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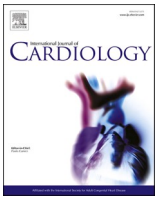

Extensive ablation for persistent atrial fibrillation patients with mitral regurgitation: Insights from the EARNEST-PVI prospective randomized trial

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ABSTRACT

Background: Extensive ablation in addition to pulmonary vein isolation (PVI) in patients with persistent atrial fibrillation (AF) has not yielded consistent results, indicating diversity in their efficacy. Mitral regurgitation (MR) associated with AF may indicate a higher prevalence of arrhythmogenic substrate, suggesting potential benefits of extensive ablation for these patients.

Methods: This post-hoc analysis of the EARNEST-PVI trial compared PVI alone versus an extensive ablation strategy (PVI-plus) in persistent AF patients, stratified by MR presence. The primary endpoint of the study was the recurrence of AF. The secondary endpoints included death, cerebral infarction, and procedure-related complications.

Results: The trial included 495 eligible patients divided into MR and non-MR groups. The MR group consisted of 192 patients (89 in the PVI-alone arm and 103 in the PVI-plus arm), while the non-MR group had 303 patients (158 in the PVI-alone arm and 145 in the PVI-plus arm). In the non-MR group, recurrence rates were similar between PVI-alone and PVI-plus arms (Log-rank $P = 0.47$, Hazard ratio = 0.85 [95%CI: 0.54–1.33], $P = 0.472$). However, in the MR group, PVI-plus was significantly more effective in preventing AF recurrence (Log-rank $P = 0.0014$, Hazard ratio = 0.40 [95%CI: 0.22–0.72], $P = 0.0021$). No significant differences were observed in secondary endpoints between the two arms.

Conclusions: For persistent AF patients with mild or greater MR, receiving PVI-plus was superior to PVI-alone in preventing AF recurrence. Conversely, for patients without MR, the effectiveness of extensive ablation was not demonstrated. These findings suggest tailoring ablation strategies based on MR presence can lead to better outcomes in AF management.

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1. Introduction

Catheter ablation has been recognized as a safe and effective intervention for treating atrial fibrillation (AF). For symptomatic AF patients, pulmonary vein isolation (PVI) is recommended as the primary rhythm control therapy. [1] While additional techniques like linear ablation or complex fractionated atrial electrograms (CFAE) ablation in addition to PVI may be considered for patients with persistent AF to target the substrate that maintains fibrillation, their effectiveness is not firmly established. [1,2] Previous studies investigating more extensive ablation approaches alongside PVI have yielded varied results, indicating a diversity in their efficacy. [3–7] We conducted a prospective randomized trial to test a non-inferiority of PVI alone in comparison with extensive approach in patients with persistent AF, but failed to achieve the primary endpoint. [8] On the contrary, the trial implicated the superiority of the extensive ablation approach. These varying previous results suggest that there may be specific individuals with persistent AF who could benefit from an extensive ablation strategy.

AF and subsequent annular enlargement can be responsible for significant mitral regurgitation (MR). [9] The severity of MR is associated with the presence of low-voltage areas (LVA) [10] considered as arrhythmogenic substrate in the left atrium. [11,12] Therefore, it is plausible that AF patients with MR may have a higher prevalence of arrhythmogenic substrate. We hypothesized that ablation methods that modify arrhythmogenic substrate may be more effective for patients with MR. We aimed to compare the effectiveness and safety of PVI-alone strategy versus an extensive ablation in stratified persistent AF patients based on the presence of MR.

2. Method

2.1. Study design

This study is a post-hoc analysis of the EARNEST-PVI trial (ClinicalTrials.gov, NCT03514693). [8,13–17] The original EARNEST-PVI trial was a prospective, multicenter, randomized, open-label, and non-inferiority trial conducted by the Osaka Cardiovascular Conference Arrhythmia Investigators. The study recruited patients with persistent AF in eight hospitals. Persistent AF was defined as a prolonged episode of AF lasting for at least 7 days but shorter than 5 years. Exclusion criteria were established as follows: age $<$ 20 or $\geq$ 80 years; sinus rhythm at enrollment; left atrial dimension $\geq$50 mm in parasternal long-axis view on echocardiography; valvular AF; history of cardiac surgery; hemodialysis; left ventricular ejection fraction (LVEF) $<$ 30%; and New York Heart Association functional classification (NYHA) 3 or 4. Patients were randomly assigned to either the PVI only strategy (PVI-alone arm) or the extensive ablation strategy with linear and/or CFAE ablation in addition to PVI (PVI-plus arm). The present post-hoc study focused on the disparity in the effectiveness of PVI-alone vs. PVI-plus between patients without MR and with MR. The overall population was further divided into 2 groups by the severity of MR (non-MR group, MR none or trace; MR group, MR mild or more severe) (Fig. 1). 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.

2.2. Study procedure

In the EARNEST-PVI trial, at the beginning of the procedure, electrical cardioversion was performed to investigate the triggers of AF originating from both the pulmonary vein (PV) and non-PV sites. [14] Before the ablation procedure, an electrophysiological study was conducted to identify the sources of AF triggers. An AF trigger was defined as an arrhythmogenic focus initiating AF at least twice with the same sequence. Triggers originating from PVs were classified as PV triggers, while those originating from other sites were classified as non-PV triggers. A mapping catheter was used to record electrograms from both PV and non-PV sites to detect the AF triggers. If AF was induced, direct current cardioversion was performed to confirm the reproducibility of AF initiation. If spontaneous recurrence of AF did not occur within 5 min after cardioversion, provocative testing was carried out, such as administering incremental doses of isoproterenol (ISP) up to 0.4 μg/kg/min. The endpoint of ISP administration was defined as systolic blood pressure $<$ 80 mmHg, heart rate in sinus rhythm $>$130 bpm, or ISP administration at 0.4 μg/kg/min for 5 min.

All ablation procedures were conducted using radiofrequency (RF) catheter ablation, with a recommended RF energy of 25-35 W in this trial. PVI was defined as the achievement of isolation of both ipsilateral PVs or individual PVs. The endpoint of PVI was a bidirectional conduction block at the end of the initial PVI procedure and after waiting $>$20 min. 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 connecting the mitral annulus to a line of PVI. The second

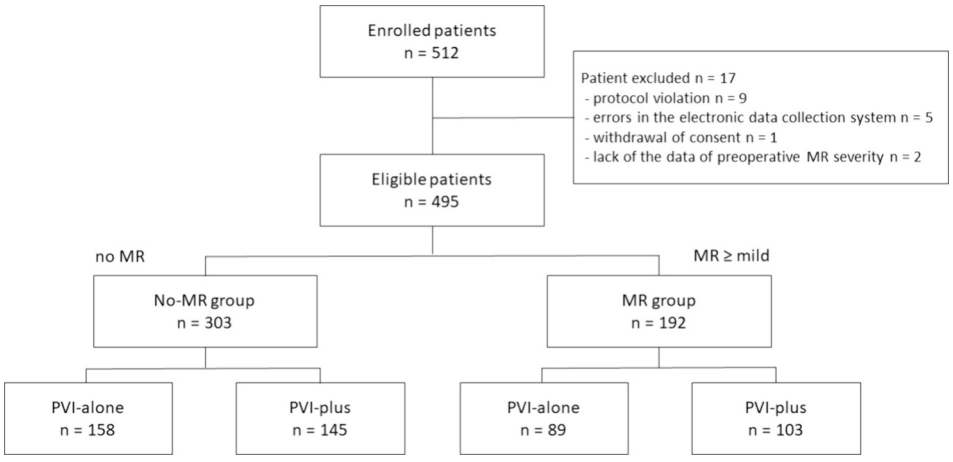

Fig. 1. Study flowchart.
The MR group includes MR severity mild and above, while the non-MR group is otherwise. The PVI-alone group performs PVI only, and the PVI-plus group performs linear ablation and/or CFAE ablation in addition to PVI. Abbreviations: MR, mitral regurgitation; PVI, pulmonary vein isolation; CFAE, complex fractionated atrial electrograms.

line was a left atrial roof or bottom line connecting a line of PVI and the opposite side. When an anterior line ablation was performed, the anterior line was recommended to be created closer to the septum so as not to interfere with the conduction of the Bachman bundle. The left atrial appendage isolation was not recommended because of the increased risk of thromboembolism. [18] The endpoint of linear ablation was a bidirectional conduction block at the end of the initial procedure and after waiting >20 min. If a patient underwent ablation of both a roof line and a bottom line, they were classified as having posterior wall isolation. For CFAE ablation, CFAE mapping was performed during AF, and automated algorithms of the three-dimensional mapping system identified CFAE sites. Detailed information about CFAE is provided elsewhere. [19] The endpoint of CFAE ablation was the elimination of CFAE sites or a rhythm change from AF to sinus rhythm, organized atrial tachycardia (AT), or atrial flutter (AFL).

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 for common atrial flutter induced by burst pacing, were allowed to perform in both groups.

2.3. Data collection and follow-up

Before performing catheter ablation, clinical data of patients were collected, including patient history, laboratory data, and transthoracic echocardiography. 12-lead electrocardiograms (ECGs) were conducted before the procedure, at discharge, and 1, 3, 6, 9, and 12 months post-procedure. Additionally, 24-h Holter ECG was performed at 6 and 12 months. Patients who experienced symptoms suggestive of AF recurrence were allowed to visit the clinics or hospitals on non-scheduled days, and an ECG was performed during each additional visit. For such patients, additional Holter ECG or event monitor recording was conducted. Transthoracic echocardiography was also performed at 12 months follow-up.

2.4. Transthoracic echocardiography

The measurement of each length was performed with a transthoracic parasternal long-axis view. The severity of mitral regurgitation was evaluated by two-dimensional echocardiographic measurements and doppler method. The type of echo machine was not limited at each facility. We recollected the data of mitral regurgitation between November and December 2023 based on the integrative approach recommended by the American Society of Echocardiography. [20]

2.5. Study endpoints

The primary endpoint of the study was the recurrence of AF, confirmed by ECG during the 1-year follow-up period following the initial procedure. Recurrence of AF was defined as documented AF, AFL, or AT lasting for >30 s, confirmed by ECG, including 12-lead ECG, 24-h 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. A second ablation was permitted in patients with AF recurrence after the blanking period. The secondary endpoints included death, cerebral infarction, and procedure-related complications.

2.6. Statistical analysis

Statistical analysis was performed using R software (version 4.3.1; R Foundation for Statistical Computing). Categorical 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 (standard deviation) or median (interquartile range) and compared using the Student's *t*-test, Mann-Whitney *U* test, or paired t-test as appropriate. The comparison of severity of MR between baseline and 12 months follow-up was conducted by Wilcoxon signed-rank test. 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 Cox proportional hazards model to estimate the impact of PVI-plus strategy in comparison with PVI-alone strategy in both groups. The interaction between the ablation strategy and the severity of MR was also estimated. Subgroup analysis was performed for the following subpopulations: type of AF (persistent vs. long-standing persistent), body mass index (< 25 vs. ≥ 25), CHA_2DS_2-VASc score (< 2 vs. ≥ 2), and diameter of left atrium (≤ 42 mm (median) vs. > 42 mm). The proportional hazards assumption of the treatment strategy for the primary endpoint was confirmed using Schoenfeld residuals (Non-MR group $P = 0.98$, MR group >0.99). 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.

3. Result

3.1. Baseline characteristics

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, one due to withdrawal of consent, two due to lack of the data of preoperative MR severity, resulting in 495 eligible patients. These eligible patients were divided into two groups based on the presence of MR: The MR group consisted of 192 patients (89 in the PVI-alone arm and 103 in the PVI-plus arm), while the non-MR group had 303 patients (158 in the PVI-alone arm and 145 in the PVI-plus arm) (Fig. 1).

The MR group was more likely to be female, older and showed lower body mass index than the non-MR group (Table 1). There were no significant differences in medications between any of the groups (Table 1).

The non-MR group showed higher levels of hemoglobin, lower levels of brain natriuretic peptides, higher left ventricular ejection fraction (LVEF), smaller left ventricular end-systolic diameter, larger left atrial diameter (LAD), larger intra ventricular septum thickness and larger posterior left ventricular wall thickness as compared to the MR group (Table 1). In the MR group, patients who underwent PVI plus had lower LVEF, larger left ventricular end-systolic diameter and larger left ventricular end-diastolic diameter, while in the non-MR group, no difference was found in the laboratory and echocardiographic data between both arms. **(**Table 1**).**

3.2. Procedure and electrophysiological study findings

The MR group more frequently performed SVC isolation and CTI ablation, accompanied by longer total ablation time and total procedure time as compared to the non-MR group. The occurrence of acute PV reconnection after a waiting period of >20 min during the initial procedure and the proportion of dormant conduction in the 4 PVs upon infusion of adenosine triphosphate were similar between the MR group and the non-MR group. In the MR group, patients in the PVI-plus arm had a smaller number of non-PV trigger ablation than those in PVI-alone arm. In the both MR and non-MR groups, patients in PVI-plus arm had a longer total ablation time, total ablation energy and total procedure time, compared to the patients in PVI-alone arm (Table 2). Details of the extensive ablation strategy are summarized in Table 3. There was no significant difference in the extensive ablation strategy between the MR group and the non-MR group.

3.3. Clinical endpoints

In the non-MR group, there was no significant difference in the

Table 1
Baseline characteristics.

	Non-MR	PVI-alone Non-MR	PVI-plus Non-MR	P alone vs plus in Non-MR	MR	PVI-alone MR	PVI-plus MR	P alone vs plus in MR	P non-MR vs MR
n	303	158	145		192	89	103		
Age	66 [57, 71]	66 [58, 71]	66 [55, 72]	0.800	68 [62, 74]	70 [64, 75]	66 [61, 72]	0.006*	<0.001*
Female	56 (18.5)	27 (17.1)	29 (20.0)	0.614	63 (32.8)	34 (38.2)	29 (28.2)	0.185	<0.001*
Body mass index	24.6 [22.7, 27.1]	24.8 [22.7, 27.2]	24.5 [22.7, 27.0]	0.817	23.7 [21.3, 25.6]	23.8 [21.4, 25.7]	23.5 [21.3, 25.5]	0.720	<0.001*
Long standing persistent AF	77 (25.4)	37 (23.4)	40 (27.6)	0.484	45 (23.4)	20 (22.5)	25 (24.3)	0.902	0.697
Duration of AF persistence (months)	4.8 [2.4, 12.2]	4.1 [2.2, 11.5]	5.0 [2.7, 13.0]	0.122	4.4 [2.0, 11.9]	3.2 [1.6, 10.8]	5.2 [2.2, 12.0]	0.113	0.300
Hypertension	184 (60.7)	98 (62.0)	86 (59.3)	0.715	114 (59.4)	51 (57.3)	63 (61.2)	0.692	0.838
Diabetes Mellitus	61 (20.1)	29 (18.4)	32 (22.1)	0.508	24 (12.5)	9 (10.1)	15 (14.6)	0.477	0.038*
Dyslipidemia	148 (48.8)	77 (48.7)	71 (49.0)	>0.999	78 (40.6)	34 (38.2)	44 (42.7)	0.626	0.090
Stroke or transient ischemic attack	26 (8.6)	11 (7.0)	15 (10.3)	0.398	18 (9.4)	9 (10.1)	9 (8.7)	0.938	0.888
Coronary artery disease	24 (7.9)	12 (7.6)	12 (8.3)	0.995	16 (8.3)	8 (9.0)	8 (7.8)	0.965	>0.999
Sick sinus syndrome	42 (13.9)	1 (0.6)	3 (2.1)	0.555	3 (1.6)	2 (2.2)	1 (1.0)	0.898	>0.999
Thyroid disease	14 (4.6)	5 (3.2)	9 (6.2)	0.324	10 (5.2)	5 (5.6)	5 (4.9)	>0.999	0.935
Chronic obstructive pulmonary disease	14 (4.6)	8 (5.1)	6 (4.1)	0.913	8 (4.2)	6 (6.7)	2 (1.9)	0.194	0.988
Chronic kidney disease	16 (5.3)	7 (4.4)	9 (6.2)	0.665	9 (4.7)	6 (6.7)	3 (2.9)	0.363	0.934
CHA2DS2-VASc	3 [2, 4]	3 [2, 4]	3 [2, 4]	0.568	3 [2, 4]	3 [3, 4]	3 [2, 4]	0.132	0.036*
CHA2DS2-VASc ≥2	171 (56.4)	86 (54.4)	85 (58.6)	0.536	131 (68.2)	68 (76.4)	63 (61.2)	0.035*	0.012*
Anticoagulation				0.566				0.817	0.672
None	1 (0.3)	0 (0.0)	1 (0.7)		0 (0.0)	0 (0.0)	0 (0.0)		
Warfarin	20 (6.6)	10 (6.3)	10 (6.9)		11 (5.7)	4 (4.5)	7 (6.8)		
DOAC	282 (93.1)	148 (93.7)	134 (92.4)		181 (94.3)	85 (95.5)	96 (93.2)		
Type of DOAC				0.544				0.844	0.336
Dabigatran	46 (16.3)	27 (18.2)	19 (14.2)		25 (13.8)	10 (11.8)	15 (15.6)		
Rivaroxaban	101 (35.8)	50 (33.8)	51 (38.1)		58 (32.0)	27 (31.8)	31 (32.3)		
Apixaban	59 (20.9)	34 (23.0)	25 (18.7)		51 (28.2)	26 (30.6)	25 (26.0)		
Edoxaban	76 (27.0)	37 (25.0)	39 (29.1)		47 (26.0)	22 (25.9)	25 (26.0)		
Antiplatelet	32 (10.6)	17 (10.8)	15 (10.3)	>0.999	21 (10.9)	11 (12.4)	10 (9.7)	0.723	>0.999
ACEi/ARB	101 (33.3)	57 (36.1)	44 (30.3)	0.350	58 (30.2)	27 (30.3)	31 (30.1)	>0.999	0.531
Calcium blocker	123 (40.6)	66 (41.8)	57 (39.3)	0.750	70 (36.5)	35 (39.3)	35 (34.0)	0.537	0.410
Bata blocker	127 (41.9)	64 (40.5)	63 (43.4)	0.688	87 (45.3)	44 (49.4)	43 (41.7)	0.356	0.515
Diuretics	56 (18.5)	27 (17.1)	29 (20.0)	0.614	49 (25.5)	28 (31.5)	21 (20.4)	0.112	0.079
Hemoglobin, g/dL	14.8 [14.0, 15.5]	15.0 [14.1, 15.7]	14.6 [13.9, 15.2]	0.028*	14.2 [13.2, 15.2]	14.2 [13.2, 15.4]	14.3 [13.4, 15.2]	0.956	<0.001*
B-type natriuretic peptide, pg/mL	135 [88, 196]	132 [88, 193]	145 [92, 197]	0.386	159 [113, 270]	159 [114, 267]	156 [113, 278]	0.969	<0.001*
Creatinine, mg/dL	0.89 [0.79, 1.01]	0.90 [0.78, 1.01]	0.89 [0.80, 1.01]	0.672	0.86 [0.77, 0.99]	0.85 [0.76, 0.98]	0.89 [0.77, 1.00]	0.410	0.271
C-reactive protein, mg/dL	0.10 [0.06, 0.20]	0.10 [0.06, 0.20]	0.10 [0.06, 0.22]	0.399	0.10 [0.06, 0.14]	0.10 [0.06, 0.15]	0.10 [0.06, 0.13]	0.535	0.170
LVEF, %	64 [60, 69]	64 [60, 68]	64 [59, 69]	0.633	62 [54, 69]	64 [57, 70]	61 [52, 67]	0.021*	0.035*
LVDD, mm	46 [43, 49]	46 [43, 49]	46 [43, 49]	0.489	47 [44, 50]	46 [44, 49]	48 [44, 52]	0.019*	0.061
LVDS, mm	30 [27, 33]	30 [27, 33]	30 [27, 33]	0.415	31 [28, 35]	30 [27, 33]	32 [28, 37]	0.008*	0.018*
Left atrial diameter, mm	42 [39, 45]	41 [39, 45]	42 [38, 45]	0.958	43 [40, 46]	43 [40, 46]	43 [40, 46]	0.942	0.004*
Mitral regurgitation				NA				0.465	<0.001*
none or trace	303 (100.0)	158 (100.0)	145 (100.0)		0 (0.0)	0 (0.0)	0 (0.0)		
mild	0 (0.0)	0 (0.0)	0 (0.0)		155 (80.7)	73 (82.0)	82 (79.6)		
mild-moderate	0 (0.0)	0 (0.0)	0 (0.0)		21 (10.9)	9 (10.1)	12 (11.7)		
moderate	0 (0.0)	0 (0.0)	0 (0.0)		13 (6.8)	7 (7.9)	6 (5.8)		
moderate-severe	0 (0.0)	0 (0.0)	0 (0.0)		3 (1.6)	0 (0.0)	3 (2.9)		
IVST, mm	9.7 [9.0, 10.7]	9.6 [9.0, 10.7]	10.0 [9.0, 10.6]	0.750	9.0 [8.0, 10.0]	9.0 [8.0, 10.0]	9.0 [8.0, 10.0]	0.711	0.010*
LVPWT, mm	9.5 [9.0, 10.4]	9.4 [8.7, 10.7]	9.6 [9.0, 10.0]	0.883	9.0 [8.0, 10.0]	9.0 [8.0, 10.0]	9.0 [8.0, 10.0]	0.804	0.001*

MR, mitral regurgitation; AF, atrial fibrillation; DOAC, direct oral anticoagulant; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic diameter; LVDS, left ventricular end-systolic diameter; IVST, intra ventricular septum thickness; LVPWT; left ventricular posterior wall thickness. * Indicates $P < 0.05$.

recurrence rate between the PVI-plus arm and the PVI-alone arm (24.4% vs. 25.2%, Log-rank $P = 0.47$, Hazard ratio = 0.85 [95%CI: 0.54–1.33], $P = 0.472$) **(**Fig. 2**A)**, whereas the recurrence rate was significantly lower in the PVI-plus arm compared to the PVI-alone arm in the MR group (17.7% vs 35.5%, Log-rank $P = 0.0014$, Hazard ratio = 0.40 [95% CI: 0.22–0.72], $P = 0.0021$) (Fig. 2**B**). There was a significant interaction between ablation strategy and presence of MR (P for interaction = 0.0415). As a sensitivity analysis, we additionally assessed the impact of the ablation strategy with adjustment by age and left atrial diameter. This analysis indicated similar findings (adjusted HR = 0.84 [95%CI: 0.54–1.32], $P = 0.456$ in the non-MR group; adjusted HR = 0.41 [95% CI: 0.23–0.74], $P = 0.0033$) in the MR group, P for interaction = 0.0438).

In subgroup analysis, an interaction between hypertension and ablation strategy was observed in the non-MR group. No significant interactions were observed in any other subgroups (Fig. 3).

The incidence of secondary endpoints, including clinical outcomes and procedure-related complications, is presented in Table 4. There

Table 2
Procedure related findings.

Procedure related findings	Non-MR	PVI-alone Non-MR	PVI-plus Non-MR	P alone vs plus in Non-MR	MR	PVI-alone MR	PVI-plus MR	P alone vs plus in MR	P non-MR vs MR
n	303	158	145		192	89	103		
Non-PV trigger ablation	15 (5.0)	10 (6.3)	5 (3.4)	0.374	13 (6.8)	10 (11.4)	3 (2.9)	0.043*	0.504
SVC isolation	4 (1.3)	2 (1.3)	2 (1.4)	>0.999	9 (4.7)	5 (5.6)	4 (3.9)	0.822	0.046*
CTI ablation	75 (24.8)	39 (24.7)	36 (24.8)	>0.999	67 (34.9)	29 (32.6)	38 (36.9)	0.636	0.020*
GP ablation	2 (0.7)	0 (0.0)	2 (1.4)	0.441	0 (0.0)	0 (0.0)	0 (0.0)	NA	0.688
ATP infusion test	153 (50.5)	84 (53.2)	69 (47.6)	0.392	105 (55.0)	50 (56.8)	55 (53.4)	0.743	0.380
Dormant conduction	22/153 (14.4)	12/84 (14.3)	10/69 (14.5)	>0.999	10/105 (9.5)	5/50 (10.0)	5/55 (9.1)	>0.999	0.332
Reconnection of 4PVs after 20 m in waiting	90 (29.7)	41 (25.9)	49 (33.8)	0.172	50 (26.2)	23 (26.1)	27 (26.2)	>0.999	0.457
Total ablation time, *sec*	2234 [1683, 3027]	1804 [1322, 2255]	2736 [2263, 3631]	<0.001*	2499 [1750, 3218]	1965 [1544, 2632]	2944.50 [2356, 3697]	<0.001*	0.018*
Total ablation energy, J	70,032 [52,799, 96,630]	56,222 [40,034, 75,556]	85,921 [66,930, 118,317]	<0.001*	73,770 [49,068, 100,539]	53,904 [45,308, 84,893]	88,335 [64,204, 116,293]	<0.001*	0.683
Total procedure time, min	153 [120, 195]	140 [109, 167]	180 [132,222]	<0.001*	170 [130,230]	160 [125, 200]	189 [140, 243]	0.005*	0.001*

MR, mitral regurgitation; PV, pulmonary vein; SVC, superior vena cava; CTI, cavotricuspid isthmus; GP, ganglionated plexi; ATP, adenosine triphosphate. * Indicates P < 0.05.

Table 3
Extensive ablation strategy.

	PVI-plus in Non-MR group	PVI-plus in MR group	*P* value
n	145	103	
Linear ablation	127 (87.6)	84 (81.6)	0.257
Roof line	126 (99.2)	84 (100.0)	>0.999
Bottom line	69 (54.3)	41 (48.8)	0.519
Anterior line	28 (22.0)	12 (14.3)	0.219
Mitral isthmus line	100 (78.7)	71 (84.5)	0.384
Other line	1 (0.8)	0 (0.0)	>0.999
CFAE ablation	18 (12.4)	20 (19.4)	0.184

MR, mitral regurgitation; CFAE, complex fractionated atrial electrograms.

were no significant differences in secondary endpoints between patients who received PVI-alone and those who received PVI-plus in either group.

3.4. AF recurrence rate by type of extensive ablation

The type of extensive ablation and AF recurrence rates are illustrated in Fig. 4. $P < 0.01$ was considered significant using the Bonferroni correction method. In the non-MR group, any additional linear ablation or CFAE ablation did not result in the improvement of recurrent rate. In the MR group, patients who underwent posterior wall isolation and mitral isthmus line ablation in addition to PVI had significantly lower recurrence rate. Other combinations of additional procedures in the PVI-plus arm also resulted in numerically lower recurrent rates.

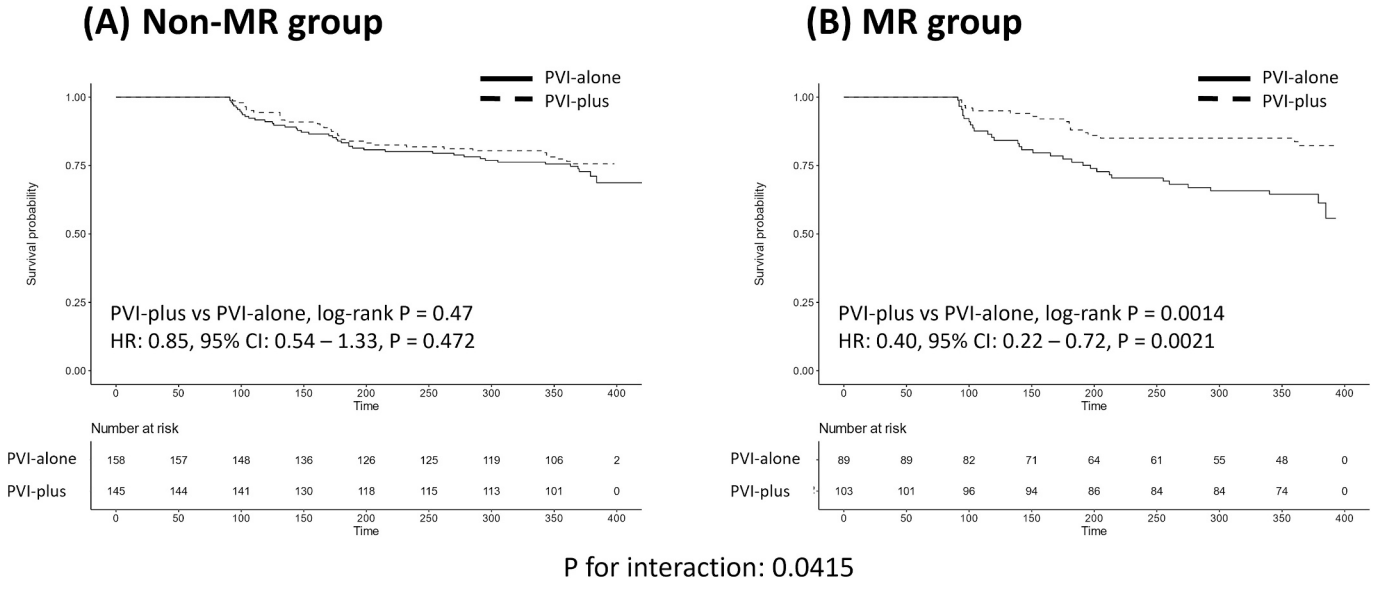

Fig. 2. Kaplan-Meier analysis.
Kaplan-Meier curve of the primary endpoint in non-MR group (A) and MR group (B). In non-MR group, there was no significant difference in the recurrence rate between the patients in the PVI-alone arm and those in the PVI-plus arm (Fig. 2A, log-rank P = 0.47; HR 0.85, 95%CI 0.54–1.33, P = 0.472), whereas the recurrence rate was significantly lower in the patients with PVI-plus arm compared to those in the PVI-alone arm in the MR group (Fig. 2B, log-rank *P* = 0.0014; HR 0.40, 95%CI 0.22–0.72, *P* = 0.0021). There is an interaction between MR and ablation strategy (P for interaction = 0.0415). Abbreviations: MR, mitral regurgitation: PVI, pulmonary vein isolation; HR, hazard ratio; CI; confidence interval.

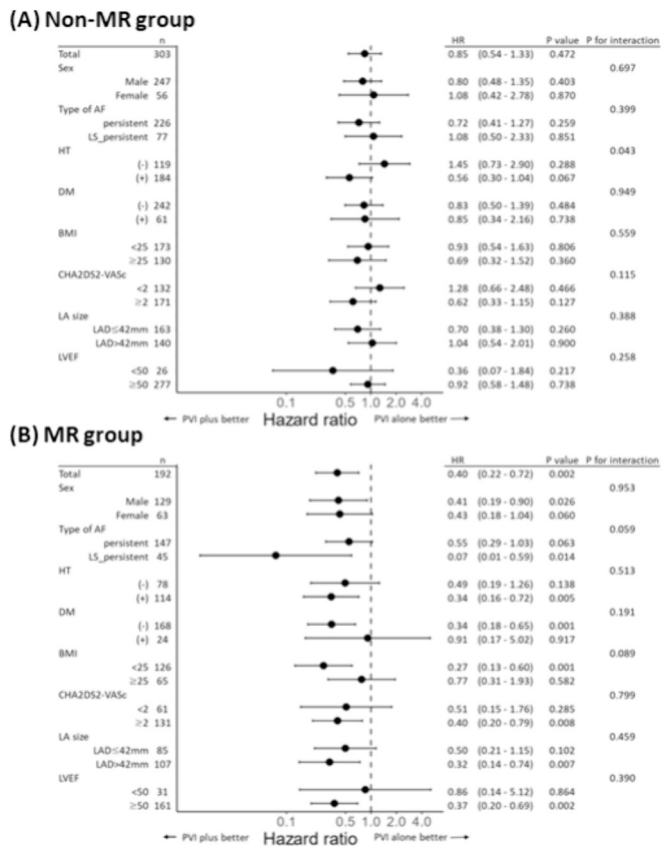

Fig. 3. Subgroup analysis of the primary endpoint.
Subgroup effects on the primary endpoint by randomized treatment strategy in the non-MR group (A), and in the MR group (B). CHA2DS2-VASc score consisted of the following points: 2 points each for age ≥ 75 years, and history of stroke, transient ischemic attack or systemic thromboembolism; 1 point each for congestive heart failure, hypertension, age of 65–74 years, diabetes mellitus, vascular disease, and female sex. Abbreviations: MR, mitral regurgitation: AF, atrial fibrillation; LS-persistent, long-standing persistent; DM, diabetes mellites; HT, hypertension; BMI, body mass index; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; CI, confidence interval; HR, hazard ratio; PVI, pulmonary vein isolation;

3.5. Change in MR severity and LAD

In the MR group, patients in the PVI-alone arm and those in the PVI-plus arm showed a significant improvement in MR severity during 12 months post-ablation **(Supplementary Figure).** In both MR and non-MR groups, both treatment arms showed a significant reduction in LAD compared to preoperative values, at 12 months after ablation**.** In the MR group, a greater reduction in LAD was observed in the PVI-plus arm compared to the PVI-alone arm (9.1% [2.5, 14.4] vs 5.1% [−1.35, 12.3], $P = 0.015$).

4. Discussion

4.1. Main findings

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 persistent AF patients with MR than PVI-alone strategy. On the other hand, in persistent AF patients without MR, the efficacy of the extensive ablation strategy was similar to the PVI-alone strategy. Our findings indicate a significant difference in its efficacy between patients without MR and those with MR. Compared to preoperative MR severity, both the PVI-alone and PVI-plus groups showed improvement at 12 months after the procedure.

4.2. Impact of the extensive ablation on patients with MR

AF is widely recognized for causing enlargement of the left atrium and mitral annulus, even in the absence of left ventricular dysfunction. [21–23] AF and subsequent annular enlargement can be responsible for significant MR, although there are various causes of MR, including mitral valve prolapse, mitral valve stenosis, left ventricular dilation, and left ventricular myocardial infarction. [9]

The severity of MR is associated with the presence of LVA in the left atrium. [10] These LVA correspond to fibrosis demonstrated by gadolinium delayed enhanced magnetic resonance imaging, indicating the presence of arrhythmogenic substrate. [11,12] The presence of MR may indicate the presence of LVA, which represents the arrhythmogenic substrate.

LVA-guided substrate modification for patients with persistent atrial fibrillation is reported to be effective compared to PVI alone. [24] LVA is

Table 4
Secondary endpoints.

	Non-MR	PVI-alone Non-MR	PVI-plus Non-MR	P alone vs plus in Non-MR	MR	PVI-alone MR	PVI-plus MR	P alone vs plus in MR	P non-MR vs MR
n	303	158	145		192	89	103		
Death	0 (0.0)	0 (0.0)	0 (0.0)	NA	1 (0.5)	0 (0.0)	1 (1.0)	>0.999	0.818
Stroke	1 (0.3)	1 (0.6)	0 (0.0)	>0.999	2 (1.0)	1 (1.1)	1 (1.0)	>0.999	0.689
Complications	6 (2.0)	1 (0.6)	5 (3.4)	0.179	8 (4.2)	4 (4.5)	4 (3.9)	0.942	0.249
Hematoma	1 (0.3)	0 (0.0)	1 (0.7)		1 (0.5)	1 (1.1)	0 (0.0)		
Bleeding	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)		
Thromboembolism	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.5)	0 (0.0)	1 (1.0)		
Pneumothorax	0 (0.0)	0 (0.0)	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)	0 (0.0)	0 (0.0)		
Pericarditis	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.5)	0 (0.0)	1 (1.0)		
Cardiac tamponade	1 (0.3)	0 (0.0)	1 (0.7)		1 (0.5)	0 (0.0)	1 (1.0)		
Phrenic nerve injury	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)		
Atrioventricular block	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.5)	1 (1.1)	0 (0.0)		
Pulmonary hypertension	0 (0.0)	0 (0.0)	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)	0 (0.0)	0 (0.0)		
Infection	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.5)	1 (1.1)	0 (0.0)		
Heart failure	1 (0.3)	0 (0.0)	1 (0.7)		0 (0.0)	0 (0.0)	0 (0.0)		
Periesophageal vagal nerve Injury	3 (1.0)	1 (0.6)	2 (1.4)		2 (1.0)	1 (1.1)	1 (1.0)		
Dermatitis	0 (0.0)	0 (0.0)	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)	0 (0.0)	0 (0.0)		

MR, mitral regurgitation.

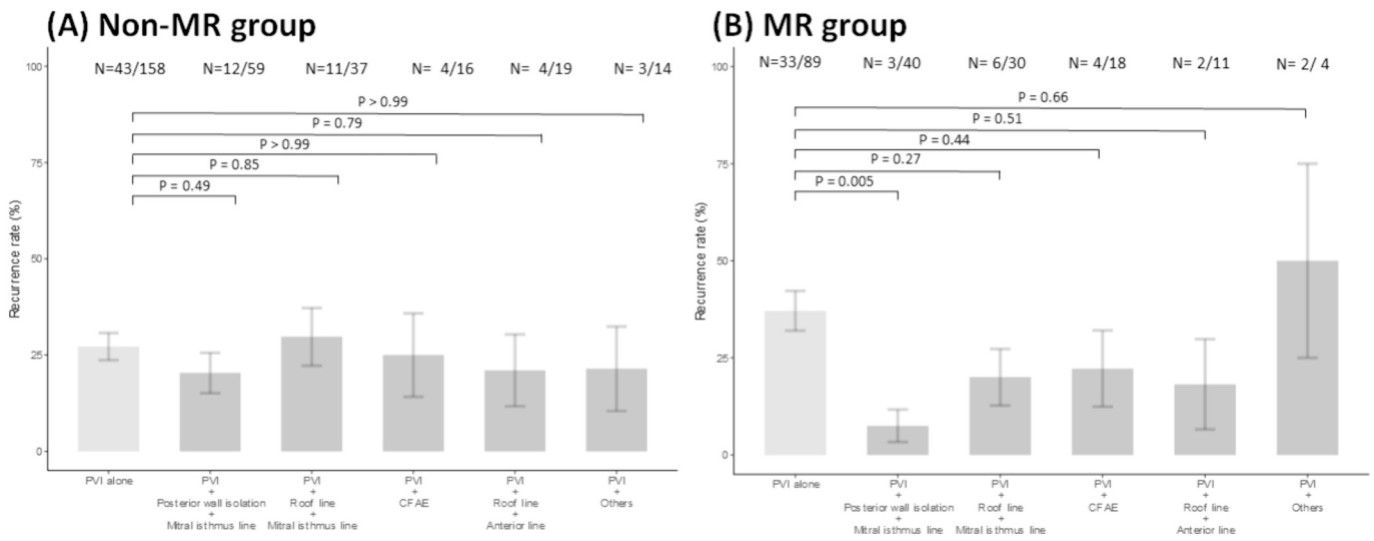

Fig. 4. Type of extensive ablation and AF recurrence.
The recurrence rate of atrial fibrillation, atrial flutter, and atrial tachycardia, according to extensive procedure types in the non-MR group (A) and the MR group (B) are illustrated as bar graphs. Error bars indicate standard error. *P* value <0.01 indicated a significance level calculated with the Bonferroni method. Abbreviations: MR, mitral regurgitation: PVI, pulmonary vein isolation; CFAE, complex fractionated atrial electrograms.

predominantly distributed in the anterior wall, septum, roof, and posterior wall. [25] Those are the locations most likely to be partially modified when performing linear ablation. CFAE is also reported to have a relationship with LVA. [26] This study performed linear ablation or CFAE ablation, albeit not LVA-guided ablation. However, it is presumed that linear ablation or CFAE ablation modifies arrhythmic substrates, such as those represented by LVA, and thus PVI-plus was effective in the MR group, where arrhythmic substrates are likely to be more prevalent.

Whether MR causes atrial fibrosis and LVA and ablation for LVA reduced the recurrence rate cannot be mentioned from the results of this study. We are currently conducting the SUPPRESS-AF trial to evaluate the efficacy of ablation for LVA. [27] From that study, we will be able to examine information on LVA and MR, and investigate the relationship between MR and LVA.

4.3. Improvement of MR after catheter ablation

The etiology of mitral regurgitation (MR) is broadly categorized into atrial functional MR (AFMR) and ventricular functional MR (VFMR). [28] Both AFMR and VFMR with atrial fibrillation show improvement in MR severity after catheter ablation. [29] AFMR is considered to have significant atrial enlargement as one of the major factors. This study found a larger LAD in the group with MR than in the group without MR. Indeed, the left atrial size is reduced through ablation. This reduction likely improves MR. However, AFMR is attributed to factors such as atrio-genic leaflet tethering, reduced annular contractility, flattened annulus, and loss of atrial systole. [30] There is potential for improvement in MR through the correction of factors other than the reduction in left atrial size. Further investigation is necessary as the data from this study does not provide conclusive evidence of MR improvement. In most cases of the EARNEST-PVI trial, preoperative CT was performed to confirm the morphology of the left atrium. We are currently working on the assessment of not only the diameter of the left atrium on echocardiography but also the overall morphology of the left atrium, the shape of the valve ring, and other factors that may have caused the MR in order to elucidate the precise mechanisms of the MR improvement.

4.4. Clinical implication

This study showed that PVI-plus is better for patients with mild or greater MR, while PVI alone is sufficient for patients without MR. Choosing the appropriate treatment method for each case can lead to lower recurrence rates and less extra invasive procedures. In any ablation strategy, ablation for patients with MR can improve their MR. Because this study is a post-hoc analysis of the prospective non-inferiority trial randomized trial, the current findings need to be considered as hypothesis-generating and re-confirmed in a prospective manner.

4.5. Limitations

Several limitations should be acknowledged. First, the study might have underestimated asymptomatic atrial fibrillation recurrence due to the follow-up method. However, since this is a randomized controlled trial, it is unlikely that its influence would be greater only in either one of the groups. Therefore, the influence on the current findings would be minimal. Second, influence of the improvement of MR severity on the subsequent clinical outcomes cannot be assessed in this study. Lastly, the initial goal of the EARNEST-PVI trial was to demonstrate that PVI alone is not inferior to any comprehensive catheter ablation approach for persistent AF. The analysis involving the extensive ablation strategy, which yielded superior results, was not part of the initial plan. Since the current study is not based on a pre-determined hypothesis, the sample size may not be sufficient. It is necessary to view the current findings as a basis for generating hypotheses. Additional prospective studies are needed to evaluate the efficacy of each comprehensive ablation method.

5. Conclusion

In patients with MR greater than or mild, PVI-plus was more effective than PVI-alone in preventing recurrent AF. In patients without MR, PVI-plus and PVI-alone were equivalent in preventing AF recurrence. In patients with MR, any ablation strategy improved their MR. These findings suggest tailoring ablation strategies based on MR presence can lead to better outcomes in AF management.

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CRediT authorship contribution statement

Akihiro Sunaga: Writing – original draft, Investigation, Conceptualization. **Yuki Matsuoka:** Writing – review & editing, Formal analysis. **Daisaku Nakatani:** Writing – review & editing, Supervision. **Katsuki Okada:** Writing – review & editing, Supervision. **Hirota Kida:** Writing – review & editing, Supervision. **Daisuke Sakamoto:** Writing – review & editing, Supervision. **Tetsuhisa Kitamura:** Writing – review & editing, Supervision. **Nobuaki Tanaka:** Investigation, Data curation. **Masaharu Masuda:** Investigation, Data curation. **Tetsuya Watanabe:** Investigation, Data curation. **Hitoshi Minamiguchi:** Investigation, Data curation. **Yasuyuki Egami:** Investigation, Data curation. **Takafumi Oka:** Investigation, Data curation. **Miwa Miyoshi:** Investigation, Data curation. **Yasuhiro Matsuda:** Investigation, Data curation. **Masato Kawasaki:** Investigation, Data curation. **Koichi Inoue:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Shungo Hikoso:** Resources, Investigation, Funding acquisition, Data curation. **Yohei Sotomi:** Supervision, Project administration. **Yasushi Sakata:** Writing – review & editing, Supervision, Resources, Funding acquisition.

Declaration of competing interest

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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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.132231.

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