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Optimal substrate modification strategies using catheter ablation in patients with persistent atrial fibrillation: 3-year follow-up outcomes

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Abstract

Objectives: This study aimed to assess the comparative efficacy of four ablation strategies on the incidence rates of freedom from atrial fibrillation (AF) or atrial tachycardia (AT) through a 3-year follow-up in patients with persistent AF.

Background: The optimal substrate modification strategies using catheter ablation for patients with persistent AF remain unclear.

Methods: Patients with persistent AF were enrolled consecutively to undergo each of four ablation strategies: (a) Group 1 (Gp 1, $n = 69$), pulmonary vein isolation (PVI) plus rotor ablation assisted by similarity index and phase mapping; (b) Gp 2 ($n = 75$), PVI plus linear ablations at the left atrium; (c) Gp 3 ($n = 42$), PVI plus the elimination of complex fractionated atrial electrograms; (d) Gp 4 ($n = 67$), PVI only. Potential confounders were adjusted via a multivariate survival parametric model.

Results: Baseline characteristics were similar across the four groups. At a follow-up period of 34.9 ± 38.6 months, patients in Gp 1 showed the highest rate of freedom from AF compared with the other three groups ($p = .002$), while patients in Gp 3 and 4 showed lower rates of freedom from AT than those of the other two groups ($p = .006$). Independent predictors of recurrence of AF were the ablation strategy ($p = .002$) and left atrial diameter (LAD) ($p = .01$).

Conclusion: In patients with persistent AF, a substrate modification strategy using rotor ablation assisted by similarity index and phase mapping provided a benefit for maintaining sinus rhythm compared with the other strategies. Both ablation strategy and baseline LAD predicted the 3-year outcomes of freedom from AT/AF

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KEYWORDS

atrial tachycardia, persistent atrial fibrillation, phase map, pulmonary vein isolation, similarity index, substrate

1 | INTRODUCTION

Atrial fibrillation (AF) is the most commonly encountered sustained arrhythmia leading to significant morbidity and mortality. Catheter ablation aiming at isolating pulmonary veins triggers from the rest of the left atrium is currently a well-accepted therapeutic strategy to treat paroxysmal AF, particularly in those patients refractory to antiarrhythmic medications.[1] For patients with persistent AF, catheter ablation is more challenging with a low successful rate of 45%–60% after 1 year.[2] These findings indicated more complicated mechanisms for the perpetuation and maintenance of AF in persistent AF than in paroxysmal AF. To improve the outcomes, catheter ablation targeting at the atrial substrate that maintains fibrillation, so-called substrate modification, is often added to pulmonary vein isolation (PVI).[3] The two most commonly used techniques for substrate modification are the deployment of linear lesions in the left atrium and focal ablation to eliminate complex fractionated atrial electrograms (CFAE).[4,5] However, the benefit of adjunctive linear ablation or CFAEs after successful PVI is debatable based on recent data from the STAR AF 2 trial.[2] Therefore, the optimal strategy of catheter ablation to treat persistent AF remains undetermined. Alternative approaches rather than linear or CFAE ablation need to be explored.

In the STAR AF 2 trial, the lack of benefits in maintaining sinus rhythm (SR) with either additional linear or CFAE ablation compared to PVI only raised the concern that additional ablation after PVI might not be feasible in patients with persistent AF.[2] For the unstable and chaotic properties of complex AF signals, phase mapping could provide spatial and temporal information that helps to reveal the electrical properties of the atrial matrix, and offering additional insight into AF mechanisms.[6] Using a novel electrogram similarity analysis and real-time phase mapping to identify the rotors/drivers, we have previously reported, from a randomized trial of patients with persistent AF, a lower AF recurrence rate using adjuvant rotor/driver ablation when compared with CFAE ablation, after PVI.[7] This finding suggested that additional ablation for the rotors/drivers after PVI guided by nonlinear phase maps improves the SR outcome. However, no PVI-alone group, which is considered so far a standard treatment for persistent AF after STAR AF 2 trial, was enrolled in that study.[7] Furthermore, the follow-up durations in the above two mentioned pivotal trials were less than 2 years and no long-term results were available.[2,7]

In the present study, we enrolled consecutive patients with persistent AF to receive one of the following treatments: (a) PVI plus driver/rotor ablation assisted by similarity index (SI) and phase maps, (b) PVI plus linear ablation, (c) PVI plus CFAE ablation, or (d) PVI only. Patients were then followed up for up to 5 years. We had two hypotheses: (1) driver/rotor ablation assisted by SI and phase mapping is superior to the other three strategies in maintaining SR; (2) substrate modification strategies and baseline left atrial diameter (LAD) predict the outcomes of freedom from AF.

2 | METHODS

This study was approved by the Institutional Review Board (IRB Number: 201305044 W and 2017-09-013BCF) of Taipei Veterans General Hospital (TVGH) in accordance with the Good Clinical Practice Guidelines.

2.1 | Study population

We retrospectively analyzed 253 consecutive patients with persistent AF undergoing procedures of catheter ablation in this institute. The definition of persistent AF was those with AF sustaining for more than 7 days, including episodes that are terminated by pharmacologic or electrical cardioversion after 7 days or more.[8] Early persistent AF is defined as AF that is sustained beyond 7 days but is less than 3 months in duration.[9] Long-lasting persistent AF was defined as AF lasting for more than 1 year when it is decided to adopt a rhythm control strategy.[8]

2.2 | Study protocol

Figure 1 shows the flow chart of the protocol. All patients with persistent AF underwent PVI by catheter ablation as the initial procedure. Patients in whom AF could be terminated after PVI did not receive further ablation, and they constituted the "PVI only" group (Group 4, $n = 67$). In patients whose AF remained sustained after PVI, they were assigned by the physicians' discrimination without randomization to one of the following three substrate modification strategies: (a) rotor/driver ablation guided by electrogram SI and phase mapping, and these patients constituted the "PVI plus SI group" (Group 1, $n = 69$); (b) linear ablation across the roof of the left atrium and in the mitral isthmus, and these patients constituted the "PVI plus line" group (Group 2, n = 75); (c) ablation of CFAE, and these patients constituted the "PVI plus CFAE" group (Group 3, $n = 42$). Figure 2 illustrates the four ablation strategies

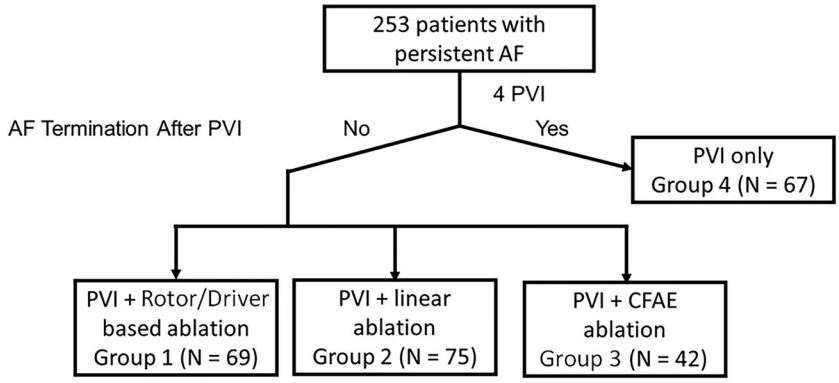

FIGURE 1 Flowchart of the study protocol for patients with persistent atrial fibrillation. CFAE, complex fractionated atrial electrograms; PVI, pulmonary vein isolation

applied to those persistent patients with AF. Before catheter ablations, antiarrhythmic medications, except for amiodarone, were discontinued for at least five half-lives, while amiodarone was stopped 2 weeks in advance. Patients all received oral anticoagulant for at least 4 weeks before catheter ablation, and they were unaware of which strategy of catheter ablation had been applied to them.

2.3 | Electrophysiological and catheter ablation procedures

All patients presented with AF at the onset of the procedure. Electro-anatomical mappings were guided by either the NavX/Velocity (Abbott, Inc.) or Carto (Biosense Webster) system using fast anatomical mapping feature in all patients. In Group 1 patients, the procedure of using electrographic similarity and phase mapping to guide substrate ablation has been reported in details (Figure 3).[10] In brief, a 3.5-mm tip irrigated catheter was used to obtain the signal characteristics of substrate during AF after PVI. The fibrillation electrographic signal was band-pass filtered (10–300 Hz) for a recording duration of 5 s. The associated envelope was processed with a proposed order-statistic filter that took into account the algorithmically identified local activity during the time window and could highlight the local activation wave (LAW). The reconstructed envelope function effectively suppress noise and far-field contamination, so it could estimate the dynamic phase changes between two consecutive activations. Nonlinear analysis was then performed to compare repetitive waveforms on a beat-to-beat basis, the similarity of which was expressed as SI. An area of high SI (> 0.5) shown in the system of three-dimensional mapping indicated the source of rotor/driver for AF maintenance, and the source was then targeted for ablation.

In Group 2 patients, complete ablation of mitral roof lines was confirmed by (1) continuous presence of double potentials along the entire length of the roof corridor during pacing of the anterior LA; (2) activation detour circumventing the right and left PVs to activate caudo-cranially the posterior wall with no conduction through the LA roof during pacing from LA.[11] After restoration to SR, ablation of the

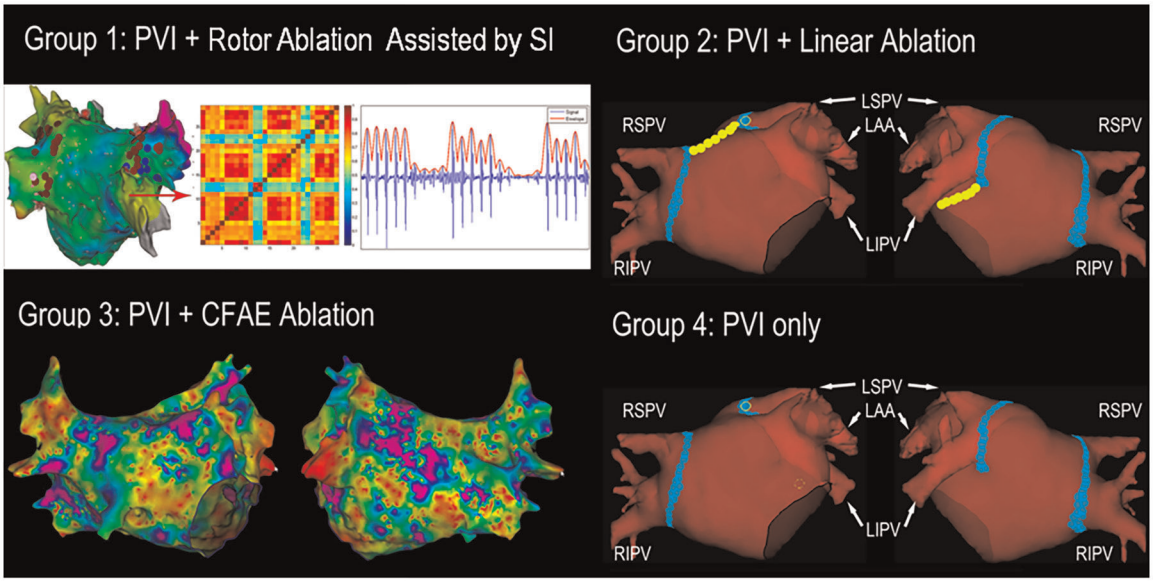

FIGURE 2 Illustrations of the four ablation strategies. CFAE, complex fractionated atrial electrograms; PVI, pulmonary vein isolation; SI, similarity index

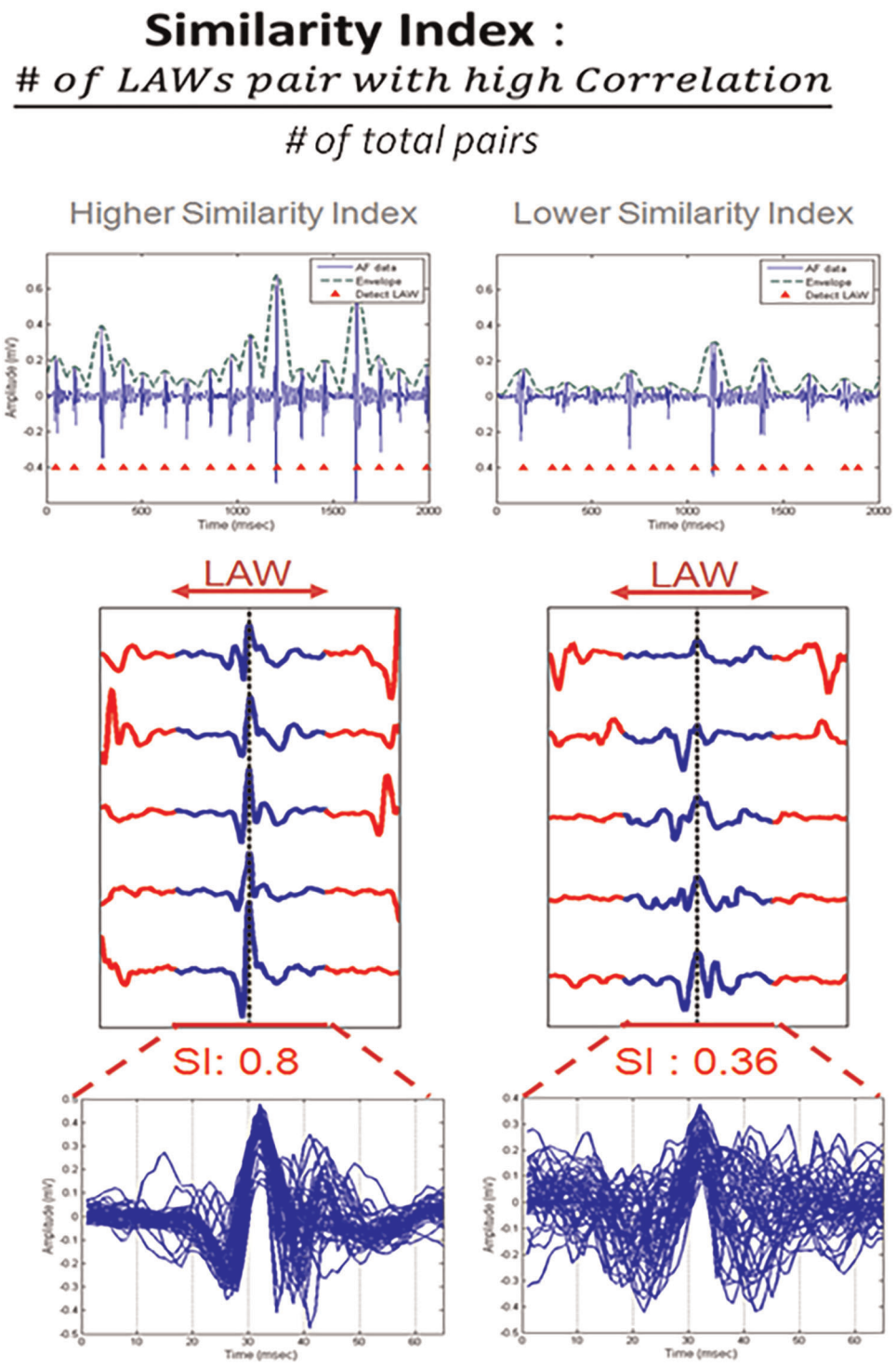

FIGURE 3 Example of rotor identification assisted by similarity index (SI). SI was quantified based on the temporal and spatial consistency of morphological repetitiveness of local activation wave (LAW). Rotors were then identified in the high SI region

right atrial cavotricuspid isthmus was performed through an ablation catheter (equipped with an 8-mm tip) to achieve bidirectional conduction block. In Group 3, CFAE ablation was confined to the areas showing continuous CFAEs, defined as an electrographic fractionation or repetitive rapid activity lasting for more than 8 s with an averaged fractionated interval of less than 50 ms over a period of 5 s at the left and right atrium. The endpoint was prolongation of the cycle length, elimination of CFAEs, or abolishment of local fractionated potentials. In this study, the ablation endpoint was restoration of SR during the procedure. If the AF could not be terminated after substrate modification, electrical cardioversion was performed to restore SR.

2.4 | Study outcomes

The primary endpoint was freedom from any atrial arrhythmia, including AF, atrial flutter, or atrial tachycardia (AT) after a blanking period based on a single procedure. The secondary endpoint was recurrence of AF after the first procedure.

2.5 | Evaluation of AF recurrence

Patients were followed up at our out-patient clinics 2 weeks after catheter ablation, and then again at intervals of one to 3 months for 3 years.[7,10] The 24-h Holter's monitoring (Philips DigiTrack XT) or 7-day cardiac event recording was arranged at each follow-up. Recurrence of atrial arrhythmia was defined as any such episode lasting more than 30 s, which was confirmed by electrocardiography three months after the index catheter ablation.

2.6 | Statistical analyses

Continuous variables were presented as mean ± standard deviation (*SD*), and categorical variables as proportion. Intergroup differences were assessed by the analysis of variance for continuous variables, and χ^2 test for categorical variables. The Cox proportional-hazards regression was used to determine hazard ratios for the outcomes. A variable with a *p* value less than .1 in the univariate analysis was put into the multivariate Cox proportional hazard regression model to evaluate risks of recurrent atrial arrhythmias. Risks were expressed in terms of hazard ratio (HR) and a 95% confidence interval (CI) against controls.

Having fitting data to the Cox model, the predicted survival proportion at any time point for a particular risk was plotted using a multivariate Cox proportional model that had been adjusted for confounders as follows: age, sex, underlying diseases of chronic obstructive pulmonary disease, chronic kidney disease, CHA_2DS_2-VASc score, left atrial size, and left ventricular ejection fraction (LVEF).[12] Statistical analyses were done using SAS software version 9.4 (SAS Institute, Inc.). Statistical significance was set at two-tailed *p* values less than .05.

3 | RESULTS

3.1 | Baseline characteristics

Table 1 shows the baseline characteristics of the four patient groups. The baseline characteristics including sex, age, and underlying diseases such as hypertension, diabetes mellitus, and heart failure were similar across the four groups. The chronicity of AF was different among the four groups ($p = .002$), with the highest percentage of persistent patients with AF in Group 4 (59.7%), and long-lasting persistent AF in Group 3 (47.6%). The highest LAD was in Group 2 compared with other groups ($p = .007$), while the LVEF ($p = .29$) and CHA_2DS_2-VASc scores ($p = .53$) were similar across the four groups.

3.2 | Ablation procedure

Table 2 shows details of the ablation procedures. The percentages of patients receiving EnSite NavX system were higher than that with the CARTO system in the four groups. All patients have completed electrical isolation of PVs and bidirectional conduction block across the cavotricuspid isthmus. The percentages of patients with AF termination during ablation procedure were 58% (Group 1), 19% (Group 2), 43% (Group 3), and 100% (Group 4) (*p* all <.01); with the highest percentage in Group 1. The percentages of patients with non-PV ectopy were similar across the four groups ($p = .76$). The procedural and ablation times were longer in Group 3 compared with other groups (both $p = .01$). The percentages of patients receiving electrical cardioversion to restore SR were 51%, 19%, 38%, and 18%, Group 1–4, respectively ($p < .01$). Two patients in Group 3 had complications (one with massive pericardial effusion released by pericardiocentesis without surgery, and the other with groin hematoma) associated with the procedure ($p = .03$).

3.3 | Catheter ablation outcomes

During follow-up duration of 34.9 ± 38.6 months, a total of 96 AF (57.1%) and 50 AT (29.8%) events had occurred. The percentages of patients receiving at least one Holter's monitoring during the follow-up duration were 62%, 63%, 69%, and 64%, Group 1–4, respectively ($p = .30$). The percentages of patients receiving at least four Holter's check-ups within the first year were 23%, 11%, 21%, and 16%, Group 1–4, respectively ($p = .21$). Table 3 shows AF recurrences based on HR from clinical factors. In univariate analysis, ablation strategies ($p < .001$), LAD ($p = .001$), and LVEF ($p = .036$) were three predictors of AF recurrence. Multivariate analysis showed that only two: that is, ablation strategies ($p = .002$) and LAD ($p = .010$) were predictors of AF recurrence. Compared with PVI plus SI strategy (ref = 1), those with PVI plus line (adjusted HR: 2.243, $p = .005$), PVI plus CFAE (adjusted HR: 3.213, $p < .001$), and PVI only (adjusted HR: 2.196, $p = .006$) were strategies associated with increased risk of AF recurrence. Figure 4 shows survival curves for AF (Figure 4A), AT (Figure 4B), and AF plus AT (Figure 4C) recurrence for the four groups using multivariate Cox proportional model. After incorporating the impacts of the confounders on the estimated survival probability, Group 1 had the lowest AF recurrence rate, while Group 3 and 4 patients had higher AF recurrence rates among the four groups ($p = .002$, Figure 4A). Among the four groups, Group 1 also had the lowest AT recurrence rate, while Group 3 had higher AT recurrence rate ($p = .006$, Figure 4B). The event-free rates for AF

TABLE 1 Baseline characteristics of patients with persistent AF

	PVI + SI (Gp 1, *n* = 69)	PVI + Line (Gp 2, *n* = 75)	PVI + CFAE (Gp 3, *n* = 42)	PVI only (Gp 4, *n* = 67)	*p* value
Age (year)	53.5 ± 10.7	52.8 ± 9.48	50.2 ± 11.1	54.6 ± 9.88	.17
Sex (male)	59 (85.5%)	63 (84%)	38 (90.5%)	59 (88.1%)	.76
Smoking (%)	14 (20.3%)	25 (35.7%)	13 (33.3%)	22 (35.5%)	.16
Alcohol drinking (%)	9 (13%)	22 (31.4%)	10 (25.6%)	14 (22.2%)	.08
Repeated procedure (%)	32 (46.4%)	20 (26.7%)	9 (21.4%)	25 (37.3%)	.02
Chronicity of AF					
Early-persistent (%)	21 (30.4%)	11 (14.7%)	3 (7.1%)	15 (22.4%)	
Persistent (%)	52 (44.9%)	35 (46.7%)	19 (45.2%)	40 (59.7%)	.002
Long-lasting (%)	17 (24.6%)	29 (38.7%)	20 (47.6%)	12 (17.9%)	
Hypertension (%)	34 (49.4%)	37 (49.3%)	18 (42.9%)	33 (49.3%)	.90
Diabetes mellitus (%)	8 (11.6%)	13 (17.3%)	4 (9.5%)	12 (17.9%)	.51
Congestive heart failure (%)	6 (8.7%)	12 (16%)	7 (16.7%)	11 (16.4%)	.50
Thyroid disease (%)	11 (15.9%)	11 (14.7%)	5 (11.9%)	8 (11.9%)	.88
Valvular heart disease (%)	3 (4.3%)	1 (1.3%)	1 (2.4%)	1 (1.5%)	.77
Chronic kidney disease (%)	1 (1.4%)	0 (0%)	1 (2.4%)	0 (0%)	.44
Gout (%)	3 (4.3%)	2 (2.7%)	0 (0%)	1 (1.5%)	.55
Dilated cardiomyopathy (%)	1 (1.4%)	2 (2.7%)	2 (4.8%)	0 (0%)	.38
LAD (mm)	42.0 ± 5.85	45.6 ± 7.36	42.5 ± 5.66	43.1 ± 6.37	.007
LVEF (%)	55.7 ± 6.07	52.5 ± 8.10	52.7 ± 9.11	54.1 ± 7.46	.29
$^{CHA}2^{DS}2$-VASc score	1.28 ± 1.22	1.19 ± 1.09	1.00 ± 0.96	1.31 ± 1.23	.53

Abbreviations: AF, atrial fibrillation; CFAE, complex fractionated atrial electrogram; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; SI, similarity index.

or AF recurrence was highest in Group 1 among the four groups (p = .003, Figure 4C).

In 15 out of the 17 long-lasting persistent AF patients in Group 1, the number of focal drivers and rotors were 3.9 and 0.4 per patient, respectively. Twenty percent of their rotors were located near the PV areas, while 8.3%, 8.7%, and 8.7% of the rotors were at left atrial appendage, mitral annulus, and left atrial roof area, respectively.

Table 4 showed the interaction analysis between ablation strategies and LAD or LVEF on the risk of AF recurrence. In patients with baseline LAD more than or equal to 40 mm, ablation strategy predicted the risk of AF recurrence (p = .02), but not predictive in those with baseline LAD less than 40 mm (p = .39), and the difference is significant (p = .01 for interaction). No significant interaction existed between ablation strategy and baseline LVEF (p = .43 for interaction).

4 | DISCUSSION

Two major findings emerged from the present study: (1) the PVI plus rotor/driver ablation strategy significantly reduced the risk of AF/AT recurrences over other strategies like PVI only, PVI plus linear, and PVI plus CFAE ablation on patients with persistent AF undergoing a long-term follow-up; (2) substrate modification strategy and baseline left ventricular function in these patients were two predictors of their atrial arrhythmia-free conditions.

4.1 | Catheter ablation strategies for persistent AF

Percutaneous catheter ablation with an anatomic approach to isolate pulmonary vein triggers at the left atrium is currently a

TABLE 2 Ablation procedures in patients with persistent AF

	PVI + SI (Gp 1, *n* = 69)	PVI + Line (Gp 2, *n* = 75)	PVI + CFAE (Gp 3, *n* = 42)	PVI only (Gp 4, *n* = 67)	*p* value
CARTO system	25 (36%)	1 (1%)[a]	4 (10%)	1 (1%)	<.01
Lasso/PentaRay catheter	2/23	0/0	0/4	0/1	
EnSite NavX system	44 (64%)	74 (99%)	38 (90%)	66 (99%)	<.01
Spiral catheter	44	74	38	66	
AF termination at procedure	40 (58%)	14 (19%)	18 (43%)	67 (100%)	<.01
Patients with non-PV ectopy	59 (85.5%)	63 (84%)	38 (90.5%)	59 (88.1%)	.76
Procedural time (min)	136 ± 43	154 ± 51	220 ± 58*	143 ± 50	.01
Ablation time (min)	88 ± 31	94 ± 33	136 ± 43*	93 ± 39	.01
Cardioversion	35 (51%)	14 (19%)	16 (38%)	12 (18%)	<.01
Complication	0 (0%)	0 (0%)	2 (4.9%)	0 (0%)	.03

Note: Complications included a pericardial effusion relieved by pericardiocentesis and a groin hematoma.

Abbreviations: AF, atrial fibrillation; CFAE, complex fractionated atrial electrograms; PV, pulmonary vein; PVI, pulmonary vein isolation; SI, similarity index.

*$p < .05$, post hoc analysis when compared with other groups.

[a]Mapping with multi-electrode ablation catheter.

well-accepted therapeutic strategy for patients with paroxysmal AF.[1] However, catheter ablation is more challenging to treat persistent AF, with less favorable outcomes.[13] Mechanisms other than pulmonary vein triggers appear to be critical in the arrhythmogenesis of persistent AF.[14] Several approaches involving atrial substrate modifications have been used to improve outcomes of catheter ablation for persistent AF. These approaches included the elimination of non-pulmonary triggers, identification of rotor/driver for ablation, elimination of CFAE, linear ablation in addition to PVI, and left atrial appendage isolation (LAAI).[8] These strategies produced unsatisfying success rates of 45%–60% after one year.[2] In the STAR AF 2 trial, patients with persistent AF randomly received either one of the following strategies: PVI alone, PVI plus ablation of CFAE, or PVI plus linear ablation. That study found similar recurrent rates of AF across the three groups, suggesting additional ablation on top of PVI did not improve AF recurrence.[2] Although LAAI might be another treatment option for patients with AF not responding to PVI, a high incidence of LAA thrombus formation was observed despite OAC use, which might offset its clinical benefit.[15] Therefore, an alternative substrate modification approach, rather than linear or CFAE ablation, is needed to improve the outcomes in these patients.

Among these substrate modification strategies, driver-guided ablation has emerged as a potential therapeutic target for ablation of persistent AF. In a pooled meta-analysis, the driver/rotor identification and ablation approach, despite using different mapping techniques and catheters, was associated with higher rates of acute AF termination (odds ratio [OR]: 4.62, $p < .001$) and lower rates of recurrence of any atrial arrhythmia (OR: 0.44, $p < .001$).[16] We have previously reported that after PVI in patients with persistent AF, atrial substrate modification guided by SI and nonlinear phase mapping is associated with a lower AF recurrence rate compared with those receiving CFAE ablation.[7] These findings suggested that substrate modification aiming at driver/rotor identification and ablation is a promising approach for persistent AF. However, the follow-up durations of previous clinical trials of atrial substrate modification were limited to less than 2 years and long-term results were unclear.[2,7] To validate the long-term efficacy of substrate modification assisted by SI and phase mapping, we observed here that PVI plus rotor/driver ablation reduced the AF recurrence risk comparing to the other three strategies in this study of up to 3-year follow-up. Our present finding showed that PVI with adjuvant rotor/driver ablation guided by SI and phase mapping had improved the long-term AF-free outcomes in patients with persistent AF.

4.2 | Technical considerations of driver/rotor mapping

A driver of a spiral wave is a rotational center with excitation propagation rotating outwards.[17] Phase mapping has been used to identify drivers presented as a phase singularity with phase transitions from a complete cycle in animal models of fibrillation.[18] Several phases mapping-guided settings, including

TABLE 3 Hazard ratios for AF recurrence after a single ablation procedure

Variables	Univariate analysis HR (95% CI)	*p* value	Multivariate analysis HR (95% CI)	*p* value
Ablation strategy				
Gp 1: PVI + SI	Ref = 1	<.001	Ref = 1	.002
Gp 2: PVI + Line	2.689 (1.573–4.596)	<.001	2.243 (1.274–3.950)	.005
Gp 3: PVI + CFAE	3.566 (2.014–6.314)	<.001	3.213 (1.782–5.793)	<.001
Gp 4: PVI only	2.156 (1.242–3.744)	<.001	2.196 (1.249–3.862)	.006
Age	0.996 (0.980–1.011)	.564		
Sex (male)	0.941 (0.588–1.506)	.799		
Repeated procedure	1.137 (0.812–1.593)	.454		
Hypertension	1.272 (0.926–1.747)	.138		
Diabetes mellitus	1.340 (0.879–2.043)	.174		
Congestive heart failure	1.216 (0.797–1.854)	.365		
Thyroid disease	1.118 (0.705–1.773)	.635		
Valvular heart disease	0.577 (0.143–2.332)	.440		
Chronic kidney disease	0.049 (0.000–27.89)	.351		
Gout	0.899 (0.286–2.819)	.855		
Dilated cardiomyopathy	1.467 (0.543–3.967)	.450		
Smoking	0.956 (0.673–1.357)	.801		
Alcohol drinking	1.182 (0.818–1.706)	.373		
LAD	1.039 (1.016–1.062)	.001	1.032 (1.007–1.057)	.010
LVEF	0.979 (0.959–0.999)	.036	0.988 (0.968–1.009)	.256
$^{CHA}2^{DS}2$-VASc score	1.079 (0.946–1.232)	.257		

Note: Items with a *p* value of <.10 in the univariate analysis was selected for multivariate analysis.
Abbreviations: AF, atrial fibrillation; CFAE, complex fractionated atrial electrogram; CI, confidence interval; HR, hazard ratio; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; SI, similarity index.

invasive focal impulse and driver modulation, noninvasive electrocardiographic imaging, and electrogram similarity/phase mapping combined techniques have been used for driver detection and ablation.[7,19] Although driver/rotor identification and ablation could reduce AF recurrence in patients with persistent AF, the results reported so far using different methodological and technical approaches for rotor mapping and ablation remain inconclusive.[20] One explanation for such discrepancy in results is related to the diversity in mapping and signal processing techniques. Such diversity leaves it unclear if these different mapping tools have detected the same drivers.[16,21]

In the present study, we used a newly-developed SI assisted with phase mapping, which has been validated to facilitate the accuracy of rotor/diver detection and ablation efficacy.[7] Our results showed an improvement in the long-term efficacy of catheter ablation for patients with persistent AF. In our previous study with an intermediate-term follow-up of 18 months using SI plus phase mapping for rotor/driver ablation, we found similar outcomes of recurrent atrial arrhythmia compared with those receiving PVI plus CFAE ablation. In the present study, the long-term (up to 3 years) outcomes of all atrial arrhythmia recurrence were significantly lower in phase mapping assisted catheter ablation comparing to the other three strategies, indicating the robust accuracy for detecting rotor/driver and hence improving the long-term outcomes. The reason why SI-assisted phase mapping showed superior efficacy in reducing AF recurrence while other trials showed neural effects with rotor ablation remained unclear.[20] One speculation is that our signal processing was based on high mathematical, stationary, repetitive electrogram configuration, which might precisely distinguish a rotor from a focal source and enable the identification of an ablation target. Further studies are warranted to confirm the efficacy of current substrate modification strategies in achieving long-term SR outcomes for patients with persistent AF.

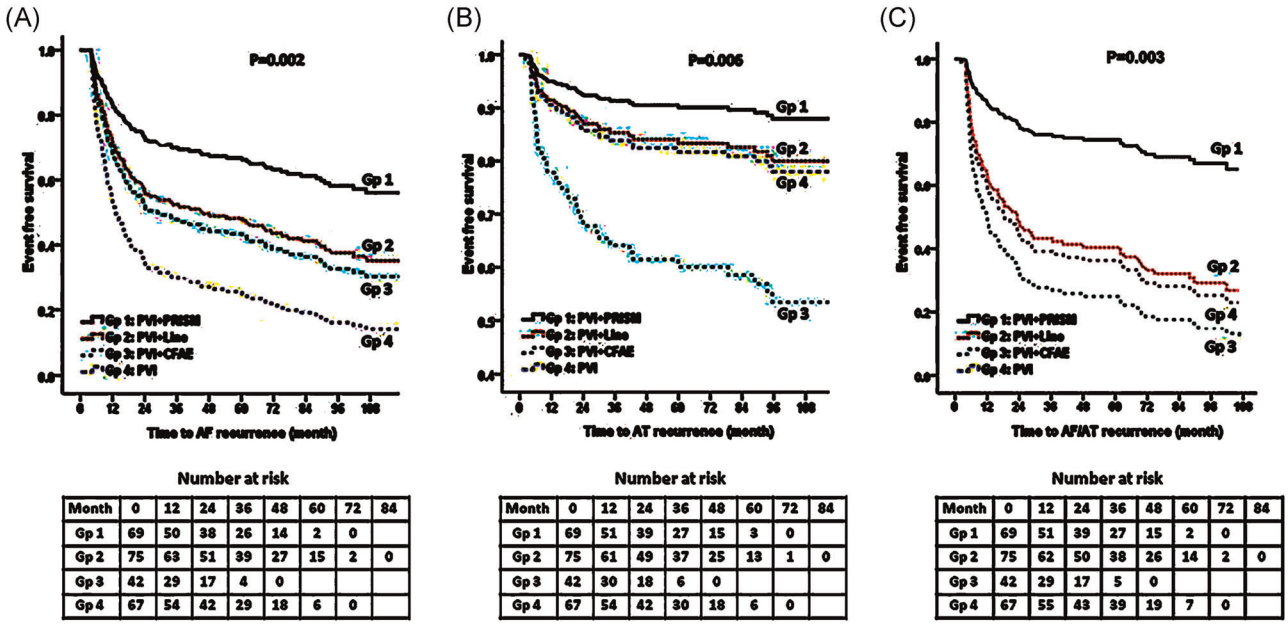

FIGURE 4 Predicted event-free survival curves adjusted by multivariate Cox proportional model for (A) AF, (B) AT, and (C) AF plus AT recurrence in the four groups of patients. AF, atrial fibrillation; AT, atrial tachycardia. The numbers of patients at risk at each time point were before model adjustment

TABLE 4 Interactions between ablation strategies and left atrial diameter or left ventricular ejection fraction on the risk of AF recurrence

Variables	HR (95% CI)	*p* value	HR (95% CI)	*p* value	*p* for LAD versus strategy
Ablation strategy[a]	LAD < 40 mm (*N* = 82)		LAD ≥ 40 mm (*N* = 171)		.01
Gp 1: PVI + SI	Ref = 1	.39	Ref = 1	.02	
Gp 2: PVI + Line	1.115 (0.363–3.420)	.85	2.887 (1.344–6.201)	.007	
Gp 3: PVI + CFAE	2.272 (0.716–7.214)	.16	3.512 (1.574–7.833)	.002	
Gp 4: PVI only	0.979 (0.331–2.899)	.97	2.766 (1.265–6.046)	.01	
Ablation strategy[b]	LVEF ≥ 40% (*N* = 226)		LVEF < 40% (*N* = 27)		.43
Gp 1: PVI + SI	Ref = 1	.01	Ref = 1	.41	
Gp 2: PVI + Line	2.777 (1.216–4.264)	.01	2.505 (0.513–12.22)	.26	
Gp 3: PVI + CFAE	3.001 (1.548–5.857)	.001	3.670 (0.589–22.85)	.16	
Gp 4: PVI only	2.016 (1.063–3.824)	.03	1.189 (0.198–7.146)	.85	

Abbreviations: CFAE, complex fractionated atrial electrogram; CI, confidence interval; HR, hazard ratio; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; SI, similarity index.

[a]Model was adjusted for LVEF.

[b]Model was adjusted for LAD.

4.3 | Catheter ablation strategy in specific group of persistent AF patients

It is currently unclear that which patient population of persistent AF may benefit from adjuvant catheter ablation on top of PVI. Enlarged left atrial size was an independent predictor of AF recurrence after PVI only without comparing different strategies in patients with persistent AF.[22] In the present study, patients with an increased left atrial size (>40 mm) showed particularly low rates of AF recurrence with rotor/driver ablation strategy assisted by SI and phase maps. This finding suggested that persistent AF patients with an increased LAD were likely the ideal patient population using rotor/driver ablation strategy. The underlying mechanism however remains unclear. One likes to speculate that atrial enlargement during atrial remodeling might allow more reentry circuits to exist within the enlarged atrial tissues and contribute to the persistence of AF.[17] Catheter ablation aiming at these stably existed or meandering rotors could adequately abolish these drivers that maintain the

persistent AF.[23] Further large scale study is warranted to verify such speculation.

5 | LIMITATIONS

Several limitations existed for the present study. First, this is a retrospective analysis and the assignment of the patients to either of the treatment groups was by the operators' discrimination without randomization. The numbers of patients in each group were small and variable. There was also an imbalance among the four groups with respect to the percentage of patients with longstanding persistent AF (17.9% in the PVI only group, and 47.6% in the CFAE group). Although the ablation procedures were performed by certified physicians, differences in experience among the physicians might lead to variable procedure times. Second, our patients had relatively low CHA_2DS_2-VASc scores (1.0–1.3), indicating low prevalences of co-morbidities in the study population. Third, the application of phase mapping was limited to selected sites rather than the whole chamber of the heart in which mapping techniques could identify the ablation targets. Extending our results to all patients with persistent AF patients should be done with caution. Finally, it remains to be explored if further substrate modifications in PVI only (Group 4) patients with either one of the three strategies even further reduce the risk of AF/AT recurrence.

6 | CONCLUSIONS

For patients whose persistent AF failed to be terminated by initial PVI, subsequent substrate modifications aiming at ablation of the rotors/drivers assisted by SI and phase mapping reduced risks of AF recurrence compared with adjuvant linear or CFAE ablation in a long term follow-up. Patients with persistent AF and enlarged atrium (>40 mm) might have a lower risk of AF recurrence by using rotor/driver ablation strategy than adjuvant linear or CFAE ablation strategy.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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