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CLINICAL RESEARCH

Persistent atrial fibrillation with left atrial low-voltage area: who benefit from additional modification?

Hengzhi Zhang †, Ning Chen †, Qiuheng Bian, Mingchuan Yuan, Gang Yang, Youmei Shen, Hongwu Chen, Weizhu Ju, Mingfang Li, Kai Gu, Nan Wu, Hailei Liu *, and Minglong Chen *

Division of Cardiology, The First Affiliated Hospital with Nanjing Medical University, Guangzhou Road, Nanjing, 210029, China

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Aims The presence of low-voltage areas (LVAs) is associated with increased recurrence rate following ablation of persistent atrial fibrillation (PeAF). However, the benefit of additional LVA modification remains controversial. This substudy of the STABLE-SR-II trial aims to explore the factors that influence the benefit of additional LVA ablation for PeAF patients with LVAs.

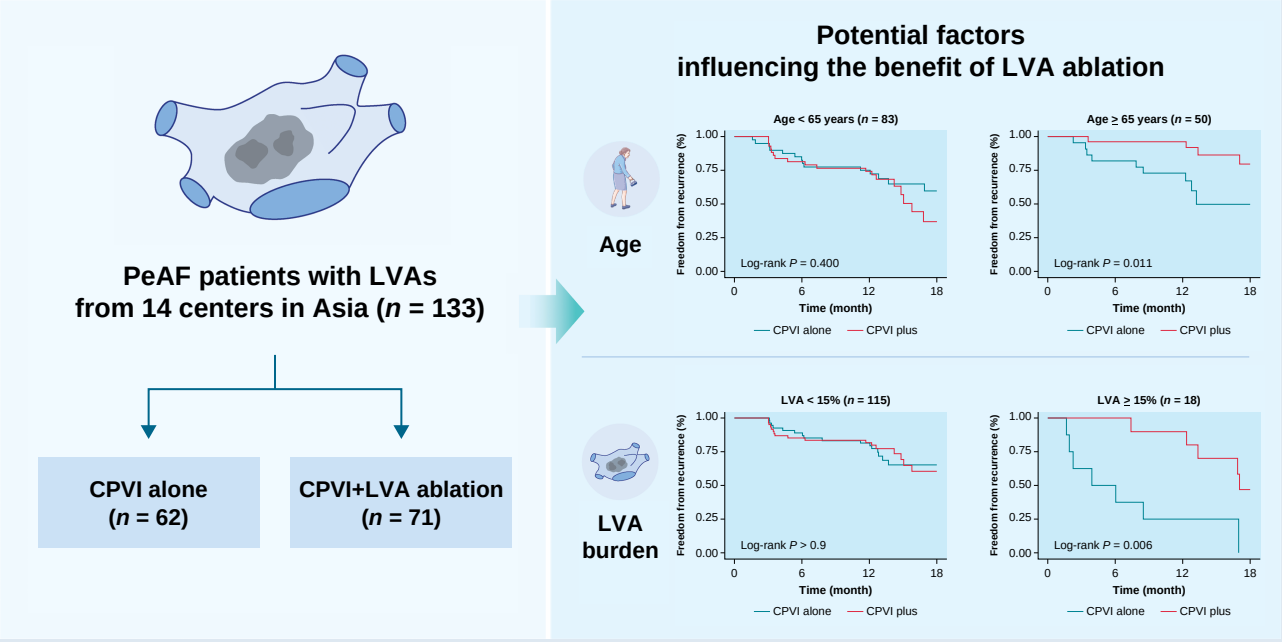
Methods and results In the STABLE-SR-II trial, PeAF patients with *de novo* ablation were randomized to receive either circumferential pulmonary vein isolation (CPVI, CPVI-alone group) or CPVI plus LVA ablation (CPVI-plus group). Patients with LVAs were included and analyzed in this substudy. The primary outcome was freedom from atrial arrhythmias 18 months after a single ablation procedure. LVAs were detected in 133 out of 276 PeAF patients (48%). Age and LVA burden were potential factors influencing the relative success of additional LVA ablation compared with CPVI alone in the univariable analysis. In multi-adjusted models, significant benefit from additional LVA ablation was found in patients aged ≥65 years [$n = 50$, hazard ratio (HR) 0.14, 95% confidence interval (CI) 0.02–0.83] or with LVA burden ≥ 15% ($n = 18$, HR 0.01, 95% CI: 0–0.44). LVA burden ≥15% was observed in 10 of 50 patients aged ≥65 years (20%) and in 8 of 83 patients aged <65 years (10%). Combined subgroup analysis demonstrated that LVA ablation was particularly beneficial for patients aged ≥65 years, regardless of LVA burden.

Conclusion LVA ablation following CPVI may provide additional benefits for older PeAF patients (≥65 years) in the first procedure.

Clinical Trial Registration NCT03448562 [CPVI Alone Versus CPVI Plus Electrophysiological Substrate Ablation in the LA During SR for the Treatment of Non-PAF (STABLE-SR_II)].

* Corresponding authors. Tel: 0086 25 68303115; fax: 0086 25 6813 6479. *E-mail address*: chenminglong@njmu.edu.cn (M.C.); *E-mail address*: liuhailei@njmu.edu.cn (H.L.)
† The first two authors contributed equally to this work as co-first authors.

Graphical Abstract



Keywords Low-voltage area • Persistent atrial fibrillation • Pulmonary vein isolation • Recurrence

What's new?

- A comprehensive analysis revealed age as a potential factor influencing the efficacy of low-voltage area (LVA) ablation beyond circumferential pulmonary vein isolation (CPVI).
- CPVI plus LVA ablation could potentially provide additional benefits for PeAF patients aged ≥ 65 years, highlighting tailored ablation strategies in PeAF patients with LVAs.

Introduction

Circumferential pulmonary vein isolation (CPVI) remains the cornerstone for atrial fibrillation (AF) ablation, with which satisfactory outcomes could be achieved in patients with paroxysmal AF.[1–3] However, for patients with persistent AF (PeAF), the long-term recurrence rate after CPVI alone remains above 40%.[4,5] Hence, adjunct strategies beyond CPVI have been developed.[5–7] While TAILORED-AF and ERASE-AF have reported improved outcomes with additional ablation,[8,9] most strategies beyond CPVI alone have yet to demonstrate consistent and significant benefits.

The unsatisfactory outcomes of these additional ablation attempts prompted a renewed focus on the pathogenesis of AF. Left atrial fibrosis has long been recognized as a key structural remodelling process contributing to the maintenance and progression of AF.[10–14] During voltage mapping, low voltage areas (LVAs) has been considered as a surrogate of local fibrosis.[15–17] However, the relationship between LVA and left atrial fibrosis is complex.[18] A previous study utilising both voltage mapping and tissue biopsy suggested that LVAs should be regarded as indicators of global voltage reduction in a diffuse pathological process.[19] Furthermore, an atrial biopsy study demonstrated that, in addition to fibrosis, other histological factors—such as increased extracellular space, myofibrillar loss, decreased myocardial nuclear density, and amyloid deposition—are also associated with atrial voltage reduction, highlighting the intricate pathological changes involved.[20] Despite this complexity, numerous studies have demonstrated that the presence of LVAs is associated with an increased risk of post-ablation AF recurrence and PeAF patients without LVAs can achieve AF-free rates comparable to those of paroxysmal AF patients following CPVI alone.[21–23]

However, the translation from these observational findings to strategies targeting left atrial fibrosis reached controversial results. The STABLE-SR-II trial, along with several other studies, revealed inconsistent results when comparing CPVI plus LVA ablation vs. CPVI alone in PeAF patients.[21,24–26] These findings raised a question for cardiac electrophysiologists: when LVAs are detected during the index procedure in PeAF patients, in whom performing the LVA modification may be beneficial?

In this study, we aimed to explore factors associated with the benefit of additional LVA ablation over CPVI alone in PeAF patients detected with LVAs, using the data from the STABLE-SR–II trial.

Methods

Study design and study population

The STABLE-SR-II trial is a multi-centre, single-blinded, randomized controlled trial comparing the effectiveness of CPVI alone vs. CPVI plus LVA ablation in patients with PeAF. Detailed information and primary results of the trial can be found in the original paper.[21] In brief, the study included participants with PeAF or long-standing PeAF refractory to at least 1 antiarrhythmic drug from 14 centres in Asia. Major exclusion criteria were: (i) Previous ablation history; (ii) not suitable for ablation (left atrium diameter ≥ 55 mm, thrombus in left atrial appendage, or severe structural heart disease); (iii) contraindications for anticoagulant therapy. All participants were 1:1 randomly assigned to CPVI alone (CPVI-alone group), or CPVI plus LVA ablation (CPVI-plus group). In this substudy, only participants with LVAs were included.

The study protocol was approved by the Institutional Review Board of the First Affiliated Hospital of Nanjing Medical University and the ethics committee at each centre.

Mapping and ablation

After local anaesthesia and transeptal puncture, CPVI was performed using an irrigated contact-force catheter (Thermocool SmartTouch, Biosense Webster) under the CARTO electroanatomic mapping system (Biosense Webster). If AF persisted after the CPVI, an electrical cardioversion was performed to restore sinus rhythm (SR). High-density voltage mapping was then conducted under SR, with a minimum of 300 points collected for each patient using a multipolar mapping catheter (Lasso SAS or PentaRay Biosense Webster) under the CONFEDENSE module. LVA was defined as a bipolar voltage between 0.1 and 0.4 mV. Regions with voltage < 0.1 mV were considered as 'dense scar', and between 0.4 and 1.3 mV were considered as transitional zones (TZs). LVA burden was calculated offline by an independent observer, as surface area with a voltage below 0.4 mV divided by the surface area of the left atrium.

In the CPVI-alone group, no further ablation was performed. In the CPVI-plus group, additional LVA ablation was then performed. Detailed protocols of LVA ablation have been previously described.[25,27] In brief, the procedure included homogenization ablation in the LVAs, defragmentation in the TZs, and dechanneling of the substrate. During dechanneling, additional short linear ablations were performed to interrupt potential conducting channels that could facilitate re-entrant activity between isolation lines, anatomical conduction barriers, and LVAs. Nevertheless, linear ablation was avoided across channels wider than 1.5 cm and contained local electrograms with amplitudes >1.3 mV. For all linear lesions, bidirectional conduction block was confirmed using differential pacing and activation mapping.

Follow-up and post-ablation management

Oral anticoagulation was continued for at least 6 months post-ablation, and anticoagulation was continued in patients with a CHA_2DS_2-VASc score ≥ 2. Antiarrhythmic drugs were discontinued 90 days after the initial procedure, except in patients with atrial tachycardia (AT)/AF recurrence. All patients received routine follow-ups, including clinic visits and 24-h Holter monitoring at 3-month (beyond the blanking period) and 6-month, as well as 7-day Holter recordings at 12-month. Afterwards, clinic visits and Holter monitoring were conducted every 6 months until the study concluded.

Outcome measurement

The primary endpoint of the study is AT/AF-free at 18 months after the procedure. AT/AF recurrence is defined as any AT/AF episodes lasting more than 30 s after a post-ablative 90-day blanking period. The recurrence rate within 18 months was compared between the two groups.

Statistical analysis

The normality of continuous variables was examined using Shapiro-Wilk test. Continuous variables with normal or non-normal distributions were reported as mean ± SD or median (quartile), respectively. Student's *t*-tests and Wilcoxon rank-sum tests were used for the comparisons of normally or non-normally distributed continuous variables, respectively. Categorical variables were compared using χ^2 tests.

Participants were categorized into subgroups according to sex, age, LVA burden, and other characteristics. An LVA burden cutoff of 15% was selected for subgroup analysis.[23] Univariable Cox proportional hazards regression models were first used within each subgroup to compare outcome rates between the CPVI-alone and CPVI-plus groups. Subgroups showing significant differences between groups were selected for further analysis, using multivariable Cox regressions and Kaplan-Meier survival analysis. In multivariable Cox Model 1, adjustments were made for age, sex, and body mass index (BMI). Model 2 included adjustments for additional covariates: AF duration, hypertension, diabetes, coronary heart disease, stroke, heart failure, chronic obstructive pulmonary disease, obstructive sleep apnoea syndrome, CHA_2DS_2-VASc score, left atrial diameter, and left ventricular ejection fraction (LVEF). Finally, a combined subgroup analysis was performed to further investigate the interactions between factors influencing the benefit of additional LVA ablation. In the concordance analysis, due to the small sample size within each subgroup, Firth's penalized partial likelihood correction for Cox regressions was applied. Compared with standard Cox regression, Firth's penalized estimation reduces bias and enhances model stability by incorporating a penalisation term, particularly in cases of limited data or rare events.[28] Given the limitation in sample size, only one adjusted model was established including age, sex, and BMI as adjusted covariates.

All statistical analyses were performed on the R software (version 4.3, R Foundation for Statistical Computing, Vienna, Austria), and a two-sided *P* value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Among 276 participants in the STABLE-SR–II trial, 133 participants (48%) were found with LVAs. Of these, 62 were assigned to the CPVI-alone group, and the remaining 71 were assigned to the CPVI-plus group (*Table 1*). No significant difference was found between the two groups regarding baseline characteristics.

Table 1 Baseline characteristics

	CPVI alone ($n = 62$)	CPVI plus ($n = 71$)	*P*
Sex, female	26 (41.9%)	31 (43.7%)	0.98
Age (years)	62.7 (54.1–67.1)	62.5 (56.2–67.0)	0.723
AF duration	7.5 (2.0–24.0)	11.0 (3.0–24.0)	0.439
BMI	26.0 (24.2–28.0)	25.5 (23.0–27.2)	0.081
Hypertension	22 (35.5%)	33 (46.5%)	0.268
Diabetes	4 (6.5%)	5 (7%)	1
NYHA function class			0.761
I	35 (56.5%)	43 (60.6%)	
II	26 (41.9%)	26 (36.6%)	
III	1 (1.6%)	2 (2.8%)	
CHA_2DS_2-VASc score	1.0 (0.0–2.0)	1.0 (1.0–2.0)	0.184
LAD (mm)	43.5 ± 5.3	41.9 ± 5.2	0.087
LVEF (%)	62.7 (60.0–65.0)	62.0 (60.0–65.0)	0.823
LVA burden (%)	4.0 (2.0–9.3)	5.0 (2.3–9.5)	0.292

BMI, body mass index; CPVI, circumferential pulmonary vein isolation; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVA, low voltage area (in left atrium).

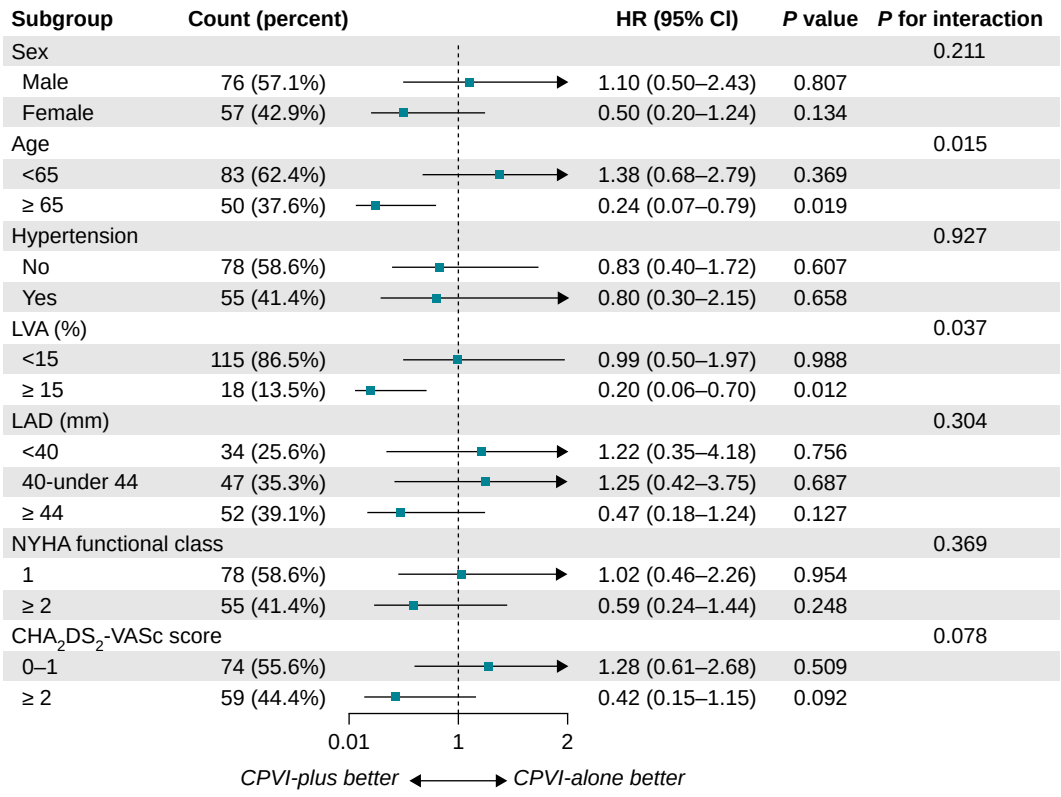


Figure 1 Subgroup analysis on the recurrence rate between ablation strategies. CI, confidence interval; HR, hazard ratio; LAD, left atrium diameter; LVA, low voltage area.

Subgroup analysis

During the follow-up period, a total of 23 (37.1%) patients in CPVI-alone group and 22 (31%) in CPVI-plus group experienced AT/AF recurrence. The relative recurrence hazards of CPVI-plus group over CPVI group in subgroups were illustrated in *Figure 1*. Among all preset subgroups analyzed, only patients aged ≥ 65 years [Hazard ratio (HR) 0.24, 95% confidence interval (CI) 0.07–0.79] or LVA burden ≥ 15% (HR 0.2, 95% CI: 0.06–0.7) have a significant lower recurrence hazard in CPVI-plus group than that in CPVI-alone group.

Kaplan-Meier curves showing comparisons of the AT/AF-free survival between patients receiving CPVI alone or CPVI plus in subgroups by age or LVA burden are provided in *Figure 2*. In patients aged < 65 years ($n = 83$), AT/AF recurrence was similar between patients receiving CPVI alone or CPVI plus (35% vs. 41.9%, $P = 0.40$ by log-rank test). In patients aged ≥ 65 years ($n = 50$), AT/AF recurrence was significantly higher in the CPVI alone group (40.9% vs. 14.2%, $P = 0.01$). In patients with LVA burden < 15% ($n = 115$), AT/AF recurrence was similar between patients receiving CPVI alone or CPVI plus (29.6% vs. 33.3%, $P > 0.9$), while CPVI plus rendered a lower recurrence rate (50.0% vs. 100%, $P = 0.006$) in patients with LVA burden ≥ 15% ($n = 18$).

Multi-adjusted models indicated the robustness of the superiority of CPVI-plus over CPVI-alone for patients who are aged ≥ 65 years or with larger LVAs (*Table 2*). In the adjusted model 2, HR was 0.03 (95% CI: 0.02–0.83) for patients ≥ 65 years old, and 0.02 (95% CI: 0–0.44) for patients with LVA burden ≥ 15%.

Combined subgroup analysis of age and LVA burden

Concordance analysis was performed to investigate the interactions between age and LVA burden (*Table 3*). In older patients (≥65 years), CPVI-plus was associated with improved outcomes both in patients who have either low or high LVA burden (adjusted HR 0.19, 95% CI: 0.02–0.93, and adjusted HR 0.05, 95% CI: 0–0.58, respectively). However, in patients with LVA burden ≥ 15%, no statistical significance was reached in patients < 65 years old (adjusted HR 0.56, 95% CI: 0.07–3.82).

Discussion

In this study, we explored factors that may influence the relative success rate of additional LVA ablation compared with CPVI alone. We found PeAF patients aged ≥ 65 years could potentially benefit from additional LVA ablation.

With the understanding that fibrosis can be detected as LVAs through voltage mapping, LVAs have traditionally been recognized as a surrogate marker for local fibrosis.[18] However, recent autopsy studies have revealed the complex relationship between LVAs and pathological changes. On one hand, LVAs indicate global voltage reduction in a diffuse pathological process rather than solely reflecting local fibrosis;[19] on the other hand, multiple pathological changes

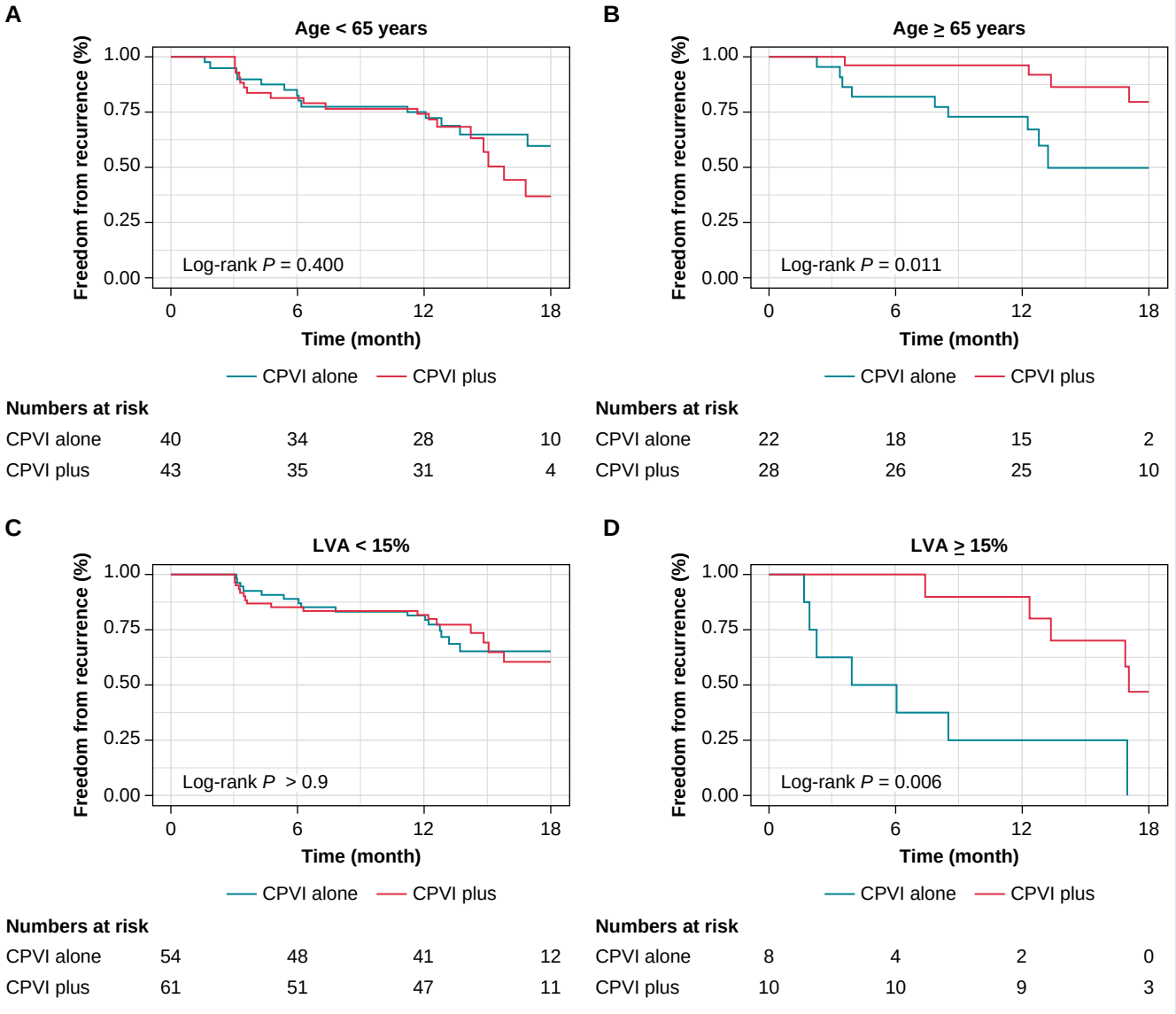


Figure 2 Kaplan-Meier analysis of the recurrence rate in different subgroups: (*A*) age < 65 years; (*B*) Age ≥ 65 years; (*C*) LVA < 15%; (*D*) LVA ≥ 15%. LVA, low voltage area.

contribute to the presence of LVAs.[20] These findings suggest that while LVAs do not strongly correlate with local fibrosis, they may provide a broader electrical representation of various pathological changes contributing to AF in the left atrium. Consequently, the presence of LVAs in the left atrium has been found to be a strong risk factor for post-ablation recurrence in PeAF patients.[22,29]

However, the benefit of LVA ablation beyond CPVI remains controversial across studies.[9,30] The STABLE-SR trial found significant benefits in PeAF patients, but the results of the subsequent STABLE-SR–II trial failed to reach statistical significance.[21,31] These trials reconfirmed CPVI as the cornerstone for AF ablation in patients without LVAs, while leaving additional LVA modification in patients with LVAs controversial. Despite recent encouraging findings,[9,31] significant methodological challenges persist in low-voltage–guided substrate modification.[2] Voltage measurements are highly variable, influenced by rhythm status, electrode size and configuration, catheter–tissue contact, atrial rate, and wavefront directionality.[32] Additionally, the criteria for defining abnormal substrate remain inconsistent, with considerable variability in low-voltage cutoffs across studies. A uniform voltage threshold fails to account for regional differences in atrial wall thickness and electrode characteristics. These limitations highlight the current uncertainty regarding the added value of additional modifications/lesions beyond CPVI.[33]

Refining through subgroup analyses, this study found that additional LVA ablation may be beneficial in PeAF with a certain burden of LVAs (≥15%). A higher AT/AF recurrence rate has been found in patients with a higher LVA burden (≥15%) than those with a lower LVA burden (<15%),[23] which potentially lead to favorable results of additional LVA modification in this population. It is worth mentioning that most of the participants in this study had LVAs <25%, so whether these findings can

Table 2 Cox regression models for the relative outcome rate across subgroups

Subgroup	Count	Univariate model		Multivariate model 1[a]		Multivariate model 2[b]	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age < 65 years	83	1.38 (0.68–2.79)	0.369	1.37 (0.67–2.78)	0.387	1.92 (0.85–4.33)	0.118
Age ≥ 65 years	50	0.24 (0.07–0.79)	0.019	0.22 (0.06–0.77)	0.018	0.14 (0.02–0.83)	0.031
LVA < 15%	115	0.99 (0.5–1.97)	0.988	0.98 (0.49–1.96)	0.956	1.56 (0.75–3.25)	0.236
LVA ≥ 15%	18	0.2 (0.06–0.7)	0.012	0.18 (0.05–0.68)	0.011	0.01 (0–0.44)	0.02

HRs of outcome risk in CPVI-plus group compared with CPVI-alone group were reported.
[a]Adjusted for age, sex, and body mass index.
[b]Adjusted for age, sex, body mass index, atrial fibrillation duration, hypertension, diabetes, coronary heart disease, stroke, heart failure, chronic obstructive pulmonary disease, obstructive sleep apnoea syndrome, CHA_2DS_2-VASc score, left atrial diameter, and left ventricular ejection fraction.
CI, confidence interval; CPVI, circumferential pulmonary vein isolation; HR, hazard ratio; LVA, low voltage area in left atrium.

Table 3 Cox regression models for the relative outcome rate across combined subgroups of LVA burden and age

Age (years)	LVA burden (%)	Count	Univariate model		Multivariate model[a]	
			HR (95% CI)	P	HR (95% CI)	P
<65	<15	75	1.66 (0.77–3.75)	0.194	1.65 (0.76–3.75)	0.204
	≥15	8	0.77 (0.12–4.02)	0.749	0.56 (0.07–3.82)	0.544
≥65	<15	40	0.19 (0.02–0.88)	0.033	0.19 (0.02–0.93)	0.039
	≥15	10	0.03 (0–0.37)	0.004	0.05 (0–0.58)	0.015

HRs of outcome risk in CPVI-plus group compared with CPVI-alone group were reported. Firth's penalized partial likelihood correction was performed on Cox models.
[a]Adjusted for age, sex, and body mass index.
CI, confidence interval; CPVI, circumferential pulmonary vein isolation; HR, hazard ratio; LVA, low voltage area in left atrium.

be extended to populations with more extensive LVA burdens remains unclear. Mohanty *et.al.*[34] reported no significant benefit by additional LVA ablation for patients with LVA > 60%.[34] Similarly, the DECAAF-II trial demonstrated that patients with a moderate LVA burden achieved more effective lesion formation compared with those with extensive fibrosis,[35] which may lead to improved outcomes in this population. Recent analyses of the DECAAF-II study have found that atrial fibrosis does not affect the left atrium uniformly and catheter ablation reduces AF burden, subsequently leading to symptom improvement post-ablation.[14,36] However, the DECAAF-II trial[25] yielded negative results across subgroups with varying levels of fibrosis burden. The underlying reasons for this discrepancy remain unclear; however, the divergent findings may result from: (i) differences in the methods used to define the diseased left atrium, with the current study utilising electrical substrate (LVAs, which may reflect various pathological changes) and DECAAF-II employing structural substrate (MRI-guided fibrosis), resulting in markedly different conceptualizations of the diseased atrium; and (ii) differences in ablation strategies, with STABLE-SR II combining LVA ablation with dechanneling, while most substrate modification strategies including DECAAF-II focused on fibrosis or LVA ablation alone.[35,37] Nevertheless, as only a small proportion of patients (13.5%) in this study had an LVA burden ≥15%, the potential benefits of additional ablation in this subgroup warrant further investigation.

In this study, age was identified as another even more important factor influencing the benefit of LVA modification. Improved outcome by LVA modification was observed in patients ≥ 65 years old, but not in younger patients. Interestingly, in the combined subgroup analysis, this benefit remained robust in patients across different LVA burdens, suggesting that age may play an independent and more important role beyond LVA burden. Previous studies have shown relatively poorer outcomes in younger new-onset AF patients,[38] as well as shared genetic factors between AF and cardiomyopathy in this population.[39,40] STABLE-SR–III trial also found LVA modification beneficial in paroxysmal AF patients aged ≥ 65 years.[31] A possible explanation may be the subtle differences in the pathophysiological process of AF between the elderly and the young: PeAF patients with LVA at a younger age may represent a distinct clinical entity, where atrial disease is more dynamic and less influenced by age-related remodelling, rendering LVA modification less beneficial.[41] Another crucial explanation is the low prevalence of LVAs in younger patients. It is well known that LVA is associated with aging.[42–44] A multicenter study demonstrated that significant left atrial LVAs are predominantly present in PeAF patients aged ≥ 60 years, which is rarely observed in younger patients (<60 years).[13] This aligns with our findings: only a small proportion of younger patients had high LVA burden (8/83, 9.6%). Given their relatively low LVA burden, younger patients may have a less arrhythmogenic substrate, which may explain the limited benefit of additional LVA modification in this population. However, due to the small number of younger patients with an LVA burden ≥15% ($n = 8$), it remains unclear whether this discrepancy reflects underlying age-related pathophysiological differences or is a result of limited statistical power in this subgroup. Future studies with larger sample sizes are needed to clarify this issue.

Overall, this study highlighted tailored ablation strategies in PeAF patients with LVAs, potentially based on age. Additional LVA ablation may be beneficial for those aged ≥ 65 years. However, these results should be interpreted with caution, as several factors limit the ability to draw definitive conclusions: First, when analyzing only patients with LVAs, no

significant difference in recurrence was observed between the CPVI-alone and CPVI-plus groups (37.1% vs. 31.0%), indicating that additional LVA modification did not consistently improve outcomes in this subset. Second, while multivariate analysis identified age and LVA burden ≥15% as potential factors influencing recurrence, only age and BMI were incorporated into one model, limiting the robustness of these findings. Lastly, the small sample size, particularly the limited number of patients with LVA burden ≥15% (10 and 8 patients in each subgroup, respectively), further restricts the statistical power of the results. Thus, larger, well-powered randomized controlled trials are needed to draw a solid conclusion.

Limitations

First, setting the presence of LVAs in the left atrium as the key inclusion criterion, participants of this substudy were selected after the randomisation step of the original trial. Although this study is based on a randomized trial, the analysis of LVA was conducted post-randomisation, which may introduce potential biases and limit the advantages of the original randomisation process. Moreover, given the multiplicity of analyses performed, the results should be interpreted with caution. Second, the sample size is small after excluding patients without LVAs, especially in subgroup of patients with an LVA burden ≥ 15% ($n = 18$), rendering the possibility of introducing Type II errors, i.e. failure to identify results that should have been significant. Third, continuous rhythm monitoring approaches such as wearable or implantable devices were not used during follow-up, which led to the underestimation of AF recurrence. However, the impact is considered minimal as the strategy is balanced between the two groups.

Conclusions

In patients with PeAF, age may be a factor influencing the potential benefit of additional LVA modification. Our findings suggest that LVA ablation following CPVI may offer added benefits for older patients (≥65 years). However, given the small sample size of patients with an LVA burden ≥15%, the potential role of LVA burden in the benefits of substrate modification remains highly uncertain. Therefore, these results should be interpreted with caution and considered as hypothesis-generating. Larger, well-powered randomized controlled trials are necessary to validate these observations and draw more definitive conclusions.

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Conflict of interest: None declared.

Data availability

Data are available on request from the authors. The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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