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CLINICAL RESEARCH

Aggressive ablation vs. regular ablation for persistent atrial fibrillation: a multicentre real-world cohort study

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Aims Current guidelines for the optimal ablation strategy for persistent atrial fibrillation (PerAF) remain unclear. While our previous RCT confirmed the favourable prognosis of aggressive ablation, real-world evidence is still lacking.

Methods and results Among 4833 PerAF patients undergoing catheter ablation at 10 centres, two groups were defined: regular ablation (PVI-only or PVI plus anatomical ablation) and aggressive ablation (anatomical plus electrogram-guided ablation), with 1560 patients each after propensity score (PS) matching. The primary endpoint was 12-month AF/atrial tachycardia (AT) recurrence-free survival off anti-arrhythmic drugs after a single procedure. Additional PS matching was performed within the regular group between PVI-only and anatomical ablation ($n = 455$ each). Furthermore, anatomical ablation from the regular group was independently matched with aggressive ablation ($n = 1362$ each). At 12 months, the aggressive group showed superior AF/AT-free survival (66.2% vs. 59.3%, $P < 0.001$; HR 0.745), similar AT recurrence (12.0% vs. 11.3%, $P = 0.539$), and significantly higher procedural AF termination (67.0% vs. 21.0%, $P < 0.001$) than regular group. Moreover, patients with AF termination had improved AF/AT-free survival (72.3% vs. 55.2%, $P < 0.001$). Safety endpoints did not differ significantly between the two groups. Both the ablation outcomes and AF termination rate showed increasing trends with the extent of ablation aggressiveness but declined with extremely aggressive ablation. After additional PS matching, within the regular group, no statistical differences were observed though AF/AT-free survival in the anatomical group was slightly higher than the PVI-only group (60.7% vs. 55.6%, $P = 0.122$); while aggressive ablation showed improved AF/AT-free survival compared to anatomical ablation alone from regular group (67.5% vs. 59.9%, $P < 0.001$).

Conclusion Aggressive ablation achieved more favourable outcomes than regular ablation, and moderately aggressive ablation may be associated with better clinical outcomes. AF termination is a reliable ablation endpoint.

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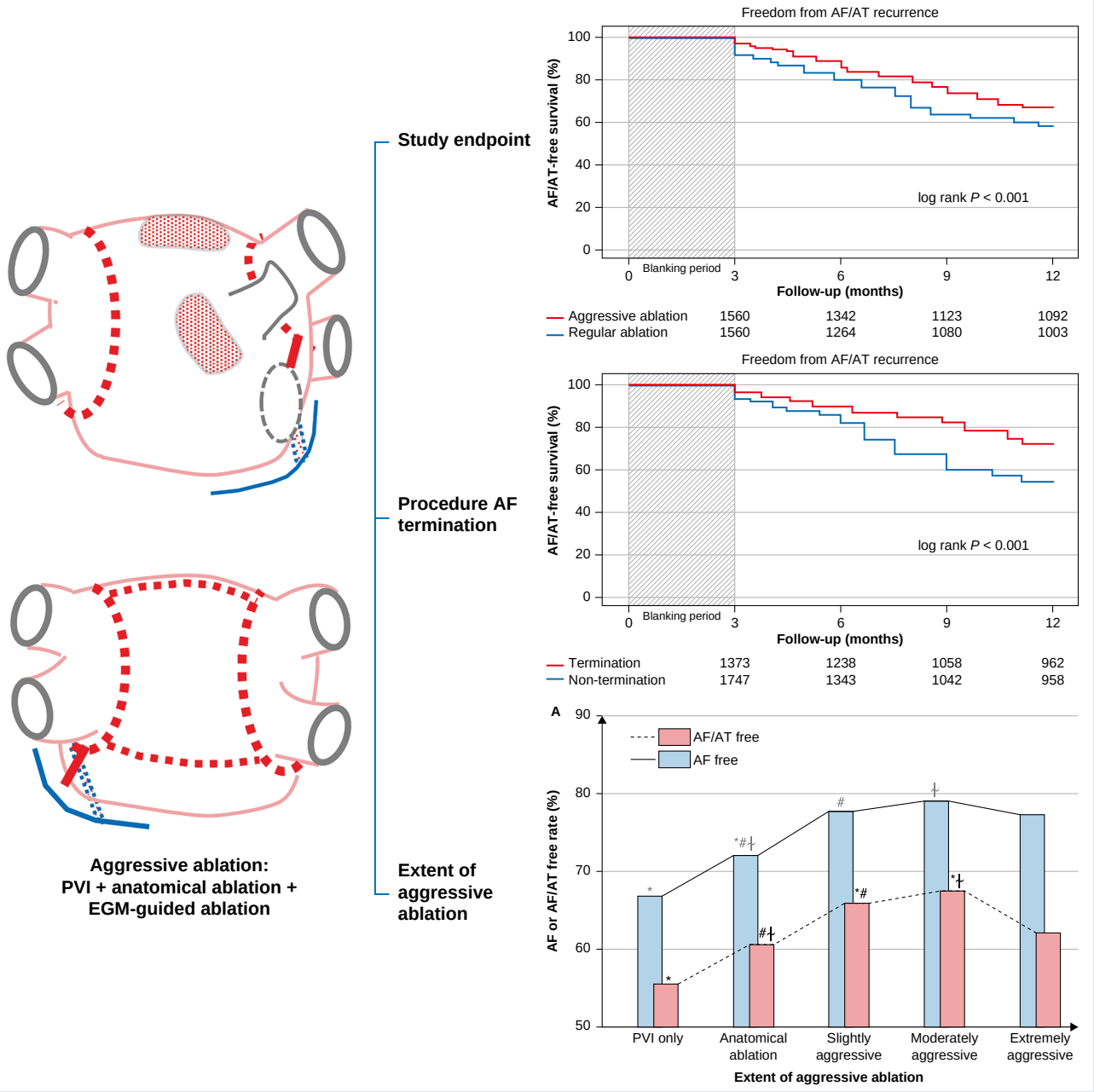
Graphical Abstract



Keywords Persistent atrial fibrillation • Aggressive ablation • Termination

What's new?

- Aggressive ablation (PVI, anatomical ablation, and EGM-guided ablation) achieved more favourable outcomes without increasing adverse events.
- AF termination is a reliable ablation endpoint for persistent AF ablation.
- Moderately aggressive ablation (two attempts of target electrogram mapping and ablation during a single ablation procedure) may provide the best clinical outcomes while the rates of freedom from AF or AF/AT recurrence and AF termination declined when extremely aggressive ablation was performed.

Introduction

Current guidelines increasingly recommend catheter ablation (CA) for the treatment of persistent atrial fibrillation (PerAF).[1–4] Although employed in PerAF[5–8] in the last decades, additional extra-pulmonary vein ablation methods, for example, linear ablation, scar-based mapping and ablation, non-PV sources ablation,[9] are often considered overly aggressive,[8–10] and ablation outcomes remain controversial, leading to a lack of consensus on strategies and endpoints in the guidelines and the latest expert consensus.[11] A widely recognized ablation approach for PerAF involves the combination of anatomical ablation and vein of Marshall (VOM) ethanol infusion, as demonstrated in the Venus study,[12]

achieving a freedom from AF rate of 49.2% after 12 months and 65.2% after multiple procedures. This success has led to the recommendation in the latest Chinese expert consensus to adopt this strategy as the first-line ablation method for PerAF,[13] and the latest Chinese RCT PROMPT-AF[14] further confirmed the superiority of this strategy than PVI alone.

Our previous randomized controlled trials indicated that, compared to regular anatomical ablation, including VOM ethanol infusion, a more aggressive strategy involving PVI, anatomical ablation, and extensive electrogram (EGM)-guided ablation may result in better outcomes and a higher procedural termination rate.[15] However, this perspective requires validation in real-world settings, and the influence of ablation aggressiveness on clinical outcomes remains uncertain. Thus, this study aims to assess the impact of the aggressive ablation strategy on the clinical outcomes of patients with PerAF, using real-world clinical data.

Methods

This retrospective real-world cohort study was conducted using data from 10 clinical sites in China, covering the medical records of 6345 patients diagnosed with 'PerAF' from 1 June 2019 to 30 June 2023. Patient data were retrieved from the electronic medical record, Hospital Information System, Laboratory Information System, and the home page of the medical record. Two researchers extracted the data to minimize bias, and a third researcher validated it to ensure accuracy.

Study design and participants

The diagnostic criteria for PerAF followed the latest clinical practice guidelines. Key inclusion criteria included undergoing CA therapy and having sufficient serum creatinine records or endpoint events. Patients with previous ablation, a significant lack of clinical diagnosis or treatment data, or those lost to follow-up were excluded. Patients who received PVI, anatomical ablation, and extensive EGM-guided ablation were assigned to the Aggressive Ablation Group (Aggressive Group), while those who underwent PVI alone or PVI plus anatomical ablation were assigned to the Regular Ablation Group (Regular Group). In the aggressive group, based on the number of EGM mapping and ablation attempt during a single procedure, patients were categorized into three groups: slightly aggressive (one attempt), moderately aggressive (two attempts), and extremely aggressive (three or more attempts).

Within the regular ablation group, additional 1:1 propensity score (PS) matching between the PVI-only cohort and the anatomical ablation cohort were performed to evaluate whether additional anatomical lesions improve outcomes over PVI alone. Anatomical ablation cohort from the regular group was also independently matched with the aggressive ablation cohort to assess whether aggressive ablation targeting EGMs offers advantages over anatomical ablation.

Electrophysiological study

Trans-oesophageal echocardiography or intra-cardiac echocardiography was performed in all patients to rule out LA thrombus. A decapolar mapping catheter (Biosense Webster, Diamond Bar, CA, USA) was positioned in the coronary sinus (CS) via the left femoral vein. Two SL1-type Swartz sheaths (St. Jude Medical, St. Paul, MN, USA) were advanced into the left atrium after two successful trans-septal punctures. Following trans-septal catheterization, systemic anti-coagulation was achieved with intravenous heparin (100 IU/kg) to maintain an activated clotting time between 300 and 350 s. Selective PV venography was performed to identify all PV ostia before ablation. The PentaRay multispline catheter (Biosense Webster, Diamond Bar, CA, USA) was used as a navigational catheter.

Ablation protocol

Regular ablation group

Catheter ablation was conducted under the guidance of a three-dimensional, non-fluoroscopic mapping system (CARTO, Biosense Webster, CA, USA). The THERMOCOOL SMARTTOUCH SF (STSF) catheter (Biosense Webster, Diamond Bar, CA, USA) and the THERMOCOOL SMARTTOUCH (ST) catheter (Biosense Webster, Diamond Bar, CA, USA) were used for ablation. Circumferential PVI was performed in all patients. The radiofrequency (RF) energy applied was 40–45 W (15–20 mL/min saline perfusion) with an ablation index of 400–450 during PVI. A minimum waiting time of 30 min was observed before verifying the PVI, confirmed by both the PentaRay catheter and the ablation catheter. Successful PVI was defined as the elimination of all PV potentials and/or atrium-PV potential dissociation.

If anatomical ablation was performed, the protocols included:

1) Linear ablation:

Linear lesions were created along the LA roof and the posterior inferior wall, linking the superior pole of the superior PVs and the inferior aspect of the inferior PVs, respectively, to achieve electrical isolation of the LA posterior box. A mitral isthmus line was then created from both the endocardium in the LA (RF: 40–45 W, 15–20 mL/min saline perfusion) and the epicardium in the CS (RF: 25 W, 25 mL/min saline perfusion) to achieve a perimetral block.

2) VOM ethanol infusion (EIVOM):

Coronary sinus venography was performed in all patients without contrast agent allergies or other contraindications to confirm the presence of the VOM. Once identified, ethanol infusion was attempted; 10 mL of 98% ethanol was delivered over 2 min through an over-the-wire angioplasty balloon (size 1.5 to 2.5 mm by 6 to 8 mm). Following ethanol injection, the ethanol-induced scar was evaluated through a repeat voltage map.

PV isolation and bidirectional block of the ablation lines were required as essential as possible in all groups.

Aggressive ablation group

In the Aggressive Group, targeted EGM mapping was performed first after PVI, followed by anatomical ablation and EGM ablation. The ablation endpoint for the aggressive group was defined as AF termination or no detectable target EGMs. If AF did not terminate after the first attempt, the operator would perform another round of EGM mapping and ablation, repeating until AF terminated or no target EGMs was detected. A single mapping and ablation attempt of targeted EGM was defined as slightly aggressive, two attempts as moderately aggressive, and three or more as extremely aggressive.

The methodology of EGM spatial-temporal analysis for driver mapping was described in our previous work.[15] The targeted EGM regions were characterized by (more details in Supplementary material online, materials):

1) Spatial-temporal dispersion activation, which spread over the AF cycle length (AFCL) across at least three adjacent bipoles and was associated with local AFCL ≤ mean AFCL;
2) Locally short cycle length activity;
3) High-frequency potentials;
4) Focal activity.

Procedure endpoint

The procedure endpoint was defined as AF termination, which was achieved by conversion to SR or a stable atrial tachycardia (AT). If AF converted to AT during the procedure, the arrhythmia was mapped and ablated until conversion to SR. If AF could not be terminated by ablation, a 150 J direct current conversion was performed. More details on the electrophysiological study and ablation protocol are provided in the Supplementary material online, Materials.

Study endpoint

The primary endpoint was defined as freedom from any AF/AT episode lasting more than 30 s after the blanking period, without the use of antiarrhythmic drugs, at the last follow-up.

Secondary outcomes included: (i) freedom from any documented AF episode lasting more than 30 s after the blanking period without antiarrhythmic drug treatment at the last follow-up; (ii) any documented AT episode lasting more than 30 s after the blanking period without antiarrhythmic drug treatment at the last follow-up; (iii) the occurrence of periprocedural adverse events.

Follow-up

Following the ablation procedure, all patients were hospitalized for at least 3 days, and cardiac rhythm was continuously monitored during the first 48 h. Anti-arrhythmic medications (amiodarone, dronedarone, or propafenone) were prescribed for 1–2 months post-ablation and were discontinued 5 half-lives before the end of the first 3 months (blanking period). Any atrial arrhythmia occurring during the blanking period was not considered a recurrence. Outpatient visits, including 48-h Holter monitoring, were scheduled at 1, 3, 6, 9, and 12 months, and every 6 months thereafter if the patient remained asymptomatic. Monthly telephone interviews were also conducted. All patients were instructed to undergo additional ECGs and 7-day Holter recordings if they experienced symptoms suggestive of tachycardia. A recurrence of atrial arrhythmia was defined as any episode lasting 30 s (symptomatic or asymptomatic), detected by ECG and/or Holter monitoring.

Statistical analysis

Differences between continuous variables with a normal distribution were expressed as mean ± standard deviation or median [inter-quartile range (IQR)] and assessed using the Student's *t*-test. Non-normally distributed variables were compared using the rank-sum test. Categorical variables were compared using the χ^2 test. For survival or time-to-event data, Kaplan–Meier survival curves were generated to illustrate patient survival in each group, with HRs and 95% CIs estimated using a Cox proportional hazards model.

Logistic regression analysis was employed to construct the PS based on whether patients received aggressive ablation or not, using covariates including age, sex, longstanding AF, hypertension, diabetes mellitus, prior stroke, coronary artery disease, heart failure, left atrial diameter (LAD), and the use of antiarrhythmic drugs (AAD). The 1:1 nearest neighbour matching method was applied to match PSs, with a maximum caliper width set to 0.25 of the PS standard deviation.

For all tests, significance was defined as $P \leq 0.05$. Statistical analyses were performed using SPSS version 22.0 and R version 3.6.2 software. Sub-group analyses of study outcomes were conducted based on AF termination, extent of ablation aggressiveness, extremely old age (>80 years), longstanding AF, ejection fraction (EF), LAD, severe valvular disease and structural heart disease.

Results

Baseline characteristics

According to the medical records, a total of 6345 patients were diagnosed with PerAF, and 4833 of these patients underwent CA. Of these, 1862 patients who received extensive electro-anatomical guided ablation were categorized into the Aggressive Group, while 2971 patients who underwent anatomical guided ablation or PVI alone were assigned to the Regular Group. After excluding patients with previous ablation procedures ($n = 605$) and those with severely incomplete treatment data ($n = 412$), 1708 patients with aggressive ablation, and 2158 patients with regular ablation (455 patients with PVI only and 1703 patients with anatomical ablation) were analysed. Following 1:1 PS matching, 3120 patients were included in the final analysis, with 1560 patients in each group. *Figure 1* summarizes the patient enrolment flow for the trial. There were no significant differences in baseline characteristics between the two groups (*Table 1*). As a result, PS matching produced a cohort that was well balanced in terms of all baseline characteristics.

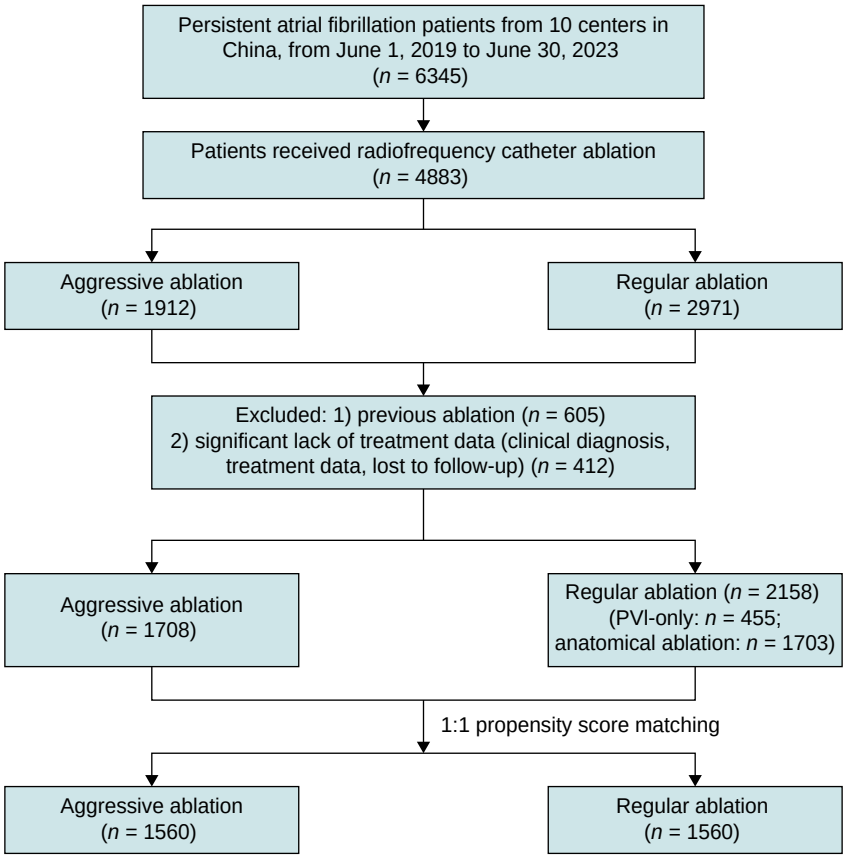


Figure 1 Study flowchart.

Table 1 Baseline characteristics after PS matching

	PS-matched (1:1) population			*P* value
	Overall after PS match (*n* = 3120)	**Aggressive group (*n* = 1560)**	**Regular group (*n* = 1560)**	
Age (years)	72.4 ± 8.9	72.5 ± 9.1	72.59 ± 9.0	0.736
Male, n (%)	1888 (60.5)	924 (59.2)	964 (61.8)	0.143
BMI, kg/m^2	24.2 ± 3.2	24.1 ± 3.3	24.3 ± 3.1	0.081
AF duration, months	7 (2–48)	8 (2–48)	6 (2–48)	0.385
Longstanding AF	1635 (52.4)	805 (51.6)	830 (53.2)	0.370
NYHA Class				
I	764 (24.5)	379 (24.3)	385 (24.6)	0.803
II	1354 (44.4)	655 (42.0)	699 (44.8)	0.112
III	702 (22.5)	364 (23.3)	338 (21.7)	0.265
IV	300 (9.6)	162 (10.4)	138 (8.8)	0.145
CHA2DS2-VASC score, n (%)				
0	405 (13.0)	198 (12.7)	207 (13.4)	0.632
1	580 (18.6)	285 (18.3)	295 (18.9)	0.645
2	652 (20.9)	332 (21.3)	320 (20.4)	0.597
3	630 (21.2)	321 (20.6)	309 (19.8)	0.593
>3	852 (27.3)	424 (27.1)	428 (27.4)	0.872
Medical history, n (%)				
Hypertension	1666 (53.4)	833 (53.4)	833 (53.4)	1.000
Diabetes mellitus	515 (16.5)	257 (16.5)	258 (16.5)	0.962
Prior stroke	398 (12.5)	191 (12.2)	207 (13.3)	0.391
Coronary artery disease	390 (12.5)	190 (12.2)	200 (12.8)	0.588
Heart failure	284 (9.1)	142 (9.1)	142 (9.1)	1.000
AADs use after ablation, n (%)				
Amiodarone	2505 (80.3)	1273 (81.6)	1232 (79.0)	0.065
Beta-blocker	1142 (36.6)	545 (34.9)	597 (38.3)	0.053
Echocardiography parameters				
LAD, mm	44.5 ± 5.3	44.3 ± 5.3	44.6 ± 5.3	0.114
LVEF, %	60.2 ± 8.2	60.4 ± 8.1	60.1 ± 7.9	0.295

BMI, body mass index; LAD, left atrial diameter; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association functional class; Scores on CHA_2DS_2-VASc, a clinical estimation of the risk of stroke among patients with atrial fibrillation, range from 0 to 9, with higher scores indicating a higher risk of stroke.

Procedural outcomes

All patients were in AF at the start of the procedure. PVI was successfully performed in all patients. In the Regular Group, 455 patients underwent PVI only, while 1105 patients received anatomical ablation. In the anatomical ablation group, 75% (892/1105) of patients successfully completed EIVOM. In the Aggressive Group, all patients completed EGM-guided ablation, with 596 patients receiving slightly aggressive ablation, 642 receiving moderately aggressive ablation, and 322 receiving extremely aggressive ablation. On average, 3.5 targeted EGM regions were ablated per patient. The most commonly mapped regions were the LA roof (22.2%), followed by the anterior wall (20.1%), posterior wall (16.3%), bottom (11.0%), LA appendage basal (9.4%), right atrium (15.4%), and other sites (5.6%). On average, 19.1 ± 7.4% of all mapped EGM regions were ablated.

There was no significant difference in the acute bidirectional block of ablation lines between the Regular and Aggressive groups [77.7% (859/1105) vs. 75.4% (1176/1560), $P = 0.159$].

Acute AF termination during the procedure was observed in 1373 patients (44.0%), with 1045 in the Aggressive Group and 328 in the Regular Group. Of these, 549 patients (40.0%) converted to SR, while 824 (60.0%) converted to AFL/AT. The Aggressive Group had a significantly higher rate of AF termination compared to the Regular Group [67.0% vs. 21.0%, $P < 0.001$] (*Table 2*). Notably, in the aggressive ablation group, 224 patients achieved AF termination during anatomical ablation, with targeted EGMs detected within the anatomical ablation regions. Thus, anatomical ablation in these cases effectively incorporated targeted EGM ablation. These 224 patients were classified into the slightly aggressive ablation sub-group. After AF termination, no further EGM ablation was performed on these patients, aside from completing the corresponding anatomical ablation.

Figure 2 lists the critical sites of procedural AF termination. Among all patients with AF termination, the key sites where AF terminated included the roof (405 patients, 29.5%), anterior wall (217 patients, 15.8%), posterior wall (152 patients, 11.1%), bottom (181 patients, 13.2%), LA appendage (161 patients, 11.7%), right atrium (127 patients, 9.2%; including 4.8% in the right atrial appendage, 2.9% in the right septum, and 1.5% in the right atrial free wall), and other sites (130 patients, 9.5%). The distribution of target EGM regions closely mirrored the distribution of AF termination sites.

Table 2 Study outcomes of aggressive ablation vs. regular ablation

	Aggressive group (n = 1560)	Regular group (n = 1560)	Absolute percentage difference (95% CI)	Hazard rate (95% CI)	*P* value
Procedure outcomes					
Procedural AF termination	1045 (67.0)	328 (21.0)	0.460 (0.429–0.491)	0.131 (0.112–0.154)	<0.001
Primary outcomes					
Freedom from AF/AT recurrence at 12 months	1032 (66.2)	925 (59.3)	0.069 (0.035–0.103)	0.745 (0.644–0.862)	<0.001
Secondary outcomes					
Freedom from AF recurrence at 12 months	1219 (78.1)	1101 (70.6)	0.076 (0.045–1.107)	0.671 (0.571–0.789)	<0.001
AT recurrence at 12 months	187 (12.0)	176 (11.3)	0.007 (−0.016–0.030)	1.071 (0.860–1.333)	0.539
Safety outcomes					
Adverse events	37 (2.4)	28 (1.8)	0.006 (−0.004–0.016)	1.329 (0.809–2.183)	0.259
Hematoma	20	15			0.395
Arteriovenous fistula	3	4			0.705
Pseudoaneurysms	5	1			0.218
Transient ischaemic attack	5	2			0.453
Pericardial effusions	4	6			0.526

AF, atrial fibrillation; AT, atrial tachycardia.

The Aggressive Group had a longer procedure time than the Regular Group (200.5 ± 36.4 vs. 180.5 ± 32.1 min, $P < 0.001$). However, the fluoroscopy time was similar between the two groups (7.4 ± 2.6 vs. 7.5 ± 3.5 min, $P = 0.620$).

Study outcomes

The study outcomes are presented in *Table 2*, with time-to-event analysis shown in *Figure 3*. At the end of the 12-month follow-up, freedom from AF/AT recurrence after the blanking period, without AADs, was achieved in 1032 (66.2%) patients in the Aggressive Group and 925 (59.3%) patients in the Regular Group (log-rank $P < 0.001$; hazard ratio [HR] 0.745, [95% CI, 0.644–0.862], with an absolute difference of 6.9% [95% CI, 3.5–10.3%]) (*Figure 3A*). Freedom from AF recurrence after the blanking period, off AADs, was also significantly higher in the Aggressive Group compared to the Regular Group (78.1% vs. 70.6%, log-rank $P < 0.001$; HR 0.671 [95% CI, 0.571–0.789], with an absolute difference of 7.6% [95% CI, 4.5–11.1%]) (*Figure 3B*). However, there was no significant difference in AT/AFL recurrence between the two groups (12.0% vs. 11.3%, log-rank $P = 0.539$; HR 1.071 [95% CI, 0.860–1.333], with an absolute difference of 0.7% [95% CI, −1.6–3.0%]).

Additionally, within the regular cohort, we matched 455 patients from the PVI-only cohort with 455 from the anatomical ablation cohort to evaluate whether additional anatomical lesions improve outcomes over PVI alone (*Table 3*). Although AF/AT-free survival at 12 months was slightly higher in the anatomical ablation group compared to the PVI-only group [60.7% vs. 55.6%, log-rank $P = 0.122$; HR 0.812 (95% CI, 0.624–1.507)], and a similar trend was also observed for AF recurrence [72.7% vs. 66.8%, log-rank $P = 0.051$; HR 0.754 (95% CI, 0.568–1.002)], neither outcome showed statistical significance.

As for anatomical ablation cohort and aggressive ablation cohort, 1:1 PS matching yielded 1362 patients each to evaluate if aggressive ablation targeting EGMs offers advantages over anatomical ablation (*Table 4*). At the end of the 12-month follow-up, the aggressive ablation group showed significantly higher rate of AF/AT free survival [67.5% vs. 59.9%, log-rank $P < 0.001$; HR 0.720 (95% CI, 0.616–0.843)] and AF-free survival [78.7% vs. 70.3%, log-rank $P < 0.001$; HR 0.639 (95% CI, 0.537–0.761)] compared to the anatomical ablation group.

Safety outcome

Adverse events occurred in 65 (2.1%) patients (*Table 2*). The most common adverse events were vascular complications, including 35 cases of hematoma at the access site, 7 arteriovenous fistulas, and 6 pseudoaneurysms. Serious adverse events included 7 transient ischaemic attacks and 10 pericardial effusions, all of which were treated conventionally with no long-term sequelae. There were no deaths or instances of PV stenosis. There was no significant difference in the incidence of adverse events between the Aggressive Group and the Regular Group ($P = 0.259$).

Sub-group analysis outcomes

We further analysed the impact of procedural AF termination on patient prognosis. Across the entire study cohort, patients who experienced AF termination had a higher rate of AF/AT-free survival [993/1373, 72.3% vs. 964/1747, 55.2%, log-rank $P < 0.001$, HR 0.596 (95% CI, 0.514–0.691)] (*Figure 4A*) and a higher rate of AF-free survival [1135/1373, 82.7% vs. 1184/1747, 67.8%, log-rank $P < 0.001$, HR 0.441 (95% CI, 0.371–0.524)] (*Figure 4B*) compared to those without AF termination at the end of the 12-month follow-up after a single ablation procedure. Similarly, AT/AFL recurrence was lower in the termination cohort [10.3% vs. 12.6%; log-rank $P = 0.047$; HR 0.798 (95% CI, 0.637–0.998)].

We also assessed the effect of the extent of aggressive ablation on study outcomes (*Table 5*).

In the Regular Group, compared to PVI alone, the anatomical ablation group showed a lower incidence of AF recurrence (72.1% vs. 66.8%, log-rank $P = 0.036$) and a higher rate of procedural AF termination (26.4% vs. 7.9%, log-rank $P < 0.001$). Although the anatomical ablation group did not show a statistically significant difference, it exhibited a slightly higher rate of freedom from AF/AT recurrence (60.8% vs. 55.6%, log-rank $P = 0.057$).

In comparison to the anatomical ablation group, both the slightly aggressive and moderately aggressive groups, with increased EGM mapping and ablation, demonstrated a significant improvement in 12-month freedom from AF/AT recurrence (66.3%, 67.9% vs. 60.8%; log-rank $P = 0.026$, 0.003, respectively) and procedural AF termination

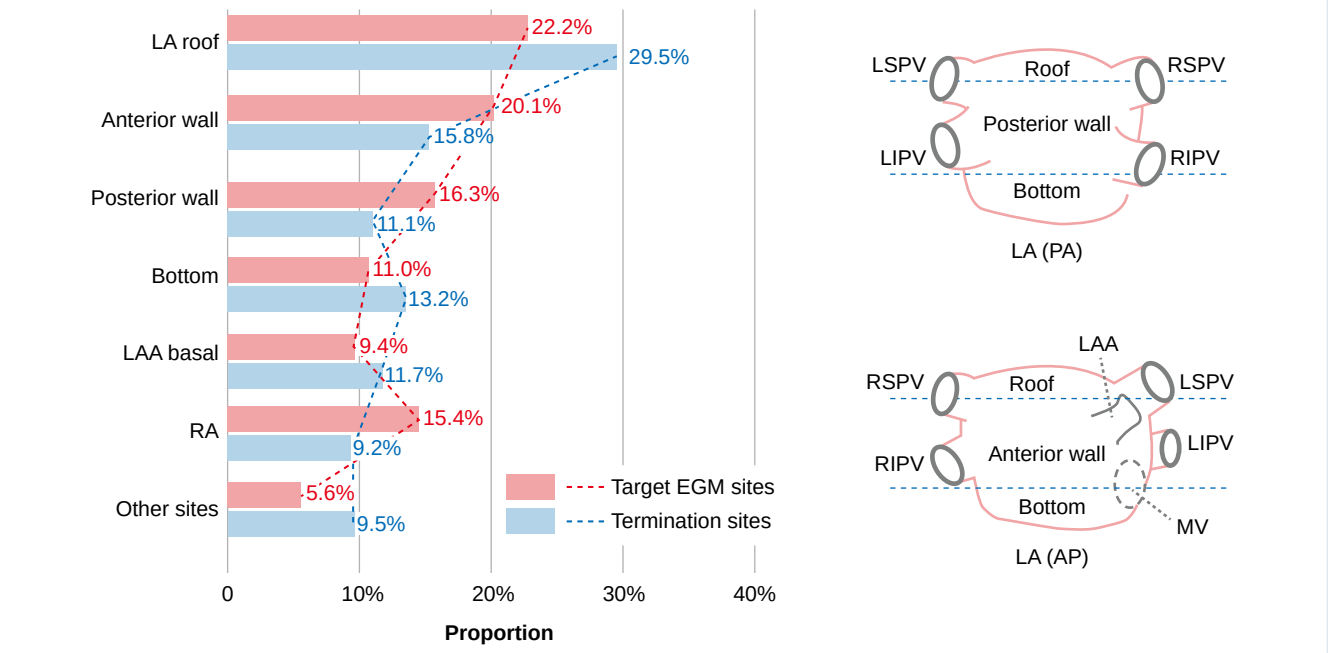


Figure 2 Target EGM sites and termination sites. LA, left atrium; LAA, left atrial appendage; RA, right atrium; EGM, electrogram; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; MV, mitral valve.

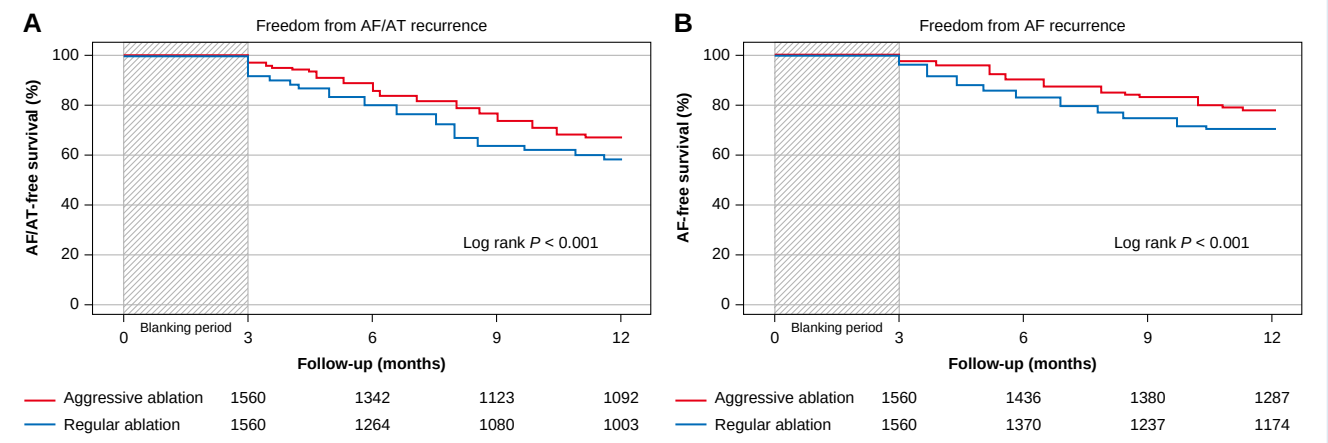


Figure 3 Time-to-event analysis of aggressive ablation. *A*) Comparison of freedom from AF/AT recurrence between Aggressive Ablation Group and Regular Ablation Group. *B*) Comparison of freedom from AF recurrence between Aggressive Ablation Group and Regular Ablation Group.

(66.8%, 70.2% vs. 26.4%; log-rank $P < 0.001$, < 0.001, respectively). However, no statistically significant differences were observed in the primary endpoints between the extremely aggressive ablation group and the anatomical ablation group (201/322, 62.4% vs. 60.8%, log-rank $P = 0.062$).

Among the three groups that underwent aggressive ablation, no statistical differences were observed in primary endpoints between the slightly aggressive and moderately aggressive ablation groups (66.3% vs. 67.9%, log-rank $P = 0.540$), nor in procedural AF termination rates (66.8% vs. 70.2%, log-rank $P = 0.055$). The extremely aggressive ablation group showed a trend towards a lower rate of AF/AT-free survival, although this was not statistically significant (62.4% vs. 67.9%, log-rank $P = 0.089$) compared to the moderately aggressive group.

The rates of freedom from AF or AF/AT recurrence and AF termination increased with the level of ablation aggressiveness but declined when extremely aggressive ablation was performed (*Figure 5*).

Additionally, a sub-group analysis of ablation results was conducted. Sub-group comparisons based on age, longstanding AF, LAD, EF, severe valvular disease, and structural heart disease are presented in *Figure 6*.

Discussion

Main findings

In this multi-centre, real-world cohort study, we found the following: (i) Compared to regular ablation (PVI or PVI plus anatomical ablation),

Table 3 Study outcomes of anatomical ablation vs. PVI-only after 1:1 PS matching

	Anatomical ablation group (n = 455)	PVI only group (n = 455)	Absolute percentage difference (95% CI)	Hazard rate (95% CI)	*P* value
Primary outcome					
Freedom from AF/AT recurrence at 12 months	276 (60.7)	253 (55.6)	0.051 (−0.013–0.115)	0.812 (0.624–1.507)	0.122
Secondary outcome					
Freedom from AF recurrence at 12 months	331 (72.7)	304 (66.8)	0.059 (0.000–0.119)	0.754 (0.568–1.002)	0.051
AT recurrence at 12 months	55 (12.7)	51 (11.2)	0.009 (−0.033–0.050)	1.089 (0.726–1.634)	0.679

PVI, pulmonary vein isolation; AF, atrial fibrillation; AT, atrial tachycardia.

Table 4 Study outcomes of aggressive ablation vs. anatomical ablation after 1:1 PS matching

	Aggressive ablation group (n = 1362)	Anatomical ablation group (n = 1362)	Absolute percentage difference (95% CI)	Hazard rate (95% CI)	*P* value
Primary outcome					
Freedom from AF/AT recurrence at 12 months	919 (67.5)	816 (59.9)	0.076 (0.040–0.112)	0.720 (0.616–0.843)	<0.001
Secondary outcome					
Freedom from AF recurrence at 12 months	1072 (78.7)	957 (70.3)	0.084 (0.051–0.117)	0.639 (0.537–0.761)	<0.001
AT recurrence at 12 months	153 (11.2)	141 (10.4)	0.009 (−0.014–0.032)	1.096 (0.860–1.396)	0.459

AF, atrial fibrillation; AT, atrial tachycardia.

aggressive ablation (PVI, anatomical ablation, and EGM-guided ablation) resulted in a higher rate of procedural AF termination and a lower rate of AF recurrence, without increasing the incidence of post-operative atrial flutter; (ii) Procedural AF termination was linked to more favourable outcomes in the ablation of PerAF; (iii) Moderately aggressive ablation may provide the best clinical outcomes.

Aggressive ablation and regular ablation

As is widely practiced in PerAF ablation,[16] anatomical ablation aims to achieve the bidirectional block of the ablation lines, with clearly defined targets and endpoints.[17] Murata *et al.*[18] reported that freedom from atrial tachyarrhythmia recurrence without anti-arrhythmic drugs after a single procedure was significantly higher in PVI + posterior wall isolation than in PVI alone (hazard ratio: 0.452, 95% confidence interval (CI): 0.308–0.664, $P < 0.001$). In the VENUS study,[12] the additional of VOM ethanol infusion increased the success rate of a single ablation by 11.2% over PVI alone, leading the latest Chinese expert consensus to recommend this strategy as an optimal method for treating PerAF.[13] Recently, Sang *et al.*[14] further confirmed the superiority of linear ablation combined with EIVOM in PerAF ablation.

In our study, PVI alone and PVI plus anatomical ablation achieved success rates of 55.6% and 60.8%, respectively, aligning with the findings of the VENUS study. As for differences between the PROMPT-AF study and our study, although AF/AT-free survival rate in anatomical ablation did not show a statistically significant difference compared to PVI-only (log-rank $P = 0.057$), the actual success rate in the anatomical group was higher, which aligns with the results from the PROMPT-AF study. The differences between the results of the PROMPT-AF study and our study can be attributed to three main factors. First, as a real-world study, the baseline characteristics of the patient populations in our research differ significantly from those in the PROMPT-AF study, including: (i) the average age of the study population in our research was older (72.4 vs. 61.3); (ii) the proportion of longstanding persistent AF patients was higher (53.3% vs. 45.9%); and (iii) the inclusion and exclusion criteria differed between the two studies, which may be more representative of real-world clinical settings. Second, in the PROMPT-AF study, 85% of patients successfully completed EIVOM, whereas about 75% of patients in our study completed it. Third, unlike the PROMPT-AF study, we did not include tricuspid isthmus ablation as a routine part of the ablation protocol.

However, regular ablation has limitations, particularly in its inability to personalize interventions to target the sustaining substrates of PerAF.[19] EGM-guided ablation, on the other hand, focuses on precisely identifying specific target potentials.[6,20] Although the clinical outcomes of EGM-guided ablation are still debated, extensive ablation is often associated with an increased risk of post-ablation atrial flutter.[21]

In our previous RCT,[15] 72% of patients who received anatomical ablation combined with EGM-guided ablation were free from AF recurrence, and the recurrence rates of AT were similar between the aggressive and anatomical ablation groups (14% vs. 18%). The current study shows a similar trend. This suggests that aggressive ablation may combine the benefits of both anatomical and EGM-guided ablation: aggressive ablation stabilizes linear ablation without increasing the risk of iatrogenic atrial flutter and targets EGM to intervene in the substrates sustaining AF. This could explain the similar distribution of target EGM regions and termination sites, contributing to a higher rate of AF termination. Additionally, although Darden *et al.*[22] reported that PVI + adjunctive was associated with a higher risk of any complication [3.0 vs. 4.5%, odds ratio (OR) 1.30, 95% CI 1.07–1.58] and major complication (0.8 vs. 1.4%, OR 1.56, 95% CI 1.10–2.21), aggressive ablation in our study does not appear to increase procedural complications, ensuring procedural safety.

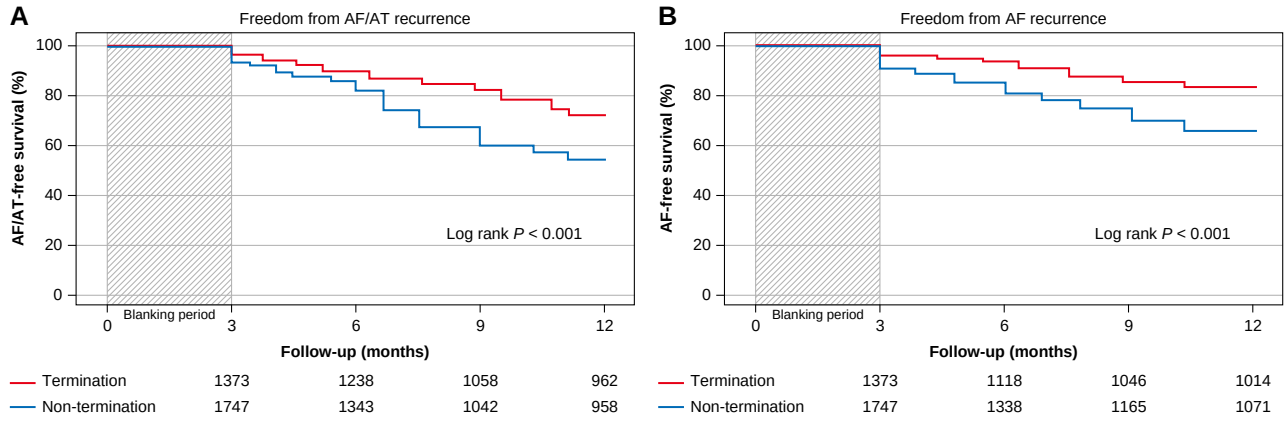


Figure 4 Time-to-event analysis of AF termination. *A*) Comparison of freedom from AF/AT recurrence between termination patients and non-termination patients. *B*) Comparison of freedom from AF recurrence between Termination patients and non-termination patients.

Table 5 Extent of aggressive ablation on study outcomes

	Regular group (n = 1560)		Aggressive group (n = 1560)		
	PVI only (n = 455)	Anatomical ablation (n = 1105)	Slightly aggressive ablation (n = 596)	Moderately aggressive ablation (n = 642)	Extremely aggressive ablation (n = 322)
Primary outcome					
Freedom from AF/AT recurrence at 12 months	253 (55.6)	672 (60.8)	395 (66.3)	436 (67.9)	201 (62.4)
Secondary outcome					
Freedom from AF recurrence at 12 months	304 (66.8)	797 (72.1)	463 (77.7)	507 (79.0)	249 (77.3)
AT recurrence at 12 months	51 (11.2)	125 (11.3)	68 (11.4)	71 (11.1)	48 (14.9)
AF termination	36 (7.9)	292 (26.4)	398 (66.8)	461 (70.2)	196 (60.9)

PVI, pulmonary vein isolation; AF, atrial fibrillation; AT, atrial tachycardia.

In our study, both clinical outcomes and procedural AF termination rates improved with increasing levels of ablation aggressiveness. However, extremely aggressive ablation was associated with a decline in procedural success and a rise in AF/AT recurrence. Extremely aggressive ablation group predominantly included patients with longstanding persistent AF, a cohort typically characterized by more advanced electrical and structural remodelling. In these patients, anatomical ablation is often more challenging, which can result in incomplete lesion formation or discontinuities in the ablation lines.[23] Furthermore, the significant atrial fibrosis present complicates EGM mapping, leading to misidentification or failure to the targeted EGMs. Given that our study purses AF termination, these patients often require repeated mapping and additional ablation procedures.

Impact of atrial fibrillation termination on ablation outcome

Recent studies have shown that PerAF is sustained by several critical drivers, and targeted ablation of these driver areas results in a high rate of acute AF termination and reduced recurrence.[6,24] Thus, procedural AF termination may reflect an intervention in the maintenance mechanisms of PerAF and could serve as a suitable ablation endpoint. However, results across studies remain inconsistent. A subanalysis of the STAR AF II trial identified AF termination as an independent predictor of reduced recurrence,[25] while long-term follow-up studies using the 'stepwise' approach also demonstrated improved outcomes in patients with procedural AF termination.[26,27] Conversely, the CHASE-AF trial reported that although AF termination was achieved in 60% of patients undergoing defragmentation, recurrence-free survival was not significantly better compared to those undergoing PVI alone.[28] Several factors should be considered when interpreting these differing results. First, many studies included CFAE ablation, though recent evidence suggests that CFAE potentials may not be an ideal target for ablation.[29,30] Second, the single-centre design of some studies[19] may limit the generalizability of their findings. Finally, the rate of AF termination can vary depending on the adjunctive ablation strategies used.

In this study, we prospectively enrolled 4883 PerAF patients who underwent various mainstream adjunctive ablation strategies across 10 electrophysiological centres. Our analysis showed that procedural AF termination was associated with reduced recurrence of AF or AF/AT, without a significant difference in AFL/AT recurrence. These results support the concept that AF termination could serve as a reliable endpoint for PerAF ablation.

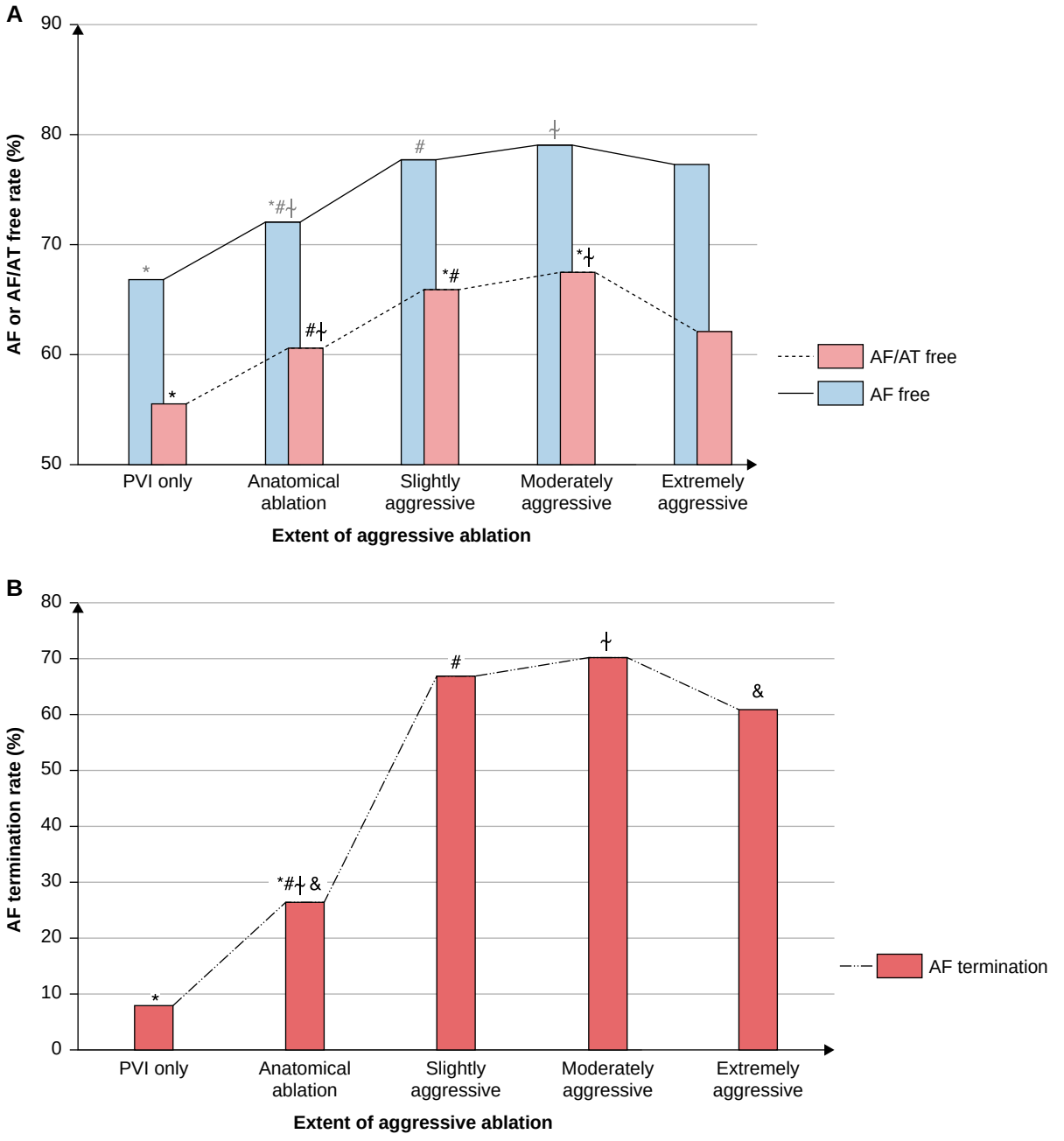


Figure 5 Impact of the extent of aggressive ablation on study outcomes. *A*) Impact of the extent of aggressive ablation on AF or AF/AT free. *B*) Impact of the extent of aggressive ablation on procedural AF termination. AF, atrial fibrillation; AT, atrial tachycardia; *#†&: log-rank $P < 0.05$.

New stepwise ablation protocol

Based on the aforementioned perspectives, we propose a new stepwise approach for ablation strategy of PerAF, incorporating PVI, EGM mapping, anatomical ablation, followed by a single round of EGM ablation or twice targeted EGM mapping and ablation, employing AF termination as the ablation endpoint.

Haissaguerre *et al*. firstly described a stepwise ablation approach for PerAF in 2005, which included pulmonary vein isolation (PVI), CFAE ablation, and linear ablation at the left atrial roof and mitral isthmus, aiming for AF termination as the endpoint.[31] However, the stepwise approach, characterized by prolonged procedural duration, excessive complexity, lack of precise ablation, and high incidence of AT recurrence, hinders its widespread adoption. Subsequent randomized controlled trials like CHASE-AF[28] and Alster-Lost-AF Trial[8] have failed to demonstrate that the stepwise strategy achieves higher success rates compared to PVI alone.

Although the procedure remains lengthy and technically complex, the new stepwise approach addresses key limitations of the conventional method, particularly in terms of precision, AT recurrence, and complications. This novel approach holds promise as a more rational ablation strategy for PerAF. However, further clinical practice is required to validate its efficacy and optimize procedures.

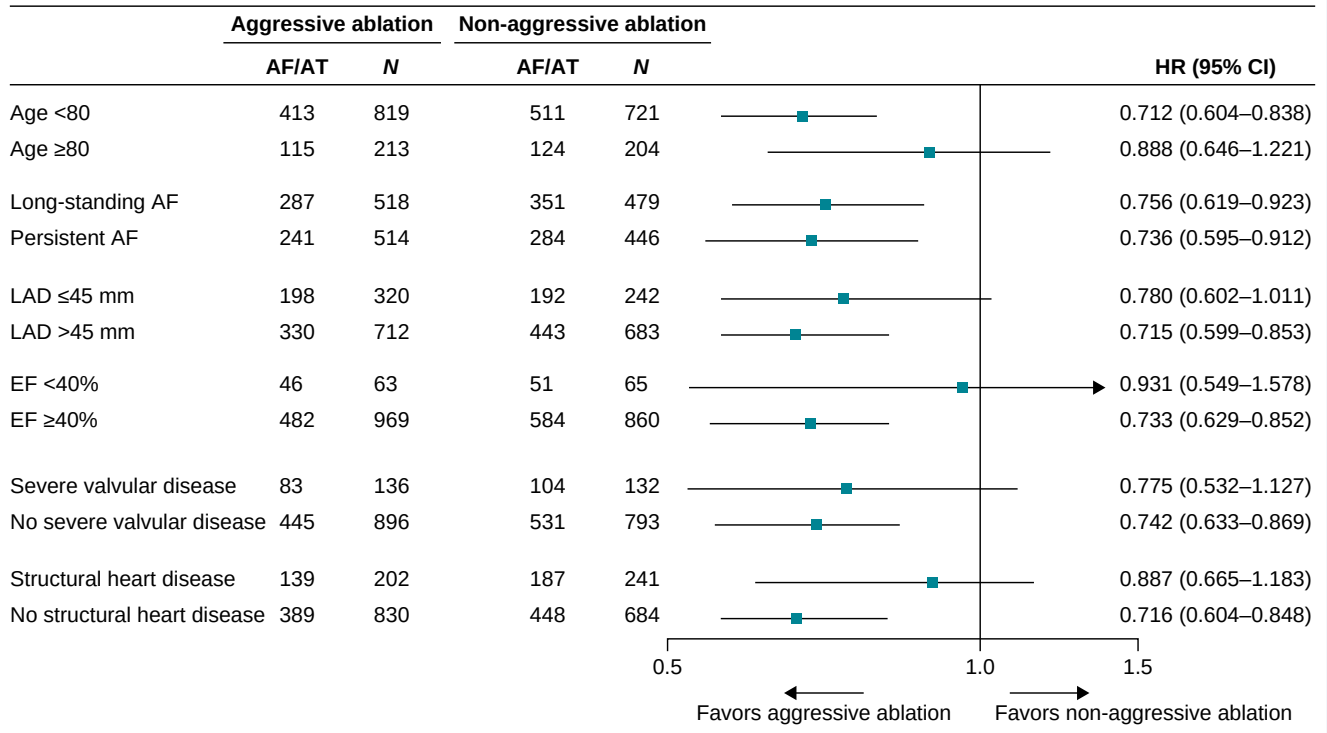


Figure 6 Sub-group analysis on ablation results. AF, atrial fibrillation; LAD, left atrial diameter; EF, ejection fraction; HR, hazard ratio.

Limitations

This study has several limitations. First, as a retrospective real-world study, it lacked randomization, particularly in terms of baseline matching when analysing the impact of ablation aggressiveness on outcomes, and the limited number of patients undergoing PVI-only ablation precluded its use as an independent control group. To address these limitations, we performed additional PS matching between the PVI only group and the anatomical ablation group, as well as between the anatomical ablation group and the aggressive ablation group separately for comparison, and analysed the PVI-only group as an independent control group in the sub-group analysis. Second, the subjectivity in identifying target EGMs may affect the reproducibility of the strategy across different centres. To address this, all operators in our study underwent standardized training to ensure consistency in EGM mapping methodology. We have also attempted to employ multi-dimensional entropy calculation tools as we previously reported[32] and software such as CARTO Finder to identify EGMs, ensuring maximum consistency in the mapping of potentials across centres. Besides, the concept of aggressiveness in EGM-guided mapping and ablation may be somewhat subjective. As a retrospective study, due to missing data in certain areas, this may be one of the most objective approaches we could have taken. We also aim to include additional quantitative parameters in future studies, such as the number of ablated EGMs and the proportion of the atrium ablated, to better evaluate the aggressiveness of the ablation. Finally, the follow-up period was limited to 12 months, preventing the identification of late AF/AT recurrences and the absence of implantable event recorders may have led to an underestimation of asymptomatic AF episodes.

Conclusion

Aggressive ablation resulted in more favourable outcomes than regular ablation, with moderately aggressive ablation potentially offering the best clinical outcomes. AF termination appears to be a reliable ablation endpoint.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: None declared.

Disclosures

None.

Data availability

The data that support the findings of this study are available from the corresponding author, Xu Liu (heartlx@sina.com), upon reasonable request.

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