

ORIGINAL RESEARCH

ATRIAL FIBRILLATION

Reduction of AF Burden After Cryoballoon Ablation in Patients With Early Persistent AF

The COOL-PER Trial



So-Ryoung Lee, MD, PhD,^{a,b} Eue-Keun Choi, MD, PhD,^{a,b} Kyung-Yeon Lee, MD,^a JungMin Choi, MD,^a Hyo-Jeong Ahn, MD,^a Soonil Kwon, MD,^c Young-Keun On, MD, PhD,^d Ji Hyun Lee, MD, PhD,^e Youngjin Cho, MD, PhD,^e Il-Young Oh, MD, PhD,^e Hong-Euy Lim, MD, PhD,^f Min-Soo Cho, MD, PhD,^g Gi-Byoung Nam, MD, PhD,^g Gregory Y.H. Lip, MD,^{b,h,i} Seil Oh, MD, PhD^{a,b}

ABSTRACT

BACKGROUND Limited data exist on reducing the atrial fibrillation (AF) burden, the regression from persistent to paroxysmal AF, and symptom improvement after cryoablation in patients with persistent AF.

OBJECTIVES This study sought to evaluate the efficacy of cryoablation in reducing the AF burden, regression to paroxysmal AF, and symptom improvement in patients with early persistent AF.

METHODS This investigator-initiated, multicenter, and prospective cohort study enrolled the patients with early persistent AF (≤ 3 years). All patients were inserted an implantable loop recorder at the time of trial entry. AF burden (percentage of time in AF) and actual AF type were evaluated during pre-cryoablation and 12-month follow-up after cryoablation. AF-related symptoms and quality of life were assessed.

RESULTS A total of 130 patients were enrolled (median age 61 years [Q1-Q3: 54-67 years]; median duration of persistent AF 6 months [Q1-Q3: 4-10 months]). The mean AF burden before cryoablation was $77 \pm 34\%$ (25.4% of high-burden paroxysmal AF; 74.6% of implantable loop recorder-confirmed persistent AF), which was reduced to $9 \pm 21\%$ after 12-month follow-up (mean $68 \pm 37\%$ of AF burden reduction; $P < 0.001$). Of the total, 38.5% had no recurrence of AF, 43.1% had a recurrence of paroxysmal AF, and 18.5% had a recurrence of persistent AF. Among those with confirmed persistent AF at baseline, 76% of patients showed regression to paroxysmal AF or no recurrence. After cryoablation, 77% of patients improved AF-related symptoms and quality of life as assessed by 36-Item Short Form Survey questionnaires.

CONCLUSIONS In patients with early persistent AF, cryoablation significantly reduced AF burden and achieved regression of AF type followed by symptom improvement. (Cryoablation for Pulmonary Vein Isolation Alone in Patients with Early Persistent AF Assessed by Continuous Monitoring [COOL-PER]; [NCT05507749](https://clinicaltrials.gov/ct2/show/study/NCT05507749)).

(JACC Clin Electrophysiol. 2025;11:1234-1247) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

From the ^aDepartment of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; ^bDepartment of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea; ^cDepartment of Internal Medicine, Seoul National University Boramae Medical Center, Seoul, Republic of Korea; ^dCardiac Arrhythmia Center, Heart Vascular and Stroke Institute, Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; ^eDepartment of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; ^fDivision of Cardiology, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea; ^gDepartment of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea; ^hDepartment of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea; ⁱDepartment of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea.

It is well established that pulmonary vein isolation (PVI) is an effective treatment for rhythm control of patients with atrial fibrillation (AF).¹⁻³ In the recent decade, efficacy and safety data of single-shot mode PVI utilizing various energies, including cryogenic energy, have been reported, especially in paroxysmal AF.^{4,5} Of these, cryoballoon ablation was noninferior in efficacy compared with radiofrequency ablation in patients with antiarrhythmic drug (AAD)-refractory paroxysmal AF, with no significant difference in safety.⁴ Recently, cryoablation has demonstrated superior efficacy in preventing atrial arrhythmia recurrence as initial therapy compared with AAD in paroxysmal AF.^{6,7} In addition, the EARLY-AF (Early Aggressive Invasive Intervention for Atrial Fibrillation) study, which followed atrial arrhythmia recurrence with implantable cardiac monitoring devices in all patients, reported a reduced risk of progression to persistent AF in patients who received cryoablation compared with AAD therapy at 3-year of follow-up.⁸

As cryoballoon ablation has become widely applied in treating patients with AF, its efficacy and safety in patients with persistent AF have been reported.⁹⁻¹¹ Persistent AF is more heterogeneous than paroxysmal AF, and the treatment response after rhythm control in patients with persistent AF is more complex than in those with paroxysmal AF.^{12,13} Although studies using continuous cardiac rhythm monitoring tools have well-documented effective AF burden reduction and inhibition of progression to persistent AF after cryoablation in patients with paroxysmal AF,^{8,14} there are limited data on actual AF burden reduction or regression to paroxysmal AF in patients with persistent AF after PVI with cryoablation, other than mere AF recurrence assessed by conventional tools such as 12-lead electrocardiogram (ECG) and 24-hour Holter monitoring.

In this study, we aimed to evaluate the efficacy of cryoablation in reducing AF burden and regression to paroxysmal AF using continuous rhythm monitoring in patients with early persistent AF.

METHODS

STUDY DESIGN. The COOL-PER (Cryoablation for pulmonary vein isolation alone in patients with early Persistent AF assessed by continuous monitoring) trial was an investigator-initiated, multicenter, single-arm, prospective study. Patients with clinically persistent AF ≤ 3 years from the onset were evaluated at 5 sites across the Republic of Korea. Before enrollment, all participants gave informed consent. The study received approval from the ethics and Institutional Review Board at each participating site, adhered to the principles outlined in the Declaration of Helsinki, and registered on ClinicalTrials.gov (NCT05507749).

INCLUSION AND EXCLUSION CRITERIA. Patients 20 to 80 years of age with drug-refractory symptomatic persistent AF ≤ 3 years were eligible for inclusion. Clinical persistent AF was defined as documented AF on 12-lead ECGs performed ≥ 7 days apart, documented 100% AF burden on 24-hour Holter monitoring, and requiring cardioversion for AF of ≥ 7 days duration. Major exclusion criteria included long-standing persistent AF, especially more than 3 years from diagnosis as persistent AF, left atrial (LA) diameter > 50 mm, left ventricular ejection fraction $< 30\%$, prior ablation or cardiac surgery for AF, a percutaneous coronary intervention or myocardial infarction in the prior 3 months, or a stroke or transient ischemic attack in the prior 6 months. Detailed exclusion criteria are presented in [Supplemental Table 1](#).

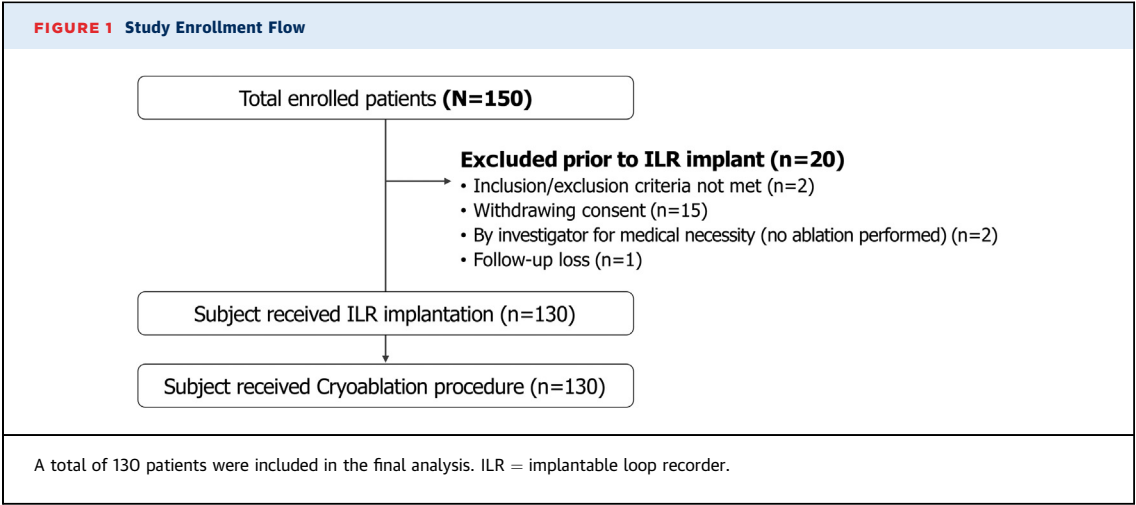
IMPLANTABLE LOOP RECORDER IMPLANTATION FOR CONTINUOUS RHYTHM MONITORING. After enrollment, all patients underwent implantable loop recorder (ILR) implantation to enable continuous cardiac rhythm monitoring (Reveal LINQ; Medtronic). ILR implantation was performed at least 7 days and up to 90 days prior to cryoablation. The monitor was equipped with an algorithm designed to detect AF, enabling continuous analysis of beat-to-beat variability in cardiac cycles. This functionality facilitated the identification of arrhythmia occurrence timing

ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug
AF = atrial fibrillation
ECG = electrocardiogram
ILR = implantable loop recorder
LA = left atrial
PVI = pulmonary vein isolation
SF-36 = 36-Item Short Form Survey

Republic of Korea; ⁸Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; ¹¹Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Chest & Heart Hospital, Liverpool, United Kingdom; and the ¹⁴Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).



and the quantification of AF burden, defined as the percentage of time spent in AF. The monitor’s settings were standardized as outlined in [Supplemental Table 2](#).^{15,16} The parameters were selected to enhance AF detection, achieving a reported sensitivity of 96.1% and a positive predictive value of 73%.^{15,16} In addition to automated detection by ILR-programmed algorithms, all arrhythmia episodes were manually adjudicated by independent, experienced electrophysiologists (E.-K.C., S.-R.L., and J.M.C.). These experts reviewed all ILR-detected events to confirm their accuracy and eliminate false positives (eg, noise or ectopic beats). Manual adjudication was cross-checked by the aforementioned electrophysiologists to ensure accurate representation of AF events and AF burden, while excluding any false positive or unconfirmed episodes.

CRYOBALLOON ABLATION PROCEDURE. The details of the cryoballoon ablation procedure have been previously elucidated.^{4,10,11,14} Details are presented in the [Supplemental Methods](#). The recommended cryoapplication duration consisted of a total of 240 seconds for each pulmonary vein, employing a freeze-thaw-freeze technique;¹⁰ nevertheless, the physician had discretion over the quantity and duration of cryoapplications. While discontinuing AADs after a 90-day post-ablation blanking period was recommended, continuation of AADs or change the type and dose of AADs during follow-up was permitted at the discretion of the treating physicians.

PATIENT FOLLOW-UP. After cryoablation, patients underwent in-office follow-up visits at intervals of 1, 3, 6, 9, and 12 months. At each visit, patients evaluated their pertinent clinical background, received a physical examination, and were assessed via a 12-lead ECG and analysis of the ILR.

ENDPOINTS. The primary endpoint was defined as the change in atrial arrhythmia burden (so-called AF burden) monitored by ILR from pre-cryoablation to post-cryoablation from day 91 (excluding a 90-day blanking period) to 12-month follow-up. Secondary endpoints were: 1) the recurrence of AF lasting more than 30 seconds for the first time between day 91 and 365 after cryoablation assessed by ILR monitor; 2) the AF recurrence pattern assessed by separating paroxysmal recurrence and persistent recurrence, with persistent recurrence defined as AF lasting more than 7 days; 3) arrhythmia-related symptoms assessed by European Heart Rhythm Association symptom classification at pre-cryoablation and 12-month follow-up²; and 4) quality-of-life surveys (36-Item Short Form Survey [SF-36] questionnaires) at pre-cryoablation and at the 12-month follow-up visit.

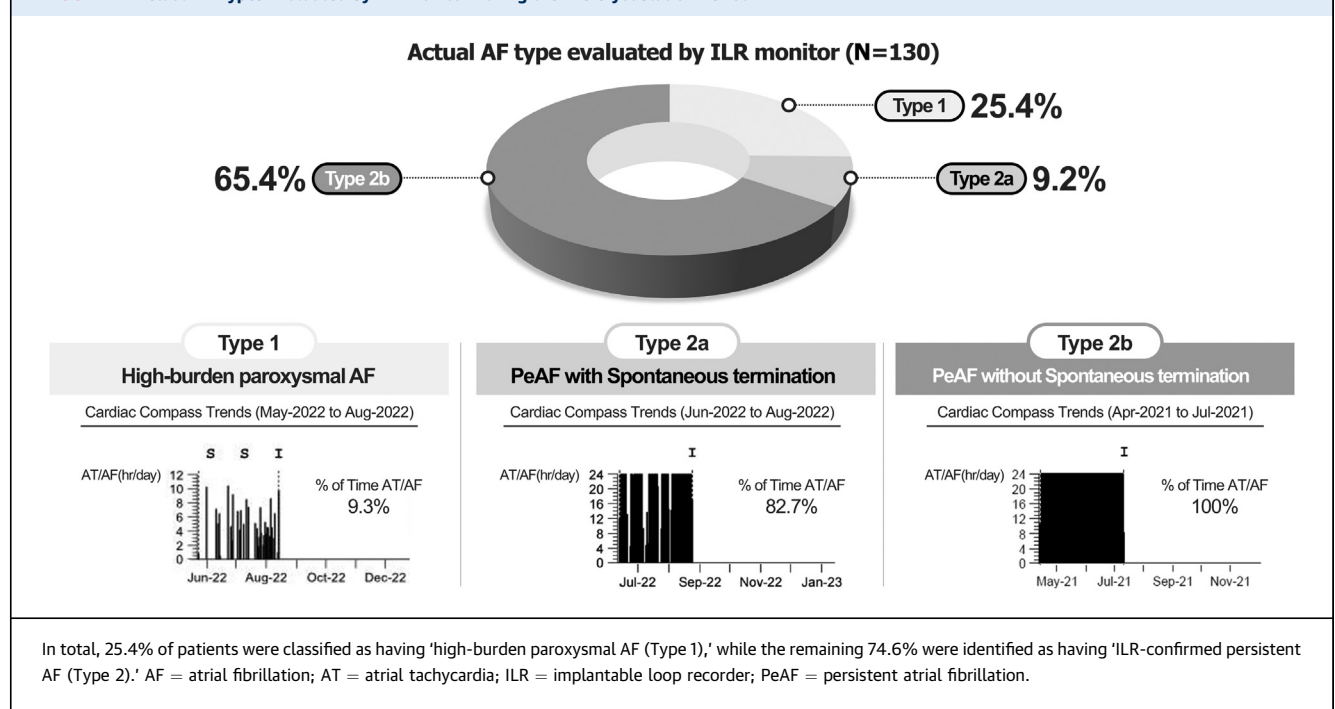
STATISTICAL ANALYSIS. Statistical analyses were performed using SPSS Statistics version 25 (IBM), Stata version 18 (StataCorp), and GraphPad Prism 9 (GraphPad Software). Continuous variables following a normal distribution were presented as mean ± SD, while non-normally distributed variables were expressed as median (Q1-Q3). A summary of baseline information, pertinent medical history, and procedure details was provided. Baseline characteristics were described for the entire study population according to baseline actual AF type. Continuous variables with a normal distribution were compared using the independent *t* test, while non-normally distributed variables were analyzed with the Wilcoxon rank sum test. Categorical variables were compared between groups using the chi-square or Fisher exact test as appropriate. The AF burden and SF-36 scores before and after cryoballoon ablation were presented as mean ± SD, and the comparison of

TABLE 1 Baseline Patient Characteristics

	Total	Type 1 High-Burden Paroxysmal AF	Type 2 ILR-Confirmed Persistent AF	P Value
Patients	130 (100)	33 (25.4)	97 (74.6)	
Age, y	61.0 (54.0-66.8)	61.0 (54.0-66.0)	61.0 (55.0-67.0)	0.502
<65 y	88 (67.7)	24 (72.7)	64 (66.0)	0.814
≥65-<75 y	40 (30.8)	9 (27.3)	31 (32.0)	
≥75 y	2 (1.5)	0 (0)	2 (2.1)	
Female	31 (23.8)	9 (27.3)	22 (22.7)	0.593
Body mass index, kg/m ²	25.9 ± 2.7	26.2 ± 2.9	25.8 ± 2.7	0.383
Persistent AF at study enrollment	130 (100)	33 (100)	97 (100)	N/A
AF on ≥2 consecutive ECGs performed 7 or more days apart	126 (96.9)	30 (90.9)	96 (99.0)	0.050
100% AF in 24-h Holter monitoring	47 (36.2)	10 (30.3)	37 (38.1)	0.022
Cardioversion before enrollment	44 (33.8)	9 (27.3)	35 (36.1)	0.356
Failed to turn sinus rhythm after cardioversion	6 (4.6)	72 (22.2)	4 (11.4)	0.586
Initial paroxysmal AF to persistent AF	42 (32.3)	14 (42.4)	28 (28.9)	0.150
Duration of AF, mo	9.0 (5.0-19.8)	10.0 (5.0-36.0)	9.0 (6.0-18.0)	1.000
Duration of persistent AF, mo	6.0 (4.0-10.0)	5.0 (3.0-9.0)	6.0 (5.0-12.0)	0.008
≤1 y	103 (79.2)	29 (87.9)	74 (76.3)	0.156
>1 y to ≤3 y	27 (20.8)	4 (12.1)	23 (23.7)	
History of atrial flutter	31 (23.8)	12 (36.4)	19 (19.6)	0.051
EHRA symptom classification				
1	4 (3.1)	1 (3.0)	3 (3.1)	0.129
2a	58 (44.6)	17 (51.5)	41 (42.3)	
2b	47 (36.2)	7 (21.2)	40 (41.2)	
3	21 (16.2)	8 (24.2)	13 (13.4)	
QoL assessed by SF-36	143.8 (119.2-163.4)	138.5 (110.9-157.8)	144.8 (127.5-164.4)	0.231
Comorbidities				
Hypertension	72 (55.4)	14 (42.4)	58 (59.8)	0.083
Diabetes mellitus	24 (18.5)	9 (27.3)	15 (15.5)	0.131
Heart failure	21 (16.2)	6 (18.2)	15 (15.5)	0.714
Coronary artery disease	8 (6.2)	4 (12.1)	4 (4.1)	0.112
Peripheral artery disease	1 (0.8)	0 (0)	1 (1.0)	1.000
Prior myocardial infarction	2 (1.5)	2 (6.1)	0 (0)	0.063
Prior stroke or TIA	11 (8.5)	2 (6.1)	9 (9.3)	0.729
Structural heart disease	9 (6.9)	1 (3.0)	8 (8.2)	0.447
CHA ₂ DS ₂ -VASc score	2.0 (1.0-2.0)	2.0 (1.0-3.0)	2.0 (1.0-2.0)	0.826
0	27 (20.8)	8 (24.2)	19 (19.6)	0.842
1	30 (23.1)	7 (21.2)	23 (23.7)	
≥2	73 (56.2)	18 (54.5)	55 (56.7)	
Serum creatinine, g/dL	1.0 (0.8-1.1)	1.0 (0.8-1.1)	1.0 (0.8-1.1)	0.894
Creatinine clearance, mL/min	78.3 ± 20.3	78.9 ± 23.2	78.1 ± 19.3	0.528
Creatinine clearance ≤50 mL/min	12 (9.2)	4 (12.1)	8 (8.2)	0.507
LVEF, %	57.0 (55.0-62.0)	57.0 (55.0-61.0)	57.0 (55.2-62.0)	0.748
<50%	10 (7.7)	3 (9.1)	7 (7.2)	0.714
LA diameter, mm	44.0 (42.0-47.0)	43.0 (41.3-46.5)	44.0 (42.0-47.0)	0.575
≥45 mm	59 (45.4)	12 (36.4)	47 (48.5)	0.270
LAVI, mL/m ²	42.7 (35.8-52.9)	46.0 (35.3-53.1)	42.4 (36.5-52.7)	0.991
Medication				
OAC, DOAC	129 (99.2)	33 (100)	96 (99.0)	1.000
OAC, warfarin	1 (0.8)	0 (0)	1 (1.0)	
Class 1c AAD	59 (45.4)	10 (30.3)	48 (49.5)	0.056
Class III AAD	68 (52.3)	22 (66.7)	46 (47.4)	
RAS blocker	39 (30)	8 (24.2)	31 (32.0)	0.403
Beta-blocker	58 (44.6)	15 (45.5)	43 (44.3)	0.911
Calcium-channel blocker	22 (16.9)	8 (24.2)	14 (14.4)	0.194

Values are n (%) or median (Q1-Q3).
AAD = antiarrhythmic drug; AF = atrial fibrillation; DOAC = direct oral anticoagulant; ECG = electrocardiogram; EHRA = European Heart Rhythm Association; ILR = implantable loop recorder; LA = left atrial; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; OAC = oral anticoagulant; QoL = quality of life; RAS = renin-angiotensin system; SF-36 = 36-Item Short Form Survey; TIA = transient ischemic attack.

FIGURE 2 Actual AF Types Evaluated by ILR Monitor During the Pre-cryoablation Period



AF burden and SF-36 scores before and after cryoballoon ablation was performed using the Wilcoxon signed rank test. The Kaplan-Meier method was employed to estimate the freedom from AF at 12 months following a 90-day blanking period. Changes in AF types from baseline to follow-up and changes in AF-related symptoms assessed by European Heart Rhythm Association symptom classification were described by Sankey plots.

All *P* values were assessed using a 2-tailed test, with statistical significance defined as a *P* value of <0.05.

DATA AVAILABILITY. All data generated or analyzed during this study are included in this paper and the [Supplemental Appendix](#). The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

RESULTS

Between January 2021 and July 2022, a total of 150 patients were screened for study enrollment; 2 patients were excluded for not meeting inclusion/exclusion criteria, 15 patients withdrew consent, 2 patients decided not to undergo cryoballoon ablation for medical reasons after study explanation, 1 patient was lost to follow-up after study explanation, and

finally 130 patients included in the study and underwent ILR implantation before cryoballoon ablation and subsequently underwent cryoballoon ablation ([Figure 1](#)).

BASELINE CHARACTERISTICS. Baseline characteristics of study patients are presented in [Table 1](#). The median age of the study patients was 61.0 years (Q1-Q3: 54.0-66.8 years), 23.8% were female, and the median CHA₂DS₂-VASc score was 2.0 (Q1-Q3: 1.0-2.0). All patients had clinically persistent AF at study enrollment, with 67.7% of patients having persistent AF at first diagnosis and 32.3% having paroxysmal AF that progressed to persistent. Of the study patients, 33.8% (n = 44) had previous cardioversion; among these, 13.6% (n = 6) failed to return to sinus rhythm after cardioversion. The median duration of AF was 9.0 months (Q1-Q3: 5.0-19.8 months) and the median duration of persistent AF was 6 months (Q1-Q3: 4.0-10.0 months); 79.2% of patients had persistent AF for 1 year or less. Atrial flutter was observed in 23.8% of patients. The median left ventricular ejection fraction was 57.0% (Q1-Q3: 55.0%-62.0%), the median LA diameter was 44.0 mm (Q1-Q3: 42.0-47.0 mm), and 45.4% of patients had an LA diameter of 45 mm or greater. All patients received adequate anticoagulation; 45.4% were prescribed a class Ic AAD and 52.3% were prescribed a class III AAD.

TABLE 2 Procedure Characteristics

	Total	Type 1 High-Burden Paroxysmal AF	Type 2 ILR-Confirmed Persistent AF	P Value
Patients	130 (100)	33 (25.4)	97 (74.6)	
Procedure time, min	70.0 (60.0-86.5)	65.0 (60.0-80.0)	73.0 (60.0-87.0)	0.268
Fluoroscopy time, min	16.7 (12.7-24.8)	16.1 (12.9-20.1)	17.2 (12.6-25.3)	0.369
Cryoablation time, min	19.3 (16.0-24.2)	19.4 (15.9-25.3)	19.3 (16.1-24.0)	0.839
Initial sinus rhythm during cryoablation	30 (23.1)	25 (75.8)	5 (5.2)	<0.001
AF but terminating during ablation	7 (5.4)	5 (15.2)	2 (2.1)	
Intraprocedural direct-current cardioversion	93 (71.5)	3 (9.1)	90 (92.8)	
CTI line	17 (13.1)	8 (24.2)	9 (9.3)	0.038
Known clinical atrial flutter	10 (7.7)	6 (18.2)	4 (4.1)	0.029
Induced atrial flutter	7 (5.4)	2 (6.1)	5 (5.2)	
Ablation other than PV antrum and CTI	1 (0.8)	0 (0)	1 (1.0) ^a	1.000
All 4 PVs success rate	126 (96.9)	32 (97.0)	94 (96.9)	1.000
Left superior PV				
Number of applications per vein	2.0 (1.0-2.0)	1.0 (1.0-2.0)	2.0 (1.0-2.0)	0.044
PV treated with single cryoablation application	59 (45.4)	20 (60.6)	39 (40.2)	0.042
Duration of cryoablation application, s	240.0 (180.0-345.0)	240.0 (180.0-300.0)	240.0 (180.0-346.3)	0.387
Left inferior PV				
Number of applications per vein	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.032
PV treated with single cryoablation application	71 (54.6)	23 (69.7)	48 (49.5)	0.044
Duration of cryoablation application, s	240.0 (180.0-270.0)	240.0 (180.0-243.8)	240.0 (180.0-296.5)	0.322
Right superior PV				
Number of applications per vein	1.5 (1.0-2.0)	1.0 (1.0-2.0)	2.0 (1.0-2.0)	0.002
PV treated with single cryoablation application	65 (50)	24 (72.7)	41 (42.3)	0.003
Duration of cryoablation application, s	240.0 (180.0-298.0)	240.0 (180.0-240.0)	240.0 (180.0-300.0)	0.138
Right inferior PV				
Number of applications per vein	2.0 (1.0-3.0)	1.0 (1.0-2.0)	2.0 (1.0-3.0)	0.027
PV treated with single cryoablation application	54 (41.5)	20 (60.6)	34 (35.1)	0.010
Duration of cryoablation application, s	260.0 (240.0-349.5)	240.0 (200.0-347.0)	268.0 (240.0-349.0)	0.382

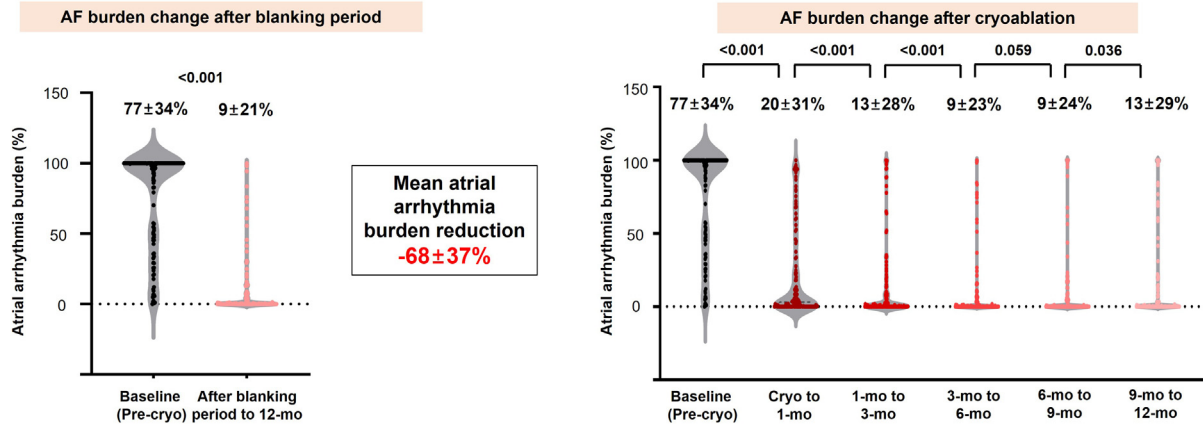
Values are n (%), median (Q1-Q3). ^aPosterior wall isolation.
AF = atrial fibrillation; CTI = cavotricuspid isthmus; ILR = implantable loop recorder; PV = pulmonary vein.

PRE-CRYOABLATION AF TYPES AND BURDEN ASSESSED BY ILR MONITOR. The median time from ILR implantation to cryoballoon ablation was 45.0 days (Q1-Q3: 25.0-64.0 days). The mean AF burden before cryoballoon ablation was $77 \pm 34\%$. The pre-cryoablation ILR AF burden distribution is shown in [Supplemental Figure 1](#); 42.3% (n = 55) had an AF burden of 100% and 22.3% (n = 29) had an AF burden between 90% and 99.9%. The remaining patients (35.4% [n = 46]) had various percentages between 0% and <90%. Although all 130 patients had persistent AF as a clinical feature, the actual ILR continuous monitoring results varied. In total, 25.4% (n = 33) of patients were classified as clinically persistent AF because they did not have AF lasting more than 7 days on ILR monitoring but had a “high-burden paroxysmal AF” (type 1) ([Figure 2](#)). The remaining 74.6% (n = 97) of patients were of persistent AF type, with AF lasting more than 7 days on the ILR monitor (type 2, “ILR-confirmed persistent AF” [hereafter “confirmed persistent AF”]), of which those with spontaneous AF termination documented on the ILR were categorized as type

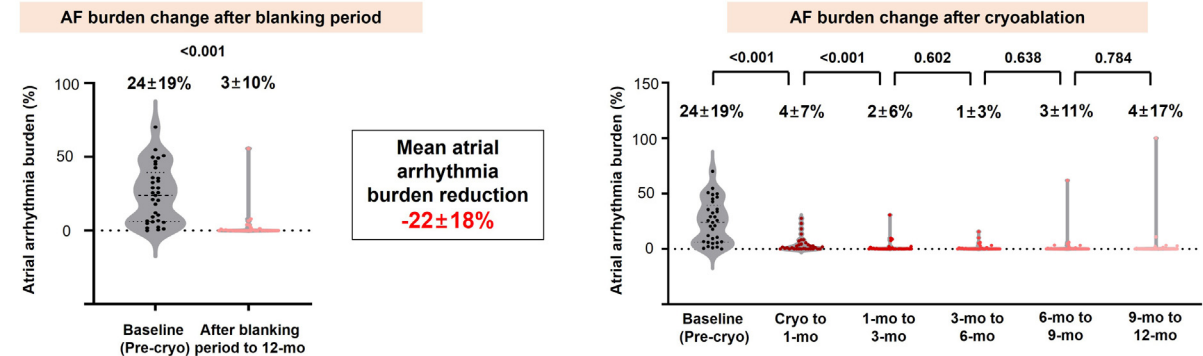
2a (9.2% [n = 12]) and those without spontaneous AF termination were classified as type 2b (65.4% [n = 85]) ([Figure 2](#)). Although there were no significant differences in baseline characteristics based on whether the actual ILR monitoring pattern was high-burden paroxysmal AF (type 1) or confirmed persistent AF (type 2), patients with type 2 had a longer duration of persistent AF, a high proportion of ECGs with 2 or more demonstrations of AF taken ≥ 7 days apart, and a higher proportion with 100% AF on Holter monitoring ([Table 1](#)). There was a trend toward a higher proportion of patients with LA diameter ≥ 45 mm in type 2, a higher proportion with initial paroxysmal AF but progressed to persistent AF in type 1, a higher proportion with atrial flutter in type 1, and a higher proportion with class III AADs in type 1, but these differences were not statistically significant ([Table 1](#)). The mean pre-cryoablation ILR AF burden for types 1 and 2 was $24.4 \pm 19.2\%$ vs $95.4 \pm 11.9\%$ ($P < 0.001$). There was no significant difference in pre-cryoablation ILR monitor duration between the two groups (median 40.0 days [Q1-Q3: 28.0-54.0 days]

FIGURE 3 AF Burden Reduction After Cryoablation

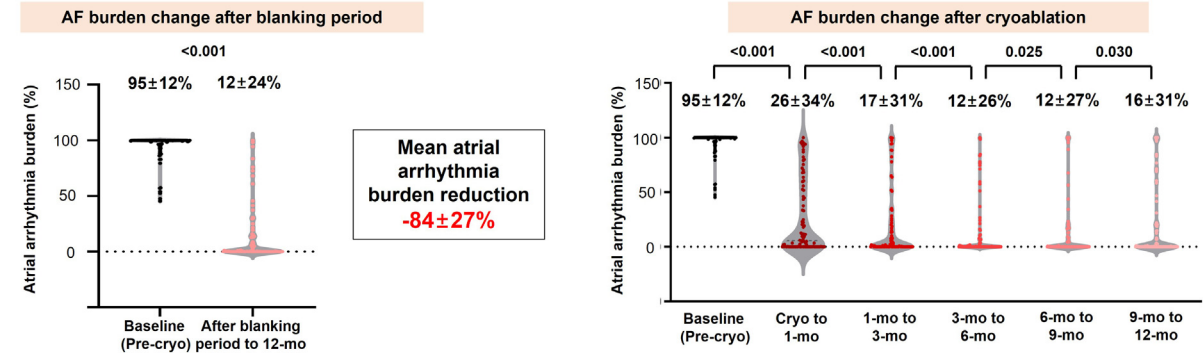
A Total



B Type 1 (High-burden paroxysmal AF)



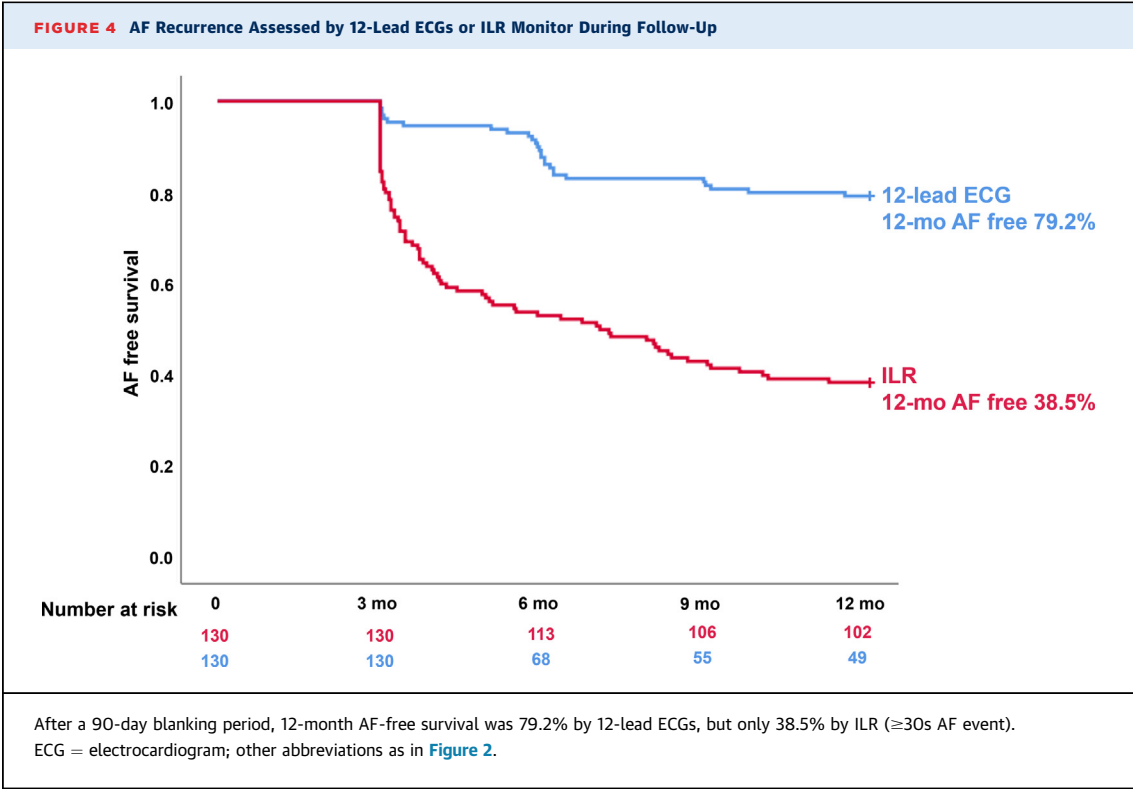
C Type 2 (ILR-confirmed persistent AF)



(A) Total. (B) High-burden paroxysmal AF. (C) ILR-confirmed persistent AF. Cryo = cryoablation; other abbreviations as in Figure 2.

in type 1 vs median 47.0 days [Q1-Q3: 24.0-70.0 days] in type 2; $P = 0.288$).

PROCEDURAL CHARACTERISTICS. The procedure characteristics are shown in Table 2. The median procedure time was 70.0 minutes (Q1-Q3: 60.0-86.5 minutes) and the cryoablation time was 19.3 minutes (Q1-Q3: 16.0-24.2 minutes), with no significant difference between types 1 and 2. Overall, 23.1% of patients were in sinus rhythm during cryoablation, 5.4% were converted to sinus rhythm during ablation, and 71.5% underwent direct current cardioversion. In type 1, a higher proportion of patients were in sinus rhythm at the time of the procedure, and a higher proportion had spontaneous AF termination during the procedure. Concomitant cavotricuspid isthmus



ablation was performed in 13.1% of patients, with a higher proportion in type 1. The acute procedure success rate was 96.9%, with no difference between the two groups, and a higher proportion of type 1 patients were isolated with a single cryoablation application in all PVs.

In the aspect of procedure-related complications, 3 (2.5%) patients had transient phrenic nerve palsy during cryoablation but recovered immediately during the procedure, and 3 (2.5%) patients had inferior lead ST-T segment changes during the procedure but recovered immediately. In 1 (0.7%) patient, the duodecapolar catheter became entrapped in the right atrium Chiari network and was removed by percutaneous procedure.

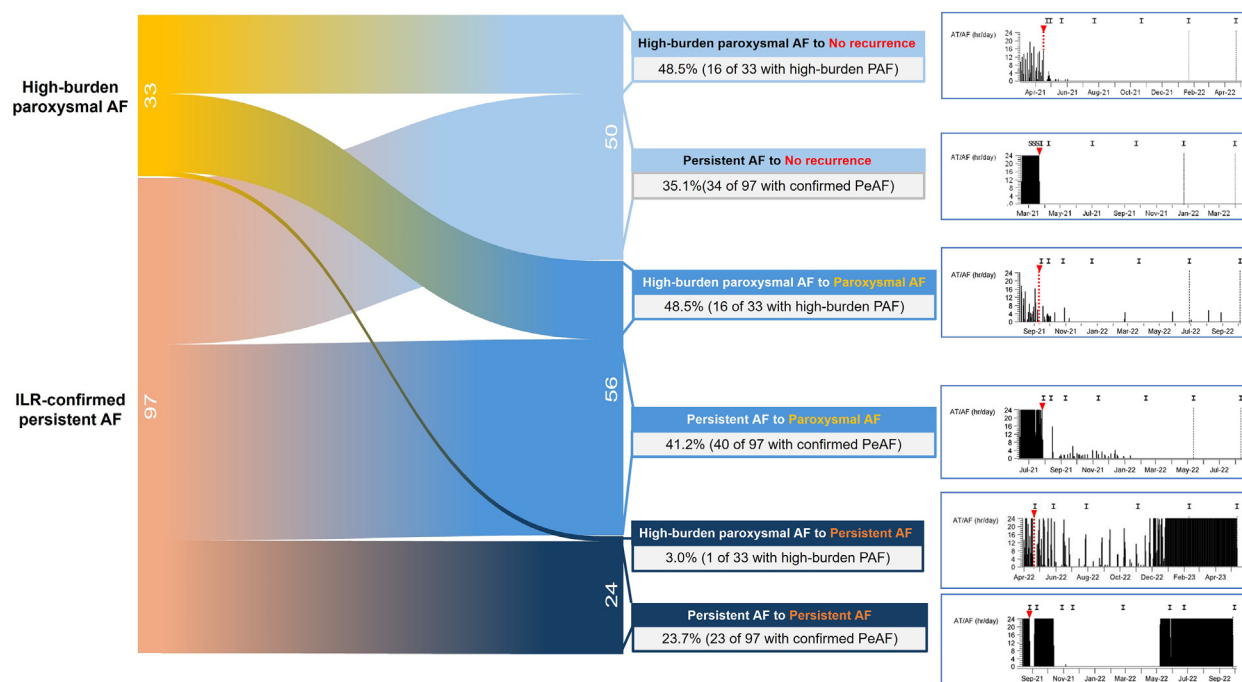
AF BURDEN CHANGES DURING FOLLOW-UP. In the overall study cohort, compared with the pre-cryoablation period, the AF burden reduced substantially from $77 \pm 34\%$ to $9 \pm 21\%$ ($-68 \pm 37\%$; $P < 0.001$) after a 90-day blanking period to a 12-month follow-up (Figure 3A). During the 3-month blanking period, AF burden substantially decreased from $77 \pm 34\%$ to $20 \pm 31\%$ at 1 month and $13 \pm 28\%$ at 3 months (Figure 3A). After the 3-month blanking period, AF burden substantially decreased up to 9 months, followed by a slight increase in the 9- to 12-month window compared with the 6- to 9-month window ($9 \pm 24\%$ vs $13 \pm 29\%$; $P = 0.036$).

The changes in AF burden by actual AF types (high-burden paroxysmal AF and confirmed persistent AF) are depicted in Figures 3B and 3C. In those with high-burden paroxysmal AF (type 1), AF burden reduced from $24 \pm 19\%$ to $3 \pm 10\%$ ($-22 \pm 18\%$ reduction compared with baseline) (Figure 3B). Among those with confirmed persistent AF (type 2), AF burden showed a more significant reduction, from $95 \pm 12\%$ to $12 \pm 24\%$ ($-84 \pm 27\%$ reduction compared with baseline) (Figure 3C).

AF RECURRENCE ASSESSED BY 12-LEAD ECGs OR ILR MONITOR DURING FOLLOW-UP. All patients completed 12-month follow-up, and AF recurrence as assessed by 12-lead ECGs performed during follow-up are presented in Figure 4. After a 90-day blanking period, 12-month AF-free survival was 79.2% assessed by 12-lead ECGs. In contrast, 12-month AF-free survival was 38.5% when recurrence was defined as the first detected AF event lasting 30 seconds or longer assessed by an ILR monitor after a blanking period (Figure 4). Supplemental Figure 2 shows the AF-free survival during follow-up by ECGs and ILR monitor according to AF types.

AF RECURRENCE TYPES. Of the 61.5% of patients with AF recurrence on ILR after a blanking period, 70% had a paroxysmal type and 30% had a persistent type (Figure 5). Type 2 persistent AF (confirmed

FIGURE 5 AF Recurrence Types Assessed by ILR Monitor



In high-burden paroxysmal AF patients (n = 33), 48.5% had no recurrence, 48.5% recurred as paroxysmal AF, and 3.0% as persistent AF. In confirmed persistent AF patients (n = 97), 35.1% had no recurrence, 41.2% regressed to paroxysmal AF, and 23.7% recurred as persistent AF. In the example ILR AF burden chart, the red arrow and dashed line indicate the timing of cryoablation. PAF = paroxysmal atrial fibrillation; other abbreviations as in [Figure 2](#).

persistent AF) showed a numerically higher recurrence rate of atrial tachyarrhythmia compared with type 1 persistent AF (high-burden paroxysmal AF) (64.9% vs 51.5%; $P < 0.171$).

Among patients with initial high-burden of paroxysmal AF (n = 33), 48.5% exhibited no recurrence of AF, 48.5% showed a recurrence as paroxysmal AF, and 3.0% experienced a recurrence as persistent AF. For patients initially diagnosed with confirmed persistent AF (n = 97), 35.1% demonstrated no AF recurrence, 41.2% regressed from persistent AF to paroxysmal AF, and 23.7% experienced a recurrence as persistent AF ([Figure 5](#)). The persistent type of recurrence was lower in those with high-burden paroxysmal AF at baseline than in those with confirmed persistent AF at baseline (3.0% vs 23.7%; $P = 0.004$).

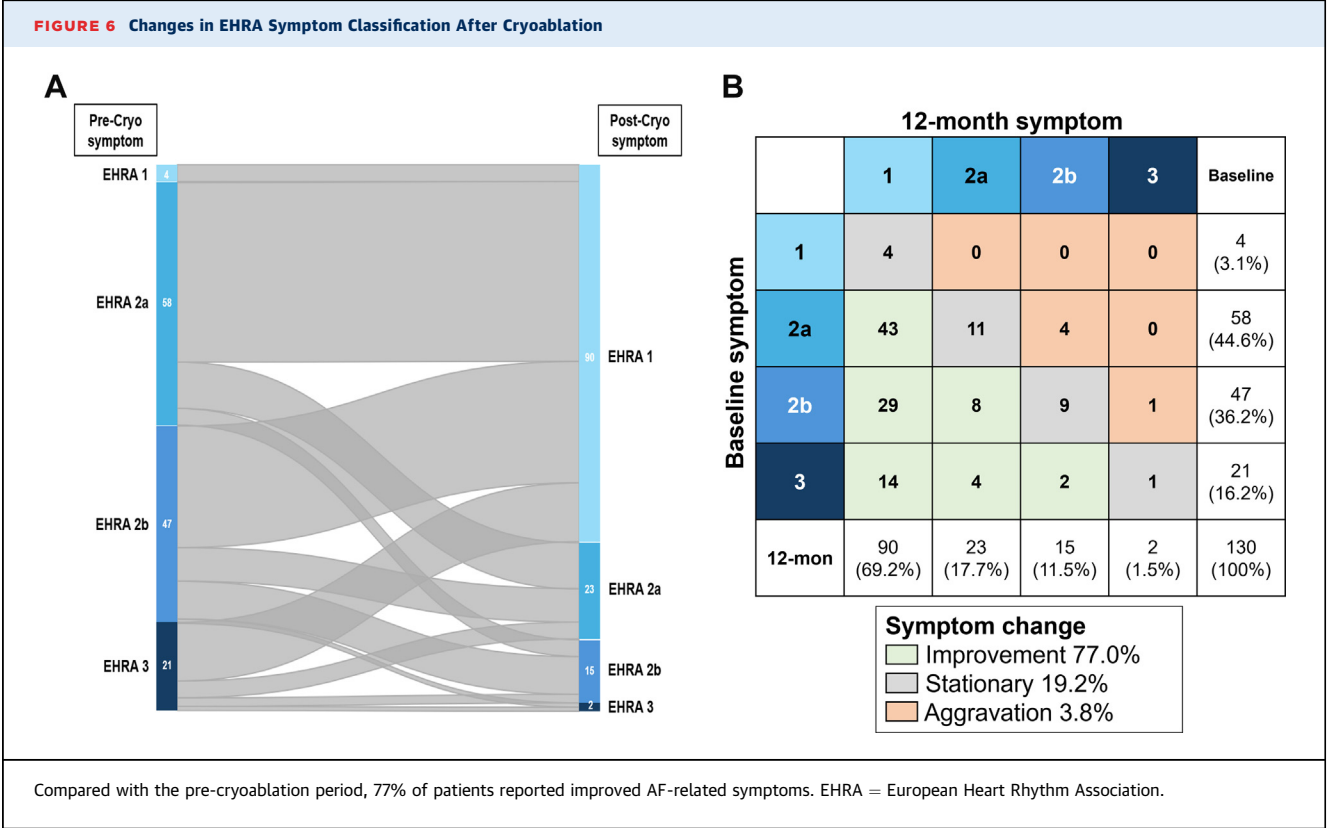
IMPROVEMENT IN AF-RELATED SYMPTOMS AND QUALITY OF LIFE AFTER CRYOABLATION. Compared with the pre-cryoablation period, 77% of patients improved AF-related symptoms ([Figure 6](#)). Improvement of symptoms was observed in 84.8% of patients in the high-burden paroxysmal AF group and 74.2% of patients in the confirmed persistent AF group ([Supplemental Figure 3](#)) Compared with the

pre-cryoablation period, improved quality of life assessed by SF-36 questionnaires was observed (total: 138 ± 35 to 155 ± 26 ; $P < 0.001$; high-burden paroxysmal AF: 132 ± 37 to 158 ± 25 ; $P < 0.001$; confirmed persistent AF group: 140 ± 34 to 155 ± 26 ; $P < 0.001$).

During follow-up, the proportion of patients without AAD therapy increased, and 41.1% of study patients discontinued AAD therapy at the 12-month follow-up ([Supplemental Figure 4](#)). The proportion of amiodarone use continuously decreased during follow-up ([Supplemental Figure 4](#)).

DISCUSSION

This analysis evaluated the actual AF burden and pattern with continuous ILR monitoring in early persistent AF. We examined changes in AF burden, pattern, symptoms, and quality of life after PVI with cryoablation. Our principal findings in this study are as follows ([Central Illustration](#)): 1) when patients with persistent AF for <3 years were monitored with ILR, 25.4% were classified as high-burden paroxysmal AF and 74.6% were classified as confirmed persistent AF; 2) compared with the preprocedure AF burden, the mean AF burden was significantly reduced from 77%



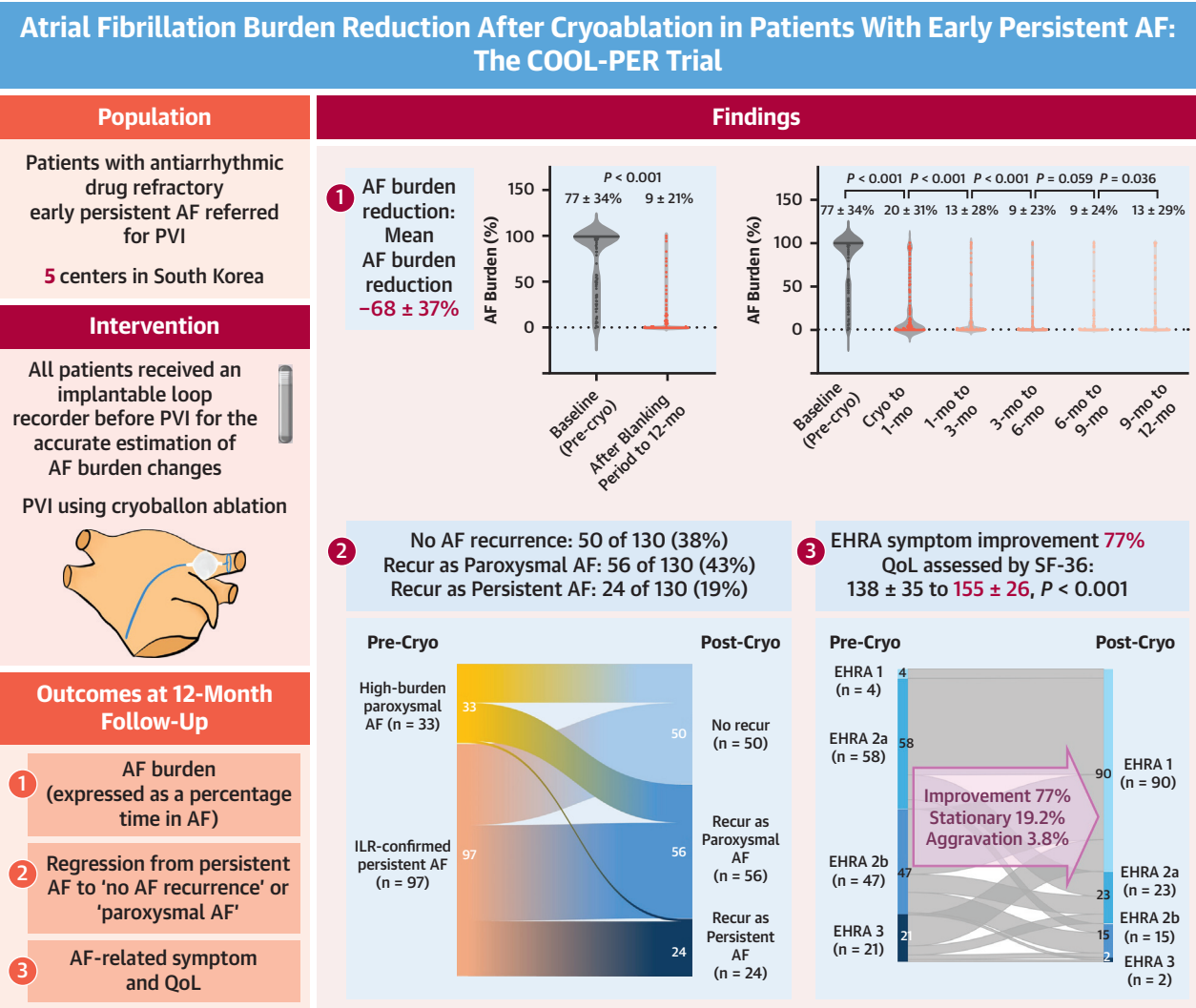
to 9% after cryoablation (average AF burden reduction of 68%); 3) after PVI with cryoablation in these patients with early persistent AF, 38.5% had no recurrence of AF, 43.1% had recurrence of paroxysmal AF, and 18.5% had recurrence of persistent AF; 4) among those with confirmed persistent AF, 75% of patients showed regression to paroxysmal AF or no recurrence, whereas 25% of patients remained in confirmed persistent AF; and 5) after cryoablation, most of patients experienced symptom and quality-of-life improvement and reduction of AAD prescription. Our study presents a novel approach: We scrutinized the authentic AF burden and pattern before and after cryoablation using an ILR in patients diagnosed with clinically persistent AF. We show that cryoablation reduced AF burden, inhibited AF recurrence, and regressed from persistent to low-burden paroxysmal AF in patients with early persistent AF.

Recent clinical trials have demonstrated that early rhythm control in patients with AF confers the advantage of markedly reducing the risk of stroke and cardiovascular-related mortality.¹⁷ According to the guidelines, catheter ablation is categorized as class 1A recommendation for enhancing symptomatic relief through rhythm control in patients with symptomatic AF unresponsive to AADs.¹⁻³ Furthermore, it is a class

1A recommendation to contemplate catheter ablation as an initial treatment option in specific patients with symptomatic paroxysmal AF, particularly those who are younger and have fewer comorbidities, aiming to improve symptoms and prevent progression to persistent AF.² Recent data indicate that initial cryoablation is more effective than AADs in suppressing AF in patients with paroxysmal AF, which supports catheter ablation as the first-line treatment in symptomatic patients with recurrent paroxysmal AF.^{3,6,7}

AF manifests as a disease with diverse clinical presentations, wherein certain patients are initially diagnosed with clinically paroxysmal AF and subsequently progress to persistent AF. In contrast, others exhibit persistent AF from the outset of diagnosis.^{18,19} Persistent forms of AF pose considerable challenges in achieving effective rhythm control and are associated with increased susceptibility to adverse clinical outcomes.^{13,20} Preferably, early identification and intervention to impede the transition from paroxysmal to persistent AF are advocated. However, comprehensive evaluation and management strategies for patients already in the persistent phase should also be addressed. Fortunately, early implementation of rhythm control has been shown to mitigate the risk of major adverse cardiovascular

CENTRAL ILLUSTRATION The Main Results of the COOL-PER Trial



Lee S-R, et al. JACC Clin Electrophysiol. 2025;11(6):1234-1247.

Atrial fibrillation (AF) burden reduction after cryoablation in patients with early persistent AF: the COOL-PER (CryOablation for PuLmonary vein isolation alone in patients with early PERsistent AF assessed by continuous monitoring) trial. AF burden was reduced after cryoablation (from $77 \pm 34\%$ at baseline to $9 \pm 21\%$ after cryoablation, $68 \pm 37\%$ of AF burden reduction; $P < 0.001$). Of the total, 38.5% had no recurrence of AF, 43.1% had a recurrence of paroxysmal AF, and 18.5% had a recurrence of persistent AF. After cryoablation, 77% of patients improved AF-related symptoms and quality of life (QoL) as assessed by 36-Item Short Form Survey (SF-36) questionnaires. EHRA = European Heart Rhythm Association; PVI = pulmonary vein isolation; recur = recurrence.

events, irrespective of whether patients present with paroxysmal or persistent AF.²¹ In this study, we have provided further evidence of early rhythm control using cryoablation, which showed a substantial reduction of AF burden, regression to paroxysmal AF, and improved quality of life in patients with early persistent AF.

Persistent AF is defined as continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion)

after ≥ 7 days.² However, not all patients underwent continuous rhythm monitoring for more than 7 days to determine if their AF was persistent. As a result, the group of patients with persistent AF might be diverse, and those with high-burden paroxysmal AF could be classified as having persistent AF in real-world clinical practice. Our study shows that a significant number of patients (25%) were identified as having high-burden paroxysmal AF using continuous rhythm monitoring.

AF characterization has evolved beyond a binary notion of presence or absence to encompass quantifiable burden.²² Precise evaluation of baseline actual AF pattern and burden, alongside quantification of the AF burden, is imperative for managing patients with persistent AF, yet remains incompletely elucidated. Discrepancies have been previously noted between clinically assigned AF types and those monitored by ILR.¹²

Our study demonstrates that cryoablation in early persistent AF was effective in promoting AF regression, echoing the findings of a study that reported that cryoablation in the EARLY-AF study prevented progression from paroxysmal AF to persistent AF more effectively than AADs.⁸

Our analysis also identifies a distinction between high-burden paroxysmal AF and confirmed persistent AF within the clinically classified persistent AF cohort. Patients with high-burden paroxysmal AF had a lower baseline AF burden but demonstrated significant reductions in AF burden following cryoablation, with half experiencing no recurrence and avoiding progression to confirmed persistent AF. In contrast, confirmed persistent AF patients, characterized by nearly 100% baseline AF burden, exhibited higher recurrence rates but still achieved significant reductions in AF burden, occasional regression to low-burden paroxysmal AF, and improvements in symptoms and quality of life.

A recent double-blind randomized clinical trial comparing PVI with cryoballoon ablation with a sham procedure in symptomatic paroxysmal and persistent AF patients has been reported.²³ In this study, an ILR was implanted at least 2 weeks prior to the procedure in all 126 participants (median pre-ablation monitoring duration 28 days [Q1-Q3: 25.8-35.5 days]). Approximately 80% of the participants had persistent AF, with a median AF duration of 25 months in the total study participants, which was longer than that of our study population. Although the study's participant criteria and objectives differ from ours, it found that, compared with the sham procedure group (mean AF burden from baseline to 6 months: 97.1% to 52.3%), the cryoballoon ablation group (mean AF burden from baseline to 6 months: 94.2% to 22.8%) showed a significantly greater reduction in AF burden. This study provides strong evidence that the effects of PVI exceed the placebo effect, demonstrating a clear reduction in AF burden. It also offers consistent findings that somewhat mitigate the limitations of our study, which lacks a comparison group.

The CIRCA-DOSE (Cryoballoon vs Contact-Force Atrial Fibrillation Ablation) trial, comparing radio-frequency ablation and various cryoablation dose

strata in patients with paroxysmal AF, meticulously monitored pre- and post-ablation AF burden using ILR.¹⁴ A subanalysis of this trial revealed that patients with low-burden paroxysmal AF experienced a marked improvement in quality of life after ablation, diminished AF burden, and a noteworthy decline in health care resource utilization in the year subsequent to the procedure.^{24,25} In a recent investigation contrasting AF ablation with medical therapy among patients with advanced heart failure, ablation led to a greater substantial reduction in baseline AF burden compared with medical therapy ($50.9 \pm 31.2\%$ to $19.6 \pm 28.0\%$ in the ablation group vs $52.4 \pm 35.2\%$ to $43.7 \pm 36.2\%$ in the medical group).²⁶ Consequently, this reduction contributed to a 76% decrease in the risk of the primary endpoint, which comprised death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation.²⁶ These two studies present distinct clinical scenarios compared with our investigation; however, they underscore the correlation between AF burden and risk of clinical endpoints, as well as AF-related symptoms and quality of life. Our findings elucidate how reducing AF burden and reverting AF patterns through cryoablation in patients with early persistent AF led to improved quality of life, symptoms, and the burden of AAD usage. Despite ongoing debates regarding the optimal ablation strategy for persistent AF patients, our study holds significance by demonstrating the efficacy of PVI with cryoablation, particularly in clinically early persistent AF.

While this study focuses on cryoballoon ablation, we acknowledge that variations in safety and efficacy may arise depending on the energy source.²⁷ Nevertheless, our data provide valuable evidence supporting the early application of PVI for rhythm control in clinically diagnosed early persistent AF patients, emphasizing its role in reducing AF burden and promoting AF-type regression. Although multiple factors influence treatment decisions, cryoballoon ablation—characterized by shorter procedure times and simplicity compared with point-by-point radio-frequency ablation—emerges as a promising rhythm control strategy. Additionally, emerging techniques like pulsed field ablation further highlight the potential for durable, safe PVI.^{5,28,29} Based on our findings, early rhythm control with PVI should be considered for early persistent AF patients, regardless of the energy source, as long as safety and durability are ensured. Further studies are needed to define the optimal energy source for PVI in these patients.

STUDY LIMITATIONS. The limitations of our study include a relatively small sample size and the single-

arm cohort design, which precludes a direct evaluation of whether reducing AF burden translates into improvements in clinical outcomes. Future studies are warranted to address these gaps by including comparisons of different rhythm control strategies (eg, AADs vs catheter ablation) or evaluating the impact of different energy sources (eg, radio-frequency ablation, cryoballoon ablation, or pulsed field ablation) for PVI on AF burden, recurrence rates, and recurrence patterns in patients with early persistent AF. Second, not all patients discontinued AADs after the blanking period, which introduces variability in postablation management and should be carefully considered when interpreting AF burden. While the decision to use AADs was left to the physician's discretion, the study protocol emphasized avoiding the initiation of more potent drugs or dose escalation postablation compared with the pre-ablation status. Nonetheless, this heterogeneity may confound the observed reduction in AF burden and warrants further attention. Third, while our study's strength is its use of ILR-based continuous monitoring to evaluate pre- and post-ablation AF burden in patients with early persistent AF, we acknowledge a limitation in the monitoring duration for pre-ablation AF burden, which was set at a minimum of 7 days and a maximum of 90 days prior to ablation. This duration may not have been sufficient to accurately capture the pre-ablation AF burden and pattern in patients with early persistent AF. This limitation should be carefully considered when interpreting the data. Fourth, while all patients had early persistent AF, individualizing the LA low-voltage zone burden and performing additional ablation according to each patient's condition might impact recurrence. However, our study did not address this aspect beyond PVI via cryoablation. Fifth, this study exclusively included Korean patients, limiting the ethnic diversity of the cohort. Therefore, the findings should be interpreted with caution when generalizing to populations with different ethnic backgrounds. Last, the slight increase in mean AF burden during the 9- to 12-month period suggests the need for separate reporting on the long-term effects of a single cryoablation procedure using extended monitoring.

CONCLUSIONS

A substantial number of patients with early persistent AF were detected as high-burden paroxysmal AF based on the continuous cardiac rhythm monitor using an ILR. Early rhythm control using cryoablation

effectively reduced the AF burden and mostly achieved regression from persistent to paroxysmal AF and symptom improvement.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was sponsored by Medtronic (IIS ERP-2020-12253). Dr Choi has received research grants or speaking fees from Abbott, Bayer, BMS/Pfizer, Biosense Webster, Chong Kun Dang, Daewoong Pharmaceutical, Daiichi-Sankyo, DeepQure, Dreamtech, Jeil Pharmaceutical, Medtronic, Samjinpharm, Samsung Electronics, Seers Technology, and Skylabs. Dr Lip has served as a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Athos, and Daiichi-Sankyo (no fees are received personally); and has served as National Institute for Health and Care Research (NIHR) Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in atrial fibrillation (grant agreement no. 899871), TARGET project on digital twins for personalized management of atrial fibrillation and stroke (grant agreement no. 101136244), and ARISTOTELES project on artificial intelligence for management of chronic long term conditions (grant agreement no. 101080189), which are all funded by the European Union's Horizon Europe Research and Innovation program. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Eue-Keun Choi, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea. E-mail: choiek17@snu.ac.kr.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study demonstrates that PVI using cryoablation is effective in significantly reducing the AF burden in patients with early persistent AF. It also shows that a substantial number of patients experienced regression from persistent to paroxysmal AF or had no recurrence of AF following the procedure.

COMPETENCY IN PATIENT CARE: The findings suggest that PVI using cryoablation can improve patient outcomes by reducing AF burden, leading to a significant improvement in AF-related symptoms and overall quality of life for patients with early persistent AF.

TRANSLATIONAL OUTLOOK: The study indicates that PVI using cryoablation may be a valuable therapeutic strategy for managing early persistent AF, with potential implications for broader clinical use in reducing the progression of AF and improving patient quality of life.

REFERENCES

1. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2024;83:109-279.
2. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42:373-498.
3. Tzeis S, Gerstenfeld EP, Kalman J, et al. 2024 European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace*. 2024;26:euae043.
4. Kuck KH, Brugada J, Fürnkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med*. 2016;374:2235-2245.
5. Reddy VY, Gerstenfeld EP, Natale A, et al. Pulsed field or conventional thermal ablation for paroxysmal atrial fibrillation. *N Engl J Med*. 2023;389:1660-1671.
6. Wazni OM, Dandamudi G, Sood N, et al. Cryoballoon ablation as initial therapy for atrial fibrillation. *N Engl J Med*. 2021;384:316-324.
7. Andrade JG, Wells GA, Deyell MW, et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. *N Engl J Med*. 2021;384:305-315.
8. Andrade JG, Deyell MW, Macle L, et al. Progression of atrial fibrillation after cryoablation or drug therapy. *N Engl J Med*. 2023;388:105-116.
9. Tondo C, Iacopino S, Pieragnoli P, et al. Pulmonary vein isolation cryoablation for patients with persistent and long-standing persistent atrial fibrillation: clinical outcomes from the real-world multicenter observational project. *Heart Rhythm*. 2018;15:363-368.
10. Boveda S, Metzner A, Nguyen DQ, et al. Single-procedure outcomes and quality-of-life improvement 12 months post-cryoballoon ablation in persistent atrial fibrillation: results from the multicenter CRYO4PERSISTENT AF trial. *JACC Clin Electrophysiol*. 2018;4:1440-1447.
11. Su WW, Reddy VY, Bhasin K, et al. Cryoballoon ablation of pulmonary veins for persistent atrial fibrillation: results from the multicenter STOP Persistent AF trial. *Heart Rhythm*. 2020;17:1841-1847.
12. Dekker LR, Pokushalov E, Sanders P, Lindborg KA, Maus B, Pürerfellner H. Continuous cardiac monitoring around atrial fibrillation ablation: insights on clinical classifications and end points. *Pacing Clin Electrophysiol*. 2016;39:805-813.
13. Bhargava M, Di Biase L, Mohanty P, et al. Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: results from a multicenter study. *Heart Rhythm*. 2009;6:1403-1412.
14. Andrade JG, Champagne J, Dubuc M, et al. Cryoballoon or radiofrequency ablation for atrial fibrillation assessed by continuous monitoring: a randomized clinical trial. *Circulation*. 2019;140:1779-1788.
15. Sanders P, Pürerfellner H, Pokushalov E, et al. Performance of a new atrial fibrillation detection algorithm in a miniaturized insertable cardiac monitor: results from the Reveal LINQ Usability Study. *Heart Rhythm*. 2016;13:1425-1430.
16. Mittal S, Rogers J, Sarkar S, et al. Real-world performance of an enhanced atrial fibrillation detection algorithm in an insertable cardiac monitor. *Heart Rhythm*. 2016;13:1624-1630.
17. Kirchhof P, Camm AJ, Goette A, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med*. 2020;383:1305-1316.
18. Chen Q, Toorop MMA, Tops LF, Lijfering WM, Cannegieter SC. Time trends in patient characteristics, anticoagulation treatment, and prognosis of incident nonvalvular atrial fibrillation in the Netherlands. *JAMA Netw Open*. 2023;6:e239973.
19. Ambrosio G, Camm AJ, Bassand JP, et al. Characteristics, treatment, and outcomes of newly diagnosed atrial fibrillation patients with heart failure: GARFIELD-AF. *ESC Heart Fail*. 2021;8:1139-1149.
20. Ganesan AN, Chew DP, Hartshorne T, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J*. 2016;37:1591-1602.
21. Goette A, Borof K, Breithardt G, et al. Presenting pattern of atrial fibrillation and outcomes of early rhythm control therapy. *J Am Coll Cardiol*. 2022;80:283-295.
22. Chen LY, Chung MK, Allen LA, et al. Atrial fibrillation burden: moving beyond atrial fibrillation as a binary entity: a scientific statement from the American Heart Association. *Circulation*. 2018;137:e623-e644.
23. Dulai R, Sulke N, Freemantle N, et al. Pulmonary vein isolation vs sham intervention in symptomatic atrial fibrillation: the SHAM-PVI randomized clinical trial. *JAMA*. 2024;332(14):1165-1173. <https://doi.org/10.1001/jama.2024.17921>
24. Samuel M, Khairy P, Champagne J, et al. Association of atrial fibrillation burden with health-related quality of life after atrial fibrillation ablation: substudy of the Cryoballoon vs Contact-Force Atrial Fibrillation Ablation (CIRCA-DOSE) randomized clinical trial. *JAMA Cardiol*. 2021;6:1324-1328.
25. Andrade JG, Macle L, Verma A, et al. Quality of life and health care utilization in the CIRCA-DOSE study. *JACC Clin Electrophysiol*. 2020;6:935-944.
26. Sohns C, Fox H, Marrouche NF, et al. Catheter ablation in end-stage heart failure with atrial fibrillation. *N Engl J Med*. 2023;389:1380-1389.
27. Kueffer T, Stettler R, Maurhofer J, et al. Pulsed-field vs cryoballoon vs radiofrequency ablation: outcomes after pulmonary vein isolation in patients with persistent atrial fibrillation. *Heart Rhythm*. 2024;21:1227-1235.
28. Turagam MK, Neuzil P, Schmidt B, et al. Safety and effectiveness of pulsed field ablation to treat atrial fibrillation: one-year outcomes from the MANIFEST-PF registry. *Circulation*. 2023;148:35-46.
29. Ekanem E, Neuzil P, Reichlin T, et al. Safety of pulsed field ablation in more than 17,000 patients with atrial fibrillation in the MANIFEST-17K study. *Nat Med*. 2024;30:2020-2029.

KEY WORDS cryoballoon ablation, implantable loop recorder, persistent atrial fibrillation

APPENDIX For an expanded Methods section and supplemental tables and figures, please see the online version of this paper.