Journal of Cardiology 74 (2019) 164–168

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

# Effect of Extensive Ablation on Recurrence in Patients with Persistent Atrial Fibrillation Treated with Pulmonary Vein Isolation (EARNEST-PVI) trial: Design and rationale

Tomoharu Dohi (MD)[a,1], Daisaku Nakatani (MD, PhD)[a,1], Koichi Inoue (MD, PhD)[b], Shungo Hikoso (MD, PhD)[a,c,*], Takafumi Oka (MD, PhD)[b], Kenichi Hayashi (PhD)[d], Masaharu Masuda (MD, PhD)[e], Yoshio Furukawa (MD)[f], Masato Kawasaki (MD)[f], Yasuyuki Egami (MD)[g], Kazunori Kashiwase (MD, PhD)[h], Akio Hirata (MD, PhD)[h], Tetsuya Watanabe (MD, PhD)[i], Miwa Miyoshi (MD, PhD)[j], Toshihiro Takeda (MD, PhD)[k], Akito Nakagawa (MD, PhD)[k], Hiroya Mizuno (MD, PhD)[a], Hitoshi Minamiguchi (MD)[a], Tetsuhisa Kitamura (MD, MSc, DrPH)[l], Shinichiro Suna (MD, PhD)[a], Takayuki Kojima (MD)[a], Hirota Kida (MAS)[a], Oeun Bolrathanak (MD)[a], Yuji Okuyama (MD, PhD)[m], Yasushi Sakata (MD, PhD, FJCC)[a] on behalf of the OCVC investigators

[a] *Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan*
[b] *Cardiovascular Center, Sakurabashi-Watanabe Hospital, Osaka, Japan*
[c] *Department of Medical Therapeutics for Heart Failure, Osaka University Graduate School of Medicine, Suita, Japan*
[d] *Keio University, Department of Mathematics, Yokohama, Japan*
[e] *Kansai Rosai Hospital Cardiovascular Center, Amagasaki, Japan*
[f] *Division of Cardiology, Osaka General Medical Center, Osaka, Japan*
[g] *Division of Cardiology, Osaka Rosai Hospital, Sakai, Japan*
[h] *Cardiovascular Division, Osaka Police Hospital, Osaka, Japan*
[i] *Department of Cardiovascular Medicine, Yao Municipal Hospital, Yao, Japan*
[j] *Department of Cardiology, Osaka Hospital, Japan Community Healthcare Organization, Osaka, Japan*
[k] *Department of Medical Informatics, Osaka University Graduate School of Medicine, Suita, Japan*
[l] *Department of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Suita, Japan*
[m] *Cardiovascular Division, Osaka Minami Medical Center, Kawachinagano, Japan*

ARTICLE INFO

*Article history:*
Received 20 October 2018
Received in revised form 13 December 2018
Accepted 18 January 2019
Available online 8 March 2019

*Keywords:*
Persistent atrial fibrillation
Catheter ablation
Recurrence
Non-inferiority trial

ABSTRACT

*Background:* Although extensive substrate modification in addition to pulmonary vein isolation (PVI) has been recommended in catheter ablation for persistent atrial fibrillation (AF), recent randomized controlled trials have not demonstrated efficacy of such additional ablations.
*Methods and study design:* The Osaka Cardiovascular Conference will conduct a multicenter, randomized, open-label trial aiming to examine whether PVI alone is non-inferior to PVI plus additional ablation such as linear ablation and/or complex fractionated atrial electrogram ablation in patients with persistent AF. The primary outcome is recurrence of AF documented by scheduled or symptom-driven electrocardiogram tests during a 1-year follow-up period after the index ablation. The key secondary endpoints include all-cause death, occurrence of symptomatic stroke, complications related to the procedure, and quality of life assessment using the 36-item Short-Form Health Survey. The clinical impact of the presence or absence of AF trigger foci, and their origins in cases with them, on the results of catheter ablation will also be investigated as an exploratory endpoint. A total of 512 patients will be enrolled and followed up to 1 year.

* Corresponding author. Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, 2-2 Yamadaoka, Suita 565-0871, Japan. Tel.: +81 6 6879 3640; fax: +81 6 6879 3639.
*E-mail address:* hikoso@cardiology.med.osaka-u.ac.jp (S. Hikoso).
[1] Drs Dohi and Nakatani contributed equally to this work.

https://doi.org/10.1016/j.jjcc.2019.01.010

*Conclusions:* The EARNEST-PVI trial is a randomized controlled trial designed to assess whether PVI alone is non-inferior to extended substrate ablation for patients with persistent AF undergoing a first catheter ablation.



## Introduction

Since the prevalence of atrial fibrillation (AF) has increased in most developed countries [1,2], now affecting one in four middle-aged adults, appropriate management of AF has become imperative. Catheter ablation is considered one of the first-line treatments for paroxysmal AF.

Ectopic atrial activity triggered in pulmonary veins is a major cause of paroxysmal AF. Therefore, catheter ablation with the objective of complete pulmonary vein isolation (PVI) has been widely performed and is highly successful for sinus rhythm maintenance [3], being reportedly more effective than antiarrhythmic drugs in paroxysmal AF patients [4,5].

Conversely, the outcomes of catheter ablation for persistent AF are worse than those for paroxysmal AF, because persistent AF is usually accompanied by more complex triggers and a more extensive arrhythmogenic substrate [6,7], which is associated with electrical and anatomical remodeling of the left atrium (LA) [8]. Therefore, additional substrate modification such as linear ablation or complex fractionated atrial electrogram (CFAE) ablation in addition to PVI during AF ablation had been considered necessary, as recommended in the previous HRS/EHRA/ECAS expert consensus statement [3]. Its effectiveness has been demonstrated in a number of meta-analyses [4,5]. However, larger-scale randomized controlled trials conducted to prove the efficacy of these empiric extensive ablations [9,10] have not demonstrated the superiority of extensive additional ablation compared to PVI alone, suggesting that PVI alone is non-inferior to empiric extensive ablation. Therefore, the efficacy and necessity of additional substrate modifications after PVI in patients with persistent AF remains controversial, and whether lines and CFAE have any remaining role in AF ablation remains unclear as described in the recent HRS/EHRA/ECAS/APHRS/SOLECE expert consensus [11], or AF guideline of the European Society of Cardiology [12]. Until now, no reports have demonstrated that PVI alone is non-inferior to empiric extensive ablation with sufficient sample size and non-inferior study design, for the prevention of AF recurrence in persistent AF.

In this multicenter, randomized trial, we aim to elucidate whether PVI alone is non-inferior to more extensive ablation with respect to the maintenance of sinus rhythms in patients with persistent AF (The EARNEST-PVI trial) with sufficient sample size for non-inferior study design. Moreover, optimal ablation strategy might be different depending on a mechanism of AF persistence [6], and PVI alone would be sufficient in patients with AF triggers only from PVs. We will divide the study population into 3 subgroups based on the presence or absence of AF triggers, and its origin in cases with them, and will investigate which ablation strategy would be more sufficient in each subgroup. This trial will be the first trial that clearly demonstrates that PVI alone is non-inferior to empirical extensive ablation for prevention of AF recurrence in the patients with persistent AF undergoing a first-time ablation.

## Methods

### *Objective*

The objective of the EARNEST-PVI trial is to examine whether PVI alone is non-inferior to PVI plus additional ablation with respect to the recurrence of AF documented by scheduled or symptom-driven electrocardiogram (ECG) tests during 1-year follow-up period after the first procedure. The clinical impact of the presence or absence of AF trigger foci, and their origins in cases with them, on the results of catheter ablation will also be investigated.

### *Study design*

The EARNEST-PVI trial is a prospective, multicenter, randomized, open-label non-inferiority trial in which patients with persistent AF will undergo a catheter ablation procedure. After providing informed consent at each hospital, patients who are eligible for the trial will be randomized to either PVI alone or PVI plus additional ablation. Randomization will be performed electronically by entering patient information into an automatic data collection system via a secure internet connection. LA dimensions will be the only adjustment factor considered in dynamic allocation to avoid bias.

This study has been registered at ClinicalTrials.gov (NCT03514693) and has been approved by the institutional review board at each participating hospital.

### *Eligibility criteria*

The study population will consist of patients with persistent AF undergoing a first-time ablation procedure. Persistent AF is defined as a sustained episode lasting ≥7 days and <5 years at enrollment. AF patients in sinus rhythm at enrollment will be excluded from this study even if they have a history of AF persisting for more than one week or a history of defibrillation to terminate AF. Inclusion and exclusion criteria are summarized in Table 1. A signed, ethics committee/institutional review board-approved informed consent form will be obtained from each patient prior to any trial-related procedure.

### *Procedures*

Anti-arrhythmic drugs will be stopped at least 5 half-lives before any procedure; amiodarone will be stopped for 60 days. All

**Table 1**
Eligibility criteria.

| Inclusion criteria |
|---|
| • Patients undergoing a first-time ablation procedure for persistent AF |
| Exclusion criteria |
| • Patients with long-standing persistent AF lasting ≥5 years |
| • Patients with left atrial dimension ≥50 mm by 2-dimensional echocardiography |
| • Patients with valvular AF (defined as the presence of mitral or aortic stenosis or regurgitation with a history of rheumatic fever or implantation of artificial heart valves) |
| • Patients who underwent prior cardiac surgery |
| • Patients aged <20 years |
| • Patients aged ≥80 years |
| • Patients receiving hemodialysis |
| • Patients with heart failure (left ventricular ejection fraction <30% and NYHA class ≥ III) |
| • Patients receiving antiarrhythmic agents before the ablation procedure (within 60 days for amiodarone, or 5 half-lives for other drugs) |
| • Patients who are not considered to be suitable candidates by the attending physician |

AF, atrial fibrillation; NYHA, New York Heart Association.

patients will undergo transesophageal echocardiography before ablation to rule out LA thrombus, and contrast computed tomography (CT) to obtain 3D images of the LA and PV. Conscious sedation, deep sedation, or general anesthesia will be chosen at the physician's discretion during procedures. All procedures will be performed via transseptal access to the LA. Heparin will be administered after the transseptal puncture to maintain an activated clotting time of >300 seconds. Multipolar diagnostic catheters (8 poles minimum) will be placed in the coronary sinus (CS) and the right atrium (RA). One or two circular mapping catheters (10 poles minimum) will be used for both mapping and confirmation of PVI. A market-approved, open irrigated-tip ablation catheter will be used for ablation and mapping. Maximum power will be ≤35 W during the ablation, and lower power will be employed on the posterior wall of the LA (25–30 W) to avoid damage to the esophagus. All procedures will be guided using a 3D cardiac mapping system (CARTO, Biosense-Webster, Diamond Bar, CA, USA; Ensite NavX, St Jude Medical, St Paul, MN, USA; or Rhythmia Mapping System, Boston Scientific Inc., Natick, MA, USA). In principle, anticoagulation therapy should be continued up to 3 months after catheter ablation, and thereafter can be continued or stopped at the discretion of the physicians.

*Identification of the origin of AF triggers*

We will perform ablation procedures after an electrophysiological study to identify the origin(s) of AF triggers. An AF trigger is defined as an arrhythmogenic focus causing initiation of AF at least twice with the same intracardiac activation sequence. Operators will attempt to detect the origin of AF triggers in patients with AF initiated after electrical cardioversion. Based on their origins, patients will be divided into three groups: PV origin, non-PV origin, and unidentified origin. The PV origin group will comprise patients with AF triggers specifically from the PVs. The non-PV group will include those with at least one AF trigger of non-PV origin regardless of the presence or absence of triggers from PVs. The unidentified origin group will include patients with no AF triggers observed during the electrophysiological study. Patients with failure of conversion to sinus rhythm will be included in the unidentified origin group.

To detect the location of the AF triggers, we will simultaneously use at least four multipolar catheters to record the electrogram from the PVs and elsewhere to search for arrhythmogenic foci. One or two circular catheters plus an ablation catheter will be placed at the ostia of two or three PVs simultaneously. If AF is induced, we will perform electronic cardioversion, confirm the reproducibility of AF initiation and investigate the origins. If premature atrial contractions initiating AF are suspected of originating from a non-PV area that is not covered by the catheters, we will change the location of the catheters and use them for mapping to attempt to search for the focus/foci as described previously [13]. If spontaneous recurrence of AF is not observed for 5 minutes after cardioversion, provocative maneuvers such as administering isoproterenol (ISP) in incremental doses of up to 0.4 μg/kg/min will be performed. The endpoint of ISP administration will be systolic blood pressure <80 mmHg, heart rate in sinus rhythm >130 bpm, or ISP administration at 0.4 μg/kg/min for 5 min. We will check for the presence or absence of AF induction for 5 minutes after ISP discontinuation. After group assignments, catheter ablation will subsequently be initiated according to the randomization strategy.

*Circumferential PV antrum isolation*

All patients will undergo PVI first. Ipsilateral circumferential PVI is the recommended PVI strategy. The success of PVI will be defined as the achievement of the dissociation of PV potentials in all PVs. Disappearance of PV potentials will be reconfirmed at the end of the procedure, a minimum of 20 minutes after the initial success of PVI. If PV potentials reappear in any PV, re-isolation will be performed. Ablation of dormant conduction evoked by rapid intravenous administration of adenosine triphosphate may be added at the discretion of the physician to establish durable LA–PV disconnection as previously described [14,15].

*Additional ablation combined with PVI*

Patients assigned to the additional ablation group will subsequently undergo CFAE ablation, linear ablation, or both; the choice of which will be decided by the physician. For CFAE ablation, CFAE mapping must be performed during AF. If AF cannot be induced or sustained, linear ablation will be used as the additional ablation strategy.

A 1-mm tipped multipolar mapping catheter will be the preferred CFAE mapping catheter. The ablation catheter may also be used in regions where the multipolar mapping catheter will have poor contact. The CFAE sites will be identified according to the automated algorithms of the 3D mapping system, which have been described and validated previously [16,17]. When the CARTO system is to be used as the mapping system, an online CFAE software module will be used to analyze a 2.5-second window of bipolar electrograms (EGMs) at each mapping site. Voltage peaks greater than the noise threshold but less than the upper threshold (0.05–0.15 mV) will be annotated. The intervals between successive peaks falling within a programmable duration (60–120 ms) will be counted, with the total defined as the interval confidence level (ICL). All sites with ICL >7 will be targeted for CFAE ablation. AF cycle length will be measured from a predetermined pair of CS recording electrodes [16]. When the Ensite NavX system is to be used, the Ensite Complex Fractionated Electrograms Algorithm will be used to measure the time between multiple discrete deflections in a local AF EGM recording over 5 seconds and average these interdeflection time intervals to calculate the mean cycle length (CL) of the local EGM during AF. The P-P sensitivity, width, and refractory value should be 0.03–0.05 mV, 15–20 ms, and 35–45 ms, respectively. The mean CL will be projected onto the LA anatomical shell as a color-coded display. Regions with mean CL <120 ms will be defined as “CFAE” based on previously published data [17]. The endpoint for CFAE ablation will be the elimination of all local CFAE sites in the LA and CS, or AF termination. AF termination will be defined as direct transition to sinus rhythm or to an organized atrial tachycardia (AT) or flutter (AFL). If AF terminates to sinus rhythm and is successfully maintained, the remaining CFAE sites will not be ablated. If AF converts to an AFL/AT, the remaining CFAE sites and isthmus or foci of AFL/AT will be ablated. CFAE ablation in the right atrium may be added at the physician's discretion.

In cases undergoing linear ablation, both roof line ablation connecting the right and left PV encircling lesions and mitral line ablation connecting the PV encircling lesion and mitral annulus will be performed. In addition to roof line ablation, bottom line ablation connecting the inferior aspect of encircling lesions for PVI may be performed to allow for electrical isolation of the posterior LA wall. For mitral line ablation, either the posterior approach (from the left inferior PV to the posterior annulus) or the anterior approach (from the left superior PV to the anterior annulus) may be used. The endpoint of linear ablation will be to achieve a complete, bidirectional block across the linear lesion. The conduction block will be rechecked at the end of the procedure or >20 minutes after the initial success of the conduction block.

The decision of whether or not to stop additional RF energy applications for safety or other reasons due to difficulties associated with eliminating all CFAE sites or creating a complete conduction block despite the operator's best efforts will be left to the discretion of the operator.

Upon completion of PVI alone or PVI plus additional ablation, inducibility of tachyarrhythmias will be evaluated using 10-s burst

pacing from the CS and RA at maximum current output (20 mA) starting at a cycle length of 400 ms and decreasing to 200 ms. ISP will be readministered to evoke non-PV AF triggers. According to the recommendations of the HRS/EHRA/ECAS expert consensus statement [3] regarding the ablation technique, physicians should ablate focal ablation or isolation of AF triggers from non-PV foci, and ablate to block the cavotricuspid isthmus (CTI) in cases with inducible CTI-dependent AFL. Ablation for clinical coexisting tachyarrhythmia such as AFL, AT, and supraventricular tachycardia will also be performed.

*Antiarrhythmic drug and repeat ablation after the ablation*

The blanking period is defined as the 3 months after the protocol therapy. The recurrence of AF during this period will not be counted, while reablation during this blanking period is defined as recurrence just after the blanking period. Use of antiarrhythmic drugs will be allowed for the first 3 months after ablation, and the choice of drug including amiodarone will be left to the discretion of investigators. The investigators will be strongly recommended to stop antiarrhythmic drugs 3 months after the ablation.

Repeat ablation will be allowed for patients with recurrence of AF with the discretion of investigators. At repeat ablation procedure, re-isolation of reconnection of PV must be performed in all cases, and re-isolation of reconnection of linear isolation, or reassessment and reablation of CFAE must be performed for extensive ablation group. Addition of linear or CFAE ablation to PVI will be allowed for reablation of PVI alone group.

*Follow-up schedule*

The study flow is summarized in Fig. 1. Before the ablation procedure, baseline information, information on atrial fibrillation, previous history, and medication history will be collected. During this visit, a blood test, transthoracic echocardiogram, and 12-lead ECG will be performed. Quality of life (QOL) will be assessed using the 36-item Short-Form Health Survey (SF-36). During the first ablation procedure, detailed information of the procedure and adverse events will be collected. Medications at discharge and any adverse events will be recorded. The blood test (hemoglobin, brain natriuretic peptide, creatinine, and C-reactive protein) and 12-lead ECG also will be repeated.

Patients will be followed up 1, 3, 6, 9, and 12 months after the ablation procedure. At each scheduled follow-up visit, a 12-lead ECG, medication assessment, and recording of any adverse events will be performed. A 24-hour Holter ECG will be acquired at 6 and 12 months. Laboratory tests, transthoracic echocardiography, and the SF-36 will be performed at 12 months.

*Study endpoints*

The primary endpoint of the study will be the recurrence of AF documented by scheduled or symptom-driven ECG tests during 1-year follow-up period after the index ablation procedure. "Recurrence of AF" is defined as the documentation of any atrial arrhythmia including AF, AFL, and/or AT lasting ≥30 seconds by 12-lead ECG or other appropriate tests.

Secondary endpoints will include the following: death from any cause, symptomatic stroke, the recurrence of AF after repeat ablation procedures, periprocedural complications, total duration of energy application, total energy delivery during the procedure, and QOL measurements according to the SF-36 test.

*Study organization and status*

*Osaka Cardiovascular Conference*

The Osaka Cardiovascular Conference (OCVC) consists of cardiologists belonging to the Osaka University Graduate School of Medicine or one of 30 affiliated hospitals in Osaka, Japan. The

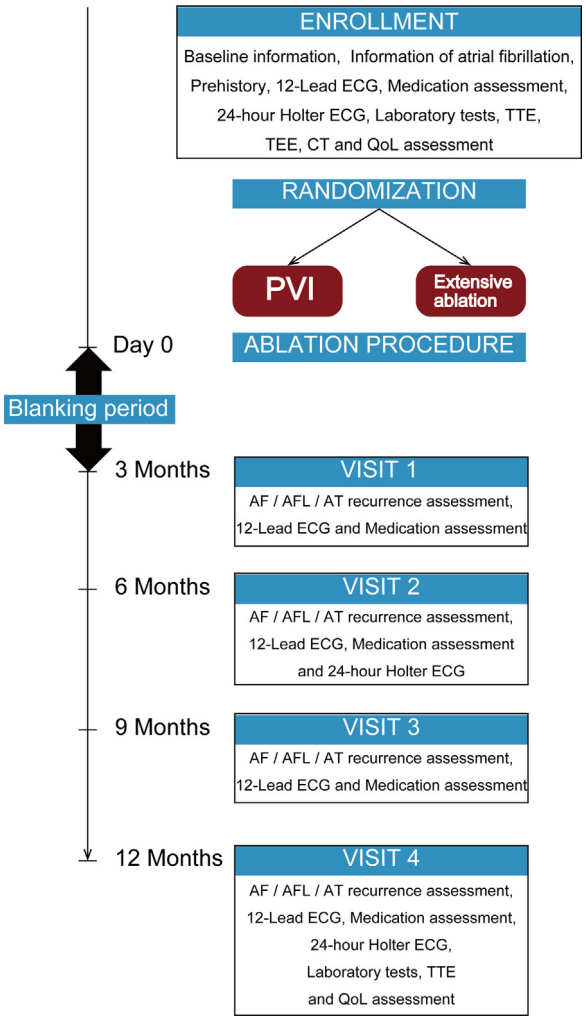


**Fig. 1.** EARNEST-PVI study design.
AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; CT, computed tomography; ECG, electrocardiography; PVI, pulmonary vein isolation; QoL, quality of life; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

OCVC was launched in 2015 to investigate clinical questions in the cardiovascular field [18]. Among the participating institutions, members of 10 high-volume hospitals that frequently perform invasive treatments for AF comprise OCVC-arrhythmia investigators and participated in the present study. Details of the study organization are shown in the Supplementary Appendix.

EARNEST-PVI started enrollment in March 2016, and completed enrollment in September 2017. Completion of the study was expected by March 2019.

*Statistical considerations*

The sample size and randomization are specified based on the concept of non-inferiority to achieve the primary objective. The null hypothesis is that the incidence rate of the primary outcome in the PVI alone group is inferior to that in the PVI plus additional ablation group. In the STAR-AF II trial, the AF recurrence rate at 18 months was 41% in the PVI-alone group [9]. The non-inferiority margin will be calculated by referring to previous studies [19,20]. Based on these values, the recurrence rate of AF is assumed to be 40% in both groups. Therefore, a sample size of 243 subjects is required to reject the null hypothesis with a power of 80% and significance level of 5% with a non-inferiority margin of 10%. The randomization ratio is 1:1. Therefore, we ultimately need a total sample size of 512 patients, allowing for some dropouts.

The full analysis set (FAS) is defined as the set of all randomized patients who meet all inclusion criteria, and its statistical evaluation is based on the intention-to-treat principle: patients should be analyzed according to the allocated treatment at randomization. The per protocol set (PPS) is defined as the set of patients of the FAS who complete the study without protocol violations.

Analysis for the primary outcome is based on the hazard ratio of the PVI alone group to the PVI plus additional ablation group for FAS and PPS. The null hypothesis will be rejected when the confidence interval for the hazard ratio lies within the non-inferiority zone. Once non-inferiority is established, a test for superiority will subsequently be conducted at a significance level of 5%. No adjustment for multiplicity will be required because of the closed testing procedure. No interim analyses will be conducted in this trial.

To identify patients in the PVI alone group whose prognoses are not inferior to those of patients in the PVI plus additional ablation group, and to compare AF recurrence rates among groups divided by the origin of AF triggers, several multivariate analyses such as the Cox proportional hazards model will be conducted.

## Summary

The EARNEST-PVI trial is a prospective, multicenter, randomized, open-label trial with non-inferiority design for patients with persistent AF undergoing first-time catheter ablation. We will compare the effects of PVI alone with PVI plus empiric additional ablation such as linear ablation, CFAE ablation, or both on the prevalence of recurrent AF documented by scheduled or symptom-driven ECG tests during 1-year follow-up period after the index ablation procedure. The result of this trial will elucidate whether PVI alone is not inferior to extensive ablation to maintain sinus rhythms, and will provide additional valuable information to develop treatment strategies for patients with persistent AF.

## Funding

This study is funded by Medtronic, Johnson & Johnson, and St. Jude Medical.

## Conflict of Interest

Dr Inoue has received honoraria from Medtronic, Johnson & Johnson, and Japan Lifeline. Dr Masuda has received honoraria from Johnson & Johnson, Boston Scientific, Medtronic, Japan Lifeline, and Abbott. Dr Mizuno has received honoraria from Biosense Webster, Medtronic, St. Jude Medical, and Japan Lifeline. Dr Minamiguchi has received an honorarium from Japan Medtronic. Dr Sakata has received research funding from Medtronic, Johnson & Johnson, and St. Jude Medical, and honoraria from Medtronic. The other authors have no conflicts of interest to report.

## Acknowledgment

We thank the clinical research coordinators for their assistance with patient data collection. All authors participated in the development and writing of the paper, reviewed and critically revised the manuscript for content, and approved the final version of the manuscript for submission.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.01.010.

## References

[1] Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129:837–47.
[2] Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nat Rev Cardiol 2014;11:639–54.
[3] Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace 2012;14:528–606.
[4] Parkash R, Tang AS, Sapp JL, Wells G. Approach to the catheter ablation technique of paroxysmal and persistent atrial fibrillation: a meta-analysis of the randomized controlled trials. J Cardiovasc Electrophysiol 2011;22:729–38.
[5] Wynn GJ, Das M, Bonnett LJ, Panikker S, Wong T, Gupta D. Efficacy of catheter ablation for persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized and nonrandomized controlled trials. Circ Arrhythm Electrophysiol 2014;7:841–52.
[6] 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.
[7] Yamaguchi T, Tsuchiya T, Fukui A, Kawano Y, Otsubo T, Takahashi Y, et al. Impact of the extent of low-voltage zone on outcomes after voltage-based catheter ablation for persistent atrial fibrillation. J Cardiol 2018;72:427–33.
[8] Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954–68.
[9] Verma A, Jiang CY, 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.
[10] Vogler J, Willems S, Sultan A, Schreiber D, Luker J, Servatius H, et al. Pulmonary vein isolation versus defragmentation: The CHASE-AF clinical trial. J Am Coll Cardiol 2015;66:2743–52.
[11] Calkins H, Hindricks G, Cappato R, Kim YH, 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.
[12] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962.
[13] Lin WS, Tai CT, Hsieh MH, Tsai CF, Lin YK, Tsao HM, et al. Catheter ablation of paroxysmal atrial fibrillation initiated by non-pulmonary vein ectopy. Circulation 2003;107:3176–83.
[14] Kobori A, Shizuta S, Inoue K, Kaitani K, Morimoto T, Nakazawa Y, et al. Adenosine triphosphate-guided pulmonary vein isolation for atrial fibrillation: the UNmasking Dormant Electrical Reconduction by Adenosine TriPhosphate (UNDER-ATP) trial. Eur Heart J 2015;36:3276–87.
[15] Okishige K, Aoyagi H, Nishimura T, Shigeta T, Nakamura T, Yamauchi Y, et al. Characteristics of dormant pulmonary vein conduction induced by adenosine triphosphate in patients with atrial fibrillation undergoing cryoballoon ablation. J Cardiol 2018;71:577–82.
[16] Porter M, Spear W, Akar JG, Helms R, Brysiewicz N, Santucci P, et al. Prospective study of atrial fibrillation termination during ablation guided by automated detection of fractionated electrograms. J Cardiovasc Electrophysiol 2008;19:613–20.
[17] Verma A, Novak P, Macle L, Whaley B, Beardsall M, Wulffhart Z, et al. A prospective, multicenter evaluation of ablating complex fractionated electrograms (CFEs) during atrial fibrillation (AF) identified by an automated mapping algorithm: acute effects on AF and efficacy as an adjuvant strategy. Heart Rhythm 2008;5:198–205.
[18] Inoue K, Suna S, Iwakura K, Oka T, Masuda M, Furukawa Y, et al. Outcomes for atrial fibrillation patients with silent left atrial thrombi detected by transesophageal echocardiography. Am J Cardiol 2017;120:940–6.
[19] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.
[20] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.