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Original Article

Extensive ablation for elderly patients with persistent atrial fibrillation: insights from the EARNEST-PVI prospective randomized trial

Yuki Matsuoka (MD) [a], Yohei Sotomi (MD, PhD) [a,*], Shungo Hikoso (MD, PhD) [a,b], Akihiro Sunaga (MD, PhD) [a], Daisaku Nakatani (MD, PhD) [a], Katsuki Okada (MD, PhD) [a,c], Tomoharu Dohi (MD, PhD) [a], Taiki Sato (MD, PhD) [a], Hirota Kida (MAS) [a], Daisuke Sakamoto (MD) [a], Tetsuhisa Kitamura (MD, MSc, DrPH) [d], Nobuaki Tanaka (MD) [e], Masaharu Masuda (MD, PhD) [f], Tetsuya Watanabe (MD, PhD) [g], Hitoshi Minamiguchi (MD) [h], Yasuyuki Egami (MD) [i], Takafumi Oka (MD, PhD) [a], Miwa Miyoshi (MD, PhD) [j], Masato Okada (MD) [e], Yasuhiro Matsuda (MD) [f], Masato Kawasaki (MD) [g], Koichi Inoue (MD, PhD) [k], Yasushi Sakata (MD, PhD, FJCC) [a], on behalf of the OCVC-Arrhythmia Investigators

[a] Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[b] Department of Cardiovascular Medicine, Nara Medical University, Nara, Japan
[c] Department of Medical Informatics, Osaka University Graduate School of Medicine, Osaka, Japan
[d] Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[e] Cardiovascular Center, Sakurabashi Watanabe Hospital, Osaka, Japan
[f] Cardiovascular Center, Kansai Rosai Hospital, Amagasaki, Japan
[g] Division of Cardiology, Osaka General Medical Center, Osaka, Japan
[h] Cardiovascular Division, Osaka Police Hospital, Osaka, Japan
[i] Division of Cardiology, Osaka Rosai Hospital, Sakai, Japan
[j] Department of Cardiology, Osaka Hospital, Japan Community Healthcare Organization, Osaka, Japan
[k] Cardiovascular Division, National Hospital Organization Osaka National Hospital, Osaka, Japan

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ABSTRACT

Background: In patients with persistent atrial fibrillation (AF), extensive ablation for substrate modification, such as linear ablation or complex fractionated atrial electrogram ablation in addition to pulmonary vein isolation (PVI) remains controversial. Previous studies investigating extensive ablation have demonstrated its varying efficacy, suggesting the possible heterogeneity of its efficacy. Aging is a major risk factor for AF and is associated with atrial remodeling. We aimed to compare the efficacy and safety of the extensive ablation strategy compared with PVI alone strategy between young and elderly patients.

Methods: This study is a post-hoc analysis of the multicenter, randomized controlled, noninferiority trial investigating the efficacy and safety of PVI-only (PVI-alone arm) compared with extensive ablation (PVI-plus arm) in patients with persistent AF (EARNEST-PVI trial). We divided the overall population into 2 groups based on age and assessed treatment effects.

Results: In the young group (age <65 years, $N = 206$), there was no significant difference in the recurrence rate between the PVI-alone group and PVI-plus group [hazard ratio (HR): 1.00, 95 % CI: 0.57–1.73, $p = 0.987$], whereas the recurrence rate was significantly lower in the PVI-plus group compared to the PVI-alone group in the elderly group (age ≥65 years, $N = 291$) (HR: 0.47, 95 % CI: 0.29–0.76, $p = 0.0021$) (p for interaction = 0.0446). There were no fatal procedural complications.

Conclusion: In patients with persistent AF, the extensive ablation strategy was more effective than the PVI-alone strategy in elderly patients, while the effectiveness of both approaches was comparable in young patients.

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* Corresponding author at: Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan.
E-mail address: sotomiyohei@gmail.com (Y. Sotomi).

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Introduction

Catheter ablation has been established as a safe and efficacious intervention for the management of atrial fibrillation (AF). Pulmonary vein isolation (PVI) is recommended as the primary approach for rhythm control therapy in symptomatic patients with AF [1]. Extensive ablation techniques for patients with persistent AF, such as linear ablation or complex fractionated atrial electrogram (CFAE) ablation in addition to PVI, may be considered but are not well established [1,2]. Prior investigations exploring more extensive ablation strategies alongside PVI have showed varying outcomes, suggesting heterogeneity of their efficacy [3–7]. Certain individuals with persistent AF might derive benefits from an extensive ablation strategy.

Aging constitutes a significant risk factor for AF [8]. Aging is correlated with atrial remodeling characterized by anatomical and structural alterations, reductions in atrial voltage with discrete areas of low voltage, widespread conduction deceleration, as well as anatomically determined functional conduction delay and block, and sinus node dysfunction during sinus rhythm [9]. With advancing age, a notable decrease in the CFAE area reflects age-related electrical remodeling, while an augmentation in the size and volume of the left atrium signifies anatomic remodeling in patients with persistent AF [10]. Elderly patients may exhibit a higher prevalence of arrhythmogenic substrates compared to younger patients. Therefore, we hypothesized that implementing an extensive ablation strategy in conjunction with PVI could yield positive outcomes for elderly patients, while a PVI-only strategy may be sufficient for maintaining sinus rhythm in young patients. This study aimed to investigate the disparity in efficacy and safety between an extensive ablation strategy and a PVI-only strategy among young and elderly patients.

Methods

Study design

This study is a post-hoc analysis of the EARNEST-PVI trial (ClinicalTrials.gov, NCT03514693), which was a prospective, multicenter, randomized, open-label, and non-inferiority trial conducted by the Osaka Cardiovascular Conference Arrhythmia Investigators [11]. Patients with persistent AF in eight hospitals were enrolled. Persistent AF was defined as lasting for at least 7 days but <5 years. The main exclusion criteria included age <20 years or ≥80 years, left atrial dimension ≥50 mm, valvular AF, history of cardiac surgery, left ventricular ejection fraction (LVEF) <30 %, and New York Heart Association classification (NYHA) ≥3. Patients were randomly assigned to either the PVI-only strategy (PVI-alone) or the extensive ablation strategy with linear and/or CFAE ablation in addition to PVI (PVI-plus). The present post-hoc study focused on the disparity in the effectiveness of PVI-alone vs. PVI-plus between young and elderly patients. We divided the overall population into 2 groups (young, age <65 years; elderly, age ≥65 years) (Fig. 1), since the elderly are defined by the age of 65 years or older in many countries including Japan [12]. All patients provided written informed consent to participate, and the study received approval from the ethics committee of each hospital. This research complied with the ethical principles laid out in the Declaration of Helsinki and received approval from the Institutional Review Boards of all hospitals. The dataset used in this sub-analysis was updated from that used in the main paper on January 11, 2021.

Study procedure

In the EARNEST-PVI trial, electrical cardioversion was initially performed to identify the triggers. Without spontaneous recurrence of AF within 5 min after cardioversion, provocative testing was carried out. All ablation procedures were conducted using radiofrequency catheter ablation. In patients assigned to the PVI-plus group, linear ablation and/or CFAE ablation was additionally performed at the discretion of the physician. For linear ablation, at least two left atrial linear lesions were required. The first line was a left atrial anterior or posterior mitral isthmus line. The second line was a left atrial roof or bottom line. Patients who underwent ablation of both a roof line and a bottom line were classified as having posterior wall isolation. The endpoint of PVI and linear ablation was a bidirectional conduction block at the end of the initial procedure and after waiting >20 min. For CFAE ablation, CFAE mapping was performed during AF. Automated algorithms of the

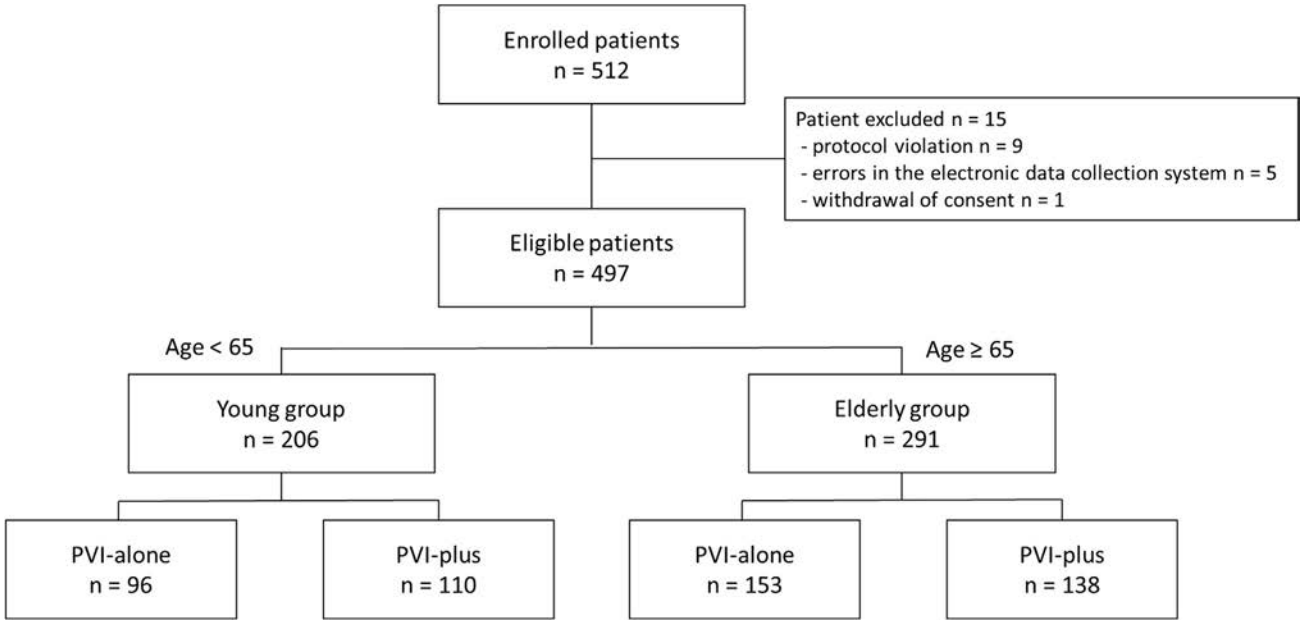

Fig. 1. Study flowchart.
A total of 512 patients were enrolled and randomized in the original trial between March 2016 and September 2017. In this study, 9 patients were excluded for protocol violation, 5 for errors in the electronic data collection system, and 1 for withdrawal of consent, leaving 497 eligible patients. These eligible patients were categorized into two groups based on their age at baseline: the young group (age <65 years) comprised 206 patients (96 in the PVI-alone group and 110 in the PVI-plus group), and the elderly group (age ≥65 years) comprised 291 patients (153 in the PVI-alone group and 138 in the PVI-plus group).
PVI, pulmonary vein isolation.

three-dimensional mapping system automatically identified CFAE sites. Detailed information about CFAE is provided elsewhere [13].

Other additional ablations, including focal ablation for non-PV triggers, ablation for paroxysmal supraventricular tachycardia, superior vena cava (SVC) isolation, and cavo-tricuspid isthmus (CTI) linear ablation, were allowed to be performed in both groups. The detail of the study procedure was described in the design paper of the EARNEST-PVI trial [14].

Data collection and follow-up

Prior to the procedure, clinical data of patient history, laboratory data, and transthoracic echocardiography were collected. Twelve-lead electrocardiograms (ECGs) were conducted before the procedure, at discharge, and 1, 3, 6, 9, and 12 months post-procedure. Additionally, 24-hour Holter ECG was performed at 6 and 12 months. Patients who experienced symptoms suggestive of AF recurrence could visit the clinics or hospitals, and an ECG was performed during each additional visit. For such patients, additional Holter ECG or event monitor recording was conducted.

Study endpoints

The primary endpoint of the study was AF recurrence within 1 year post-procedure, defined as AF, atrial flutter, or atrial tachycardia lasting over 30 s confirmed by ECG, including 12-lead ECG, 24-hour Holter ECG, or event recorders. A blanking period of 3 months was implemented. The use of antiarrhythmic drugs was permitted during the blanking period but not recommended thereafter. Prescription of antiarrhythmic drugs was at the discretion of the physician. The secondary endpoints included death, cerebral infarction, and procedure-related complications.

Statistical analysis

Statistical analysis was performed using R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria). Categorical

Table 1
Patient background and medical history.

	Young	Young PVI-alone	Young PVI-plus	*p*-Value (Young)[a]	Elderly	Elderly PVI-alone	Elderly PVI-plus	*p*-Value (Elderly)[a]	*p*-Value (Young vs elderly)[b]
n	206	96	110		291	153	138		
Age	57.50 [52.25,61.00]	58.00 [52.50,61.00]	57.00 [52.25,61.75]	0.881	71.00 [68.00,75.00]	72.00 [68.00,75.00]	71.00 [67.25,75.00]	0.286	<0.001
Female	28 (13.6)	14 (14.6)	14 (12.7)	0.854	93 (32.0)	49 (32.0)	44 (31.9)	>0.999	<0.001
Body mass index	24.86 [23.12,27.39]	24.91 [23.24,27.41]	24.80 [22.99,27.28]	0.967	23.71 [21.62,25.96]	23.88 [21.89,26.45]	23.45 [21.48,25.25]	0.205	<0.001
Family history of AF	19 (9.2)	12 (12.5)	7 (6.4)	0.202	19 (6.5)	11 (7.2)	8 (5.8)	0.808	0.346
AF duration (months)	4.6 [2.5–11.2]	4.3 [2.4–10.9]	4.7 [2.6–11.9]	0.449	4.7 [2.1–12.6]	3.6 [1.9–12.1]	5.3 [2.6–13.1]	0.072	0.861
Long-standing persistent AF	49 (23.8)	21 (21.9)	28 (25.5)	0.661	75 (25.8)	38 (24.8)	37 (26.8)	0.802	0.690
Hypertension	108 (52.4)	48 (50.0)	60 (54.5)	0.609	191 (65.6)	102 (66.7)	89 (64.5)	0.790	0.004
Diabetes mellitus	26 (12.6)	11 (11.5)	15 (13.6)	0.795	59 (20.3)	27 (17.6)	32 (23.2)	0.304	0.035
Dyslipidemia	101 (49.0)	53 (55.2)	48 (43.6)	0.129	126 (43.3)	59 (38.6)	67 (48.6)	0.110	0.241
Smoking				0.929				0.525	0.007
None	69 (33.5)	31 (32.3)	38 (34.5)		126 (43.3)	65 (42.5)	61 (44.2)		
Current	37 (18.0)	18 (18.8)	19 (17.3)		27 (9.3)	17 (11.1)	10 (7.2)		
Past	100 (48.5)	47 (49.0)	53 (48.2)		138 (47.4)	71 (46.4)	67 (48.6)		
History of heart failure	32 (15.5)	16 (16.7)	16 (14.5)	0.821	60 (20.6)	30 (19.6)	30 (21.7)	0.761	0.187
History of percutaneous coronary intervention	4 (1.9)	1 (1.0)	3 (2.7)	0.712	19 (6.5)	8 (5.2)	11 (8.0)	0.479	0.029
Peripheral artery disease	2 (1.0)	2 (2.1)	0 (0.0)	0.419	7 (2.4)	3 (2.0)	4 (2.9)	0.890	0.401
History of stroke	8 (3.9)	3 (3.1)	5 (4.5)	0.869	31 (10.7)	13 (8.5)	18 (13.0)	0.287	0.009
Sleep apnea syndrome	27 (13.1)	12 (12.5)	15 (13.6)	0.973	26 (8.9)	11 (7.2)	15 (10.9)	0.372	0.181
Thyroid disease	8 (3.9)	3 (3.1)	5 (4.5)	0.869	16 (5.5)	7 (4.6)	9 (6.5)	0.638	0.539
Chronic obstructive pulmonary disease	7 (3.4)	5 (5.2)	2 (1.8)	0.340	15 (5.2)	9 (5.9)	6 (4.3)	0.745	0.474
Chronic kidney disease	3 (1.5)	1 (1.0)	2 (1.8)	>0.999	22 (7.6)	12 (7.8)	10 (7.2)	>0.999	0.004
CHA2DS2-VASc score				0.789				0.715	<0.001
0	65 (31.6)	32 (33.3)	33 (30.0)		0 (0.0)	0 (0.0)	0 (0.0)		
1	83 (40.3)	37 (38.5)	46 (41.8)		45 (15.5)	24 (15.7)	21 (15.2)		
2	35 (17.0)	15 (15.6)	20 (18.2)		86 (29.6)	44 (28.8)	42 (30.4)		
3	18 (8.7)	11 (11.5)	7 (6.4)		92 (31.6)	53 (34.6)	39 (28.3)		
4	3 (1.5)	0 (0.0)	3 (2.7)		41 (14.1)	19 (12.4)	22 (15.9)		
5	2 (1.0)	1 (1.0)	1 (0.9)		18 (6.2)	10 (6.5)	8 (5.8)		
6	0 (0.0)	0 (0.0)	0 (0.0)		6 (2.1)	2 (1.3)	4 (2.9)		
7	0 (0.0)	0 (0.0)	0 (0.0)		2 (0.7)	1 (0.7)	1 (0.7)		
8	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)	1 (0.7)		
DR-FLASH score				0.559				0.743	<0.001
1	4 (1.9)	1 (1.0)	3 (2.7)		0 (0.0)	0 (0.0)	0 (0.0)		
2	63 (30.6)	32 (33.3)	31 (28.2)		3 (1.0)	2 (1.3)	1 (0.7)		
3	88 (42.7)	43 (44.8)	45 (40.9)		59 (20.3)	28 (18.4)	31 (22.5)		
4	38 (18.4)	16 (16.7)	22 (20.0)		105 (36.2)	56 (36.8)	49 (35.5)		
5	13 (6.3)	4 (4.2)	9 (8.2)		83 (28.6)	48 (31.6)	35 (25.4)		
6	0 (0.0)	0 (0.0)	0 (0.0)		31 (10.7)	14 (9.2)	17 (12.3)		
7	0 (0.0)	0 (0.0)	0 (0.0)		9 (3.1)	4 (2.6)	5 (3.6)		

Continuous values are shown as median with interquartile range (median [25th percentile, 75th percentile]). Categorical values are given as the number and percentage of positive findings per number of studied patients (N (%)). CHA2DS2-VASc score consisted of the following points: 2 points each for age ≥75 years, and history of stroke, transient ischemic attack, or systemic thromboembolism; 1 point each for congestive heart failure, hypertension, age of 65–74 years, diabetes mellitus, vascular disease, and female sex. The DR-FLASH score was calculated from the prevalence of: diabetes, renal dysfunction (estimated glomerular filtration rate <90 ml/min/1.73 m^2), persistent form of AF, left atrial diameter >45 mm, age >65 years, female sex, and hypertension.
PVI, pulmonary vein isolation; AF, atrial fibrillation.

[a] Comparison between PVI-alone and PVI-plus in each group.

[b] Comparison between all patients in the young group and the elderly group.

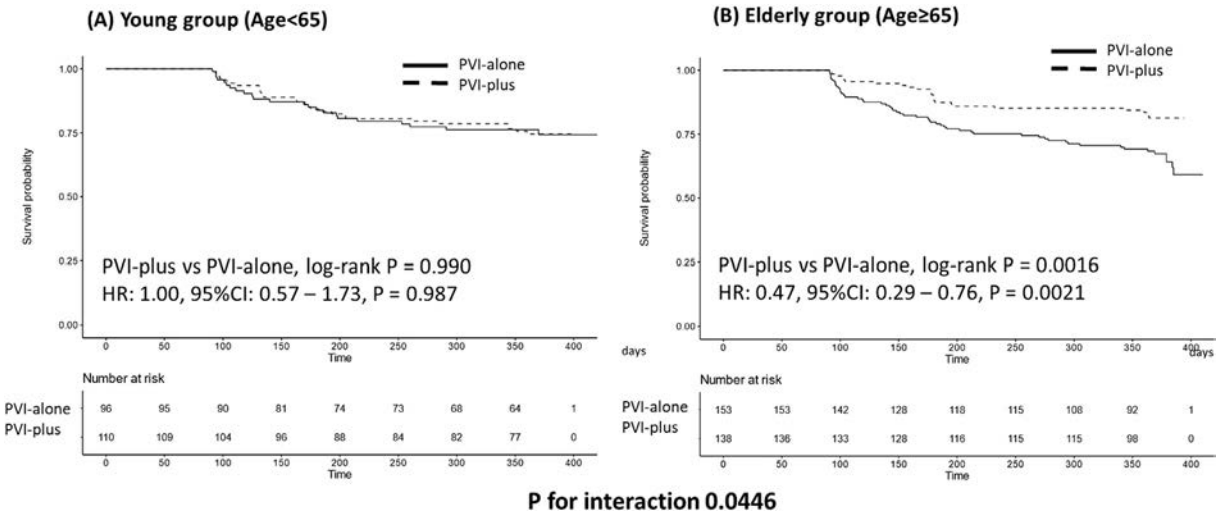

Fig. 2. Kaplan-Meier analysis.
Kaplan-Meier curve of the primary endpoint in the young group (A) and the elderly group (B). In the young group, there was no significant difference in the recurrence rate between the PVI-alone group and the PVI-plus group (A, log-rank $p = 0.99$; HR 1.00, 95 % CI 0.57–1.73, $p = 0.987$), whereas the recurrence rate was significantly lower in the PVI-plus group compared to the PVI-alone group in the elderly group (B, log-rank $p = 0.0016$; HR 0.47, 95 % CI 0.29–0.76, $p = 0.0021$) (p for interaction = 0.0446).
PVI, pulmonary vein isolation; HR, hazard ratio; CI, confidence interval.

variables were presented as counts (percentages) and compared using the chi-squared test or Fisher's exact test, as appropriate. Continuous variables were reported as mean (SD) or median (interquartile range) and compared using the Student's *t*-test or Mann-Whitney *U* test, as appropriate. The recurrence rate was calculated using the Kaplan-Meier method, and the comparison of survival curves between the PVI-alone and PVI-plus groups in each cohort was conducted using the log-rank test. We used a univariable Cox proportional hazards model to estimate the impact of PVI-plus in comparison with PVI-alone in the young and the elderly groups, respectively. The interaction between the ablation strategies and age was also estimated. Subgroup analysis was performed for the following sub-populations: sex (male vs female), type of AF (persistent vs. long-standing persistent), hypertension (yes vs. no), diabetes (yes vs. no), body mass index (<25 vs. ≥25), CHA_2DS_2-VASc score (<2 vs. ≥2), and diameter of left atrium (≤45 mm vs. >45 mm). The proportional hazards assumption of the treatment strategy for the primary endpoint was confirmed using Schoenfeld residuals ($p > 0.05$). Hazard ratio (HR) for the main effect of the PVI-plus strategy across different age levels was estimated using a univariable Cox proportional hazards model, with age flexibly modeled using restricted cubic splines (with 3 knots). Confidence intervals were estimated using the delta method. Significance was defined as p-values < 0.05, and the significance level was adjusted using the Bonferroni method in a multiple comparison procedure, with p-values < 0.01 indicating significance.

Results

A total of 512 patients were enrolled in this study between March 2016 and September 2017. Nine patients were excluded due to protocol violation, five due to errors in the electronic data collection system, and one due to withdrawal of consent, resulting in 497 eligible patients (PVI-alone, $n = 249$; PVI-plus, $n = 248$). These eligible patients were divided into two groups based on their baseline age: the young group (age <65 years) consisted of 206 patients (PVI-alone, $n = 96$; PVI-plus, $n = 110$), and the elderly group (age ≥65 years) consisted of 291 patients (PVI-alone, $n = 153$; PVI-plus, $n = 138$) (Fig. 1). Table 1 and Online Table 1 show the background characteristics and medication of the patients before catheter ablation, respectively. In comparison to the young group, the elderly group had a higher proportion of female patients, lower body mass index, a higher prevalence of hypertension, history of percutaneous coronary intervention, stroke, and chronic kidney disease. Additionally, a greater number of patients in the elderly group were prescribed antiplatelet drugs, dihydropyridine calcium channel blockers, and diuretics. Among the direct oral anticoagulants, apixaban was more frequently used in the elderly group. Laboratory data before ablation revealed that patients in the elderly group had lower hemoglobin levels and higher levels of brain natriuretic peptides. Echocardiography findings before ablation showed that patients in the elderly group had a smaller left ventricular diameter, thinner walls, and a higher prevalence of mitral regurgitation (Online Table 2). There were no differences in baseline characteristics between patients undergoing PVI-alone and those undergoing PVI-plus in both young and elderly groups.

Procedure and electrophysiological study findings

All patients were allowed to undergo non-PV trigger ablation, SVC ablation, and CTI isolation. Online Table 3 provides a summary of the data, indicating that the frequency of these procedures was comparable between patients in the young and elderly groups. There were no

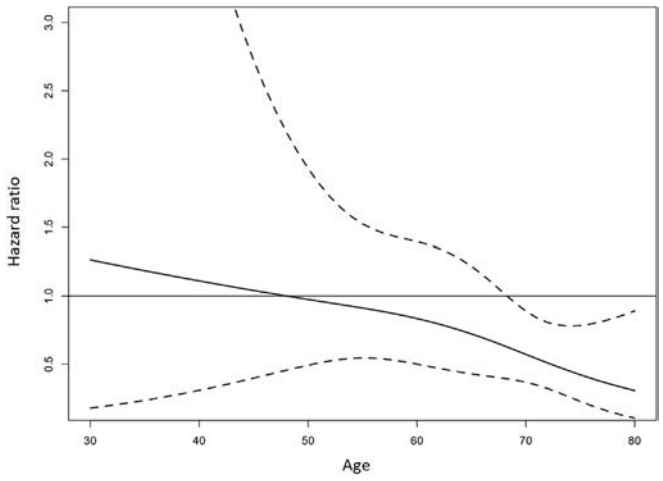

Fig. 3. Treatment effect of PVI-plus vs. PVI-alone across a range of ages for the primary outcome. Cubic spline curve of the hazard ratio for primary outcome as a function of age. The solid line indicates the hazard ratio of PVI-plus compared with PVI-alone and the dashed lines indicate a 95 % confidence interval.
PVI, pulmonary vein isolation.

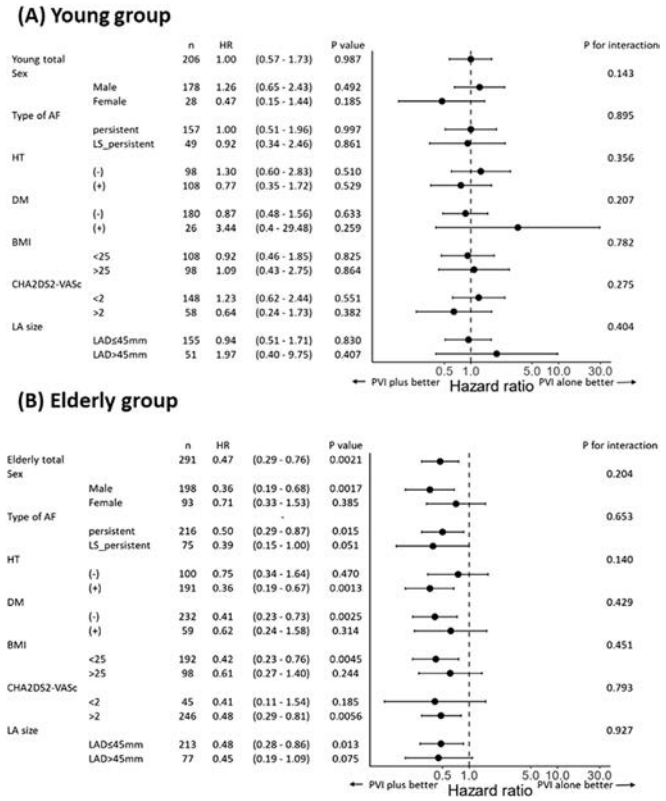

Fig. 4. Subgroup analysis of the primary endpoint. Subgroup effects on the primary endpoint by randomized treatment strategy in the young group (A), and in the elderly group (B). CHA2DS2-VASc score consisted of the following points: 2 points each for age ≥75 years, and history of stroke, transient ischemic attack, or systemic thromboembolism; 1 point each for congestive heart failure, hypertension, age of 65–74 years, diabetes mellitus, vascular disease, and female sex.
AF, atrial fibrillation; BMI, body mass index; DM, diabetes mellitus; HT, hypertension; LA, left atrium; LS-persistent, long-standing persistent; LAD, left atrial diameter; HR, hazard ratio; PVI, pulmonary vein isolation.

significant differences in total ablation time, total ablation energy, and total procedure time between the young and elderly groups. Details of the extensive ablation strategy are summarized in Online Table 4.

Clinical endpoints

Median follow-up period was 365.0 [305.0–378.0] days. The use of anti-arrhythmic drugs at discharge is summarized in Online Table 5. Although anti-arrhythmic drugs were not permitted after the 3-month blanking period, 39 patients continued at 1-year follow-up (Online Table 6). The percentage of patients who underwent Holter ECG is shown in Online Table 7.

In the young group, there was no significant difference in the 1-year recurrence rate between the PVI-alone group and the PVI-plus group [PVI-alone 23/96 (24.0 %) vs PVI-plus 27/110 (24.5 %), log-rank $p = 0.99$; HR 1.00, 95 % CI 0.57–1.73, $p = 0.987$, Fig. 2A], whereas the 1-year recurrence rate was significantly lower in the PVI-plus group compared to the PVI-alone group in the elderly group [PVI-alone 53/153 (34.6 %) vs PVI-plus 24/138 (17.4 %), log-rank $p = 0.0016$; HR 0.47, 95 % CI 0.29–0.76, $p = 0.0021$, Fig. 2B] (p for interaction = 0.0446). The treatment effect of PVI-plus versus PVI-alone across different age ranges for the primary outcome is depicted in Fig. 3. The PVI-plus strategy becomes more effective with the increasing age of the patients. The effect of treatment on the primary endpoint of AF recurrence is illustrated in Fig. 4 for each subgroup in both age groups. The treatment effect was consistent across all subgroups with no significant interactions.

The incidence of secondary endpoints, including clinical outcomes and procedure-related complications, is presented in Online Table 8 and Table 2, respectively. There were no significant differences in secondary endpoints between patients who received PVI-alone and those who received PVI-plus in either age group.

Type of extensive ablation and AF recurrence

The type of extensive ablation and AF recurrence rates are illustrated in Online Fig. 1; $p < 0.01$ was considered significant using the Bonferroni correction method. In the young group, any additional linear ablation or CFAE ablation did not result in the improvement of recurrence rate. In the elderly group, all additional procedures showed a trend toward improving the recurrence rate, albeit statistically non-significantly. Posterior wall isolation along with mitral isthmus line ablation showed the numerically lowest recurrence rate. The success rate of linear conduction block in the initial procedure is shown in Online Table 9.

Table 2
Procedure-related complications.

	Young	Young PVI-alone	Young PVI-plus	*p*-Value (young)[a]	Elderly	Elderly PVI-alone	Elderly PVI-plus	*p*-Value (elderly)	*p*-Value (young vs elderly)[b]
N	206	96	110		291	153	138		
Complications	4 (1.9)	2 (2.1)	2 (2.8)	>0.999	10 (3.4)	3 (2.0)	7 (5.1)	0.257	0.473
Hematoma	1 (0.5)	1 (1.0)	0 (0)		1 (0.3)	0 (0)	1 (0.7)		
Bleeding	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)		
Thromboembolism	0 (0)	0 (0)	0 (0)		1 (0.3)	0 (0)	1 (0.7)		
Pneumothorax	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)		
Arteriovenous fistula	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)		
Pericarditis	0 (0)	0 (0)	0 (0)		1 (0.3)	0 (0)	1 (0.7)		
Cardiac tamponade	0 (0)	0 (0)	0 (0)		2 (0.6)	0 (0)	2 (1.4)		
Phrenic nerve injury	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)		
Atrioventricular block	0 (0)	0 (0)	0 (0)		1 (0.3)	1 (0.7)	0 (0)		
Pulmonary hypertension	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)		
Left atrial-esophageal fistula	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)		
Infection	0 (0)	0 (0)	0 (0)		1 (0.3)	1 (0.7)	0 (0)		
Heart failure	0 (0)	0 (0)	0 (0)		1 (0.3)	0 (0)	1 (0.7)		
Periesophageal vagal nerve injury	3 (1.5)	1 (1.0)	2 (1.8)		2 (0.7)	1 (0.7)	1 (0.7)		
Dermatitis	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)		
Allergy	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)		

Categorical values are given as the number and percentage of positive findings per number of studied patients (N (%)).
PVI, pulmonary vein isolation.
[a] Comparison between PVI-alone and PVI-plus in each group.
[b] Comparison between all patients in the young group and the elderly group.

Discussion

This substudy of the EARNEST-PVI trial demonstrated that the extensive ablation approach, which includes linear and/or CFAE ablation along with PVI, was more effective in elderly patients with persistent AF. On the other hand, in young patients with persistent AF, the efficacy of the extensive ablation strategy was similar to the PVI only strategy. Our findings indicate a significant heterogeneity in its efficacy between young and elderly patients.

Arrhythmogenic substrates in elderly patients

Previous studies have established a correlation between aging and remodeling in the left atrium in patients with AF [10,15,16]. The initial alterations in atrial remodeling typically manifest as changes in electrophysiological and ion channel characteristics, which may be reversible. In addition, progressive atrial remodeling leads to irreversible structural changes such as atrial dilatation and fibrosis [17]. Structural remodeling can cause non-uniform local myocardial electrical activity, forming more micro-reentry loops. This change further causes conduction block and uncoordinated contraction, finally resulting in the development of AF [17]. Fibrosis can be objectively assessed by delayed enhanced magnetic resonance imaging (DE-MRI) [18]. The DECAAF trial ($N = 272$), a multicenter, prospective, observational cohort study, demonstrated that left atrial fibrosis estimated by DE-MRI was independently associated with procedural outcomes in patients undergoing AF ablation, even after adjusting established baseline covariates [19]. Another surrogate marker of arrhythmogenic substrates, low voltage area, can be detected by 3D electroanatomic maps during the ablation procedure. The low voltage area is reportedly related with DE-MRI and atrial fibrosis [20,21]. The DR-FLASH score, which incorporates several clinical factors including diabetes, renal dysfunction (estimated glomerular filtration rate <90 ml/min/1.73m^2), persistent form of AF, left atrial diameter >45 mm, age >65 years, female sex, and hypertension, has been reported to be a valuable tool for predicting the presence of low voltage areas in the left atrium [22,23]. In this study, the rate of female sex and prevalence of hypertension and diabetes was higher in the elderly group than in the young group. These factors including age contributed to higher DR-FLASH score in the elderly group compared to the young group, indicating a potential higher prevalence of low voltage area in the elderly group (Table 1).

Patients with more arrhythmogenic substrates may theoretically benefit from intensive substrate modification strategy by extensive ablation. Stratification by age may enable the easy identification of patients who benefit from extensive ablation strategy.

Comparison with previous trials

The current findings are inconsistent with the previous reports. The STAR AF II trial, a multicenter randomized trial ($N = 589$), showed no difference in recurrence between CFAE or linear ablation as an adjunctive procedure to PVI [6]. The subgroup analysis of this study divided the patients into those with age ≤60 years versus >60 years. This subgroup analysis consistently showed similar effectiveness of additional ablation strategy to PVI isolation only. The CAPLA randomized clinical trial ($N = 338$), which compared PVI with posterior wall isolation versus PVI alone in persistent AF patients could not establish the superiority of the extensive ablation strategy over the simple PVI, either [24]. The subgroup analysis stratified by age of 65 years showed consistent results with the overall population where the addition of posterior wall isolation to PVI did not significantly improve freedom from atrial arrhythmia compared with PVI alone [24]. In contrast to these previous data, our study showed the superiority of the extensive ablation strategy for patients with persistent AF, although the original trial was of a non-inferiority design [11]. This was largely driven by the results in elderly patients, as presented in this study. Subgroup analysis of the previous trials by age did not show any small signals implying the superior efficacy of the extensive ablation in elderly patients. However, because the main results differed in the first place, it would be challenging to have some reasonable insights into the reasons for these dissimilarities.

One of the possible explanations would presumably be the higher success rate of linear conduction block in the initial procedure in our study. This is further prominent in elderly patients than in the young patients, albeit not statistically significant (Online Table 9). Given that the linear ablation was robust, it would work better in the elderly patients by the mechanisms we mentioned above. And also, the elderly PVI-alone group was less likely to undergo the ATP infusion test than the young PVI-alone group, and the procedural time was 10 min shorter, meaning that waiting time after PVI was shorter. This may have prevented the elderly PVI-alone group from coping more adequately with acute PV reconnection than the young PVI-alone group. This mechanism possibly made the effect of the extensive ablation strategy more pronounced in the elderly group. In addition, the results might have been influenced by difference in patient characteristics. In our study, there was a low proportion of cases with long-standing persistent AF (25.8 %), a relatively short duration of AF persistence (median 4.7 months), a small left atrial diameter (median 42 mm), and a lower body mass index (median 24.3 kg/m^2) compared to previous studies. The patients included in our study might have had less advanced left atrial structural remodeling compared to patients in previous studies. The present findings need to be reconfirmed by prospective randomized trials.

Safety of extensive catheter ablation

An extensive catheter ablation strategy is recognized to entail various risks. Firstly, posterior wall isolation may occasionally result in esophageal injury. Low body mass index has been identified as an independent predictor [25]. Secondly, left anterior wall line ablation can sometimes lead to conduction delay in the left atrial appendage and cause sinus dysfunction due to coronary spasms in the sinus node artery [26]. Previous meta-analyses have indicated a higher incidence of procedural complications in elderly patients [27,28]. In our study, the overall population had a low rate of procedural complications, but the rate was numerically higher in the elderly group compared to the young group. There was no significant difference in complication rates between patients undergoing PVI-alone and PVI-plus in the young group, whereas in the elderly group, patients with PVI-plus had a numerically higher rate of complications, albeit not statistically significant, compared to those with PVI-alone. The rate of stroke during the follow-up period was higher in the elderly group as expected, given the association of stroke incidence with advancing age. However, the stroke rate was similar between patients undergoing PVI-alone and PVI-plus in both age groups. It is worth noting that no fatal complications occurred in the elderly group of our study. Our findings suggest that the extensive ablation strategy was safe in both groups. However, elderly patients should particularly be treated with extra caution.

Clinical implications

The present investigation has provided evidence regarding the effectiveness and safety of implementing the extensive ablation strategy, especially in elderly patients. For elderly patients, the extensive ablation approach may be considered as a primary treatment strategy to decrease the recurrence of AF and the necessity for re-ablation. On the other hand, the PVI-alone approach may suffice for younger patients in maintaining sinus rhythm. Avoiding unnecessary ablation procedures may reduce procedural duration, costs, and complications in young patients. Our team reported other factors which were important for stratifying patients such as DR-FLASH score [23] and UPLIFT modeling [29]. Although the result of this study did not simply justify the

extensive ablation strategy for all elderly patients with persistent AF, it showed that age can be one of the important and useful factors to decide the strategy. Stratifying the patients with persistent AF based on age is easy and practical, holding clinical significance.

Limitation

Firstly, this trial did not employ implantable cardiac monitors to detect AF recurrence, which might have resulted in an underestimation of the primary endpoint. Additional ECG tests might not have been utilized for patients with asymptomatic AF. In addition, the percentage of patients who underwent Holter ECG was significantly lower in patients in the young group than those in the elderly group (Online Table 7). This also might affect the recurrence rate of AF. The recurrence rate of AF especially in young patients might be more underestimated than that of elderly patients. The results of analyses comparing the elderly and young patients should be interpreted with caution. Secondly, we did not distinguish the mode or type of recurrence. We uniformly counted all AF, atrial flutter or atrial tachycardia lasting over 30 s as recurrence. Thirdly, patients with age ≥80 years were excluded in the original trial, which limits the generalizability of the study findings to all elderly patients. Fourthly, our study focused on an East Asian population, thus restricting the generalizability of the results to other populations. Finally, the original purpose of the EARNEST-PVI trial was to establish the non-inferiority of PVI-alone compared to any extensive catheter ablation for persistent AF. The identification of superiority in the extensive ablation strategy was a post-hoc finding, necessitating the interpretation of the current results as hypothesis-generating. Further prospective investigations are necessary to assess the effectiveness of each extensive ablation strategy.

Conclusion

In patients with persistent AF, the extensive ablation strategy was more effective than the PVI-alone strategy in elderly patients, while the effectiveness of both approaches was comparable in young patients.

Data availability

Our study data will not be made available to other researchers for purposes of reproducing the results because of institutional review board restrictions.

Declaration of competing interest

Y. Sotomi has received grants from Roche Diagnostics, FUJIFILM Toyama Chemical, TOA EIYO, Bristol-Myers Squibb, Biosense Webster, Abbott Medical Japan, and NIPRO, and personal fees from Abiomed, Abbott Medical Japan, AstraZeneca, Amgen Astellas BioPharma, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Boston Scientific Japan, Bayer, Daiichi Sankyo, Eli Lilly, Novartis, TERUMO, Medtronic, and Pfizer Pharmaceuticals. S. Hikoso has received grants from Roche Diagnostics, FUJIFILM Toyama Chemical, Actelion Pharmaceuticals; and personal fees from AstraZeneca, Daiichi Sankyo, Astellas Pharma, Bayer, Pfizer Pharmaceuticals, Boehringer Ingelheim Japan, Kowa Company, and Ono Pharmaceutical. D. Nakatani has received personal fees from Roche Diagnostics. T. Dohi has received grants from Medtronic, Johnson & Johnson, and Abbott, during the conduct of the study. A. Sunaga has received grants from Medtronic, Johnson & Johnson, and Abbott, during the conduct of the study and personal fees from Bayer, Daiichi Sankyo, and Medtronic, outside the submitted work. M. Masuda has received personal fees from Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, Boston Scientific, Abbott, Nihon Kohden, Otsuka Pharmaceutical, AstraZeneca, and Medtronic, outside the submitted work. T. Watanabe has received personal fees from Biosense Webster, Abbott, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Bayer, Daiichi Sankyo, Nihon Kohden, and Fukuda Denshi, outside the submitted work. H. Minamiguchi has received grants from Medtronic, Johnson & Johnson, and Abbott, during the conduct of the study, and personal fees from Medtronic, Abbott, Johnson & Johnson, Nihon Kohden, Biotronik, Japan Lifeline, Daiichi Sankyo, Bayer, Pfizer, Squibb, Boehringer Ingelheim, Kowa, Ono Pharmaceutical, and Otsuka Pharmaceutical, outside the submitted work. Y. Egami has received personal fees from Japan Lifeline and Medtronic, and non-financial support from Johnson & Johnson, Abbott, and Medtronic, outside the submitted work; T. Oka has received personal fees from Medtronic, Biotronik, Abbott, Daiichi Sankyo, Beyer, Bristol-Myers Squibb, Boehringer Ingelheim, MSD, and AstraZeneca, outside the submitted work. Y. Matsuda has received personal fees from Daiichi Sankyo, Boehringer Ingelheim, Bayer, Medtronic, and Biotronik, outside the submitted work. M. Kawasaki has received personal fees from Medtronic, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Bristol-Myers Squibb, and Abbott, and grants from Osaka Heart Club, outside the submitted work. K. Inoue has received personal fees from Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, and Medtronic, outside the submitted work. Y. Sakata has received personal fees from Otsuka Pharmaceutical, Ono Pharmaceutical, Daiichi Sankyo, Mitsubishi Tanabe Pharma Corporation, AstraZeneca K.K. and Actelion Pharmaceuticals, and grants from Roche Diagnostic, FUJIFILM Toyama Chemical, Bristol-Myers Squibb, Co, Biosense Webster, Inc., Abbott Medical Japan, Otsuka Pharmaceutical, Daiichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation, Astellas Pharma, Kowa Company, Boehringer Ingelheim Japan, and Biotronik. Other authors have nothing to disclose.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, we used ChatGPT in order to proof read the text. After using this tool, we reviewed and edited the content as needed and take full responsibility for the content of the publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2024.09.001.

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