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Low-voltage-area ablation for persistent atrial fibrillation: a randomized controlled trial

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Low-voltage areas (LVAs) in the left atrium may promote atrial fibrillation (AF), but the efficacy of LVA ablation for preventing arrhythmia has not been determined. In the present study, we carried out a multicenter, randomized controlled trial (SUPPRESS-AF) to investigate the efficacy of LVA ablation in patients with persistent AF who had left atrial LVAs. Patients with persistent AF and left atrial LVAs that covered ≥5 cm^2 of the left atrial surface on a voltage map after pulmonary vein isolation (PVI) were randomized to undergo LVA ablation (PVI + LVA-ABL group) or not (PVI-alone group) in a 1:1 fashion. Recurrence of AF or atrial tachycardia (AT) was monitored using 24-h Holter electrocardiography (ECG) and twice-daily portable ECG recordings. The primary endpoint was freedom from AF or AT recurrence without antiarrhythmic drug use during 1 year of follow-up. Of 1,347 patients (1,003 males and 344 females) who underwent initial ablation for AF, patients with left atrial LVAs were assigned to the PVI + LVA-ABL (n = 170) or the PVI-alone group (n = 171). Although the PVI + LVA-ABL group demonstrated a numerically higher rate of freedom from AF or AT recurrence compared with the PVI-alone group (61% (95% confidence interval (CI) = 53–68%) versus 50% (95% CI = 42–57%)), this difference did not reach statistical significance (P for log(rank) test = 0.127). There was no difference in the procedure-related serious adverse events between the two groups (1.7% versus 1.8%, P < 0.0001). In conclusion, LVA ablation in addition to PVI did not significantly reduce 1-year AF or AT recurrence in patients with persistent AF with left atrial LVAs. Future studies are needed to identify patients who may receive greater benefit from LVA ablation.

Pulmonary vein isolation (PVI) is a standard procedure in ablation for persistent atrial fibrillation (AF), but its therapeutic effect is unsatisfactory[1–3]. Although several pre-specified anatomical ablations or local electrogram-guided ablations have been investigated, none has been determined to be effective[3–5]. Atrial myocardial degeneration such as fibrosis is reported to form extrapulmonary vein AF substrate[6–8]. As the degree of myocardial degeneration in each case varies from site to site[9], individualized ablation techniques guided by myocardial degeneration may be effective. Magnetic resonance imaging has demonstrated regional consistency between low-voltage areas (LVAs) and areas with delayed gadolinium enhancement, representing increased extracellular volume such as fibrosis[10–12]. More recently, histological analysis has revealed that atrial myocardial degeneration is observed as an electrophysiological abnormality, including voltage reduction[13]. Based on these findings, ablation guided by LVAs may reduce AF substrates, leading to the suppression of AF recurrence.

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Several clinical trials have explored the efficacy of LVA ablation in addition to PVI in patients with persistent AF, but the results have been inconsistent[14–16]. A major criticism of these previous studies was their design, which assigned patients to treatment and nontreatment groups without knowledge of the presence of LVAs. Consequently, these studies may not have sufficiently examined the specific impact of LVA ablation.

To address this issue, we designed a study that specifically enrolled patients with identified LVAs. Randomization was conducted for patients with LVAs at the time of the procedure. The purpose of the present study was to explore the efficacy of LVA ablation in addition to PVI in patients with persistent AF and the presence of LVAs.

Results

A randomized controlled SUPPRESS-AF trial included patients undergoing initial ablation for persistent AF with left atrial LVAs on the voltage map after PVI. The patients were randomly assigned in a 1:1 ratio to undergo LVA ablation (PVI + LVA-ABL group) or not (PVI-alone group). Patients were followed for 12 months using v24-h Holter ECG at 6 and 12 months after ablation and twice-daily rhythm checks with portable ECG from 6 months to 12 months after ablation.

Patients and follow-up

Of 1,347 patients who underwent initial ablation for persistent AF between June 2019 and August 2022, left atrial LVAs were detected in 343 (25.5%) patients (Fig. 1). A total of 342 patients were randomly assigned to either the LVA-ABL group (170 patients) or the PVI-alone group (172 patients) and safety outcomes were assessed. Patient enrollment ended when the target sample size was reached. After excluding one patient who was found to have a history of thromboembolism after randomization and judged ineligible to participate in the study, the efficacy endpoint was assessed in 171 patients. During the 1-year follow-up period, 17 patients dropped out as a result of lack of daily ECG or loss to follow-up at the outpatient clinic. The follow-up protocol was completed in 324 (94.7%) patients. Twice-daily ECG recordings were done almost exactly as pre-specified with a recording rate of 96.0% (81.2%, 100.0%). Antiarrhythmic drugs used during the follow-up period are shown in Extended Data Table 1.

Baseline characteristics in the two groups were well balanced (Table 1). The mean age was about 74 years and nearly half of the patients were female. Most patients had an AF duration ≤1 year. The mean left atrial diameter was about 44 mm.

Procedural characteristics

Total procedure time, total radiofrequency application time and total applied energy were significantly greater in the PVI + LVA-ABL group than in the PVI-alone group (Table 2). First-pass left- and right-sided PVI rates were nearly 90% in both groups, with no difference between the groups. Mean LVA size was comparable between the two groups. Radiofrequency application time for LVA ablation was approximately 11 ± 5 min and complete LVA ablation was achieved in 78% of patients. Reasons for incomplete LVA ablation were concerns about damage to the esophagus and physiological conduction system, including the His bundle and anterior transverse conduction (Bachman's bundle) in 29 patients, excessively extensive LVAs in 4 patients and inability to manipulate the ablation catheter to some LVAs in 4 patients. Ablation for regular AT was more frequently performed in the PVI + LVA-ABL group (details of AT origin are in Extended Data Table 2).

Efficacy endpoints

Kaplan–Meier curves, on the primary endpoint of freedom rate from AF or AT recurrence without antiarrhythmic drug use after a single ablation procedure, showed no statistical difference between groups (*P* for log(rank) test = 0.127; Fig. 2). At 1 year, the freedom rate from AF or AT recurrence was 61% (95% CI = 53–68%) in the PVI + LVA-ABL group and 50% (95% CI = 42–57%) in the PVI-alone group (Fig. 2a). The hazard ratio (HR) of the PVI + LVA-ABL group to the PVI-alone group was 0.781 (95% CI = 0.564–1.083). HRs adjusted for participating hospitals are listed in Extended Data Table 3.

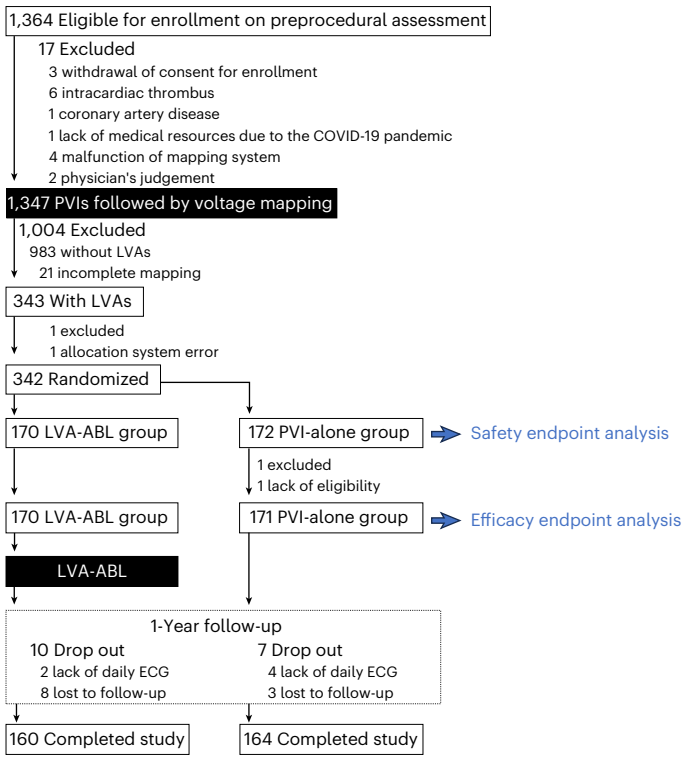

Fig. 1 | Patient flow. Of 1,347 patients who underwent initial ablation for persistent AF, left atrial LVAs were detected in 343 (25.5%) patients. A total of 342 patients were randomly assigned to either the PVI + LVA-ABL (170 patients) or the PVI-alone group (172 patients) and safety outcomes were assessed. After excluding 1 patient who was found to have a history of thromboembolism after randomization and judged ineligible to participate in the study, the efficacy endpoint was assessed in 170 patients in the LVA-ABL group and 171 patients in the PVI-alone group. During the 1-year follow-up period, 17 patients dropped out. The follow-up protocol was completed in 324 (94.7%) patients.

During a follow-up period of 1 year, 23 of 170 (13.5%) patients in the PVI + LVA-ABL group and 28 of 171 (16.4%) patients in the PVI-alone group underwent multiple ablation procedures: 2 procedures in 20 and 27 patients and 3 procedures in 3 and 1 patients, respectively. The secondary endpoint of freedom rate from AF or AT recurrence without antiarrhythmic drug use, after multiple ablation procedures at 1 year, was 68% (95% CI = 60–75%) in the PVI + LVA-ABL group and 57% (95% CI = 49%–65%) in the PVI-alone group (*P* for log(rank) test = 0.143; HR = 0.763 (95% CI = 0.526–1.106); Fig. 2b). Freedom rates from AF or AT recurrence with antiarrhythmic drug use after single or multiple ablation procedures did not differ between groups (Extended Data Fig. 1).

Post hoc analysis revealed that, among patients who developed the primary endpoint of AF or AT recurrence after single ablation, the proportion of AT on the first AF- or AT-detected ECG was higher in the PVI + LVA-ABL group (36% (95% CI = 24–49%)) than in the PVI-alone group (18% (95% CI = 10–30%), *P* = 0.029; Extended Data Fig. 2).

Subgroup analysis

Pre-specified subgroup analysis suggested that the efficacy of LVA ablation was demonstrated in patients aged ≥75 years and those with a CHA_2DS_2-VASc score ≥ 4, New York Heart Association (NYHA) functional class ≥II, left atrial diameter ≥45 mm, no diabetes mellitus and LVA size ≥20 cm^2 (Fig. 3).

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Table 1 | Baseline characteristics

	PVI+LVA-ABL	PVI-alone
	n=170	*n*=171
Age, years	73.8±6.8	74.7±6.1
Female, *n* (%)	85 (50)	82 (48)
Body mass index, kg per m^2	23.7±4.1	23.7±3.8
Heart rate, beats per min	81.4±17.2	81.7±17.1
Systolic blood pressure, mmHg	126±17	126±17
AF period, days	189 (83, 662)	180 (87, 602)
Duration of AF persistence, d	115 (63, 342)	110 (59, 290)
Long-standing persistent AF[a], *n* (%)	38 (22)	32 (19)
Hypertension, *n* (%)	117 (68)	125 (74)
Diabetes mellitus, *n* (%)	42 (25)	35 (21)
Congestive heart failure, *n* (%)	54 (32)	49 (29)
NYHA functional class II, *n*	35	33
NYHA functional class III, *n*	4	3
NYHA functional class IV, *n*	0	0
Stroke, *n* (%)	15 (9)	19 (11)
Vascular disease, *n* (%)	3 (2)	4 (2)
Myocardial infarction, *n* (%)	4 (2)	3 (2)
NT-pro BNP, pg per ml	1150 (737, 1874)	1008 (653, 1578)
eGFR, ml per min per 1.73 m^2	60.5±17.0	60.5±14.7
CHA_2DS_2-VASc score	3.4±1.3	3.5±1.5
Anticoagulants		
Direct oral anticoagulants, *n* (%)	166 (98)	162 (95)
Warfarin, *n* (%)	2 (1)	9 (5)
Antiarrhythmic drugs, n (%)	9 (5)	13 (8)
Echocardiography		
Left atrial diameter, mm	44.1±5.4	43.6±5.5
Left ventricular ejection fraction, %	55.8±10.7	57.4±10.4

Continuous data are expressed as the mean ± s.d. or median (interquartile range). eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal prohormone of brain natriuretic peptide. [a]Long-standing persistent AF was defined as persistent AF lasting for >1 year.

Table 2 | Procedural characteristics

	PVI+LVA-ABL	PVI alone	*P*[a]
	n=170	*n*=171	
Total procedure time, min	192.1±72.8	163.8±59.1	<0.001
Total ablation time, s	2461±916	1761±575	<0.001
Total applied radiofrequency energy, kJ	86.2±27.0	63.2±19.8	<0.001
Deflectable sheath, *n* (%)	134 (79)	134 (78)	>0.999
Mapping catheter			
Circular catheter, *n* (%)	23 (14)	21 (12)	0.749
Radiating catheter, *n* (%)	147 (87)	150 (88)	
Mapping points, *n*	1876±761	1843±772	0.689
Mapping time, min	18.5±8.1	17.4±7.0	0.163
LVA size, cm^2	13.2 (8.5–21.5)	14.0 (8.7–24.3)	0.800
Left atrial surface area size, cm^2	164.5 (136.8, 195.8)	158.2 (132.6, 185.0)	0.129
LVA ablation	170 (100)	0	
Applied energy, kJ	21.5 (13.2, 30.6)		
Ablation time, s	648±357		
Complete homogenization, *n* (%)	133 (78)		
Pulmonary vein isolation, *n* (%)	170 (100)	171 (100)	
First-pass isolation (left side), *n* (%)	151 (89)	149 (87)	0.740
First-pass isolation (right side), *n* (%)	147 (87)	151 (88)	0.628
Nonpulmonary-vein AF trigger ablation, *n* (%)	9 (5)	17 (10)	0.152
Superior vena cava, *n* (%)	3 (2)	5 (3)	0.723
Right atrium, *n* (%)	2 (1)	4 (2)	0.685
Left atrium, *n* (%)	5 (3)	7 (4)	0.770
Coronary sinus, *n* (%)	1 (1)	1 (1)	>0.999
Cavo-tricuspid isthmus ablation, *n* (%)	43 (25)	40 (23)	0.706
For clinical AFL, *n* (%)	6 (4)	4 (2)	0.542
For induced AFL, *n* (%)	36 (21)	35 (21)	0.895
As empirical ablation, *n* (%)	1 (1)	1 (1)	>0.999
Ablation of regular AT, *n* (%)	28 (17)	12 (7)	0.007
Perimitral AT, *n* (%)	6 (4)	3 (2)	0.336
Roof-dependent AT, *n* (%)	5 (14)	3 (19)	0.502
Other ATs, *n* (%)	24 (14)	10 (6)	0.012

Continuous data are expressed as the mean ± s.d. or median (interquartile range). AFL, atrial flutter. [a]*P* for comparison between groups using the two-sided, unpaired Student's *t*-test for continuous variables and the two-sided χ^2 test or Fisher's exact test for categorical variables.

Safety endpoints

There was no difference between the two groups in the safety endpoints of bleeding events, symptomatic stroke or death from any cause, except for periprocedural adverse events, which tended to be more often observed in the PVI + LVA-ABL group than in the PVI-alone group (Extended Data Table 4). Details of periprocedural adverse events are shown in Extended Data Table 5. All six heart failure cases recovered quickly with drug therapy and were discharged after an extended hospital stay of 2–9 d. There was no difference in procedure-related serious adverse events between the two groups. Case presentations of procedure-related serious adverse events are shown in Extended Data Table 6.

Discussion

Several randomized controlled trials have demonstrated inconsistent results on the efficacy of LVA ablation in patients with persistent AF. The STABLE-SR-II trial included 279 patients with persistent AF (133 (47.7%) patients had left atrial LVAs) and reported that LVA ablation in addition to PVI did not improve rhythm outcomes[15]. The ERASE-AF trial studied 324 patients with persistent AF, including 118 (36.4%) patients with atrial LVAs, and demonstrated fewer AF or AT recurrences in patients allocated to the PVI + LVA-ABL group than in those with PVI alone[16]. In contrast, the SUPPRESS-AF trial was uniquely designed such that patients with left atrial LVAs on the voltage map after PVI were randomized, allowing efficient validation of the effect of LVA ablation. Durable PVI was ensured by radiofrequency ablation guided by Visitag Surpoint and a resulting high first-pass PVI ratio[17,18]. In addition, to avoid underestimating AF or AT recurrence, twice-daily portable ECG monitoring, which is known to increase the AF detection rate after ablation[19], was incorporated into follow-up ECG monitoring. The study was adequately powered to detect a pre-estimated difference in primary outcome between the two groups.

The LVA is an area of intense atrial tissue degeneration, which is thought to play a role in the development and persistence of AF[6,10–13].

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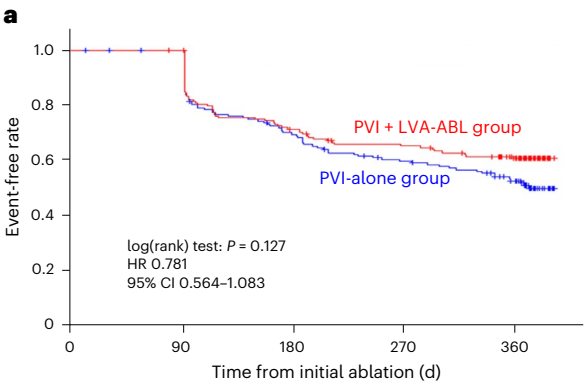
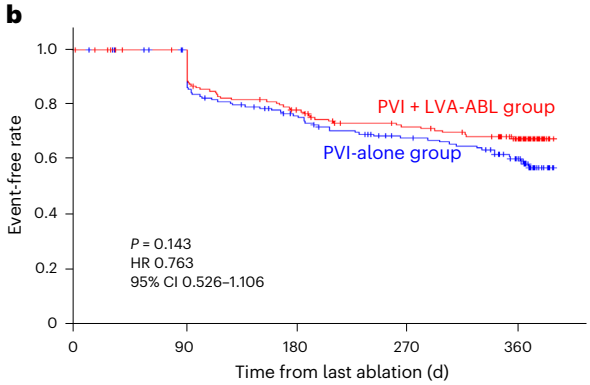


Number at risk (*n*)

PVI + LVA-ABL	170	169	118	105	80
PVI-alone	171	168	115	96	74



Number at risk (*n*)

PVI + LVA-ABL	170	161	122	105	81
PVI-alone	171	161	115	95	74

Fig. 2 | AF or AT recurrence-free rate. a, Kaplan–Meier graph showing the primary endpoint of AF or AT recurrence-free rates after the initial ablation without antiarrhythmic drug use. **b**, Kaplan–Meier graph showing the secondary endpoint of AF or AT recurrence-free rates after multiple ablations without antiarrhythmic use. Comparison of the PVI + LVA-ABL group versus the PVI-alone group was performed using the two-sided, log(rank) test. The unadjusted HR and 95% CI of AF or AT recurrence in the PVI + LVA-ABL group, compared with the PVI-alone group, are also shown.

The rationale for LVA ablation is that it can selectively modify diseased myocardium, which has individual differences in distribution. However, the SUPPRESS-AF trial failed to show statistical significance of the efficacy of adding LVA ablation to PVI, despite the numerical superiority of the PVI + LVA-ABL group. This suggests that the trial was underpowered to show the resulting efficacy of additional LVA ablation, which was less than initially estimated. Possible reasons why the efficacy of LVA ablation was lower than expected were as follows: first, the essential question of whether LVA ablation can reduce AF substrates has not been fully resolved. All LVAs may not play as an arrhythmogenic substrate and eliminating electrical activity by LVA ablation does not necessarily lead to suppression of the arrhythmic substrate. Second, the atrial arrhythmogenic substrate may not always be confined within LVAs. LVA ablation may therefore leave other substrates that can sustain AF, leading to failure to suppress AF in some cases. This idea is supported by the observation of not a few ATs arising from non-LVA sites such as the right atrium in the PVI + LVA-ABL group. In addition, several clinical studies reported the entire left atrial electrical remodeling (voltage reduction and electrical conduction velocity decrease) in patients with local voltage reduction or LVAs[13,20,21]. Third, extensive ablation, including LVA ablation, can increase iatrogenic ATs by generating re-entrant substrates such as electrical scars and slow conduction channels[22–25]. In the present study, patients in the PVI + LVA-ABL group underwent more AT ablations during the initial ablation and had a higher proportion of AT among AF or AT recurrences during 1 year of follow-up than those in the PVI-alone group. ATs after LVA ablation could have been reduced by using the methods in ERASE-AF[16], including connecting nonconducting structures with linear ablation and achieving electrophysiological endpoints such as loss of local capture at a given lesion and bidirectional conduction block for linear ablation.

On the other hand, the efficacy of LVA ablation was demonstrated in subgroups of patients aged ≥75 years, with a CHA_2DS_2-VASc score ≥4, left atrial diameter ≥45 mm and LVA size ≥20 cm^2. Some inferences about the possibility that LVA ablation suppressed AF can be made from the finding that efficacy was greater in patients with advanced atrial remodeling. The importance of LVA as an AF substrate may increase the more extensive it becomes, resulting in LVA ablation having a substantial impact. Alternatively, extensive left atrial ablation itself may effective for the modification of diffuse AF substrate. The opposite view is that maintenance of sinus rhythm cannot be expected even via LVA ablation in patients with extremely advanced atrial remodeling. However, such patients were a minority in the present study where patients had relatively less advanced atrial remodeling in terms of left atrial size and AF duration.

The present study also sheds light on the safety issue of LVA ablation. Procedure time was approximately half an hour longer in the PVI + LVA-ABL group than in the PVI-alone group. Serious, procedure-related, adverse event rates were not increased with the addition of LVA ablation. On the other hand, the incidence of all periprocedural adverse events tended to be higher in the PVI + LVA-ABL than in the PVI-alone group (11 (95% CI = 6.5%) versus 4 (95% CI = 2.3%) patients (odds ratio (OR) = 2.91 (95% CI = 0.91–9.31))) and a larger study may well have found a difference in safety endpoints. The tendency toward a difference between the two groups was mainly the result of minor complications, such as the incidence of heart failure, that were easily managed with medications and complications at the inguinal puncture site, which were probably caused by the longer procedure time and more extensive ablation.

Several limitations of the present study warrant mention. First, as the study was conducted at institutions in Japan, some limitations in generalizing the findings to other populations may be present. Second, several participants dropped out from follow-up visits or portable electrocardiogram recording, possibly because the study was conducted across the coronavirus disease (COVID)-19 pandemic period. Third, AF or AT recurrence was monitored by discontinuous ECG monitoring, giving rise to the possibility that asymptomatic episodes of AF or AT might have been missed. In addition, AF burden, which has recently been considered a meaningful efficacy outcome after ablation, could not be measured. Fourth, the divergence in the Kaplan–Meier curves suggests the possible efficacy of LVA ablation, but was statistically underpowered to detect a difference that was smaller than assumed when the protocol was created. When calculated from the recurrence rates of the LVA ablation and non-ablation groups obtained in the present study, a sample size of 630 cases for each study arm would have demonstrated a significant difference. Fifth, LASSO NAV and PentaRay NAV have different electrode properties in terms of interelectrode spacing and arrangement and the recorded signals would not be identical. As a result, the arrhythmogenic implication of LVAs may differ between the two mapping catheters.

In conclusion, LVA ablation in addition to PVI did not significantly reduce 1-year AF or AT recurrence in patients with persistent AF who underwent initial ablation and had left atrial LVAs. Given that

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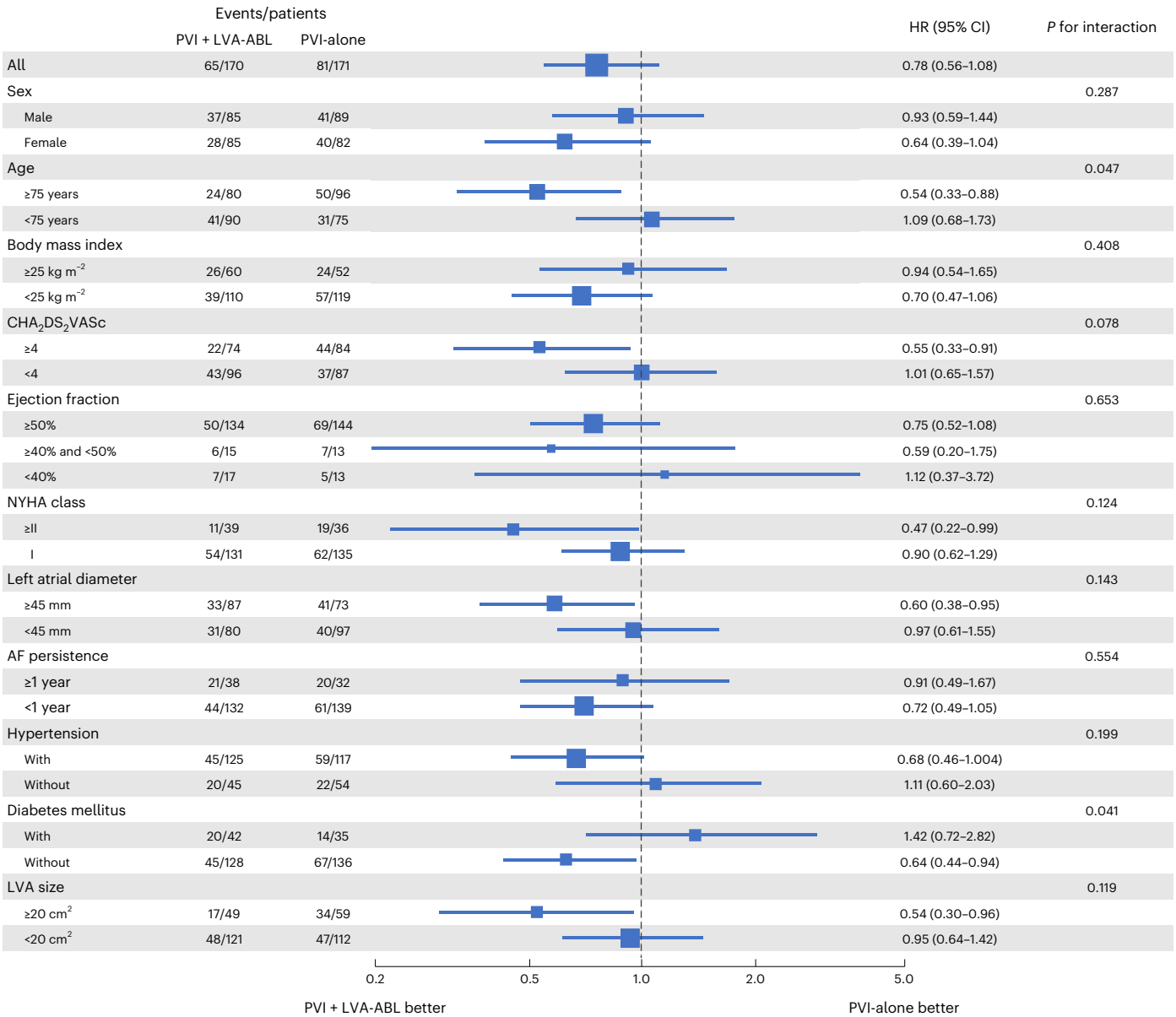

Fig. 3 | Impact of LVA ablation in addition to PVI in pre-specified subgroups. Forest plots displaying unadjusted HRs (center squares) and 95% CIs (error bands) of AF or AT recurrence in the PVI + LVA-ABL group compared with the PVI-alone group, as stratified according to pre-specified subgroups. *P* values for Wald's test for interaction was also presented. Patients aged ≥75 years, with a CHA_2DS_2VASc score ≥4, NYHA functional class ≥II, left atrial diameter ≥45 mm, no diabetes mellitus and LVA size ≥20 cm^2 had lower AF or AT recurrence rates in the PVI + LVA-ABL group than in the PVI-alone group.

the efficacy of LVA ablation may depend on patient characteristics, future studies on improving patient selection for more effective LVA ablation are needed.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-03674-y.

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Methods

Trial design

A prospective, investigator-initiated, multicenter, randomized, open-label SUPPRESS-AF trial was conducted at eight centers in Japan. The trial protocol has been described previously[26]. Protocol creation, data monitoring and collection and primary data analysis were performed by the steering team of Osaka Cardiovascular Conference (Osaka University). Roles and responsibilities were agreed among collaborators ahead of the research. Local researchers and clinical research coordinators who were trained before and during the study were involved in the conduct of the study and data management at each site. Data collection was conducted using an electronic data capture system (DATATRAK ONE, Datatrack International). The Osaka University Ethics Committee conducted the central review and approval of the protocol (approval no. 18211) on behalf of other facilities, except for Osaka National Hospital, which conducted the ethics review and approved the protocol (approval no. 21056) independently. The study was sponsored by Biosense Webster through the Investigator Initiated Studies (IIS) program, which had no role in the conduct of the study except for review and approval of protocol creation. The present study complied with the Declaration of Helsinki. The trial protocol and statistical analysis plan are available in the Supplementary Information.

Trial participants

Patients undergoing initial ablation for persistent AF were considered for enrollment. Exclusion criteria were age <20 years, left atrial diameter ≥55 mm, history of cardiac surgery, valvular AF, hemodialysis, contraindication to ablation, contraindication to anticoagulant therapy, history of stroke or systemic embolism within the last 6 months, treatable cause of AF, pregnancy and physician's judgment of unsuitability for enrollment.

Before the ablation procedure, provisional registration was made and an informed consent form was obtained. Patients with left atrial LVAs (defined as areas with a bipolar peak-to-peak voltage <0.50 mV) covering ≥5 cm^2 of the left atrial surface on the voltage map after PVI were then fully enrolled in the study. They were randomly assigned in a 1:1 ratio to LVA ablation after PVI (PVI + LVA-ABL group) or PVI alone (PVI-alone group) immediately after voltage mapping. Randomization allocation was computer generated through a central concealed process and each site was informed online. A minimization method using participating hospitals as an adjustment factor was used so as not to cause large deviation within each hospital.

Interventions

Catheter ablation was performed under a carefully established procedural protocol to minimize variability among facilities and operators. An electroanatomical mapping system (CARTO 3, Biosense Webster) was used for catheter navigation, ablation guidance and mapping. Ipsilateral encircling PVI was performed in all patients using an open-irrigated ablation catheter with a contact force sensor (Thermocool Smarttouch SF, Biosense Webster). Radiofrequency energy application was guided using a Visitag Surpoint module (Biosense Webster). Target Visitag Surpoint was set at ≥425 for the anterior wall and ≥375 for the posterior wall with an interlesion distance of ≤4 mm[27]. Throughout the ablation procedure, the following VISITAG module setting was used: (1) catheter stability range of motion ≤2 mm, (2) catheter stability duration >5 s or (3) contact force ≥5 g (time ≥25%). After the waiting time of ≥20 min, both entrance and exit blocks were confirmed at each ipsilaterally isolated PV. Electrical cardioversion was performed in cases where AF persisted at the end of the PVI procedure.

After the PVI, left atrial voltage mapping was performed under 100 p.p.m. pacing from the high right atrium. Magnetic sensor-enabled, multielectrode mapping catheters with a 1-mm electrode size (LASSO NAV or PentaRay NAV, Biosense Webster) were used. Mapping points were automatically acquired using the Confidense Module (Biosense Webster) until all color gaps on the voltage map were filled in the following setting: cycle length filtering ±30 ms; local activation time stability 3 ms; position stability 2 mm; density 1 mm; tissue proximity indicator off; and fill and color interpolation threshold 10 mm. LVAs were defined as areas with a bipolar peak-to-peak voltage of <0.5 mV. The scar level was set at 0.05 mV. The area of the LVA was manually measured using the area measurement tool of the CARTO system and, when the total of the LVA area exceeded 5 cm^2, it was judged that the left atrium LVA was present.

In the PVI + LVA-ABL group, homogenization ablation covering all LVAs was performed, except for scar areas where mapping points with voltage <0.05 mV concentrated. LVAs located at the posterior wall were allowed to be isolated with top (roof) and bottom lines. Each radiofrequency application was guided by a Visitag Surpoint of ≥350 with an interlesion distance of <6 mm. It was acceptable to omit ablation to sites where ablation could impair physiological electrical conduction system or damage collateral structures, including the esophagus.

After completion of these procedures, induction of AF or AT by atrial burst stimulation and intravenous administration of isoproterenol was performed. Induced AT and nonpulmonary-vein AF triggers could be ablated at the discretion of the attending operator. In addition, cavo-tricuspid isthmus ablation was permitted when tricuspid isthmus-dependent atrial flutter was clinically observed.

Follow-up

Patients were followed for 12 months and were required to visit a cardiology outpatient clinic at 6 and 12 months for medical assessment. A standard 12-lead electrocardiogram in the supine resting position and 24-h Holter ECG during the course of daily life was performed before each outpatient visit. Holter ECG was recorded using two leads: CM5 and NASA. In addition, twice-daily and symptom-driven ECG recordings for 30 s were performed with a portable electrocardiogram (HCG 901 or HCG 801; Omron) from 6 months to 12 months. Patients were instructed to place the electrodes in contact with the index finger and the anterior chest at a few centimeters below the nipple. The portable electrocardiogram recorder is approved by health authorities such as those in the European Union and Japan, and has been used in several clinical studies[28,29].

AF or AT recurrence was defined as the occurrence of one of the following events: (1) AF or AT indicated on a scheduled or symptom-triggered electrocardiogram or (2) AF or AT of at least 30-s duration on Holter ECG monitoring. AF or AT episodes during the 3 months after the initial or repeat ablation were not included as recurrence events (blanking period). Antiarrhythmic drug use was not recommended for 3 months after the ablation procedure.

Repeat ablations were allowed for recurrent AF or AT. The procedure was required to be in accordance with the pre-specified protocol. In short, re-isolation of reconnected pulmonary veins followed by left atrial voltage mapping was performed. Ablation targeting residual LVAs was conducted in the PVI + LVA-ABL group, but not in the PVI-alone group. There were no protocol restrictions on other ablation procedures, which could be performed at the discretion of the operator.

Endpoints

The primary endpoint of the study was the recurrence of AF or AT without antiarrhythmic drug use during the 1-year follow-up period after the index ablation procedure. The secondary efficacy endpoint was recurrent AF or AT after repeat ablations. Safety endpoints included death from any cause, symptomatic cerebrovascular stroke or bleeding events during the 1-year follow-up period and any periprocedural adverse events. In addition, procedure-related serious adverse events, including cardiac tamponade, stroke or systemic thromboembolism, esophageal fistula, major bleeding and death, were also defined as safety endpoints. Bleeding events were defined as major bleeding in the ISTH bleeding criteria[30] and bleeding requiring hospitalization. Serious adverse events

were defined as events that led to death, threatened life or required hospitalization or an extended hospital stay period for treatment.

Statistical analysis

The time to event was compared with the assumption of 1-year AF or AT recurrence-free rates of 75% in the PVI + LVA-ABL group and 60% in the PVI-alone group (HR = 0.56). With a randomization ratio of 1:1, a sample size of 155 participants in each group was required to reject the null hypothesis with a power of 80% and a significance level of 5%. A total sample size of 340 patients was estimated to be required, allowing for some dropouts.

Continuous data are expressed as the mean ± s.d. or median (interquartile range). Categorical data are presented as absolute values and percentages. Analyses were based on the intention-to-treat principle. In primary and secondary efficacy endpoints, unadjusted survival curves were estimated using the Kaplan–Meier method and compared with the use of log(rank) tests. The 1-year AF or AT recurrence-free rate and its 95% CI after the initial or repeat ablation were calculated using Greenwood's formula. Unadjusted HRs and 95% CIs derived from Cox's proportional-hazards models were used in primary and secondary efficacy endpoints and subgroup analysis. HRs adjusted for the eight participating hospitals (classified into four groups: the top three hospitals with the highest number of enrolled cases and the remaining five hospitals) were also calculated. For each subgroup analysis, Wald's test for interaction was performed. Safety endpoints were analyzed using Fisher's exact test. All tests were conducted at a two-sided α level of 0.05. Procedural characteristics were compared using the unpaired Student's *t*-test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. All analyses were performed using commercial software (SAS v.9.4, SAS Institute Inc.).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The datasets from the present study are not publicly available due to concerns about patient confidentiality and proprietary considerations. Deidentified individual patient-level clinical data will be available on request for academic use with appropriate consideration of patient confidentiality. Responses to enquiries will be made within 1 week. All requests for datasets should be directed to the corresponding author at masuda-masaharu@kansaih.johas.go.jp.

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Author contributions

M.M., T.W., H.M., Y.E., S.H., T.D., K.I. and Y. Sakata designed the study. M.M., A.S., S.H., T.D., K.I. and Y. Sotomi. organized and complied the study. M.M., A.S., N.T., T.W., H.M., Y.E., T.O., T.M., T.K., M.O., Y.M. and K.T. performed the clinical research at their respective institutions and contributed to data acquisition. M.M. wrote the paper with an input from all authors. T.Y. performed all statistical analyses. All authors contributed to the interpretation of the results and to paper development and approval of the paper.

Competing interests

Unrelated to the research, M.M. received honoraria from Medtronic and Daiichi Sankyo. M.H. received honoraria from Medtronic and Abbott and technical guidance fees from Phillips and Cook Medical. I.K. received honoraria from Johnson and Johnson. S.Y received honoraria from Nippon Boehringer Ingelheim. The other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-025-03674-y.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-025-03674-y.

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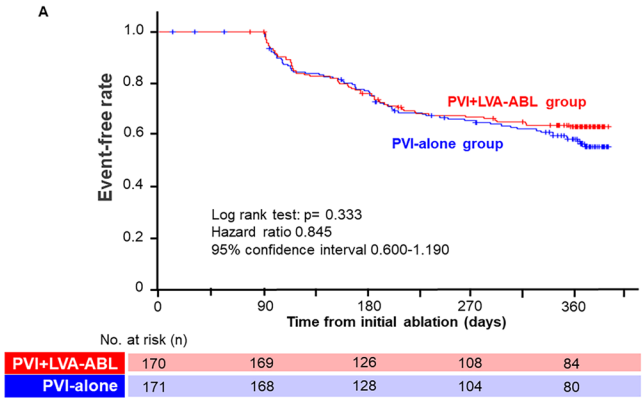
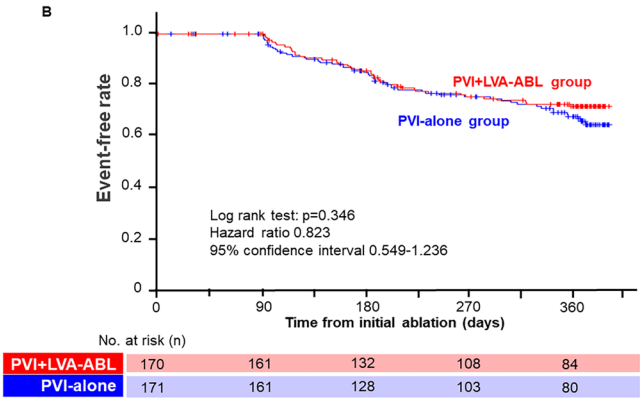


No. at risk (n)

PVI+LVA-ABL	170	169	126	108	84
PVI-alone	171	168	128	104	80



No. at risk (n)

PVI+LVA-ABL	170	161	132	108	84
PVI-alone	171	161	128	103	80

Extended Data Fig. 1 | AF/AT-recurrence-free rate with antiarrhythmic use. **a**, Kaplan-Meier graph showing AF/AT-recurrence-free rates after the initial ablation with antiarrhythmic drug use. **b**, Kaplan-Meier graph showing AF/AT-recurrence-free rates after the multiple ablations with antiarrhythmic use. Comparison of the PVI+LVA-ABL group versus PVI-alone group was performed using the two-sided log-rank test. Unadjusted hazard ratios and two-sided 95% CIs of AF/AT recurrence in the PVI+LVA-ABL group compared with the PVI-alone group are also shown. AF/AT indicates atrial fibrillation or atrial tachycardia. AT indicates atrial tachycardia; AF, atrial fibrillation.

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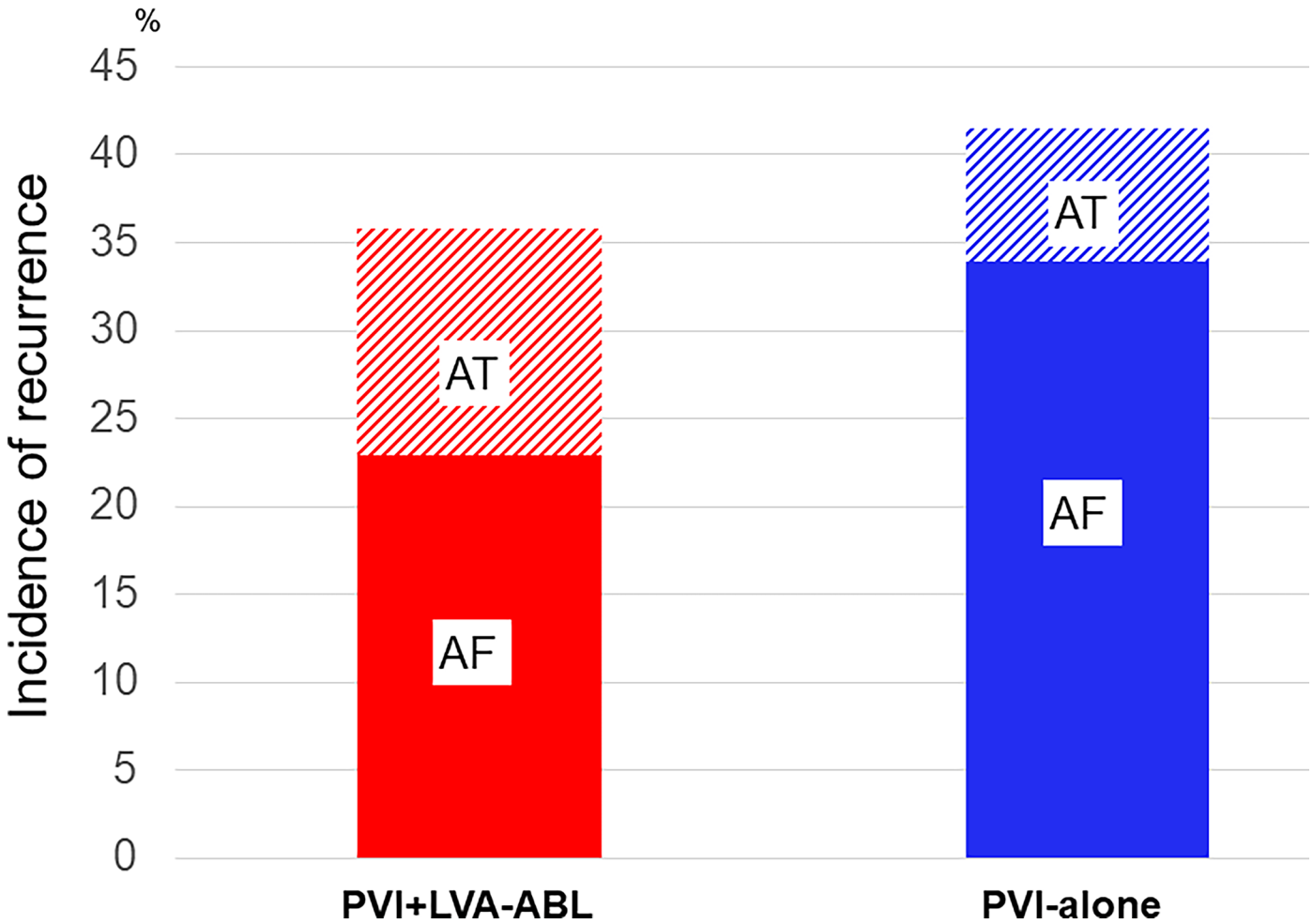

Extended Data Fig. 2 | Type of recurred atrial tachyarrhythmias. Proportion of AT on the first-AF/AT-detected ECG was higher in the PVI+LVA-ABL group (36% [24%–49%]) than in the PVI-alone group (18% [10%–30%], p = 0.029). AT indicates atrial tachycardia; AF, atrial fibrillation.

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Extended Data Table 1 | Antiarrhythmic drug use

	PVI+LVA-ABL n=170	PVI-alone n=171
Baseline		
All, n (%)	9 (5.3)	13 (7.6)
Class I, n (%)	4 (2.4)	7 (4.0)
Class III, n (%)	3 (1.8)	6 (3.5)
3 months after the procedure		
All, n (%)	27 (16.7)	21 (12.9)
Class I, n (%)	4 (2.5)	4 (2.3)
Class III, n (%)	23 (14.2)	17(9.9)
6 months after the procedure		
All, n (%)	21 (12.7)	18 (10.9)
Class I, n (%)	1 (0.6)	3 (1.8)
Class III, n (%)	20 (12.1)	15 (9.0)
12 months after the procedure		
All, n (%)	20 (12.7)	17 (10.7)
Class I, n (%)	3 (1.9)	4 (2.5)
Class III, n (%)	17 (10.8)	13 (8.2)

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Extended Data Table 2 | Origin of ATs that were attempted to be ablated during the initial ablation

	PVI+LVA-ABL	PVI-alone
Left atrium, n	8	6
Right atrium, n	11	3
Bi atria, n	2	0
Coronary sinus, n	2	0
Atrioventricular nodal reentrant tachycardia, n	2	1
Unknown, n	2	1

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Extended Data Table 3 | HRs of AF or AT recurrence in the PVI+LVA-ABL group to PVI-alone group adjusted for participating hospitals

	Hazard ratio	95% confidence interval
Without antiarrhythmic drug use after a single ablation procedure	0.790	0.569 - 1.095
Without antiarrhythmic drug use after multiple ablation procedures	0.777	0.535 - 1.127
With antiarrhythmic drug use after a single ablation procedure	0.850	0.603 - 1.198
With antiarrhythmic drug use after multiple ablation procedures	0.831	0.553 - 1.248

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Extended Data Table 4 | Safety endpoints

	PVI+LVA-ABL n=170	PVI-alone n=172	p[a]
Adverse events during 1-year follow up			
Bleeding events, n (%)	6 (3.5)	2 (1.2)	0.173
Symptomatic stroke, n (%)	4 (2.4)	2 (1.7)	0.723
Death from any cause, n (%)	2 (1.2)	2 (1.2)	>0.999
Periprocedural adverse events, n (%)	11 (6.5)	4 (2.3)	0.069
Procedure-related serious adverse events, n (%)	3 (1.7)	3 (1.8)	>0.999
Cardiac tamponade, n (%)	0	1 (0.6)	
Stroke or systemic embolism, n (%)	0	1 (0.6)	
Esophageal fistula, n (%)	1 (0.6)	0	
Major bleeding, n (%)	2 (1.2)	1 (0.6)	
Death, n (%)	0	0	

[a]p for comparison between groups using the two-sided Fisher's exact test.

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Extended Data Table 5 | Periprocedural adverse events

	PVI+LVA-ABL n=170	PVI-alone n=172
Total	11 (6.5)	4 (2.3)
*Groin hematoma necessitating intervention**	2 (1.2)	0
Bleeding events	0	0
Ischemia stroke or systemic thromboembolism	0 (0)	1 (0.6)
Pneumothorax	0	0
Arteriovenous fistula	0	0
Pericarditis	0	1 (0.6)
Cardiac tamponade	0	1 (0.6)
Phrenic nerve injury	0	0
Atrioventricular block	0	0
Sick sinus syndrome	0	0
Pulmonary stenosis	0	0
Esophageal fistula	1 (0.6)	0
Gastric dilatation	0	0
Infection	0	0
Coronary spasm	1 (0.6)	0
Heart failure	5 (2.9)	1 (0.6)
Dermatitis	0	0
Allergy to drugs	0	0
Blood transfusion	1 (0.6)	1 (0.6)
Aspiration pneumonia	1 (0.6)	0

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Extended Data Table 6 | Procedure-related serious adverse events

Randomized group	Event	Description of event
PVI-alone	Cardiac tamponade	Hypotension (systolic blood pressure of 70 mmHg) was observed at the end of the ablation procedure. Cardiac echocardiography revealed significant pericardial effusion. Pericardiocentesis was performed, and 500 ml of blood was drained. After the intravenous administration of prothrombin complex, hemostasis was quickly obtained. The patient recovered well and discharged from the hospital 12 days after the ablation procedure.
PVI-alone	Stroke	The patient complained of visual field loss in the right eye 3 days after the ablation procedure. Magnetic resonance imaging revealed cerebral infarction of the occipital lobe. The patient is followed conservatively and there is no further progression of symptoms.
PVI+LVA-ABL	Esophageal fistula	Ablation lesions of pulmonary vein isolation, roof line and bottom line were created with ablation index of 400-450 at left atrial posterior wall under esophageal temperature monitoring. When esophageal temperature reached 40 degrees Celcius, radiofrequency energy application was aborted. The patient visited emergency room 20 days after the ablation procedure, and complained of chest pain, fever, and fatigue. Computed tomography revealed pericardial effusion and pneumomediastinum, and following esophagography showed perforation of the esophagus into the pericardial space. The patient underwent esophagectomy and reconstructive surgery, but the intraoperative findings did not clarify the ablation site that caused the esophageal injury. Subsequent infection and prolonged wound healing prolonged the hospital stay, requiring 9 months of inpatient care. The patient was eventually discharged home, unable to take food orally and requiring enteral nutrition through an enterostomy.
PVI+LVA-ABL	Major bleeding	The patient visited an emergency room 8 days after the ablation procedure, and complained of right lower extremity pain. Computed tomography revealed intramuscular hemorrhage. Emergent angiography identified the bleeding artery, followed by catheter coil embolization. Hemostasis was successfully obtained. The patient recovered well and discharged from the hospital.
PVI-alone	Major bleeding	The patient had chronic renal anemia due to solitary kidney after the surgery for renal cancer. After the ablation procedure, the patient received a transfusion of 2 units of concentrated red blood cells due to further progression of anemia.
PVI+LVA-ABL	Major bleeding	The patient visited emergency room 6 days after the ablation procedure, and complained of general fatigue. Blood test showed anemia, and further examination including colonoscopy found active bleeding from the colonic mucosa. Endoscopic hemostatic procedure was performed, and the patient is doing well afterwards.

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Reporting on sex and gender	The data on biological sex (Female or Male) was collected and presented in the manuscript. The study participants consisted of 167 females and 174 males. The efficacies of low-voltage-area ablation stratified by sex group are presented in Figure 3. No data on gender (social attribute) was collected.
Reporting on race, ethnicity, or other socially relevant groupings	We did not use socially relevant groupings.
Population characteristics	Patients with persistent atrial fibrillation and left atrial low-voltage areas. Mean age was approximately 74 years old, and nearly half of patients were Female.
Recruitment	The participants were recruited at 8 hospitals. Participation in the study was advanced to patients deemed appropriate by the physician, and the decision to participate was made of the patient's own free will. Patients were informed about the study at the time of obtaining consent form for the ablation procedure. Therefore, patients who were perceived by their physicians to be or were actually uncooperative with the study activities were excluded, possibly due to selection bias.
Ethics oversight	The Osaka University Ethics Committee conducted the central review and approval of the protocol (approval number #18211) on behalf of other facilities, except for Osaka National Hospital, which conducted the ethics review and approved the protocol (approval number #21056) independently.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We assumed 1-year AF/AT recurrence-free rates of 75% in the PVI+LVA-ABL group and 60% in the PVI-alone group. With a randomization ratio of 1:1, a sample size of 155 subjects in each group was required to reject the null hypothesis with a power of 80% and a significance level of 5%. A total sample size of 340 patients was estimated to be required, allowing for some dropouts.
Data exclusions	We excluded some participants according to pre-defined exclusion criteria (please see the study protocol). The reasons for exclusion are shown in Figure 1.
Replication	Two analysts independently carried out statistical analysis each time to ensure that identical results were obtained. In terms of ensuring reproducibility,processes related to data handling, such as the derivation of variables and the replacement of data , were recorded. The process of creating data sets for analysis and the results of the analysis were checked (double-checking) by the responsible person.
Randomization	The participants were randomly assigned in a 1:1 ratio to PVI+LVA-ABL group or PVI-alone group immediately after voltage mapping. Randomization allocation was computer generated, and each site was informed online.
Blinding	For the researcher, blinding was not possible because the ablation procedures were different between allocated groups. For the participants, the benefit of knowing the details of the ablation procedure they received was also high, and blinding was not thought to be appropriate.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	UMIN-CTR, https://www.umin.ac.jp/ctry. UMINUMIN000035940
Study protocol	Please see the protocol in the supplemental materials
Data collection	Local researchers and clinical research coordinators who were trained before and during the study were involved in the conduct of the study and data management at each site. Data collection was conducted using an electronic data capture system (DATATRAK ONE, Datatrack International, OH, USA).
Outcomes	The outcomes were discussed among the researchers and finally adopted the standard that has been used in similar studies. The primary outcome was selected as the off-drug AF/AT recurrence rate at 1 year, which was considered the most suitable for determining the efficacy of LVA ablation. The clinically significant on-drug AF/AT recurrence rate and safety endpoints were selected as secondary outcomes. For the assessment of the outcomes, 12 lead ECG, 24-h Holter ECG, twice daily portable ECG recordings, and clinical observation for safety endpoints were used.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*