Korean Circ J. 2024 Oct;54(10):619-633
https://doi.org/10.4070/kcj.2024.0044
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Original Research

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Long-term Outcome of Cryoballoon Ablation in Korean Patients With Atrial Fibrillation: Real-World Experience From the Cryo Global Registry

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OPEN ACCESS

Received: Jan 29, 2024
Revised: Apr 5, 2024
Accepted: May 7, 2024
Published online: Jun 10, 2024

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AUTHOR'S SUMMARY

Atrial fibrillation (AF), the most common form of atrial arrhythmia (AA), presents a growing healthcare challenge in Korea. Catheter ablation has emerged as a fundamental treatment modality for AF. This study aimed to assess the long-term effectiveness beyond 12 months, symptomatic burden, quality of life, and healthcare utilization following cryoballoon ablation (CBA) in Korean patients, along with identifying predictors of AA recurrence. Moreover, the study highlights a notable association between the timing of ablation and the incidence of arrhythmia-free survival at the 2-year follow-up, suggesting CBA as a potential initial rhythm control therapy for Korean patients with AF.

ABSTRACT

Background and Objectives: Atrial fibrillation (AF), the most common atrial arrhythmia (AA), is an increasing healthcare burden in Korea. The objective of this sub-analysis of the Cryo Global Registry was to evaluate long-term efficacy, symptom burden, quality of life (QoL), and healthcare utilization outcomes and factors associated with AA recurrence in Korean patients treated with cryoballoon ablation (CBA).
Methods: Patients were treated and followed up according to local standard-of-care in 3 Korean hospitals. Kaplan-Meier estimates were used in analyzing (1) efficacy defined as freedom from ≥30 second recurrence of AA at 24 months, (2) healthcare utilization, and (3) predictors of 24-month AA recurrence. Patient-reported QoL (using European Quality of Life-5 Dimensions-3 Levels) and predefined AF-related symptoms were assessed at baseline and 24-month follow-up.
Results: Efficacy was 71.9% in paroxysmal AF (PAF) and 49.3% in persistent AF (PsAF) patients ($p<0.01$). A larger left atrial diameter (LAD), an increased time from AF diagnosis to CBA, and PsAF were independent predictors of AA recurrence. The percentage of patients with no AF symptoms significantly increased from baseline (24.5%) to 24-month (89.5%)

Trial registration
ClinicalTrials.gov Identifier: NCT02752737

Funding
This work was sponsored by Medtronic, Inc.

Conflict of Interest
Dr. Jada M Selma, Fred J Kueffer, Dr. Kelly A van Bragt, and Valentine Obidigbo are employees of Medtronic. The remaining authors have no conflicts of interest pertaining to this manuscript to declare.

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions
Conceptualization: Oh IY; Formal analysis: Obidibo V; Investigation: Lim HE, Oh IY, On YK; Validation: Kueffer FJ; Writing - original draft: Ahn HB, Selma JM; Writing - review & editing: Lim HE, Oh IY, On YK, Kueffer FJ, van Bragt KA.

follow-up (p<0.01). Improvement in QoL from baseline to 24 months was not statistically different between AF cohorts. PAF patients experienced greater freedom from repeat ablations (93.9% vs. 81.4%) and cardiovascular hospitalizations (91.3% vs. 72.5%, p<0.001 for both).

Conclusions: In alignment with global outcomes, CBA is an effective treatment for AF in the Korean population, with patients possessing a large LAD and not receiving ablation soon after diagnosis being the most at risk for AA recurrence.

Trial registration: ClinicalTrials.gov Identifier: NCT02752737

Keywords: Atrial fibrillation; Catheter ablation; Cryotherapy; Republic of Korea

INTRODUCTION

Atrial fibrillation (AF) affects approximately 1% to 2% of the overall population and is a rapidly increasing healthcare burden in Korea and worldwide.[1)] Catheter ablation is superior to antiarrhythmic drug (AAD) therapy in maintaining sinus rhythm and improving quality of life (QoL) in AAD-refractory or AAD-naive patients.[2)] In addition to radiofrequency ablation (RFA), cryoballoon ablation (CBA) with the Arctic Front Advance catheter has become a “gold standard” for AF ablation. Specifically, CBA has been shown to be more effective than RFA in preventing repeat ablations, direct-current cardioversions, all-cause rehospitalizations, and cardiovascular rehospitalizations post-procedure.[3)]

Reporting on long-term outcomes following CBA in Asian populations is limited.[4)] Lim et al.[5)] conducted a sub-analysis of the Cryo Global Registry evaluating the safety and efficacy of index CBA in the Korean population at 12-month follow-up. However, with AF being a progressive disease, there is a need to implement longer follow-up duration in ablation studies. Therefore, this analysis sought to determine long-term efficacy, safety, QoL, and healthcare utilization outcomes as well as factors influencing atrial arrhythmia (AA) recurrence in Korean patients over a 24-month period following CBA.

METHODS

Ethical statement

Local Institutional Review Boards and ethics committees at each participating center granted approval for the study (Samsung Medical Center IRB 2019-02-061, Seoul National University Bundang Hospital B-1903/562-303, and Hallym University Sacred Heart Hospital 2019-04-025), and patients provided written informed consent before enrolling in the registry.

Study design

The Cryo Global Registry (NCT02752737) is an ongoing prospective, multicenter post-market registry designed to assess the outcomes of AF ablation procedures that utilize the Arctic Front (Advance) family of cryoablation catheters (Medtronic, Inc., Minneapolis, MN, USA). An international committee of physicians supervised data quality, analyses, and publication milestones. The principles outlined in the Declaration of Helsinki (2013) and Good Clinical Practices were followed for data collection.

Patient population

All individuals aged ≥18 years scheduled for a planned CBA procedure were eligible for participation in the registry, and no exclusions were made based on pre-existing characteristics. In this analysis, patients were consecutively enrolled between April 2019 and May 2020 at 3 Korean hospitals. All patients were treated with index pulmonary vein isolation (PVI). Patients were categorized according to their AF disease status in alignment with current guidelines, including[6]: paroxysmal AF (PAF, AF that ends spontaneously or with intervention within 7 days of onset), persistent AF (PsAF, continuous AF lasting >7 days but ≤12 months), or long-standing PsAF (LsPsAF, continuous AF lasting >12 months). Due to considerations of low sample size, LsPsAF patients were combined with PsAF patients from the 3 hospitals for statistical analysis.

Cryoballoon ablation procedure

Each CBA-PVI procedure conducted adhered to the local standard-of-care in Korea and in accordance with standard procedural methods as previously described.[5] Briefly, following transeptal access, a 28-mm CBA catheter (Arctic Front Advance; Medtronic, Inc.) was maneuvered into the left atrium (LA) via a dedicated 15-F outer diameter steerable sheath (FlexCath Advance Steerable Sheath; Medtronic, Inc.). In one patient, an additional 23-mm CBA catheter was used. An over-the-wire technique, using a J-tip guidewire or a specialized circular mapping catheter (Achieve [Advance]; Medtronic, Inc.), was employed to introduce the CBA catheter in the LA. The number and duration of cryoapplications was determined by the operator, and PVI was confirmed via entrance and/or exit block.

Right-sided ablations were recommended to be accompanied by phrenic nerve monitoring and cryoapplications were stopped upon a diminished diaphragmatic response. Operator discretion determined pre- and intra-procedural imaging, acute PVI chemical testing, esophageal temperature monitoring, and additional ablations beyond PVI (performed with focal cryoablation and/or RFA). Left atrial diameter (LAD) was determined by pre-procedural imaging according to standard hospital practices. Operators dictated periprocedural anti-coagulation and pre- and post-ablation AADs utilization. Patient discharge was conducted according to local standard-of-care and hospital practices.

Patient follow-up and study endpoints

Follow-up was conducted according to the standard-of-care practice of each hospital. Monitoring of patients was conducted through a combination of telephone communication and in-person appointments. Patients were obligated to attend annual evaluation visits. The rhythm monitoring method was not protocol dictated and included a variety of approaches, including 12-lead electrocardiograms (ECGs), Holter monitors, trans-telephonic monitors, and implanted cardiac devices.

Following a 90-day blanking period, the primary effectiveness of the CBA procedure was assessed by the 24-month freedom from AF and AA (defined as AF, atrial flutter, and atrial tachycardia) lasting at least 30 seconds. Patient baseline characteristics were assessed to determine if they predicted AA recurrence. All adverse events from enrollment to end of follow-up were documented.

All adverse events from enrollment to end of follow-up were documented. The primary safety endpoint was the rate of serious procedure-or device-related adverse events. Events that caused death or a severe decline in health were physician-categorized as serious.

Healthcare utilization was defined as freedom from repeat ablation, cardiovascular-related hospitalization, and cardioversion at 24-months. Predefined AF-related symptoms and QoL, measured by the European Quality of Life-5 Dimensions-3 Levels (EQ-5D-3L), were reviewed at baseline and 24-month follow-up. Utilization of any Class I/III AAD was reviewed at pre-ablation, hospital discharge, and 24-month follow-up.

Statistical analysis

Continuous variables were expressed as mean and standard deviation, while categorical variables were presented as counts and percentages. Baseline and procedural characteristics of PAF and PsAF patients were compared by employing a 2-sample t-test for continuous variables and an exact test for categorical variables. The 24-month freedom from AF recurrence, overall AA recurrence, repeat ablation, rehospitalization, and cardioversion were estimated using the Kaplan-Meier method. The standard error was computed using Greenwood's formula. Separate log-rank tests were conducted to evaluate the AF recurrence rate, overall AA recurrence rate, repeat ablation rate, rehospitalization rate, and cardioversion rate between PAF and PsAF patients. Predictors of AA recurrence were calculated using multivariable Cox regression analysis. Significant predictors from the multivariable analysis were further assessed using Kaplan-Meier methods. Changes in QoL and AF-related symptoms between timepoints were evaluated using a one-sample t-test. McNemar's test was used to assess the AAD prescription in the analysis cohort. Statistical significance was defined as $p<0.05$. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics

A total of 299 patients were enrolled (n=150 PAF and n=149 PsAF). Baseline characteristics are displayed in **Table 1**. Both AF cohorts were similar in age, sex, body mass index, and

Table 1. Patient baseline characteristics

Subject characteristics	PAF (n=150)	PsAF* (n=149)	Total subjects (n=299)	p value†
Age (years)	60±11	61±10	60±11	0.35
Female sex	40 (26.7)	34 (22.8)	74 (24.7)	0.50
Diagnosed with AF (years)	2.3±2.8	3.3±3.1	2.8±3.0	<0.01
Number of failed AADs	1.2±0.7	1.2±0.5	1.2±0.6	0.66
BMI (kg/m^2)	25±3	25±3	25±3	0.09
Left ventricular ejection fraction (%)	61±7	57±9	59±8	<0.01
Left atrial diameter (mm)	41±6	45±7	43±7	<0.01
CHA_2DS_2-VASc score	1.7±1.4	2.0±1.4	1.8±1.4	0.04
Diabetes	23 (15.3)	31 (20.8)	54 (18.1)	0.23
Hypertension	64 (42.7)	88 (59.1)	152 (50.8)	<0.01
History of atrial flutter	35 (23.3)	28 (18.8)	63 (21.1)	0.40
History of atrial tachycardia	6 (4.0)	1 (0.7)	7 (2.3)	0.12
Prior atrial flutter ablation	3 (2.0)	0 (0.0)	3 (1.0)	0.25
Prior PVI	0 (0.0)	0 (0.0)	0 (0.0)	NA
Prior myocardial infarction	1 (0.7)	3 (2.0)	4 (1.3)	0.37
Prior stroke/transient ischemic attack	16 (10.7)	14 (9.4)	30 (10.0)	0.85
History of coronary artery disease	21 (14.0)	7 (4.7)	28 (9.4)	<0.01

Values are presented as number (%) or mean ± standard deviation.
AAD = antiarrhythmic drug; AF = atrial fibrillation; BMI = body mass index; NA = not available; PAF = paroxysmal atrial fibrillation; PsAF = persistent atrial fibrillation; PVI = pulmonary vein isolation.
*PsAF and long-standing-PsAF patient data pooled; †The t-test for continuous variables, Fisher's exact test for binary variables.

number of failed AADs at baseline. PAF patients were diagnosed with AF for a significantly shorter duration (2.3±2.8 years) than PsAF patients (3.3±3.1 years, p<0.01). The PAF cohort had a larger left ventricular ejection fraction (61±7% vs. 57±9%, p<0.01), smaller LAD (41±6 mm vs. 45±7 mm, p<0.01), lower CHA_2DS_2-VASc score (1.7±1.4 vs. 2.0±1.4, p=0.04), and lower proportion of patients with hypertension (42.7% vs. 59.1%, p<0.01) compared to PsAF patients. However, coronary artery disease (14.0% vs. 4.7%, p<0.01) occurred more often in PAF compared to PsAF patients.

Procedural characteristics

The procedural characteristics are presented in **Table 2**. The total procedure time in the PAF group was shorter than the in the PsAF group (71±17 minutes vs. 82±23 minutes, p<0.01). Similarly, left atrial dwell time (48±17 minutes vs. 63±25 minutes) and total fluoroscopy time (23±14 vs. 31±29, p<0.01 for both) were shorter in the PAF cohort compared to PsAF patients. Esophageal temperature monitoring was performed in 117 (78%) PAF patients and 78 (52.3%) PsAF patients, while phrenic nerve monitoring via pacing and palpation of the phrenic nerve was performed in all (100%) patients. The PAF cohort underwent less imaging assessment, such as pre-procedural computed tomography or magnetic resonance imaging (56.0% vs. 71.8%) and intracardiac echocardiography (ICE; 42.7% vs. 62.4%), in comparison to the PsAF cohort (p<0.01 for both). Overall, a high rate of acute PVI was successfully achieved, with 97.3% in the PAF group and 98.7% in the PsAF group (p=0.68). Non-pulmonary vein (PV) ablations were not statistically different between the AF cohorts (p=1.0).

A total of 1209 veins were treated, with an average of 1.5±1.0 applications per vein. PAF patients experienced shorter cryoapplications (159±51 vs. 175±57 seconds, p<0.001) in comparison to PsAF patients (**Supplementary Table 1**). Following CBA, no patients were discharged on the same day as the procedure, and the total length of hospital stay did not vary between PAF and PsAF patients (1.2±1.0 vs. 1.1±0.6 days, p=0.36, **Supplementary Table 2**).

Table 2. Procedural characteristics

Procedure characteristics	PAF (n=150)	PsAF* (n=149)	Total subjects (n=299)	p value†
Total procedure time‡ (minutes)	71±17	82±23	76±21	<0.01
Left atrial dwell time§ (minutes)	48±17	63±25	56±23	<0.01
Total fluoroscopy time (minutes)	23±14	31±29	27±23	<0.01
Esophageal temperature monitored	117 (78.0)	78 (52.3)	195 (65.2)	<0.01
Phrenic nerve monitored	150 (100.0)	149 (100.0)	299 (100.0)	1.00
Pacing/palpate	150 (100.0)	149 (100.0)	299 (100.0)	
Diaphragm stimulation	30 (20.0)	72 (48.3)	102 (34.1)	
CMAP	62 (41.3)	36 (24.2)	98 (32.8)	
Pre-procedural CT or MRI	84 (56.0)	107 (71.8)	191 (63.9)	<0.01
Intracardiac echocardiography	64 (42.7)	93 (62.4)	157 (52.5)	<0.01
Successful PVI	146 (97.3)	147 (98.7)	293 (98.0)	0.68
Non-PV ablations	4 (2.7)	4 (2.7)	8 (2.7)	1.00
Left-sided trigger	1 (0.7)	3 (2.0)	4 (1.3)	
Superior vena cava trigger	2 (1.3)	0 (0.0)	2 (0.7)	
Other (1 PSVT, 1 LV anterior wall ablation)	1 (0.7)	1 (0.7)	2 (0.7)	
Cavotricuspid isthmus ablation	28 (18.7)	38 (25.5)	66 (22.1)	

Values are presented as number (%) or mean ± standard deviation.
CMAP = Compound Motor Action Potential; CT = computerized tomography; LV = left ventricle; MRI = magnetic resonance imaging; PAF = paroxysmal atrial fibrillation; PsAF = persistent atrial fibrillation; PSVT = paroxysmal supraventricular tachycardia; PV = pulmonary vein; PVI = pulmonary vein isolation.
*PsAF and long-standing-PsAF patient data pooled.
†The t-test for continuous variables, Fisher's exact test for binary variables.
‡Total procedure time is defined as time of first venous access to time of last cryocatheter removal.
§Left atrium dwell time is defined as time from first cryoablation catheter insertion to last cryoablation catheter removal.

Efficacy

Recurrence of arrhythmias

Following a 90-day blanking period, freedom from ≥30 second recurrence of AF and AA at 24 months occurred in 79.2% (95% confidence interval [CI], 71.8–84.9%) and 71.9% (95% CI, 64.0–78.4%) of the PAF cohort compared to 54.8% (95% CI, 46.4–62.5%) and 49.3% (95% CI, 41.0–57.1%) in the PsAF cohort, respectively (**Figure 1A and B**). PsAF patients experienced significantly more AF and AA recurrence than PAF patients (p<0.01 for both). AF occurred as the first type of arrhythmia recurrence in nearly half (41.6%) of the PsAF cohort and only 13.3% of the PAF cohort (**Figure 1C**).

Predictors of atrial arrhythmia recurrence

Using multivariable Cox regression analysis, PsAF (hazard ratio [HR], 1.70; 95% CI, 1.10–2.63; p<0.01), LAD >43 mm (HR, 1.04; 95% CI, 1.01–1.07; p=0.01), and longer time-to-ablation (HR, 1.30; 95% CI, 1.07–1.58; p<0.01) were found to be independent predictors of AA recurrence (**Supplementary Table 3**). To depict the relationship between LAD and AA recurrence (**Figure 2A**), a cutoff value of 43 mm (median LAD) was utilized to divide the cohort into 2 sub-groups: LAD <43 mm and LAD ≥43 mm. Freedom from AA recurrence at 24

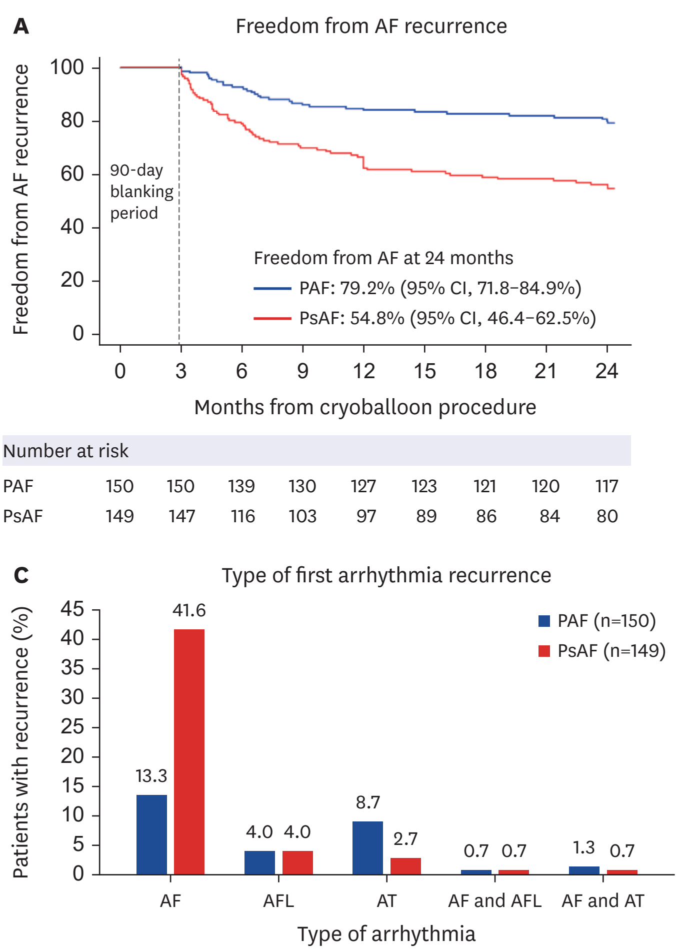
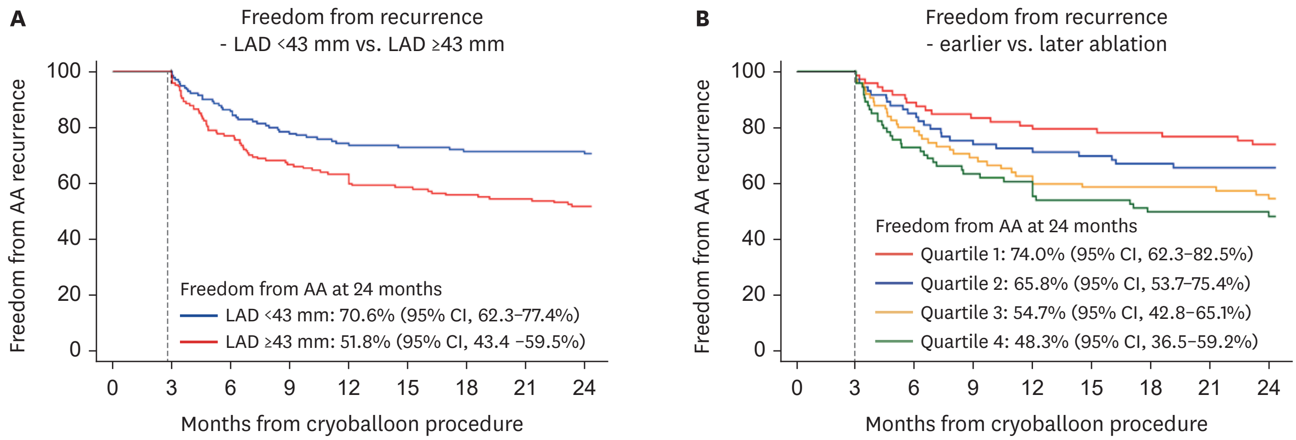


Figure 1. Freedom from AA recurrence at 24 months. Kaplan-Meier estimate of 24-month freedom from ≥30-second recurrences of (A) AF and (B) AA after a 90-day blanking period in PAF (blue line) and PsAF (red line) patients treated with cryoballoon ablation (PAF vs. PsAF, p<0.01 for both). (C) Type of first arrhythmia recurrence in patients with PAF (blue bars) and PsAF (red bars). Data from PsAF and long-standing PsAF patients are pooled.
AA = atrial arrhythmia; AF = atrial fibrillation; CI = confidence interval; PAF = paroxysmal atrial fibrillation; PsAF = persistent atrial fibrillation.



Number at risk									
LAD <43 mm	140	140	121	110	104	100	97	96	96
LAD ≥43 mm	150	148	113	99	93	86	82	80	76

Number at risk									
Quartile 1	74	73	65	62	59	58	57	56	54
Quartile 2	74	74	62	55	53	50	48	47	47
Quartile 3	76	75	60	52	47	44	44	44	42
Quartile 4	74	74	54	47	45	39	35	34	34

Figure 2. Freedom from recurrence from AA recurrence depending on LAD and time of ablation. Kaplan-Meier estimate of 24-month freedom from ≥30-second recurrences of AA after a 90-day blanking period depending on (A) LAD and (B) timing of cryoballoon ablation. A total of 290/299 patients were divided into LAD <43 mm (blue line) and LAD ≥43 mm (red line) groups. A total of 298/299 patients were stratified based on quartiles for AF diagnosis to ablation time (quartile 1: 0–7.5 months, red line [n=74]; quartile 2: 7.6–20.1 months, blue line [n=74]; quartile 3: 20.2–49.0 months, yellow line [n=76]; and quartile 4: 49.1–164.9 months, green line [n=74]). LAD and AF diagnosis to ablation time is significantly associated with AF/atrial tachycardia/AFL recurrence (p<0.01 for both).
AA = atrial arrhythmia; AF = atrial fibrillation; AFL = atrial flutter; CI = confidence interval; LAD = left atrial diameter.

months was 70.6% (95% CI, 62.3–77.4%) in the LAD <43 mm cohort (n=140) and 51.8% (95% CI, 43.4 –59.5%) in the LAD ≥43 mm cohort (n=150).

To depict longer time from AF diagnosis, subjects were divided into quartiles based on time from AF diagnosis to enrollment in the study. Time from diagnosis to ablation quartiles were 0 to 7.5 months, 7.6 to 20.1 months, 20.2 to 49.0 months, and 49.1 to 164.9 months. Notably, freedom from recurrence at 24 months increased significantly with shorter durations from diagnosis to CBA, measuring 74.0% (95% CI, 62.3–82.5%), 65.8% (95% CI, 53.7–75.4%), 54.7% (95% CI, 42.8–65.1%), and 48.3% (95% CI, 36.5–59.2%) from quartile 1 to 4, respectively (p<0.01).

Safety

As presented in **Table 3**, Two serious device- or procedure-related adverse events were observed in 2 PAF patients (0.7%), including an incision site hematoma and a vascular pseudoaneurysm. Of note, no atrioesophageal fistula, pericardial tamponade, and PV stenosis were reported, and all 3 cases of phrenic nerve injuries (PNIs, 1.0%) were resolved within 6 months post-ablation. There were 2 events in the primary safety outcome in the PAF group, but fewer serious non-procedure-related events occurred in the PAF group.

Patient follow-up and antiarrhythmic drug usage

AAD usage significantly decreased from 82.9% at procedure discharge to 59.8% at 24-month follow-up (p<0.001, **Figure 3A**). However, PAF patients were prescribed AADs at lower rate at 24 months (49.7% vs. 70.2%, p<0.001). **Figure 3B** displays the type and frequency of rhythm monitoring performed in patients during the follow-up period. Patients were monitored an average of 4.7 times, with all patients undergoing at least one 12-lead ECG. Furthermore,

Table 3. Safety events

Adverse events	PAF (n=150)	PsAF (n=149)	Total subjects (n=299)	p value†
Serious device-or-procedure-related adverse events	2 (2, 1.3)	0 (0, 0.0)	2 (2, 0.7)	0.50
Vascular pseudoaneurysm	1 (1, 0.7)	0 (0, 0.0)	1 (1, 0.3)	
Incision site hematoma	1 (1, 0.7)	0 (0, 0.0)	1 (1, 0.3)	
Non-serious procedure-related adverse events	4 (3, 2.0)	1 (1, 0.7)	5 (4, 1.3)	0.62
Phrenic nerve injury	2 (2, 1.3)	1 (1, 0.7)	3 (3, 1.0)	
Urinary retention	1 (1, 0.7)	0 (0, 0.0)	1 (1, 0.3)	
Haemoptysis	1 (1, 0.7)	0 (0, 0.0)	1 (1, 0.3)	
Serious non-procedure-related adverse events	28 (22, 14.7)	75 (53, 35.6)	103 (75, 25.1)	<0.001
Appendicitis	0 (0, 0.0)	1 (1, 0.7)	1 (1, 0.3)	
Arrhythmia supraventricular	1 (1, 0.7)	2 (2, 1.3)	3 (3, 1)	
Atrial fibrillation	12 (12, 8.0)	51 (37, 24.8)	63 (49, 16.4)	
Atrial flutter	2 (2, 1.3)	6 (6, 4.0)	8 (8, 2.7)	
Atrioventricular block first degree	0 (0, 0.0)	1 (1, 0.7)	1 (1, 0.3)	
Cardiac failure	1 (1, 0.7)	0 (0, 0.0)	1 (1, 0.3)	
Cerebral hemorrhage	0 (0, 0.0)	1 (1, 0.7)	1 (1, 0.3)	
Chest pain	0 (0, 0.0)	1 (1, 0.7)	1 (1, 0.3)	
Cholecystitis acute	1 (1, 0.7)	0 (0, 0)	1 (1, 0.3)	
Coronary artery disease	0 (0, 0.0)	1 (1, 0.7)	1 (1, 0.3)	
Coronary artery stenosis	0 (0, 0.0)	1 (1, 0.7)	1 (1, 0.3)	
Femoral neck fracture	1 (1, 0.7)	0 (0, 0.0)	1 (1, 0.3)	
Gastritis	1 (1, 0.7)	0 (0, 0.0)	1 (1, 0.3)	
Hematochezia	0 (0, 0.0)	1 (1, 0.7)	1 (1, 0.3)	
Hashimoto's encephalopathy	1 (1, 0.7)	0 (0, 0.0)	1 (1, 0.3)	
Hypertrophic cardiomyopathy	1 (1, 0.7)	0 (0, 0.0)	1 (1, 0.3)	
Inguinal hernia	0 (0, 0.0)	1 (1, 0.7)	1 (1, 0.3)	
Mitral valve incompetence	1 (1, 0.7)	0 (0, 0.0)	1 (1, 0.3)	
Pneumonia	2 (2, 1.3)	1 (1, 0.7)	3 (3, 1)	
Quadriplegia	0 (0, 0.0)	1 (1, 0.7)	1 (1, 0.3)	
Sinus node dysfunction	2 (2, 1.3)	3 (3, 2.0)	5 (5, 1.7)	
Thermal burn	1 (1, 0.7)	0 (0, 0.0)	1 (1, 0.3)	
Traumatic hemothorax	0 (0, 0.0)	1 (1, 0.7)	1 (1, 0.3)	
Urinary tract infection	0 (0, 0.0)	1 (1, 0.7)	1 (1, 0.3)	
Ventricular extrasystoles	0 (0, 0.0)	1 (1, 0.7)	1 (1, 0.3)	
Ventricular tachycardia	1 (1, 0.7)	0 (0, 0.0)	1 (1, 0.3)	

Results are presented as number of events (number of subjects, % subjects).
PAF = paroxysmal atrial fibrillation; PsAF = persistent atrial fibrillation.
†Exact test.

ECG monitoring was performed 3 or more times in 89.0% of the study population. Holter and continuous monitoring was utilized in 193 (64.5%) and 27 patients (9%), respectively (**Supplementary Table 4**).

Arrhythmia symptoms and quality of life

At baseline, 75.5% of patients reported one or more symptoms, with palpitations being the most prevalent. Twenty-four-months post CBA, the symptom burden significantly decreased to 10.5%, with no cases of rapid heartbeat, fatigue, or syncope reported (**Figure 3C**). According to the EQ-5D index and visual analog scale (VAS) scores, PAF patients had a lower QoL at baseline in comparison to PsAF patients ($p<0.01$ for both, **Table 4**). However, QoL improvement from baseline to 24-month follow-up was not statistically different between PAF and PsAF patients for both the EQ-5D index ($p=0.75$) and VAS scores ($p=0.12$).

Healthcare utilization

Regarding healthcare utilization at 24 months, the PAF group experienced a higher freedom from repeat ablations (93.9%; 95% CI, 88.7–96.8% vs. 81.4%; 95% CI, 74.0–86.8%) and

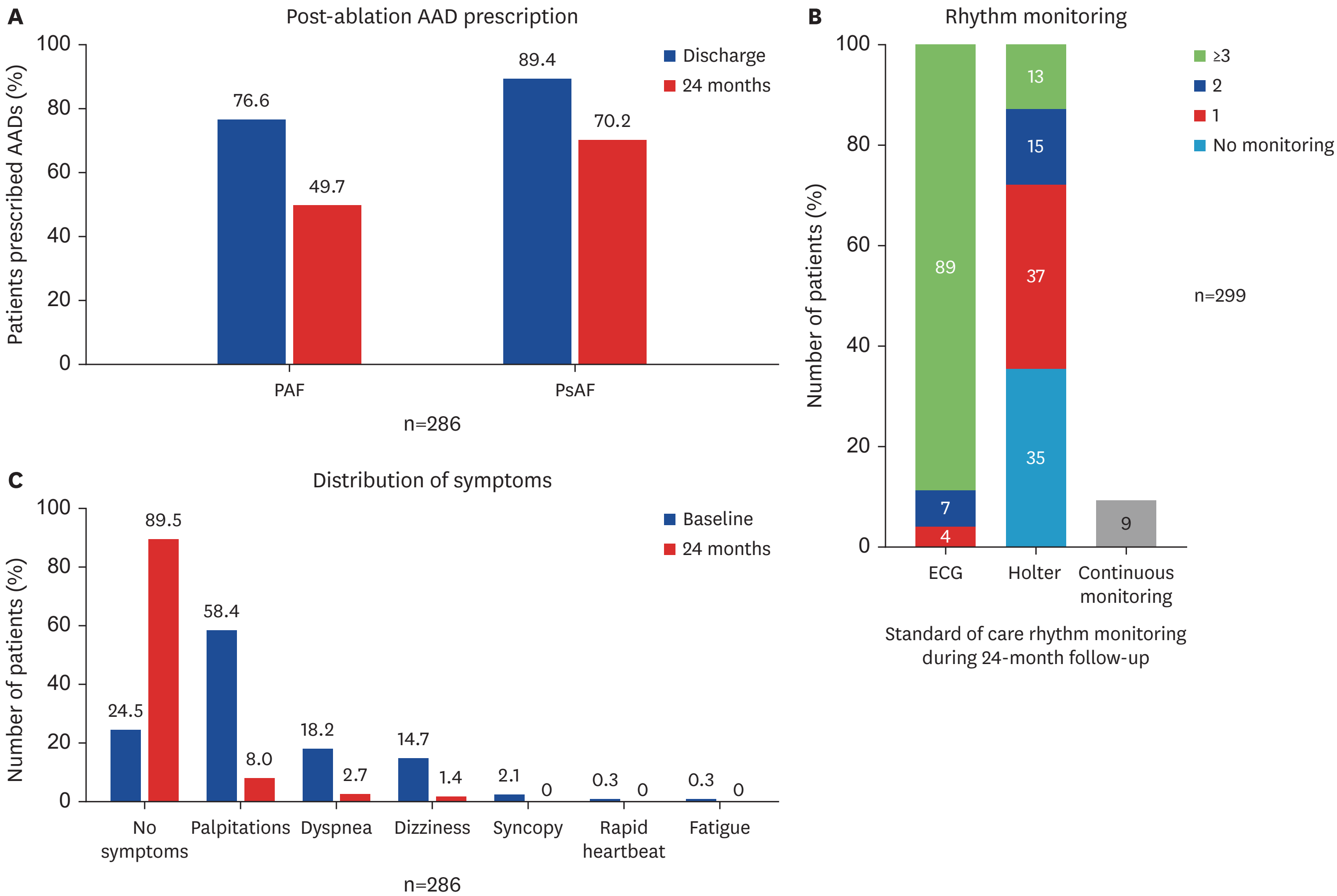


Figure 3. Post-procedure follow-up and AF-related symptoms. (A) AAD prescription in 286/299 PAF and PsAF patients at discharge (blue bars) and at 24 months (red bars). (B) Percentage of 299 patients monitored for atrial arrhythmia recurrences with none (aqua), one (red), 2 (blue) or 3 or more (green) 12-lead ECGs or Holter monitoring events over the 12-month follow-up period. Proportion of patients with continuous monitoring (pacemaker/implantable cardiac monitor) are shown in gray. (C) Distribution of AF-related symptoms in 286/299 patients at baseline (blue bars) and 24 months (red bars).
AAD = antiarrhythmic drug; AF = atrial fibrillation; ECG = electrocardiogram; PAF = paroxysmal atrial fibrillation; PsAF = persistent atrial fibrillation.

Table 4. Quality of life

	PAF (n=144)	PsAF (n=141)	p value
EQ-5D index (n=285*)			
Baseline	0.78±0.24	0.86±0.22	<0.01†
24 months	0.92±0.17	0.94±0.14	0.75‡
Absolute difference	0.14±0.25	0.09±0.23	
VAS (n=285*)			
Baseline	74±17	81±12	<0.01†
24 months	71.2±17.9	76.5±16.3	0.12‡
Absolute difference	80.0±11.1	82.9±11.4	

EQ-5D = European Quality of Life-5 Dimensions; PAF = paroxysmal atrial fibrillation; PsAF = persistent atrial fibrillation; VAS = visual analogue scale.
*The 285/299 subjects completed an EQ-5D questionnaire at baseline and 24 months.
†The t-test comparing EQ-5D score/VAS score at baseline between PAF and PsAF.
‡Linear model, dependent variable change in EQ5D/VAS, covariates = baseline atrial fibrillation type, baseline EQ-5D score/VAS score.

cardiovascular-related hospitalization (91.3%; 95% CI, 85.4–94.8% vs. 72.5%; 95% CI, 64.4–79.0%) in comparison to the PsAF group (p<0.001 for both, **Figure 4A and B**). Freedom from cardioversion did not vary between the AF cohorts (p=0.115, **Figure 4C**).

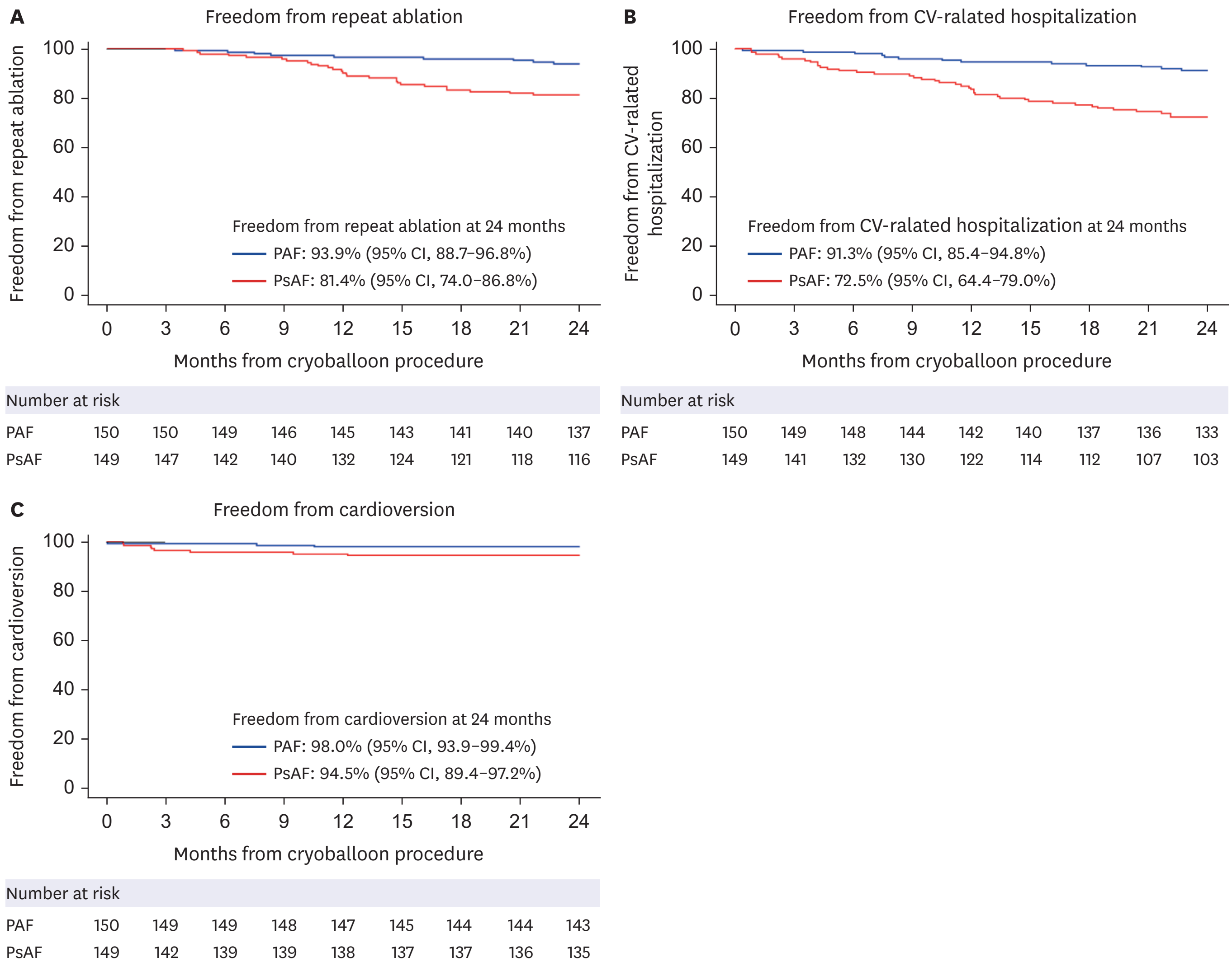


Figure 4. Freedom from repeat ablations, hospitalization, and cardioversions at 24 months. Kaplan-Meier estimate of 24-month freedom from (A) repeat ablation, (B) CV-related hospitalization, and (C) cardioversion in PAF (blue lines) and PsAF (red lines) patients treated with cryoballoon ablation.
CI = confidence interval; CV = cardiovascular; PAF = paroxysmal atrial fibrillation; PsAF = persistent atrial fibrillation.

DISCUSSION

Long-term outcomes of CBA in the Asian population have been under-investigated. Therefore, the aim of this sub-analysis of the Cryo Global Registry was to address this evidence disparity. This work is the first multicenter study to evaluate 2-year outcomes of CBA in real-world clinical practice in Korea. The data showed not only that CBA is efficacious and safe in PAF and PsAF patients, but also, the data demonstrated that the treatment reduced AAD usage, improved patient QoL, and decreased healthcare utilization post-ablation. Moreover, lower freedom from AA recurrence following CBA was found to be significantly associated with a LAD ≥43 mm and increased time from AF diagnosis to ablation. These results were further supported in PsAF patients, who had a significantly longer AF diagnosis duration and a larger LAD (45±7 mm), experienced higher AF and AA recurrence at 24 months compared to PAF patients. The predictors of AF recurrence identified in the Korean population after CBA (baseline AF type, time-to-ablation, and LAD) were congruent with predictors identified in a recent meta-analysis of predictors of recurrence after CBA.[7)]

The Korea cohort of the Cryo Global Registry differs from the global cohort in efficacy and safety.[8)] CBA was more efficacious in preventing AA recurrence in PAF than PsAF patients in both the global and Korean cohorts; however, despite PAF patients in the Korean cohort having a shorter AF diagnosis to ablation time (2.3±2.8 years vs. 3.2±4.3 years), they experienced a lower efficacy rate (71.9% vs. 86.4%) in comparison to patients in the global population. Yet, patients in the Korean cohort were monitored more frequently, with 89% of the group undergoing 3 or more 12-lead ECGs over 24 months in comparison to only 37% of the global group. Additionally, only 79.9% of the global cohort were monitored at least once during the follow-up period in comparison to 100% of the Korean cohort. Thus, the lower treatment success observed in the Korean cohort could be due to more recurrent AAs being detected as a result of a more rigorous monitoring strategy.

Despite, these differences in efficacy, patients from both cohorts reported a significant improvement in QoL from baseline to follow-up. Fewer patients suffered a serious procedure-related adverse event in the Korean cohort (0.7%) in comparison to the global cohort (3.4%), with 0.5% of the latter and 0% of the former experiencing PNI. Although phrenic nerve monitoring was performed in 99.1% of the 2,922 global patients; only 87.9% received pacing/palpate monitoring in comparison to 100% of Korean patients. Though none of the modalities have been successful in preventing PNI, using Compound Motor Action Potential (CMAP) has been shown to effectively reduce PNI. Therefore, it is anticipated that incorporating CMAP alongside pacing/palpation could prevent PNI, leading to safer cryoablation procedures.[9)]

Although the utilization of esophageal temperature monitoring varied greatly between the 2 cohorts (65.2% Korea vs. 37.3% global); neither group was afflicted with an atrioesophageal fistula. The absence of cardiac tamponade in the Korean population (but presence within 0.4% of the global population) could be due to the increased utilization of ICE (52.5% vs. 26.3%) in the Korean sub-study. In addition to cardiac tamponade, ICE can assist in diminishing pericardial effusion, PV stenosis, and atrioesophageal fistulas by providing clinicians with real-time visualization of cardiac anatomy and catheter positioning.[9-11)] In a meta-analysis of 19 catheter ablation studies, a trend for decreasing complication was observed in studies that utilized ICE vs. those that did not; however, due to the infrequency of peri-procedural complications, it is difficult to assess if the absence of ICE significantly leads to more adverse events.[9)]

Outcomes in the Korean cohort are comparable to 12- and 24-month results from other regional analyses of Asian populations.[12-15)] Following a 2-year follow-up, Kimura et al.[12)] observed that 86.7% of a Japanese PAF cohort experienced freedom from AA post CBA. Although this result is higher than our PAF efficacy rate, the Japanese study[12)] only conducted rhythm monitoring for about 2/3 of the patients while 100% of our study cohort underwent at least one 12-lead ECG. Given this aspect, the 24-month performance of PAF patients in our study is adequately comparable. Similar to our results, Choi et al.[13)] reported a significant difference in efficacy rates between Korean PAF and PsAF patients treated with CBA (80.4% vs. 56.2%). Furthermore, a study in Taiwan demonstrated that PsAF patients are at greater risk for AF recurrence following CBA in comparison to PAF patients, with only 51.5% of PsAF remaining free of AF at 12-month follow-up.[14)] In terms of patient follow-up care, our study varied greatly from a single-center study in Korea, in which only a mere 9.0% of patients were administered AADs at discharge; however, after a mean follow-up of 9.8±5.1 months, AAD utilization increased to 21.8%.[15] Whereas, our study witnessed a decrease in AAD utilization 24 months post CBA. This discrepancy in regional standard-of-care can be attributed to a center effect, and this variation is further elucidated by a registry analysis of 1,261 patients in East Asia (including China, Japan, South Korea, and Taiwan) that reported AADs being prescribed at discharge to 52.9% of the study population.[16]

This study demonstrated that an increased time from AF diagnosis to ablation and a LAD ≥43 mm leads to lower freedom from AA recurrence. There is no definitive criterion for the cut-off value of LAD that impacts AA recurrence post-cryoablation, and thus, there are a variety of values proposed in literature. While a retrospective, single-center study of American patients determined that LAD >40 mm is a predictor of AA recurrence[17]; a global meta-analysis found the cutoff to be 45 mm.[18] Though there are fewer studies among Asian patients, a retrospective study conducted in Taiwan concluded a LAD ≥47 mm put patients at greater risk for AA recurrence post CBA.[14] However, since there are various prognostic factors affecting the recurrence of AA, further investigation is necessary to determine a conclusive cut-off value.

All 4 aforementioned studies also ascertained that a lengthy duration of AF before ablation and/or PsAF is a predictor of AA recurrence. Subsequently, the impact of diagnosis-to-ablation time on recurrence is well recognized.[19,20] In this study we observed a meaningful decrease in the freedom from AA as the diagnosis-to-ablation time increased, confirming the significant univariate nature of AF persistency in relation to recurrence that has been witnessed previously in PsAF patients.[21] The predictive capacity of recurrence for LAD and time of intervention is likely connected with atrial remodeling, which has been thought to lead to continuing electrical volatility in the atria.[6] Neumann et al.[22] even identified LAD as the sole predictor of sinus rhythm maintenance in PAF patients treated with CBA within 5 years. Atrial fibrosis in the LA drives AF progression, is higher in PsAF patients, and is associated with a higher rate of recurrence.[23,24] An enlarged LA and prolonged progression of AF promote PV reconnections, electrical and structural remodeling, and prevents effective electrical isolation of the AF substrate.[25] In fact, the 2012 HRS/EHRA/ECAS Consensus Statement on Catheter and Surgical Ablation of AF established LAD and AF classification (i.e., PAF, PsAF, and LsPsAF) as the top 2 predictors of recurrence, which is consistent with the data from this current Korean study of longer-term efficacy.[6]

This study has several limitations. Firstly, there was no established protocol for rhythm monitoring, which is crucial for evaluating efficacy. However, 12-lead ECG was performed 3 or more times during the follow-up period in 89% of patients. Holter monitoring was conducted in 64% of patients and continuous monitoring was performed in 9% of patients. These monitoring protocols were found to be comparable to those used in the Cryo-FISRT, EARLY-AF, and STOP-AF First studies, which investigated CBA as a first-line treatment for AF.[26-28] Furthermore, monitoring was performed at least once in 100% of the study population. (**Supplementary Table 4**). Secondly, this is a real-world data that reflects standard of care. The reason for the use of certain ablation techniques, ablation target, or ablation parameters is not collected. Thirdly, while it has been demonstrated that LAD and time of diagnosis to cryoablation have a significant impact on the recurrence of AA, the study did not account for potential interactions of LAD with other variables that might influence recurrence. Also, women accounted for a relatively small proportion of the overall patient population at 24.7%. However, considering the fact that gender did not have a significant impact on the 24-month efficacy and safety outcomes of the Cryo Global Registry,[29] this is a minor issue. Lastly, though this analysis demonstrates the safety of CBA, the low incidence of adverse events precludes conclusive evidence of significant differences between PAF and PsAF groups.

This study demonstrates that CBA is a safe and effective treatment that reduces symptom burden and improves QoL for PAF and PsAF patients in Korea. Furthermore, with the established relationship between the recurrence rate of AA, LAD, and the time from diagnosis to cryoablation, early application of CBA for AF patients could be expected to lead to a more favorable prognosis.

ACKNOWLEDGMENTS

The authors sincerely thank the Cryo Global Registry Korea site staff for their commitment and contributions to the study. The authors also thank Jihyun Jung, Hae Lim, and Ryan Radtke from Medtronic for their support of the trial and generation of this manuscript.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Cryo energy application

Supplementary Table 2
Length of hospital stay post-ablation

Supplementary Table 3
Multivariable Cox regression analysis: predictors of atrial arrhythmia recurrence

Supplementary Table 4
Monitoring methods per atrial fibrillation type

REFERENCES

1. Lee SR, Choi EK, Han KD, Cha MJ, Oh S. Trends in the incidence and prevalence of atrial fibrillation and estimated thromboembolic risk using the CHA_2DS_2-VASc score in the entire Korean population. *Int J Cardiol* 2017;236:226-31. PUBMED | CROSSREF
2. Andrade JG, Wells GA, Deyell MW, et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. *N Engl J Med* 2021;384:305-15. PUBMED | CROSSREF
3. Kuck KH, Fürnkranz A, Chun KR, et al. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. *Eur Heart J* 2016;37:2858-65. PUBMED | CROSSREF
4. Ganesan AN, Shipp NJ, Brooks AG, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc* 2013;2:e004549. PUBMED | CROSSREF
5. Lim HE, Oh IY, Kueffer FJ, van Bragt KA, On YK. Cryoballoon catheter ablation in Korean patients with paroxysmal and persistent atrial fibrillation: one year outcome from the Cryo Global Registry. *Korean Circ J* 2022;52:755-67. PUBMED | CROSSREF
6. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* 2024;149:e1-156. PUBMED | CROSSREF

7. Song W, Lv T, Zhang N, Li G, Tse G, Liu T. Long-term efficacy and safety of cryoballoon ablation of atrial fibrillation: a systematic review and meta-analysis. *Pacing Clin Electrophysiol* 2024;47:49-57. PUBMED | CROSSREF

8. Chun KR, Okumura K, Scazzuso F, et al. Safety and efficacy of cryoballoon ablation for the treatment of paroxysmal and persistent AF in a real-world global setting: results from the Cryo AF Global Registry. *J Arrhythm* 2021;37:356-67. PUBMED | CROSSREF

9. Goya M, Frame D, Gache L, et al. The use of intracardiac echocardiography catheters in endocardial ablation of cardiac arrhythmia: meta-analysis of efficiency, effectiveness, and safety outcomes. *J Cardiovasc Electrophysiol* 2020;31:664-73. PUBMED | CROSSREF

10. Kuwahara T. Intracardiac echocardiography in catheter ablation for atrial fibrillation: it is better to see what you are doing? *J Atr Fibrillation* 2015;7:1215. PUBMED

11. Dello Russo A, Russo E, Fassini G, et al. Role of intracardiac echocardiography in atrial fibrillation ablation. *J Atr Fibrillation* 2013;5:786. PUBMED

12. Kimura M, Kobori A, Nitta J, et al. Cryoballoon ablation for paroxysmal atrial fibrillation in Japan: 2-year safety and efficacy results from the Cryo AF Global Registry. *J Interv Card Electrophysiol* 2022;64:695-703. PUBMED | CROSSREF

13. Choi JH, Park SJ, Park KM, Kim JS, On YK. Efficacy and safety of cryoballoon pulmonary vein isolation for paroxysmal and persistent atrial fibrillation: a comparison with radiofrequency ablation. *PLoS One* 2022;17:e0265482. PUBMED | CROSSREF

14. Wu SJ, Li CH, Weng CJ, et al. Efficacy of cryoballoon ablation for atrial fibrillation and recurrence predictors in an asian cohort. *J Pers Med* 2022;12:732. PUBMED | CROSSREF

15. Pak HN, Park JW, Yang SY, et al. Cryoballoon versus high-power, short-duration radiofrequency ablation for pulmonary vein isolation in patients with paroxysmal atrial fibrillation: a single-center, prospective, randomized study. *Circ Arrhythm Electrophysiol* 2021;14:e010040. PUBMED | CROSSREF

16. Scazzuso F, Ptaszynski P, Kaczmarek K, et al. Regional variations in patient selection and procedural characteristics for cryoballoon ablation of atrial fibrillation in the Cryo Global Registry. *J Interv Card Electrophysiol* 2023;67:493-501. PUBMED | CROSSREF

17. Bavishi AA, Kaplan RM, Peigh G, et al. Patient characteristics as predictors of recurrence of atrial fibrillation following cryoballoon ablation. *Pacing Clin Electrophysiol* 2019;42:694-704. PUBMED | CROSSREF

18. Quan D, Huang H, Kong B, Li Q, Liao J, Wang G. Predictors of late atrial fibrillation recurrence after cryoballoon-based pulmonary vein isolation: a meta-analysis. *Kardiol Pol* 2017;75:376-85. PUBMED | CROSSREF

19. Lawin D, Stellbrink C, Chun K, et al. Efficacy and safety outcomes of early versus late cryoballoon ablation of atrial fibrillation-24-months-results from the Cryo Global Registry. *EP Europace* 2023;25:euad122.682. CROSSREF

20. Chew DS, Black-Maier E, Loring Z, et al. Diagnosis-to-ablation time and recurrence of atrial fibrillation following catheter ablation: a systematic review and meta-analysis of observational studies. *Circ Arrhythm Electrophysiol* 2020;13:e008128. PUBMED | CROSSREF

21. Ciconte G, Ottaviano L, de Asmundis C, et al. Pulmonary vein isolation as index procedure for persistent atrial fibrillation: one-year clinical outcome after ablation using the second-generation cryoballoon. *Heart Rhythm* 2015;12:60-6. PUBMED | CROSSREF

22. Neumann T, Wójcik M, Berkowitsch A, et al. Cryoballoon ablation of paroxysmal atrial fibrillation: 5-year outcome after single procedure and predictors of success. *Europace* 2013;15:1143-9. PUBMED | CROSSREF

23. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA* 2014;311:498-506. PUBMED | CROSSREF

24. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002;54:230-46. PUBMED | CROSSREF

25. Helms AS, West JJ, Patel A, et al. Relation of left atrial volume from three-dimensional computed tomography to atrial fibrillation recurrence following ablation. *Am J Cardiol* 2009;103:989-93. PUBMED | CROSSREF

26. Su WW, Reddy VY, Bhasin K, et al. Cryoballoon ablation of pulmonary veins for persistent atrial fibrillation: results from the multicenter STOP Persistent AF trial. *Heart Rhythm* 2020;17:1841-7. PUBMED | CROSSREF

27. Chierchia GB, Pavlovic N, Velagic V, et al. Quality of life measured in first-line therapy during the Cryo-FIRST study: a comparison between cryoballoon catheter ablation versus antiarrhythmic drug therapy. *Eur Heart J* 2020;41:ehaa946.0436. CROSSREF

28. Andrade JG, Champagne J, Deyell MW, et al. A randomized clinical trial of early invasive intervention for atrial fibrillation (EARLY-AF) - methods and rationale. *Am Heart J* 2018;206:94-104. PUBMED | CROSSREF

29. Khelae SK, Kyoung-Ryul Chun J, Drephal C, et al. PO-679-05 differences in atrial fibrillation cryoballoon ablation by gender: 24-month outcomes from the Cryo AF Global Registry. *Heart Rhythm* 2022;19:S354-5. CROSSREF