Catheter Ablation With Morphologic Repetitiveness Mapping for Persistent Atrial Fibrillation

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Abstract

**IMPORTANCE** Catheter ablation for persistent atrial fibrillation (AF) has shown limited success.

**OBJECTIVE** To determine whether AF drivers could be accurately identified by periodicity and similarity (PRISM) mapping ablation results for persistent AF when added to pulmonary vein isolation (PVI).

**DESIGN, SETTING, AND PARTICIPANTS** This prospective randomized clinical trial was performed between June 1, 2019, and December 31, 2020, and included patients with persistent AF enrolled in 3 centers across Asia. Data were analyzed on October 1, 2022.

**INTERVENTION** Patients were assigned to the PRISM-guided approach (group 1) or the conventional approach (group 2) at a 1:1 ratio.

**MAIN OUTCOMES AND MEASURES** The primary outcome was freedom from AF or other atrial arrhythmia for longer than 30 seconds at 6 and 12 months.

**RESULTS** A total of 170 patients (mean [SD] age, 62.0 [12.3] years; 136 men [80.0%]) were enrolled (85 patients in group 1 and 85 patients in group 2). More group 1 patients achieved freedom from AF at 12 months compared with group 2 patients (60 [70.6%] vs 40 [47.1%]). Multivariate analysis indicated that the PRISM-guided approach was associated with freedom from the recurrence of atrial arrhythmia (hazard ratio, 0.53 [95% CI, 0.33-0.85]).

**CONCLUSIONS AND RELEVANCE** The waveform similarity and recurrence pattern derived from high-density mapping might provide an improved guiding approach for ablation of persistent AF. Compared with the conventional procedure, this novel specific substrate ablation strategy reduced the frequency of recurrent AF and increased the likelihood of maintenance of sinus rhythm.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT05333952

Key Points

**Question** Do periodicity and similarity (PRISM) mapping improve ablation results for persistent atrial fibrillation (AF)?

**Findings** This single-blinded randomized clinical trial enrolled 170 patients, including 85 receiving PRISM mapping and 85 receiving a standard approach. The PRISM-guided approach was associated with freedom from the recurrence of AF.

**Meaning** The specified substrate modification guided by PRISM mapping may eliminate AF sources and maintain sinus rhythm.

Invited Commentary

Supplemental content

Author affiliations and article information are listed at the end of this article.
Introduction

Atrial fibrillation (AF) is the most frequently diagnosed arrhythmia and causes significant morbidity and mortality worldwide. Pulmonary vein isolation (PVI) is the cornerstone of AF ablation, although it remains associated with suboptimal results for persistent AF. The optimal ablation strategy for persistent AF remains undetermined, and an alternative approach should be explored. A new driver-guided method has emerged as an alternative approach, and other various mapping methods have yielded some encouraging results in small populations.

Previous prospective studies by Lin et al. and Narayan et al. evaluated the substrate modification guided by repetitive and/or organized similar electrography to eliminate rotors and focal sources. From these studies, electrogram similarity analysis could be used to detect regions with stable activation waveforms in the atria regardless of the spatial wavefront propagations. In a previous study, Lin et al. developed a mapping software to assess regional electrograms by periodicity (repeated time evolution pattern of multiple activation waves) and similarity (the degree of waveforms resembling each other), consequently named PRISM, and the PRISM-guided approach improved freedom from AF in a case-control study. We performed a prospective and multicenter trial to test the hypothesis that adding PRISM-guided ablation to PVI for persistent AF may increase the chances of maintaining sinus rhythm.

Methods

Study Design and Patient Enrollment

This study was a multicenter, randomized clinical trial, conducted at 3 hospitals, including 2 centers in Taiwan (Taipei Veterans General Hospital in Taipei and Tzu-Chi General Hospital in Hualien) and 1 center in Japan (Makiminato Central Hospital in Makiminato). The trial protocol is found in Supplement 1. This was a preplanned analysis of the parent trial and follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical studies. This study was designed to determine the efficacy of additional ablation based on regional electrograms assessed using PRISM in patients with persistent AF. Patients with persistent AF referred for ablation between June 1, 2019, and December 31, 2020, were enrolled. Patients were tracked until October 1, 2022. This study was approved by the institutional review board of the Taipei Veterans General Hospital. Written informed consent was obtained from all patients.

Inclusion and Exclusion Criteria

Information on patient sex was obtained from patient identity cards; data on race and ethnicity were not collected. Patients with persistent AF who were symptomatic and had intolerance of at least 1 class I or III antiarrhythmic medication were included in the study. Patients younger than 20 years were excluded from this study. Patients who underwent a previous maze procedure or with a left atrial (LA) thrombus and those with spontaneous AF termination before the procedure were also excluded from this study.

Allocation and Trial Procedures

The rhythm-control effectiveness of 2 ablation strategies for treating persistent AF was compared (PRISM-guided approach and the conventional strategy). Simple randomization was applied based on a single sequence of random assignment generated in each trial center, with a total assigned number of 86 in Taiwan and 84 in Japan (Figure 1). Patients were randomly assigned in a 1:1 ratio to PRISM mapping and ablation (group 1) or the conventional approach (group 2). The assignment to the intervention or the control group was decided prior to the procedure. Computed tomography of the pulmonary vein with 3-dimensional reconstruction and transesophageal echocardiography were performed prior to the procedures. Due to the nature of ablation procedures, the study could not be performed in a double-blind manner. The methodology of the PRISM mapping and ablation
strategy has been described in a previous publication7 (see eMethods and eFigures 1 and 2 in Supplement 2). The duration of recording bipolar electrograms is at least 10 seconds for this study. The analysis of PRISM value takes less than 5 minutes in this trial. The patients with a high PRISM value area within the PV or the PV vicinity without involving the LA body were classified as undergoing a type 1 PRISM strategy. The other patients with high PRISM value area in the LA body were classified as undergoing a type 2 PRISM strategy.

Wide Circumferential PVI and Substrate Ablation Based on PRISM

Patients assigned to group 1 underwent PRISM mapping using a mapping catheter (PentaRay; Johnson & Johnson) in the entire LA before PVI. The calculated PRISM value was then displayed in our custom software (Figure 2 and Figure 3). Wide circumferential PVI encircling the high PRISM area in the PV vicinity was performed at the Taipei Veterans General Hospital and Hualien Tzu-Chi General Hospital (n = 45).7 The radiofrequency energy was applied with a contact force range of 5 to 25 g with a maximum power of 25 to 40 W and a duration of 20 to 40 seconds in a power control mode. Pulmonary vein isolation was performed using a 28-mm cryoballoon ablation catheter (Arctic Front Advance and Arctic Front Advance Pro; Medtronic, Inc) in the Makiminato Central Hospital (n = 40). If the PRISM area was in the PV vicinity outside the lesion created by cryoablation, extension of the isolation line was performed using an ablation catheter (ThermoCool SmartTouch SurroundFlow [STSF]; Biosense Webster, Inc). If AF was not terminated during PVI, additional ablation with STSF was applied to the high PRISM areas (>315 milliseconds) with highly repetitive electrogram morphology, except if they were in the left atrial appendage area (Figure 2 and Figure 3 and eFigures 3 and 4 in Supplement 2).

The end point of the local ablation site was AF organization or termination, decreased PRISM (<=315 milliseconds, similar to the nearby region), or decreased electrogram voltage of less than 0.2 mV. Remapping of the ablation site was performed to confirm the elimination of high PRISM signals if AF persisted after the PRISM-guided approach. Cardioversion was performed to restore sinus rhythm. If AF was resolved into stable atrial tachycardia and/or flutter, the atrial tachycardia and/or flutter was mapped and ablated. Substrate mapping was performed after sinus rhythm was restored. According to the operator’s decision, the roofline gap or the mitral line gap was targeted by STSF with a confirmed bidirectional block. Non-PV triggers (if inducible) were mapped and ablated in all patients as by Higa et al11 (eMethods in Supplement 2).

Figure 1. Flowchart Describing Eligibility, Randomization, and Follow-Up of Study Patients

AF indicates atrial fibrillation.
Conventional Approach
Patients assigned to group 2 underwent LA geometry mapping using the PentaRay mapping catheter before PVI. Pulmonary vein isolation was performed using the STSF in the Taipei Veterans General Hospital and Hualien Tzu-Chi General Hospital (n = 41). In the Makiminato Central Hospital, PVI was performed using a 28-mm cryoballoon ablation catheter (n = 44). Cardioversion was applied to restore sinus rhythm if AF was not terminated during PVI. If AF was resolved into stable atrial tachycardia and/or flutter, the atrial tachycardia and/or flutter was mapped and ablated. Non-PV triggers (if inducible) were mapped and ablated in all patients as reported by Higa et al11 (eMethods in Supplement 2).

Clinical End Points
The study's primary end point was freedom from AF or other atrial tachyarrhythmias after a blanking period based on a single procedure. The secondary end points were (1) procedural termination, (2) recurrence of all atrial arrhythmias after the index procedure, and (3) safety (procedural complications).

Statistical Analysis
Normally distributed data are presented as mean (SD) values. Continuous variables were compared using the independent 2-tailed t test. Nonnormally distributed variables were compared using the Mann-Whitney test. Categorical variables are presented as number (percentage), and the χ² test was

Figure 2. Application of Catheter Ablation Based on the Type 1 Periodicity and Similarity (PRISM) Map

[Diagram images showing PRISM maps and ablation outcomes]

A, The PRISM map reveals only a high PRISM area within the left pulmonary vein (PV). B, The recurrent plot demonstrates a high PRISM value (>315 milliseconds) in the left PV and low PRISM value in the anterior wall. C, Pulmonary vein isolation enclosing the PRISM area was performed without substrate modification. The atrial fibrillation was terminated during left PV isolation. Bi indicates bipolar voltage; Carto, 3-dimensional electroanatomical mapping system (CARTO; Biosense Webster, Inc, and Johnson & Johnson); and LSPV, left superior pulmonary vein.
used for comparing the percentages between groups. The Kaplan-Meier method with the log-rank test examined the recurrence-free survival curve. Cox proportional hazards regression was also used to compare the risk between the 2 groups, with results expressed as hazard ratios with 95% CIs. Variables with an absolute standardized difference exceeding 0.10 were selected into the multivariable Cox proportional hazards regression for adjustment. Statistical significance was set at 1-sided \( P < .05 \). Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc).

**Results**

**Patient Characteristics**

One hundred and seventy patients (136 men [80.0%] and 34 women [20.0%]; mean [SD] age, 62.0 [12.3] years) with a diagnosis of persistent AF were enrolled for this study (Table 1). Hypertension was diagnosed in 105 patients (61.8%), hyperlipidemia in 24 (14.1%), type 2 diabetes in 34 (20.0%), coronary artery disease in 11 (6.5%), and thyroid dysfunction in 20 (11.8%). Twenty-eight patients (16.5%) received prior PVI for AF before enrollment (mean [SD] duration, 3.4 [2.3] years). Pulmonary vein reconnections were found in all 28 patients with prior PVI. Eighty-five patients were assigned to group 1, and the other 85 were assigned to group 2. There were no significant differences in the baseline characteristics, echocardiographic parameters, and type of persistent AF between the groups. All participants completed the 1-year follow-up, and data assessment was completed.

**Figure 3. The Application of Catheter Ablation Based on the Type 2 Periodicity and Similarity (PRISM) Map**

A, The PRISM map reveals a high PRISM area outside the pulmonary vein (PV) or vicinity (appendage, posterior wall, and mitral area). B, The recurrent plot demonstrates a high PRISM value (>315 milliseconds) in the posterior wall and mitral area. Pulmonary vein isolation was performed and the atrial fibrillation (AF) persisted. C, Additional PRISM ablation is performed over the posterior wall and mitral area. After posterior wall ablation, the AF was terminated during ablation over the mitral area. Bi indicates bipolar voltage; Carto, 3-dimensional electroanatomical mapping system (CARTO; Biosense Webster, Inc, and Johnson & Johnson).
Mapping Data
A mean (SD) of 528.25 (89.15) electrograms per patient (group 1) were used for PRISM analysis. An area with a PRISM value more than 315 milliseconds was defined as high PRISM area. Of the 85 patients assigned to group 1, 157 (mean [SD], 1.8 [0.6] per person) high PRISM areas were identified within the PV or PV vicinity and 143 (mean [SD], 1.7 [1.5] per person) within the LA body. In 28 patients in group 1 (32.9%), only high PRISM areas within the PV and PV vicinity were classified as type 1 PRISM. In the other 57 patients of group 1 (67.1%), a high PRISM area was identified in both the PV or PV vicinity and the LA body, which was classified as a type 2 PRISM. The high PRISM area of LA was summarized in eFigure 4 in Supplement 2.

In group 1, wide circumferential PVI was performed on all patients, successfully eliminating 157 high PRISM areas within or near the PV (mean [SD], 1.8 [0.6] per person). During PVI, 14 patients (16.5%) experienced AF termination (13 in type 1 PRISM and 1 in type 2 PRISM). In the 57 patients with type 2 PRISM, the high PRISM area in the LA was approached after PVI. A total of 122 high PRISM areas of LA (122 of 143 [85.3%]) were eliminated in the LA. Atrial fibrillation was terminated during PRISM-guided LA ablation in 6 patients. In 18 patients, the residual high PRISM area (n = 21) was not ablated. The PRISM area was not ablated due to location within the LA appendage (n = 12), location close to the esophagus (n = 4), and AF termination before completing the high PRISM area (n = 5). Among patients in group 2, the conventional PVI was successfully performed in all the patients. There were no significant differences in procedural parameters between the groups (Table 2 and eTable 1 in Supplement 2).

Non-PV triggers were identified in 8 patients in group 1 (9.4%) and 12 patients in group 2 (14.3%), without significant difference (P = .35). The details were summarized in eFigure 5 in Supplement 2.

No patient refused follow-up after catheter ablation. Rhythm follow-up data were obtained from implanted device recordings (pacemakers or defibrillators) in 2 patients in group 1 (2.4%) and in 3 in group 2 (3.5%). No significant monitoring differences were recorded between the groups. Patients without implanted devices underwent a regular follow-up involving 12-lead electrocardiography and 24-hour Holter monitoring.

Intraprocedural Outcome and Complication
Atrial fibrillation terminated into sinus rhythm or atrial tachycardia and/or flutter in 20 patients (23.5%) in group 1 and 11 patients (12.9%) in group 2 (P = .11). Group 1 patients experienced AF termination during PVI in 14 patients (16.5%) and during PRISM-guided substrate modification in 6 patients.

### Table 1. Patient Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 85)</th>
<th>Group 2 (n = 85)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>61.9 (11.8)</td>
<td>62.0 (12.9)</td>
<td>.95</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>68 (80.0)</td>
<td>68 (80.0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Women</td>
<td>17 (20.0)</td>
<td>17 (20.0)</td>
<td></td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.5 (3.5)</td>
<td>26.6 (4.1)</td>
<td>.80</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52 (61.2)</td>
<td>53 (62.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>12 (14.1)</td>
<td>12 (14.1)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>21 (24.7)</td>
<td>13 (15.3)</td>
<td>.18</td>
</tr>
<tr>
<td>CAD</td>
<td>4 (4.7)</td>
<td>7 (8.2)</td>
<td>.54</td>
</tr>
<tr>
<td>CHF</td>
<td>14 (16.5)</td>
<td>15 (17.6)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>7 (8.2)</td>
<td>13 (15.3)</td>
<td>.22</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>26 (30.6)</td>
<td>26 (30.6)</td>
<td>&gt;.99</td>
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<td>LAD, mean (SD), mm</td>
<td>44.2 (6.1)</td>
<td>43.9 (5.9)</td>
<td>.70</td>
</tr>
<tr>
<td>LVEF, mean (SD), %</td>
<td>55.1 (12.6)</td>
<td>56.9 (11.0)</td>
<td>.33</td>
</tr>
<tr>
<td>Longstanding persistent AF, No. (%)</td>
<td>64 (75.3)</td>
<td>58 (68.2)</td>
<td>.39</td>
</tr>
<tr>
<td>CHA2DS2-VAS score, mean (SD)</td>
<td>1.4 (1.4)</td>
<td>1.4 (1.1)</td>
<td>.86</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; BMI, body mass index (weight in kilograms divided by height in meters squared); CAD, coronary artery disease; CHA2DS2-VAS, congestive heart failure, hypertension, age 75 years (doubled), diabetes, stroke or TIA or thromboembolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65 to 75 years, sex category (female); CHF, congestive heart failure; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

* Unless otherwise indicated, data are expressed as No. (%) of patients.

* Indicates continuous AF lasting for 1 year or more.

* Indicates clinicalestimation of the risk of stroke in patients with AF. Scores range from 0 to 9, and higher scores indicate a greater risk.
patients (7.1%). During PVI, 2 patients (2.4%) experienced organized flutter. Two patients (2.4%) experienced organized flutter during PRISM-guided substrate modification. In group 2, 11 patients (12.9%) had their AF terminated through conventional PVI. Conventional PVI terminated AF into organized atrial tachycardia in 3 (3.5%) and sinus rhythm in 8 (9.4%). A summary of additional linear ablation and/or substrate medication is provided in Table 2.

There were no major adverse events reported in either group. In 2 patients (1 in group 1 and 1 in group 2), a femoral vessel complication required surgical repair. One patient from group 1 had pericarditis requiring medication. One case of pulmonary edema was reported in group 1 following the procedure. In group 1, 3 patients overall (3.5%) experienced complications compared with 1 patient in group 2 (1.2%) (P = .31).

### Midterm and Long-Term Outcomes

More group 1 patients achieved freedom from AF at 12 months compared with group 2 patients (60 of 85 [70.6%] vs 40 of 85 [47.1%]). Multivariate analysis indicated that the PRISM-guided approach was associated with freedom from the recurrence of atrial arrhythmia (hazard ratio, 0.53 [95% CI, 0.33-0.85]). There was a clinical recurrence of AF in 22 of 85 patients in group 1 (25.9%) and 25 of 85 patients in group 2 (29.4%) 6 months after the ablation (P = .73). During the 12-month follow-up, 25 patients in group 1 (29.4%) and 45 of 85 patients in group 2 (52.9%) experienced clinical AF recurrence (P = .003). A recurrence of clinical atrial tachycardia 6 months after ablation was documented in 6 patients in group 1 (71%) and 4 patients in group 2 (4.7%) (P = .75). After 12 months of monitoring, 6 patients in group 1 (7.1%) and 6 patients in group 2 (7.1%) had clinical atrial tachycardia recurrences (P > .99).

### Table 2. Patient Procedural Parameters and Outcome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 85)</th>
<th>Group 2 (n = 85)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior PVI</td>
<td>12 (14.1)</td>
<td>16 (18.8)</td>
<td>.54</td>
</tr>
<tr>
<td>General anesthesia</td>
<td>61 (71.8)</td>
<td>65 (76.5)</td>
<td>.60</td>
</tr>
<tr>
<td>Cryoablation for PVI</td>
<td>40 (47.1)</td>
<td>44 (51.8)</td>
<td>.65</td>
</tr>
<tr>
<td>Roofline block</td>
<td>39 (45.9)</td>
<td>43 (50.6)</td>
<td>.65</td>
</tr>
<tr>
<td>Mitral line block</td>
<td>9 (10.6)</td>
<td>8 (9.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Box isolation</td>
<td>3 (3.5)</td>
<td>3 (3.5)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>CTI line block</td>
<td>72 (84.7)</td>
<td>73 (85.9)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>PRISM within PV ostium</td>
<td>28 (32.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PRISM ablation not complete</td>
<td>18 (21.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Non-PV triggers</td>
<td>8 (9.4)</td>
<td>12 (14.1)</td>
<td>.35</td>
</tr>
<tr>
<td>Termination during ablation</td>
<td>20 (23.5)</td>
<td>11 (12.9)</td>
<td>.11</td>
</tr>
<tr>
<td>AAD in the blanking period</td>
<td>82 (96.5)</td>
<td>84 (98.8)</td>
<td>.62</td>
</tr>
<tr>
<td>AAD at 6 mo</td>
<td>61 (71.8)</td>
<td>59 (69.4)</td>
<td>.87</td>
</tr>
<tr>
<td>AAD at 12 mo</td>
<td>43 (50.6)</td>
<td>50 (58.8)</td>
<td>.36</td>
</tr>
<tr>
<td>AT recurrence within 6 mo&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 (7.1)</td>
<td>4 (4.7)</td>
<td>.75</td>
</tr>
<tr>
<td>AT recurrence within 12 mo&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 (7.1)</td>
<td>6 (7.1)</td>
<td>&gt;.99</td>
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<tr>
<td>AF recurrence within 6 mo</td>
<td>22 (25.9)</td>
<td>23 (26.4)</td>
<td>.73</td>
</tr>
<tr>
<td>AF recurrence within 12 mo</td>
<td>25 (29.4)</td>
<td>45 (52.9)</td>
<td>&lt;.003</td>
</tr>
<tr>
<td>AF and/or AT recurrence within 6 mo&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26 (30.6)</td>
<td>29 (34.1)</td>
<td>.74</td>
</tr>
<tr>
<td>AF and/or AT recurrence within 12 mo&lt;sup&gt;b&lt;/sup&gt;</td>
<td>28 (32.9)</td>
<td>49 (57.6)</td>
<td>.002</td>
</tr>
<tr>
<td>Procedure time, mean (SD), min</td>
<td>145.7 (34.7)</td>
<td>137.5 (33.3)</td>
<td>.12</td>
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<td>Mapping time for PRISM, mean (SD), min</td>
<td>6.1 (1.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ablation time for PRISM in LA, mean (SD), min</td>
<td>3.5 (3.2)</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Complication</td>
<td>3 (3.5)</td>
<td>1 (1.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Femoral vascular complication</td>
<td>1 (1.2)</td>
<td>1 (1.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Acute decompensated heart failure</td>
<td>1 (1.2)</td>
<td>0</td>
<td>&gt;.99</td>
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<tr>
<td>Pericarditis</td>
<td>1 (1.2)</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; AT, atrial tachycardia, which included atrial tachycardia and atrial flutter; CTI, cavotricuspid isthmus; LA, left atrium; NA, not applicable; PRISM, periodicity and similarity; PV, pulmonary vein; PVI, pulmonary vein isolation.

<sup>a</sup> Unless otherwise indicated, data are expressed as No. (%) of patients.

<sup>b</sup> Includes atrial flutter.
The prevalence of clinical overall atrial arrhythmia recurrence, including AF and/or atrial tachycardia, 6 months after ablation was 26 of 85 patients (30.6%) for group 1 and 29 of 85 patients (34.1%) for group 2 ($P = .74$). The prevalence of clinical overall atrial arrhythmia recurrence 12 months after ablation was 28 of 85 patients (32.9%) for group 1 and 49 of 85 patients (57.6%) for group 2 ($P = .002$).

**Variables Associated With Long-Term Recurrence**
During a mean (SD) follow-up of 20.9 (6.7) months, the Kaplan-Meier survival curves showed that group 1 had fewer AF recurrences and overall atrial arrhythmia recurrences than group 2 (eFigure 6 in Supplement 2). Between the groups, there was no significant difference in AF recurrence at 6 months or atrial tachycardia recurrence at 6 and 12 months. One patient died of a noncardiovascular event 24 months after ablation (group 1). According to the results of multivariable analyses of Cox proportional hazards regression (eTable 2 in Supplement 2), PRISM-guided treatment and the absence of non-PV triggers were independently associated with better AF- and/or atrial tachycardia-free survival.

**Discussion**

**Main Findings**
This randomized clinical trial describes a novel method for additional substrate modification for patients with persistent AF or long-standing persistent AF. This is a prospective multicenter study, the results of which can be considered as an extension of previous results reported on the PRISM-guided approach. The addition of the PRISM-guided approach compared with catheter ablation with the conventional approach increased the likelihood of remaining free of AF at 12 months post procedure. These positive results provide an optimal guide for additional ablation for persistent AF. PRISM mapping can provide a guide for clinical electrophysiologists to develop patient-specific strategies. For example, substrate modification might not be required in patients with PRISM areas within PV only (type 1 PRISM).

**Comparison With Previous Studies and the Latest Approaches for Mapping AF Drivers**
There are several newly developed methods for AF driver mapping. These new mapping systems can detect AF drivers and have significant technical differences related to signal acquisition and processing compared with PRISM. Several different mapping methods are used to determine AF drivers. First, the stochastic trajectory analysis of ranked signals (STAR) mapping method determines the earliest sites of activation from unipolar signals. Ablation guided by STAR mapping produced a favorable clinical outcome (80% freedom from AF) in a small cohort and warranted testing through a randomized clinical trial. Second, the AcQMap (High-Resolution Imaging and Mapping System [Acutus Medical, Inc]) full-chamber, noncontact mapping system displays continuous chaotic activation during AF and identifies targets. The single-arm study resulted in freedom from AF in 73% of patients after a single procedure. Third, CardioNXT technologies stitch local unipolar electrograms from high-density AF mapping together to form a coherent panoramic AF map and identify the driver based on individual conduction vectors within the full atrial chamber. The substrate ablation based on CardioNXT resulted in 74% remaining AF free. Fourth, CARTOFINDER (Biosense Webster, Inc) uses high-resolution sequential endocardial electrogram-based mapping (without phase transformation) to identify focal and rotational activities in persistent AF. The previous case-controlled study demonstrated a better AF freedom rate with a CARTOFINDER-guided approach compared with the conventional approach (70.0% vs 30.0%; $P < .001$). Fifth, a spatiotemporal dispersion (Volta Medical) mapping study tagged and ablated only regions displaying electrogram dispersion during AF. This approach resulted in 85% remaining AF-free after a mean (SD) of 1.4 (0.5) procedures/patient. Sixth, electrographic flow mapping (Ablamap; Ablacon Inc)
aimed to identify active AF sources during AF ablation procedures. The randomized clinical studies were lacking for the above-mentioned strategies.

We describe the features of AF drivers using 4-dimensional spatiotemporal signals, and we have quantified a repetitive pattern of time and demonstrated a spatial distribution of it by high-density PRISM mapping derived using either single or multiple electrodes catheters. Nevertheless, simultaneous mapping with multiple electrodes not only significantly reduced the procedure time but also minimized the likelihood of unreliable PRISM values occurring at a single site during point-by-point mapping.

Our study focused on evaluating the efficacy of PVI with additional targeted drivers identified through PRISM mapping without extensive substrate modification. The procedural AF termination may not reflect the long-term outcome. The factors influencing AF termination and long-term success are complex and not fully understood. Therefore, the procedural end point of AF termination is still controversial in the consensus. In the present study, the AF termination rate was not high compared with those of previous studies. The termination of AF during ablation can result from eliminating focal drivers and modifying the atrial substrate sustaining AF. After successful AF ablation, the atrial substrate might be reversible in patients with persistent or long-lasting persistent AF. The reasons for the failure to achieve acute termination in these cases could be multifactorial, including substrate complexity and untargeted drivers.

Limitations
This study had several limitations. First, some patients in both groups underwent ablation beyond PVI, including linear ablation and ablation at other locations. Second, the right atrium was not mapped in this study, which might underestimate drivers in that location. Third, the follow-up based on symptoms, 24-hour Holter monitoring, and 7-day event recorder could affect the success rate by underestimating asymptomatic recurrences. Fourth, the study enrolled 28 patients (16.5%) receiving prior PVI, which might affect the durability of PVI in the present study.

Conclusions
In this randomized clinical trial of persistent AF ablation, the waveform similarity and recurrence pattern derived from high-density mapping might provide an improved guiding approach for persistent AF ablation. Compared with the conventional procedure, our novel specific substrate ablation strategy reduced the frequency of recurrent AF and increased the likelihood of maintenance of sinus rhythm.
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REFERENCES


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SUPPLEMENT 2.
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