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Pulmonary Vein Isolation With Optimized Linear Ablation vs Pulmonary Vein Isolation Alone for Persistent AF
The PROMPT-AF Randomized Clinical Trial

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IMPORTANCE Success rates of pulmonary vein isolation (PVI) are modest for persistent atrial fibrillation (AF). Additional linear ablation beyond PVI has not been proved superior to PVI alone in randomized trials. Ethanol infusion of the vein of Marshall (EIVOM) facilitates ablation at the mitral isthmus and may lead to improved effectiveness of a linear ablation strategy.

OBJECTIVE To determine whether linear ablation with radiofrequency energy combined with EIVOM added to PVI improves sinus rhythm maintenance compared with PVI alone in patients with persistent AF.

DESIGN, SETTING, AND PARTICIPANTS The PROMPT-AF trial is an investigator-initiated, multicenter, open-label, randomized trial involving 12 tertiary hospitals in China. A total of 498 patients aged 18 to 80 years, with AF persisting for more than 3 months, undergoing first-time AF ablation, were enrolled and randomized from August 27, 2021, to July 16, 2023.

INTERVENTIONS Patients were randomized to undergo PVI alone or PVI plus EIVOM and linear ablation (intervention). The latter group first underwent EIVOM, followed by PVI and linear ablation of the left atrial roof, mitral isthmus, and cavotricuspid isthmus.

MAIN OUTCOMES AND MEASURES The primary end point was freedom from any documented atrial arrhythmias lasting more than 30 seconds, without the use of antiarrhythmic drugs within 12 months. Secondary outcomes included freedom from atrial arrhythmia recurrence, AF, atrial arrhythmia recurrence after multiple procedures, and documented atrial tachycardia or atrial flutter with or without antiarrhythmic drugs; AF burden; and improvement in quality of life. Patients were monitored with wearable single-lead electrocardiographic (ECG) patches, worn for 24 hours a week, supplemented by symptom-triggered ECGs and Holter monitoring.

RESULTS Among 498 randomized patients, 495 (99.4%) were included in the primary analysis (mean age, 61.1 years [SD, 9.7] years, 361 male [72.9%]). After 12 months, 174 of 246 patients (70.7%) assigned to undergo PVI plus EIVOM and linear ablation and 153 of 249 patients (61.5%) assigned to undergo PVI alone remained free from atrial arrhythmias without taking antiarrhythmic drugs (hazard ratio, 0.73; 95% CI, 0.54-0.99, $P = .045$). The intervention effect was consistent across all prespecified subgroups. The comparison of secondary outcomes did not demonstrate significant results.

CONCLUSION Among patients with persistent AF, linear ablation combined with EIVOM in addition to PVI significantly improved freedom from atrial arrhythmias within 12 months compared with PVI alone.

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Visual Abstract
Editorial
Supplemental content

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Pulmonary vein isolation (PVI) has been the cornerstone of catheter ablation for the treatment of atrial fibrillation (AF). However, PVI alone is less effective for persistent AF compared with paroxysmal AF, notably in patients with episodes lasting longer than 3 months. Therefore, many ablation strategies extending beyond PVI have been considered for persistent AF.[1-4] Linear ablation, derived from the Cox-Maze surgical technique, is one of the strategies employed in this context. Nevertheless, the incremental benefit of linear ablation beyond PVI for persistent AF has not been demonstrated in prospective randomized trials, primarily due to difficulties in achieving durable lesions.[2,5,6] Achieving mitral isthmus block remains a significant challenge despite optimal contact force sensing and power settings.[7] Creation of linear lesion using radiofrequency ablation may be proarrhythmic and may increase the incidence of left atrial tachycardias,[8] limiting the application of linear ablations when treating persistent AF.

Prospective multicenter studies of linear ablation with durable bidirectional conduction block are needed. Ethanol infusion via the vein of Marshall (EIVOM) effectively creates chemical lesions affecting both epicardial and endocardial mitral isthmus.[9] The Vein of Marshall Ethanol for Unablated Persistent AF (VENUS) trial[10,11] has demonstrated the potential benefits of EIVOM in improving rhythm outcomes in patients with persistent AF, with post hoc analyses suggesting a correlation between these outcomes and successful mitral isthmus block. However, a linear ablation strategy optimized with EIVOM alongside PVI compared with PVI alone has yet to be compared in a randomized clinical trial. Although the latest expert consensus indicated that EIVOM may be reasonable for persistent AF ablation, it is still categorized as an area of uncertainty.[1]

The Prospective Randomized Comparison Between Upgraded 2C3L Versus PVI Approach for Catheter Ablation of Persistent Atrial Fibrillation (PROMPT-AF) trial aimed to evaluate the efficacy of a linear ablation strategy with radiofrequency energy—incorporating mitral isthmus, left atrial roof, and cavotricuspid isthmus ablation—combined with EIVOM and PVI. This study investigated whether this combined approach is more effective than PVI alone in maintaining sinus rhythm in patients with persistent AF.

Key Points

Question Does the addition of linear ablation combined with ethanol infusion via the vein of Marshall (EIVOM) to pulmonary vein isolation (PVI) improve rhythm outcomes for patients with persistent atrial fibrillation (AF)?

Findings In this randomized clinical trial that included 498 patients with persistent AF undergoing first-time ablation, linear ablation combined with EIVOM significantly improves freedom from atrial arrhythmia recurrence without antiarrhythmic drugs (70.7% vs 61.5%; hazard ratio, 0.73).

Meaning Linear ablation combined with EIVOM provides additional benefit in rhythm outcomes for the ablation of persistent AF.

Methods

Trial Design

The PROMPT-AF trial was an investigator-initiated, multicenter, open-label, randomized study conducted across 12 tertiary hospitals in China. The principal investigators and the steering committee have designed the trial, with details published elsewhere.[12] The full protocol and statistical analysis plan are available in Supplement 1. Ethics approval has been obtained from the institutional review boards of each participating center. This study followed the Consolidated Standards of Reporting Trials (CONSORT) guideline.

Study Population

Patients were eligible for inclusion if they were aged 18 to 80 years, diagnosed with persistent AF (with a sustained AF episode of at least 3 months), refractory to at least 1 antiarrhythmic drug, and had no prior history of AF ablation. Exclusion criteria included paroxysmal AF, a left atrial diameter greater than 60 mm, a left ventricular ejection fraction of less than 30%, a life expectancy of less than 1 year, and any contraindication to catheter ablation or anticoagulation. Detailed inclusion and exclusion criteria are provided in Supplement 1.

Randomization

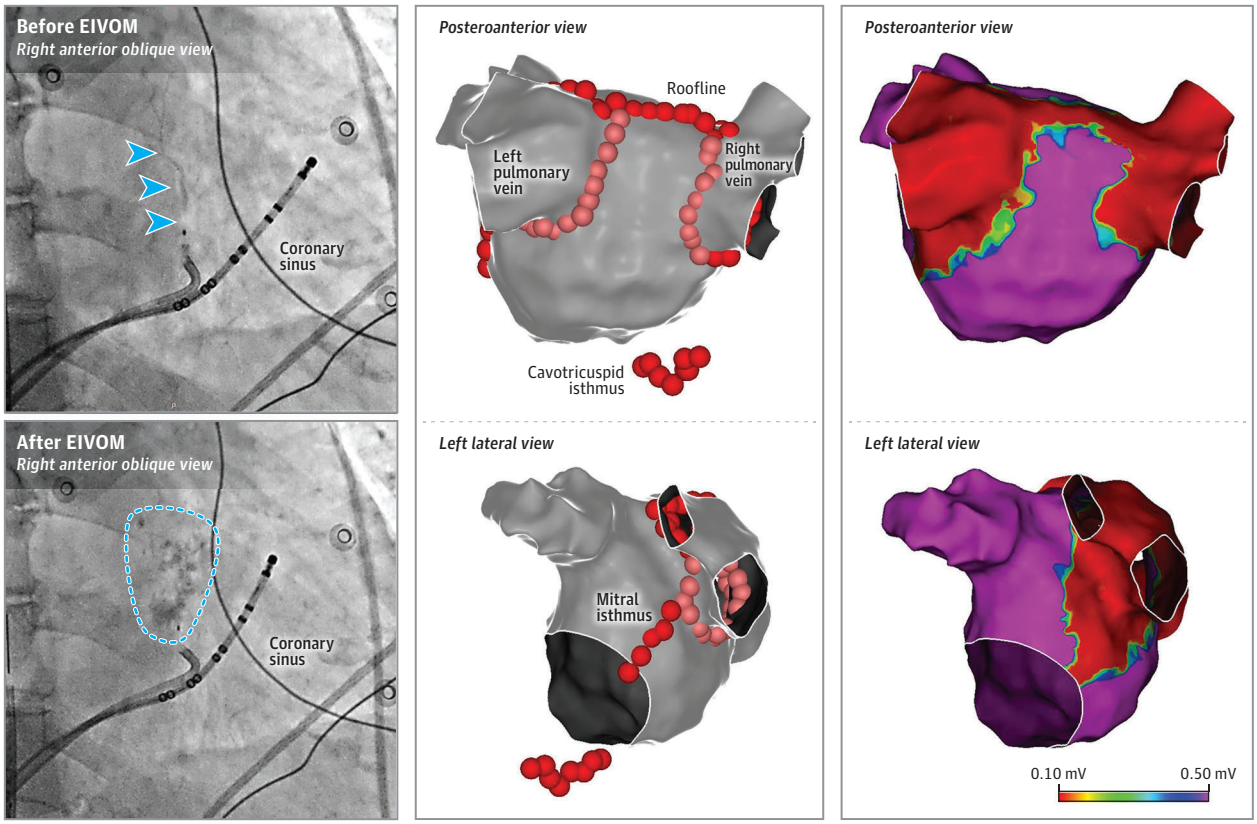
Patients were randomly assigned in a 1:1 ratio to PVI plus EIVOM and linear ablation or to PVI alone. Randomization was performed using a computerized central randomization system. The randomization used minimization, including an 80% probabilistic element with stratification for the randomization site and sex. The randomization was hosted by the Heart Health Research Center in Beijing, China.

Study Procedures

Patients assigned to the intervention (PVI plus EIVOM and linear ablation) underwent EIVOM first, followed by bilateral PVI and linear ablation at the mitral isthmus, left atrial roof, and cavotricuspid isthmus, as depicted in **Figure 1**. Technical details regarding EIVOM and linear ablation have been described elsewhere[13] and in Supplement 1. The procedural end point was successful PVI and bidirectional block of the ablation lines, validated through differential pacing techniques and activation mapping after restoring sinus rhythm. For patients assigned to PVI alone, the procedural end point focused solely on PVI without additional substrate ablation. For both randomized groups, cardioversion was conducted if sinus rhythm was not restored after ablation. If organized atrial tachycardia was identified during the ablation procedure, ablation targeting critical isthmus or focal activation was allowed. A fixed procedural flow for each group is detailed in Supplement 1.

All ablations in this study were performed using a 3-dimensional anatomical mapping system (CARTO, Biosense-Webster Inc) with irrigated-tip, contact force catheters (ThermoCool SMARTTOUCH Catheter or ThermoCool SMARTTOUCH Surround Flow Catheter, Biosense-Webster Inc) using a power control mode. Ablation index was employed to guide lesion quality, targeting values of 500 to 550 in the anterior wall, 350 to 400 in the posterior wall, 450 to 500 in the

Figure 1. Linear Ablation Combined With Ethanol Infusion via the Vein of Marshall in Addition to Pulmonary Vein Isolation



A, EIVOM was the first step of the procedure. The upper panel shows the selective VOM venography (blue arrows) acquired via an over-the-wire balloon. The lower panel shows contrast staining (blue chain) after ethanol infusion. B, After EIVOM, bilateral pulmonary vein isolation (PVI) and linear ablation in the roof, mitral isthmus, and cavotricuspid isthmus were performed. C, Voltage map at the end of the procedure.

cavotricuspid isthmus and roofline, and 550 to 600 in the mitral isthmus.[7,14]

Study Outcomes

The primary end point of the study was freedom from any documented atrial arrhythmia, including AF, atrial tachycardia or atrial flutter episodes lasting longer than 30 seconds without antiarrhythmic drugs, for 12 months after the index ablation procedure, excluding a 3-month blanking period. The continuation or reinitiation of class I or class III antiarrhythmic drugs after the 3-month postablation blanking period, as well as electric cardioversion or catheter ablation for any atrial arrhythmias, were considered treatment failures for the primary end point.

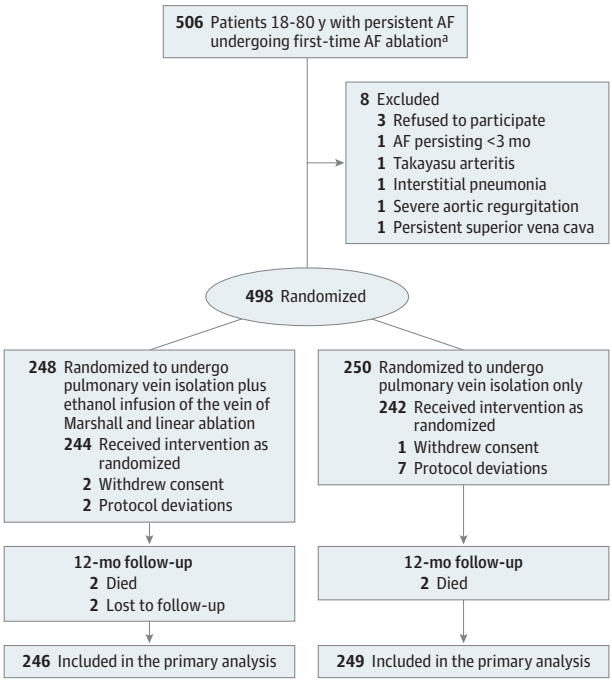
Secondary end points with or without antiarrhythmic drugs included freedom from atrial arrhythmias, atrial arrhythmias following repeated ablation, atrial tachycardia or flutter and assessment of AF burden during the 12 months after the procedure (percentage of time in AF, in single-lead electrocardiographic [ECG] patches and Holter monitorings), also excluding the 3-month blanking period. Changes in quality of life from baseline to 12 months after the procedure were evaluated using the AF Effect on Quality of Life (AFQT) and the EuroQol Health-Related Quality-of-Life 3-Level (EQ-5D-3L) instruments. Additionally, acute and subacute procedural complications were documented. Detailed definitions for the secondary end points are provided in the study protocol (Supplement 1).

Patient assessments were conducted at 1, 3, 6, and 12 months following the initial ablation. Antiarrhythmic drugs were discontinued after the blanking period. Anticoagulation therapy was maintained for a minimum of 3 months after the procedure and thereafter according to guideline recommendations.[15,16] Continuous rhythm monitoring was performed using a single-lead ECG patch that patients were required to wear for a period of at least 24 hours each week during the entire 12 months of follow-up. Additional rhythm data—including but not limited to Holter monitoring, other licensed wearable devices, and symptom-triggered ECGs—were also collected. Atrial arrhythmias identified by wearable devices were adjudicated by 2 independent physicians who were blinded to the randomization.

Statistical Analysis

The statistical analysis plan was published prior to data availability. Sample size estimation was based on findings from previous studies, anticipating atrial arrhythmia recurrence in 40% for PVI plus EIVOM and linear ablation and 55% for PVI alone.[17]

Figure 2. Patient Recruitment and Study Flow of the PROMPT-AF Trial



AF indicates atrial fibrillation.

[a]Screening log was not systematically collected from the participating centers

A total of 224 patients included in each group would provide 90% power at a 2-sided type I error probability of .05. Accounting for a 10% loss to follow-up, a target enrollment of 249 patients per group was deemed necessary.

The primary analysis was performed according to the modified intention to treat principle, including all consented participants who had been randomized and had undergone an ablation procedure. Crossovers were not permitted for the initial ablation. We assessed time to first recurrence by the Kaplan-Meier product limit method and compared groups with the log-rank test, with patients censored at death, lost to follow-up, or 12 months after the procedure. The proportional hazard assumption was examined by the scaled Schoenfeld residuals test. Cox proportional hazard regression was applied to estimate hazard ratios (HRs). Stratified log-rank test, as well as Cox proportional hazard regression adjusted for stratification factors, were performed as a sensitivity analysis. We did no interim analyses. Subgroup analyses have been prespecified in the study protocol (Supplement 1), and interactions between each subgroup factor and treatment arm were also assessed.

Continuous baseline variables were presented as mean (SE) or as percentiles (median, 25th, and 75th percentiles) if skewed. Discrete variables were summarized as frequencies and percentages. The *t* test or the nonparametric Wilcoxon rank-sum test was employed as appropriate for comparisons of continuous variables. For group comparisons of discrete baseline variables, Pearson χ^2 test or Fisher exact test was used as appropriate. A 2-sided *P* value of less than .05 was considered statistically significant. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc).

Table 1. Baseline Characteristics of Study Population

	No. (%) of patients	
	PVI + EIVOM and linear ablation (n = 246)	PVI alone (n = 249)
Age, mean (SD), y	61.3 (9.9)	61.0 (9.5)
≥65	103 (41.9)	97 (39)
Female	66 (26.8)	68 (27.3)
Male	180 (73.2)	181 (72.7)
Duration of persistent AF diagnosis, median (IQR), months	12 (5-24)	12 (4-24)
Long-standing persistent AF[a]	113 (45.9)	89 (35.7)
Hypertension	136 (55.3)	130 (52.2)
Diabetes	32 (13)	27 (10.8)
Ischemic stroke or TIA	14 (5.7)	17 (6.8)
Coronary heart disease[b]	11 (4.5)	5 (2)
Heart failure	22 (8.9)	31 (12.4)
New York Heart Association >II[c]	13 (5.3)	7 (2.8)
CHA_2DS_2-VASc score, median (IQR)[d]	1 (1-2)	1 (0-2)
LA diameter		
Mean (SD), mm[e]	42.8 (6.1)	42.8 (4.5)
>45 mm[e]	84 (34.1)	83 (33.3)
Ejection fraction, mean (SD), %[e]	61.3 (7.6)	61.1 (8)
Ejection fraction <50%[e]	15 (6.1)	19 (7.6)

Abbreviations: AF, atrial fibrillation; EIVOM, ethanol infusion via the vein of Marshall; LA, left atrium; PVI, pulmonary vein isolation; TIA, transient ischemic attack.

[a] Defined as AF persisting more than 12 months.

[b] Defined as any coronary stenosis of 50% or more under coronary angiography or computed tomographic angiography.

[c] A categorization of cardiac function, ranging from class I to class IV. Higher class indicates worse cardiac function.

[d] A score assessing individual risk of ischemic stroke in patients with nonvalvular AF, ranging 0 ≈ 9. A higher score indicates higher risk of ischemic stroke.

[e] Echocardiogram was performed at baseline before the procedure.

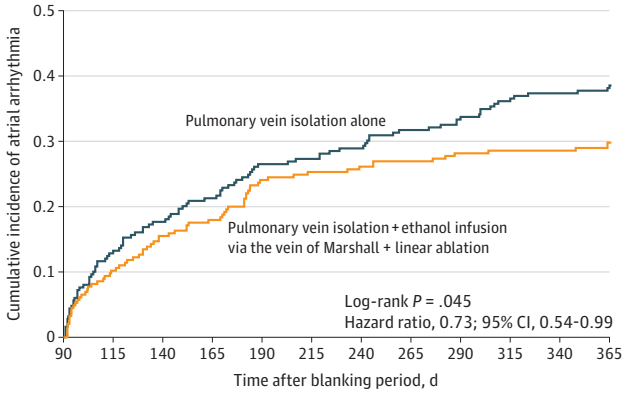
Results

Patients

A total of 498 patients (mean age, 61.1 [SD, 9.7] years, 361 male [72.9%]) were enrolled and randomized from August 27, 2021, to July 16, 2023 (**Figure 2**). Among these, 495 patients completed the procedure and were included in the primary analysis; the other 3 patients withdrew consent before ablation. Two of 246 patients (0.8%) randomized to the intervention group and 7 of 249 patients (2.8%) randomized to PVI alone who had undergone but had not adhered to the assigned ablation protocol (details in eTable 1 in Supplement 2) were included in the primary analysis as randomized. Baseline characteristics are detailed in **Table 1**.

During the follow-up period, 2 patients in intervention group dropped out after the procedure, and 4 patients died (2 in each group). During the 12-month follow-up, the mean (SD) rhythm monitoring time for the study population was 13.0 (8.0) hours per week, with no significant difference between groups (12.7 [8.7] hours for the intervention group vs 13.4 [8.4] hours for the PVI alone group, *P* = .39). Further details regarding

Figure 3. Freedom From Recurrence of Atrial Arrhythmias Without Antiarrhythmic Drugs



Cumulative No.												
Pulmonary vein isolation + ethanol infusion via the vein of Marshall + linear ablation												
Event	0	25	38	44	59	62	64	66	69	70	70	72
Death	0	0	0	0	0	0	0	0	0	0	0	2
Atrial fibrillation	0	23	36	41	47	50	51	53	56	56	57	58
Redo procedure	0	1	5	6	7	8	9	10	10	10	11	11
Pulmonary vein isolation alone												
Event	0	33	44	53	66	68	72	79	84	91	93	96
Death	0	0	0	0	0	1	2	2	2	2	2	2
Atrial fibrillation	0	27	34	42	48	49	54	62	64	70	74	75
Redo procedure	0	7	7	9	9	9	10	16	17	17	18	20

Table 2. Primary and Secondary Outcomes

	No. (%)		(95% CI)		
	PVI + EIVOM and linear ablation (n = 246)	PVI alone (n = 249)	Absolute difference	Hazard ratio	*P* value
Primary outcome without antiarrhythmic drugs : 12-mo freedom from					
Atrial arrhythmias after single ablation	174 (70.7)	153 (61.5)	9.2 (1.0 to 17.6)	0.73 (0.54 to 0.99)	.045
Secondary outcome with or without antiarrhythmic drugs: 12-mo freedom from					
Atrial arrhythmias	180 (73.2)	161 (64.7)	8.5 (0.4 to 16.6)	0.74 (0.53 to 1.01)	.06
AF	188 (76.4)	174 (69.9)	6.5 (−1.2 to 14.3)	0.77 (0.55 to 1.09)	.14
Atrial arrhythmias after multiple ablations	191 (77.6)	181 (72.7)	5.1 (−2.6 to 12.6)	0.81 (0.57 to 1.16)	.31
AFL or AT	212 (86.2)	206 (82.7)	3.5 (−2.9 to 9.8)	0.79 (0.51 to 1.24)	.25

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; EIVOM, ethanol infusion via the vein of Marshall; PVI, pulmonary vein isolation.

rhythm monitoring adherence are provided in eFigure 1 in Supplement 2.

Procedural Characteristics

The procedural characteristics are presented in eTable 2 in Supplement 2. The combination of linear ablation plus EIVOM was associated with a longer mean (SD) procedure time (188.0 [54.1] min vs 140.8 [39.7] min, *P* < .001) and fluoroscopy time (15.9 [26.3] min vs 5.1 [5.9] min, *P* < .001). Bilateral PVI was successfully achieved in all patients except for 2 patients (1 in each group).

Among patients in the intervention group, EIVOM was successfully performed in 209 patients (85%). The VOM was not visualized under venography in 30 patients (12.2%), whereas VOM cannulation failed in another 7 patients due to complicated anatomy. Complete linear block was achieved in 233 patients (94.3%) for the cavotricuspid isthmus, 215 patients (87.4%) for the roofline, and 215 patients (87.4%) for the mitral isthmus. Additional ablation with the coronary sinus was performed in 154 patients (62.6%) to achieve mitral isthmus block.

Primary Analysis

Within 12 months of the procedure, freedom from any documented atrial arrhythmia—including AF, atrial tachycardia, or atrial flutter episodes lasting longer than 30 seconds, in the absence of antiarrhythmic drugs—was achieved in 174 patients (70.7%) randomized to the intervention group and 153 patients (61.5%) randomized to PVI alone. The HR was 0.73 (95% CI, 0.54-0.99; *P* = .045; **Figure 3**). The test for proportional hazard assumption is shown in eFigure 2 in Supplement 2. The Cox proportional hazard regression with stratification of sex and randomization site and the stratified log-rank tests are shown in eTable 3 in Supplement 2.

Secondary End Points

Secondary outcomes are described in **Table 2** and eFigures 3 through 6 in Supplement 2. Freedom from any atrial arrhythmia recurrence, with or without antiarrhythmic drugs, was achieved in 180 patients (73.2%) assigned to the intervention and 161 (64.7%) assigned to PVI alone (HR, 0.74; 95% CI, 0.53-1.01). The number of patients free from AF episodes was 188

Table 3. Procedure-Related Adverse Events

	No. of adverse events	
	PVI + EIVOM and linear ablation	PVI
Cardiac		
Tamponade		
Requiring pericardiocentesis	1	1
Requiring surgery	1	0
Pericarditis or pericardial effusion not requiring drainage[a,b]	7	0
Coronary event[c]	1	1
Third-degree atrioventricular block	0	1
Vascular		
Pseudoaneurysm of femoral artery	1	1
Deep venous thrombosis	1	0
Other		
Postprocedural fever	1	1
Antiarrhythmic drugs related complication	0	1

Abbreviations: EIVOM, ethanol infusion via the vein of Marshall; PVI, pulmonary vein isolation.

[a] Diagnosis of pericarditis should meet at least 2 of the following criteria: pericarditis chest pain; pericardial rubs; incident widespread ST elevation or PR suppression on surface electrocardiograph (ECG); or pericardial effusion.

[b] Defined as mild to moderate pericardial effusion without ECG changes and pericarditis chest pain, identified by opportunistic or other symptom-triggered echocardiograms within 30 days after the procedure.

[c] Including transient ST-T elevation with chest pain during the procedure, which does not require further coronary intervention or prolonged hospitalization.

(76.4%) in the intervention group and 174 (69.9%) in the PVI alone group (HR, 0.77; 95% CI, 0.55-1.09). Additionally, 34 patients (13.8%) in the intervention group and 43 patients (17.3%) in the PVI alone group had documented atrial flutter or atrial tachycardia (HR, 0.79; 95% CI, 0.51-1.24). During the 12-month follow-up, 11 patients in intervention group and 20 in the PVI alone group underwent a redo ablation. Freedom from atrial arrhythmia recurrence after multiple procedures at 12-month was achieved in 191 patients (77.6%) in the intervention group and 181 (82.7%) in PVI alone group (HR, 0.81; 95% CI, 0.57-1.16).

The median of AF burden throughout the 12-month follow-up, excluding the 3-month blanking period but including patients taking antiarrhythmic drugs or after redo procedures, was 0.0% (IQR, 0.0% to 0.0%) for the intervention group and 0.0% (IQR, 0.0% to 0.1%) for the PVI alone (P = .67). Improvement in quality of life after the procedure observed at 12 months in both groups is shown in eTable 4 in Supplement 2, without intergroup difference. For AFEQT the median was −26 (IQR, −46 to −10) vs −27 (IQR, −44 to −11; P = .94), and for EQ-5D-3L, the median was 10 (IQR, 0 to 20) vs 10 (IQR, 0 to 25; P = .08).

Prespecified Subgroup Analysis

The comparison of the primary outcome was conducted in 8 prespecified subgroups, including age 65 years or older, sex, long-standing persistent AF (AF persisting ≥1 year), left atrial diameter 45 mm or more, left atrial volume greater than the 50th percentile of the study population, heart failure, left ventricular ejection fraction less than 50%, and the presence of low-voltage areas in the left atrium. The effect of the intervention remained consistent across all subgroups (eFigure 7 in Supplement 2).

Adverse Events

Procedure-related adverse events are described in **Table 3**. There was no significant difference in the overall incidence of procedural-related adverse events between groups (P = .15). However, 7 patients assigned to the intervention group experienced pericarditis or pericardial effusion compared with none in the PVI alone group.

All serious adverse events throughout the study are described in eTable 5 in Supplement 2, without significant intergroup difference (P = .36). Four patients died during the 12-month follow-up. All deaths occurred after the blanking period. Three patients died after atrial arrhythmia recurrence, and 1 patient died without atrial arrhythmia recurrence. In patients randomized to intervention group, 1 patient died of COVID-19 infection and 1 patient died of myocardial infarction. Among patients randomized to PVI alone, 1 died of intracranial bleeding and 1 died of heart failure. All deaths were considered unrelated to the procedure by the event committee.

Discussion

The PROMPT-AF trial is the first randomized study to demonstrate that a linear ablation strategy including EIVOM in addition to PVI significantly reduced atrial arrhythmia recurrence compared with PVI alone. Specifically, freedom from atrial arrhythmia recurrence without antiarrhythmic drugs was achieved in 70.7% of patients assigned to PVI plus EIVOM and linear ablation compared with 61.5% assigned to PVI alone. The finding remained consistent across all prespecified subgroups.

Although various linear ablation strategies have been explored, none have conclusively improved rhythm outcomes when added to PVI in randomized trials.[2,4] Linear ablation targeting anatomical isthmuses aims to eliminate the substrate maintaining AF through atrial compartmentalization, effectively preventing the proliferation of AF drivers within the atria.[18] This approach has shown promising results in surgical ablation.[19] However, when applied to catheter ablation, the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II[2] (STAR-AF II) study failed to demonstrate additional benefit of linear ablation over PVI alone, primarily due to less durable linear lesions. Besides not using contact-force-sensing catheters, the lack of benefit with linear lesions in STAR-AF II may also be explained by the use of radiofrequency alone.

Mitral isthmus ablation represents a significant technical challenge that hinders the broader clinical application of linear ablation strategies, even with the progress in power settings and contact-force technology.[7] Perimitral flutter subsequent to the unblocked or less durable mitral isthmus lesion has been identified as the most common type of recurrent

tachycardia in patients undergoing linear ablation.[20,21] Epicardial conduction via the ligament of Marshall hampers the achievement and validation of mitral isthmus block.[22-25] The use of EIVOM not only abolishes epicardial conduction but also facilitates mitral isthmus ablation by creating chemical lesions in the mid to distal mitral isthmus where reconnections are most prevalent,[26] thereby reinforces the durability of mitral isthmus lesions.[27] Randomized trials have also shown that EIVOM significantly enhances the mitral isthmus block rate and reduces the incidence of acute reconnections,[28,29] leading a current expert consensus to recommend its use to support mitral isthmus ablation.[1] In this study, mitral isthmus block was achieved in 87.4% patients, compared with only 75% in the STAR-AF II trial, which may, in part, explain the discrepancy of the results between the 2 trials. Meanwhile, EIVOM may also benefit persistent AF ablation in other aspects, including facilitating left pulmonary vein isolation,[30] eliminating nonpulmonary vein triggers,[31] and modulating cardiac autonomic nerves,[32] although these effects have only been reported in small observational studies.

Linear ablation strategies optimized with EIVOM for persistent AF have only been preliminarily assessed for feasibility and safety in observational studies.[13,33] Although the VENUS[10] randomized trial indicated a benefit of EIVOM in conjunction with catheter ablation, it was not a pure comparison with PVI alone because more than 95% of patients overall underwent either posterior wall isolation or ablation of complex fractionated electrograms. Notably, a post hoc analysis of the VENUS trial revealed an interaction between mitral isthmus block and the effects of EIVOM,[11] further supporting the establishment of a linear ablation strategy combined with EIVOM.

Despite these improvements, there remains potential for further refinement of this ablation strategy to enhance atrial compartmentalization and prevent arrhythmia recurrence. In the present study, 12.6% of mitral isthmus attempts did not achieve linear block, which could be partly attributed to undetectable VOM or difficulties in VOM cannulation. Additionally, residual conduction along the annulus side of the mitral isthmus, particularly through epicardial connections via the coronary sinus myocardial sleeves, often remains unaddressed during the procedure.

This current trial also highlighted that the roofline block was achieved in only 87.7%, indicating that this area may pose an underestimated challenge when performing linear ablation. The presence of adipose tissue between the septopulmonary and septoatrial bundles complicates the creation of transmural lesions in this region.[34] Residual epicardial conduction may also pose a risk for macroreentrant tachycardias.[35] Targeting the thinner areas of the posterior wall with a floor line could better intercept the anatomical isthmus, although this approach carries an increased risk of esophageal injury. Meanwhile, targeting the posterior wall alone may be insufficient.[4] Macroreentrant tachycardias are frequent after posterior wall ablation.[8,36] In the extended follow-up of CAPLA trial,[36] flutters dependent on mitral or cavotricuspid isthmus after posterior wall ablation accounted for 17.3% and 11.5% of the redo procedure in the PVI plus posterior wall isolation group, respectively, indicating the importance of integrated anatomical ablation strategy. The ongoing Marshall Ethanolization, Pulmonary Vein Isolation and Line Completion for Ablation of Persistent Atrial Fibrillation (Marshall-PLAN) randomized trial (NCT04681872), which employs a similar lesion set to this current trial, may yield further insights for clinical practice. Moreover, the advent of pulsed field ablation allows for the ability to create posterior wall lesions with increased safety and efficacy.[37] The feasibility of linear ablation with pulsed field energy is also being investigated,[38] and pulsed field ablation may ultimately play a role in addressing the VOM. Whether an ablation strategy including linear lesions using pulsed field ablation is superior to PVI alone remains to be confirmed in randomized trials.

Although adding a linear ablation strategy optimized with EIVOM to PVI improves success rate of catheter ablation for persistent AF, it comes at a cost. This approach inevitably increases procedural time and fluoroscopy exposure, which could be improved as the operators gets more technically proficient about EIVOM and linear ablation. Although the incidence of procedural adverse events did not differ significantly between groups, 7 patients assigned to PVI plus linear ablation experienced pericarditis or pericardial effusion not requiring drainage, which may result in additional medical therapy and prolonged hospitalization, compared with none in PVI group.

Limitations

The present trial has several limitations. First, implantable loop recorders for continuous monitoring of the primary end point were not used. This may underestimate atrial arrhythmia recurrence and explain the relatively high success rate for a persistent AF population. Patients wore single-lead ECG patches for a 24-hour period each week. These wearable devices are noninvasive, making them more acceptable to patients and contributing to a less selective enrollment process. Furthermore, based on a post hoc analysis from the Cryoballoon Versus Contact-Force Irrigated Radiofrequency Catheter Ablation (CIRCA-DOSE) trial,[39] the 13-hour-weekly average monitoring time aligns well with loop recorders in assessing AF burden. Second, the PROMPT-AF trial exclusively included patients with persistent AF lasting longer than 3 months. As a result, these findings may not be generalizable to patients with shorter episodes of persistent AF.

Conclusions

Among patients with persistent AF, linear ablation combined with EIVOM in addition to PVI significantly improved freedom from atrial arrhythmias within 12 months compared with PVI alone.

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