

Original Research



Real-World Outcomes of Cryoballoon vs. Radiofrequency Ablation in Atrial Fibrillation: A Multicenter Propensity-Matched Analysis of Short- and Long-term Efficacy

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OPEN ACCESS

Received: Jun 24, 2025

Revised: Feb 14, 2026

Accepted: Mar 4, 2026

Published online: Mar 25, 2026

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AUTHOR'S SUMMARY

Despite the widespread use of both cryoballoon ablation and radiofrequency ablation in atrial fibrillation, limited real-world data exist comparing their long-term outcomes. This multicenter propensity-matched analysis addresses this unmet need by evaluating efficacy across diverse subgroups over a 3-year period. Our findings provide clinically relevant insights into the durability of rhythm control strategies and inform decision-making tailored to individual patient profiles.

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Funding

This research was supported by the Korean Heart Rhythm Society (KHRS 2021-3).

Conflict of Interest

The authors have no financial conflicts of interest.

Data Sharing Statement

The data analyzed during the current study are not publicly available due to restrictions imposed by the Institutional Review Board to protect participant privacy and confidentiality. Sharing of data is not permitted under the terms of the ethical approval granted for this study.

Author Contributions

Conceptualization: Kim Y, Jeong JH, Park J, Kim DH, Shim J; Data curation: Kim Y, Jeong JH, Lim HE, Oh IY, Cha MJ, Lee SR, Kim JY, Kwon CH, Lee SH, Kim KH, Yang PS, Kim JH, Roh SY, Park J, Kim DH, Shim J; Formal analysis: Kim Y, Jeong JH, Kim DH,

ABSTRACT

Background and Objectives: Thermal energy-based catheter ablation techniques, including cryoballoon ablation (CBA) and radiofrequency ablation (RFA), are widely utilized for rhythm control in patients with atrial fibrillation. However, direct comparisons of CBA and RFA using real-world data are limited. This study aims to evaluate the short- and long-term outcomes of CBA and RFA.

Methods: A total of 4,868 patients who underwent procedures between January 2018 and July 2022 were selected from the Korean CBA Registry and a multicenter RFA cohort. The primary outcome was the atrial tachyarrhythmia recurrence. To reduce selection bias, 1:1 propensity score matching (PSM) was performed, yielding 1,843 patients in each group.

Results: After PSM, RFA demonstrated significantly lower recurrence rates compared with CBA at both 1 year (20.9% vs. 27.9%; hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.61–0.79) and 3 years (31.9% vs. 35.2%; HR, 0.72; 95% CI, 0.65–0.81). In multivariable Cox regression analysis, RFA was independently associated with lower recurrence risk, with a 30% relative risk reduction at 1 year (HR, 0.70; 95% CI, 0.61–0.80) and a 27% relative risk reduction at 3 years (HR, 0.73; 95% CI, 0.65–0.81). When cavotricuspid isthmus (CTI) ablation was performed in addition to pulmonary vein isolation (PVI), recurrence rates were comparable between RFA and CBA.

Conclusions: In this large, multicenter real-world cohort, RFA consistently demonstrated more favorable short- and long-term outcomes than CBA, even after PSM and multivariable adjustment. However, outcomes were comparable when CTI ablation was additionally performed, underscoring the importance of procedural strategies beyond PVI.

Keywords: Atrial fibrillation; Catheter ablation; Cryoablation; Radiofrequency ablation

INTRODUCTION

Catheter ablation is a well-established therapy for atrial fibrillation (AF), reducing both symptoms and adverse cardiovascular outcomes.^{1,2)} Cryoballoon ablation (CBA) for early paroxysmal atrial fibrillation (PAF) significantly reduced atrial arrhythmia recurrence compared to antiarrhythmic drugs, establishing catheter ablation as a first-line rhythm control strategy in PAF.³⁾ Whereas radiofrequency ablation (RFA) requires point-by-point lesion formation, CBA achieves pulmonary vein isolation (PVI) with a single-shot energy delivery, resulting in a shorter learning curve and reduced procedure time.

While comparisons of CBA and RFA in PAF revealed the non-inferiority of CBA in terms of atrial arrhythmia recurrence, leading to its widespread use as a first-line ablation strategy,⁴⁾ there is limited evidence supporting its effectiveness in persistent atrial fibrillation (PeAF) or cases with advanced left atrial (LA) remodeling. Prospective studies comparing CBA and RFA in PeAF have reported no significant differences in efficacy.^{5,6)} However, these studies had small sample sizes and only assessed atrial arrhythmia recurrence over short periods, potentially underestimating any differences between the 2 ablation strategies.⁶⁾ Additionally, catheter ablation in PAF suggests that CBA is less effective than RFA in preventing progression to PeAF.⁷⁾ Although the long-term outcomes of CBA have been previously studied,⁸⁾ direct comparisons with RFA remain limited, and real-world data in clinical settings are also underexplored.

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Despite the conflicting results regarding atrial arrhythmia recurrence, CBA remains widely used as a first-line ablation strategy in a clinical setting. Therefore, this study aims to investigate the efficacy of CBA compared to RFA using a large-scale, real-world dataset, exploring differences according to AF type and the severity of LA remodeling.

METHODS

Ethical statement

The research adhered to the principles of the latest version of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Ewha Womans University Mokdong Hospital (IRB No. 2022-02-017) and the Institutional Review Boards of all participating hospitals.

Study cohort

This study utilized data from 2 prospective and retrospective cohorts. Patients in the CBA group were recruited from a multicenter, prospective, observational CBA registry cohort (Korean Heart Rhythm Society) across 12 tertiary hospitals (with 36 electrophysiologists) in South Korea. Similarly, patients in the RFA group were recruited from a multicenter, retrospective RFA cohort across 8 South Korean tertiary hospitals (with 24 electrophysiologists). AF diagnosis was confirmed via 12-lead electrocardiography (ECG) or Holter ECG. The criteria for ablation were consistent across both thermal energy ablation groups, while drug-refractory symptomatic AF was confirmed despite at least 6 weeks of standard doses of class Ic or III antiarrhythmic drugs. Patients who could not tolerate antiarrhythmic drugs due to side effects or sick sinus syndrome were also eligible. The study included 4,868 subjects between January 2018 and July 2022. Among the 4,868 patients eligible for evaluation during the study period, we included patients aged 20 to 85 years who underwent de novo ablation, excluding those with incomplete data (**Figure 1**).

Catheter energy ablation procedure

In the CBA group, cryoenergy was delivered using either a 28- or 23-mm balloon (second-generation Arctic Front Advance; Medtronic, Seoul, Korea). A transseptal puncture was initially performed to access the left atrium through a 15-Fr deflectable sheath (FlexCath; Medtronic). Cryoenergy delivery was initiated after identifying the PV potential using a circular mapping catheter (Achieve; Medtronic). Superior vena cava (SVC) pacing was used to monitor phrenic nerve injury during right-sided PVI.

If typical atrial flutter (AFL) was documented on a 12-lead ECG at any time before index procedure, cavotricuspid isthmus (CTI) ablation was performed. In cases where typical AFL was not documented on 12-lead ECG, CTI ablation was performed if CTI-dependent flutter was induced during the peri-procedural electrophysiology study. CTI ablation was carried out using radiofrequency with an open-irrigated catheter at 25 to 40 W and was considered successful when the bidirectional block was confirmed during pacing maneuvers.

In the RFA group, PVI was the primary procedural goal, using available irrigation catheters in accordance with practice guidelines for catheter ablation. An open-irrigated 4 mm tip ablation catheter was used, set to a power of 25–40 W, with lower power settings employed when ablating the posterior, inferior, or carina regions of the pulmonary vein (Navistar Thermocool SF/Thermocool Smart Touch; Biosense Webster, Irvine, CA, USA; Flexibility;

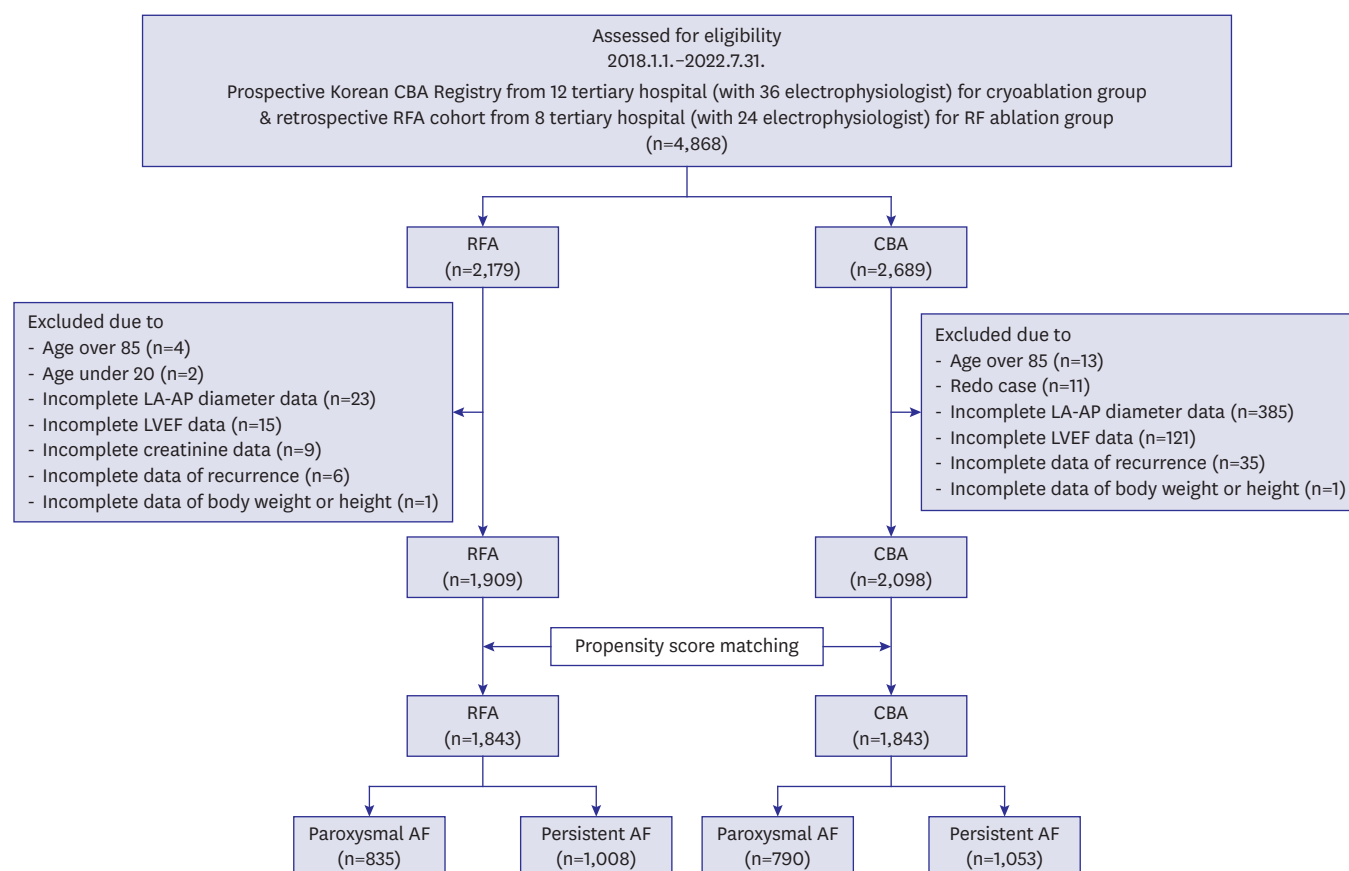


Figure 1. Schematic flow chart for patient selection.

AF = atrial fibrillation; CBA = cryoballoon ablation; LVEF = left ventricular ejection fraction; RFA = radiofrequency ablation.

Abbott, Chicago, IL, USA). For the Smart Touch catheter, contact force was maintained between 5 and 20 g. Electro-anatomical mapping of the atria and pulmonary veins was undertaken using two different 3D mapping systems (CARTO-3; Biosense Webster; EnSite NavX; Abbott). CTI ablation was performed as described above, and prophylactic line ablation was conducted at the operator's discretion in some patients.

The procedure followed general practice guidelines, but detailed procedural choices, such as sedation or general anesthesia, use of intracardiac echocardiography, cryoenergy delivery time, post-ablation testing methods, and use of non-PV trigger studies, were determined by the operator. When non-PV triggers were identified, or at the operator's discretion, additional ablation beyond PVI was performed. The detailed strategies other than CTI ablation are described in the subsequent section.

Data collection, subgroup definition, and outcomes

We collected data on patients' AF type, demographic data, and comorbidities. Thromboembolic events were defined as any occurrence of stroke, transient ischemic attack, or other thromboembolic events, while vascular events were defined as prior myocardial infarction, peripheral artery disease, or aortic plaque. Echocardiography performed within 3 months prior to ablation was reviewed to evaluate LA diameter and left ventricular ejection fraction (LVEF). LA diameter was measured in the parasternal long-axis M-mode view at left ventricular

end-systole. Procedural details were classified into PVI only and PVI plus. The PVI plus comprised additional ablation strategies, including CTI line ablation, complex fractionated atrial electrograms ablation, posterior wall isolation, roof line ablation, LA appendage isolation, anterior line ablation, perimitral isthmus ablation, and SVC isolation. For subgroup analysis, patients were classified according to AF type; PAF vs. PeAF. Classification by LA diameter was based on previous studies, with patients stratified into groups of ≥ 45 mm and < 45 mm.^{9|10)}

The primary outcome of this study was the recurrence of atrial tachyarrhythmia, defined as any atrial tachyarrhythmia detected during follow-up via 12-lead ECG or Holter ECG, including AF, AFL, and atrial tachycardia. The 90 days following the index procedure were considered the blanking period. Patients were seen in the clinic within 2 weeks of discharge and attended regular follow-ups every 3–6 months, during which a 12-lead ECG check was performed. Routine screening for AF recurrence using Holter ECG was conducted according to guideline and local protocols.¹¹⁾

Statistical analysis

Categorical variables were presented as numbers and frequencies, and continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile ranges. Group comparisons were made using the χ^2 test, Student's t-test, and Mann–Whitney U test as appropriate. Kaplan–Meier survival analysis was used to compare primary outcomes, with differences tested using nonparametric log-rank tests.

For multivariable analysis, Cox proportional hazard models were used to calculate hazard ratios (HRs) and confidence intervals (CIs), testing for interactions among subgroups. The variables included in the multivariable analysis were AF type, age, sex, body mass index (BMI), left atrial anteroposterior (LA-AP) diameter, serum creatinine, and CTI ablation. For subgroup analyses, patients were stratified by AF type (PAF vs. PeAF), LA diameter (< 45 mm vs. ≥ 45 mm), age (< 75 vs. ≥ 75 years), sex, BMI (< 25.0 vs. ≥ 25.0), LVEF ($< 40\%$ vs. $\geq 45\%$), diabetes mellitus (DM), and chronic kidney disease (CKD).

To reduce selection bias, a propensity score matching (PSM) analysis was performed. Each thermal energy ablation group was matched at a 1:1 ratio using Greedy Nearest Neighbor Matching. Covariates included in the propensity score (PS) model were age, sex, BMI, AF type, and LA size. After PSM, the standardized mean difference for all variables was < 0.1 , indicating balanced groups. Statistical significance was set at 2-sided p values < 0.05 . All statistical analyses were performed using SPSS (version 27; SPSS Inc., Chicago, IL, USA), SAS 9.4 (SAS Institute, Cary, NC, USA), and R Statistical software (version 4.3.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

The baseline characteristics of the study cohort are summarized in **Table 1**. In the RFA group, 53.3% of patients had PeAF, compared to 59.4% in the CBA group. The mean age of the patients was 62.0 years, and the CBA group had significantly more males (77.3%). No significant differences were found between the groups in CHA2DS2-VASc scores or comorbidities, except for hypertrophic cardiomyopathy. Additionally, the CBA group contained more patients with larger LA sizes.

Table 1. Baseline characteristics before and after PSM

	Before PSM			After PSM			SMD
	RFA (n=1,909)	CBA (n=2,098)	p value	RFA (n=1,843)	CBA (n=1,843)	p value	
AF type			<0.001			0.114	0.049
PAF	891 (46.7)	852 (40.6)		835 (45.3)	790 (42.9)		
PeAF	1,018 (53.3)	1,246 (59.4)		1,008 (54.7)	1,053 (57.1)		
Demographics							
Age	62.0 (55.0–68.0)	62.0 (56.0–68.0)	0.034	62.0 (55.0–68.0)	62.0 (55.0–68.0)	0.719	0.017
Sex			0.003			0.359	0.031
Female	511 (26.8)	477 (22.7)		468 (25.4)	443 (24.0)		
Male	1,398 (73.2)	1,621 (77.3)		1,375 (74.6)	1,400 (76.0)		
Body weight (kg)	70.9 (63.0–79.0)	72.0 (64.0–79.7)	0.003	71.0 (63.0–79.0)	71.4 (63.2–79.0)	0.567	0.021
Height (cm)	168.0 (161.0–174.0)	168.0 (161.3–173.0)	0.902	168.0 (161.0–174.0)	168.0 (161.0–173.0)	0.471	0.020
BMI (kg/m ²)	25.2 (23.2–27.1)	25.5 (23.6–27.7)	<0.001	25.3 (23.3–27.3)	25.3 (23.5–27.4)	0.31	0.041
Creatinine	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.002	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.069	0.004
CHA2DS2 VASc score	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.805	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.257	0.034
CHA2DS2 VA component	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.580	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.290	0.026
Comorbidity							
HF	483 (25.3)	513 (24.5)	0.559	472 (25.6)	439 (23.8)	0.222	0.042
HTN	1,128 (59.1)	1,199 (57.1)	0.226	1,107 (60.1)	1,037 (56.3)	0.021	0.077
DM	394 (20.6)	456 (21.7)	0.419	389 (21.1)	395 (21.4)	0.841	0.008
Previous stroke/TIA	208 (10.9)	249 (11.9)	0.359	203 (11.0)	214 (11.6)	0.603	0.019
Myocardial infarction	21 (1.1)	28 (1.3)	0.597	20 (1.1)	25 (1.4)	0.550	0.025
PAOD	7 (0.4)	11 (0.5)	0.611	7 (0.4)	10 (0.5)	0.627	0.024
CKD	90 (4.7)	113 (5.4)	0.37	90 (4.9)	104 (5.6)	0.338	0.034
SSS	82 (4.3)	99 (4.7)	0.57	78 (4.2)	90 (4.9)	0.385	0.031
HCMP	24 (1.3)	45 (2.1)	0.042	24 (1.3)	37 (2.0)	0.121	0.055
ICD implantation	14 (0.7)	15 (0.7)	1	14 (0.8)	12 (0.7)	0.844	0.013
Pacemaker implantation	41 (2.1)	50 (2.4)	0.694	38 (2.1)	45 (2.4)	0.505	0.026
Echocardiographic findings							
Pre LA-AP diameter (mm)	42.7 (39.0–47.0)	44.0 (39.0–48.0)	<0.001	43.0 (39.0–47.2)	43.0 (39.0–48.0)	0.401	0.056
LA ≥45 mm	712 (37.3)	926 (44.1)	<0.001	709 (38.5)	752 (40.8)	0.157	0.048
Pre LVEF (%)	57.5 (52.5–59.0)	59.5 (55.1–64.0)	<0.001	57.5 (52.5–59.0)	59.5 (55.5–64.0)	<0.001	0.402
EF ≤40%	99 (5.2)	103 (4.9)	0.743	99 (5.4)	89 (4.8)	0.5	0.025

Values are presented as median (interquartile range) or number (%).

AF = atrial fibrillation; BMI = body mass index; CBA = cryoballoon ablation; CKD = chronic kidney disease; DM = diabetes mellitus; EF = ejection fraction; HCMP = hypertrophic cardiomyopathy; HF = heart failure; HTN = hypertension; ICD = implantable cardioverter-defibrillator; LA = left atrial; LA-AP = left atrial anteroposterior; LVEF = left ventricular ejection fraction; PAF = paroxysmal atrial fibrillation; PAOD = peripheral arterial occlusive disease; PeAF = persistent atrial fibrillation; PSM = propensity score matching; RFA = radiofrequency ablation; SMD = standardized mean difference; SSS = sick sinus syndrome; TIA = transient ischemic attack.

In the RFA group, 36.0% of patients underwent only PVI, while 81.4% of CBA patients underwent only PVI. Among the RFA group, the majority of the PVI plus group underwent CTI line ablation, accounting for 56.3% of all treatments. In the CBA group, no other ablation strategy was used in the PVI plus group apart from CTI line ablation (**Supplementary Figure 1**).

PSM was performed to adjust for baseline variables between the 2 thermal energy ablation groups. After 1:1 PSM, a total of 1,843 patients were included in each group. After matching, there were no significant differences in baseline characteristics between the groups, except for pre-procedure LVEF. However, when divided into groups with an ejection fraction of 40% or less, no significant differences were observed (**Table 1**). A histogram with an overlaid density plot comparing the cohorts before and after PSM is presented in **Supplementary Figure 2**, and the standardized mean differences for all used covariates were within 0.1.

Atrial tachyarrhythmia recurrence

In terms of atrial tachyarrhythmia recurrence, the PS-matched cohort showed a trend similar to that observed in the pre-matching data (**Table 2**). The 1-year recurrence rate was higher in the CBA group than the RFA group, a trend which persisted when analyzed by AF type or in

Table 2. Atrial tachyarrhythmia recurrence rate according to the AF type or LA-AP diameter

	Before PSM			After PSM		
	RFA	CBA	p value	RFA	CBA	p value
1 year atrial tachyarrhythmia recurrence						
AF type						
PAF	124/891 (13.90)	160/852 (18.80)	0.006	118/835 (14.10)	148/790 (18.70)	0.012
PeAF	269/1,018 (26.40)	428/1,246 (34.30)	<0.001	267/1,008 (26.50)	367/1,053 (34.90)	<0.001
LA-AP diameter (mm)						
<45	195/1,197 (16.30)	238/1,172 (20.30)	0.011	187/1,134 (16.50)	219/1,091 (20.10)	0.029
≥45	198/712 (27.80)	350/926 (37.80)	<0.001	198/709 (27.90)	296/752 (39.40)	<0.001
PAF & LA-AP <45 mm	78/682 (11.40)	96/647 (14.80)	0.066	72/629 (11.40)	92/617 (14.90)	0.710
PAF & LA-AP ≥45mm	46/209 (22.00)	64/205 (31.20)	0.034	46/206 (22.30)	56/173 (32.40)	0.028
PeAF & LA-AP <45mm	117/515 (22.70)	142/525 (27.00)	0.107	115/505 (22.80)	127/474 (26.80)	0.145
PeAF & LA-AP ≥45mm	152/503 (30.20)	286/721 (39.70)	<0.001	152/503 (30.20)	240/579 (41.50)	<0.001
3 years atrial tachyarrhythmia recurrence						
AF type						
PAF	195/891 (21.90)	214/852 (25.10)	0.111	186/835 (22.30)	195/790 (24.70)	0.252
PeAF	406/1,018 (39.90)	533/1,246 (42.80)	0.164	402/1,008 (39.90)	454/1,053 (43.10)	0.136
LA-AP diameter, mm						
<45	298/1,197 (24.90)	321/1,172 (27.40)	0.167	285/1,134 (25.10)	296/1,091 (27.10)	0.283
≥45	303/712 (42.60)	426/926 (46.00)	0.164	303/709 (42.70)	353/752 (46.90)	0.106
PAF & LA-AP <45 mm	123/682 (18.00)	131/647 (20.20)	0.305	114/629 (18.10)	126/617 (20.40)	0.304
PAF & LA-AP ≥45 mm	72/209 (34.40)	83/205 (40.50)	0.204	72/206 (35.00)	69/172 (39.90)	0.322
PeAF & LA-AP <45 mm	175/515 (34.00)	190/525 (36.20)	0.455	171/505 (33.90)	170/474 (35.90)	0.511
PeAF & LA-AP ≥45 mm	231/503 (45.90)	343/721 (47.60)	0.570	231/503 (45.90)	284/579 (49.10)	0.305

Values are presented as event/total (%).

AF = atrial fibrillation; CBA = cryoballoon ablation; LA-AP = left atrial anteroposterior; PAF = paroxysmal atrial fibrillation; PeAF = persistent atrial fibrillation; PSM = propensity score matching; RFA = radiofrequency ablation.

patients with an LA-AP diameter. At 1 year, recurrence rates were significantly higher with CBA in the subgroup with an LA diameter ≥45 mm ($p=0.028$ and $p<0.001$, respectively). When comparing recurrence by both AF type and LA size, no significant difference was found in 1-year recurrence rates regardless of AF type with an LA size of <45 mm ($p=0.710$ and $p=0.145$, respectively). At 3 years, no statistically significant difference in recurrence rates was observed between the two groups, regardless of AF type ($p=0.252$ and $p=0.136$, respectively). Similarly, no significant differences were observed in the 3-year recurrence rates when comparing results based on an LA-AP diameter ≥ 45 mm ($p=0.283$ and $p=0.106$, respectively). The atrial tachyarrhythmia recurrence rates by other subgroups are presented in **Supplementary Table 1**.

After PSM, RFA was associated with a significantly lower 1-year recurrence rate compared with CBA (HR, 0.69; 95% CI, 0.61–0.79; **Figure 2A**). At 3 years, RFA also demonstrated a lower recurrence rate than CBA (HR, 0.72; 95% CI, 0.65–0.81; **Figure 2B**).

To assess the contribution of specific variables to the primary outcome, we performed an additional analysis focusing on CTI ablation. This was done because CTI ablation was the only adjunctive procedure performed in the CBA group and also represented the most common PVI plus ablation strategy in the RFA group (**Supplementary Figure 3**). Among patients in the RFA group, 1,187 patients (64.4%) underwent PVI plus ablation. In contrast, 357 patients (19.4%) in the CBA group underwent PVI plus ablation, all of whom received CTI ablation only. CTI ablation was performed in 1,046 patients (56.8%) in the RFA group, accounting for 88.1% of all PVI plus cases. Post-matching, the highest 1-year and 3-year recurrence rates were observed in the CBA group that underwent only PVI, with significant differences among the 4 groups. However, no significant differences in 1-year and 3-year recurrence rates were observed between the two groups that underwent both CTI and

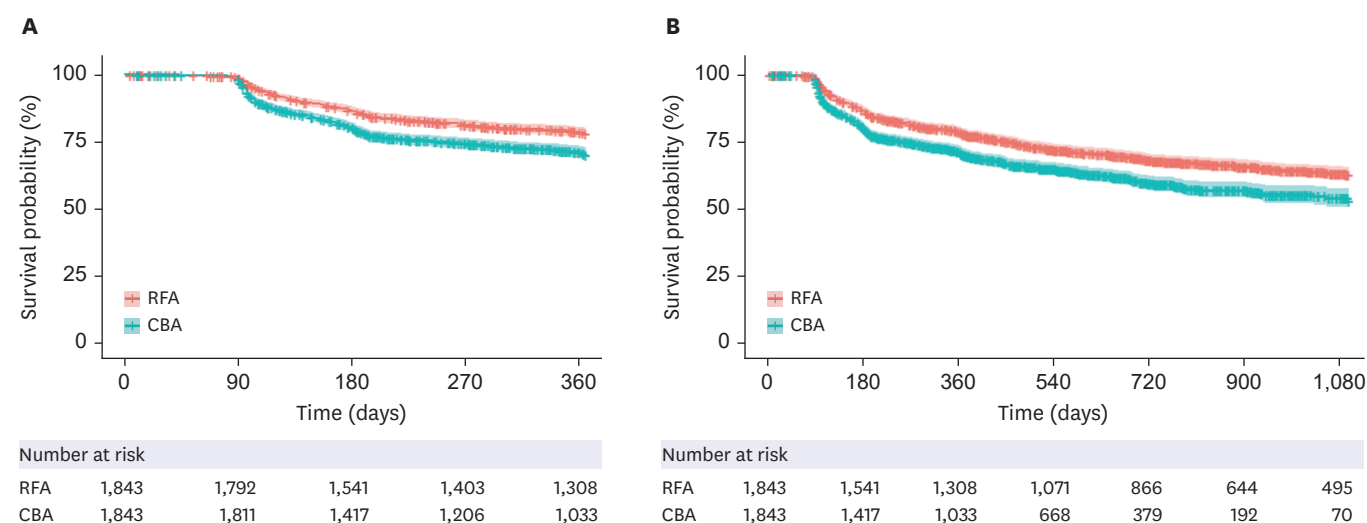


Figure 2. Kaplan–Meier event free survival curve of atrial tachyarrhythmia recurrence after propensity score matching. (A) Kaplan–Meier curves of event free survival for 1 year, (B) Kaplan–Meier curves of event free survival for 3 years. CBA = cryoballoon ablation; RFA = radiofrequency ablation.

PVI (Log-rank $p=0.848$ and Log-rank $p=0.920$, respectively; **Figure 3**). The differences in recurrence rates associated with PVI plus ablation, including CTI ablation, are presented in **Supplementary Figure 4**.

Based on the before PS-matched data, the Kaplan–Meier event-free survival curve for 1-year recurrence, stratified by AF type and LA size, showed no significant difference between the 2 thermal ablation groups in patients with PAF and an LA-AP diameter <45 mm

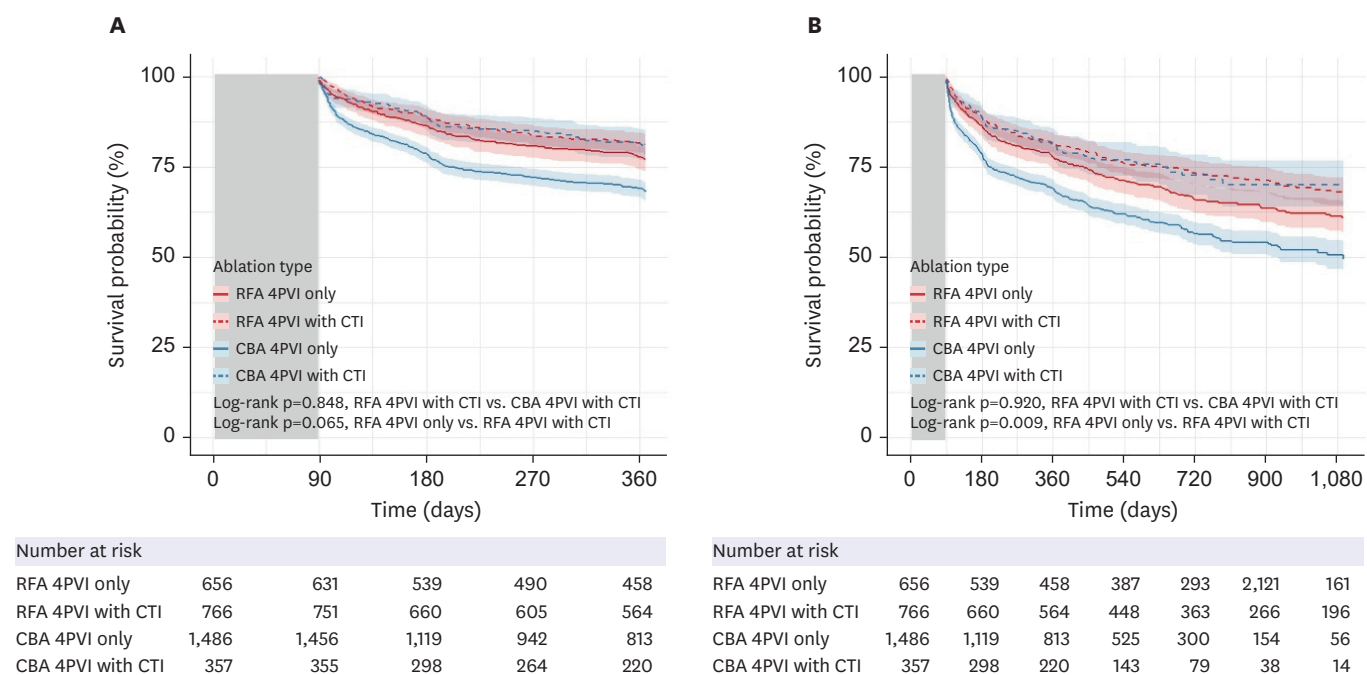


Figure 3. Kaplan–Meier event-free survival curve of atrial tachyarrhythmia recurrence based on the performance of CTI line ablation after propensity score matching. (A) Kaplan–Meier curves of event-free survival for 1 year, (B) Kaplan–Meier curves of event-free survival for 3 years. CBA = cryoballoon ablation; CTI = cavotricuspid isthmus; PVI = pulmonary vein isolation; RFA = radiofrequency ablation.

Table 3. Multivariable Cox regression analysis

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
1 year recurrence of RFA	0.693 (0.607–0.791)	<0.001	0.699 (0.612–0.798)	<0.001
3 years recurrence of RFA	0.723 (0.646–0.809)	<0.001	0.727 (0.649–0.814)	<0.001

The variables considered in the multivariable analysis included atrial fibrillation type, age, sex, body mass index, left atrial anteroposterior diameter, and serum creatinine.

CI = confidence interval; HR = hazard ratio; RFA = radiofrequency ablation.

(**Supplementary Figure 5A**). In all other groups, atrial tachyarrhythmia recurrence was significantly lower in the RFA group compared to the CBA group (**Supplementary Figure 5B-D**).

Multivariable analysis

Multivariable analyses were conducted using the PS-matched cohort to assess the impact of various factors on recurrence.

Multivariable analysis revealed that the 1-year recurrence risk for RFA was 30% lower (HR, 0.70; 95% CI, 0.61–0.80; **Table 3**) and the 3-year recurrence risk was 27% lower (HR, 0.73; 95% CI, 0.65–0.81; **Table 3**), compared to CBA. These associations remained materially unchanged after adjustment for CTI ablation (**Supplementary Table 2**). Detailed results of the multivariable Cox regression analysis, including adjusted HRs with 95% CIs and p values for all covariates in the model, are summarized in **Supplementary Table 3**.

Subgroup analysis

To investigate the impact of various factors, we performed subgroup analyses using the pre-matching data.

Subgroup analysis showed that the 1-year recurrence risk and 3-year recurrence risk did not differ significantly across subgroups, with p-for-interaction not significant for AF type, LA diameter (<45 vs. ≥45 mm), age (<75 vs. ≥75 years), sex, BMI (<25.0 vs. ≥25.0 kg/m²), LVEF (<40% vs. ≥45%), DM, or the presence of CKD (**Supplementary Figure 6**). However, subgroup analysis showed favorable 1-year outcomes for RFA regardless of AF type or LA size.

DISCUSSION

This study's key findings are: 1) RFA demonstrated significantly lower recurrence rates at 1 year among patients with LA diameter ≥45 mm; 2) After PSM, RFA showed significantly higher event-free survival compared with CBA; 3) CTI ablation performed alongside PVI reduced recurrence rates in both groups, with no significant differences between RFA and CBA when CTI ablation was additionally performed; 4) Multivariable analysis demonstrated a lower recurrence risk in the RFA group at both 1 year (HR, 0.70; 95% CI, 0.61–0.80) and 3 years (HR, 0.73; 95% CI, 0.65–0.81), while subgroup analysis revealed no significant differences across various clinical factors.

CBA is a well-established rhythm control strategy for PAF. Its proven non-inferiority to RFA, combined with the limited benefits of ablation beyond PV isolation, has led to its increased use as a first-line option for catheter ablation.⁴⁾¹²⁾¹³⁾ A prospective study of CBA for PeAF (duration <6 months) demonstrated significant quality of life improvements and reduction of atrial arrhythmia recurrence.¹⁴⁾ However, the efficacy of CBA has been less

assessed in early PeAF, and it has not been compared directly to RFA. A randomized trial comparing RFA and CBA in a small cohort showed no significant difference in 1-year atrial arrhythmia recurrence.⁶⁾ Notably, this study included only patients with PeAF and was conducted with a strict PVI-centered strategy, thereby excluding the potential impact of adjunctive ablation beyond PVI or operator-driven decisions that may influence long-term outcomes in real-world practice. Additionally, transitioning from binary assessments of atrial arrhythmia recurrence to evaluating atrial arrhythmia burden suggests CBA may be less effective in preventing AF progression.⁷⁾¹⁵⁾ Nevertheless, in real-world practice, CBA has been widely used not only in PAF but also in PeAF, primarily due to its shorter procedure time.

The differential effects of CBA may be attributed to several mechanisms. First, point-by-point ablation may result in more effective lesion formation for PVI than single-shot ablation. Although rare, anatomical variations in pulmonary veins—such as common pulmonary veins, middle pulmonary veins, large pulmonary veins, or shallow angles of the right pulmonary vein¹⁶⁾—may restrict effective pulmonary vein occlusion and lesion formation via cryoballoon, which has a uniform, spherical shape, and limited balloon size options. This could explain the higher atrial arrhythmia recurrence rates observed in CBA, even when limited to PVI.

Second, the impact of additional ablation beyond PVI in the RFA group may explain the significant differences in atrial arrhythmia recurrence. In stratified analysis, additional CTI ablation resulted in lower recurrence rates, regardless of ablation modality. These patients had both typical AFL and AF, so ablation of AFL in addition to PVI likely reduced the chance of atrial arrhythmia recurrence compared to patients with only AF. Furthermore, CTI ablation may have additional effects, such as modifying the right atrial ganglionated plexus.¹⁷⁾ In the CRYALAL randomized trial, adjunctive right atrial linear ablation including CTI ablation was also associated with less frequent long-term recurrence compared with CBA with PVI alone (HR, 0.66; 95% CI, 0.46–0.94; $p=0.022$).¹⁸⁾ While ablation beyond PVI did not reveal generalized benefits for AF, ablating non-PV triggers or modifying substrates in selected patients may have contributed to recurrence reduction.¹⁹⁾²⁰⁾ The more frequent use of non-PV ablation in the RFA group may have affected the differential effects of CBA in advanced or PeAF.

In this study, we compared the efficacy of CBA and RFA using a real-world database. Even after adjusting for baseline characteristics, we found that RFA showed significantly lower recurrence rates of atrial arrhythmia during follow-up. Heeger et al.⁸⁾ identified LA diameter as an independent predictor of long-term outcomes following CBA (HR, 1.20; 95% CI, 1.04–1.39; $p=0.014$), and our study similarly demonstrated higher recurrence rates in patients with an LA diameter ≥ 45 mm. However, in both multivariable and subgroup analyses, the outcomes were consistently more favorable for RFA compared with CBA, irrespective of LA size. As shown in a previous study of PeAF patients, in which CBA with PVI alone resulted in a high long-term recurrence rate of 53.1%,¹⁸⁾ our findings support the evidence that, given the pathophysiology of AF and the complexities of atrial remodeling, CBA with PVI alone may have insufficient long-term efficacy.

Therefore, when choosing the energy source for PVI, the spectrum of atrial remodeling should be considered in addition to the AF type. Single-shot ablation might be sufficient for true PAF without advanced atrial remodeling, but point-by-point ablation should be considered in patients with advanced atrial remodeling, even if the AF is not persistent. In particular, our study showed that the addition of CTI ablation was associated with

improved post-CBA outcomes. However, it is important to note that CTI ablation was performed only when typical AFL was documented or induced during the procedure. This interpretation is consistent with previous studies demonstrating that prophylactic CTI ablation in patients with paroxysmal AF without documented typical AFL does not reduce atrial tachyarrhythmia recurrence compared with PVI alone.²¹⁾²²⁾ Similar to the findings of the STAR AF II trial,¹³⁾ the addition of PVI plus ablation in the RFA group did not lead to an overall improvement in recurrence outcomes. However, when the analysis was limited to patients who underwent CTI ablation, a statistically significant reduction in 3-year recurrence was observed, with the cohort including patients who received CTI ablation empirically. These findings indicate that adjunctive ablation strategies vary in their contribution to long-term efficacy; therefore, a more selective, indication-based approach is necessary for ablation performed beyond PVI.

This study has several limitations. First, a unified continuous rhythm monitoring was not performed after catheter ablation. The outcome was defined as a binary event (a recurrence of atrial arrhythmia lasting more than 30 seconds), which may not accurately reflect the overall atrial arrhythmia burden. A reduction in AF burden after catheter ablation is a more important prognostic predictor, and future studies should assess the efficacy of catheter ablation regarding AF burden.¹⁵⁾ In the CIRCA-DOSE trial, RFA showed greater clinical benefits in reducing AF progression in general PAF.⁷⁾ Thus, the difference between RFA and CBA may be more pronounced if quantitative AF burden was assessed as an outcome in our cohort. Second, because procedures were performed across 12 CBA and 8 RFA centers, variability in procedural protocols may have affected the outcomes and should be considered when interpreting the results.

In this large, multicenter real-world cohort, RFA consistently demonstrated more favorable short- and long-term outcomes than CBA, even after PSM and multivariable adjustment. However, outcomes were comparable when CTI ablation was additionally performed, highlighting the importance of procedural strategies beyond PVI and supporting the notion that CTI ablation should not be omitted in patients with clearly documented AFL.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to all the investigators from the Korean Heart Rhythm Society for their invaluable contributions to the Cryoablation Registry database in the Republic of Korea.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Atrial tachyarrhythmia recurrence rate according to the subgroup

Supplementary Table 2

Multivariable Cox regression analysis

Supplementary Table 3

Full results of multivariable Cox regression analysis after propensity score matching

Supplementary Figure 1

The comparison on ablation strategies between two groups. (A) RFA, (B) CBA.

Supplementary Figure 2

PS distribution shown as histogram with overlaid densitogram before and after PSM.

Supplementary Figure 3

The comparison on ablation strategies between two groups after propensity score matching.

Supplementary Figure 4

Kaplan–Meier event-free survival curves for atrial tachyarrhythmia recurrence according to the performance of PVI plus ablation after propensity score matching. (A) Kaplan–Meier curves of event free survival for 1year, (B) Kaplan–Meier curves of event free survival for 3 years.

Supplementary Figure 5

Kaplan–Meier event-free survival curve of 1-year atrial tachyarrhythmia recurrence differentiated by AF type and left atrial size. (A) PAF and LA-AP diameter <45 mm, (B) PAF and LA-AP diameter ≥45 mm, (C) PeAF and LA-AP diameter <45 mm, (D) PeAF and LA-AP diameter ≥45 mm.

Supplementary Figure 6

Multivariate Cox regression analysis for finding out risk factor of recurrence according to the subgroup. (A) 1 year atrial tachyarrhythmia recurrence, (B) 3 years atrial tachyarrhythmia recurrence.

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