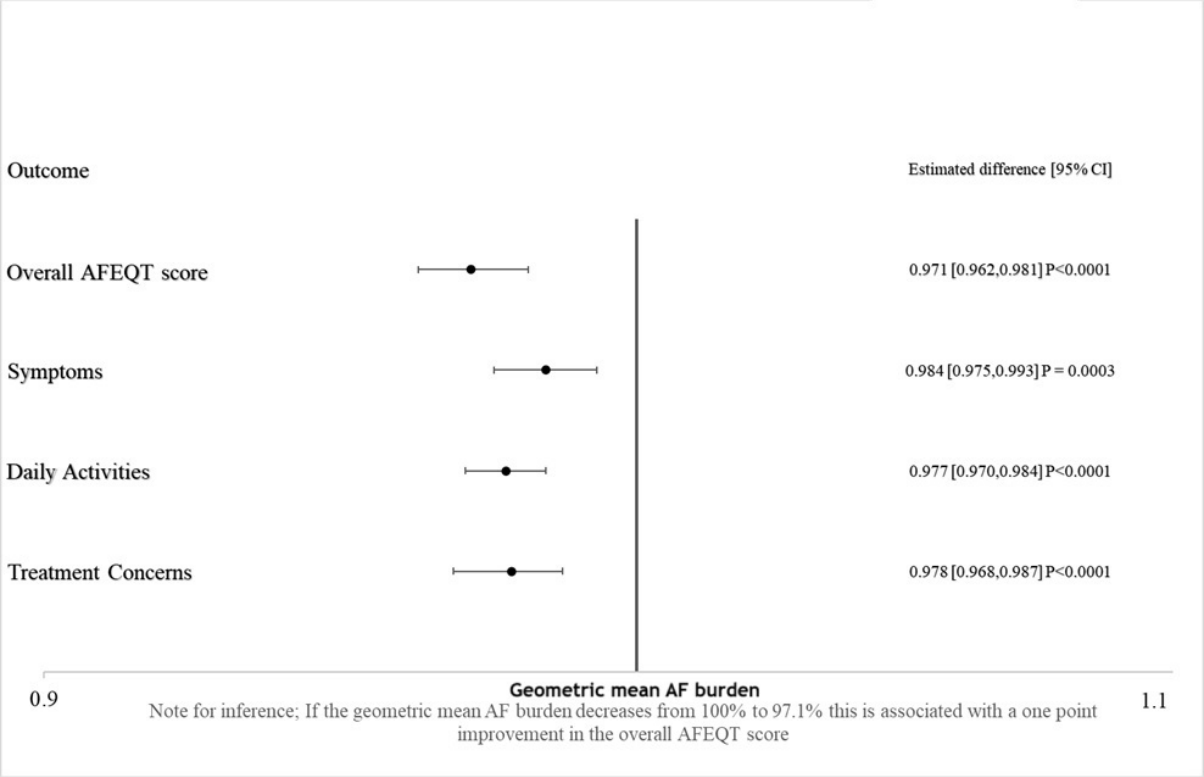

Figure 15: Relationship between geometric mean AF burden and AFEQT estimated in a model including time period and randomised group

MAFSI

There was a statistically significant relationship observed between the change in the geometric mean AF burden and the total Mayo AF-Specific Symptom Inventory (MAFSI) severity and frequency scores (Estimate 1.115, 95% CI, 1.070 to 1.163 ; P <.0001 and estimate 1.097, 95% CI, 1.064 to 1.132 ; P<.0001 respectively, Figure 16 and Table 21). As MAFSI is an adverse symptom score, a positive estimate indicates an improvement, reflecting a reduction in AF burden with improving symptom severity and frequency.

With regard to patient reported symptoms there was a statistically significant association between the geometric mean AF burden and palpitations, dizziness, shortness of breath, tiredness, unable to exercise and weakness (Table 19). There was no significant relationship

between the geometric mean AF burden and reported chest pain, slow heartbeat and fainting (Table 19).

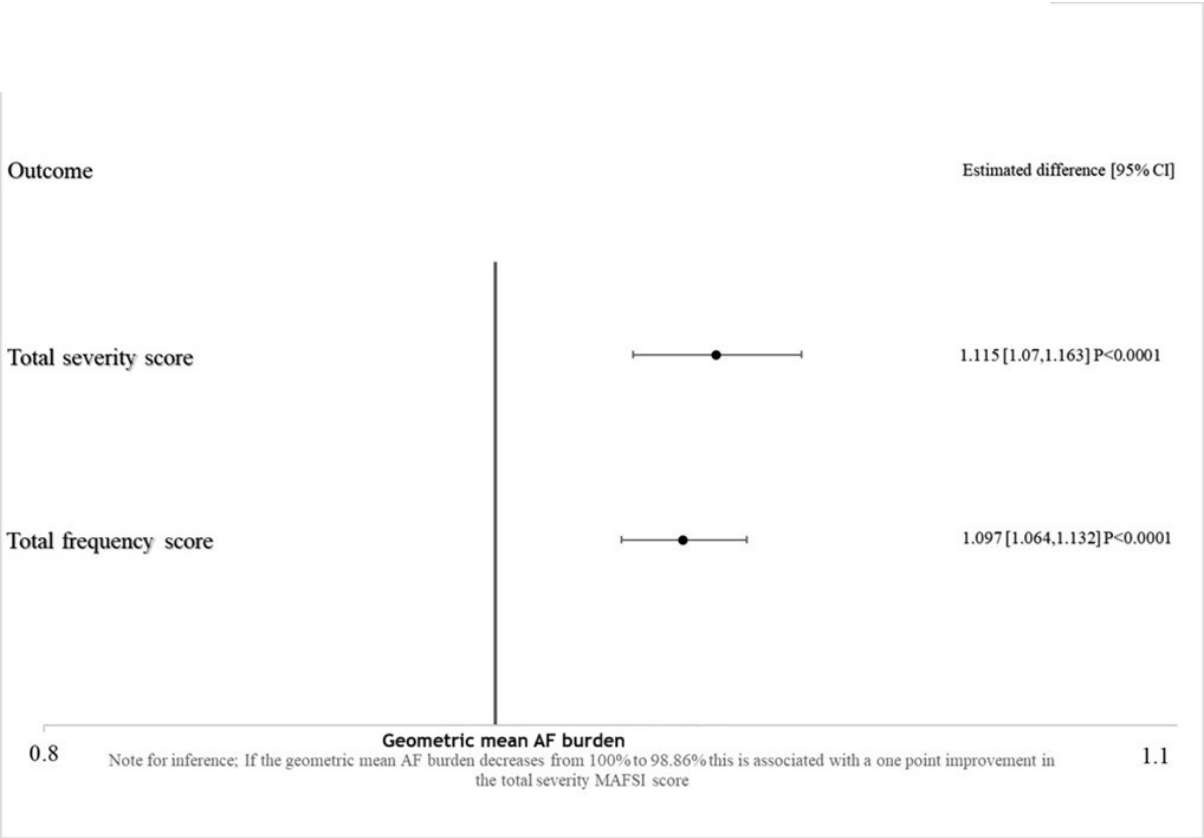

Figure 16: Relationship between geometric mean AF burden and total MAFSI scores estimated in a model including time period and randomised group

Table 19: Effect estimates for MAFSI subscales presented as the change in AF burden associated with a 1-point change in the MAFSI score

MAFSI	Estimate	Lower 95% CI	Upper 95% CI	P
Palpitations Severity	1.258	0.992	1.595	0.0577
Palpitations Frequency	1.346	1.115	1.624	0.002
Slow Heart Rate Severity	1.185	0.882	1.594	0.258
Slow Heart Rate Frequency	1.139	0.933	1.392	0.199
Fainting Severity	1.790	0.901	3.553	0.096
Fainting Frequency	1.170	0.695	1.972	0.552
Dizziness Severity	1.510	1.160	1.966	0.003
Dizziness Frequency	1.505	1.221	1.855	0.0002
Chest Pain Severity	1.227	0.915	1.645	0.169
Chest Pain Frequency	1.146	0.904	1.452	0.258
Shortness of Breath Severity	1.678	1.336	2.107	<.0001
Shortness of Breath Frequency	1.647	1.385	1.957	<.0001
Unable to Exercise Severity	1.565	1.275	1.921	<.0001
Unable to Exercise Frequency	1.407	1.201	1.648	<.0001
Tired Severity	1.844	1.443	2.356	<.0001
Tired Frequency	1.583	1.327	1.888	<.0001
Weakness Severity	1.683	1.320	2.145	<.0001
Weakness Frequency	1.610	1.352	1.918	<.0001
Flushed Severity	1.273	0.991	1.636	0.059
Flushed Frequency	1.211	1.000	1.465	0.050

SF-36

There was a statistically significant association observed with improvements in the geometric mean AF burden and the SF-36 health change scores at six months (Estimate 0.979, 95% CI, 0.971 to 0.987; P<.0001). There was also a statistically significant association observed between the geometric mean AF burden and physical and social functioning scores of the SF-36 scale. (Table 20 and 21)

Table 20: Effect estimates are presented as the change in AF burden associated with a 1-point improvement in the 36-Item Short Form Health Survey (SF-36) score.

SF36 Scale	Estimate	Lower 95% CI	Upper 95% CI	P
General Health	-0.155	-0.356	0.046	0.130
Physical Functioning	-0.265	-0.423	-0.107	0.001
Role Limit Physical Health	-0.128	-0.228	-0.027	0.013
Role Limit Emotional Health	-0.101	-0.201	0.000	0.051
Fatigue	-0.385	-0.577	-0.193	0.0001
Emotional Wellbeing	-0.154	-0.416	0.108	0.247
Social Functioning	-0.208	-0.371	-0.045	0.013
Pain	-0.103	-0.265	0.059	0.212
Health Change	-0.336	-0.501	-0.171	<.0001

Table 21:Interaction between randomised group and quality of life assessed and model fit.

Outcome	P_Imp in model fit with treat*QoL interaction	Interaction term (95% CI; p)
SF36 Scale		
General Health	Model Worse	NA
Physical Functioning	Model Worse	NA
Role Limit Physical Health	Model Worse	NA
Role Limit Emotional Health	Model Worse	NA
Fatigue	Model Worse	NA
Emotional Wellbeing	Model Worse	NA
Social Functioning	Model Worse	NA
Pain	Model Worse	NA
Health Change	Model Worse	NA
AFEQT Scores		
Overall	Model Worse	NA
Symptoms	Model Worse	NA
Daily Activities	Model Worse	NA
Treatment Concerns	Model Worse	NA
Treatment Control AF	0.45	NA
Treatment Relieves Symptoms	0.33	NA
MAFSI		
Total Severity	Model Worse	NA
Total Frequency	Model Worse	NA
Palpitations Severity	0.03	1.871 (1.109 to 3.155; p=0.019)
Palpitations Frequency	0.01	1.797 (1.186 to 2.724; p=0.006)
Slow Heart Rate Severity	0.0004	3.961 (1.863 to 8.422; p=0.0004)
Slow Heart Rate Frequency	0.0001	2.781 (1.674 to 4.620; p=0.0001)
Fainting Severity	NE	NE
Fainting Frequency	0.09	2.594 (0.261 to 25.806; p=0.413)

Dizziness Severity	0.43	NA
Dizziness Frequency	0.14	NA
Chest Pain Severity	0.1	1.826 (0.939 to 3.551; p=0.076)
Chest Pain Frequency	0.53	NA
Shortness of Breath Severity	Model Worse	NA
Shortness of Breath Frequency	Model Worse	NA
Unable to Exercise Severity	Model Worse	NA
Unable to Exercise Frequency	Model Worse	NA
Tired Severity	0.22	NA
Tired Frequency	Model Worse	NA
Weakness Severity	Model Worse	NA
Weakness Frequency	Model Worse	NA
Flushed Severity	0.28	NA
Flushed Frequency	0.84	NA

6.5 Discussion

This substudy of the SHAM-PVI trial presents valuable insights into the relationship between AF burden, and quality of life in patients with symptomatic AF taking into account the placebo effect of pulmonary vein isolation which has not been studied before. In this substudy there was a clear relationship between AF burden and quality of life metrics including the AFEQT score, MAFSI score and SF36 scale. We also demonstrated that there was no evidence of a systematic difference between the treatment and sham intervention groups in the behaviour of the quality-of-life scores.

Reduction in AF Burden and Quality of Life Improvements

The primary outcome of the SHAM-PVI study showed a statistically significant reduction in AF burden in the PVI group compared to the sham intervention group. This result was consistent in both subgroups of AF patients including paroxysmal AF and persistent AF patients.(136)

This study further demonstrates a clear association between AF burden and improvements in multiple quality of life and symptom based metrics. These results are consistent with prior literature. In a sub analysis of the CIRCA-DOSE study, Samuel et al. reported a statistically significant relationship between reductions in AF burden and improvements in health-related quality of life metrics.(81) In both studies, lower AF burden post-ablation correlated with better AFEQT scores, reinforcing the concept that symptom relief is not solely dependent on complete elimination of AF episodes but is influenced by overall arrhythmia burden reduction. Additionally, Samuel et al. identified a dose-response relationship, where a 30.2% relative reduction in AF burden from baseline resulted in a clinically meaningful improvement in AFEQT score.(81)

A major distinction between the studies is the inclusion of a sham control group in the SHAM-PVI study, which allowed for a more rigorous evaluation of the placebo effect. Whilst the CIRCA-DOSE study showed that catheter ablation effectively reduces AF burden and improves quality of life albeit in a population of paroxysmal AF patients, the study lacked a sham intervention group.(126) It could be argued that some of the reported improvements could be partially influenced by either the placebo effect, treatment expectancy or psychological factors. Although there were quality of life improvements in both the ablation and sham intervention groups in this trial, this can be explained by the fact that the sham intervention group also received a cardioversion during the procedure if they were in AF and there was also the influence of antiarrhythmic therapy which was restarted to a greater extent in the sham intervention group than the ablation group in the follow-up period.(136)

In addtion to the inclusion of a sham controlled group, a major strength of this study is the use of implantable loop recorders for continuous rhythm monitoring to assess AF burden. The continuous monitoring of AF burden using an implantable loop recorder overcomes the

limitations of intermittent monitoring such as Holter monitoring or patient only reported events, which are prone to recall bias and under-detection of arrhythmia burden.

The findings advocate for a move away from the traditional binary classification of ablation success and the conventional definition of treatment success or failure based solely on a 30-second AF recurrence.(140) Our data highlights the clinical importance of AF burden as a more detailed and valuable measure for informing rhythm control strategies. In the context of the SHAM-PVI trial, where continuous AF monitoring allowed precise quantification of arrhythmic burden, it was demonstrated that even partial reductions in AF burden are strongly associated with improvements in quality of life. This suggests that rhythm control decisions in clinical practice and future clinical trials should consider AF burden rather than rely exclusively on the binary endpoint of AF recurrence.

Symptom-Specific Effects

An important aspect of this study was the assessment of symptom-specific changes associated with AF burden. The MAFSI analysis showed that overall symptom frequency and severity correlated with AF burden and symptoms such as palpitations, dizziness, shortness of breath, tiredness, inability to exercise, and weakness were statistically significantly associated with changes in AF burden. This reinforces the hypothesis that reducing AF burden has a direct impact on symptomatic relief and functional capacity.

However, there was a lack of a statistically significant correlation between AF burden and symptoms such as chest pain, slow heart rate, and fainting suggesting that these symptoms may be influenced by factors beyond the arrhythmic burden itself and due to alternative medical causes. This finding is relevant for clinical practice, as it underscores the importance of an individualised patient assessment when considering pulmonary vein isolation for symptom

relief. However, these symptoms were relatively infrequent and the analyses may therefore have been underpowered, raising the possibility of a type II error.

Interaction Between AF Burden, Quality of life, and Treatment Group

In this substudy we conducted an interaction assessment between randomized group assignment and the relationship between AF burden and quality of life outcomes. The findings indicated that whilst AF burden reduction consistently correlated with quality of life improvements, the interaction terms for treatment assignment were not statistically significant for most quality of life parameters.

This suggests that the relationship between AF burden and quality of life was relatively stable across both treatment arms. The minor improvements observed in the model fit with treatment interaction for certain MAFSI subscales were driven by the predominance of those symptoms in the control group and the absense of symptoms in the treatment group rather than by a true effect of treatment assignment.

Overall quality of life

In this analysis we saw a clear relationship between AF burden and physcial and social functioning of the SF-36 scale. This is consistent with previous literature. In a sub-analysis of the Substrate versus Trigger Ablation for Reduction in AF (STAR AF) trial, there were significant improvements in physical health (24%) and mental health (19%) component scores from baseline to 12 months after ablation ($p<0.05$) for all of the ablation strategies. (141) In addition Terricabras et al conducted a sub-study of the STAR AF II trial and showed that there was a statistically significant improvement in quality of life using the SF-36 and EuroQol Health-Related Quality of Life 5-Dimension-3-Level questionnaire in all three ablation

arms.(142) Greater reductions in AF burden were associated with greater quality of life improvements which is similar to the results shown by this sub analysis of the SHAM-PVI trial. (142)

Although a statistically significant relationship was observed between AF burden and the physical functioning domains of the SF-36 this association was not seen with role limitations due to emotional health or the emotional wellbeing domain. In contrast, Al-Kaisey et al. reported statistically significant improvements in psychological distress following catheter ablation vs those randomzied to medical therapy, however, the study was not blinded and may be more susceptible to expectancy effects and biases.(134)

6.6 Limitations

This study has limitations. Whilst this trial provides robust evidence for the strong relationship between AF burden and quality of life, the follow-up duration was limited to six months, and longer-term assessments are needed to evaluate the durability of observed effects. Mark et al. reported clinically important and significant improvements in quality of life at 12 months in the CABANA trial however this trial did not include a sham intervention.(7)

In addition to the short follow-up, the effect of AF burden on other metrics such as heart failure admissions, stroke and mortality could not be studied. Furthermore the baseline AF burden was assessed over a relatively short period of time and thus the AF burden may have been underrepresented in the paroxymsal AF patients. The study also only included cryoablation and thus the results may not be generalized to other ablative technologies such as radiofrequency and pulsed field ablation. Lastly the results can not be generalized to patients with long-

standing persistent atrial fibrillation, severe heart failure or those with severely dilated left atriums as these patients were excluded.

6.7 Conclusion

In this secondary analysis of the SHAM-PVI trial there was a significant relationship between AF burden and improvements in AFEQT scores, MAFSI scores and SF-36 scores. The study provides robust evidence for the use of AF burden as a marker of success and further reinforces that pulmonary vein isolation exhibits no placebo effect.

7 Discussion and Synthesis

7.1 Summary of studies

In this thesis, the effectiveness of pulmonary vein isolation in patients with symptomatic AF was tested against a sham intervention. Despite numerous clinical trials advocating pulmonary vein isolation as a treatment modality for symptomatic AF, to date the technique had not been tested against a sham procedure with blinding of patients and physicians.

The SHAM PVI trial had numerous outcomes to assess the placebo effect of pulmonary vein isolation. The primary outcome was AF burden using continuous monitoring between the end of month 3 and end of month 6 post-randomisation between the ablation group and sham intervention group. Secondary outcomes 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. Overall quality of life was compared using the 36-Item Short Form Health Survey (SF-36). Arrhythmia recurrence end points included time to any atrial tachyarrhythmia stratified by the length of episode (more than 30 s and more than 7 days) and time to symptomatic atrial tachyarrhythmia in the follow-up period. In a sub analsyis of the SHAM-PVI trial I also assessed the interaction between AF burden and AF symptom specific metrics and overall quality of life.

7.2 The need for a sham controlled study

The practice of blinding, especially within the framework of randomised controlled trials, is essential for reducing bias. In unblinded studies, there is a potential for both patients and investigators to unintentionally affect the perceived or reported efficacy of an intervention.(143) In addition ineffective blinding is associated with overestimation of true treatment effects.(144)

Double-blind randomised controlled trials, in which both the patient and the physicians are unaware of the treatment allocation, are regarded as the gold standard in clinical research.(145) They minimise the influence of observer and participant expectations, reduce differences in follow-up treatment, and enhance the validity of reported outcomes. Without adequate blinding, treatment effects may be overstated or inaccurate, resulting in erroneous conclusions that could improperly influence clinical practice and guideline recommendations.

In procedural studies such as catheter ablation, it was previously believed that full blinding was not feasible. However, the SHAM-PVI trial refuted this assertion and demonstrated that while patient blinding presented challenges, it was achievable.(136) Furthermore sham-controlled trials in procedures such as vertebroplasty and arthroscopy have revealed limited or absent therapeutic benefit beyond placebo, prompting a major shift in their clinical use. (146,147)Thus double-blind randomised controlled trials ensure that clinical recommendations are accurate, evidence-based, and patient-centred.

Although catheter ablation, especially pulmonary vein isolation, has shown superiority over medical therapy, the lack of a sham-controlled trial left an important gap in understanding its true efficacy. This becomes particularly relevant in AF, where symptoms are subjective and can fluctuate over time, further complicating interpretation of results.

As highlighted by Ozeke et al, AF ablation potentially mirrors earlier patterns observed in renal denervation for hypertension, where initial enthusiasm was tempered by the SYMPLICITY HTN-3 trial's negative findings. (10,116,125)There has also been instances reported where patients continue to remain free of arrhythmias despite pulmonary vein reconnection. Additionally, there are cases where patients experience symptom improvement without a significant reduction in arrhythmias. Björkenheim et al. and Wokhlu et al. have both shown that quality-of-life improvement following ablation can occur independently of rhythm

outcomes.(102,104) The DISCERN-AF study also demonstrated a high proportion of asymptomatic episodes post-ablation, raising further the question of a placebo effect. (103)

Recognising the limitations of previous AF ablation studies, the National Heart, Lung, and Blood Institute advocated for the design and implementation of a sham-controlled study in AF ablation. (118) Thus despite ethical, logistical, and funding concerns, sham controlled trials are crucial for distinguishing treatment effects from placebo responses, especially in procedures with risks and high costs.

7.3 Studies

7.3.1 The SHAM-PVI study

Pulmomary vein isolation is indicated for symptom improvement in patients with atrial fibrillation. (3) However the symptomatic improvement that patients report post ablation may be due to a placebo effect or other factors such as the effect of concurrent medical therapy. The SHAM-PVI study was designed to determine if pulmonary vein isolation exhibits a placebo response. The study was designed to recruit the minimum number of patients required to test the null hypothesis and for no longer than necessary. The sham treatment needed to be acceptable to patients for recruitment and to minimise risk. The design aimed to reduce crossovers, which had complicated the interpretation of previous trials. (88)

The study met its primary endpoint with pulmonary vein isolation resulting in a significant and 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 the study demonstrated the effectiveness of pulmonary vein isolation against a sham intervention.

7.3.2 The Effect of Atrial Fibrillation Burden on Quality of Life in Patients Undergoing Pulmonary Vein Isolation

In this sub study of the SHAM-PVI study I showed there to be a clear relationship between AF burden and symptom specific metrics including the AFEQT score, MAFSI score and overall quality of life measured by the SF-36 instrument. I also demonstrated that there was no evidence of a systematic difference between the treatment and sham intervention groups in the behaviour of the quality-of-life scores.

7.4 Implications of results

The results of the SHAM-PVI study were not a surprise to the electrophysiology community however the results reassured non electrophysiologists including general cardiologists and primary care physicians that AF ablation is effective when tested against a sham intervention and that pulmonary vein isolation results in a significant decrease in AF burden with associated improvement in symptoms and overall quality of life. The results reinforce the current guideline recommendations for AF ablation including The European Society of Cardiology guidelines which currently give a class 1 recommendation for pulmonary vein isolation for rhythm control in symptomatic paroxysmal atrial fibrillation refractory or intolerant to at least one class I or III antiarrhythmic drug and a 2a recommendation for pulmonary vein isolation as a first-line therapy for symptomatic paroxysmal AF, as an alternative to antiarrhythmics, considering patient preference and operator expertise.(122) With regard to persistent AF the European Society of Cardiology currently give a 2a recommendation for pulmonary vein isolation in symptomatic persistent AF after failure of or intolerance to AADs and a 2b recommendation for pulmonary vein isolation as first-line therapy for selected patients with persistent atrial fibrillation.(122)

Since its introduction in the year 2000, pulmonary vein isolation has been adopted on a global scale, with hundreds of thousands of patients undergoing this procedure. The results of the SHAM-PVI trial provide reassurance to both physicians and patients by demonstrating that the symptomatic improvement following ablation exceeds that seen with a sham procedure. The findings provide additional evidence supporting catheter ablation for symptomatic AF and demonstrate the importance of rigorous, placebo-controlled trials in assessing interventional therapies.

Given that there are substantial costs associated with catheter ablation, both in terms of procedural expense and healthcare resource utilisation, the confirmation of a true therapeutic benefit has important implications not only for clinical practice but also for health policy and economic modelling.(148,149) Thus sham-controlled studies such as the SHAM-PVI study are essential to ensure that healthcare systems invest in interventions that provide genuine patient benefit and cost-effectiveness.

7.5 Dissemination of Results

I presented the results of SHAM-PVI study as a late breaking clinical trial at the European Society of Cardiology conference in September 2024 with simultaneous publication in The Journal Of The American Medical Association.(136) The results of the trial were widely publicised and discussed with press articles, podcasts and comments on X (formally known as Twitter). (Appendix 10.5 and 10.6)

7.6 Appraisal of the SHAM-PVI results

Although the results of the SHAM-PVI study were positive, there were suggested modifications and criticisms of the design which I address.

7.6.1 Was the primary outcome AF burden the right one ?

The study was designed with AF burden measured by continuous monitoring as the primary outcome. AF burden is considered the gold standard for measuring intervention success. Certainly implantable loop recorders overcome the limitations of intermittent monitoring such as Holter Monitoring. Catheter ablation has been demonstrated to significantly enhance quality of life, irrespective of ablative efficacy, which is defined as the absence of recurrence of episodes lasting 30 seconds or longer. Consequently, time to AF was not selected as a primary outcome.(104) Indeed the most recent European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on catheter and surgical ablation of atrial fibrillation strongly advises AF burden as an outcome especially in clinical trials.(150) In the sub-analysis of the SHAM-PVI trial it was also clearly demonstrated that AF burden and symptoms and quality of life are closely correlated. Estimating the effectiveness of pulmonary vein isolation using a quality of life measure also posed challenges during the study design, as there had not been a sham-controlled study in AF ablation prior to this research.

7.6.2 Was the trial ethical ?

Following the publication of the trial, some members of the medical community raised concerns about the ethical implications of the study. Considering the inherent risks associated with interventional procedures and the significant costs involved, one might question whether it is unethical not to conduct a sham-controlled study to definitively establish its efficacy.

Patient feedback was considered during the study design phase to reduce risk and enhance participant retention. Consequently, the study duration was set at 6 months, as patients indicated that a longer timeframe could result in higher dropout and crossover rates.

The study received ethical approval from a national research ethics committee. One of the primary questions raised by the committee was why such a study had not been conducted previously. The underlying reasons for this were multifaceted, including securing financial support. Moreover, there was a widespread belief within the scientific community that executing a sham-controlled study in the area of ablation presented significant challenges. (118)However, the success of trials such as ORBITA and SYMPLICITY HTN-3 demonstrated that, with careful planning and the engagement of patients, funders, and sponsors, such studies are indeed feasible. In the end, the SHAM-PVI trial contradicted the prevailing opinion from the medical community and demonstrated that sham-controlled studies in the area of AF ablation are viable.

7.6.3 Did the Sham intervention group receive adequate placebo ?

One of the criticisms of the SHAM-PVI trial was that the sham intervention group did not undergo a transseptal puncture, and therefore may not have received an adequate placebo. However, blinding was rigorously assessed immediately after the procedure using the Bang Blinding Index, which confirmed that blinding was maintained in both groups.

During the design phase, patient feedback revealed that the most perceptible steps during an AF ablation procedure were groin access and phrenic nerve stimulation. As a result, these elements were incorporated into the sham procedure to simulate the experience of an AF ablation without performing a transseptal puncture. Including a transseptal puncture in the sham arm was deemed unnecessary for mimicking the procedural experience and would have

significantly increased procedural risk. The intention throughout the trial was to minimise risk to participants.

It has been argued that a transseptal puncture which is required to perform pulmonary vein isolation might alter left-to-right shunting and thereby affect left atrial pressure. This may potentially improve symptoms such as shortness of breath.(151)This is unlikely to have had a significant impact on the trial results. Furthermore, other common AF-related symptoms, such as palpitations and dizziness, would not be influenced by a transseptal puncture.

7.6.4 Was the follow-up long enough?

The SHAM-PVI study employed a six-month follow-up period, which was intentionally chosen to minimise patient risk and facilitate recruitment. During the study design phase, patients expressed that they would unlikely consent to participate in a sham-controlled trial lasting longer than six months. While the standard follow-up duration for AF ablation studies is typically one year, these studies often suffer from high crossover rates, which makes interpretation of their results difficult. In contrast, the SHAM-PVI trial experienced no crossovers. At the end of the study, 95% of patients who had been randomised to the sham intervention group proceeded to receive an ablation procedure.

7.7 Further work

Although the results of the SHAM-PVI trial were conclusive, several important questions remain. Firstly, the study utilised only cryoballoon ablation as the energy source for pulmonary vein isolation. The potential placebo-controlled effects of other modalities, including radiofrequency energy and the newer pulsed field ablation technologies, remain uncertain at

this time. Additional research is needed to examine these techniques in similar sham-controlled environments.

Since the publication of the SHAM-PVI study, pulsed field ablation has emerged as a promising and exciting new technology. Due to its tissue specificity and favourable safety profile, it presents a viable alternative to thermal energy sources.(152) However, it remains uncertain whether pulsed field ablation provides superior outcomes compared to cryoablation used in the SHAM-PVI trial. This uncertainty highlights the need for future randomised trials to focus on this comparison.

8 Conclusion

In this thesis I conducted the SHAM-PVI trial and assessed the long-term outcomes of AF ablation in patients with continuous monitoring. Pulmonary vein isolation has been adopted widely as the treatment choice for patients with symptomatic AF. Despite its widespread adoption over the last two decades, there has not been a placebo-controlled study proving its efficacy. Given the evidence gap, the SHAM-PVI study was conducted to investigate the impact of the placebo effect in patients undergoing pulmonary vein isolation.

The electrophysiology community welcomed the study results, proving the efficacy of pulmonary vein isolation. The study results demonstrated a significant reduction in AF burden when compared to the sham intervention. This reduction was accompanied by improvements in symptoms and overall quality of life.

From a methods perspective, the trial highlights the critical role of blinding and sham control intervention in studies with a procedural component. Invasive therapies like pulmonary vein isolation can have a strong placebo effect, highlighting the importance of distinguishing between actual physiological benefits and perceived improvements. The study has ensured that treatment recommendations for patients with atrial fibrillation are evidence-based and patient-centered. The European Cardiac Arrhythmias Society has given catheter ablation a class 1 indication for the treatment of atrial fibrillation, based on the SHAM-PVI results. (162)

Furthermore, I assessed the relationship between AF burden and quality of life based on data from the SHAM-PVI study, which showed a clear association between AF burden, symptoms, and quality of life.

In conclusion, interventions for AF should be held to the same rigorous standards as those in other medical specialties, via through placebo-controlled trials. This gold-standard approach ensures that the evidence base for such interventions is robust, ultimately improving patient outcomes.

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10 Appendix

10.1 Statistical analysis plan

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

Statistical analysis plan 06/02/2024

Rajdip Dulai

Nick Freemantle

For the purposes of data analysis, all analysis shall be based on the intention to treat population on available data. Missing data will not be imputed as part of the principal analyses. We will also undertake threshold analyses that is assume a poor outcome in one arm but a good one in the other arm, and vice versa. All analysis shall be performed after locking of the electronic database.

Baseline analysis

Baseline demographics and procedural parameters will be summarized and presented as mean +/- standard deviation or medians with interquartile range (IQR) for continuous variables and absolute number and percentages for categorical data.

Primary endpoint analysis

The primary endpoint is defined as the AF burden at 6 months, captured over the period 3 to 6 months. The primary analysis will compare the AF burden between each group at 6 months follow up post randomisation using a generalised mixed model, including baseline and post intervention observations for each subject and parameterised to identify the period (baseline or post randomisation) and the randomised condition in the post treatment period. The stratification factor (Persistent versus PAF) will be included in this and all other statistical models for prespecified outcomes. The generalised mixed model will utilise an identity link and Gaussian error structures. Observations within a patient will be linked with a random intercept term and the denominator degrees of freedom for the principal analysis will be derived from the number of patients rather than the number of observations. It is our expectation from previous experience that the distribution of data will follow a log(e) linear distribution, and so the generalised mixed model will include the log(e) AF burden. The log(e) AF burden shall be back transformed and presented as a geometric mean.

The first 3 months of follow-up is defined as the blanking period therefore the AF burden in this period will not be used.

In supportive analyses, the effect of randomised therapy will be described in each subgroup of the stratification factor (Persistent versus PAF), and a test for interaction presented.

Secondary endpoint analysis

1. **Time to event analysis**

The time to event of each defined secondary outcome will be compared and summarised between the two groups using the Kaplan–Meier estimator. The log-rank test will be used to compare the survival functions between the groups. We will fit Cox Constant Proportional Odds models and a hazard ratio (HR) and 95 percent confidence interval (95% CI) will be calculated. The constancy assumption will be evaluated using the Supremum. If the constancy assumption is not met, and cannot be achieved by modifying the model with time dependent variables or other modifications the hazard ratio will not be reported. Events during the first 3 months of follow up shall be censored. The following time to events shall be tested

- Time to any atrial tachyarrhythmia lasting more than 30 seconds
- Time to any atrial tachyarrhythmia lasting more than 7 days
- Time to symptomatic atrial tachyarrhythmia

2. Number of atrial arrhythmia episdoes

The number of atrial arrhythmia episodes (as listed below) shall be compared between the two groups using Poisson Mixed models with random effects as the participant level to address expected overdispersion (extra Poissonian variability).

Number of AF activations

Number of AT activations

Number of SR / ST activations

Number ectopy activations

Number of AF episodes

Number of PAF episodes

Number of persistent AF episodes

3. AF specific quality of life scores

The following AF specific quality of life scores shall be presented.

- AF Effect On Quality-Of-Life Questionnaire (AFEQT) which includes 6 domains: overall score, symptom score, daily activity score, treatment concern score and two treatment satisfaction scores.
- Mayo *AF*-Specific Symptom Inventory (*MAFSI*) which includes a total frequency score and total severity score. Sub scores for the following symptoms will be also be presented: palpitations / heart fluttering / racing, slow heart beat, light-headedness / dizziness, fainting / blackout / loss of consciousness, chest pain / pressure or fullness without palpitations, shortness of breath, unable to exercise, tired / lack of energy, weakness and feeling warm / flushed
- European Heart Rhythm Association (EHRA) symptom classification which includes 4 scores: 1 -no symptoms, 2- 'mild symptoms' normal daily activity not affected, 3 'severe symptoms' normal daily activity affected and 4 - 'disabling symptoms' normal daily activity discontinued.

The analysis of AFEQT and MAFSI will be analysed using the analogous mixed models as described for the primary outcome. Values for each post intervention time point will be examined (3 and 6 months), with the models including the baseline period.

Point estimates for each treatment group and treatment group mean differences (ablation – sham treatment) with 95% confidence intervals (CIs) will be generated for each time point. The assessment will be based on the treatment group difference at month 6.

The EHRA scores will be compared between the randomised groups at 3 months and 6 months using Fisher's Exact Test.

4. Overall quality of life score

The SF-36 score shall be presented as a measure of overall quality of life. The following domain scores shall be presented: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, general health and health change.

The SF36 scores shall be analyzed using the previously described generalized repeated measures mixed model. The treatment effects will be examined at 3 months and 6 months, accounting for the baseline value.

5. Health care utilisation

The number of patients undergoing cardioversions and emergency department visits during the follow up periods shall be presented and compared between groups using Fisher's Exact Test.

6. Medication treatment

The number of patients restarted on antiarrhythmic medications during the follow up period shall be presented and compared between groups using Fisher's exact Test. All Fisher's Exact Tests will describe the mid p value.

7. Procedure related complications / adverse events

Procedure related complications and adverse events shall be presented and compared between the groups using Fisher's Exact Test.

Blinding Assessment

Frequency distribution of patients and staff perception of treatment received immediately post procedure, at three months and six months follow-up will be provided. We will utilise the BANG Index to describe the extent to which blinding appears intact. (115)

Multiple comparisons and significance levels

Given the number of secondary outcomes there is a multiplicity of analysis to be performed. The widths of the 95% confidence intervals will not be 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. Thus if the primary analysis is statistically significant then the secondary analyses may be considered to describe the manner in which the treatment worked. If the primary analysis is neutral then, regardless of nominal significance, the secondary analyses will be considered exploratory and descriptive. Although a significance level of 0.05 (/2) shall be used, a conservative approach shall be taken when interpreting secondary outcomes taking into account the degree of significance and consistency across outcomes. The actual significance level shall be reported for all outcomes except when $p < 0.0001$.

Sub analysis and future analysis

Once the main analysis has been published it is intended that a full sub analysis of outcomes in paroxysmal AF and persistent AF patients is performed using the same statistical analysis described. Further an analysis of outcomes during the blanking period will be analysed and published.

10.2 Publications arising from this thesis

- Pulmonary Vein Isolation vs Sham Intervention in Symptomatic Atrial Fibrillation: The SHAM-PVI Randomized Clinical Trial

  Dulai R, Sulke N, Freemantle N, Lambiase PD, Farwell D, Srinivasan NT, Tan S, Patel N, Graham A, Veasey RA

  JAMA. 2024 Sep 2;332(14):1165-73. doi: 10.1001/jama.2024.17921.

- A randomised sham-controlled study of pulmonary vein isolation in symptomatic atrial fibrillation (The SHAM-PVI study) : study design and rationale

  Rajdip Dulai, Stephen S Furniss, Neil Sulke, Nick Freemantle, Pier D Lambiase, David Farwell, Neil T Srinivasan, Stuart Tan, Nikhil Patel, Adam Graham, Rick A Veasey

  Clin Cardiol. 2023 Aug;46(8):973-980. doi: 10.1002/clc.24066

- The Association Between Atrial Fibrillation Burden and Quality of Life: A Substudy of the SHAM-PVI Trial

  Dulai R, Sulke N, Freemantle N, Lambiase PD, Farwell D, Srinivasan NT, Tan S, Patel N, Graham A, Veasey RA

  JACC Clin Electrophysiol. 2025 Oct 20:S2405-500X(25)00741-8.

  doi: 10.1016/j.jacep.2025.09.013.

10.3 Presentations and abstracts arising from this thesis

- Pulmonary Vein Isolation vs Sham Intervention in Symptomatic Atrial Fibrillation: The SHAM-PVI Randomized Clinical Trial

  European Society of Cardiology Congress 2024

- UK clinical trials: The SHAM-PVI Study

  BHRS Scientific Sessions 2025

- The SHAM-PVI trial

  Heart Rhythm Congress 2024

- Insights from the SHAM-PVI trial

  The Eighteenth Annual Scientific Congress of the European Cardiac Arrhythmia Society 2025

- The Effect of Atrial Fibrillation Burden on Quality of Life in Patients Undergoing Pulmonary Vein Isolation: A Sub-study of the SHAM-PVI Trial

  Royal Society of Medicine Presidents Prize 2025

- A randomised sham-controlled study of pulmonary vein isolation in symptomatic atrial fibrillation (The SHAM-PVI study) : study design and rationale

  The 16th European Cardiac Arrhythmia Society Congress 2023

- The sham atrial fibrillation ablation study: protocol and design

  Royal Society of Medicine 2022

10.4 Other publications during thesis studies

- A retrospective analysis of frailty status on atrial fibrillation catheter ablation outcomes

  Dulai R, Uy CP, Sulke N, Patel N, Veasey RA.

  Pacing Clin Electrophysiol. 2023 Aug;46(8):855-860. doi: 10.1111/pace.14768

- A randomized comparison of retrograde left-sided versus anterograde right-sided ablation of the atrioventricular junction

  Rajdip Dulai, Neil Sulke, Stephen S. Furniss, Anura Malaweera, Pier D. Lambiase, Nikhil Patel, Rick A. Veasey

  Clin Cardiol. 2023 Jul;46(7):785-793. doi: 10.1002/clc.24038

- Immediate implantable loop recorder implantation for detecting atrial fibrillation in cryptogenic stroke

  Rajdip Dulai, Jacqui Hunt, Rick A Veasey, Chemindra Biyanwila, Barbora O'Neill, Nikhil Patel

  J Stroke Cerebrovasc Dis. 2023 Mar;32(3):106988.

- Long Term outcomes of percutaneous atrial fibrillation ablation in patients with continuous monitoring

  Sulke N, Dulai R, Freemantle N, Sugihara C, Podd S, Eysenck W, Lewis M, Hyde J, Veasey RA, Furniss SS

  Pacing Clin Electrophysiol. 2021 Jul;44(7):1176-1184

- The long-term effect of thermal-guided second-generation cryoablation in paroxysmal and persistent atrial fibrillation

  Dulai R, Uy CP, Kassir Y, Maravilla VA, Patel N, Furniss S, Sulke N, Veasey RA

  Indian Pacing Electrophysiol J. 2021 Sep-Oct;21(5):261-266

- The effect of second-generation cryoablation without electrical mapping in persistent AF using continuous monitoring

  Rajdip Dulai, Neil Sulke, Stephen Furniss, Rick A Veasey

  J Interv Card Electrophysiol. 2021 Mar;60(2):175-182

10.5 SHAM-PVI press articles

The SHAM-PVI trial has featured on various news websites including:

1. https://francais.medscape.com/voirarticle/3612230
2. https://www.medscape.com/viewarticle/better-late-than-never-sham-pvi-shows-af-ablation-works-2024a1000iet
3. https://www.healio.com/news/cardiology/20240906/pulmonary-vein-isolation-benefits-patients-with-atrial-fibrillation-vs-sham-procedure
4. https://www.physiciansweekly.com/pulmonary-vein-isolation-yields-reduction-in-a-fib-burden/
5. https://espanol.news/la-ablacion-de-la-fibrilacion-auricular-da-resultados-en-el-primer-estudio-controlado-con-placebo/
6. https://scienmag.com/pulmonary-vein-isolation-vs-sham-intervention-in-symptomatic-atrial-fibrillation/
7. https://www.eurekalert.org/news-releases/1056199
8. https://www.medpagetoday.com/meetingcoverage/esc/111763
9. https://www.escardio.org/The-ESC/Press-Office/Press-releases/Mainstay-ablation-procedure-for-atrial-fibrillation-shows-substantial-benefit-over-sham-procedure
10. https://www.tctmd.com/news/sham-pvi-catheter-ablation-improves-objective-measure-af-burden
11. https://www.emjreviews.com/cardiology/news/sham-pvi-trial-confirms-efficacy-of-ablation-procedure-for-atrial-fibrillation-esc-2024/
12. https://cardiacrhythmnews.com/sham-pvi-mainstay-ablation-procedure-atrial-fibrillation-placebo-esc-2024/

10.6SHAM-PVI podcasts

The SHAM-PVI trial has featured on various podcasts including:

1. https://www.heartrhythm365.org/AssetListing/The-Lead-Episode-77-A-Discussion-of-Pulmonary-Vein-Isolation-vs-Sham-Intervention-in-Symptomatic-Atrial-Fibrillation-11398/The-Lead-Episode-77-Video-51594
2. https://www.medscape.com/viewarticle/better-late-than-never-sham-pvi-shows-af-ablation-works-2024a1000iet
3. https://www.heartrhythm365.org/Public/Catalog/Details.aspx?id=9fU75kJFOlNV2%2bUKXGREQA%3d%3d&returnurl=%2fUsers%2fUserOnlineCourse.aspx%3fLearningActivityID%3d9fU75kJFOlNV2%252bUKXGREQA%253d%253d
4. https://www.youtube.com/watch?v=8y8xOrR3lDo