

Original Research



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Cryoballoon Ablation for Elderly Patients With Atrial Fibrillation: Results From the Korean Cryoballoon Registry

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AUTHOR'S SUMMARY

Cryoballoon ablation (CBA) is considered an effective rhythm control treatment for atrial fibrillation (AF), and its use is increasing exponentially. However, data regarding the efficacy and safety of CBA in very elderly patients remain limited. This study, based on data from the Korean CBA registry, demonstrated that elderly patients with AF, despite a higher burden of comorbidities, achieved comparable long-term rhythm outcomes and complication rates to those of younger patients. Given its standardized techniques and short learning curve, CBA may be an effective rhythm control strategy for elderly patients with AF who are often concerned about drug-related adverse events.

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Conflict of Interest

The authors have no financial conflict of interest.

Data Sharing Statement

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

Author Contributions

Conceptualization: Lim HE; Data curation: Kang DS, Yang PS, Kim JH, Kim KH, Kim JY, Lee SR, Park J, Lee SH, Kwon CH, Cha MJ, Shim J, Oh IY, Han SJ, Lim HE; Formal analysis: Kang DS, Yang PS; Funding acquisition: Lim HE; Investigation: Kang DS, Yang PS, Kim JH, Kim KH, Kim JY, Lee SR, Park J, Lee SH, Kwon CH, Cha MJ, Shim J, Oh IY, Han SJ, Lim HE; Methodology: Kang DS, Yang PS, Lim HE; Resources: Lim HE; Software: Kang DS; Supervision: Kim JH, Kim KH, Kim JY, Lee SR, Park J, Lee SH, Kwon CH, Cha MJ, Shim J, Oh IY, Han SJ, Lim HE; Visualization: Kang DS; Writing - original draft: Kang DS, Yang PS; Writing - review & editing: Lim HE.

ABSTRACT

Background and Objectives: Cryoballoon ablation (CBA) is considered an effective rhythm control treatment for atrial fibrillation (AF) and is increasing exponentially. However, data regarding the efficacy and safety of CBA in elderly patients are limited.

Methods: A total of 2,652 patients (55.2% with non-paroxysmal AF) from the Korean CBA registry database with follow-up of ≥ 12 -months after de novo CBA were divided into 2 groups based on age (< 75 and ≥ 75 years old). Procedure related complications and clinical outcomes were compared.

Results: Compared to the control group ($n=2,403$), the elderly group ($n=249$) had female predominance (41.8% vs. 21.1%, $p<0.001$), a higher CHA₂DS₂-VASc scores (4.0 [3.0–5.0] vs. 2.0 [1.0–3.0]; $p<0.001$), and a higher prevalence of heart failure (33.3% vs. 21.9%; $p<0.001$) and chronic kidney disease (42.2% vs. 10.4%; $p<0.001$). A total of 120 procedure-related minor complications were reported, but no significant difference was observed between the 2 groups (6.4% vs. 4.3%; $p=0.18$). Recurrence of atrial tachyarrhythmias was observed in 67 patients (27.2%) in the elderly group and 788 patients (33.3%) in the control group. After adjusting for confounding variables, the freedom from atrial tachyarrhythmias during 24-month was similar between the 2 groups (67.0% vs. 62.7%; adjusted hazard ratio, 0.91; 95% confidence interval, 0.62–1.34; $p=0.63$).

Conclusions: CBA showed a reasonable efficacy and safety profile in elderly population with AF, comparable to that in younger patients.

Keywords: Atrial fibrillation; Cryoballoon ablation; Elderly

INTRODUCTION

Atrial fibrillation (AF) is a prevalent arrhythmia, particularly among the elderly, and its incidence increases significantly with age.^{1,2)} As of 2017, the global prevalence of AF was estimated at 37.6 million, with projections indicating a rise of over 60% by 2050, largely driven by an aging population.³⁾ AF affects 10–17% of individuals aged 80 years and older, a demographic that poses unique challenges due to the presence of multiple comorbidities.⁴⁾ Despite advances in catheter ablation techniques, there is hesitancy in performing catheter ablation in this population due to concerns regarding safety and efficacy. Since pulmonary vein isolation (PVI) is establishing the primary strategy for AF ablation, cryoballoon ablation (CBA) may be the first option due to its relative simplicity, short learning curve, and similar efficacy to radiofrequency catheter ablation (RFCA). Large-scale clinical trials proved the favorable outcomes of CBA; however, they included only a small number of elderly patients, leaving a gap in the evidence regarding the management of AF in this growing segment of the population.^{5,6)}

From a large multicenter CBA registry, therefore, we aim to evaluate the efficacy, safety, and long-term success rates of CBA in elderly patients with AF compared to those younger than 75 years old, thereby providing clinical decision-making for rhythm control management in the very elderly population with AF.

METHODS

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki (2013), and the requirement for informed consent was waived by the Hallym University Sacred Heart Hospital Institutional Review Board (IRB) approvals of the participating institutions (IRB No. 2020-01-010). Procedures were performed following the ethical standards of the research committee.

Study population

The Korean CBA registry consisted of cohort data from 12 tertiary institutes in South Korea from May 2018 to June 2022. A total of 2,689 patients who underwent de novo CBA for treatment of drug refractory AF were consecutively recruited. Patients were divided into elderly and control groups based on the age of 75 years. Patients who had contraindication for long-term anticoagulation or were lost to follow-up during the 90-day blanking period after CBA were excluded from the analysis.

Cryoballoon ablation procedure

The CBA procedure generally conformed to the practice guidelines for CBA of AF, and detailed approaches and dosing protocols, including cryoenergy delivery time or number, fluoroscopic or intracardiac echocardiographic guidance for balloon positioning and occlusion, use of general anesthesia, and post-ablation testing, were applied based on the discretion of each operator. In performance of all procedures, a 15-F steerable sheath (FlexCath Advance Steerable Sheath; Medtronic Inc., Dublin, Ireland) was used for introduction of a 28-mm CBA catheter (Arctic Front Advance; Medtronic Inc.) into the left atrium (LA). The CBA catheter was manipulated in LA over a dedicated inner-lumen circular mapping catheter (Achieve, Medtronic Inc.), which was used to record pulmonary vein (PV) potentials. The CBA catheter was inflated and advanced towards the antral surface of each PV. Freezing was initiated upon antral occlusion of the targeted PV. The number of cryoenergy applications and the duration of freezing were determined according to the discretion of each operator and PVI was confirmed by blocking the entrance and exit after CBA. Diaphragmatic stimulation with continuous pacing of the ipsilateral phrenic nerve was performed during performance of right-sided CBA to avoid phrenic nerve paralysis. Freezing was immediately stopped upon detection of an attenuated diaphragmatic response. Additional RFCA of the cavotricuspid isthmus was performed based on the operator's decision. Periprocedural anticoagulation regimen and discontinuation or reinitiation of antiarrhythmic drugs was determined according to the discretion of each operator, and patients were discharged according to the hospital's standard-of-care practice.

Data collection and primary endpoint

AF-related clinical variables including demographic factors, medical history, and clinical characteristics and procedure-related parameters were obtained. Data of echocardiography which was performed within 3 months before CBA procedure were collected. The LA diameter was measured in the M-mode parasternal long-axis view at the end-systole of left ventricle. AF duration was defined as time period from the first diagnosis of AF to the date of CBA. Heart failure (HF) was defined as any symptoms or sign of HF combined with raised natriuretic peptides or left ventricular ejection fraction $\leq 50\%$. The first 3 months after CBA were designated as a blanking period. The primary efficacy endpoint was the recurrence of any atrial tachyarrhythmias lasting ≥ 30 seconds including AF, atrial tachycardia, and atrial

flutter after 3 months of the blanking period. The primary safety endpoint was the incidence of any procedure-related complications.

Patient follow-up

Antiarrhythmic drugs were prescribed during the 3-month blanking period to prevent early recurrence, but were discontinued at the physician's discretion if sinus rhythm was maintained. Anticoagulants were mandatorily prescribed for 3 months after CBA, and their continued use thereafter was determined based on the patient's risk of stroke and systemic embolism. Patients were followed up at the outpatient clinic at 1, 3, 6, 9, and 12 months and every 3–6 months thereafter or whenever symptoms occurred after CBA according to the current guideline and the standard-of-care method used in their hospitals. Follow-up monitoring was performed according to the current guideline and the standard-of-care practice for each hospital. Rhythm monitoring was performed using any of the following methods, including 12-lead electrocardiogram (ECG), Holter or a single-lead ECG patch recording, or insertable cardiac monitor.

Statistical analysis

Continuous variables were reported as medians (interquartile range), and categorical variables as numbers (percentages). The Kaplan-Meier method was used to estimate the recurrence rate of atrial tachyarrhythmias over 24 months. Univariate- and multivariate Cox proportional-hazards regression models were used to calculate unadjusted and adjusted hazard ratios (HRs) for atrial tachyarrhythmia recurrence, respectively. The multivariate model included baseline characteristics listed in **Table 1** with the exception of CHA₂DS₂-VAsC

Table 1. Baseline characteristics of the elderly and control groups

	Elderly (n=249)	Control (n=2,403)	p
Follow-up duration (months)	20.0 (12.5–27.9)	20.0 (12.3–28.3)	0.96
AF duration (months)	23.6 (11.7–54.9)	23.2 (10.1–48.0)	0.25
Age (years)	77.0 (76.0–80.0)	61.0 (55.0–66.0)	<0.001
Sex, male	145 (58.2)	1,897 (78.9)	<0.001
Non-paroxysmal AF	129 (51.8)	1,334 (55.5)	0.29
Left atrial diameter (mm)	43.0 (39.0–48.0)	43.0 (39.0–48.0)	0.94
LV ejection fraction (%)	61.0 (55.0–64.3)	60.0 (56.0–64.0)	0.41
LV E/e'	11.0 (9.0–13.0)	9.0 (7.0–11.0)	<0.001
CHA ₂ DS ₂ -VAsC score	4.0 (3.0–5.0)	2.0 (1.0–3.0)	<0.001
CHDS ₂ -VSc score*	2.0 (1.0–3.0)	1.0 (1.0–2.0)	<0.001
Hypertension	168 (67.5)	1,356 (56.4)	0.001
Diabetes mellitus	74 (29.7)	494 (20.6)	0.001
Heart failure	83 (33.3)	526 (21.9)	<0.001
Stroke/TIA	47 (18.9)	264 (11.0)	<0.001
Coronary artery disease	35 (14.1)	182 (7.6)	0.001
Chronic kidney disease	105 (42.2)	250 (10.4)	<0.001
End-stage kidney disease	3 (1.2)	64 (2.7)	0.24
Oral anticoagulants			<0.001
Warfarin	1 (0.4)	236 (9.8)	
NOAC	245 (98.4)	2,150 (89.5)	
Dose reduction of NOAC			<0.001
No	194 (77.9)	1,768 (73.6)	
Yes	52 (20.9)	388 (16.1)	
Antiarrhythmic drugs before CBA	4 (1.6)	158 (6.6)	0.003
Class IC	0 (0.0)	42 (26.6)	
Class III	4 (100.0)	116 (73.4)	

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

AF = atrial fibrillation; CBA = cryoballoon ablation; LV = left ventricle; NOAC = non-vitamin K antagonist oral anticoagulant; TIA = transient ischemic attack.

*The CHDS₂-VSc score was calculated by excluding the points attributed to age from the CHA₂DS₂-VAsC score.

score and age. Subgroup and sensitivity analyses were conducted as follows: First, the same analyses were repeated for each type of AF. Second, stepwise selection based on the Akaike Information Criterion was performed, including age and sex as mandatory variables, to select the most appropriate multivariate model. Third, to account for differences in baseline characteristics, overlap weighting based on propensity scores was applied instead of the multivariate Cox regression model. Fourth, the group classification criterion was modified from 75 years to 80 years for the analysis. All statistical analyses were performed using R version 4.2.1 (www.R-project.org, The R Foundation, Vienna, Austria), with a $p < 0.05$ considered statistically significant.

RESULTS

Patient characteristics

Among the 2,689 patients, 5 patients who could not take long-term anticoagulants and 32 patients whose follow-up was lost during the 3-month blanking period after CBA were excluded. A total of 249 elderly (9.4%) and 2,403 control (90.6%) patients were included in the analysis, with their baseline characteristics summarized in **Table 1**. The median age was 62.0 years (56.0–68.0), with 1,463 patients (55.2%) presenting with non-paroxysmal AF. The median duration from AF diagnosis to CBA was 23.3 months (10.2–49.1). Compared to the control group, the elderly group had a higher predicted stroke risk (CHA₂DS₂-VASc score, 4.0 [3.0–5.0] vs. 2.0 [1.0–3.0], $p < 0.001$), and this difference remained significant even after excluding the contribution of age (CHDS₂-VSc score, 2.0 [1.0–3.0] vs. 1.0 [1.0–2.0], $p < 0.001$). Furthermore, the elderly group had higher E/e' values on pre-procedural transthoracic echocardiography (11.0 [9.0–13.0] vs. 9.0 [7.0–11.0], $p < 0.001$), and a higher prevalence of HF (33.3% vs. 21.9%, $p < 0.001$) and chronic kidney disease (42.2% vs. 10.4%, $p < 0.001$).

Procedural characteristics

Table 2 shows the procedure characteristics and complications. PVI was successfully achieved through CBA in all enrolled patients. The elderly group was less likely to undergo general anesthesia during the procedure compared to the control group (24.5% vs. 33.0%, $p = 0.01$) and were more frequently subjected to cavotricuspid isthmus ablation (28.1% vs. 21.1%, $p = 0.01$). A total of 120 procedure-related complications were reported, but no significant difference was observed between the 2 groups (6.4% vs. 4.3%, $p = 0.18$). Although 5 cases (2.0%) of pericardial effusion, 2 cases (0.8%) of puncture site hematoma, and 6 cases (2.4%) of transient phrenic nerve palsy occurred in the elderly group, these did not differ significantly from the control group. Notably, no major complications requiring additional intervention, such as stroke, atrio-esophageal fistula, PV stenosis, or death, were observed.

Clinical outcomes

Table 3 shows the clinical outcomes after index CBA. During a median follow-up period of 20.0 months (12.3–28.3), events of atrial tachyarrhythmias were observed in 67 patients (27.2%) in the elderly group and 788 patients (33.3%) in the control group. The median time to recurrence was 5.7 months (3.4–12.1) and 5.6 months (3.4–10.5) for the elderly and control groups, respectively. No death events occurred during the follow-up period. **Figure 1** shows the Kaplan-Meier curves for the freedom from atrial tachyarrhythmias during 24-month after index CBA. After adjusting for the influence of confounding variables, freedom from atrial tachyarrhythmias during 24 months was not significantly different between the elderly group (67.0%; 95% confidence interval [CI], 60.1–74.7%) and the control group (62.7%;

Table 2. Procedural characteristics and related complications of the elderly and control groups

	Elderly (n=249)	Control (n=2,403)	p
ICE use	221 (88.8)	2,219 (92.3)	0.06
General anesthesia	61 (24.5)	792 (33.0)	0.01
Cavotricuspid isthmus ablation	70 (28.1)	507 (21.1)	0.01
Procedure-related complications			
Total	16 (6.4)	104 (4.3)	0.18
Pericardial effusion	5 (2.0)	17 (0.7)	0.07
Cardiac tamponade	2 (0.8)	6 (0.2)	0.36
Puncture site complication	2 (0.8)	24 (1.0)	1.00
Requiring intervention	0 (0.0)	5 (0.2)	1.00
Phrenic nerve palsy	6 (2.4)	43 (1.8)	1.00
Permanent phrenic nerve paralysis	0 (0.0)	0 (0.0)	1.00
Hemoptysis	2 (0.8)	9 (0.4)	1.00
Gastroparesis	0 (0.0)	7 (0.3)	0.84
Complete atrioventricular block	0 (0.0)	1 (0.0)	1.00
Pneumothorax	0 (0.0)	0 (0.0)	1.00
Pneumonia	0 (0.0)	0 (0.0)	1.00
Atrial-esophageal fistula	0 (0.0)	0 (0.0)	1.00
Pulmonary vein stenosis	0 (0.0)	1 (0.0)	1.00
During index hospitalization			
Cardiac surgery	1 (0.4)	1 (0.0)	0.45
Acute myocardial infarction	1 (0.4)	0 (0.0)	0.16
Cardiac arrest	0 (0.0)	0 (0.0)	1.00
Stroke	0 (0.0)	3 (0.1)	1.00
Death	0 (0.0)	1 (0.0)	1.00

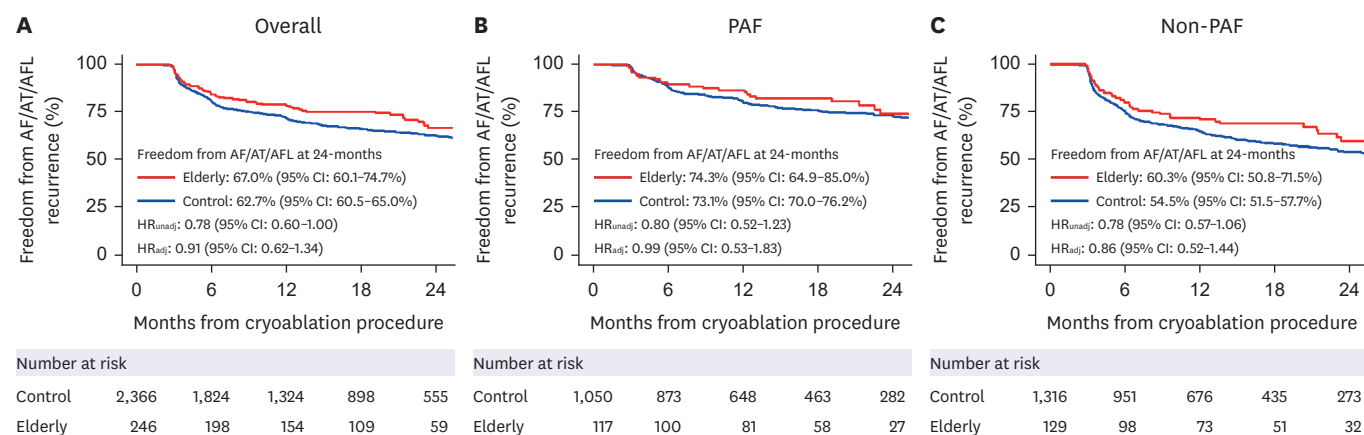
ICE = intracardiac echocardiography.

Table 3. Comparison of clinical outcomes

	Overall (n=2,652)	Elderly (n=249)	Control (n=2,403)
Early recurrence	40 (1.5)	3 (1.2)	37 (1.5)
Duration until detection (months)	5.6 (3.4–10.6)	5.7 (3.4–12.1)	5.6 (3.4–10.5)
Atrial tachyarrhythmias	855 (32.7)	67 (27.2)	788 (33.3)
Type of recurrence			
AF	750 (87.7)	51 (76.1)	699 (88.7)
AFL/AT	241 (28.2)	25 (37.3)	216 (27.4)

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

AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia.

**Figure 1.** Freedom from atrial tachyarrhythmias during 24 months. Kaplan-Meier estimates of freedom from atrial tachyarrhythmias (AF, AT, or AFL) during 24 months after a 90-day blanking period in octogenarians (red line) or controls (blue line) treated with CBA. HR_{unadj} and HR_{adj} are calculated from univariate and multivariate Cox regression models, respectively. The multivariate model include all baseline characteristics from Table 1 with the exception of CHA₂DS₂-VASc score and age.AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia; CI = confidence interval; HR_{adj} = adjusted hazard ratio; HR_{unadj} = unadjusted hazard ratio; PAF = paroxysmal atrial fibrillation.

95% CI, 60.5–65.0%; adjusted HR [HR_{adj}], 0.91; 95% CI, 0.62–1.34; $p=0.63$; **Figure 1A**). This trend was consistent among both paroxysmal AF patients (HR_{adj} , 0.99; 95% CI, 0.53–1.83; $p=0.97$; **Figure 1B**) and non-paroxysmal AF patients (HR_{adj} , 0.86; 95% CI, 0.52–1.44; $p=0.58$; **Figure 1C**). The results remained consistent across various sensitivity analyses: in the multivariate model with stepwise selection applied (HR_{adj} , 0.90; 95% CI, 0.61–1.32; $p=0.59$; **Supplementary Table 1**), when baseline differences between the 2 groups were adjusted using overlap weighting (HR_{adj} , 0.90; 95% CI, 0.69–1.18; $p=0.45$), and when the group classification criterion was set at 80 years (HR_{adj} , 0.91; 95% CI, 0.37–2.26; $p=0.85$; **Supplementary Table 2**).

DISCUSSION

Clinical data about CBA in very elderly Asian population with AF is very limited. Based on the Korean CBA Registry, the principal findings of the present study are as follows: First, the elderly group accounted for 9.4% of patients who underwent index CBA for AF, and successful PVI was achieved in all patients. Second, despite the higher burden of comorbidities in the elderly group, there was no significant difference in the freedom from atrial tachyarrhythmias between the elderly and control groups over a median follow-up period of 20 months. Third, procedure-related adverse events were mild and the rates were similar between the 2 groups.

As the population ages, both the prevalence and average age of patients with AF are increasing, posing frequent challenges to physicians in clinical practice.¹⁾²⁾ Although major studies emphasizing the benefits of catheter ablation for drug refractory AF have been recently published, elderly patients comprised only a small proportion of participants, making it controversial to extrapolate these conclusions directly to older populations.⁶⁻⁸⁾ A post-hoc analysis from the CABANA trial, which compared drug therapy and catheter ablation with mortality-inclusive outcomes, reported that the prognostic benefit of catheter ablation was not observed in patients aged 75 and older (HR, 1.39; 95% CI, 0.75–2.85).⁹⁾ Additionally, a real-world data-based study that examined the comparative effectiveness of AF treatment strategies by age showed that initiating early rhythm control, including catheter ablation, beyond the age of 70 did not have a significant protective association.¹⁰⁾

Given the expected life expectancy of elderly population, symptom control and the reduction of AF burden are likely the primary indications for choosing rhythm control, particularly catheter ablation.¹¹⁾ From RFCA to the development of new technologies like CBA, procedural approaches have consistently demonstrated outstanding outcomes in maintaining sinus rhythm and improving quality of life.⁵⁾⁶⁾ Although the concept that elderly patients can consistently benefit from the effects of CBA remains controversial, several previous small-scale studies have supported this idea. Over a one-year follow-up period, Abugattas et al.¹²⁾ and Vermeersch et al.¹³⁾ found that 81.1% and 59.0% of elderly patients, respectively, maintained normal sinus rhythm after CBA, with no significant difference compared to the control. Additionally, a 2019 CBA study with a longer follow-up period reported no difference in AF recurrence rates after 3 years between patients aged 75 and older and the control group.¹⁴⁾ These findings are consistent with our results.

Recently, AF ablation is exponentially increasing based on data regarding the superior rhythm control effect, the increasing prevalence, the significant proportion of symptomatic patients,¹⁵⁾ and the serious drug-related adverse events due to impaired renal/hepatic

metabolism.¹⁶⁾ However, the inherent invasive nature and the potential for irreversible complications associated with the procedure still make physicians hesitant to proceed it. Particularly, reports indicating that frail individuals not only experience reduced effectiveness of the procedure but also face a higher risk of procedure related complications lead to the underutilization of invasive procedure,¹⁷⁻¹⁹⁾ especially considering the characteristic lean bodyweight prevalent among East Asians.²⁰⁾²¹⁾ From this perspective, CBA, which has a shorter learning curve and procedure time compared to RFCA, and offers standardized and consistent techniques, may be an excellent first choice for AF ablation.⁵⁾²²⁾ A meta-analysis of 16 clinical trials indicated that CBA tends to result in fewer groin site complications, pericardial effusions, and cardiac tamponade.²³⁾ Another meta-analysis showed that while elderly patients who underwent RFCA experienced more overall and cerebrovascular complications, those who received CBA did not show an age-related increase in complications.²⁴⁾ Abdin et al.²⁵⁾ and Hartl et al.²⁶⁾, who reported no procedure-related deaths or atrioesophageal fistulas in elderly AF patients treated with CBA, also supported our findings. One of the most common scenarios during CBA is phrenic nerve injury, with an incidence rate of about 4%.²⁷⁾ In the present study, transient phrenic nerve palsy occurred in 49 (1.8%) patients, making it the most common complication. However, no permanent paralysis was observed in either age group, demonstrating that CBA can be safely performed even in elderly patients

It is well known that the prevalence of AF increases with age, and as of 2022, 12.9% of Koreans aged 80 and older had already been diagnosed with AF.²⁾ Nevertheless, octogenarian patients accounted for only 2.5% of those registered in the Korean CBA Registry. Furthermore, considering that East Asians are often underrepresented in pivotal clinical trials, it suggests that the Asian AF population is one of the most underserved groups in AF treatment.²⁸⁾ Therefore, the results of the present study could provide important evidence supporting the effectiveness of CBA in this population.

This study has several limitations. First, it may not be generalizable that CBA is an optimal rhythm control strategy for very elderly patients with AF because our findings were based on data from tertiary hospitals with extensive experience in AF ablation. Also, despite the high burden of comorbidities in the elderly group, they exhibited a similar benefit-risk profile to the control group. This may suggest that patients likely to benefit from AF ablation were selectively included. Second, detailed procedural characteristics that could act as confounding factors, including procedure time, freeze duration or number per vein, and time-to-isolation among PVs, were not investigated. Third, consistent follow-up protocols, including rhythm monitoring, across institutions and groups could not be ensured. This limitation raises the possibility of overestimating the efficacy and safety profile of CBA in certain groups. Fourth, the number of elderly patients might have been insufficient to adequately assess the efficacy and safety of CBA. Additionally, the study did not investigate the use of antiarrhythmic drugs, cardioversion, or repeat procedures after CBA. Further large-scale, multicenter cohort data are needed to address these issues.

In elderly population with AF, despite a higher burden of comorbidities, the long-term rhythm outcomes after index CBA did not show significant differences compared to younger patients, and a similar level of procedure-related complications was observed. Therefore, CBA may be an effective rhythm control strategy for elderly AF patients.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Hazard ratios for atrial tachycarrhythmia recurrence according to cox regression models

Supplementary Table 2

Results from the sensitivity analyses

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