Clinical Profile and Outcome of Patients Undergoing Cryoablation for Atrial Fibrillation in a Tertiary Centre in South India

Dr. Sudipta Mondal

PDF (Cardiac Electrophysiology) Thesis

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DEPARTMENT OF CARDIOLOGY

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

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A THESIS SUBMITTED BY

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TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

In partial fulfillment of the requirements for the award of

PDF (CARDIAC ELECTROPHYSIOLOGY)

2024

Declaration by the student

CERTIFICATE

I, Dr Sudipta Mondal, hereby certify that I have personally carried out the work in the thesis titled **Clinical Profile and Outcome of Patients Undergoing Cryoablation for Atrial Fibrillation in a Tertiary Centre in South India,** in the Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum.

I further declare that before this date, no part of this thesis has been submitted for the award of any other degree or diploma.



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The thesis titled **Clinical Profile and Outcome of Patients Undergoing Cryoablation for Atrial Fibrillation in a Tertiary Centre in South India,** was carried out under my direct guidance and supervision, and no part of this thesis was submitted for awarding any degree or diploma, before this date.

Clearance from the Institutional Ethics Committee was obtained for conducting this study.



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List of Abbreviations

1.	ACC	American College of Cardiology
2.	ACEi	Angiotensin converting enzyme inhibitor
3.	AF	Atrial fibrillation
4.	AFL	Atrial Flutter
5.	AHA	American Heart Association
6.	AT	Atrial Tachycardia
7.	CT	Computed tomography
8.	CTI	Cavo-tricuspid Isthmus
9.	DOAC	Direct oral anticoagulant
10.	EF	Ejection fraction
11.	ESC	European Society of Cardiology
12.	HCM	Hypertrophic cardiomyopathy
13.	HF	Heart failure
14.	HFpEF	HF with preserved ejection fraction
15.	HFrEF	HF with reduced ejection fraction
16.	HRS	Heart Rhythm Society
17.	LCV	Left common pulmonary vein
18.	LIPV	Leftt inferior pulmonary vein
19.	LUPV	Left upper pulmonary vein
20.	NT-proBNP	N-terminal pro-B-type natriuretic peptide
21.	PAF	Paroxysmal atrial fibrillation
22.	PsAF	Persistent atrial fibrillation
23.	PVI	Pulmonary vein isolation
24.	RIPV	Right inferior pulmonary vein
25.	RUPV	Right upper pulmonary vein
26.	SGLT2i	Sodium Glucose Transporter 2 inhibitor
27.	TTI	Time-to-isolation.
28.	VKA	Vitamin K antagonist

Synopsis of the study

Background: Cryoballoon ablation is a frequently employed treatment strategy for patients with atrial fibrillation (AF).

Aims and objective: This report details the safety and efficacy of cryoballoon ablation for the treatment of atrial fibrillation (AF) in a South Indian cohort of patients undergoing cryoablation at a tertiary referral center.

Methods: This retrospective observational study included patients with paroxysmal atrial fibrillation (PAF) or persistent atrial fibrillation (PsAF) treated with cryoballoon catheter ablation according to standard clinical practice. The primary efficacy endpoints were freedom from AF and freedom from AF/atrial flutter (AFL)/atrial tachycardia (AT) lasting ≥30 seconds. The primary safety endpoint was the occurrence of serious procedure-related adverse events during the mean follow-up period of 30 months (April 2022 to October 2024).

Results: The cohort had a mean age of 55 ± 14 years, was 77% male, had a CHA2DS2VASc score of 1.63 ± 1.53, and had been diagnosed with AF for a mean of 2.93 ± 3.25 years prior to cryoablation. Patients with paroxysmal AF (PAF) comprised 75.8% of the total cohort. The PAF subgroup had a significantly larger mean left atrial (LA) diameter (36 mm vs. 42 mm; $P < 0.01$), lower LVEF (63% vs. 57%; $P = 0.016$), fewer presyncope episodes (6% vs. 30%; $P = 0.048$), and higher amiodarone use (69% vs. 22%; $p < 0.01$). Cavo-tricuspid isthmus line ablation was performed in 12% of patients, and other radiofrequency (RF) touch-up ablations were performed in 17% of subjects during the index procedure of PVI. Occurrence of atrial arrhythmia at the beginning (88% vs 30%, P <0.01) and persistent arrhythmia after the procedure requiring cardioversion (69% vs 6%, P <0.01), both were significantly higher in persistent AF group. In the 66 subjects included in the procedure analysis cohort, two serious procedure-related events (3.03%) occurred (PNI and moderate pericardial effusion, both resolved with conservative management). Freedom from recurrence of atrial arrhythmia at 12 month was 71% (95% CI 55-81%), with significant difference between PAF 84% (95% CI 68-92%) and PsAF PAF 34% (95% CI 10-60%) groups. Presence of atrial arrhythmia at the beginning of the study (87% vs

51%) and failure to terminate after completion of ablative procedure, requiring electrical cardioversion impose a higher risk (83% vs 28%) of recurrence**.** No difference was found between PVI and PVI+ groups**.**

Conclusions

1. Cryoballoon ablation demonstrated efficiency, safety, and effectiveness in treating patients with paroxysmal and persistent atrial fibrillation when performed according to standard-of-care techniques.
2. 12-month atrial arrhythmia-free survival rates were significantly higher in patients with paroxysmal AF compared to those with persistent AF.
3. Pre-procedural atrial arrhythmias and post-procedural atrial arrhythmias requiring cardioversion are associated with a higher risk of recurrence compared to patients without these conditions.
4. Major procedural adverse effects were comparable to those reported in global standards.

Introduction

Introduction

AF is the most common sustained arrhythmia encountered in clinical practice. It is a chronic and progressive disorder initially characterised by exacerbations and remissions leading to reductions in quality of life (QOL) with AF comparable to that observed in patients with chronic heart failure or receiving chronic haemodialysis. Furthermore, AF is associated with an increased risk of stroke and heart failure, leading to reduced overall survival.[1–3] The contemporary goals of AF management are improving arrhythmia-related symptoms and QOL, as well as reducing the morbidity and healthcare utilisation associated with AF.[4]

Over the past 20 years, catheter ablation, which is centred on the electrical isolation of triggering foci within the pulmonary veins, is superior to AAD therapy when AADs have been ineffective, or are contraindicated or poorly tolerated.[5]

The EAST-AFNET 4 trial recently tested an early rhythm-control strategy in patients with newly diagnosed AF (enrolled median 36 days after AF diagnosis). This trial predominantly employed pharmacological rhythm control, demonstrating that early rhythm control significantly reduced the composite primary outcome of cardiovascular death, stroke, and hospitalisation for worsening heart failure and acute coronary syndrome by 21% (from 5.0% per year to 3.9% per year) but increased serious adverse events related to AAD therapy (4.9% versus 1.4% in the usual care group).[6]

In contrast, The EARLY-AF trial sought to evaluate the role of initial cryoballoon ablation versus initial AAD therapy as the first treatment of AF in AAD-naïve patients.[7] While the majority of patients enrolled in the EAST-AFNET 4 trial were treated with AAD therapy (only 8.0% and 19.4% undergoing AF ablation at baseline and 2 years of follow-up), the EARLY-AF trial demonstrated that an initial cryoballoon ablation approach was superior to AADs for the outcomes of atrial tachyarrhythmia recurrence, arrhythmia burden and QOL.

On this background of emerging evidence favouring the growing utility of cryoablation in the management of AF, SCTIMST has performed >50 cases of cryoablation as per standard guidelines. We propose to document the clinical-investigational profile of patients undergoing cryoablation for AF in our institution, as well as the short-term and intermediate outcomes in this cohort of patients.

RATIONALE AND JUSTIFICATION FOR THIS STUDY

While the safety and efficacy of cryoablation procedures have been well-established in Western populations, data regarding these outcomes in the subcontinent remain limited. This paucity of data has consequently restricted the widespread application of this procedure within the subcontinent's population. This study aims to address this knowledge gap by documenting the safety and efficacy profile of cryoablation in this region, alongside insights into both short-term and intermediate-term outcomes.

Review of literature

Review of literature

Atrial fibrillation (AF) is a prevalent cardiac condition with significant implications for healthcare services across both primary and secondary care settings. Its prevalence is projected to double within the coming decades due to population aging, increasing comorbidity burden, heightened awareness, and advancements in detection technologies.

While the effects of AF vary among individuals, its associated morbidity remains a serious concern. Patients may experience a range of debilitating symptoms and diminished quality of life. Although the links between AF and stroke or heart failure are well established, AF is also associated with other thromboembolic events, including subclinical cerebral damage (potentially leading to vascular dementia) and thromboembolism affecting various organs, all of which contribute to the increased mortality risk associated with AF.

A range of comorbidities and risk factors typically drive the onset and progression of AF. Optimal AF management necessitates early and dynamic management of these contributing factors. Failure to do so can lead to recurrent AF episodes, treatment failure, poor patient outcomes, and inefficient use of healthcare resources. The European Society of Cardiology (ESC) AF practice guidelines have evolved into the AF-CARE framework (Atrial Fibrillation—[C] Comorbidity and risk factor management, [A] Avoid stroke and thromboembolism, [R] Reduce symptoms by rate and rhythm control, [E] Evaluation and dynamic reassessment).(Van Gelder et al., 2024) This framework prioritizes comorbidity and risk factor management as the foundational element, applicable to all AF patients regardless of their thromboembolic risk or presenting symptoms. Subsequent considerations include stroke and thromboembolism prevention ([A]), symptom reduction through rate and rhythm control ([R]), and individualized evaluation and dynamic reassessment ([E]) to account for the evolving nature of AF and associated conditions.

Patient empowerment is crucial for achieving optimal outcomes in long-term conditions like AF, promoting treatment adherence, and facilitating timely intervention for changes in clinical status. A patient-centered, shared decision-making approach enables management strategies tailored to individual needs, particularly important in AF where some therapies improve clinical outcomes

while others primarily address symptoms and quality of life. Enhanced education and awareness, for both patients and healthcare professionals, are essential to mitigate the impact of AF on individuals and healthcare systems.

Definitions:

Atrial fibrillation (AF) is a highly prevalent heart rhythm disorder characterized by uncoordinated atrial activation, resulting in ineffective atrial contraction. On a surface electrocardiogram (ECG), AF is identified by the absence of distinct, regular P waves and irregular ventricular activation, leading to unpredictable RR intervals in the absence of atrioventricular block. **Table 1** provides the classification of AF based on temporal patterns. It is important to note that these categories describe observed AF episodes and do not necessarily reflect the underlying pathophysiological mechanisms. Patients may progress through these categories sequentially, or require periodic reclassification based on their individual clinical course. Over time, some individuals with AF develop atrial and ventricular remodeling, which can render attempts at rhythm control ineffective. In such cases, or when patients and clinicians jointly decide to pursue rate control, AF is called permanent AF.(Alam et al., 2012)

Temporal classification	**Definition**
First-diagnosed AF	AF that has not been diagnosed before, regardless of symptom status, temporal pattern, or duration.
Paroxysmal AF	AF which terminates spontaneously within 7 days or with the assistance of an intervention. Evidence suggests that most self-terminating paroxysms last <48 h.
Persistent AF	AF episodes which are not self-terminating. Many intervention trials have used 7 days as a cut-off for defining persistent AF. Long-standing persistent AF is arbitrarily defined as continuous AF of at least 12 months' duration but where rhythm control is still a treatment option in selected patients, distinguishing it from permanent AF.
Permanent AF	AF for which no further attempts at restoration of sinus rhythm are planned, after a shared decision between the patient and physician.

Table A. Definitions and classifications for the temporal pattern of AF

Diagnosis:

In many cases, AF diagnosis is uncomplicated, such as when typical symptoms coincide with characteristic ECG findings on a standard 12-lead ECG, clearly indicating the need for AF management. However, diagnosis becomes more complex in cases of asymptomatic episodes or when AF is detected by long-term monitoring devices, especially those that do not provide an ECG . To prevent misdiagnosis, this task force reiterates the recommendation that ECG documentation is mandatory for initiating AF risk stratification and management. In current practice, ECG confirmation can be obtained through various means: not only when AF is evident on a standard 12-lead ECG, but also through single-lead and multiple-lead devices that provide ECG recordings . This excludes non-ECG wearables and other devices that typically utilize photoplethysmography. It is important to note that many pivotal AF trials required two or more ECGs documenting AF, or a pre-existing AF diagnosis, prior to randomization. The duration of AF required for diagnosis on monitoring devices is not definitively established. While a standard 12-lead ECG records 10 seconds, a duration of 30 seconds or more on single-lead or multiple-lead ECG devices has generally been accepted, although supporting evidence is limited.

Symptoms:

Symptoms associated with AF episodes are diverse and extend beyond the commonly recognized palpitations. While asymptomatic AF episodes can occur, the majority (90%) of AF patients report experiencing symptoms of varying severity. Even in symptomatic individuals, some AF episodes may remain asymptomatic. Importantly, the presence or absence of symptoms does not correlate with the risk of stroke, systemic embolism, or mortality. However, symptoms do significantly impact patient quality of life. Although cardiac-specific symptoms like palpitations are less frequent than non-specific symptoms such as fatigue, they significantly detract from quality of life. While women are often underrepresented in AF clinical trials, existing data suggests that women with AF tend to experience more pronounced symptoms and report lower quality of life. Compared to the general population, AF patients report a greater burden of anxiety and more severe depression, with these symptoms being particularly prevalent in women with AF.

Adverse events associated with AF:

Atrial fibrillation is associated with a range of serious adverse events. Patients with AF also experience elevated rates of hospitalization and complications arising from coexisting medical conditions. Heart failure is the most common non-fatal outcome, affecting approximately half of all AF patients over time. Two meta-analyses have demonstrated a four- to five-fold increase in the relative risk (RR) of heart failure in AF patients compared to those without AF (RR, 4.62; 95% CI, 3.13–6.83 and RR, 4.99; 95% CI, 3.0–8.22).(Odutayo et al., 2016; Ruddox et al., 2017) Ischemic stroke (RR, 2.3; 95% CI, 1.84–2.94), ischemic heart disease (RR, 1.61; 95% CI, 1.38–1.87), and other thromboembolic events represent the next most frequent adverse impacts of AF.(Van Gelder et al., 2024) These thromboembolic events typically involve arterial thromboembolism (preferred over the term "systemic"), although venous thromboembolism is also associated with AF. Furthermore, AF increases the risk of cognitive impairment and dementia. The age-specific incidence of hospital admission increased notably in older age groups.

AF is also associated with increased mortality. In 2017, AF contributed to over 250,000 deaths globally, with an age-standardized mortality rate of 4.0 per 100,000 people (95% uncertainty interval 3.9–4.2).(Dai et al., 2021) Heart failure-related death is the most frequent cause of death in AF patients, exhibiting complex relationships with both cardiovascular and non-cardiovascular diseases. Compared to sinus rhythm, AF is associated with up to a two-fold increased risk of all-cause mortality (RR, 1.95; 95% CI, 1.50–2.54) and cardiovascular mortality (RR, 2.03; 95% CI, 1.79–2.30). Even in the absence of major thromboembolic risk factors, the incidence of death is 15.5 per 1,000 person-years in individuals with AF exposure, compared to 9.4 per 1,000 person-years without (adjusted HR, 1.44; 95% CI, 1.38–1.50; $P < .001$). Patients experiencing OAC-related bleeding events, both minor and major (as defined by the International Society on Thrombosis and Haemostasis scale), exhibit higher mortality. Despite OAC use, AF patients retain a substantial residual risk of death, emphasizing the importance of addressing concomitant diseases.

AF management:

The 2024 ESC Guidelines for the management of AF have synthesized and built upon previous approaches to establish core management principles aimed at facilitating guideline implementation and, consequently, improving patient care and outcomes. While evidence suggests that clinical support tools can aid best-practice management, it is crucial to recognize that such tools serve only as guides, and all patients require individualized care.(Van Gelder et al., 2024) The AF-CARE approach encompasses established AF management principles within a systematic, time-oriented framework comprising four essential treatment pillars. Collaborative management with each patient forms the foundation of AF-CARE. Importantly, it acknowledges the growing body of evidence indicating that AF therapies are most effective when associated health conditions are addressed. Therefore, a thorough assessment for comorbidities and risk factors ([C]) is crucial and should be conducted in all patients diagnosed with AF. The next step focuses on stroke and thromboembolism prevention ([A]) in at-risk patients, emphasizing the appropriate use of anticoagulant therapy. Subsequently, the focus shifts to reducing AF-related symptoms and morbidity through effective heart rate and rhythm control ([R]), which, in select patients, may also reduce hospitalizations or improve prognosis. The potential benefits and associated risks of rhythm control should be considered for all patients at each healthcare encounter. Given the dynamic nature of AF and its related comorbidities, individualized and dynamic evaluation and re-evaluation ([E]) are essential. Due to the variability in treatment response and the evolving pathophysiology of AF with age and advancing comorbidities, reassessment should be integrated into standard care pathways to prevent adverse patient outcomes and improve population health.

A. Avoid stroke and thromboembolism

Atrial fibrillation, regardless of its classification as paroxysmal, persistent, or permanent, is a significant risk factor for thromboembolism.(Wolf et al., 1991) Without treatment, and depending on individual patient characteristics, AF increases the risk of ischemic stroke five-fold, with AF implicated in one of every five strokes. Consequently, the standard approach should be to offer oral anticoagulation (OAC) to all eligible patients, except those deemed to be at low risk of incident stroke or thromboembolism. The efficacy of OAC in preventing ischemic

stroke in AF patients is well documented. Antiplatelet agents alone (aspirin or aspirin combined with clopidogrel) are not recommended for stroke prevention in AF. Percutaneous left atrial appendage occlusion (LAAO) is an alternative device-based intervention designed to prevent ischemic stroke in patients with atrial fibrillation in a selected group.(Glikson et al., 2020)

B. Reduce symptoms by rate and rhythm control

Rate control: The optimal heart rate target for patients with atrial fibrillation (AF) varies depending on the clinical context, symptom burden, presence of heart failure, and whether rate control is used in conjunction with a rhythm control strategy. The RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation) randomized controlled trial (RCT), which studied patients with permanent AF, demonstrated that lenient rate control (target heart rate <110 bpm) was non-inferior to a stricter approach (<80 bpm at rest; <110 bpm during exercise; Holter monitoring for safety) regarding a composite outcome of clinical events, NYHA class, and hospitalization.(Groenveld et al., 2011) A post-hoc combined analysis of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and RACE (Rate Control versus Electrical cardioversion) studies yielded similar findings. Consequently, lenient rate control represents an acceptable initial strategy unless patients experience ongoing symptoms or there is suspicion of tachycardia-induced cardiomyopathy, in which cases stricter heart rate targets may be warranted.(Van Gelder et al., 2006) AV nodal ablation is smother strategy in elected group of patients.

Rhythm control: Rhythm control strategies aim to restore and maintain sinus rhythm using therapies such as cardioversion, antiarrhythmic drugs (AADs), percutaneous catheter ablation, endoscopic and hybrid ablation, and open surgical approaches. Rhythm control should always be implemented as part of the broader AF-CARE approach, not as an isolated strategy.

In patients experiencing acute or worsening hemodynamic instability attributed to AF, rapid electrical cardioversion is recommended. For other patients, a wait-and-see approach, allowing for spontaneous conversion, may be considered as an alternative to immediate cardioversion. The Rate Control versus Electrical Cardioversion Trial 7–Acute Cardioversion versus Wait and See (RACE 7 ACWAS) trial, conducted in patients with recent-onset symptomatic AF without hemodynamic compromise, demonstrated that a wait-and-see approach for spontaneous

conversion within 48 hours of symptom onset was non-inferior to immediate cardioversion at a 4-week follow-up.(Pluymaekers et al., 2019) Since landmark trials published over 20 years ago, the primary rationale for considering long-term rhythm control therapy has been symptom reduction. Older studies indicated that implementing a rhythm control strategy using AADs did not reduce mortality or morbidity compared to a rate control-only strategy and could potentially increase hospitalization rates. Conversely, multiple studies have shown that rhythm control strategies positively impact quality of life once sinus rhythm is maintained. Therefore, if the presence of AF-related symptoms is uncertain, attempting to restore sinus rhythm is a reasonable initial step. In symptomatic patients, factors favoring rhythm control should be considered, including suspected tachycardiomyopathy, a short AF history, a non-dilated left atrium, and patient preference.

Rhythm control strategies have advanced significantly due to increased experience with the safe use of antiarrhythmic drugs, consistent use of OAC, improvements in ablation technology, and enhanced identification and management of risk factors and comorbidities. The ATHENA trial (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg twice daily for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter) demonstrated that dronedarone significantly reduced the risk of cardiovascular hospitalization or death compared to placebo in patients with paroxysmal or persistent AF.(Hohnloser et al., 2009) The CASTLE-AF trial (Catheter Ablation versus Standard Conventional Treatment in Patients With Left Ventricle Dysfunction and AF) showed that a rhythm control strategy using catheter ablation could improve mortality and morbidity in select patients with heart failure with reduced ejection fraction (HFrEF) and an implanted cardiac device.(Marrouche et al., 2018) In end-stage HFrEF, the CASTLE-HTx trial (Catheter Ablation for Atrial Fibrillation in Patients With End-Stage Heart Failure and Eligibility for Heart Transplantation) found, in a single center, that catheter ablation combined with guideline-directed medical therapy significantly reduced the composite outcome of all-cause death, left ventricular assist device implantation, or urgent heart transplantation compared to medical treatment alone. However, the CABANA trial (Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation) did not find a significant difference in mortality and morbidity between catheter ablation and standard rhythm and/or rate

control drugs in symptomatic AF patients older than 64 years or younger than 65 years with stroke risk factors.(Packer et al., 2019) The EAST-AFNET 4 (Early treatment of Atrial fibrillation for Stroke prevention Trial) reported that implementing a rhythm control strategy within one year, compared to usual care, significantly reduced the risk of cardiovascular death, stroke, or hospitalization for heart failure or acute coronary syndrome in patients older than 75 years or with cardiovascular conditions.(Kirchhof et al., 2020) Notably, rhythm control in EAST-AFNET 4 was primarily achieved with antiarrhythmic drugs (80% of patients in the intervention arm), while usual care consisted of rate control, with rhythm control only considered for uncontrolled AF-related symptoms. Patients in EAST-AFNET 4 had cardiovascular risk factors but were at an early stage of AF, with over 50% in sinus rhythm and 30% asymptomatic at baseline.

Catheter ablation:

Catheter ablation effectively prevents AF recurrence, reduces AF burden, and improves quality of life in symptomatic patients with paroxysmal or persistent AF who are intolerant of or unresponsive to AADs. Multiple RCTs support catheter ablation as a first-line rhythm control strategy in patients with paroxysmal AF, demonstrating a similar risk of adverse events compared to initial AAD treatment.(Van Gelder et al., 2024) However, the superiority of first-line ablation over drug therapy in persistent AF remains unclear. Catheter ablation may also be beneficial for patients experiencing symptoms due to prolonged pauses following AF termination, where non-randomized data suggests symptom improvement and avoidance of pacemaker implantation.

Pulmonary vein isolation (PVI) remains the cornerstone of AF catheter ablation, but the optimal ablation strategy for non-paroxysmal AF is not yet established. Emerging technologies, such as pulsed field ablation, use high-amplitude electrical pulses to ablate myocardium via electroporation with high tissue specificity. A single-blind RCT involving 607 patients found pulsed field ablation to be non-inferior to conventional radiofrequency or cryoballoon ablation for efficacy and safety endpoints. Regarding the timing of ablation, a small RCT found that delaying catheter ablation by 12 months (with optimized medical therapy) in patients with

paroxysmal or persistent AF did not impact arrhythmia-free survival compared to ablation within one month.

As with any rhythm control strategy, many patients are unsuitable for catheter ablation due to factors such as left atrial dilatation, which reduce the likelihood of a positive outcome. Definitive evidence supporting the prognostic benefit of catheter ablation is required before this invasive procedure can be considered for truly asymptomatic patients. As previously noted, the CABANA trial did not demonstrate a benefit of catheter ablation over medical therapy, although high crossover rates and low event rates may have confounded the results. Therefore, only highly selected asymptomatic patients should be considered for catheter ablation, and only after a thorough discussion of the associated risks and potential benefits of delaying AF progression. Randomized trials have demonstrated that AF catheter ablation in patients with HFrEF significantly reduces arrhythmia recurrence and increases ejection fraction, with improvements in clinical outcomes and mortality observed in select patients. Several factors, including AF type, left atrial dilatation, and the presence of atrial and/or ventricular fibrosis, can refine patient selection to maximize the benefits of AF catheter ablation in HFrEF patients. The prognostic value of catheter ablation in patients with heart failure with preserved ejection fraction (HFpEF) is less established than in HFrEF.

Recent registries and trials report varying rates of peri-procedural serious adverse events associated with catheter ablation (2.9%–7.2%), with a very low 30-day mortality rate (<0.1%). Operator experience and procedural volume at the ablation center are crucial, as they are associated with complication rates and 30-day mortality.

Cryoablation:

For the treatment of symptomatic paroxysmal atrial fibrillation (PAF), catheter ablation is considered a first-line therapy, with pulmonary vein isolation (PVI) serving as a fundamental and standard approach for both paroxysmal and persistent AF.

Radiofrequency catheter ablation (RFCA) has been a cornerstone of arrhythmia treatment, including PVI for AF. Cryoablation has been employed in cardiac surgery for decades and has been used transvenously for arrhythmia treatment since the 2000s.

Cryoablation gained significant prominence with its application in AF therapy. The introduction of cryoballoon ablation (CBA) for pulmonary vein (PV) isolation represented a technological advancement, enabling single energy applications to create encircling lesions at the PV antral level, contrasting with the point-by-point energy delivery characteristic of conventional RFCA. The FIRE AND ICE trial demonstrated the non-inferiority of the cryoballoon to irrigated-tip radiofrequency ablation (RFA) in terms of efficacy and safety, establishing CBA as one of the most widely adopted ablation technologies for AF treatment.(Kuck et al., 2016)

Biophysics:

Cryothermal energy induces tissue changes characterized by intracellular and extracellular ice crystal formation, osmotic cellular damage, microvascular injury leading to hemorrhage, and subsequent inflammation, ischemia, fibrosis, and apoptosis in the surrounding tissue. Unlike radiofrequency ablation (RFA) lesions, cryoablation lesions preserve tissue architecture, including fibrocytes and collagen, while exhibiting significantly fewer large vascular structures or endocardial damage.(Whittaker, 1984)

This characteristic of preserving tissue architecture makes cryoablation preferable for reducing the risk of structural damage during ablation of specific arrhythmias, such as atrioventricular nodal reentrant tachycardia or tachycardias originating near the His bundle. This preservation also contributes to the lower risk of cardiac perforation and thrombogenicity compared to RFA.

Cryothermal energy is generated by refrigerant injected through a fine tube. The refrigerant vaporizes at the cryoablation catheter tip, freezing the adjacent tissue. During freezing, the catheter tip adheres to the tissue, ensuring stable energy delivery. The cryoballoon employs the same cryoenergy production mechanism, but with a balloon-tipped catheter.

The first-generation Arctic Front™ cryoballoon system (Medtronic, Minneapolis, MN, USA), commercially available since 2010, comprises inner and outer balloons, a central lumen for a guide wire and contrast injection, a thermocouple for inner balloon temperature monitoring, and lumens for cryorefrigerant intake and exhaust. Pressurized nitrous oxide (N2O) is delivered to the distal aspect of the inner balloon, reducing the temperature to a maximum of −80°C. Heat is

absorbed from the surrounding tissue, and the cryorefrigerant returns to the console through a vacuum lumen.(Andrade et al., 2012)

The first-generation cryoballoon (CB-1) had an equatorial cooling region that could result in incomplete PV encirclement (Figure 1). To address this limitation, the second-generation cryoballoon (CB-2), Arctic Front Advance™ (Medtronic), was developed. While maintaining similar basic structures, CB-2 features a modified refrigerant injection system that provides more homogenous cooling across the entire distal hemisphere, including the tip.(Metzner et al., 2015) This modification improved the one-year success rate and reduced complication rates compared to CB-1.

Cryoballoons are available in 23 mm and 28 mm sizes. The 28-mm size is generally preferred to avoid complications associated with deep balloon placement within the PVs. The appropriate size is selected based on individual PV anatomy. A single interatrial septal puncture is sufficient for CBA, as the spiral Achieve™ (Medtronic) catheter for PV electrogram recording is inserted through the cryoballoon's central guide wire lumen. The Achieve™ mapping catheter is positioned before cryoballoon insertion.

Ablation procedure:

The septal puncture technique is similar to that used for RFA with a standard transseptal sheath, but a low anterior septal puncture is recommended to provide more space for cryoballoon movement and better support for the PVs, particularly the right inferior PV. Intracardiac echocardiography (ICE) is strongly recommended during septal puncture to ensure safety.

The inserted standard transseptal sheath is replaced with a steerable transseptal sheath (FlexCath Advance™; Medtronic) with a 12-Fr inner diameter and 15-Fr outer diameter over a long, stiff guidewire. This stiffer steerable sheath is designed to steer and support the cryoballoon throughout the procedure. Both the cryoballoon and Achieve™ mapping catheter can be inserted through the sheath. To prevent cardiac damage, the Achieve™ catheter should lead the cryoballoon outside the sheath during movement within the left atrium, as both the cryoballoon and sheath distal tips are rigid.

Once the cryoballoon is positioned near a PV, achieving complete PV occlusion with the balloon's distal hemisphere is crucial. The cryoballoon should be inflated outside the PV and advanced to the PV antrum for proper fitting. While the inflated cryoballoon rarely causes cardiac damage due to low pressure, inflation within the PV should be avoided. PV angiography with 1–2 mL of contrast injection should be performed to verify complete PV sealing by the balloon. If contrast leakage is observed, the balloon can be repositioned. If the balloon fits the PV without leakage, a slight withdrawal can be performed to induce leakage, confirming appropriate antral positioning. Improper positioning within the PV can increase the risk of complications involving surrounding structures, such as phrenic nerve injury (PNI).

After appropriate balloon positioning, the Achieve™ mapping catheter can be adjusted to optimize PV recordings. Electrical PV isolation is detectable, and the time required to achieve it can serve as an indicator of long-term PVI success.

During cryoenergy application, balloon compliance changes, and the cooled cryoballoon adheres to the surrounding tissue. Therefore, the cryoballoon should not be moved during cryoenergy delivery to prevent cardiac damage. Experts recommend an initial 180-second ablation with CB-2, but the optimal cryoenergy application duration remains undetermined.

Esophageal temperature and diaphragmatic motion during phrenic nerve stimulation should be monitored to prevent complications.

Since the release of the first-generation cryoballoon (CB-1) in 2010 and the more advanced CB-2 in 2012, numerous studies have demonstrated comparable efficacy between CBA and RFA. The 2016 publication of the FIRE AND ICE trial, a large randomized controlled study including both CB-1 and CB-2, provided significant evidence supporting the non-inferiority of CBA to RFA in terms of efficacy and overall safety.(Kuck et al., 2016) Given the advancements in cryoballoon technology from CB-1 to CB-2 and the evolution of RFA from simple irrigated-tip catheters to force-sensing catheters, comparing the efficacy and safety of CB-2 with contact-force RFA catheters is warranted, despite the limited number of studies directly addressing this comparison.

A systematic review was conducted to compare CBA with RFA for AF ablation.(Jin and Wang, 2018) Studies comparing CBA and RFA were identified through searches of PubMed, EBSCO,

Web of Science, and the Cochrane Library. Studies using only CB-1 or predominantly CB-1 in the CBA group were excluded. Only studies evaluating atrial tachyarrhythmia (ATA) recurrence during follow-up were included in the analysis. A total of 12 studies, encompassing 4,228 unique patients, met the inclusion criteria.

Of the 12 included studies, 7 used only CB-2 in the cryoablation group, while 5 used CB-2 in a median of 41% of patients (range, 30.7–80.4%). Six studies exclusively used force-sensing RFA catheters, while the remaining studies did not specify the type of RFA catheter used. Persistent AF was present in 383 of the 4,228 patients (9%).

Acute Procedural Success

Electrical PVI during the index procedure was assessed in 8 studies. Acute procedural success rates ranged from 98.4% to 100% in the CB-2 group and from 97.4% to 100% in the RFA group, with a median success rate of 99% in both groups. No significant difference was observed between the two groups.

Recurrence of ATA During Follow-Up

Studies were included only if patients were followed for at least 3 months. Nine studies reported a 12-month follow-up period, while the remaining studies used follow-up periods ranging from 3 to 18 months.

ATA recurrence after a single procedure was similar between the two groups (12 studies; 4,228 patients; 25.2% CB-2 vs. 29.5% RFA; odds ratio [OR], 0.81; 95% confidence interval [CI], 0.62–1.05; p=0.11). When the RFA group was limited to force-sensing RFA, no significant difference was found between the CB-2 and force-sensing RFA groups (6 studies; 1,507 patients; 19.5% CB-2 vs. 18.3% RFA; OR, 1.08; 95% CI, 0.83–1.40; p=0.58).

Procedural and Fluoroscopy Time

While some patients in the CB-2 group underwent procedures with electroanatomical mapping, most RFA procedures were performed with this technology. However, precise numbers for electroanatomical mapping use were not available.

Procedural time ranged from 73.5±16 minutes to 192.9±44 minutes in the CB-2 group and from 118.5±15 minutes to 283.7±78.0 minutes in the RFA group. The CB-2 group had significantly shorter procedure times (mean difference [MD], −37.59 minutes; 95% CI, −56.78, −18.4; $p<0.001$). Fluoroscopy time ranged from 13.8±4 minutes to 39.8±14.9 minutes in the CB-2 group and from 15.8±6 minutes to 73.0±30.1 minutes in the RFA group. Although the CB-2 group had shorter fluoroscopy times, the difference was small (MD, −3.1 minutes; 95% CI, −6.93, −0.73; $p=0.11$) (Figure 3B).

Complications

Phrenic Nerve Injury (PNI)

Transient PNI was evaluated in 11 studies, and permanent PNI was evaluated in 9 studies. Transient PNI is relatively common in CBA, occurring in a median of 5% of patients (range, 0.99–17.3%) across 11 studies involving 2,088 patients. Permanent PNI occurred in only 4 studies, with a median incidence of 1% (range, 0.26–2.5%). In contrast, only 2 cases of transient PNI (0.1%) occurred in the RFA group (1,854 patients), and no cases of permanent PNI were reported. Transient PNI was significantly more frequent in the CB-2 group (OR, 9.69; 95% CI, 4.18–22.49; $p<0.001$). To mitigate PNI risk, phrenic nerve function monitoring is crucial, especially during right superior PV (RSPV) ablation, where the risk is highest. Right phrenic nerve stimulation with palpation of diaphragmatic contractions or monitoring of diaphragmatic compound motor action potential recordings can be used.(Mondésert et al., 2014) These methods can reduce the PNI rate to below 1.5%.

Other Serious Complications

Serious complications such as cardiac tamponade, gastrointestinal bleeding, documented esophageal ulcer, and thromboembolic events like stroke occurred significantly less frequently in the CB-2 group (0.78% vs. 2.53% in the RFA group; OR, 0.39; 95% CI, 0.23–0.68; $p<0.001$).

Esophageal temperature monitoring is strongly recommended during CBA to prevent esophageal injury. While large controlled trials have not definitively confirmed the benefit of terminating

cryoenergy application based on esophageal temperature limits, discontinuing cryoablation should be considered when the esophageal temperature falls to 21–25°C.

While the safety and efficacy of cryoablation procedures have been well-established in Western populations, data regarding these outcomes in the subcontinent remain limited. This paucity of data has consequently restricted the widespread application of this procedure within the subcontinent's population. This study aims to address this knowledge gap by documenting the safety and efficacy profile of cryoablation in this region, alongside insights into both short-term and intermediate-term outcomes.

Materials and methods

Materials and methods

HYPOTHESIS: Cryoablation is a safe and effective procedure with good clinical outcomes in selected patients with atrial fibrillation.

AIM: To investigate the clinical profile and short and intermediate outcomes of patients undergoing cryoablation for AF in a South Indian tertiary center.

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OBJECTIVES:

Primary Objective:

- To assess the efficacy of cryoablation in achieving freedom from atrial fibrillation episodes during the follow-up period.

Secondary Objectives:

- To evaluate the clinical profile of patients undergoing cryoablation for AF, including demographics, comorbidities, and prior antiarrhythmic medication use.
- To assess the procedural success rate and document any peri-procedural complications associated with cryoablation.

METHODOLOGY

Study Design: Single-center retrospective observational study.

Study period: April 2022 to October 2024 (30 months)

Study setting: Department of Cardiology, Sree Chitra Tirunal Institute of Medical Sciences and Technology (SCTIMST), Trivandrum

Sample size: 66 (All patients who underwent cryoablation)

Inclusion Criteria:

- Symptomatic AF documented by electrocardiogram (ECG) and underwent AF cryoablation as per standard guidelines.

Exclusion Criteria:

Not applicable

Methodology:

- Baseline data collected on demographics, medical history, comorbidities, AF characteristics (duration, type), medications, and quality of life scores using validated instruments.
- Pre-procedural workup details, including echocardiography (including LA volume), chest X-ray, and CT scan with pulmonary vein assessment (including LA volume), documented.
- Procedural details: fluoroscopy time, cryoablation energy delivered, and any complications encountered during the procedure.
- Post-procedural data: monitoring for arrhythmia recurrence, need for additional antiarrhythmic medications, length of hospital stay, and any adverse events within 30 days.
- Follow-up conducted at regular intervals (e.g., 1 month, 3 months, 6 months, 12 months) to assess for sustained freedom from AF episodes and document any long-term complications.

Statistical analysis:

Categorical data will be summarized as frequencies and percentages, and groups will be compared using the Chi-square test / Fischer exact test. Descriptive data for continuous variables will be presented as mean +/- SD or median with range when appropriate. Analyses of continuous data will be performed with the use of a Paired t-test for parametric distribution. A p-value of < 0.05 will be considered statistically significant. The primary endpoint (freedom from AF episodes) will be analyzed using Kaplan-Meier curves and compared between groups using log-rank tests. Secondary outcomes will be analyzed with appropriate statistical methods depending on data distribution.

ETHICAL JUSTIFICATION

Data regarding the safety and effectiveness of cryoablation in AF is limited with no Indian studies to date. The results of this study will immensely help in upgrading the quality of care of patients with atrial fibrillation.

Results and analysis

Results and analysis

Baseline characteristics

Sixty-six subjects were enrolled between April 2022 and October 2024, with a mean follow-up of 15.3 months (SD 8.8 months). Baseline clinical characteristics, procedural details, efficacy, safety, and short-term outcomes were analyzed. Baseline patient characteristics are detailed in **Table 1**. The cohort had a mean age of 55 ± 14 years, was 77% male, had a CHA2DS2VASc score of 1.63 ± 1.53, and had been diagnosed with AF for a mean of 2.93 ± 3.25 years prior to cryoablation. The prevalence of typical atrial flutter, atrial tachycardia, and tachy-brady syndrome was 12%, 9%, and 18%, respectively. Beta-blockers (88%) were the most commonly prescribed pre-procedural medication, followed by amiodarone (33%) and flecainide (27%). All patients experienced palpitations as the predominant symptom, with 24% reporting paroxysmal presyncope. Key comorbidities included hypertension (44%), diabetes (29%), hypothyroidism (18%), dyslipidemia (20%), significant coronary artery disease (12%), and obstructive sleep apnea (23%). No patients in the cohort were chronic alcoholics or binge drinkers. Structural heart disease was present in 26% of patients, including 13% with concentric left ventricular hypertrophy (LVH), 1.5% with apical hypertrophic cardiomyopathy (HCM), and 4.5% with mitral valve prolapse (**Table 2**). Overall, 24% of patients exhibited either concentric or eccentric LVH. Mean atrial diameter and left ventricular ejection fraction (LVEF) were 38 mm and 62%, respectively. Patients with paroxysmal AF (PAF) comprised 75.8% of the total cohort. The PAF subgroup had a significantly larger mean left atrial (LA) diameter (36 mm vs. 42 mm; $P < 0.01$), lower LVEF (63% vs. 57%; $P = 0.016$), fewer presyncope episodes (6% vs. 30%; $P = 0.048$), and higher amiodarone use (69% vs. 22%; $p < 0.01$). Other baseline characteristics were similar between the subgroups. Prior ablation history has been depicted in **Table 3.**

Preprocedural cardiac computed tomography (CT) was performed in 97% of the cohort, excluding two patients. In one patient, a history of kidney transplantation contraindicated contrast CT. In the other, significant diabetic nephropathy precluded CT. CT imaging revealed a mean left atrial (LA) volume of 97 mL (SD 32 mL), with significantly greater LA dilation in the persistent AF (PsAF) group compared to the paroxysmal AF (PAF) group (116 mL vs. 92 mL, $p = 0.011$). The majority of the cohort (82%) had four pulmonary veins, while 18% had five. The additional pulmonary veins were left middle (1.5%) and right middle (16.7%) pulmonary veins.

Common pulmonary veins were observed in 24% of the cohort, with left-sided common veins being the most prevalent.

Subject characteristics	**Total cohort (N = 66)**	**Paroxysmal AF (N = 50)**	**Persistent AF (N = 16)**	***P*-value**
Male sex (N [%])	50 (77.27)	38 (76.00)	13 (81.25)	0.476
Age in years (mean ± STD)	55.19 (13.79)	54.84 (13.62)	56.31 (14.71)	0.713
CHA_2DS_2-VASc Score (mean ± SD)	1.63 (1.53)	1.56 (1.50)	1.87 (1.66)	0.479
Years diagnosed with AF (mean ± SD)	2.93 (3.25)	2.73 (2.83)	3.58 (4.36)	0.362
History of atrial flutter (N [%])	8 (12.12)	6 (12.00)	2 (12.50)	0.628
History of atrial tachycardia (N [%])	6 (9.09)	6 (12.00)	0 (0)	0.175
Tachy-brady syndrome (N [%])	12 (18.18)	12 (24.00)	0 (0)	0.093
Left atrial diameter in mm (mean ± SD)	37.83 (6.32)	36.42 (5.54)	42.25 (6.75)	0.0009
Left ventricular hypertrophy (N [%])	16 (24.24)	13 (26)	3 (18.75)	0.412
Structural heart disease (N [%])	17 (25.76)	14 (28)	3 (18.75)	0.351
Left ventricular ejection fraction in % (mean ± SD)	61.95 (8.9)	63.44 (6.65)	57.31 (3.31)	0.016
Hypertension (N [%])	29 (43.94)	9 (56.25)	20 (40.00)	0.254
Diabetes (N [%])	19 (28.79)	7 (43.75)	12 (24.00)	0.129
Dyslipidaemia (N [%])	13 (19.70)	11 (22.00)	2 (12.50)	0.332
Hypothyroidism (N [%])	12 (18.18)	8 (16.00)	4 (25.00)	0.319
Coronary artery disease (N [%])	8 (12.12)	7 (14.00)	1 (6.25)	0.372
Sleep apnoea (N [%])	15 (22.73)	10 (20)	5 (31.25)	0.350
Palpitations (N [%])	66 (100)	50 (100)	16 (100)	NA
Presyncope (N [%])	16 (24.24)	15 (30.00)	1 (6.25)	0.048
Prior medications (N [%]) Amiodarone Beta blockers Flecainide	 22 (33.33) 58 (87.88) 18 (27.27)	 11 (22.00) 46 (92.00) 15 (30.00)	 11 (68.75) 12 (75.00) 3 (18.75)	 0.001 0.090 0.296
Cardiac CT (N [%]) LA volume (mean ± STD) No. of Pulmonary veins 5 Additional pulmonary veins LMPV RMPV Common pulmonary veins LCV RCV	64 (96.97) 97.64 (31.49) 12 (18.18) 12 (18.88) 1 (1.52) 11 (16.67) 16 (24.24) 14 (21.21) 1 (1.52)	50 (100) 92.27 (24.82) 11 (22.00) 11 (22.00) 1 (2.00) 10 (20.00) 11 (22.00) 9 (18.00) 1 (2.00)	14 (87.5) 116.07 (44.21) 1 (6.25) 1 (6.25) 0 (0.00) 1 (6.25) 5 (31.25) 5 (31.25) 0 (0.00)	0.056 0.011 0.188 0.188 0.572 0.572 0.355 0.579 0.579

Table 1. Baseline patient characteristics

Structural Heart disease	N = 66 (%)
Total	17 (25.76)
Left ventricular hypertrophy	13 (19.70)
Mitral valve prolapse	3 (4.5)
Hypertrophic cardiomyopathy	1 (1.5)

Table 2. Presence of structural heart disease in the study cohort

Prior ablation	NO [Total 6]
Cavotricuspid Isthmus	1
Cavotricuspid isthmus and Left WACA	1
Pulmonary vein isolation – RFA	1
Left atrial flutter	1
Atrioventricular nodal reentrant tachycardia	1
Right ventricular outflow tract ventricular tachycardia	1

Table 3. Prior ablation history in the study cohort (N=66)

Procedure characteristics

Procedurals data are detailed in **Table 4**. All patients were treated with the Arctic Front Advance (second-generation) catheter (100%), and a 28 mm cryoballoon was used in all procedures (100%). Intraprocedural three-dimensional (3D) electroanatomical mapping was performed in all cases. Intracardiac echocardiography (ICE) was used in 26% of the cohort. Phrenic nerve function was monitored during all ablations using a pace and palpate technique with compound muscle action potential (CMAP) monitoring. The mean left atrial (LA) dwell time was 61 ± 19 minutes, and the average fluoroscopy time was 40 ± 17 minutes. All targeted pulmonary veins (PVs) were acutely isolated during the index procedure. However, documentation of PV potential disappearance during cryoapplication was observed in only 36% of patients. Cavo-tricuspid isthmus line ablation was performed in 12% of patients, and other radiofrequency (RF) touch-up ablations were performed in 17% of subjects during the index procedure (**Table 5**). Minimum esophageal temperature was achieved during cryoapplication most often in LIPV (26%) followed by LUPV (26%) and RIPV (24%). However, lowest numerical values were observed during LCV cryoapplication (27.78, SD 1.72 degree Celsius). Mean Cryoballoon application time for LUPV, LIPV, LCV, RUPV and RIPV are 273s, 210s, 333s, 190s and 185s, respectively. Mean time-to-isolation (PV potential disappearance during cryoballon application) for LUPV, LIPV, LCV, RUPV and RIPV are 44s, 46s, 41s, 37s and 43s, respectively. Nadir temperature during cryoapplication was usually less than -40 degree Celsius in all veins. Atrial arrhythmia at the beginning of the procedure was noted in as high as 44% of the cohort. Atrial arrhythmia persisted after the procedure in 21% of the cohort for which electrical cardioversion

was done. All patients were in sinus rhythm after cardioversion. Occurrence of atrial arrhythmia at the beginning (88% vs 30%, P <0.01) and persistent arrhythmia after the procedure requiring cardioversion (69% vs 6%, P <0.01), both were significantly higher in persistent AF group.

Procedural characteristics	**Total cohort (N =66)**	**Paroxysmal AF (N = 50)**	**Persistent AF (N = 16)**	**P- Value**
Prior Radiofrequency ablation (N [%])	6 (9.09)	5 (10.00)	1 (6.25)	0.548
Ablation tools				
28mm Cryoballoon (N [%])	66 (100)	50 (100)	16 (100)	NA
Arctic Front Advance (N [%])	66 (100)	50 (100)	16 (100)	NA
Achieve Mapping Catheter	66 (100)	50 (100)	16 (100)	NA
Left atrial dwell time in minutes (mean ± SD)	60.80 (19.28)	62.76 (20.09)	54.68 (15.51)	0.146
Total fluoroscopy time in minutes (mean ± SD)	40.17 (16.97)	39.44 (15.47)	42.43 (21.42)	0.543
General Anaesthesia (N [%])	66 (100)	50 (100)	16 (100)	NA
Intra-procedural 3D electroanatomical mapping (N [%])	66 (100)	50 (100)	16 (100)	NA
Intracardiac echocardiography (N [%])	17 (25.76)	13 (26.00)	4 (25.00)	0.608
Esophageal temperature monitoring (N [%])	66 (100)	50 (100)	16 (100)	NA
Minimum oesophageal temperature Frequency (N [%])				
LUPV	17 (25.76)	13 (26.00)	4 (25.00)	0.787
LIPV	22 (33.33)	16 (32.00)	6 (37.50)	
LCV	6 (9.09)	6 (12.00)	0 (0)	
RUPV	4 (6.06)	3 (6.00)	1 (6.25)	
RIPV	16 (24.24)	11 (22.00)	5 (31.25)	
RMPV	1 (1.52)	1 (2.00)	0 (0)	
Minimum oesophageal temperature observed degree C (mean ± SD)				
LUPV	31.45 (2.28)	31.43 (2.36)	31.5 (2.34)	0.392
LIPV	29.72 (3.01)	29.92 (3.21)	29.21 (2.60)	
LCV	27.78 (1.72)	27.78 (1.72)	N/A	
RUPV	33.42 (1.23)	33.36 (1.50)	33.6 (0)	
RIPV	30.36 (3.43)	31.17 (3.45)	28.6 (2.94)	
RMPV	33.6 (0)	33.6 (0)	N/A	
Phrenic nerve monitoring				
Pacing/ Palpate	66 (100)	50 (100)	16 (100)	NA
Diaphragm stimulation	66 (100)	50 (100)	16 (100)	NA
CMAP	66 (100)	50 (100)	16 (100)	NA
Pulmonary vein Isolation				
Pulmonary vein Isolation +	19 (28.78)	12 (24)	7 (43.75)	0.129
CTI	8 (12.12)	4 (8.00)	4 (25)	0.142
Others	11 (16.66)	8 (16.00)	3 (18.75)	

PV potential disappearance during Cryoapplication (N [%])	24 (36.36)	18 (36.00)	6 (37.50)	0.914
Cryoballoon application time (mean ± SD)				
LUPV	272.66 (115.73)	270.88 (105.95)	278.53 (148.47)	0.836
LIPV	209.48 (60.36)	208.97 (64.65)	211 (47.39)	0.917
LCV	332.6 (125.33)	346.57 (120.01)	300 (158.74)	0.619
RUPV	189.59 (61.02)	197.08 (61.76)	166.18 (53.87)	0.077
RIPV	184.77 (60.96)	185.04 (59.69)	183.93 (66.81)	0.950
Time-to-Isolation (mean ± SD)				
LUPV	44.13 (18.67)	46.3 (19.35)	36 (13.94)	0.168
LIPV	46.27 (31.50)	49.71 (33.08)	28.5 (11.31)	0.133
LCV	40.55 (24.47)	45.71 (8.92)	22.5 (24.74)	0.262
RUPV	37.43 (24.44)	39.02 (26.62)	32 (24.44)	0.430
RIPV	42.72 (25.70)	41.83 (26.57)	45.4 (25.70)	0.709
ADDITIONAL VEIN	27.80 (8.78)	27.80 (8.78)	NA	NA
Nadir temperature (mean ± SD)				
LUPV	-47.25 (6.23)	-46.55 (6.08)	-49.53 (6.42)	0.132
LIPV	-44. 06 (4.91)	-43.71 (4.35)	-45.07 (6.39)	0.393
LCV	-49.97 (10.85)	-51.71 (11.55)	-45.9 (9.71)	0.470
RUPV	-48.46 (5.91)	-48.02 (5.77)	-49.87 (6.32)	0.278
RIPV	-46.71 (6.99)	-46.88 (6.87)	-46.18 (7.56)	0.733
Atrial arrhythmia at the beginning of the procedure (N [%])	29 (43.94)	15 (30.00)	14 (87.50)	<0.001
Atrial arrhythmia at the end of the procedure (N [%])	14 (21.21)	3 (6.00)	11 (68.75)	<0.001

Table 4. Procedural characteristics

LUPV- left upper pulmonary vein, LIPV- left inferior pulmonary vein, LCV- left common pulmonary vein, RUPV- right upper pulmonary vein, RIPV- right inferior pulmonary vein, RMPV- right middle pulmonary vein, CTI- cavotricuspid isthmus

PVI +	No (19)	Recurrence
CTI	8	1
Left Carinal ablation	3	0
RIPV	2	1
RUPV	1	0
Mitral Isthmus	1	0
Posterior LA	1	1
LA roof	1	0
Anterior LA flutter	1	1
Coronary Sinus Tachycardia	1	0

Table 5. Additional radiofrequency ablation

LA- left atrium, pulmonary vein, RUPV- right upper pulmonary vein, RIPV- right inferior pulmonary vein, RMPV- right middle pulmonary vein, CTI- cavotricuspid isthmus

Safety

In the 66 subjects included in the procedure analysis cohort, two serious procedure-related events (3.03%) occurred. Recurrence of arrhythmia was not classified as a procedural adverse event. One patient developed moderate pericardial effusion, which resolved with conservative management. No major access site complications were observed. One subject (1.5%) experienced phrenic nerve injury (PNI) that persisted at discharge; however, this resolved completely by the one-month follow-up visit. No procedure-related strokes or transient ischemic attacks occurred. A complete list of serious adverse events is provided in **Table 6**.

Major complication	No 2/66 (3.03%)	Managed by
Phrenic nerve palsy	1	Conservative [resolved]
Moderate pericardial effusion	1	Conservative [resolved]

Table 6. Major procedure related complications

Efficacy:

Freedom from recurrence of atrial arrhythmia at 12 month was 71% (95% CI 55-81%), with significant difference between PAF 84% (95% CI 68-92%) and PsAF PAF 34% (95% CI 10-60%) groups. (**Figure 1, 2).** Although taking a cut-off of LA dimension 40mm did not difference in outcome, an incremental association was found between dilated LA and atrial arrhythmia recurrence. (**Figure 3).** Presence of atrial arrhythmia at the beginning of the study (87% vs 51%) and failure to terminate after completion of ablative procedure, requiring electrical cardioversion impose a higher risk (83% vs 28%) of recurrence (**Figure 4, 5).** No difference was found between PVI and PVI+ groups (**Figure 6, 7).**

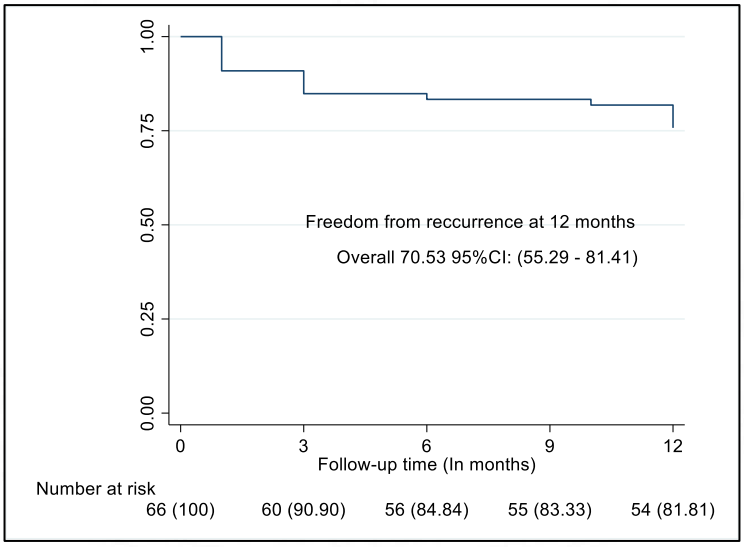


Figure 1. Kaplan – Meyer 12 month estimate of freedom from atrial arrhythmia (AF/ AT/ AFL) recurrence

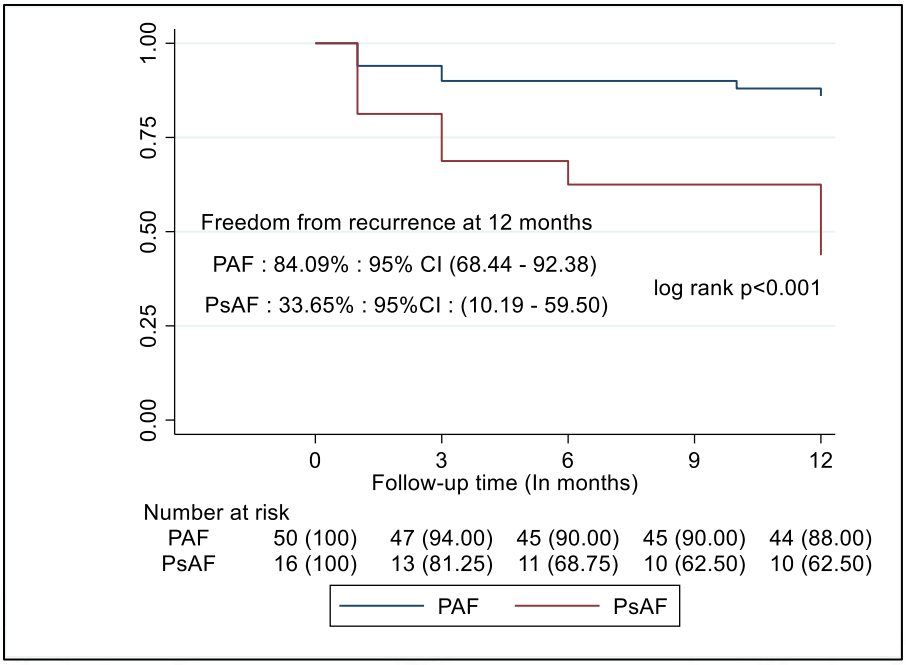


Figure 2. Kaplan – Meyer 12 month estimate of freedom from atrial arrhythmia (AF/ AT/ AFL) recurrence in PAF and PsAF groups

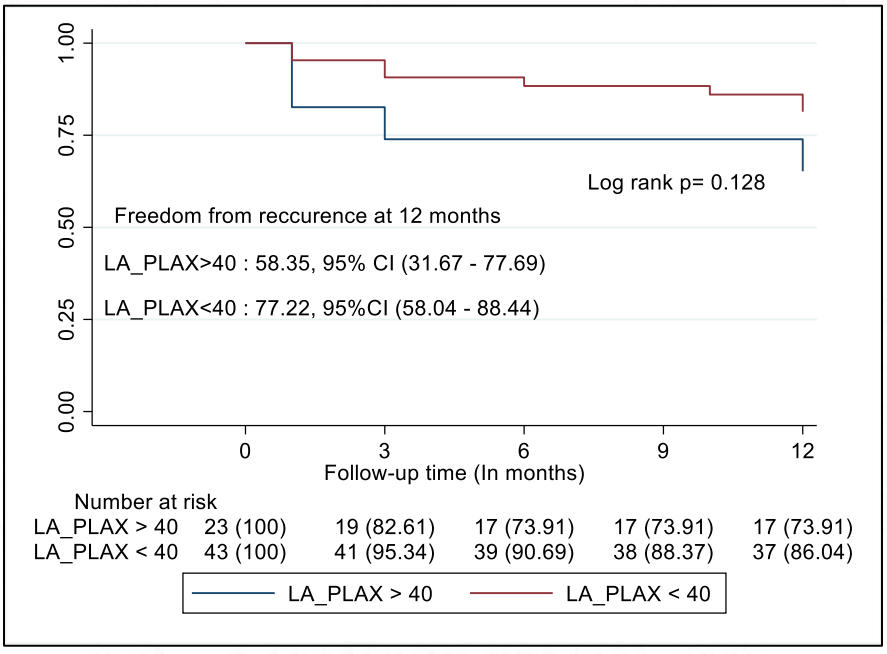


Figure 3. Kaplan – Meyer 12 month estimate of freedom from atrial arrhythmia (AF/ AT/ AFL) recurrence in dilated and non-dilated LA (40mm) by 2D- echocardiogram (PLAX – Parasternal long axis view)

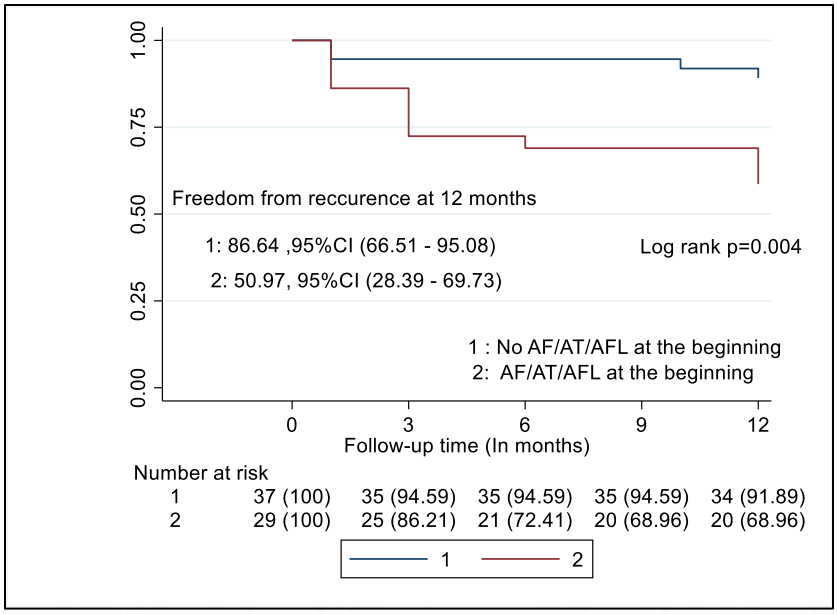


Figure 4. Kaplan – Meyer 12 month estimate of freedom from atrial arrhythmia (AF/ AT/ AFL) recurrence in terms of comparison between atrial arrhythmia at the beginning of the study vs sinus rhythm at the beginning of the study.

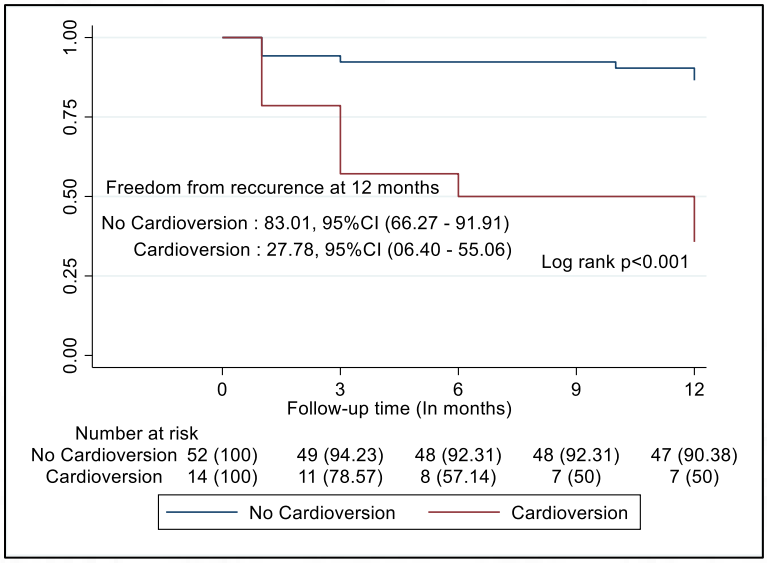


Figure 5. Kaplan – Meyer 12 month estimate of freedom from atrial arrhythmia (AF/ AT/ AFL) recurrence in terms of comparison between atrial arrhythmia at the end of the study requiring electrical cardioversion vs sinus rhythm at the end of the study

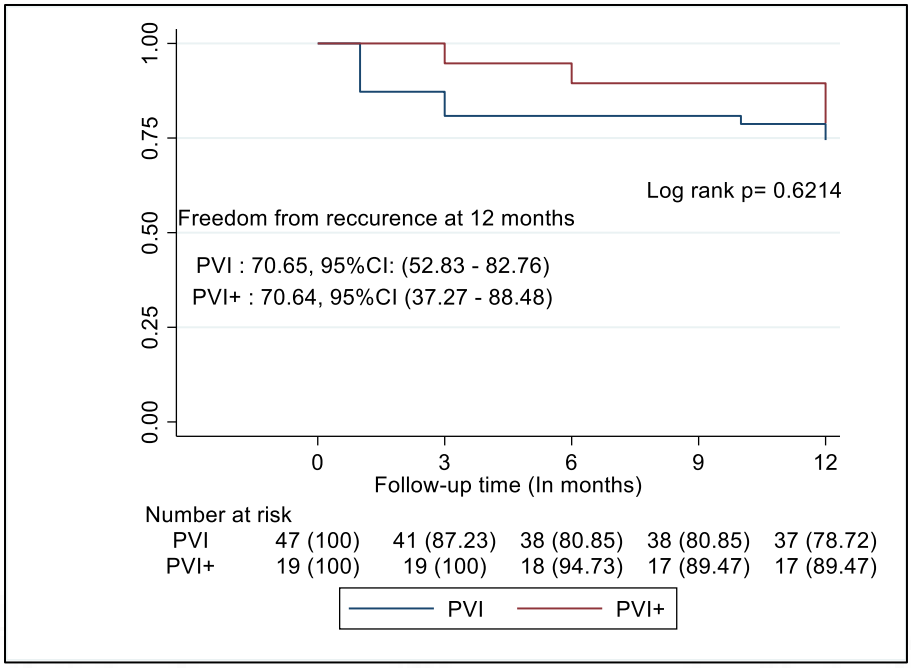


Figure 6. Kaplan – Meyer 12 month estimate of freedom from atrial arrhythmia (AF/ AT/ AFL) recurrence in terms of comparison between PVI only vs additional RF ablation

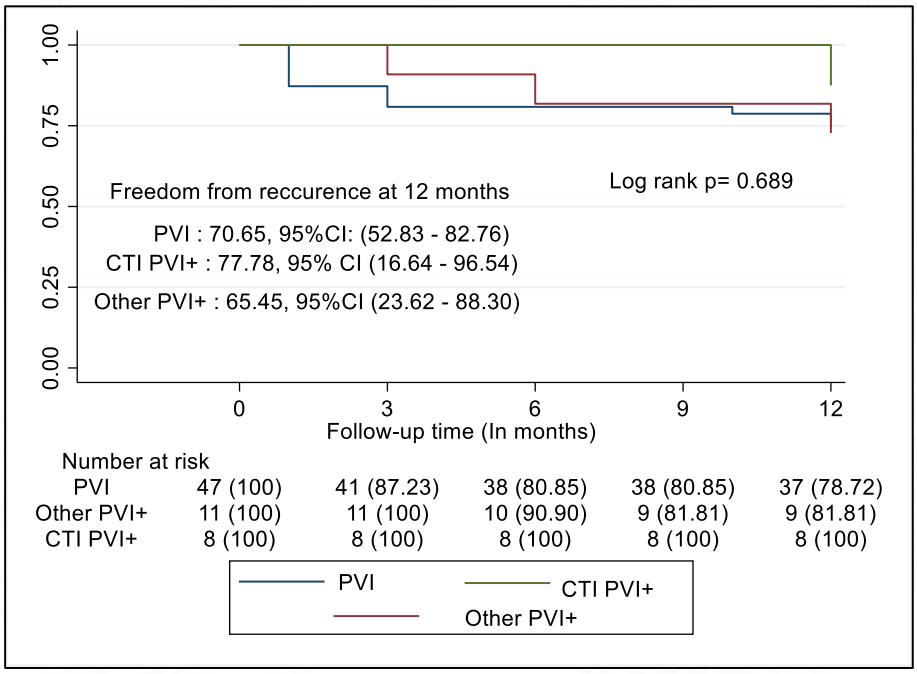


Figure 7. Kaplan – Meyer 12 month estimate of freedom from atrial arrhythmia (AF/ AT/ AFL) recurrence in terms of comparison between PVI only vs additional RF ablation

Discussion

Discussion

To our knowledge, this cohort represents the first and largest assessment of an Indian population undergoing cryoballoon ablation for AF treatment, with a 12-month follow-up. Cryoablation in this diverse cohort of patients with PAF and PsAF was performed safely, with a 3.03% rate of procedure-related serious adverse events (including a 1.5% rate of phrenic nerve injury), and efficiently, with a mean LA dwell time of 61 ± 19 minutes and a mean fluoroscopy time of 40 ± 17 minutes. Freedom from AF/AT/AFL at 12 months was 86.4% (95% CI: 84.3%–88.3%) for the PAF cohort and 70.9% (95% CI: 64.6%–76.4%) for the PsAF cohort. These findings demonstrate the safety and effectiveness of cryoballoon ablation for AF treatment when delivered according to varying global standard-of-care practices.

Consistent with findings from controlled clinical trials, patients with PsAF in this study exhibited baseline characteristics indicative of more advanced AF disease, including greater left atrial (LA) dilation, reduced left ventricular function, and increased amiodarone use, compared to patients with PAF.(Boveda et al., 2018; Su et al., 2020) Regardless of AF classification, standard-of-care treatment resulted in a consistent and efficient procedure, with an average total LA dwell time of 61 ± 19 minutes. Specifically, a PVI-only approach was frequently employed (71%) for both PAF and PsAF patients, reinforcing the essential role of PVI in treating all forms of AF.(Calkins et al., 2017) While previous studies have reported shorter procedural times with conscious sedation, general anesthesia was used in all patients in this study, aligning with initial cryoablation studies and mitigating procedural challenges during the initial phase of experience in this region.(Wasserlauf et al., 2016) The use of conscious sedation is expected to increase in the future. Similarly, preprocedural CT imaging and intraprocedural electroanatomical mapping were performed in nearly all patients. Intracardiac echocardiography (ICE) use (26%) was primarily limited to the initial phase of experience and in challenging cases (e.g., difficult transseptal puncture or ruling out left atrial appendage (LAA) thrombus).(Sagone et al., 2019) The ability to perform effective cryoballoon ablation with minimal adjunctive tools is a challenge, particularly in resource-constrained environments, given the increasing AF patient population. Future improvements in this area are anticipated.

The overall major procedure-related side effect rate (3.03%) was numerically lower than that reported in recent global studies.(Boveda et al., 2018; Kuck et al., 2016; Su et al., 2020) Notably,

the rates of PNI at discharge (1.5%) and cardiac tamponade/pericardial effusion (1.5%) were low. Phrenic nerve monitoring was employed in 100% of procedures, likely contributing to the low PNI rate, consistent with contemporary findings.(Knight et al., 2019; Mörtsell et al., 2019; Su et al., 2018) Previous studies have also documented low rates of cardiac tamponade/pericardial effusion following cryoballoon ablation, and this study further corroborates the low risk of this event in typical clinical practice. Importantly, no procedure-related deaths were reported in this registry, signifying an improvement in the safety of atrial fibrillation ablation procedures since the 2010 survey by Cappato et al., which reported a 0.15% procedure-related mortality rate.(Cappato et al., 2010).

Freedom from recurrence of atrial arrhythmia at 12 month was 71% (95% CI 55-81%), with significant difference between PAF 84% (95% CI 68-92%) and PsAF PAF 34% (95% CI 10-60%) groups. This outcome in PAF is in concordance with one of the latest global AF registry.(Chun et al., 2021) The relatively inferior outcome in terms of recurrence observed in patients with persistent atrial fibrillation (PsAF) may be attributed to the fact that a significant proportion of chronic patients with long-standing AF have undergone ablation with the advent of newer cryoablation technology. This trend is likely to improve in subsequent patient cohorts. Although a cut-off of 40 mm for left atrial (LA) dimension did not reveal a significant difference in outcome, an incremental association between LA dilatation and atrial arrhythmia recurrence was observed. This finding supports the notion of progressive atrial remodeling, which has been previously established in the literature.

The presence of atrial arrhythmia at the beginning of the study (87% vs. 51%) and the failure to terminate atrial arrhythmia following the ablation procedure, necessitating electrical cardioversion, were associated with a significantly higher risk of recurrence (83% vs. 28%). This likely reflects the chronic and resistant nature of the disease, which exhibits an intrinsic propensity for recurrence due to established substrate.

Summary and Conclusions

Conclusions

The conclusions drawn from this study are as follows:

- The Arctic Front Cardiac Cryoablation System has achieved global adoption. This study demonstrates its robust safety, efficacy, and efficiency across a diverse patient population with atrial fibrillation (AF) when cryoballoon ablation is performed in accordance with local standards of care.
- Left atrial dilatation may signify advanced disease progression in the natural history of AF, potentially associated with a higher risk of recurrence.
- The left and right inferior pulmonary veins are particularly susceptible to significant reductions in esophageal temperature (below 30 degrees Celsius), with the least observed in the left common pulmonary vein.
- 12-month atrial arrhythmia-free survival rates were significantly higher in patients with paroxysmal AF compared to those with persistent AF.
- Pre-procedural atrial arrhythmias and post-procedural atrial arrhythmias requiring cardioversion are associated with a higher risk of recurrence compared to patients without these conditions.
- Major procedural adverse effects were comparable to those reported in global standards.
- No significant difference in recurrence rates was observed between patients who underwent pulmonary vein isolation (PVI) alone and those who received additional ablation strategies during the procedure.

Limitation

Limitations

This retrospective, non-randomized, observational study is subject to potential limitations. Study cohort was relatively small. Patient selection bias may have influenced the results. Furthermore, monitoring for atrial arrhythmia recurrence was not standardized across all patients. Since patient and physician discretion determined follow-up schedules, asymptomatic and other atrial arrhythmias may have been underreported. However, this study provides valuable insights into the real-world clinical experience of patients and providers. Notably, 12-month follow-up data were unavailable for all patients treated with cryoballoon ablation within the study period, which may potentially impact the reported efficacy outcomes.

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Annexures

Format for CV of the Investigators

First name: **Sudipta**	Middle name:	Last name: **Mondal**
Date of birth: 04.10.1991		Male
Professional Mailing Address (Include Institution name)		Study Site Address (Include Institution name)
PDF, Cardiac electrophysiology Dept of Cardiology SCTIMST		Dept of Cardiology, SCTIMST
Mobile Number:	7686906481	
Email:	sudiptamondalnrs@gmail.com	

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
DM Cardiology	2023	SCTIMST, Trivandrum, KL
DNB General Medicine	2019	NBE, New Delhi
MD General Medicine	2019	North Bengal Medical College, Siliguri
MBBS	2014	Nil Ratan Sircar Medical College, Kolkata

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration

TCMC Reg: 80886, dated 10.09.2021

West Bengal Medical Council: 73195, dated 30.06.2015

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
January 2024	**PDF, Cardiac EP**	SCTIMST, Trivandrum, Kerala
January 2021	**SR, DM Cardiology course**	SCTIMST, Trivandrum, Kerala
June 2019	**SR, Medicine**	Murshidabad MC, Berhampore, WB
May 2016	**JR, Medicine**	North Bengal Medical College, Darjeeling, WB

Brief summary of relevant research experience:

1. Clinical Profile Of AES Cases In A Tertiary Care Center Of North Bengal. **Int J Sci Res.** 2021 Jul 1;10(7):71–3
2. Epidemiological Review and Sensitivity Patterns of CBNAAT Testing for Tuberculosis in a Teaching Hospital of Eastern India. **JIMA** 2020;18(12):43-48.
3. Etiological study of seizure disorders among patients attending the epilepsy clinic of an urban center in Eastern India. **JIMA** 2020;18(7):43-45.
4. Establishing Normal Echocardiographic Measurements In Healthy Indian Newborn Infants. **Asia Pac J Paediatr Child Health** 2021;4:11-17.

Current project/s at hand

Sudipta Mondal Signature	Date: 22.06.2024 Place: SCTIMST, Trivandrum, Kerala

Plagiarism report

Clinical Profile and Outcome of Patients Undergoing Cryoablation for Atrial Fibrillation in a Tertiary Centre in South India

by Kaviya Mohan

General metrics

50,827	7,256	373	29 min 1 sec	55 min 48 sec
characters	words	sentences	reading time	speaking time

Score

89

This text scores better than 89% of all texts checked by Grammarly

Writing Issues

237	79	158
Issues left	Critical	Advanced

Plagiarism

2 %

13 sources

2% of your text matches 13 sources on the web or in archives of academic publications

Proforma

DATA COLLECTION PROFORMA

Age: **Gender:** **Project ID no:**

Weight:

Height:

BSA:

BMI:

Baseline diagnosis:

Comorbidities:

Etiology of AF:

Duration of AF:

History of prior DC version:

Relevant blood investigations:

ECHO parameters:

LA size	
LVEF	
LVH	
MVA	
RVSP	
TAPSE	
LAVI	

CT scan parameters:

PV anatomy:

Additional pulmonary veins:

LA volume:

DRUG THERAPY:	
Rate control medications:	
Beta-blockers	
Calcium channel blockers	
Digoxin	
Ivabradine	
Anti-arrhythmic therapy:	
Amiodarone	
Flecainide	
Anti-platelet therapy:	
Aspirin	
Clopidogrel	
Anti-coagulation therapy:	
Warfarin	
Apixaban	
Dabigatran	
Rivaroxaban	
Other relevant medications:	

Cryoablation procedure details:
Date:
Case Start Time:
Transseptal Time:
AFA pro in left atrium:
AFA pro out of the left atrium:
LA dwell time:
Case end time:
Indication:
Total Fluoro time:
Imaging used for PVI:
Catheters used:
PVI or PVI plus:

- Posterior wall of LA inclusion

Diaphragmatic palsy (Transient/ Persistent)
Intraprocedural AF conversion to SR

Vein	TIME TO REACH -30	TTI (sec)	Nadir Temp	Freeze Duration (min)	Esophagus Start Temp	Esophagus End Temp	Time to zero
LSPV # 1							
LSPV # 2							
LSPV # 3							
LSPV # 4							
LIPV # 1							
LIPV # 2							
LIPV # 3							
LIPV # 4							
RIPV # 1							
RIPV # 2							
RIPV # 3							
RIPV # 4							
RSPV # 1							
RSPV # 2							
RSPV # 3							
RSPV # 4							

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
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Institutional Ethics Committee

CDSCO Registration No: ECR/189/Inst/KL/2013/RR-24
DHR Registration No: EC/NEW/INST/2022/2775

SCT/IEC/2285/NOVEMBER-2024 27.11.2024

Dr. Sudipta Mondal
Post Doctoral Fellow
Department of Cardiology
SCTIMST, Thiruvananthapuram

Dear Dr. Sudipta Mondal,

The Institutional Ethics Committee held on 2nd November, 2024, reviewed and discussed your application to conduct the study titled "**CLINICAL PROFILE AND OUTCOME OF PATIENTS UNDERGOING CRYOABLATION FOR ATRIAL FIBRILLATION IN A TERTIARY CENTRE IN SOUTH INDIA (IEC /2285)**".

Principal Investigator	Dr. Sudipta Mondal, PDF – Cardiac Electrophysiology, Department of Cardiology, SCTIMST
Co-Principal Investigator(s)	Dr. Narayanan Namboodiri KK, Professor, Department of Cardiology, SCTIMST Dr. Abhilash SP, Professor, Department of Cardiology, SCTIMST Dr. Jyothi Vijay MS, Assistant Professor, Department of Cardiology, SCTIMST
Duration of the study	2 years and 6 months

The following members of the Ethics Committee were present at the meeting held on 2nd November, 2024

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Annapurna.Y	MD	Female	Basic Medical Scientist	No
2.	Dr. Manoj Murhekar	MD (Preventive & Social Medicine)	Male	Social Scientist	No
3.	Dr. Indu PV	MBBS, DPM, MPhil, PhD	Female	Clinician	No
4.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
5.	Smt. Rekha Radhakrishnan	M.A (Eng.); B.Ed	Female	Lay person	No
6.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
7.	Dr. Syam K	MBBS, MD, DM	Male	Clinician	Yes
8.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
9.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairman, IEC, SCTIMST*
2. *IEC Application Form*
3. *Proforma*
4. *Study Consent Form in English and Malayalam*
5. *Patient Information Sheet in English and Malayalam*
6. *Declaration form*
7. *CV of PI and Co-PIs*
8. *Study Proposal*

Revised submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST*
2. *Amendment as per IEC recommendations*
3. *Study Proposal*
4. *Proforma*
5. *CV of PI and Co-PIs*
6. *Declaration form*

IEC Decision
The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Dr. G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM