



# Optimal single procedure strategy of pulmonary vein isolation with cryoballoon or radiofrequency and non-pulmonary vein triggers ablation for non-paroxysmal atrial fibrillation<sup>☆</sup>

Giichi Nitta<sup>a,\*</sup>, Junichi Nitta<sup>b</sup>, Osamu Inaba<sup>a</sup>, Akira Sato<sup>a</sup>, Yukihiro Inamura<sup>a</sup>, Tomomasa Takamiya<sup>a</sup>, Masahiko Goya<sup>c</sup>, Tetsuo Sasano<sup>c</sup>

<sup>a</sup> Department of Cardiology, Japanese Red Cross Saitama Hospital, 1-5 Shintoshin, Chuo-ku, Saitama 330-8553, Japan

<sup>b</sup> Department of Cardiology, Sakakibara Heart Institute, 3-16-1 Asahi-cho, Fuchu City, Tokyo 183-0003, Japan

<sup>c</sup> Department of Cardiovascular Medicine, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

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## ABSTRACT

**Background:** Limited data exist on pulmonary vein isolation (PVI) using cryoballoon (CB) or radiofrequency (RF) ablation and additional non-pulmonary vein trigger ablation for non-paroxysmal atrial fibrillation (non-PAF). We aimed to assess the outcomes of first-stage catheter ablation for non-PAF patients.

**Methods:** Initial PVI was performed on 734 non-PAF patients (age:  $64 \pm 10$  years; male: 584 (80%)) between September 2014 and June 2018 [315 (43%), CB ablation; 419 (57%), RF catheter]. A logistic regression model was used to match 257 pairs (514 patients) according to the propensity scores (CB or RF group). After PVI, additional non-PV trigger ablation was performed if induced by isoproterenol. We analysed the clinical outcomes of both groups.

**Results:** The mean procedural time was significantly shorter in the CB group (125 [range, 89–165] min) than in the RF group (190 [160–224] min;  $P < 0.001$ ). The 1-year Kaplan-Meier event rate revealed similar atrial fibrillation-free survival rates between the two groups (CB: 77.9%, RF: 82.3%; log-rank  $P = 0.111$ ). The additional ablation percentage for non-PV foci (CB: 39%, RF: 41%;  $P = 0.653$ ) and complication incidence (CB: 5%, RF: 4%;  $P = 0.670$ ) were also similar.

**Conclusions:** In non-PAF patients, the combination strategy of PVI using CB or RF ablation and non-PV trigger ablation achieved comparable outcomes.

## 1. Introduction

Atrial fibrillation (AF) is associated with considerable morbidity and mortality, possibly causing stroke or heart failure. Progression from paroxysmal AF (PAF) to non-PAF worsens clinical outcomes [1]. Catheter ablation (CA) for AF is an established sinus rhythm maintenance treatment without antiarrhythmic drugs (AADs) [2,3]. Pulmonary vein isolation (PVI) is a standard strategy to eliminate AF triggers originating from the pulmonary vein (PV), and additional ablation for non-PV triggers has also been proven effective. The main methods of PVI are radiofrequency (RF) or cryoballoon (CB) ablation. RF ablation is applied by a point-by-point heating technique, whereas CB ablation is applied by a simple-step freezing technique. Kuck et al. reported the non-inferiority

of CB ablation over RF ablation regarding PAF efficacy and safety [4]. Recent studies have demonstrated the efficacy of PVI and ablation of additional non-PV triggers with RF for non-PAF [5–7]. Nevertheless, the PVI with CB ablation combination strategy for non-PAF has not been established [8–12]. We hypothesised that this single procedure of PVI with CB or RF and non-PV trigger ablation beyond PVI for non-PAF patients could be safe and effective, because it is already established for PAF. The objective of this study was to assess the outcomes of first-stage catheter ablation for non-PAF patients.

## 2. Methods

This single-centre retrospective cohort study (September 2014 to

<sup>☆</sup> All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

\* Corresponding author at: Department of Cardiology, Japanese Red Cross Saitama Hospital, 1-5 Shintoshin, Chuo-ku, Saitama 330-8553, Japan.

E-mail address: [ginitta@yahoo.co.jp](mailto:ginitta@yahoo.co.jp) (G. Nitta).

June 2018) included 2131 patients with AF undergoing initial PVI. AF was classified as PAF or non-PAF, and non-PAF was further divided into persistent AF (continuous AF > 7 days, <1 year) or longstanding persistent AF (uninterrupted AF  $\geq$  1 year), defined by the current guidelines and depending on AF duration [2,3]. All non-PAF patients were eligible. Patients who underwent repeat CA or surgical ablation or CA for procedures other than RF or CB ablation for initial PVI, without exact follow-up data, or on haemodialysis were excluded. Moreover, those with left atrial (LA) thrombus, left atrial appendage (LAA), abnormal thyroid function, or any procedural contraindications were also excluded. All patient data were obtained from the institution's database.

This study was approved by the Japanese Red Cross Saitama Hospital's institutional review board (21-G). Informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

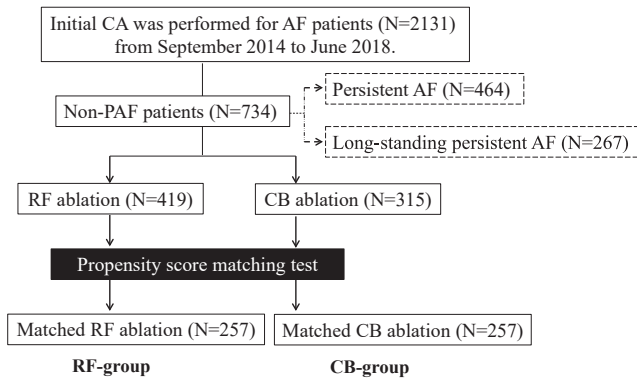
Procedural management at our hospital has been previously reported [7,10–17]. Blood tests, chest radiography, and electrocardiography were performed preoperatively. Transthoracic echocardiography and contrast-enhanced computed tomography (CT) with three-dimensional LA construction were used to screen for cardiac function and structural abnormality. This enabled the physicians to choose between CB and RF ablation based on the anatomical structure of the PV and the left atrium. The physicians deduced that completion of PVI using the CB ablation occlusion technique would be difficult in patients with a common PV stem, altered PV diameter, and remodelling-related LA or LA antrum enlargement. All non-PAF patients underwent transoesophageal echocardiography for intra-cavitary thrombi absence confirmation, especially with LA or LAA, within a week preoperatively. Oral anticoagulants were taken for at least 1 month, and AADs were discontinued for at least 1 week preoperatively. Warfarin was continued throughout the procedure to achieve an international normalised ratio of 2–3; oral anticoagulant administration was also continued for at least 3 months and proton-pump inhibitors for 2 months post-procedure. All procedures included initial PVI as the procedural endpoint and were performed with patients under deep midazolam and pentazocine-induced sedation and with continuous propofol infusion. All the patients including both RF and CB groups were inserted into the esophageal temperature monitor via the nose. A 6-French (Fr) 20-pole 4-site mapping catheter (2-, 8-, 2-, and 8-pole for the superior vena cava [SVC], right atrium, coronary sinus [CS] ostium, and CS, respectively) (BeeAT Cath; Japan Lifeline, Tokyo, Japan) was inserted through the right subclavian vein into the CS as a pacing, recording, and intracardiac defibrillation diagnostic catheter during CA. The mapping catheter's distal portion was placed in the CS and cavotricuspid isthmus, with the proximal portion in the crista terminalis and SVC. The CA protocol has recently been described [7,14,17]. In patients undergoing PVI with RF, an 8.5-Fr long sheath (SLO; Abbott Medical, Minneapolis, MN, USA) and 11.5-Fr steerable sheath (Agilis; Abbott Medical) were inserted through the right femoral vein, while an 8.5-Fr long sheath (SLO) and a 15-Fr steerable sheath (FlexCath Advance; Medtronic, Minneapolis, MN, USA) were inserted in patients undergoing PVI with CB ablation. An arterial line was inserted through the right femoral artery to monitor blood pressure. A transseptal puncture was performed using the modified Brockenbrough fluoroscopic guidance technique and an RF needle (powered transseptal needle; Japan Lifeline). Subsequently, a heparin bolus and continuous infusion were administered to achieve an activated clotting time of 300–350 s during the procedure. A temperature probe (SensiTherm Multi Probe; Abbott Medical) was inserted through the nasal cavity and positioned within the oesophagus to monitor oesophageal temperatures during the procedure.

Post-transseptal puncture, a 15-Fr steerable long sheath (FlexCath Advance; Medtronic) was inserted into the LA. A 28-mm second-generation CB (Arctic Front Advance; Medtronic) was placed in the LA via the steerable sheath by inserting a spiral 20-mm mapping catheter

(Achieve; Medtronic) to the summit. A 10-polar circular mapping catheter (Inquiry; Abbott Medical) was positioned in the SVC via the other 8.5-Fr long sheath (SLO). The CB was inflated near the ostium of each PV, and a circular mapping catheter was positioned into the PV. The degree of PV occlusion was confirmed by contrast medium injection. Freezing was started following CB application with a cycle of 180–240 s. [Fig. 2A] During the freezing of the right PVs, phrenic nerve pacing was stimulated, and freezing was immediately terminated in the case of phrenic palsy, if the temperature of the CB fell below  $-60^{\circ}\text{C}$  or that of the oesophagus fell below  $15^{\circ}\text{C}$ . The PVI procedure endpoint was defined as proof of the bidirectional conduction block between each PV and LA and was indicated by the absence of both local PV potentials (entrance block) and local capture of the PV during LA pacing (exit block). This was confirmed by the spiral mapping catheter in each PV and the 20-pole 4-site mapping catheter in the CS. One or more bonus-freezes were performed at the physician's discretion when PVI was not completed, or the required PVI completion time was  $> 60$  s. In cases of PVI failure with the CB, additional PV touch-up ablation was performed using a non-irrigation RF catheter (Thermocool [Biosense Webster], Flexibility [Abbott Medical], CoolPath [Abbott Medical], or Ablaze [Japan Lifeline]).

Post-transseptal puncture, the 8.5-Fr long sheath (SLO) and an 11.5-Fr steerable sheath (Agilis; Abbott Medical) were inserted into the LA. Pulmonary venography and oesophagography were performed with contrast medium injection for the anatomical position and the PV, LA, and oesophagus relationship assessment. A 10- or 20-polar circular mapping catheter (Inquiry; Abbott Medical or Lasso; Biosense Webster) was positioned in the LA via an 8.5-Fr long sheath (SLO) while an irrigated ablation catheter with a 3.5-mm tip, with or without contact-force sensing (Thermocool [Biosense Webster]; Flexibility [Abbott Medical] and CoolPath [Abbott Medical]) was positioned. All RF procedures were performed under three-dimensional electroanatomic mapping system (CARTO system; Biosense Webster or Ensite NavX system; Abbott Medical) guidance. Before starting CA, cardioversion was attempted for restoration of sinus rhythm in most patients. Extensive encircling PVI (EPPVI) or PVI plus LA posterior wall isolation was performed at the physician's discretion. [Fig. 2B, C, D] PVI plus LA posterior wall isolation included wide antral circumferential PVI with posterior lines extending to the LA posterior wall mid portion. A single vertical LA posterior wall line was drawn with the right posterior wall line adjacent to the left posterior wall line on the left or right side of the oesophagus to avoid procedural oesophageal injury. This approach of PVI plus LA posterior wall isolation (PWI) can potentially isolate a larger PV antrum area and a part of the LA posterior wall compared to that of EPPVI and PVI with the CB. The RF energy was the output of the point-by-point technique under fluoroscopic guidance, the three-dimensional mapping system, and the local voltage on the intracardiac electrocardiogram. The energy (25–35 W) or ablation time (20–30 s) was adjusted according to the regions (each aspect of the PV or LA posterior wall). If dormant conduction of the PV was confirmed after intravenous adenosine administration, additional electrical reconnection ablation was performed. The endpoint of EPPVI or PVI plus LA PWI was defined as proof of the bidirectional conduction block and PVI with the CB. This method has been described previously [7,14,15].

Upon completion of PVI (CB or RF), non-PV trigger induction was attempted by continuous high-dose intravenous isoproterenol infusion and atrial burst pacing. [Fig. 3] Non-PV triggers were defined as the origin of the atrial premature beats, which initiate AF or focal atrial tachycardia (AT) and appear to have a short-run pattern ( $>3$  beats). After induction, both groups underwent additional ablation for non-PV triggers with an irrigated or a non-irrigated catheter. The locations of non-PV triggers were identified using a 20-pole, 4-site mapping catheter (BeeAT), a 20-polar circular mapping catheter, and an ablation catheter. The isoproterenol protocol for inducing non-PV triggers has been reported [7,13–16]. In some cases of non-PV triggers from the LA being induced or if additional touch-up RF ablation for the PV was needed



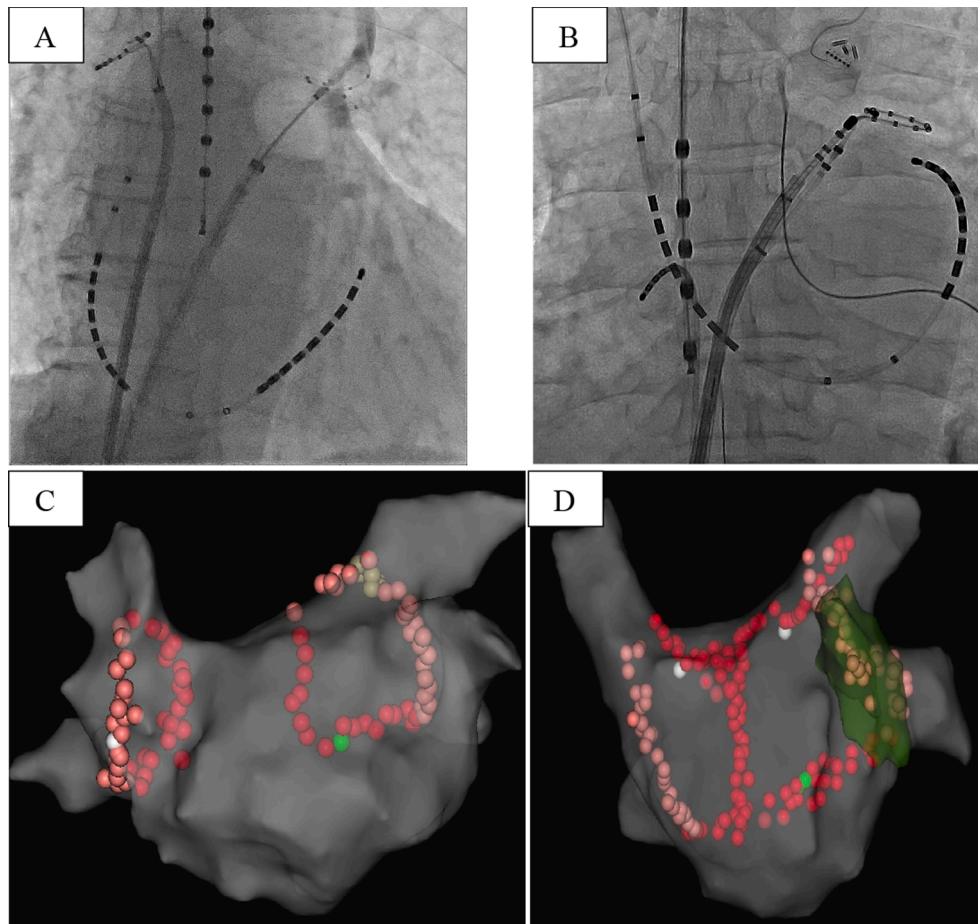
**Fig. 1.** Study population and patient enrolment AF: atrial fibrillation, CB: cryoballoon, non-PAF: non-paroxysmal atrial fibrillation, PVI: pulmonary vein isolation, RF: radiofrequency ablation.

post-CB ablation, additional PVI plus PWI with the RF catheter was performed at the physician's discretion. After the non-PV trigger ablation, the endpoint of the procedure was terminated after confirming that no more than three consecutive episodes of PACs were induced even after another isoproterenol protocol.

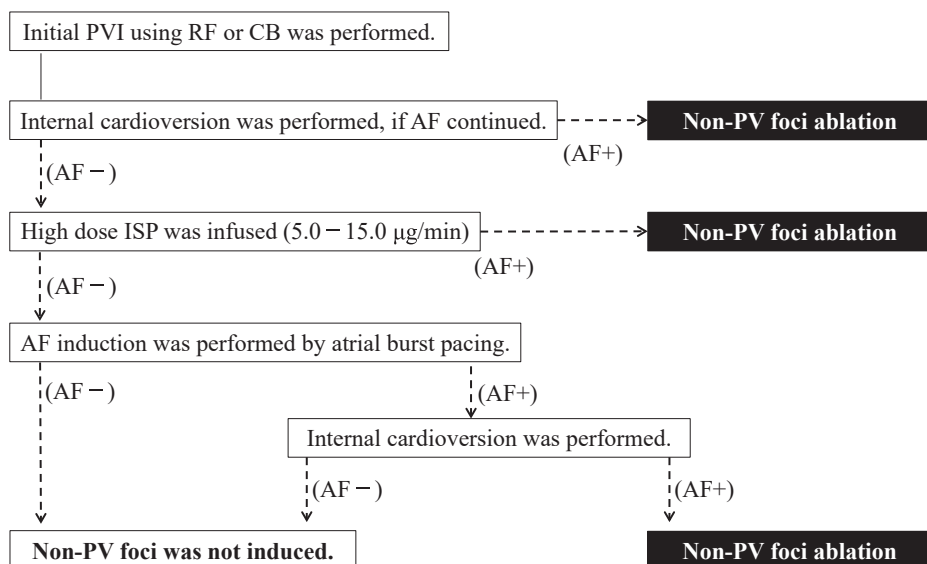
All patients continued anticoagulants ( $\geq 3$  months), depending on their CHADS<sub>2</sub> score. Atrial tachyarrhythmia within a blanking period within 3 months post-procedure was not regarded as an instance of recurrence, and AADs were typically discontinued within the period

unless an early recurrence was observed. Any atrial tachyarrhythmia lasting 30 s following the blanking period was regarded as recurrence. Maintaining sinus rhythm without AAD use was defined as clinical success. All patients were followed up at our hospital for 2–3 weeks post-discharge, every 1–3 months up to 12 months, and every 6 months thereafter. Intensive interviews were obtained, and 12-lead electrocardiograms were performed at each time-point, with 24-h Holter monitor recordings performed at 3 and 12 months. Patients were asked to call or visit our hospital when experiencing arrhythmia recurrence symptoms. CT was performed to evaluate PV stenosis at 12 months post-CA. Our primary endpoint was freedom from AF/AT recurrence at 1 year following the initial procedure in both groups, and the recurrence factors were assessed.

Propensity score matching using logistic regression was performed to reduce basal characteristic differences between CB and RF ablation patients based on age, sex, type of AF, presence of hypertension, diabetes mellitus, cerebral infarction, and congestive heart failure, LA diameter (LAD), and body mass index (BMI). Nearest-neighbour matching without replacement was performed, and score-matched pairs identical to the first two decimal places were used in the analyses. To compare baseline characteristics, Mann-Whitney U tests, Student's t-tests, and chi-square tests were performed. Data were summarised as mean  $\pm$  standard deviation or median [25th and 75th percentiles (%)]. The Kaplan-Meier method was used to calculate the 1-year event rate estimates, and the log-rank test was used to analyse between-group treatment efficacy. Predictors of AF recurrence were evaluated using univariate and multivariate Cox hazard regression analyses. Values were assessed using linear univariate and multivariate regression analyses.



**Fig. 2.** PVI by using CB and RF [A] The approach of PVI by using CB. [B] The approach of PVI by using RF. [C] EEPVI: Extensive encircling PVI or [D] PVI plus LA posterior wall isolation was performed. The red tags indicate the isolation line by the RF energy. CB: cryoballoon, LA: left atrium, PVI: pulmonary vein isolation, RF: radiofrequency. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



**Fig. 3.** Isoproterenol protocol for the non-PV trigger induction and ablation. Non-PV foci were identified to be the origin of atrial premature beats that initiated sustained or non-sustained AF. If AF continued after initial PVI using RF or CB was performed, internal cardioversion was performed to convert the AF to sinus rhythm. If AF could not be stopped after internal cardioversion, CFAE-guided catheter ablation for unmappable non-PV foci was performed until AF was terminated spontaneously or by internal cardioversion. After AF terminated, high dose ISP was infused continuously at a dose of approximately 0.06 to 0.2 mg per hour for 1 min. If AF could not be provoked, AF induction was performed by atrial burst pacing at the distal CS for 240 ms per 8 beats, and the time was reduced by 20 ms at every time point until 140 ms. Similarly, the pacing site was changed to the HRA if AF could not be provoked. If AF occurred, internal cardioversion was performed, and the presence of non-PV foci was assessed after AF stopped. AF, atrial fibrillation; CB: cryoballoon, CFAE, complex fractionated atrial electrogram; CS, coronary sinus; HRA, high right atrium; ISP: isoproterenol, Non-PV foci: non-pulmonary vein foci, PV, pulmonary vein; PVI: pulmonary vein isolation, RF: radiofrequency.

**Table 1**  
Baseline characteristics of patients after propensity score matching.

	RF (n = 257)	CB (n = 257)	P
Age (years)	63.3 ± 9.9	63.4 ± 10.3	0.906
Male sex	216 (84%)	206 (80%)	0.300
BMI (kg/m <sup>2</sup> )	25.4 ± 4.3	25.0 ± 4.0	0.284
Persistent AF (<1 year)	174 (68%)	179 (70%)	0.704
Long-standing AF	83 (32%)	78 (30%)	0.704
Duration of AF (months)	6 (3–24)	6 (2–14)	0.159
HT	148 (58%)	145 (56%)	0.859
DM	44 (17%)	39 (15%)	0.632
CI	18 (7%)	17 (7%)	0.98
CHF	40 (16%)	41 (16%)	0.98
CHADS <sub>2</sub>	1.12 ± 0.96	1.11 ± 1.04	0.895
CHADS <sub>2</sub> -VASC	1.96 ± 1.30	1.94 ± 1.44	0.872
BNP level (pg/mL)	104 (6–179)	100 (58–180)	0.726
EF (%)	58.5 ± 11.9	59.8 ± 12.3	0.205
LAD (mm)	41.4 ± 5.9	41.0 ± 6.0	0.552
Cre level (mg/dl)	0.90 (0.78–1.03)	0.87 (0.78–1.00)	0.350

\*Values are presented as mean ± standard deviation or median (25th and 75th percentiles [%]).

+AF: atrial fibrillation, BMI: body mass index, BNP: brain natriuretic peptide, CB: cryoballoon, CHF: congestive heart failure, CI: cerebral infarction, Cre: creatinine, DM: diabetes mellitus, EF: ejection fraction, HT: hypertension, LAD: left atrial diameter, RF: radiofrequency.

The associated variables in the univariate analysis ( $P \leq 0.10$ ) were entered into the final multivariate model. Analyses were performed using the R software program (version 3.6.1; The R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org>). All  $P$ -values were two-sided, and  $P < 0.05$  was considered significant.

### 3. Results

A total of 734 non-PAF patients (467 [64%], persistent AF; 267 [36%], longstanding AF) underwent initial PVI during the study period. Among them, 419 (57%) with AF underwent RF ablation and 315 (43%) underwent CB ablation. After performing propensity score matching, 257 pairs with RF (RF group) or CB (CB group) ablation were matched (Fig. 1). Both groups were similar (Table 1).

Table 2 shows the procedural and complication occurrence characteristics. The non-PV trigger induction and additional ablation required

**Table 2**  
Characteristics of procedures and occurrence of complications.

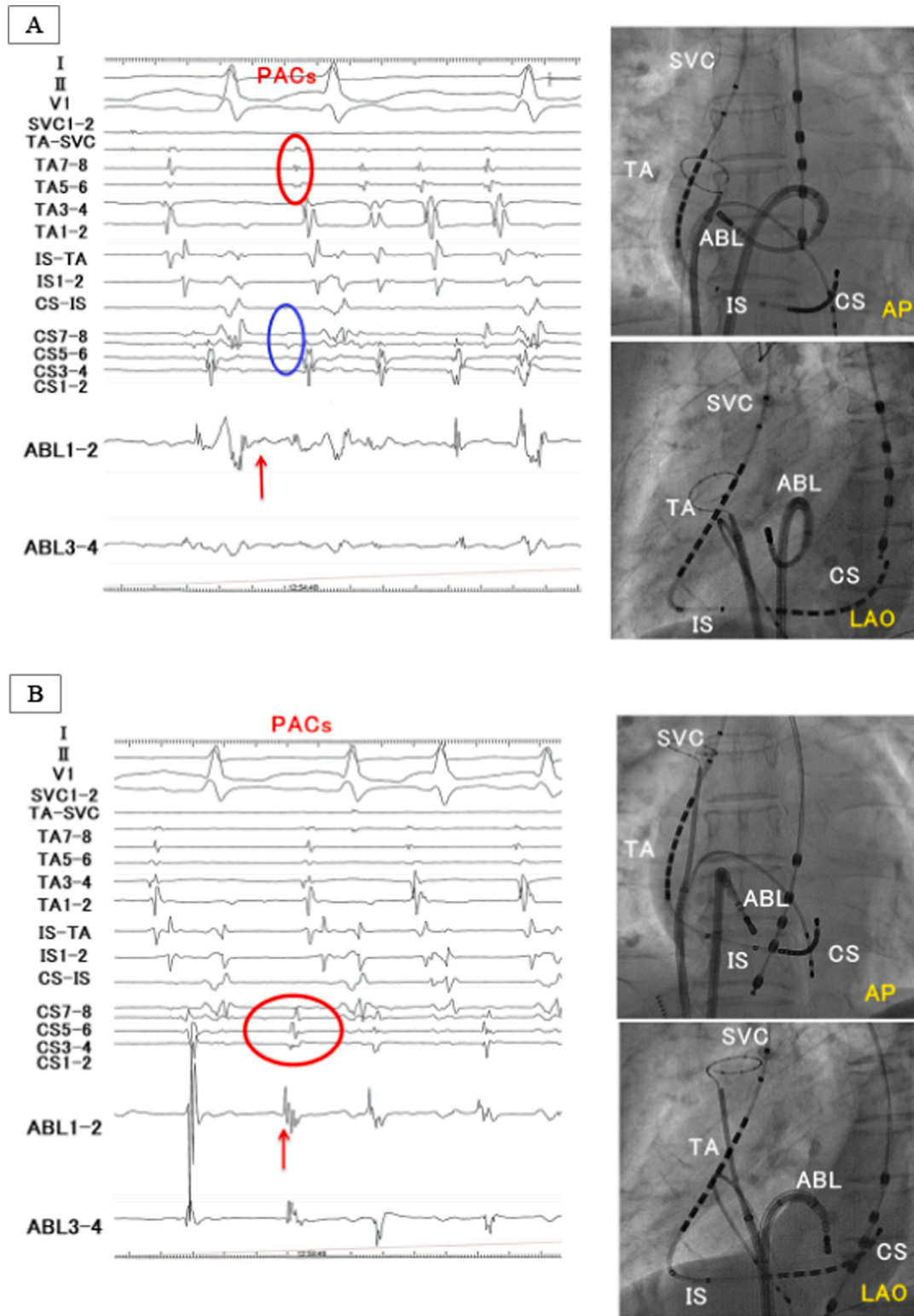
	RF (n = 257)	CB (n = 257)	P
PVI complete	257 (100%)	257 (100%)	0.98
PV touch-up	–	35 (14%)	–
- LSPV touch-up		9 (PVs)	
- LIPV touch-up		4 (PVs)	
- RIPV touch-up		18 (PVs)	
- RSPV touch-up		10 (PVs)	
CTI	40 (16%)	38 (15%)	0.902
LA posterior isolation	246 (96%)	30 (12%)	<0.01
Add non-PV ablation	105 (41%)	100 (39%)	0.653
SVC	45 (18%)	45 (18%)	0.98
RA	36 (14%)	31 (12%)	0.600
LA	28 (11%)	43 (17%)	0.073
IAS	35 (14%)	37 (14%)	0.899
Mitral isthmus	7 (3%)	4 (2%)	0.381
CFAE	18 (7%)	13 (5%)	0.362
Complication	10 (4%)	12 (5%)	0.67
Cardiac tamponade	3	2	0.98
Hematoma/fistula	0	1	0.98
Blood pneumothorax	0	0	0.98
Esophageal injury	2	0	0.411
Phrenic nerve injury	3	7	0.351
Cerebral vascular disease	2	2	0.98
Severe bleeding	0	1	0.98
Pulmonary vein stenosis	4	0	0.045
Death	0	0	0.98

\*Values are presented as mean ± standard deviation.

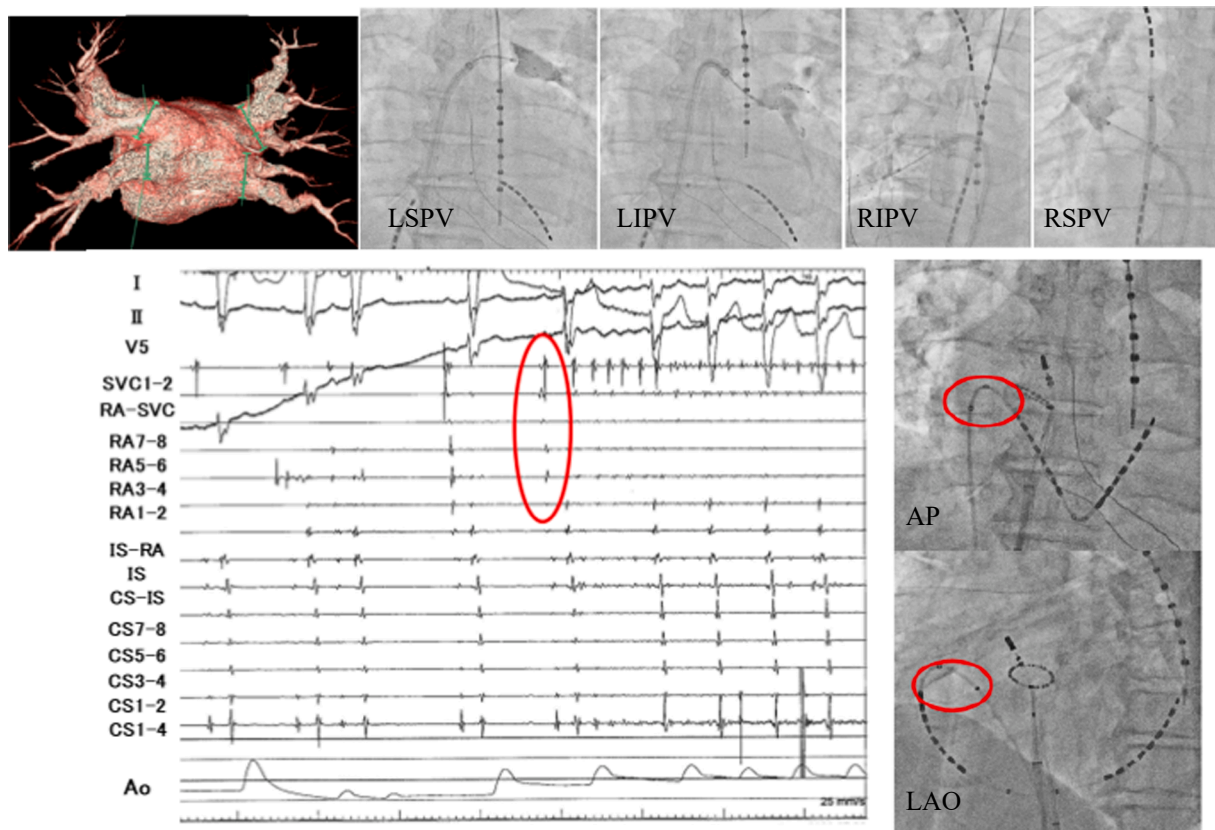
+CB: cryoballoon, CFAE: continuous fractionated atrial electrogram, CTI: cavotricuspid muscle, IAS: interatrial septum, LA: left atrium, LIPV: left inferior pulmonary vein, LSPV: left superior pulmonary vein, PV: pulmonary vein, PVI: pulmonary vein isolation, RA: right atrium, RF: radiofrequency, RIPV: right inferior pulmonary vein, RSPV: right superior pulmonary vein, SVC: superior vena cava.

were similar between the two groups (RF: 41%, CB: 39%;  $P = 0.653$ ). Among the induced non-PV triggers, the LA triggers were higher in the CB group ( $P = 0.073$ ). Additionally, cavo-tricuspid isthmus ablation for common type atrial flutter was similar between the two groups (RF: 16%, CB: 15%;  $P = 0.902$ ; Table 2). The representative cases of non-PV trigger induction from different sites, and CB and RF PVI plus non-PV trigger induction were shown in the figures [Fig. 4A, B, Fig. 5].

The total procedural (190 [160–224] min vs. 125 [89–165] min,  $P <$



**Fig. 4.** Non-PV trigger induction from different sites. [A] An example of the non-PV induction. Atrial tachycardia was initiated incessantly after the infusion of high dose ISP. the earliest site of excitation in the 20-pole 4-site mapping catheter (BeeAT) was the TA on the intracardiac electrocardiogram, which was indicated near atrial septum. And the area was further identified with the ablation catheter or the ring catheter. Non-PV trigger from atrial septum was identified as the earliest site of excitation. Additional non-PV ablation for the atrial septum from the left atrium side was performed and the AT was stopped. [B] The AT was also initiated from the right atrium side and the earliest site of excitation was identified by the potential of the ablation catheter. Additional non-PV ablation for the site was performed and the AT was stopped. ABL: ablation, AF: atrial fibrillation, AP: antero-posterior, AT: atrial tachycardia, CB: cryoballoon, CS: coronary sinus, IS: internal septum, ISP: isoproterenol, LAO: left anterior oblique, PAC: premature atrial contraction, PAF: paroxysmal atrial fibrillation, RF: radiofrequency, SVC: superior vena cava, TA: tricuspid annulus.



**Fig. 5.** PVI plus non-PV trigger induction and ablation. The representative case of CB PVI plus non-PV trigger induction and ablation. PVI was completed by using CB. AF was initiated incessantly after the infusion of high dose ISP. The earliest site of excitation in the 20-pole 4-site mapping catheter (BeeAT) was the RA on the intracardiac electrocardiogram, which was indicated near RA. Non-PV trigger from RA was induced and identified. Additional non-PV ablation for the site was performed, and then, the AF was stopped. AF: atrial fibrillation, AP: antero-posterior, CB: cryoballoon, ISP: isoproterenol, LAO: left anterior oblique, LIPV: left inferior pulmonary vein, LSPV: left superior pulmonary vein, Non-PV foci: non-pulmonary vein foci, PV: pulmonary vein, PVI: pulmonary vein isolation, RA: right atrium, RF: radiofrequency, RIPV: right inferior pulmonary vein, RSPV: right superior pulmonary vein.

**Table 3**  
Outcomes of procedures in non-PAF patients.

	RF group (n = 257)	CB group (n = 257)	P
Procedure time (min)	190 [160–224]	125 [89–165]	<0.001
Radiation time (min)	73 [57–92]	38 [23–61]	<0.001
Early recurrence (<3 months)	65 (27%)	92 (38%)	0.011
Early recurrence (AF)	52 (20%)	76 (30%)	0.025
Early recurrence (AT/AFL)	13 (5%)	16 (6%)	0.851
Recurrence at 1-year	45 (18%)	56 (21.8)	0.267
Recurrence at 1-year (AF)	32 (13%)	41 (16%)	0.312
Recurrence at 1-year (AT/AFL)	13 (5%)	15 (6%)	0.693
Recurrence during whole period	65 (25%)	78 (31%)	0.202
Recurrence during whole period (AF)	50 (20%)	59 (23%)	0.388
Recurrence during whole period (AT/AFL)	15 (6%)	19 (7%)	0.595
Perform 2nd session	45 (18%)	52 (20%)	0.499
Observational period (day)	836 [547–1127]	615 [403–1079]	<0.001
Death during the follow-up	3 (1.2%)	4 (1.6%)	0.98

\*Values are presented as mean  $\pm$  standard deviation or median (25th and 75th percentiles [%]).

<sup>†</sup>CB: cryoballoon, d: days, min: minutes, PAF: paroxysmal atrial fibrillation, RF: radiofrequency.

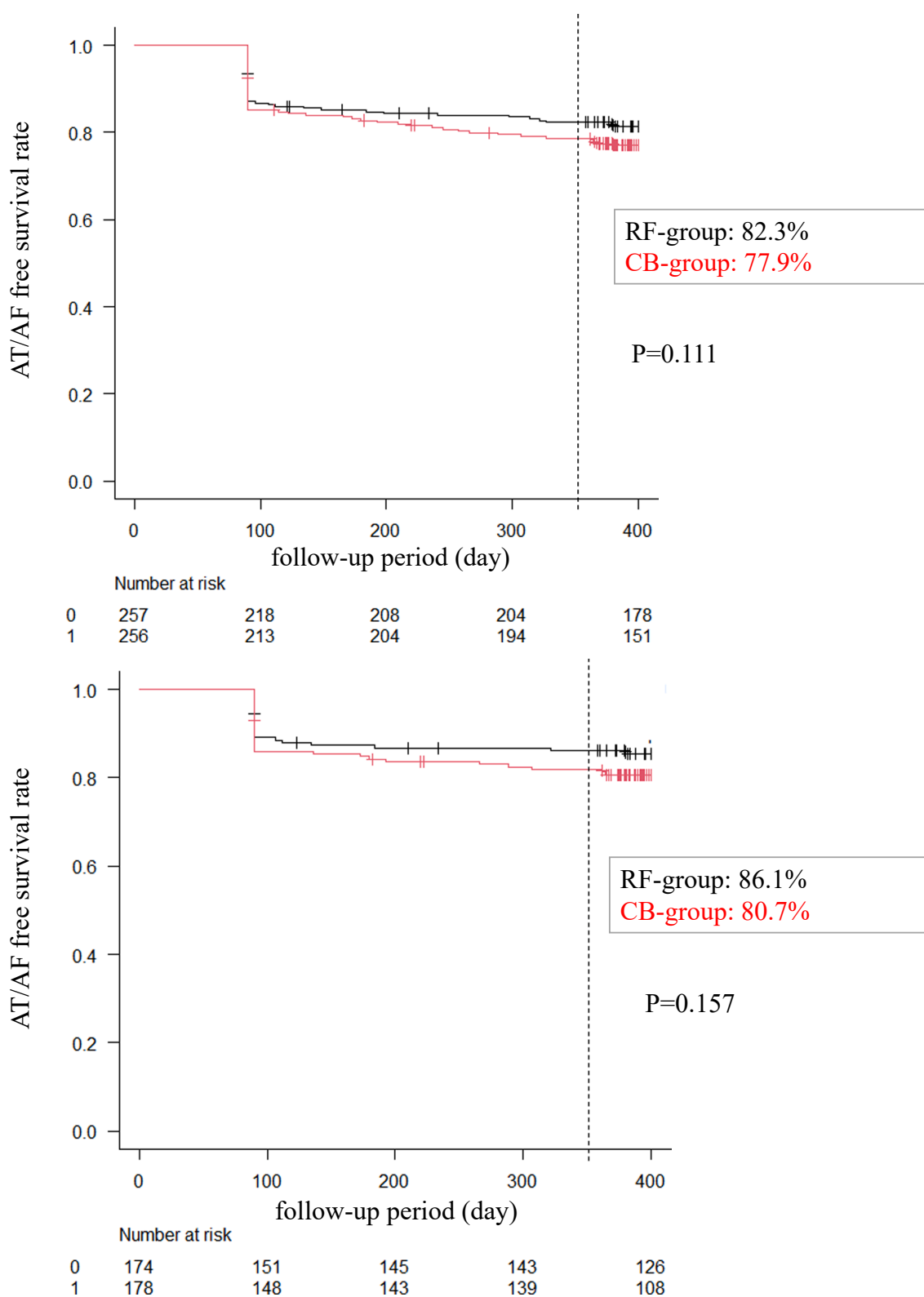
0.001) and radiation (73 [57–92] min vs. 38 [23–61] min,  $P < 0.001$ ) times were significantly shorter in the CB group than in the RF group, with both groups reporting similar complication rates (RF: 4%, CB: 5%;  $P = 0.670$ ). Cerebral vascular disease included cerebral infarctions or cerebral hemorrhages that occurred in the perioperative period.

Hematoma/fistula implied the complication of the puncture site hematoma/fistula. Esophageal injury, which was identified in 2 patients in the RF group, implied transient gastroesophageal peristalsis disturbance, and we observed reversible improvement during the follow-up period. Pulmonary vein stenosis was identified in 4 patients in the RF group (2 patients: LIPV 90 %stenosis, 2 patients: RSPV 75%), but all were asymptomatic, and were not performed the extension of the stenosis. No deaths occurred during the procedure, as all patients had complete recovery post-CA during the follow-up period (Table 3).

The median follow-up period was significantly shorter in the CB group than in the RF group (615 vs. 836 days;  $P < 0.001$ ). Early recurrence within 3 months post-procedure was observed more frequently in the CB group than in the RF group (38% vs. 27%;  $P = 0.011$ ). AT/AF recurrence at 1 year was similar between the two groups (RF: 18%, CB: 22%;  $P = 0.267$ ) and throughout the entire follow-up period (RF: 25%, CB: 31%;  $P = 0.202$ ). The number of patients with repeat ablation post-AF recurrence was also similar between the two groups (RF: 18%, CB: 20%,  $P = 0.499$ ; Table 3).

The AF-free survival rate was similar between the two groups (1-year Kaplan-Meier event rate, RF: 82.3% and CB: 77.9%; log-rank  $P = 0.111$ ; Fig. 6A). After classification into persistent and longstanding AF based on AF duration, AF-free survival rates were similar (persistent AF, RF: 86.1%, CB: 80.7%;  $P = 0.157$ ; Fig. 6B; longstanding persistent AF, RF: 74.4%; CB: 71.6%;  $P = 0.354$ ; Fig. 2C, D). Seven patient (CB: 4, RF: 3;  $P = 0.98$ ) deaths during the entire follow-up period were unrelated to the procedure (Table 3).

The AT/AF recurrence predictor in the univariate analysis was the longer AF duration ( $P < 0.001$ ), and other factors, such as enlarged LAD



**Fig. 6.** Kaplan-Meier curve analysis Kaplan-Meier AF/AT-free survival curves of patients maintaining a sinus rhythm without AADs after the first procedure. RF and CB rates in A) non-PAF patients and B) patients with persistent AF. Subgroup analyses of C) patients with longstanding persistent AF in the RF and CB groups and D) the AF types. AADs: antiarrhythmic drugs, AF: atrial fibrillation, AT: atrial tachycardia, CB: cryoballoon, PAF: paroxysmal atrial fibrillation, RF: radiofrequency.

( $P = 0.068$ ) or non-PV induction ( $P = 0.061$ ), showed no association. Moreover, age ( $P = 0.246$ ), sex ( $P = 0.115$ ), employment of CB ( $P = 0.125$ ), PVI plus LA posterior isolation ( $P = 0.124$ ), and CHADS<sub>2</sub> score

( $P = 0.476$ ) showed no association. In the Cox proportional hazard model, longer AF duration (hazard ratio [HR]: 1.01, 95% confidence interval [CI]: 1.00–1.02,  $P < 0.001$ ) was an independent predictor of

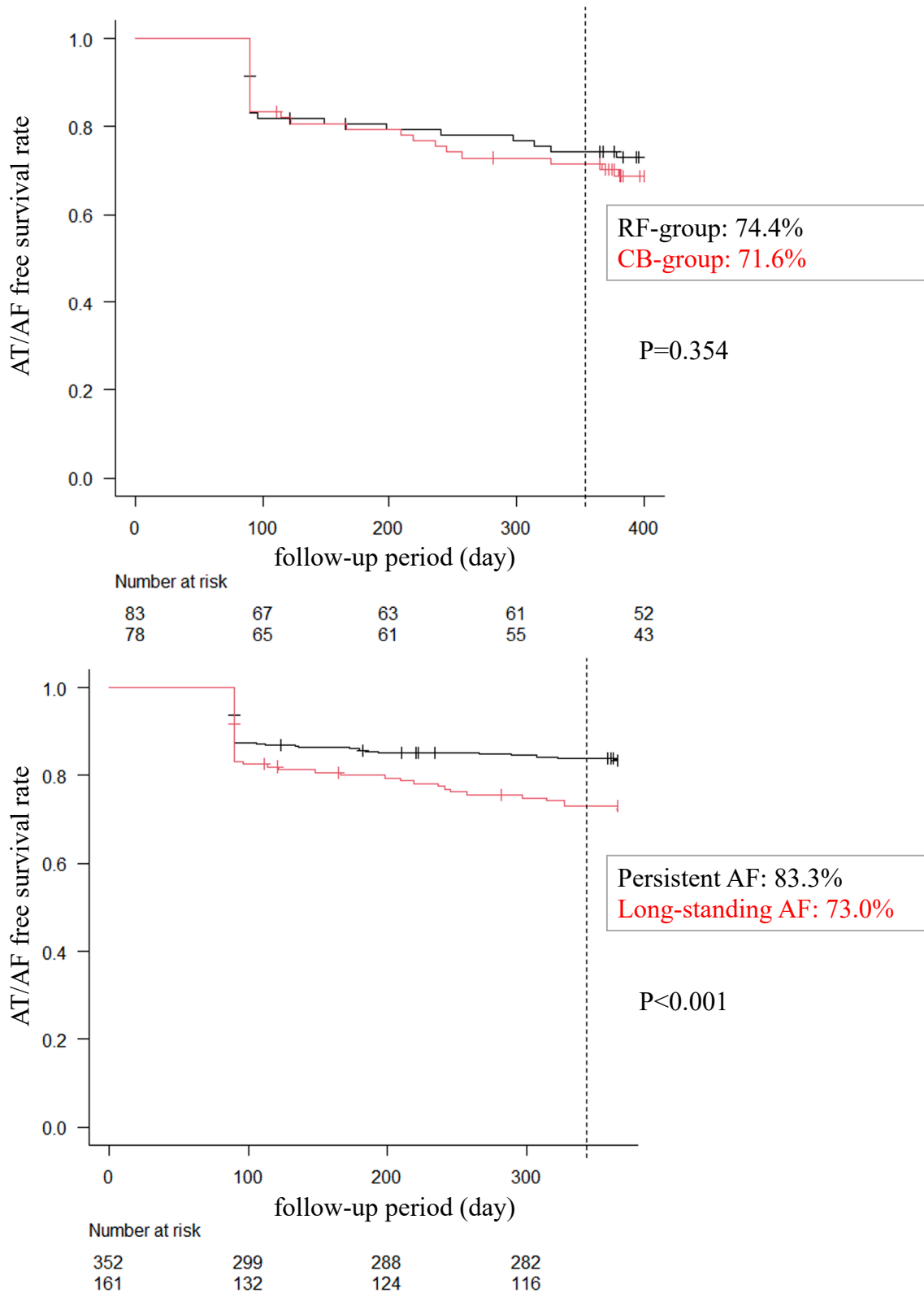


Fig. 6. (continued).

atrial arrhythmia recurrence among non-PAF patients post-CA (Table 4).

#### 4. Discussion

To the best of our knowledge, this is the first study that demonstrates comparable first-stage CA outcomes between non-PAF patients

undergoing PVI with CB and those undergoing PVI with RF ablation and additional non-PV trigger ablation. The post-procedure success rate was similar between the two groups, with appropriate patient selection and sample size. Our study substantiates the safety and efficacy of both procedures, confirming our hypothesis. Recent studies have reported a shorter procedural time for the CB group than for the RF group



**Table 4**  
Predictors of atrial tachyarrhythmia recurrence in patients with non-PAF.

	Univariate			Multivariate		
	HR	95 %CI	P	HR	95 %CI	P
Age (years)	1.01	0.99–1.03	0.246			
Male	1.38	0.93–2.05	0.115			
BMI (kg/m <sup>2</sup> )	1.01	0.97–1.05	0.797			
AF duration (months)	1.01	1.01–1.02	<0.001	1.01	1.00–1.02	<0.001
HT	1.07	0.76–1.49	0.711			
DM	0.99	0.62–1.58	0.977			
CI	0.99	0.72–1.38	0.99			
CHF	1.19	0.77–1.85	0.437			
CHADS <sub>2</sub>	1.06	0.90–1.25	0.476			
CHADS <sub>2</sub> -vasc	1.07	0.95–1.21	0.264			
BNP (pg/ml)	1.00	0.99–1.00	0.788			
EF (%)	1.01	0.99–1.03	0.128			
LAD (mm)	1.03	0.99–1.05	0.068	1.03	1.00–1.06	0.056
Cre (mg/dl)	0.99	0.76–1.29	0.943			
Cryoballoon	1.29	0.93–1.80	0.125			
LA posterior wall isolation	0.77	0.56–1.07	0.124			
Non-PV induction and ablation	1.37	0.99–1.91	0.061	1.23	0.86–1.83	0.237
Procedure time (min)	1.00	0.99–1.01	0.129			
Radiation time (min)	1.00	0.99–1.01	0.109			
Complication	1.71	0.90–3.26	0.103			

The predictors of atrial recurrence (atrial tachycardia or AF) were evaluated by using the univariate and multivariate cox-hazard regression analysis. Values were assessed by using linear univariate and multivariate regression analysis. The associated variables in univariate analysis ( $P \leq 0.10$ ) were entered into the final multivariate model.

AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; CHF, congestive heart failure; CI, cerebral infarction; Cre, Creatinine; DM, diabetes mellitus; EF, ejection fraction; HT, hypertension; LA, left atrium, LAD, left atrial diameter; PAF, paroxysmal atrial fibrillation.

[4,18,19,21]. The baseline LA size in this cohort was not relatively enlarged for non-PAF patients, compared with those of other recent studies [10,20]. The method of selecting PVI with CB or RF according to the LA size was reported, and CB ablation was recommended for AF patients without enlarged LA owing to its shorter procedure time and efficacy [13]. Our study also indicates that the physician's preprocedural use of CB or RF under heart anatomy guidance could be helpful to achieve the comparable success rates among non-PAF patients without enlarged LA by remodelling. These CB data and strategy with less operator-dependent technique variability and shorter procedure times contribute to making CB ablation for non-PAF patients possible at lower centres.

During our study, additional ablation for non-PV triggers was routinely performed, and induction of non-PV triggers was similar between the two groups. Almost 40% of non-PAF patients experienced induced non-PV triggers, and additional non-PV ablation with RF was performed post-PVI using RF or CB ablation. The non-PV foci induction from the LA was higher in the CB group than in the RF group, which may be reflected by the potentially larger isolation area of the LA in RF ablation (PVI plus LA posterior isolation) [7]. Generally, non-PV triggers were observed in 10%–30% of PAF patients, more frequently in non-PAF, female patients, or patients with low BMI [6,16,27,28]. In this study, patients who were induced non-PV triggers after PVI and performed additional non-PV ablation have a higher atrial tachycardia recurrence rate than those without induced non-PV triggers (Table 4). The non-PV trigger ablation efficacy has been reported and the results of the mappable non-PV ablation were nearly equal to those without induced non-PV triggers, although the total procedural and fluoroscopic time were prolonged. [5,6,7,15,16,28,29] This knowledge of the induced non-PV trigger frequency necessitates the CA strategy

development for non-PAF patients beyond the PVI procedure. This study suggests two methods beyond PVI: a first-stage procedure with RF ablation or a time-saving procedure with CB ablation for PV and RF ablation for non-PV triggers. Considering the finding that non-PV induction was not the predictor of atrial tachyarrhythmia recurrence (Table 4), it may be implied that non-PV induction does not correlate to the outcome or induced non-PV triggers were mostly eliminated by additional ablation. Recent reports on CB ablation strategies beyond PVI have expanded applications including LA PWI, SVC isolation, and LAA isolation, enabling us to perform the first-stage procedure [22–26]. Further studies are required after initial CA in non-PAF patients to assess differences in recurrence factors or electrophysiological findings of repeat ablation, such as PV reconnection or other recurrent triggers between the two groups.

The factors influencing recurrence when physicians perform the CA procedure for non-PAF patients is important. Among non-PAF patients, longer AF duration was an independent predictor of atrial arrhythmia recurrence, whereas the use of CB or RF ablation and PVI plus LA PWI was not. Sawhney et al. also reported longer AF duration and enlarged LAD as factors affecting recurrence in non-PAF patients undergoing CB ablation [10].

The results of patients with longstanding and persistent AF are shown in the sub-analysis (Supplementary Appendix, Tables S1–S3); post-procedure success rates were lower, and induction of non-PV triggers was higher in longstanding persistent AF (>50% of longstanding persistent AF cases required additional non-PV ablation compared to persistent AF cases). These data could aid in CA performance guidance in patients with longstanding persistent AF. Further large-scale studies on CA in a similar patient population are required to establish and develop the strategy.

#### 4.1. Study limitations

This study had some limitations. The exact AF duration could not be confirmed in any patient, although the AF types were classified. Some were presumed or registered with AF duration based on data from the latest medical checkup or from the primary care physician. Continuous observational period monitoring was not performed, which could have caused us to miss arrhythmia recurrence possibly reflected in the relatively better success rates. Additionally, isolation areas between the RF and CB groups were potentially different. In most patients in the RF group, areas were isolated from a part of the LA posterior wall in addition to the PV, whereas, in those in the CB group, this was not noted. The left atrium of each group was relatively healthy (LAD 41 mm) for the AF duration (mean duration was 6 months) and the large proportion of the long-standing AF (30%). This may be reflected by the patient selection that CB ablation was not performed for patients with a common PV stem, altered PV diameter, and remodelling-related LA or LA antrum enlargement by referring to the TTE or CT with 3D LA construction, and those patients performed with RF ablation were not matched after propensity score matching. The longstanding persistent AF duration between RF and CB ablation was significantly different, possibly reflected in the selection bias at the physician's discretion or restriction of CB usage for PAF at that time. Finally, the total fluoroscopy time was higher in the RF group than in the CB group, contrary to other reports [4,11,21]. This possibly reflects our hospital's tendency to depend on fluoroscopic guidance and insufficiency of three-dimensional mapping to identify the exact location of a catheter affected by respiratory fluctuation under deep sedation. The greater reliance on the fluoroscopy guide in our hospital may have resulted in considerably longer fluoroscopic times, in parallel with longer procedure times in the RF group than in the CB group.

#### 5. Conclusion

The combination strategy of PVI with CB and that with RF guided by

anatomical features and non-PV trigger ablation achieved comparable outcomes in non-PAF patients. The non-PV triggers were observed in almost 40% of the non-PAF patients.

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### Disclosures

The authors declare that there are no conflicts of interest.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

### Data availability

Our deidentified participant data in the Kaplan-Meier curve analysis will be shared after publication of this paper on a request basis for anyone under approval of the corresponding author via E-mail. The data can be applicable for the analysis of propensity score matching and will be shared as Excel files via e-mail.

### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2022.101021>.

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