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ORIGINAL RESEARCH

Extended Period Outcomes of Posterior Box Isolation in 4 Randomized Atrial Fibrillation Catheter Ablation Trials

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ABSTRACT

BACKGROUND Catheter-based electrical posterior box isolation (POBI) and circumferential pulmonary vein isolation (CPVI) do not improve the rhythmic outcomes of atrial fibrillation catheter ablation in previous studies with 12 to 24 months of follow-up.

OBJECTIVES The authors analyzed the long-term rhythm outcomes of our 4 previously conducted randomized controlled trials comparing CPVI alone vs CPVI plus additional POBI using the intention-to-treat principle.

METHODS The authors analyzed 575 AF patients included in our 4 previous randomized controlled trials. We compared clinical recurrence defined as recurrent atrial arrhythmia after the index procedure. In patients who underwent a repeat procedure because of recurrence after the index procedure, the mechanism of recurrence was analyzed.

RESULTS After a median follow-up of 48 months, there were no significant differences in the clinical recurrence or major adverse cardiac events between the CPVI alone and CPVI plus POBI groups. The procedure time was significantly longer, and the atrial tachycardia recurrence rate was higher in the CPVI plus POBI group. In the patients who experienced clinical recurrence, there were no significant differences in the rates of cardioversion or need for repeat procedures between the groups. In patients who underwent a repeat procedure because of recurrence after the index procedure ($n = 64$), the pulmonary vein reconnection rate did not differ, but re-entrant atrial tachycardia was more common in the CPVI plus POBI group, while extrapulmonary vein triggers were more common in the CPVI alone group.

CONCLUSIONS The addition of POBI to CPVI did not improve the long-term rhythm outcomes in patients undergoing atrial fibrillation catheter ablation. (The Evaluation for Prognostic Factors After Catheter Ablation of Atrial Fibrillation, NCT02138695; Evaluation of Proper Radiofrequency Catheter Ablation Strategy for the Patients Who Were Changed to Paroxysmal Atrial Fibrillation From Persistent Atrial Fibrillation, NCT02176616; Comparison of Circumferential Pulmonary Vein Isolation Alone Versus Linear Ablation in Addition to Circumferential Pulmonary Vein Isolation for Catheter Ablation in Persistent Atrial Fibrillation: Prospective Randomized Controlled Trial, NCT02721121; Comparison of Circumferential Pulmonary Vein Isolation and Complex Pulmonary Vein Isolation Additional Linear Ablation for Recurred Atrial Fibrillation After Previous Catheter Ablation: Prospective Randomized Trial [RILI Trial]; NCT02747498 (JACC Asia. 2025;5:285–295)

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ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug

AF = atrial fibrillation

AFCA = atrial fibrillation catheter ablation

AT = atrial tachycardia

CPVI = circumferential pulmonary vein isolation

ECG = electrocardiogram

LA = left atrium

MACE = major adverse cardiovascular event(s)

PAF = paroxysmal atrial fibrillation

PeAF = persistent atrial fibrillation

POBI = catheter-based electrical posterior box isolation of left atrium

PV = pulmonary vein

RCT = randomized controlled trial

The effectiveness of atrial fibrillation catheter ablation (AFCA) is steadily growing. AFCA helps improve the quality of life of the patients by reducing the frequency of atrial fibrillation (AF) episodes and maintaining a stable sinus rhythm.[1] Furthermore, AFCA has beneficial effects in reducing the risk of heart failure-induced mortality.[2] Because most triggers develop from the pulmonary veins (PVs), circumferential pulmonary vein isolation (CPVI) can separate the triggers from the substrate; it is regarded as the cornerstone technique of AFCA in patients with paroxysmal atrial fibrillation (PAF). However, the efficacy of CPVI diminishes in patients with persistent atrial fibrillation (PeAF), which could be possibly attributed to changes in the substrate as the duration of AF increases. The creation of additional lesions has been widely tested to reduce the risk of arrhythmia recurrence. The large randomized controlled trial (RCT), STAR AF II (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II), revealed that linear ablation or ablation of a complex fractionated electrogram has no benefit on the rhythm outcomes in patients with PeAF.[3]

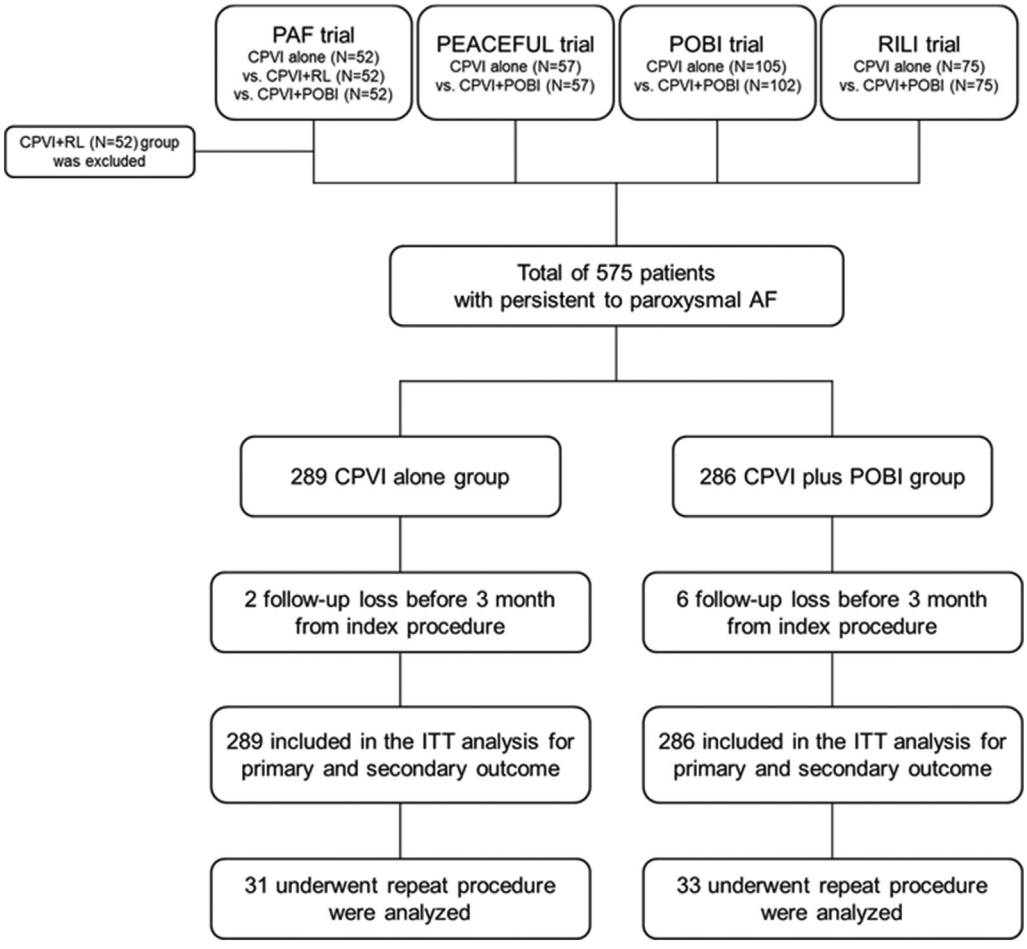
Although there were promising results in some reports,[4,5] subsequent studies have shown that electrical isolation of the left atrial posterior wall (posterior box isolation [POBI]) in persistent AF has not yielded the desired outcomes.[6-9] In a recent RCT, the addition of posterior wall isolation to CPVI in patients with persistent AF did not lead to an improvement in the rhythm outcome at the 12-month follow-up.[10] These RCTs, with follow-up durations of 16 to 24 months, provide insufficient evidence regarding the long-term effects of additional POBI. To address this gap, we conducted an extended analysis of rhythm outcomes based on the intention-to-treat principle in 4 previously conducted RCTs that compared the outcomes of CPVI alone with those of CPVI in addition to POBI. Furthermore, additional procedures in patients with recurrent atrial arrhythmia after index procedure were analyzed to identify the mechanisms of recurrence.

METHODS

STUDY DESIGN. Data from 4 previous RCTs, namely PAF (The Evaluation for Prognostic Factors After Catheter Ablation of Atrial Fibrillation), PEACEFUL (Evaluation of Proper Radiofrequency Catheter Ablation Strategy for the Patients Who Were Changed to Paroxysmal Atrial Fibrillation From Persistent Atrial Fibrillation), POBI (Comparison of Circumferential Pulmonary Vein Isolation Alone Versus Linear Ablation in Addition to Circumferential Pulmonary Vein Isolation for Catheter Ablation in Persistent Atrial Fibrillation: Prospective Randomized Controlled Trial), and RILI (Comparison of Circumferential Pulmonary Vein Isolation and Complex Pulmonary Vein Isolation Additional Linear Ablation for Recurred Atrial Fibrillation After Previous Catheter Ablation: Prospective Randomized Trial), were analyzed. Participants in the 4 trials were followed up for an extended period from enrollment to April 10, 2023. The protocols for the 4 trials are described in Supplemental Table 1. Basically, 4 trials were RCTs that examined the effectiveness of POBI in patients with drug-refractory nonvalvular AF. The PAF trial was a study of patients with paroxysmal AF. The PEACEFUL trial was a study of patients with persistent AF who changed to paroxysmal AF after taking antiarrhythmic drugs (AADs). The POBI trial was a study of patients with persistent AF. The RILI trial was a study of recurred AF patients who had previously undergone CPVI. The baseline and procedure-related characteristics of each trial are described in Supplemental Tables 2 to 5.

The exclusion criteria were patients with the following: 1) rheumatic valvular disease; 2) significant structural heart disease other than left ventricular hypertrophy; 3) an enlarged left atrium (LA) ≥60 mm; and 4) history of cardiac surgery. Before all ablation procedures, the absence of LA thrombi was confirmed using transesophageal echocardiography or computed tomography (CT), and the anatomies of the LA and PVs were visually defined using 3-dimensional (3D) CT scans (64-channel, Light Speed Volume CT, Philips, Brilliance 63). All AADs were discontinued after at least 5 half-lives. The studies were performed using open-label, prospective, randomized protocols. Randomization was performed by core laboratory clinical research coordinators (Yonsei University), and informed consent was obtained from the physicians at each participating institution. Both the patients and physicians were blinded to the initial allocation, and the rhythm outcome was registered by the research coordinators based on Holter and electrocardiogram (ECG) documentation. This protocol was approved by the Institutional Review Boards of each hospital and registered in clinicaltrials.gov (PAF trial from the Yonsei AF Ablation Cohort, NCT02138695; PEACEFUL

FIGURE 1 Flow Chart of the Study



Excluding the 52 patients in the PAF (Paroxysmal Atrial Fibrillation) trial who underwent only roof line (RL) and pulmonary vein isolation were performed without a posterior-inferior line, a total of 575 patients across the 4 trials were included in the study analysis. The primary and secondary outcomes were analyzed with intention to treat (ITT) in the circumferential pulmonary vein isolation (CPVI) alone (n = 289) and CPVI plus posterior box isolation (POBI) (n = 286) groups. In patients with recurrence of atrial arrhythmia, repeat procedure was performed in 31 and 33 patients, respectively. The mechanism of recurrence identified during repeat procedure was also analyzed. AF = atrial fibrillation; PEACEFUL = Evaluation of Proper Radiofrequency Catheter Ablation Strategy for the Patients Who Were Changed to Paroxysmal Atrial Fibrillation From Persistent Atrial Fibrillation; RILI = Comparison of Circumferential Pulmonary Vein Isolation and Complex Pulmonary Vein Isolation Additional Linear Ablation for Recurred Atrial Fibrillation After Previous Catheter Ablation: Prospective Randomized Trial.

trial, NCT02176616; POBI trial, NCT02721121; and RILI trial, NCT02747498). Except for the PAF trial, which was conducted in 3 groups, the remaining 3 trials were conducted in 2 groups based on the AFCA method: CPVI alone and CPVI plus POBI (with or without an anterior line) groups. Because the PAF trial was conducted in 3 groups based on the AFCA method, namely CPVI alone, CPVI plus roof line, and CPVI plus POBI, the CPVI plus roof line group was excluded from this analysis (Figure 1).

ELECTROPHYSIOLOGY MAPPING AND AFCA. A Prucka CardioLab Electrophysiology system (General Electric Medical Systems, Inc) was used to record intracardiac electrograms. Merged images from 3D electroanatomical mapping system (NavX, Abbott, Inc, CARTO system, Biosense Webster) and 3D spiral

CT scans were used for AFCA in all patients. After the transseptal puncture, pulmonary venograms in the right and left anterior oblique views were obtained. The details of the AFCA technique and strategy were described in our previous study.[6-9,11] Intravenous heparin was administered for systemic anticoagulation to maintain an activated clotting time of 350 to 400 seconds during the procedure. The esophageal temperature was monitored in all patients, and its cutoff value was defined as 38.4 °C during radiofrequency (RF) energy delivery on the LA posterior wall. An open-irrigated tip deflectable catheter (FlexAbility, Abbott Inc; TactiCath, Abbott Inc; ThermoCool SmartTouch, Biosense Webster Inc) was used. The RF power for AFCA varied between 25 and 60 W. Using the Carto 3D system, an adequate lesion formation was defined as an ablation index of 450 or more for PV isolation and 400 or more for posterior wall isolation, and using the NavX 3D system, an adequate lesion formation was defined as follows: 1) more than 50% of the reduction of bipolar voltage amplitude; 2) no sharp potential; 3) more than 10 Ω of impedance drop. All patients underwent antral circumferential ablation around the PVs. In patients randomized to the CPVI plus POBI group, we created a roof and posterior-inferior line that spanned from one side to the opposite, connecting the CPVI ablation sites on both sides. In patients who underwent repeated ablation procedures because of clinical recurrence, the reconnection at the previous ablation site and mechanism of recurrence were thoroughly investigated. Electrical reisolation of the PV was performed in patients with reconnected PV, and the critical isthmus causing re-entry was ablated in patients with re-entrant tachycardia. After protocol-based ablation, AF or atrial tachycardia (AT) was induced using 10 seconds of high-current burst pacing (10 mA, pulse width 5 ms; Bloom Associates) from the high right atrial electrodes. This commenced at a pacing cycle length of 250 ms and was gradually reduced to 120 ms. Isoproterenol (5 to 20 μg/min depending on beta-blocker use with a target heart rate of 120 beats/min) was infused for at least 3 minutes before induction, and this was maintained for 3 minutes after the induction of AF or AT. If sustained AF or AT was induced, internal cardioversion was performed using biphasic shock (2-20 J) with R-wave synchronization (Lifepak12, Physiocontrol Ltd). The procedure was ended when there was no immediate AF recurrence within 10 minutes of isoproterenol infusion, with or without cardioversion. If further AF triggers were observed under the isoproterenol effect, the potential location of the extra-PV triggers was determined based on contact bipolar electrograms, and quick and detailed 3D-activation mapping was conducted with a multielectrode catheter. Based on the 3D mapping of the extra-PV foci, those foci were ablated at 35 to 50 W for 10 seconds in each lesion until elimination.

FOLLOW-UP AND RHYTHM MONITORING. All patients were required to administer oral anticoagulants for a minimum duration of 3 months after the procedure. The use of AADs was initially allowed; however, it was discouraged after the initial 3 months. Repeated ablation was permitted in patients with recurrent atrial arrhythmias refractory to AAD. Patients were followed up in the outpatient clinic at 1, 3, 6, and 12 months, and regularly every 6 months thereafter or upon symptom recurrence. An ECG was conducted during each visit, and 24-hour Holter monitor recordings were performed at 3 and 6 months, followed by subsequent monitoring every 6 months. Additional Holter monitoring or event recordings were performed when patients experienced palpitations, suggesting arrhythmia recurrence. Holter analysis and adjudication were performed by an individual who was blinded to the study group assignment. The details of follow-up are described in Supplemental Table 6.

ENDPOINTS. The primary endpoint was clinical recurrence beyond 3 months postprocedure, defined as any episode of atrial arrhythmia (AF or AT) lasting at least 30 seconds. The secondary endpoint was episode of AF, AT, and major cardiac adverse events (MACE), defined as a composite of cardiac death, ischemic stroke, acute coronary syndrome, and hospitalization for heart failure. Additional outcomes, such as AAD use, cardioversion, and repeated procedures in patients with clinical recurrence, were also analyzed. In patients who underwent repeated procedures, the mechanisms of arrhythmia, previous ablation site reconnection, and extra PV triggers were identified.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD or median (IQR), whereas categorical variables are presented as frequencies and percentages. Continuous variables were compared using the Student's *t*-test or Mann-Whitney *U* test. Categorical variables are depicted as percentages of the total group and were compared using either the chi-square test or Fisher exact test. The primary and secondary outcomes were analyzed according to the intention-to-treat principle. Kaplan-Meier curves and log-rank tests were used to analyze the cumulative incidence of the outcomes. Before performing the Cox regression analysis, Schoenfeld's test was performed to determine if there was a violation of the

TABLE 1 Baseline and Procedure-Related Characteristics of The Patients

	CPVI Alone (n = 289)	CPVI Plus POBI (n = 286)	*P* Value
Clinical characteristics			
Age, y	59.0 (52.0-66.0)	59.0 (52.0-66.0)	0.685
Male	224 (77.5)	224 (78.3)	0.893
Paroxysmal AF	100 (34.6)	93 (32.5)	0.659
Persistent AF	189 (65.4)	193 (67.5)	
CHA_2DS_2-VASc score	1.0 (1.0-2.0)	1.0 (0.0-2.0)	0.327
Congestive heart failure	49 (17.0)	53 (18.5)	0.700
Hypertension	140 (48.4)	124 (43.4)	0.254
Diabetes mellitus	55 (19.0)	39 (13.6)	0.102
Stroke/TIA	34 (11.8)	34 (11.9)	1.000
Vascular disease	16 (5.5)	21 (7.3)	0.476
Hb, g/dL	14.5 (13.2-15.2)	14.5 (13.3-15.6)	0.332
Creatinine, mg/dL	1.0 (0.8-1.1)	0.9 (0.8-1.0)	0.236
LA AP diameter, mm	42.0 (38.0-46.0)	43.0 (38.0-47.0)	0.224
LA volume index, mL/m^2	35.3 (29.0-44.3)	38.0 (31.0-48.0)	0.055
LV ejection fraction, %	62.0 (57.5-67.0)	63.0 (57.5-66.0)	0.882
E/e′	9.3 (8.0-12.0)	9.0 (7.4-11.3)	0.094
LVEDD, mm	50.0 (47.0-53.0)	50.0 (47.0-53.0)	0.671
LVMI, g/m^2	90.0 (78.2-102.7)	91.4 (79.2-104.9)	0.780
Procedure-related characteristics			
Procedure time, min	162.0 (124.5-195.0)	181.0 (148.0-216.0)	<0.001
Ablation time, s	3,932.0 (1,855.5-4,827.5)	4,987.0 (2,372.0-6,137.0)	<0.001
Contact force sensing catheter use	41 (14.2)	30 (10.5)	0.222
Ablation lesions			
Posterior box isolation (%/BDB%)	0 (0.0)	236 (100/82.5)	<0.001
Linear ablation at LA, other than POBI	12 (4.2)	127 (44.4)	<0.001
Lateral mitral isthmus line	2 (0.7)	19 (6.6)	<0.001
Anteroseptal line	9 (3.1)	12 (4.2)	0.639
Anterolateral line	2 (0.7)	108 (37.8)	<0.001
Cavo-tricuspid isthmus line	276 (95.5)	279 (97.6)	0.265
SVC to RA septal line	173 (59.9)	180 (62.9)	0.502
Major complication	10 (3.5)	7 (2.4)	0.638
Cardiac tamponade	4 (1.4)	1 (0.3)	0.375
Sinus node dysfunction	0 (0.0)	3 (1.0)	0.243
Phrenic nerve palsy	0 (0.0)	2 (0.7)	0.474
Arteriovenous fistula	2 (0.7)	1 (0.3)	1.000
Atrio-esophageal fistula	1 (0.3)	0 (0.0)	1.000
Pulmonary vein stenosis	3 (1.0)	0 (0.0)	0.251

Values are median (Q1-Q3) or n (%).

AF = atrial fibrillation; AP = anteroposterior; BDB = bidirectional block; CPVI = circumferential pulmonary vein isolation; Hb = hemoglobin; LA = left atrium; LV = left ventricle; LVEDD = left ventricular end-diastolic dimension; LVMI = left ventricular mass index; POBI = posterior box isolation; RA = right atrium SVC = superior vena cava; TIA = transient ischemic attack.

proportional hazard assumption. Univariate and multivariate Cox regression analysis was performed to obtain the HRs and 95% CIs. A 2-sided *P* value <0.05 was considered statistically significant. Statistical analyses were performed using R software version 4.3.1 (R Foundation for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS AND PROCEDURE-RELATED CHARACTERISTICS. After excluding 52 participants who underwent only roof line ablation in the PAF trial, 575 patients were included in the analysis. The numbers of participants in the CPVI alone and CPVI plus POBI groups were 289 and 286, respectively. The mean age of the enrolled participants was 58.5 ± 10.7 years and 77.9% were men. The median follow-up duration was 48.6 months (Q1-Q3: 26.3-69.0 months). Overall, the demographic and clinical characteristics were balanced between the groups (Table 1). Successful CPVI was achieved in all of the patients. POBI was performed in all patients enrolled in the CPVI plus POBI group, and a bidirectional block

TABLE 2 Event Rate of Clinical Recurrence and its Rhythm Management

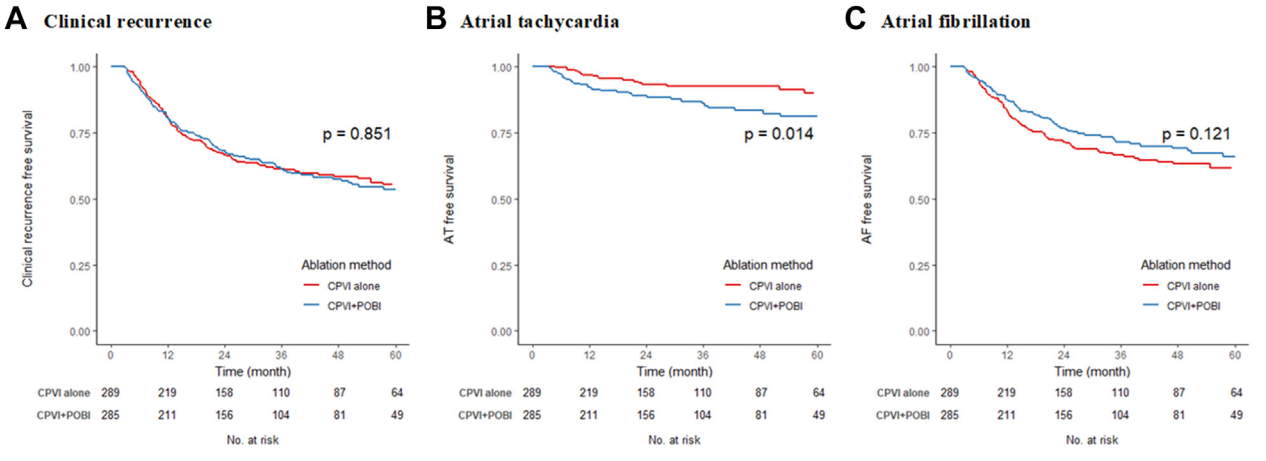
	CPVI Alone (n = 289)	CPVI Plus POBI (n = 286)	*P* Value
Clinical recurrence	124 (42.9)	118 (41.3)	
Total follow-up period (person-y)	914.1	865.0	
100 person-y event rate	13.56	13.64	
Atrial tachycardia[a]	19 (15.3/6.6)	36 (30.5/12.6)	
Atrial fibrillation[a]	105 (84.7/36.3)	82 (69.5/28.7)	
Rhythm management for recurrence	**(n = 124)**	**(n = 118)**	
Antiarrhythmic drug	92 (74.2)	91 (77.1)	0.704
Cardioversion	42 (33.9)	55 (46.6)	0.059
Repeat RF catheter ablation[b]	31/102 (30.4)	33/104 (31.7)	0.955

Values are n (%) unless otherwise indicated. [a]Presented as % of recurrence/% of total. [b]Insufficient information for performance of repeated procedure (other hospital): 22 for CPVI only, 14 for CPVI plus POBI.
RF = radiofrequency; other abbreviations as in Table 1.

of the posterior wall was confirmed in 236 (82.5%) patients. The procedure and ablation times were longer in the CPVI plus POBI group. Contact force sensing catheter was used in 71 (12.3%). Although the proportion of ablations conducted in right atrium (cavotricuspid isthmus ablation or linear ablation from superior vena cava to the atrial septum) did not differ between the 2 groups, lateral mitral isthmus line and anterolateral line ablations were more frequently performed in the CPVI plus POBI group than those in the CPVI alone group. There were no significant differences in the major complications during or after the procedure between the CPVI alone and CPVI plus POBI groups (3.5% vs 2.4%, respectively; $P = 0.638$).

PRIMARY ENDPOINT. There was no significant difference in the clinical recurrence rate between the CPVI alone and CPVI plus POBI groups (124 [42.9%] vs 118 [41.3%], respectively; log-rank $P = 0.855$) (Table 2, Figure 2A). In each of the 4 trials, there was no significant difference in the clinical recurrence rate between the CPVI alone and CPVI plus POBI groups (Supplemental Figure 1). The recurrence of AT was higher in the CPVI plus POBI than that in the CPVI alone group (36 [12.6%] vs 19 [6.6%], respectively; log-rank $P = 0.014$) (Figure 2B). There was no significant difference in the AF recurrence between the CPVI alone and CPVI plus POBI groups (105 [36.3%] vs 82 [28.7%], respectively; log-rank $P = 0.122$) (Figure 2C). These results were similar when comparing the complete POBI group to the CPVI alone group (Supplemental Figure 2). Because there was a violation of proportional hazard assumption in Schoenfeld's test for clinical recurrence and AF recurrence, Cox regression analysis was performed only for AT recurrence. In multivariate Cox regression analysis, POBI was significantly associated with AT recurrence (HR: 2.70 [95% CI: 1.45-5.04]; $P = 0.002$) (Table 3). Among the patients underwent CPVI with POBI, clinical recurrence, especially AF recurrence, was higher in the group that underwent additional linear ablation in LA (Supplemental Figure 3). However, additional linear ablation group has higher

FIGURE 2 Kaplan-Meier Curve for Clinical Recurrence, AT, and AF



(A) Clinical recurrence; (B) atrial tachycardia (AT); and (C) AF. The incidence of clinical recurrence and recurrence as AF did not differ between the 2 groups. Recurrence as AT occurred more frequently in the CPVI plus POBI than in the CPVI alone group. Abbreviations as in Figure 1.

proportion of persistent AF and larger LA size (Supplemental Table 7).

SECONDARY ENDPOINT. MACE occurred in 20 patients (4.1%). There was no significant difference in the cumulative incidence of MACE in the CPVI alone and CPVI plus POBI groups (11 vs 9, respectively; log-rank $P = 0.675$) (**Figure 3**, Supplemental Table 8). The individual outcomes of MACE did not differ between the 2 groups (Supplemental Figure 4).

RHYTHM MANAGEMENT AFTER CLINICAL RECURRENCE. There was no significant difference in the rhythm management for clinical recurrence (**Table 2**). The percentage of those using AAD after recurrence were 74.2% in the CPVI alone and 77.1% in the CPVI plus POBI group ($P = 0.704$). The cardioversion rate was 33.9% in the CPVI alone and 46.6% in the CPVI plus POBI group ($P = 0.059$). The repeated procedure was performed in 30.4% and 31.7% of the patients in the CPVI alone and CPVI plus POBI groups, respectively ($P = 0.955$).

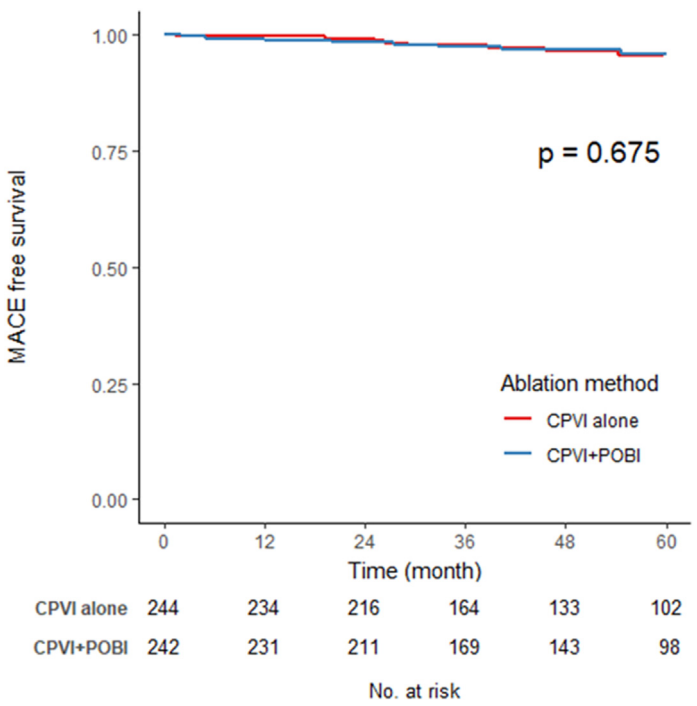
RHYTHM OUTCOMES AND MECHANISMS OF ARRHYTHMIA AT THE REPEAT PROCEDURES. After the index procedure, 64 patients underwent repeat ablation procedure because of recurrent atrial arrhythmia refractory to antiarrhythmic drug. Ablation lesions in repeat ablation were described in **Table 4**. The clinical recurrence after repeat ablation was 18 (58.1%) in the CPVI alone group and 13 (39.4%) in the CPVI plus POBI group. The mechanisms of recurrence differed between the CPVI alone and CPVI plus POBI groups (**Table 5**). The main mechanism of recurrence in the CPVI alone group was AF (51.6% in the CPVI alone vs 21.2% in the CPVI plus POBI group; $P = 0.018$), while re-entrant AT was the main mechanism of recurrence in the CPVI plus POBI group (42.4% in the CPVI plus POBI vs 9.7% in the CPVI alone group; $P = 0.007$). The PV reconnection rate (80.6% in the CPVI alone vs 81.8% in the CPVI plus POBI group; $P = 0.933$) and incidence of focal AT (9.7% in CPVI alone vs 9.1% in the CPVI plus POBI group; $P = 1.000$) did not differ between the 2 groups. Excluding patients in whom conduction block was not checked, reconnection rate of roof line was 35.5% and posterior-inferior line was 60%. Enduring POBI was observed in 11 (36.7%) patients at the time of redo ablation procedure. Among the patients who underwent isoproterenol provocation after CPVI (n = 38), extra-PV triggers were more commonly observed in the CPVI alone group (42.9%) than in the CPVI plus POBI group (5.9%; $P = 0.012$).

TABLE 3 Cox Regression Analysis for Atrial Tachycardia

	Univariate		Multivariate	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.00 (0.97-1.02)	0.948		
Sex	0.69 (0.39-1.22)	0.198	0.81 (0.41-1.59)	0.535
Body mass index	1.00 (0.91-1.09)	0.927		
Persistent AF	0.79 (0.46-1.35)	0.394		
Hypertension	1.11 (0.66-1.89)	0.689		
Diabetes mellitus	1.16 (0.58-2.30)	0.671		
Hemoglobin	0.83 (0.70-0.99)	0.039	0.85 (0.69-1.05)	0.128
Creatinine	1.01 (0.51-2.01)	0.980		
LA AP diameter	0.99 (0.95-1.03)	0.631		
LV ejection fraction	1.02 (0.98-1.05)	0.343		
E/e′	1.03 (0.97-1.10)	0.354		
POBI	1.98 (1.13-3.45)	0.016	2.70 (1.45-5.04)	0.002
CTI block	0.94 (0.23-3.86)	0.930		
SVC-RA septal line	0.66 (0.39-1.13)	0.130	0.78 (0.42-1.44)	0.419

CTI = cavotricuspid isthmus; other abbreviations as in Table 1.

FIGURE 3 Kaplan-Meier Curve for Major Adverse Cardiac Events



The incidence of major adverse cardiac events (MACE) defined as composite of cardiac death, stroke, acute coronary syndrome, and hospitalization for heart failure, did not differ between the 2 groups. *Cases with no information on MACE (other hospital) were excluded (CPVI alone, n = 45 and CPVI plus POBI, n = 44). Abbreviations as in Figure 1.

TABLE 4 Ablation Lesions and Rhythm Outcomes of Repeat Ablation

	CPVI Alone (n = 31)		CPVI Plus POBI (n = 33)	
Ablation lesions in repeat ablation[a]				
Posterior box isolation (%/BDB%)	19 (61.3/51.6)		33 (100.0/78.8)	
Linear ablation at LA, other than POBI	11 (35.5)		21 (63.6)	
Lateral mitral isthmus line	2 (6.5)		7 (21.2)	
Anteroseptal line	3 (9.7)		4 (12.1)	
Anterolateral line	8 (25.8)		18 (54.5)	
Cavo-tricuspid isthmus line	31 (100.0)		33 (100.0)	
SVC to RA septal line	26 (83.9)		28 (84.8)	
Preprocedure Diagnosis	**AT (n = 6)**	**AF (n = 25)**	**AT (n = 14)**	**AF (n = 19)**
Rhythm outcome of repeat ablation				
No recurrence	2 (33.3)	11 (44.0)	10 (71.4)	10 (52.6)
Recurrence as AT	2 (33.3)	4 (16.0)	3 (21.4)	5 (26.3)
Recurrence as AF	2 (33.3)	10 (40.0)	1 (7.1)	4 (21.1)
Clinical recurrence	18 (58.1)		13 (39.4)	

Values are n (%) unless otherwise indicated. [a]Ablation lesions in repeat ablation include ablation lesions in index procedure.
Abbreviations as in Table 1.

DISCUSSION

MAIN FINDINGS. In the present study, the extended follow-up period after AFCA revealed a clinical recurrence rate exceeding 40%, with no significant difference between the 2 groups. However, recurrence as AT was more frequent in the additional POBI group than that in the CPVI-alone group (**Central Illustration**). Re-entrant AT was the predominant mechanism of recurrence in the POBI group, underscoring the challenging limitation of linear ablation posing re-entry from reconnection. Interestingly, extra-PV triggers were more frequent in the CPVI alone group than in the CPVI plus POBI group.

PREVIOUS RCTs REGARDING THE ROLE OF POBI IN AF ABLATIONS. Given that the main elements in the AF mechanism are triggers and atrial substrates, CPVI is widely recognized as a cornerstone procedure in most AF cases. However, in the case of progressive AF, particularly in the context of PeAF, there tends to be a more advanced atrial substrate and additional triggers beyond PVs. Several trials have been conducted to devise adjunctive ablation strategies that modify substrates in patients with AF in addition to CPVI. Several studies have reported benefits of linear ablation in addition to CPVI in PeAF.[12-14] In the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Part II Trial, the efficacy of a CPVI alone strategy was evaluated against combinations involving CPVI with linear ablation and CPVI with focal ablation targeting complex fractionated electrograms in patients with PeAF; however, the outcome proved to be unsatisfactory.[3] As a method to reduce atrial substrate, the achievement of electrical isolation of the LA posterior wall by adding roof and posterior-inferior lines to PV isolation has been examined in several studies. Mun et al[11] reported that adding roof and posterior-inferior lines to CPVI in patients with PAF did not improve the rhythm outcomes. Yu et al[7] reported that although the additional linear ablation did not improve the rhythm outcomes, the subgroup with POBI achieving complete bidirectional block showed a favorable rhythm outcome in patients with PeAF who changed to PAF after using AADs. The efficacy of POBI was assessed in 3 RCTs, namely the POBI, PEACEFUL, and RILI trials, where a complete block of POBI was achieved by touch-up ablation of the remnant potentials on the LA posterior wall in patients with PeAF, PeAF to PAF after using AAD, and recurred AF after previous CPVI.[6,8,9] However, the results of the 3 trials were negative. The CAPLA (Catheter Ablation for persistent atrial fibrillation: A Multicenter randomized trial of Pulmonary vein isolation vs PVI with posterior left atrial wall isolation) trial revealed that compared with CPVI alone, adding posterior wall isolation to CPVI did not improve the freedom from atrial arrhythmia in patients with PeAF at 12 months.[10] In a subgroup analysis of a meta-analysis of 10 RCTs comparing the clinical outcomes of CPVI plus posterior wall isolation vs CPVI alone, the addition of posterior wall isolation to CPVI in patients with nonparoxysmal AF reduced the atrial arrhythmia over a mean follow-up of 15.7 months.[15] Our findings provide additional evidence regarding the long-term outcomes of POBI and mapping of non-PV trigger by AF or AT induction using isoproterenol. Because the presence of non-PV

trigger can affect rhythm outcome, removing the non-PV trigger would have further narrowed the baseline difference between the 2 groups and allowed for a fairer comparison. And, mapping of non-PV trigger allowed us to find the difference in non-PV triggers between 2 groups.

POTENTIAL ANTI-AF MECHANISMS OF POBI. In this study, although the addition of POBI did not improve the long-term rhythm outcomes, the instances of AF recurrence were lower in the CPVI plus POBI group, albeit without reaching statistical significance. A substudy of the CAPLA trial revealed that compared with CPVI alone, adding POBI to PVI in patients with rapid posterior wall activity was associated with a significant reduction in arrhythmia recurrence at 12 months.[16] Furthermore, a recent meta-analysis of prior RCTs provided additional evidence supporting the potential anti-AF effects of POBI.[17] There is substantial evidence that the LA posterior wall plays an important role in AF. Because the LA posterior wall embryonically originates from the same tissue as the PV, it serves as a substrate and site of AF triggers.[18] The orientation of myocardial fibers at the junction between the LA posterior wall and PVs is heterogeneous, resulting in varying conduction velocity and refractoriness.[19] Accordingly, re-entry is easily formed in the LA posterior wall. In addition, the LA posterior wall contains ganglionated plexi, which includes a high density of autonomic neurons and contributes to AF.[20] Theoretically, POBI is expected to play a multipotent role by reducing the trigger burden, modifying the substrate, and influencing certain ganglionated plexi. In the current study, we observed a reduction in the right-sided extra-PV triggers. This finding suggests that modification of the ganglionated plexi near the LA posterior wall may have an effect in suppressing the firing of extra-PV triggers affected by autonomic tones. However, the result of a higher incidence of AT in the CPVI plus POBI group than that in the CPVI alone group suggests that achieving enduring and sustained electrical isolation of the posterior box remains challenging although POBI effectively reduces the critical mass and suppressing the extra-PV triggers. Pambrun et al[21] reported that conduction gaps along the roof line are common (33%) and are associated with maintained epicardial conduction through the septopulmonary bundle. Another potential obstacle for achieving long-lasting POBI might be the epicardial adipose tissue volume. Kim et al[22] reported that a larger epicardial adipose tissue volume was associated with a greater POBI reconnection rate. The low electrical and thermal conductivity of the adipose tissue may hinder the penetration of radiofrequency current and heat to the underlying tissue.

TABLE 5 Mechanism of Arrhythmia of the Repeated Procedure

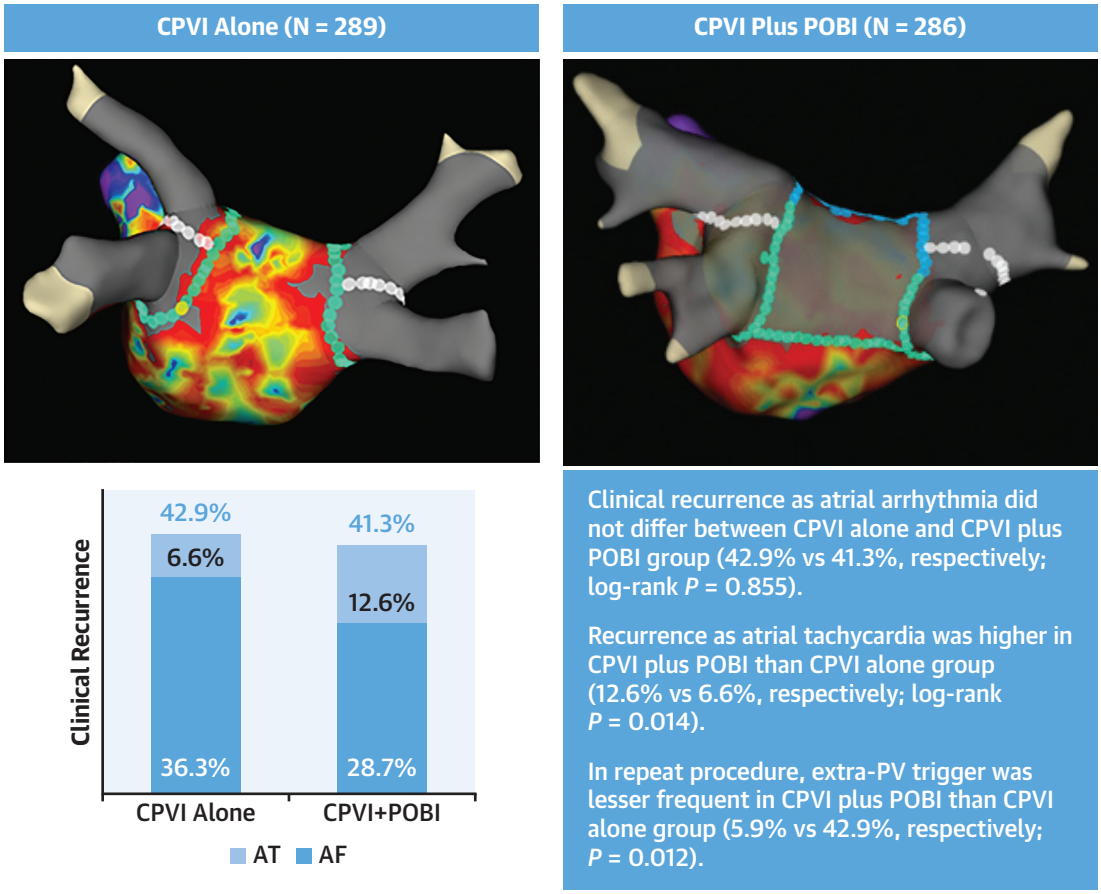
	CPVI Alone (n = 31)	CPVI Plus POBI (n = 33)	*P* Value
Mechanisms of arrhythmia			
Atrial fibrillation	16 (51.6)	7 (21.2)	0.018
Re-entrant atrial tachycardia	3 (9.7)	14 (42.4)	0.007
Perimitral re-entry[a]	2 (66.7/6.5)	11 (78.6/33.3)	
Micro-re-entry at LAPW[a]	2 (66.7/6.5)	2 (14.3/6.1)	
Micro-re-entry at LAA base[a]	1 (33.3/3.2)	0 (0.0)	
Micro-re-entry at RA[a]	0 (0.0)	2 (14.3/6.1)	
Re-entry at SVC[a]	0 (0.0)	1 (7.1/3.0)	
Multiple re-entry circuit			
2 circuits[a]	0 (0.0)	2 (14.3/6.1)	
3 circuits[a]	1 (33.3/3.2)	0 (0.0)	
Focal atrial tachycardia	3 (9.7)	3 (9.1)	1.000
Multiple mechanism	4 (12.9)	4 (12.1)	1.000
Noninducible or unknown	8 (25.8)	9 (27.3)	1.000
Reconnections of previous ablation site			
Any PV reconnection	25 (80.6)	27 (81.8)	1.000
Number of reconnected PV ≤2	16 (51.6)	16 (48.5)	
Number of reconnected PV ≥3	9 (29.0)	11 (33.3)	
Roof line reconnection[b]	0/0 (0.0)	11/31 (35.5)	
Posteroinferior line reconnection[b]	0/0 (0.0)	18/30 (60.0)	
CTI reconnection[b]	6/27 (22.2)	5/33 (15.2)	0.712
Isoproterenol induced extra-PV triggers[c]	9/21 (42.9)	1/17 (5.9)	0.012
Superior vena cava	1 (4.8)	0 (0.0)	0.975
Coronary sinus	1 (4.8)	0 (0.0)	0.975
Bachmann's bundle	1 (4.8)	0 (0.0)	0.975
Atrial septum	2 (9.5)	0 (0.0)	0.445
Multifocal or unmappable	4 (19.0)	1 (5.9)	0.315

Values are n (%) unless otherwise indicated. In the RILI (Comparison of Circumferential Pulmonary Vein Isolation and Complex Pulmonary Vein Isolation Additional Linear Ablation for Recurred Atrial Fibrillation After Previous Catheter Ablation: Prospective Randomized Trial), patients who underwent trido procedures were assessed (n = 4). [a]% of re-entry atrial tachycardia/% of repeat procedures. [b]Line reconnection: (bidirectional block)/(test to confirm BDB). [c]Inducible extra-PV trigger/isoproterenol infusion and ramp pacing test.

CTI = cavotricuspid isthmus; LAA = left atrial appendage; LAPW = left atrial posterior wall; LR = late recurrence; PV = pulmonary vein; other abbreviations as in Table 1.

FUTURE DIRECTIONS TO IMPROVE THE OUTCOME OF AF ABLATION. The recurrence rate was approximately 40% in both groups even after achieving successful AFCA, and the repeated procedure data showed approximately 80% reconnection rates of any PV in both groups. In contrast, the reconnection rates of the roof and posterior-inferior line were 65.5% and 35%, respectively, in the CPVI plus POBI group. Given the potential for PV reconnection to have a significant impact on AF recurrence, the true effect of POBI may be obscured or underestimated. Therefore, it is essential to achieve the solid isolation of PVs before evaluating the impact of POBI. A comparative analysis of contemporary technologies such as pulsed-field ablation against RF catheter ablation may be necessary to determine their efficacy in achieving

CENTRAL ILLUSTRATION **Extended Period Rhythm Outcome of Circumferential Pulmonary Vein Isolation vs Circumferential Pulmonary Vein Isolation Plus Posterior Box Isolation**



The top row shows representative ablation lesions of circumferential pulmonary vein isolation (CPVI) alone (left) and CPVI plus posterior box isolation (POBI) (right). The bottom bar plot shows that recurrence as atrial tachycardia was more common in the CPVI plus POBI group, although clinical recurrence did not differ between the 2 groups. AF = atrial fibrillation; AT = atrial tachycardia; PV = pulmonary vein.

solid PV isolation. Recently, studies comparing pulsed field ablation and RF ablation in PV isolation have been accumulating.[23] Posterior wall isolation has also been studied with pulsed field ablation and found negative results, but long-term results are needed to determine whether durable isolation is maintained.[24]

STUDY LIMITATIONS. First, because we included a PAF trial, the impact of POBI could be less pronounced in patients with PAF, as they may have a lesser atrial substrate. Second, there were 44% of patients in the CPVI plus POBI group who received lateral mitral or anterior lines, which can be proarrhythmic. Third, our results cannot be generalized because the median follow-up durations of the 4 trials were heterogeneous. AF recurrence is more likely to be detected in patients with a longer follow-up period, because aging is one of the risk factors for AF occurrence. Fourth, in the 18% of CPVI plus POBI group, complete POBI was not achieved despite additional ablation at inside of LA posterior wall. Fifth, the precise assessment of the AF burden was limited by the reliance on regular 12-lead ECG and Holter monitoring despite conducting routine rhythm follow-ups for all the enrolled patients. The majority

of clinical recurrences occurred within 12 months after index procedure in this study. Because the follow-ups beyond 12 months after the index procedure were performed less frequently than those within 12 months, less intensive follow-up may have contributed to these results.

CONCLUSIONS

The addition of POBI to CPVI did not improve the long-term rhythm outcomes in patients who underwent AFCA. Notably, the addition of POBI to CPVI was associated with increased AT recurrence and concurrent reduction in extra-PV triggers in this patient population. These findings emphasize the importance of comprehensive evaluation when optimizing procedural strategies for improved outcomes in the context of AFCA.

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KEY WORDS atrial fibrillation, catheter ablation, long-term, posterior box isolation, recurrence

APPENDIX For supplemental tables and figures, please see the online version of this paper.