Clinical Impact of Eliminating Non-Pulmonary Vein Triggers in Patients with Persistent Atrial Fibrillation: Highlights on Non-Pulmonary Vein Foci and Premature Atrial Contraction

Short title: **Non-PV trigger targeted ablation for PEAF**

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Abstract:

Backgrounds: The role of non-pulmonary vein (PV) triggers ablation in persistent atrial fibrillation (PEAF) was suggested but it is still under debate.

Objectives: We aimed to assess the effectiveness of non-PV trigger targeted ablation for patients with PEAF.

Methods: Consecutive patients with PEAF undergoing catheter ablation (CA) between January 2015 and April 2017 were enrolled. Isoproterenol plus adenosine challenge was performed to provoke non-PV triggers. Non-PV triggers were defined as the non-PV foci inducing AF and/or frequent premature contraction (non-PV PAC) from other than PVs. Three groups were defined: group 1 (n=186) without non-PV triggers; group 2 (n=65) with non-PV triggers that could be completely eliminated with CA; group 3 (n=49) with non-PV triggers still inducible after CA. Primary endpoint was freedom from any atrial tachyarrhythmia (ATa) recurrence.

Results: A total of 300 patients (230 males, age 64±10) were enrolled. Mean follow-up period was 27±10 months. Freedom from ATa recurrence at 1- and 2 years were significantly lower in group 3 compared to the other 2 groups (group 1; 74.7%, 67.2% vs. group 2; 75.8%, 68.3% vs. group 3: 52.1%, 38.6%, P=0.0005), irrespective of the type of non-PV triggers (non-PV PAC vs. non-PV foci initiating AF). On multivariate analysis, unsuccessful elimination of

non-PV trigger was an independent predictor for ATa recurrence (HR 1.80 [95%CI:1.07-2.95], P=0.026).

Conclusions: Successful non-PV trigger elimination can improve the ATa recurrence rate in PEAF ablation. ATa recurrence rate is higher, if non-PV foci or even non-PV PAC remains in patients with PEAF.

Key words: persistent atrial fibrillation, non-pulmonary vein trigger, non-pulmonary vein foci,

Introduction:

Pulmonary vein (PV) isolation (PVI) has become the established treatment strategy regardless of the type of atrial fibrillation (AF)[1]. However, AF can be initiated from ectopic beats originating from other than PVs (the so called non-PV triggers) at a constant rate, which clusters at superior vena cava (SVC), left atrial anterior wall (LAAW), left atrial posterior wall (LAPW), left inter atrial septum (LIAS), right inter atrial septum (RIAS), right atrial free wall (RAFW), coronary sinus, ligament of Marshall (CS/LOM), and left atrial appendage (LAA)[2-4]. In such cases, additional ablation targeting non-PV foci inducing AF has been reported to improve the outcome of catheter ablation for paroxysmal AF (PAF)[5].

Moving forward to persistent atrial fibrillation (PEAF), the clinical data on non-PV triggers targeted catheter ablation (CA) has been still controversial. Beyond the fact of lacking established endpoint in the procedure, a relatively low range of 10-20%[6-8] incident rate of non-PV foci inducing AF has been supposed to limit an indication of the systematic strategy. In contrast, expanding the target of non-PV trigger on the residual reproductive frequent premature atrial contraction originating from other than PVs which did not induce AF (non-PV PAC), the incident increases to a wide range of 21–60% in PEAF[3,6]. Although such a trigger beat has been also reported to be associated with the AF perpetuation[9], the little is known about the clinical impact of CA targeting these comprehensive triggers. Therefore, we

aimed to assess the clinical impact of eliminating non-PV triggers, not only non-PV foci inducing AF but also non-PV PAC, among patients with PEAF.

Methods:

Study population:

In this study, we included consecutive patients with PEAF who underwent the initial CA under non-PV triggers targeted strategy between January 2015 and April 2017. The patients with prior AF ablation were excluded from this analysis. PEAF was defined as that lasting longer than 7 days, not self-terminating, and usually requiring medical intervention[1]. Long-standing AF, which was refractory to cardioversion or persisted for longer than 1 year[1], was also included in the study population.

All patients signed a written informed consent according to the institutional guidelines of Kokura Memorial Hospital and the data entered in registry was approved by the ethical committee.

Procedure setting

Antiarrhythmic drugs (AADs) were discontinued for at least 5 half-lives before the procedure. Transesophageal echocardiography was performed to exclude left atrial (LA) or

LAA thrombus. The procedure involved inserting a 20-pole catheter (BeeAT; Japan Lifeline, Tokyo) through the right jugular vein. The proximal portion was positioned along the SVC and lateral RAFW, and the distal portion was placed in CS. A 10-pole catheter was positioned at the His-bundle area to record the His-bundle potential. Following the standard Brockenbrough technique, we introduced a 10-pole circular mapping catheter (EP Star Libero; Japan Lifeline) and the multipole mapping catheter (Pentaray or Lasso; Biosense Web-star, Diamond Bar, CA, or Advisior; Abbot Medical, St. Paul, MN) on the bi-lateral PV ostium. An ablation catheter was set in the left inferior vein ostium. An electroanatomical mapping system (CARTO3; Biosense Web-ster or EnSite NavX; Abbot Medical) was used to provide additional guidance and to minimize fluoroscopy time.

Induction Protocol of non-PV triggers

Induction protocol of non-PV triggers was demonstrated in Figure 1. After bilateral PVI, all catheters were positioned on each non-PV site (Figure 2A, B). Intracardiac cardioversion was performed to observe the spontaneous ectopic beat following AF termination. Then, adenosine triphosphate (ATP, 20–60mg) was intravenously injected to induce AF. After, isoproterenol (ISP, starting at 4 μ g and incrementing every 2 minutes to 6, 12, and 20–30 μ g) was continuously infused to provoke non-PV triggers[2] until the targeted heart rate with more

than 130 bpm or with 30% increase from basic heart rate. Additional ATP infusions were performed thereafter to check the dormant conduction and iteratively to provoke non-PV triggers. If AF was not initiated by the ATP and ISP infusion, sustained AF was forcibly induced by rapid atrial pacing during ISP infusion. Following restoration of sinus rhythm by intracardiac cardioversion, we investigated whether there some ectopic trigger beats showed up.

Definition of non-PV triggers; non-PV foci and non-PV PAC

Non-PV foci was defined as the premature beat originating from other than PVs which induced AF lasting >30s[5]. Non-PV PAC was defined as reproducible ectopic beats that were constantly observed with the same intra-atrial activation patterns from other than PVs but that did not initiate any ATa lasting >10s[3]. Non-PV trigger was defined as non-PV foci and/or non-PV PAC[2,4]. Solitary premature atrial contraction was excluded if it was not confirmed as reproducible by the intracardiac electrogram.

Catheter ablation

PVI was performed using 2 circular lines encircling the ipsilateral PVs[10] with a 3.5-mm or 4-mm open-irrigated-tip ablation catheter (ThermoCool Smart Toutch; Biosense Webster, Flex

Ability; Abott Medical). We created a LA roof and floor linear lesions to prevent roof-dependent atrial tachycardia when the bilateral PVI circles were within 1 cm. A cavo-tricuspid isthmus linear ablation was routinely performed. When a non-PV trigger was identified (Figure 2 C), additional ablation was performed aiming on the most preceding ectopic sites under the guidance of three-dimensional mapping system (Figure 2 E, F). For non-PV trigger from SVC, luminal isolation was performed. For LAPW, a combination of focal area ablation and a box-shaped linear ablation combining roof and floor linear ablations were performed. For other lesions, a focal application was delivered. Power delivery during radiofrequency ablation was adjusted for each ablation site (i.e anterior left LA; 30W, posterior LA; 25W).

Patient classification

The patients were divided into 3 groups as followings: group 1 comprised patients with PEAF in whom non-PV trigger was not inducible; group 2 comprised patients with PEAF in whom non-PV triggers were induced and all of them were successfully eliminated; group 3 comprised patients with PEAF in whom non-PV triggers were induced and any of them remained.

Follow-up

Patients were observed in the hospital for 2 days after the procedure. After discharge, patients were evaluated in the outpatient clinic at 1 month, 3 months, and every 1 to 3 months with 24-hour Holter monitoring or 2-week cardiac event recording after the procedure at appropriate times. AADs were discontinued after prescribing for 3 months following the procedure. The first 3 months after the ablation was considered the blanking period. Any recorded ATa sustained more than 30 seconds were treated as recurrences.

Study outcome measures

The primary endpoint in the present study was the recurrence of an ATa more than 3 months after initial non-PV trigger targeted ablation. The secondary endpoint was the identical evaluation in patients with non-PV foci and non-PV PAC respectively.

Statistical analysis

For baseline characteristics, continuous variables were reported as mean ± standard deviation (SD) or median and percentiles, and compared by using the independent student's t-test or Mann-Whitney U-test. Categorical variables were reported as numbers and percentages, and analyzed by using the Chi-square test or Fisher's exact test. Kaplan– Meier survival analysis with a log-rank test was used to assess the recurrence of ATa. Cox hazard

proportional analysis was used for multivariate analysis. Selection of a priori variables was based on previous literature and clinical importance according to the event number. In all analyses, $P<0.05$ was considered significant. Bonferroni method was used in multiple comparison among the 3 groups. Analyses were conducted using R (version 3.3.1, The R Foundation for Statistical Computing, Vienna, Austria.)

Results

Baseline and electrophysiologic characteristics

The baseline characteristics in the 3 groups were shown in table 1. The patient population consisted of 300 patients (mean age 64 ± 10 years; 76.3% male, group 1 n=186, group 2 n=65, group 3 n=49). On multiple comparison, mean age was the lowest in group 1 (62 ± 10 vs. group 2; 66 ± 10, $P<0.0001$, vs. group 3; 69 ± 7, $P=0.044$) and gender difference was also significant between group 1 and group 3 (male: 80.7% vs. group 3; 58.3%, $P=0.0071$). Although there was no statistic difference in CHADS2 score, the mean CHA2DS2-VASC score was the highest in group 3 (2.9 ± 1.4 vs. group 1; 2.0 ± 1.5, $P=0.0009$, vs. group 2; 1.2 ± 1.0, $P=0.0123$).

Incidence and distribution of non-PV foci

A total of 189 non-PV Trigger were identified in 114 patients (38.0%). Twenty-five non-PV triggers (13 non-PV foci and 12 non-PV PACs) were unidentified. Non-PV foci was documented in 50 patients (16.7%) and non-PV PAC were documented in 64 patients (21.3%). The localization and distribution of non-PV triggers in each group was summarized in Table 2.

The most frequent non-PV trigger located in SVC (17%). More frequent non-PV triggers were recorded numerically in group 3. The statistical difference in distribution of non-PV triggers between group 2 and 3 was found in SVC (group 2: 63.1% vs. group 3: 20.4%, $P<0.0001$), RA free wall (group 2: 3.1% vs. group 3: 14.3%, $P=0.0373$) and LIAS (group 2: 4.6% vs. group 3: 20.4%, $P=0.0148$). These differences showed the same tendency in non-PV PAC (SVC; group 2: 47.7% vs. group 3: 14.3%, $P=0.0002$, RA free wall; group 2: 0.0% vs. group 3: 10.2%, $P=0.013$, LIAS; group 2: 0.0% vs. group 3: 10.2%, $P=0.013$, respectively).

Catheter ablation procedure

Procedural characteristics was summarized in Table 3. Electrical PVI was completed in all patients. In group1, roof linear ablation was performed in 14 cases (7.5%) based on the operator's decision because of the short distance between the top of left and right sided PV isolation lines. In 9 of 14 cases, inferior linier ablation was additionally performed by

physician's preference because of short distance between the bottoms of bilateral PVs. Successful elimination of non-PV triggers was achieved in all cases for SVC and LAPW. Among the open anatomies, the presence of non-PV trigger from LIAS was the predictor for unsuccessful elimination (OR: 4.13, 95% CI:1.05-21.0, P=0.0425) on multivariate analysis. The rate of SVC isolation was higher in group 2 (57.6% vs. group 3; 25.0%, P=0.0005). Conversely, the rates of RA and LA focal ablation were higher in group 3 (RA focal ablation; 43.8% vs. group 2; 21.2%, P=0.01, LA focal ablation; 20.8% vs. group 2; 6.1%, P=0.223). Procedures related complications occurred in three cases (2 cardiac tamponade and 1PV stenosis in group 1).

Clinical follow up

During the mean follow-up period of 27±10 months, 112 patients (37.3%) had ATa recurrence (AF, 108 pts, atrial tachycardia 3 pts and right atrial flutter 1 pts). Kaplan–Meier survival analysis demonstrated that the single-procedure freedom from ATa recurrence at 1- and 2- years were 74.7% and 67.2% in group 1, 75.8% and 68.3% in group 2, 52.1% and 38.6% in group 3, respectively (adjusted P=0.0005, figure 3). The recurrence rate was significantly higher in group 3 than in group 1 (P=0.0009) and in group 2 (P=0.0049), while that was similar between groups 1 and 2 (P=1.000).

On multivariate analysis, unsuccessful non-PV trigger elimination (Hazard Ratio (HR): 1.80, 95% Confidence Interval (CI): 1.07 – 2.95, P=0.026), long-standing PEAF (HR: 2.61, 95% CI: 1.68 – 3.96, P<0.0001) and non-PV trigger from RIAS (HR: 1.97, 95% CI: 1.06 – 3.47, P=0.032) were predictors for ATa recurrence.

In the patients with non-PV triggers, freedom from ATa recurrence was the lowest in group 3 both in patients with non-PV foci (group 2; 70.4%, 61.1% vs. group 3; 43.5%, 29.0%, P = 0.0274, Figure 4A) and with non-PV PAC (group 2; 84.2%, 78.3% vs. group 3; 53.9%, 41.7%, P=0.0022, Figure 4B).

Discussion

Main findings

Firstly, if non-PV triggers could be completely eliminated, the ATa recurrence rate was similar to that of patients without non-PV trigger. Secondly, in our non-PV trigger targeted ablation for PEAF, unsuccessful elimination of non-PV triggers, long-standing PEAF and non-PV trigger from RIAS were predictors for ATa recurrence. Lastly, regardless of the type of non-PV triggers (non-PV foci or non-PV PAC), the ATa recurrence was significantly higher in patients with unsuccessful elimination. To our best knowledge, this study is the first report that evaluated the clinical impact of eliminating non-PV PAC in patients with PEAF.

Feasibility of non-PV trigger targeted ablation

In general, "triggers" play an important role in AF initiation, whereas "substrates" in AF maintenance. Our non-PV trigger targeted ablation has been previously proved effective in non-PV foci targeted CA for PAF[5]; the combination of the established luminal SVC isolation, focal area ablation for LIAS/RIAS/RAFW/LAAW and enclosing area ablation for LAPW aiming potential substrate modification. The additional indication of this strategy for comprehensive non-PV triggers demonstrated the similar feasibility on PEAF.

As for the triggers, SVC is one of the most common non-PV sites[11]. This is consistent with the embryologic origin of the SVC from "the sinus venous" (the same as sinoatrial node) that can explain the arrhythmogenic properties of this structure. LAPW is also reported a frequent non-PV site and additional benefit of its isolation over PVI in PEAF have been reported in previous study[12]. This structure includes mainly PV antrum and has the embryologic origin deriving from primordial pulmonary vein[13,14]. In fact, these two locations were the most frequent non-PV trigger sites in the present study[8].

Focal area ablation was applied for open anatomy (LIAS/RIAS/RAFW/LAAW). Complete elimination of non-PV triggers in these lesions remained still challenging with several reasons, such as the complication risk of atrial-ventricular conducting system injury, perforating thick

cardiac muscle, and the difficulty in precise identification of non-PV triggers due to anatomical mismatch with catheter design. In fact, the presence of non-PV trigger from LIAS was the predictor for unsuccessful elimination. Moreover, the presence of non-PV trigger from RIAS was a predictor for ATa recurrence. This can be explained by the difficulty in catheter manipulation on LIAS around the transseptal puncture site and in ablating non-PV triggers near the atrial-ventricular conducting system.

Regarding to arrhythmogenic substrate, some studies have indicated variations in the effective refractory period, decremental conduction properties, and multiple conduction pathways as substrates in the PVs, PV-LA antrum and left atrial tissue in PEAF[15-17] in which LAPW had been reported to play an important role as substrates, including conduction delay, and drivers[18,19]. Based on this theory, LAPW isolation can contribute to both trigger elimination and substrate modification in case of non-PV trigger originating from LAPW.

Comparison with prior studies

Previous report suggested the positive impact of ablation for PEAF targeting non-PV foci inducing AF[7,20]. In these reports, non-PV PAC was excluded from the analysis. Nakamaru et al. described that remaining non-PV PAC had a limited impact on freedom from ATa recurrence[3]. Our data resulted in the different conclusion that successful elimination of non-

PV PAC had also positive impact. To explain this result, several considerations can be added. Firstly, the main cohort in the present study was focused on patients with PEAF. Secondly, the induction protocol of non-PV triggers was more aggressive; iterative ATP infusions, compulsive AF induction and frequent use of high-dose ISP. Indeed, the more frequent appearance of non-PV triggers (38%) compared to the previous report (24.4%) was detected. Thus, different patient background and induction protocol were considered to be possible explanations for the result of the present study.

Clinical implication

Although, various ablation strategies for substrate modification have been proposed in PEAF ablation over the last two decades: from linear lesions to potential electrical phenomena (rotors, focal impulses) and specific myocardial regions (low-voltage substrate)[15-19,21], none of empirical use of these strategies have proven superiority to PVI in randomized study for patients with PEAF. On the contrary, in the non-PV triggers targeted ablation strategy, the additional ablation site is inevitably individualized for each patient based on demand, namely "tailored concept", which can provide the clinical benefit to the wide spread patient cohort.

One of the future tasks in non-PV trigger targeted ablation is to reveal the potential non-PV triggers' area in the optimal method under sinus rhythm. The previous report describes that

non-PV foci in LA arose from the degenerated LA[22]. Combination with the low-voltage map might predispose the potential non-PV triggers.

Another future task is to overcome the difficulty in eliminating multiple non-PV triggers. PEAF was reported to have the higher incidence of multiple non-PV triggers compared to PAF[8]. In our data, 15.2% of patients had unidentified non-PV trigger. Most of all were due to either interspersed multiple distribution or spontaneous decrease without ablation. The important key to identify non-PV trigger site is to find the most preceding electrical activity while ectopic beats show up. For this purpose, the more electrodes should be positioned so that more locational information of non-PV triggers can be recorded simultaneously. Therefore, double-lasso catheter technique[23] is recommended in our strategy. Furthermore, contemporary prevalence of multielectrode mapping catheters and the improved accuracy of locational information with high-resolution mapping systems might enable a more precise identification of non-PV triggers.

Limitation

There are several limitations to the present study. Firstly, this is a single center retrospective study. The second limitation is the unequal numbers of patients in each group. Moreover, there were statistical differences in the gender and age categories. However, this is consistent

with previous review that these two characters were associate with the prevalence of non-PV triggers[4]. Therefore, we directly compared each group without statistical deliberate adjustment. Thirdly, LAA was one of the anatomies of non-PV trigger origin with their prevalence increasing in patients with non-paroxysmal AF[24]. We excluded LAA from ablation target, because high incidence of LAA thrombosis after LAA isolation[25] was reported and LAA closing device was clinically not available at that time in our country. Finally, the analysis was performed only for the initial procedure. The cohort bias could have existed due to non-inducibility of non-PV triggers during the initial procedure.

Conclusion

Successful non-PV trigger elimination can improve the ATa recurrence rate to the similar result of PVI for the patients without non-PV trigger in PEAF ablation. ATa recurrence rate is higher, if non-PV foci or even non-PV PAC remains inducible in patients with PEAF ablation.

Reference:

1 Calkins H, Hindricks G, Cappato R, Kim Y-H, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14:e275–444.

2 Santangeli P, Marchlinski FE. Techniques for the provocation, localization, and ablation of non–pulmonary vein triggers for atrial fibrillation. Heart Rhythm 2017;14:1087–96.

3 Nakamaru R, Okada M, Tanaka N, Tanaka K, Ninomiya Y, Hirao Y, et al. Outcomes After Atrial Fibrillation Ablation in Patients With Premature Atrial Contractions Originating From Non-Pulmonary Veins. JACC: Clinical Electrophysiology 2019;5:1319–27.

4 Gianni C, Mohanty S, Trivedi C, Di Biase L, Natale A. Novel concepts and approaches in ablation of atrial fibrillation: the role of non-pulmonary vein triggers. EP Europace 2018;20:1566–76.

5 Hayashi K, An Y, Nagashima M, Hiroshima K, Ohe M, Makihara Y, et al. Importance of non-pulmonary vein foci in catheter ablation for paroxysmal atrial fibrillation. Heart Rhythm

2015;12:1918–24.

6 Lin W-S, Tai C-T, Hsieh M-H, Tsai C-F, Lin Y-K, Tsao H-M, et al. Catheter Ablation of Paroxysmal Atrial Fibrillation Initiated by Non–Pulmonary Vein Ectopy. Circulation 2003;107:3176–83.

7 Santangeli P, Zado ES, Hutchinson MD, Riley MP, Lin D, Frankel DS, et al. Prevalence and distribution of focal triggers in persistent and long-standing persistent atrial fibrillation. Heart Rhythm 2016;13:374–82.

8 Elayi CS, Di Biase L, Bai R, Burkhardt JD, Mohanty P, Santangeli P, et al. Administration of Isoproterenol and Adenosine to Guide Supplemental Ablation After Pulmonary Vein Antrum Isolation: Administration of Isuprel/Adenosine After Pulmonary Vein Antrum Isolation. J Cardiovasc Electrophysiol 2013;24:1199–206.

9 Kurotobi T, Iwakura K, Inoue K, Kimura R, Okamura A, Koyama Y, et al. Multiple Arrhythmogenic Foci Associated With the Development of Perpetuation of Atrial Fibrillation. Circ Arrhythm Electrophysiol 2010;3:39–45.

10 Takahashi A, Iesaka Y, Takahashi Y, Takahashi R, Kobayashi K, Takagi K, et al. Electrical Connections Between Pulmonary Veins: Implication for Ostial Ablation of Pulmonary Veins in Patients With Paroxysmal Atrial Fibrillation. Circulation 2002;105:2998–3003.

11 Tsai C-F, Tai C-T, Hsieh M-H, Lin W-S, Yu W-C, Ueng K-C, et al. Initiation of Atrial Fibrillation by Ectopic Beats Originating From the Superior Vena Cava: Electrophysiological Characteristics and Results of Radiofrequency Ablation. Circulation 2000;102:67–74.

12 Kumagai K, Toyama H, Ashihara T. Impact of Box Isolation on Rotors and Multiple Wavelets in Persistent Atrial Fibrillation. Circ J 2020;84:419–426.

13 Patti G, Pengo V, Marcucci R, et al.: The left atrial appendage: from embryology to prevention of thromboembolism. Eur Heart J 2017; 38: 877–887.

14 Beigel R, Wunderlich NC, Ho SY, et al. The Left Atrial Appendage: Anatomy, Function, and Noninvasive Evaluation. JACC: Cardiovascular Imaging 2014; 7:1251–1265.

15 Jaïs P, Hocini M, Macle L, Choi K-J, Deisenhofer I, Weerasooriya R, et al. Distinctive Electrophysiological Properties of Pulmonary Veins in Patients With Atrial Fibrillation. Circulation 2002;106:2479–2485.

16 Kumagai K, Ogawa M, Noguchi H, Yasuda T, Nakashima H, Saku K. Electrophysiologic properties of pulmonary veins assessed using a multielectrode basket catheter. Journal of the American College of Cardiology 2004;43:2281–2289.

17 Rolf S, Kircher S, Arya A, Eitel C, Sommer P, Richter S, et al. Tailored Atrial Substrate Modification Based on Low-Voltage Areas in Catheter Ablation of Atrial Fibrillation. Circ Arrhythm Electrophysiol 2014;7:825–33.

18 Markides V, Schilling RJ, Ho SY, Chow AW, Davies DW, Peters NS. Characterization of left atrial activation in the intact human heart. Circulation 2003; 107: 733–739.

19 Kalifa J, Tanaka K, Zaitsev AV, Warren M, Vaidyanathan R, Auerbach D, et al. Mechanisms of wave fractionation at boundaries of high-frequency excitation in the posterior left atrium of the isolated sheep heart during atrial fibrillation. Circulation 2006;

113: 626–633.

.

20 Inoue K, Kurotobi T, Kimura R, Toyoshima Y, Itoh N, Masuda M, et al. Trigger-Based Mechanism of the Persistence of Atrial Fibrillation and Its Impact on the Efficacy of Catheter Ablation. Circ Arrhythm Electrophysiol 2012;5:295–301.

21 Verma A, Jiang C, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to Catheter Ablation for Persistent Atrial Fibrillation. N Engl J Med 2015;372:1812–22.

22 Kawai S, Mukai Y, Inoue S, Yakabe D, Nagaoka K, Sakamoto K, et al. Non-Pulmonary Vein Triggers of Atrial Fibrillation Are Likely to Arise from Low-Voltage Areas in the Left Atrium. Sci Rep 2019;9:12271.

23 Ouyang F, Ernst S, Chun J, Bänsch D, Li Y, Schaumann A, et al. Electrophysiological Findings During Ablation of Persistent Atrial Fibrillation With Electroanatomic Mapping and Double Lasso Catheter Technique. Circulation 2005;112:3038–48.

24 Hocini M, Shah AJ, Nault I, Sanders P, Wright M, Narayan SM, et al. Localized reentry

within the left atrial appendage: arrhythmogenic role in patients undergoing ablation of persistent atrial fibrillation. Heart Rhythm 2011;8:1853–61.

25 Rillig A, Tilz RR, Lin T, Fink T, Heeger C-H, Arya A, et al. Unexpectedly High Incidence of Stroke and Left Atrial Appendage Thrombus Formation After Electrical Isolation of the Left Atrial Appendage for the Treatment of Atrial Tachyarrhythmias. Circ Arrhythm Electrophysiol 2016;9(5):e003461.

Figure legends

Figure 1: Induction protocol of non-PV triggers.

Figure 2: Procedural course of non-PV trigger induction.

(A), (B): Initial catheter positionings at non-PV trigger induction with AP (A) and RAO (B) views on fluoroscopy. Two spiral mapping catheters were placed on LAPW and LIAS. Ablation catheter was placed on LAAW. A 10-pole catheter was positioned on RAFW.

(C): Intracardiac electrogram at the moment of non-PV foci induction. White arrows indicate the most preceding electrical activity on LIAS

(D): Catheter positionings on the fluoroscopy of figure 2 C.

(E), (F): Identified non-PV trigger site on the local activation map with LAO (E) and RAO (F) views using three-dimensional mapping system. Red balls indicate focal area ablation sites.

AP = anteroposterior; RAO = right-anterior-oblique; LAO = left-anterior-oblique

Figure 3: Freedom from ATa recurrence after non-PV trigger targeted ablation in patients with PEAF.

Figure 4: Freedom from ATa recurrence after catheter ablation in patients with non-PV foci

(A) and non-PV PAC (B).

Table 1: Patient characteristics

Patient characteristics	Group 1, N = 186	Group 2, N = 65	Group 3, N = 49	P value
Age, years	**62 ± 10	66 ± 10	69 ± 7	<0.0001
Gender, Male, %	*80.7%	77.3%	*58.3%	0.0051
BMI, kg/m^2	24.7 ± 4.0	24.8 ± 3.5	24.5 ± 3.4	0.908
AF burden, years	2.6 ± 3.8	3.2 ± 4.6	3.0 ± 5.0	0.160
Long standing AF, %	14.0%	19.7%	27.1%	0.086
Left atrial diameter, mm	43.0 ± 6.1	44.7 ± 5.8	43.6 ± 5.3	0.128
Left ventricular ejection fraction, %	59.7 ± 9.3	57.7 ± 9.7	61.4 ± 6.9	0.090
Hypertension, %	57.5 %	60.6 %	66.7 %	0.508
Diabetes mellitus, %	15.6 %	10.6 %	14.6 %	0.610
History of stroke / TIA, %	9.6 %	6.2 %	18.0 %	0.107
Vascular disease, %	5.9 %	3.0 %	2.1 %	0.572
Heart failure, %	21.0 %	21.2 %	25.0%	0.829
HCM, %	3.8 %	3.0 %	2.1 %	1.000
DCM, %	1.6 %	0%	2.1 %	0.625
Valvular disease, %	5.4 %	7.6 %	4.2 %	0.767
$CHADS_2$ score	1.2 ± 1.1	1.2 ± 1.0	1.6 ± 1.3	0.153
≧ 2, %	36.9 %	25.4 %	40.0 %	0.432
CHA_2DS_2-VASc score	2.0 ± 1.5	2.0 ± 1.4	**2.9 ± 1.4	0.0027
≧ 2, %	60.0 %	58.5 %	**88.0 %	0.0012
≧ 3, %	37.1 %	37.9 %	54.2 %	0.091
≧ 4, %	15.1 %	20.0 %	28.0 %	0.125
Preprocedural Medication				
Antiarrhythmic drug (AAD), %	57.5 %	45.5 %	43.8 %	0.097
Class I AAD, %	14.0 %	10.6 %	2.1 %	0.054
Amiodarone, %	8.7 %	1.5 %	4.0 %	0.110
Bepridil, %	35.0 %	36.4 %	39.6 %	0.835
Beta blocker, %	42.5 %	45.5 %	47.9 %	0.767
ACE-I/ ARB, %	43.3 %	44.4 %	46.0 %	0.941
Vitamin K antagonist, %	12.9 %	13.6 %	12.5 %	0.982
DOACs, %	87.1 %	86.4 %	87.5 %	

BMI = Body mass index; AF = Atrial fibrillation; TIA = Transient ischemic attack; HCM = Hypertrophic cardiomyopathy; DCM = Dilated cardiomyopathy; ACE-I = Angiotensin-converting-enzyme inhibitors; ARB = Angiotensin II receptor blocker+ DOAK = Direct oral anticoagulants

* Statistically different from another asterisk

** Statistically different from other two groups

Table 2: Distribution and localization of non-PV foci in each group

	Group2, N=65	Group3, N=49	P	Total, N=300
SVC (non-PV trigger), %	63.1%	20.4%	<0.0001	17.0%
SVC (non-PV foci), %	15.4%	6.1%	0.147	4.3%
SVC (non-PV PAC only), %	47.7%	14.3%	0.0002	12.7%
RA free wall (non-PV trigger), %	3.1%	14.3%	0.0373	3.0%
RA free wall (non-PV foci), %	3.1%	4.1%	1.000	1.3%
RAA free wall (non-PV PAC), %	0.0%	10.2%	0.013	1.7%
RIAS (non-PV trigger), %	18.5%	30.6	0.131	8.7%
RIAS (non-PV foci), %	10.8%	12.2%	0.806	4.3%
RIAS (non-PV PAC), %	7.7%	18.4%	0.086	4.7%
LIAS (non-PV trigger), %	4.6%	20.4%	0.0148	4.3%
LIAS (non-PV foci), %	4.6%	8.2%	0.467	2.3%
LIAS (non-PV PAC), %	0.0%	10.2%	0.013	1.7%
LAPW (non-PV trigger), %	36.9%	40.8%	0.673	14.7%
LAPW (non-PV foci), %	13.9%	16.3%	0.713	5.7%
LAPW (non-PV PAC), %	20.0%	22.5%	0.751	8.0%
LAAW (non-PV trigger), %	7.7%	10.2%	0.743	3.3%
LAAW (non-PV foci) %	4.6%	6.1%	0.876	2.0%
LAAW (non-PV PAC), %	3.1%	4.1%	1.000	1.3%
CS/MV/LOM (non-PV trigger), %	4.6%	12.2%	0.170	3.0%
CS/MV/LOM (non-PV foci), %	0.0%	4.1%	0.183	0.7%
CS/MV/LOM (non-PV PAC), %	4.6%	8.2%	0.461	2.3%
Unidentified non-PV trigger, %	--	51.0%	--	8.0%

PV = Pulmonary vein; PAC = premature atrial contractions

Table 3: Procedural characteristics

Procedural characteristics	Group 1, N = 186	Group 2, N = 65	Group 3, N = 49	P value
Procedure time, min	**133 ± 42	156 ± 34	163 ± 50	<0.0001
Fluoroscopic time, min	*16.6 ± 10.3	23.0 ± 16.4	*25.1 ± 21.9	<0.0001
Successful PV isolation, %	100%	100%	100%	--
AF initiation from PV, %	19.4 %	10.6 %	10.4 %	0.129
From septal sided PV, %	11.8 %	9.1 %	4.2 %	0.317
From lateral sided PV, %	17.7 %	6.1 %	8.3 %	0.032
From bilateral PV, %	3.2 %	3.0 %	2.1 %	1.000
AF initiation from non-PV trigger, %	--	43.9 %	60.4 %	0.082
Non-PV PAC, %		56.1 %	39.6 %	
				Adjusted P value (group 2 vs. 3)
Additional ablation				
Roof line ablation, %	7.5 %	39.4 %	33.3 %	0.508
Inferior line ablation, %	4.8 %	33.3 %	25.0 %	0.337
Mitral isthmus line ablation, %	0.0 %	4.6 %	10.4 %	0.278
Anterior line ablation	0.0%	1.5 %	2.1 %	1.000
Superior vena cava isolation, %	0.0 %	57.6 %	25.0 %	0.0005
Right atrial focal ablation, %	0.0 %	21.2 %	43.8 %	0.01
Left atrial focal ablation, %	0.0 %	6.1 %	20.8%	0.0223

Table 4: Multivariate analysis for ATa recurrence

	Unadjusted HR, (95% CI)	P value	Adjusted HR, (95% CI)	P value
Age > 75	1.07 (0.57 – 1.85)	0.810	1.05 (0.59 – 2.02)	0.872
Gender, Male	1.09 (0.71 – 1.72)	0.713	1.53 (0.97 – 2.52)	0.071
CHA_2DS_2-VASC score ≧ 2	1.05 (0.71 – 1.56)	0.821		
Left atrial diameter > 50mm	1.25 (0.73 – 2.02)	0.400	1.12 (0.64 – 1.85)	0.680
Long standing PEAF	2.50 (1.63 – 3.73)	<0.0001	2.61 (1.68 – 3.96)	<0.0001
Unsuccessful non-PV trigger elimination	2.25 (1.46 – 3.39)	0.0004	1.80 (1.07 – 2.95)	0.026
Non-PV trigger from SVC	0.79 (0.45 – 1.30)	0.369	0.66 (0.36 – 1.11)	0.125
Non-PV trigger from RAFW	2.61 (1.02 – 5.47)	0.046	1.27 (0.45 – 3.07)	0.627
Non-PV trigger from RIAS	2.11 (1.21 – 3.45)	0.010	1.97 (1.06 – 3.47)	0.032
Non-PV trigger from LIAS	2.27 (1.02 – 4.38)	0.046	1.06 (0.47 – 2.65)	0.891
Non-PV trigger from LAAW	1.08 (0.33 – 2.57)	0.880		
Non-PV trigger from LAPW	1.61 (0.98 – 2.55)	0.060	1.26 (0.72 – 2.10)	0.410
Non-PV trigger from CS/LOM	2.96 (1.16 – 6.20)	0.027	2.06 (0.74 – 4.92)	0.154

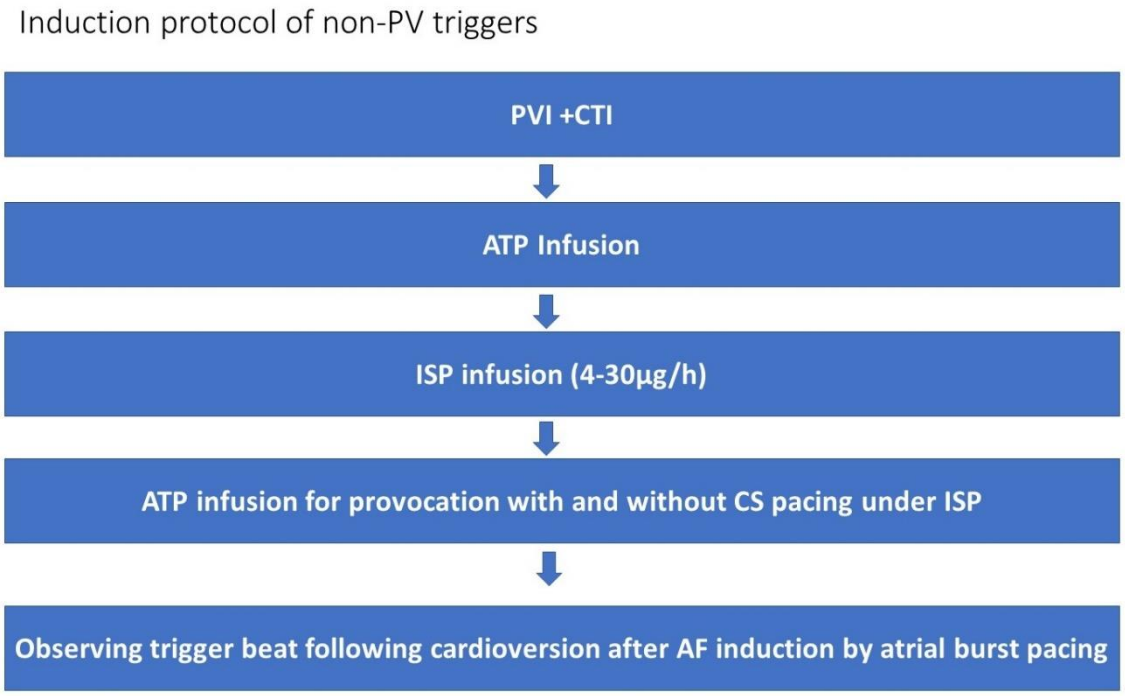

Induction protocol of non-PV triggers
PVI +CTI
ATP Infusion
ISP infusion (4-30μg/h)
ATP infusion for provocation with and without CS pacing under ISP
Observing trigger beat following cardioversion after AF induction by atrial burst pacing

Figure 1

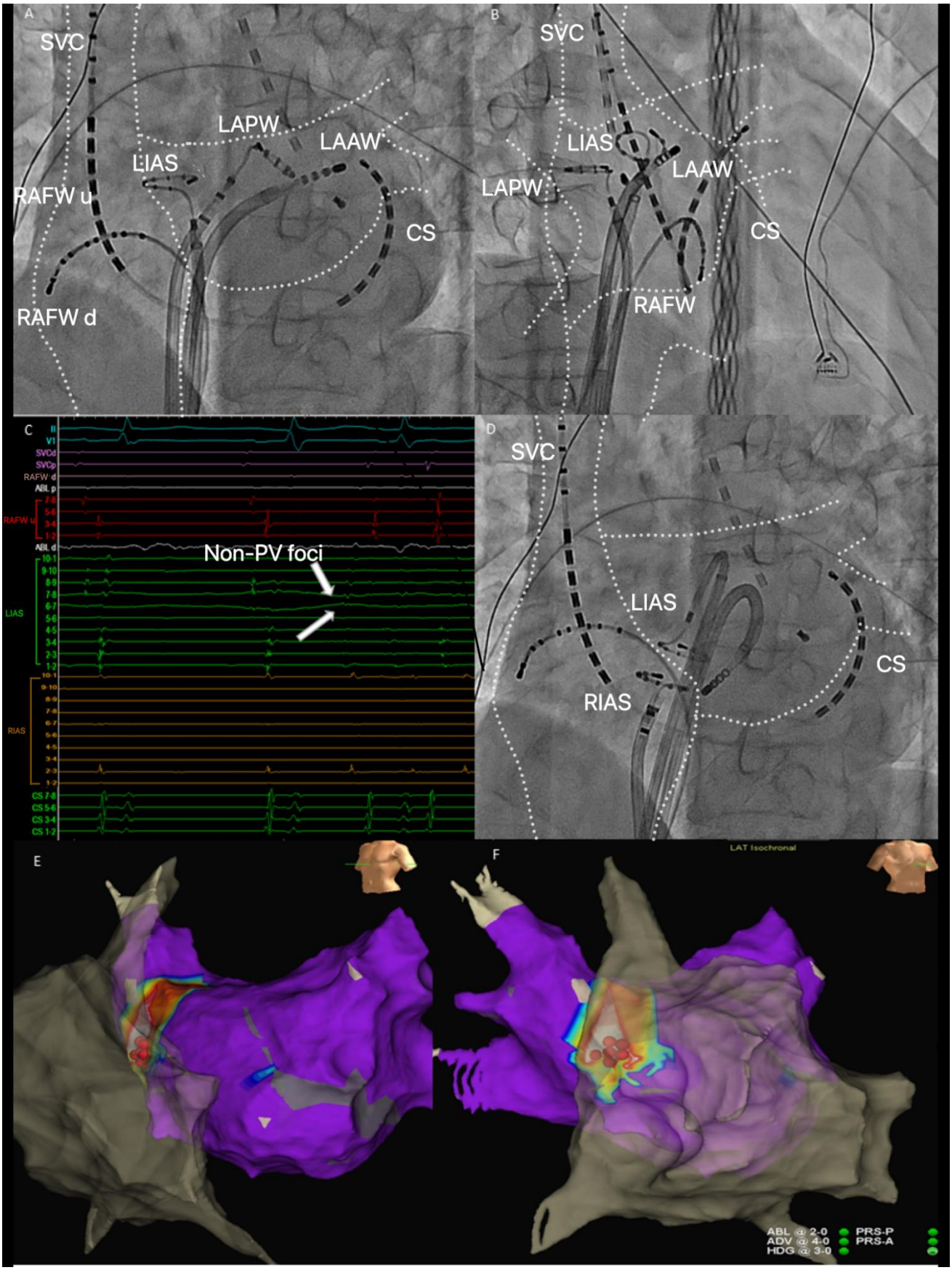
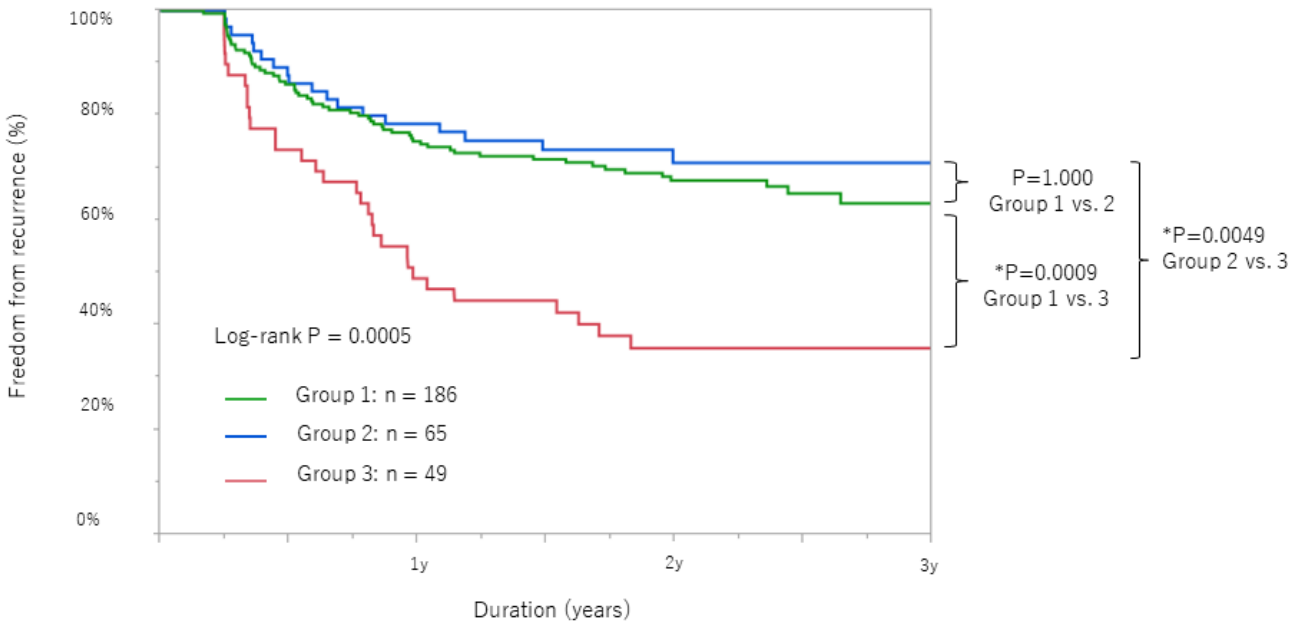

A
SVC
LAPW
LAAW
LIAS
RAFW u
CS
RAFW d
B
SVC
LIAS
LAAW
LAPW
CS
RAFW
C
II
V1
SVCd
SVCp
RAFW d
ABL p
RAFW u
ABL d
LIAS
RIAS
CS 7-8
CS 5-6
CS 3-4
CS 1-2
Non-PV foci
D
SVC
LIAS
CS
RIAS
E
F
LAT Isochronal
ABL @ 2-0
ADV @ 4-0
HDG @ 3-0
PRS-P
PRS-A

Figure 2

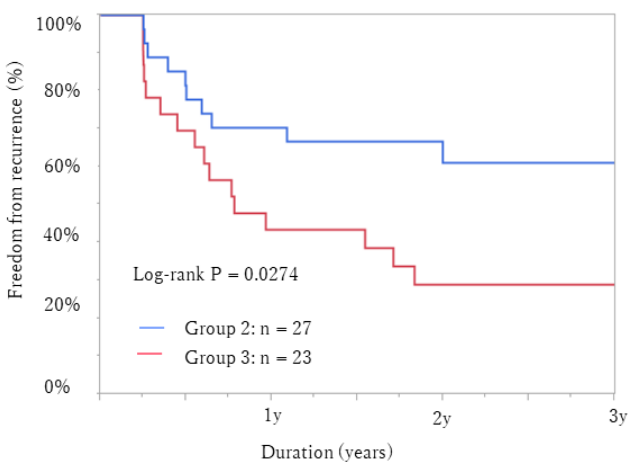
Freedom from ATa recurrence after non-PV trigger ablation in patients with PEAF



Number at risk	0y	0.5y	1 y	1.5y	2y	2.5y	3y
Group 1	186	160	138	120	91	44	24
Group 2	66	58	52	42	30	14	8
Group 3	48	38	25	21	12	8	3

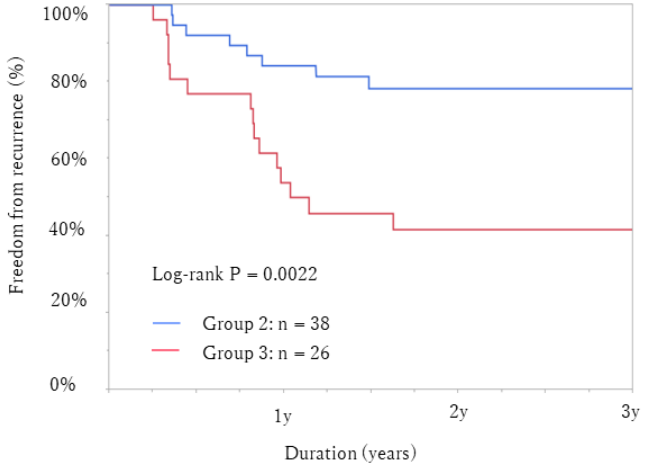
Figure 3

(A) Freedom from ATa recurrence after catheter ablation in patients with non-PV foci



Number at risk	0y	0.5y	1 y	1.5y	2y	2.5y	3y
Group 2	27	22	20	17	12	8	5
Group 3	23	17	11	9	5	3	1

(B) Freedom from ATa recurrence after catheter ablation in patients with non-PV PAC



Number at risk	0y	0.5y	1 y	1.5y	2y	2.5y	3y
Group 2	38	35	33	26	19	7	3
Group 3	26	21	15	12	8	6	3

Figure 4