Journal of the American Heart Association

ORIGINAL RESEARCH

De Novo Pulmonary Vein Isolation by Means of Pulsed Field Versus Conventional Thermal Ablation of Paroxysmal Atrial Fibrillation in Women: Safety, Efficiency, and Efficacy

Valentina Ribatti, MD, PhD; Antonio Dello Russo, MD, PhD; Stefania Riva, MD; Maurizio Malacrida, MSc; Stefano Bianchi, MD; Francesco Solimene, MD; Saverio Iacopino, MD; Antonio De Simone, MD; Antonio Rossillo, MD; Gemma Pelargonio, MD, PhD; Giulio Zucchelli, MD; Ruggero Maggio, MD; Maurizio Russo, MD; Domenico Pecora, MD; Matteo Bertini, MD, PhD; Stefano Bandino, MD; Mario Volpicelli, MD; Paolo Compagnucci, MD, PhD; Valerio De Sanctis, MD; Matteo Anselmino, MD, PhD; Roberto Rordorf, MD; Gianluca Zingarini, MD; Giovanni Rovaris, MD; Elena Agus, MD; Sakis Themistoclakis, MD; Gianfranco Mitacchione, MD; Roberta Mea, MD; Yari Valeri, MD; Claudio Tondo, MD, PhD; Michela Casella, MD, PhD

BACKGROUND: Women are frequently underrepresented in studies investigating atrial fibrillation (AF) ablation. We evaluated the acute efficacy, safety, and mid-term outcomes of de novo paroxysmal AF ablation in female patients using a pentaspline pulsed-field ablation (PFA) versus thermal-based technologies.

METHODS: In a cohort of consecutive female patients with paroxysmal AF undergoing de novo pulmonary vein isolation, enrolled in the ATHENA-CHARISMA (Advanced Technologies For Successful Ablation of AF in Clinical Practice - Catheter Ablation of Arrhythmias With High-DensityMapping System in the Real WorldPractice) registries, thermal ablation systems (radiofrequency or cryoablation) were compared to the PFA by means of a propensity score matching (ratio 1:1:1).

RESULTS: One-thousand one female patients (mean age 63±10 years, mean left ventricular ejection fraction 60.8±6%) were included: 376 (37.6%) underwent cryoablation ablation, 342 (34.2%) radiofrequency ablation, and 283 (28.3%) PFA. Propensity score matching yielded 684 patients (228 per group). The PFA group had significantly shorter skin-to-skin time (60 [50–75] minutes) compared with both radiofrequency (120 [90–145] minutes, $P<0.001$) and cryoablation (75 [60–100] minutes, $P<0.001$), while fluoroscopy time was similar among groups (15 [11–21] minutes for PFA, 14 [10–20] minutes for cryoablation, $P=0.599$ versus PFA and 14 [9–20] minutes for radiofrequency, $P=0.454$ versus PFA). Overall complication rate was 3.4% and it was significantly higher after thermal ablation than PFA (4.6% versus 0.9%, OR, 5.5, 95% CI, 1.3–23.5, $P=0.0227$). During a median follow-up of 413 [277–589] days, 139 (20.3%) patients experienced AF recurrence. The Kaplan–Meier estimated freedom from AF at 1-year follow-up was 86.8% with PFA, 84.6% with cryoablation, and 83.3% with radiofrequency (log-rank P value: 0.839).

CONCLUSIONS: Among this cohort of female patients, de novo paroxysmal AF using a pentaspline PFA system demonstrated significantly shorter procedural times, and a lower complication rate compared with thermal ablation systems. One-year follow-up revealed comparable rates of AF freedom across all ablation modalities.

Correspondence to: Valentina Ribatti, MD, Department of Clinical Electrophysiology & Cardiac Pacing, Monzino Cardiological Center, IRCCS, Via Carlo Parea, 4, 20138 Milan, Italy. Email: valentina.ribatti@cardiologicomonzino.it and Michela Casella, MD, PhD, Cardiology and Arrhythmology Clinic, Marche University Hospital, Via Conca 71, 60126, Ancona, Italy. Email: michelacasella@hotmail.com

This manuscript was sent to Shaan Khurshid, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Presented in part at Heart Rhythm 2025 in San Diego, California, April 24-April 27, 2025, and published in abstract form [10.1016/j.hrthm.2025.03.983].

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.125.041873

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

REGISTRATION: ATHENA (Advanced Technologies For Successful Ablation of AF in Clinical Practice). URL: http://clinicaltrials.gov/; Unique identifier: NCT05617456. CHARISMA (Catheter Ablation of Arrhythmias With High-Density Mapping System in the Real World Practice). URL: http://clinicaltrials.gov/; Unique Identifier: NCT03793998.

Key Words: atrial fibrillation ■ catheter ablation ■ electroporation ■ female sex ■ pulsed-field ablation ■ thermal ablation ■ women

CLINICAL PERSPECTIVE

What Is New?

- In this cohort of female patients, pulsed-field ablation for treatment of paroxysmal atrial fibrillation was associated with a shorter procedural time and lower complication compared with thermal ablation.
- Atrial fibrillation recurrence during follow up was comparable across all ablation modalities while atrial tachycardia/atrial flutter recurrences were less frequent in patients treated with pulsed-field ablation than in those treated with thermal ablation.

What Are the Clinical Implications?

- In female patients undergoing ablation for paroxysmal atrial fibrillation, use of a pentaspline pulsed-field ablation system was associated with shorter procedures, fewer complications, and similar rate of atrial fibrillation recurrence compared with thermal ablation, suggesting potential advantages for procedural efficiency and long-term rhythm outcomes in this population.

Nonstandard Abbreviations and Acronyms

AT	atrial tachycardia
ATHENA	Advanced TecHnologies For Successful Ablation of AF in Clinical Practice
ATL	atrial flutter
CHARISMA	Catheter Ablation of Arrhythmias With High-Density Mapping System in the Real World Practice
PFA	pulse-field ablation

Women are often underrepresented in randomized clinical trials, including those investigating atrial fibrillation (AF) ablation, and are less likely than men to undergo interventional procedures.[1] This disparity highlights potential sex-based differences in treatment strategies.[2] Sex-specific variations in the risks and benefits of catheter ablation for AF remain a topic of debate, given the distinct differences in AF incidence, clinical presentation, and management between men and women.[3,4]

Notably, thermal ablation procedures for AF have been associated with higher rates of arrhythmia recurrence and post-procedural complications in women compared with men.[1,5,6]

Pulsed field ablation (PFA), a novel non-thermal ablation modality based on irreversible cellular electroporation, has recently become available for clinical application. PFA has garnered significant attention due to its unique safety profile and efficient lesion delivery.[7,8] Data from a large observational registry evaluating the initial post-approval use of PFA for AF treatment suggest no significant sex-based differences in clinical effectiveness or safety.[9] However, the comparative efficacy and safety of PFA versus conventional thermal ablation techniques in the specific subset of women remain inadequately characterized. In addition, in most of the published works the comparison between groups or analysis of predictive factors included a sex analysis, this in fact determined the loss of the relevant aspect of a structured evaluation specific to the female universe. With our study we aimed to evaluate the acute efficiency, safety, and mid-term outcomes of AF ablation in female patients only using a pentaspline PFA system compared to thermal-based ablation technologies.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Population and Study Design

Consecutive female patients with paroxysmal AF undergoing de novo pulmonary vein isolation and enrolled in the ATHENA (Advanced Technologies For Successful Ablation of AF in Clinical Practice) and CHARISMA (Catheter Ablation of Arrhythmias With High-Density Mapping System in the Real World Practice) registries at 20 Italian centers from January 2020 to January 2024. The ATHENA registry is a prospective, multicenter, non-randomized post-market study in which patients indicated to AF ablation are treated according to the

standard care followed by each center. During the 12 months follow-up period, clinical atrial fibrillation recurrence, occurrence of all kind of atrial arrhythmias and of all adverse events in the study population are collected. The CHARISMA study is a non-randomized, multicenter, prospective study in which consecutive patients indicated for different kind of arrhythmias are enrolled, with the aim to describe the Italian clinical practice in relation to the ablation approach. For current analysis purpose, from all kinds of patients indicated to different arrhythmia ablation, female patients with indication to AF ablation were included. The choice for ablation modality was based on the operators' preference and the availability of technology in their center.

In the present analysis, the population was stratified into 3 groups according to thermal ablation systems (radiofrequency or cryoablation) or pulsed-field ablation system and then were compared by means of a propensity score matching in a 1:1:1 ratio. Only patients undergoing ablation of the PVs alone were included, patients undergoing additional lesions outside the veins (ie, posterior wall, mitral isthmus, roof, etc) were not included in the analysis. All patients were followed up at the enrolling center, from the time of first ablation to the last follow-up visit. The studies complied with the Declaration of Helsinki; the locally appointed ethics committee approved the research protocol, and informed consent was obtained from all patients.

Ablation Procedure

PFA Group

all procedures were performed under either deep conscious sedation or general anesthesia. The choice of anesthesia protocol was guided by the operator's preference, expertise, and the patient's overall health status.[10–13] Anticoagulation was administered in adherence to the most recent guidelines.[14] After the transseptal puncture, procedural activated clotting times were maintained at a minimum of 300 seconds through the administration of intravenous heparin bolus or continuous infusion. The procedure involved the utilization of the penta-splines 12F over-the-wire PFA catheter (FARAWAVE™, Boston Scientific Inc, St. Paul, MN) with the FARAPULSE™ PFA system (Boston Scientific Inc, St. Paul, MN). PVI was performed by means of 4 applications in a basket configuration and 4 applications in a flower configuration per PV, as described elsewhere.[10–13] Between pairs of PFA applications, the catheter was rotated by about 30°/45° after the first two applications in each configuration, to cover the entire PV circumference. Ablation was performed by using an amplitude setting of 2.0 kV for each of the 4 PVs. Additional lesions at PVs were deployed per physician's discretion.

Radiofrequency Group

a 3D-electroanatomical mapping system (Carto 3, Biosense Webster; EnSite NavX, Abbott or Rhythmia, Boston Scientific) was used to guide mapping and ablation in all cases. Left atrial electroanatomic mapping and PVI were achieved via a multipolar catheter and an open- irrigated radiofrequency ablation catheter according to center/operator's preferences. Radiofrequency ablation was performed with a power of >45 W.

Cryoablation Group

After transseptal catheterization, the cryoablation-balloon was inserted into the left atrium via the steerable sheath. Mapping of the PVs was performed by means of the dedicated mapping catheter advancing into each PV ostium and positioned as proximally as possible, in order to record PV potentials. A 28-mm or 31-mm was advanced, inflated, and positioned at each PV antrum. Protocol-directed cryoablation was administered for 180 seconds or 240 seconds, based on the operator's preference. If isolation was achieved within ≤60 seconds, a 180-second freeze was employed; otherwise, a 240-second freeze was applied. If PV isolation did not occur after the second freeze, the decision to proceed with additional lesions was taken based on the other parameters according to operator feedback, by instances when time to isolation data were unavailable or when proper contact/occlusion was achieved.

Post-Ablation Management

Follow-up evaluations were conducted at outpatient clinics at 1, 3, 6, and 12 months post-procedure, or as needed in response to patient complaints. These assessments comprised a detailed review of medical history, physical examination, 12-lead electrocardiography, Holter monitoring (24-hour, 48-hour, or 7-day), and evaluation for adverse events.

Any atrial tachyarrhythmia defined as episodes >30 s was considered a recurrence. Recurrence was assessed with a standard ECG or Holter ECG monitoring or by interrogation of implantable loop recorders or implanted devices, if applicable. Additionally, any symptoms following ablation were deemed to warrant Holter ECG monitoring. The primary endpoint of this analysis is the freedom from atrial arrhythmia recurrence at 1-year follow-up. During the initial 3-month period post-ablation (the blanking period), occurrences of AF or atrial tachycardia (AT) or atrial flutter (AFL) were not classified as recurrences. The differentiation of the classification of arrhythmias, AF and AT/AFL is based on the evaluation of ECG or Holter ECG monitoring recording according to the conventional criteria of AF and AT/AFL suggested by the current guidelines.[14]

Anticoagulation and antiarrhythmic therapies were maintained following the ablation. At the 3-month follow-up, decisions regarding the continuation of anticoagulation therapy were guided by the patient's stroke risk, while the ongoing use of antiarrhythmic drugs was determined at the treating physician's discretion. Major adverse events, including cardiac tamponade, air embolism, stroke, transient ischemic attack, atrio-esophageal fistula, and mortality, were recorded. The relationship between each adverse event and the procedure and/or device was assessed by the respective participating center.

Statistical Analysis

Descriptive statistics are reported as means±SD for normally distributed continuous variables, or medians with 25th to 75th percentiles in the case of skewed distribution. Normality of distribution was tested by means of the nonparametric Kolmogorov–Smirnov test. Differences between mean data were compared by means of a t-test for Gaussian variables, and the F-test was used to check the hypothesis of equality of variance. The Mann–Whitney non-parametric test was used to compare non-Gaussian variables. Differences in proportions were compared by applying $\chi 2$ analysis or Fisher's exact test, as appropriate. Univariable Cox proportional hazards models were used to determine the association between procedural parameters and the occurrence of atrial arrhythmia events during the follow-up period, and to estimate the hazard ratios (HRs) with 95% CIs. The cumulative probability of arrhythmia recurrence was displayed by means of the Kaplan–Meier method, and the log-rank test was used to compare cumulative events. To reduce confounding, we performed 1:1 nearest-neighbor propensity score matching without replacement. Given the 3 treatment groups (PFA, cryoablation, radiofrequency), we conducted separate pairwise logistic regressions (PFA versus cryoablation, PFA versus radiofrequency, cryoablation versus radiofrequency) to estimate propensity scores based on the following covariates: age, history of atrial arrhythmias, chronic kidney disease, chronic obstructive pulmonary disease, heart failure, hypertension, coronary/peripheral artery disease, history of thromboembolic event, left atrial dimension, left ventricular ejection fraction, and sleep apnea. From the 3 matched cohorts, we identified patients common to all comparisons, resulting in a final matched population of 684 patients (n=228 per group; 1:1:1 ratio). After matching, standardized mean differences for all covariates were <0.1, indicating good balance. All statistical analyses were performed by means of R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population and Procedural Characteristics

A total of 1001 female patients were included: 376 (37.6%) underwent cryoablation ablation, 342 (34.2%) radiofrequency ablation, and 283 (28.3%) PFA. After propensity score matching, the analysis was restricted to 684 patients in a 1:1:1 ratio: 228 (33%), PFA group versus 228 (33%), cryoablation group versus 228 (33%), radiofrequency group. Baseline clinical variables and procedural parameters of the unmatched and matched cohort study groups were reported in Table S1 and Table 1.

Table 1. Baseline Clinical Characteristics of the Propensity Score-Matched Population Presented for the Entire Population and According to Matched Cohort Study Groups: Radiofrequency, Cryoablation and PFA

Parameter	Overall population (n=684)	Cryoablation (n=228)	Radiofrequency (n=228)	PFA (n=228)	*P* value
Age, y	63.4±9	63.3±9	62.9±9	63.9±9	0.496
Left Atrial volume, mL	33.0±10	32.2±10	33.4±10	33.2±10	0.581
LVEF, %	60.1±6	60.2±6	60.0±7	60.1±5	0.951
History of AT/AFL, n (%)	63 (9.2)	19 (8.3)	23 (10.1)	21 (9.2)	0.811
Structural heart disease (non-ischemic), n (%)	32 (4.7)	7 (3.1)	15 (6.6)	10 (4.4)	0.201
Coronary artery disease, n (%)	34 (5.0)	13 (5.7)	9 (3.9)	12 (5.3)	0.669
CKD, n (%)	2 (0.3)	0 (0.0)	1 (0.4)	1 (0.4)	0.606
COPD, n (%)	13 (1.9)	3 (1.3)	5 (2.2)	5 (2.2)	0.731
History of HF, n (%)	8 (1.2)	2 (0.9)	3 (1.3)	3 (1.3)	0.881
Sleep apnea, n (%)	13 (1.9)	4 (1.8)	3 (1.3)	6 (2.6)	0.578
Hypertension, n (%)	295 (43.1)	92 (40.4)	106 (46.5)	97 (42.5)	0.407
Stroke/TIA, n (%)	16 (2.3)	6 (2.6)	5 (2.2)	5 (2.2)	0.938
Antiarrhythmics, n (%)	353 (51.6)	120 (52.6)	115 (50.4)	118 (51.8)	0.895

Data are reported as median [IQ range, Q1–Q3] or number (percentage). AT indicates atrial tachycardia; AFL, atrial flutter; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; LVEF, left ventricular ejection fraction; PFA, pulsed-field ablation; and TIA, transient ischemic attack.

Table 2. Procedural Details of the Propensity Score-Matched Population Presented for the Entire Population and According to Matched Cohort Study Groups: Radiofrequency, Cryoablation, and PFA

Parameter	Overall population (n=684)	Cryoablation (n=228)	Radiofrequency (n=228)	PFA (n=228)	*P* value
Mapping system used, n (%)	285 (41.7)	22 (9.6)	228 (100.0)	35 (15.4)	<0.001
Intracardiac echocardiography, n (%)	157 (23.0)	16 (7.0)	68 (29.8)	73 (32.0)	<0.001
Skin-to-skin (primary operator) time, min	80 [60–120]	75 [60–100]	120 [90–145]	60 [50–75]	<0.001
Total fluoroscopy time, min	14.1 [10–20]	14 [10–20]	14 [9–20]	15 [11–21]	0.887
Left atrium dwell time, min	20 [13–28]	16 [12–25]	25 [14–35]	18 [13–23]	<0.001

Data are reported as median [IQ range, Q1–Q3] or number (percentage). LA indicates left atrium; and PFA, pulsed-field ablation.

Procedural Efficiency

The median skin-to-skin time, fluoroscopy time and left atrium dwell time were 80 [60–120] minutes, 14.1 [10–20] minutes and 20 [13–28] minutes, respectively. A 3D-mapping system was used to guide the ablation and validate the lesion set in all the radiofrequency procedures (n=228, 100%), while its use was less frequent in both PFA (n=35, 15.4%, *P*<0.001) and cryoablation (n=22, 9.6%, *P*<0.001) procedures. The PFA group (Table 2) had significantly shorter skin-to-skin time (60 [50–75] minutes) and left atrium dwell time (18 [13–23] minutes) compared with thermal energy sources (skin-to-skin time: 100 [70–120] minutes, *P*<0.001; left atrium dwell time: 20 [12–30] minutes, *P*=0.0002, respectively) while fluoroscopy time was similar between groups (15 [11–21] minutes for PFA versus 14 [10–20] minutes for thermal energy sources, *P*=0.449). Considering energy sources separately, the PFA group exhibited significantly shorter skin-to-skin time compared with both radiofrequency (120 [90–145] minutes, *P*<0.001) and cryoablation (75 [60–100] minutes, *P*<0.001), while fluoroscopy time was similar among groups (14 [10–20] minutes for cryoablation, *P*=0.599 versus PFA and 14 [9–20] minutes for radiofrequency, *P*=0.454 versus PFA). Left atrium dwell time was longer during radiofrequency procedures (25 [14–35] minutes) than both cryoablation (16 [12–25] minutes, *P*<0.0001 versus radiofrequency) and PFA (*P*<0.0001 versus radiofrequency, *P*=0.802 versus cryoablation). Figure 1 reports procedural times according to the energy source adopted during the procedure and Figure S1 provides procedural times for the unmatched population.

Ablation Outcome and Predictors of Atrial Arrhythmia Recurrence During Follow-Up

During a median follow-up of 413[277–589] days, 99 (14.5%) patients experienced AF recurrence, 29 (4.2%) an AT/AFL recurrence, and 40 (5.8%) experienced both events, resulting in 168 (24.6%) patients who suffered overall an AF/AT/AFL recurrence after the 90-day blanking period. At 1-year follow-up the rate of AF/AT/AFL recurrence, AF or AT/AFL recurrence rate was 18.6% (n=127), 15.1% (n=103) and 42 (6.1%), respectively. The Kaplan–Meier estimated freedom from AF at 1-year follow-up was 84.9%, with similar rate between PFA

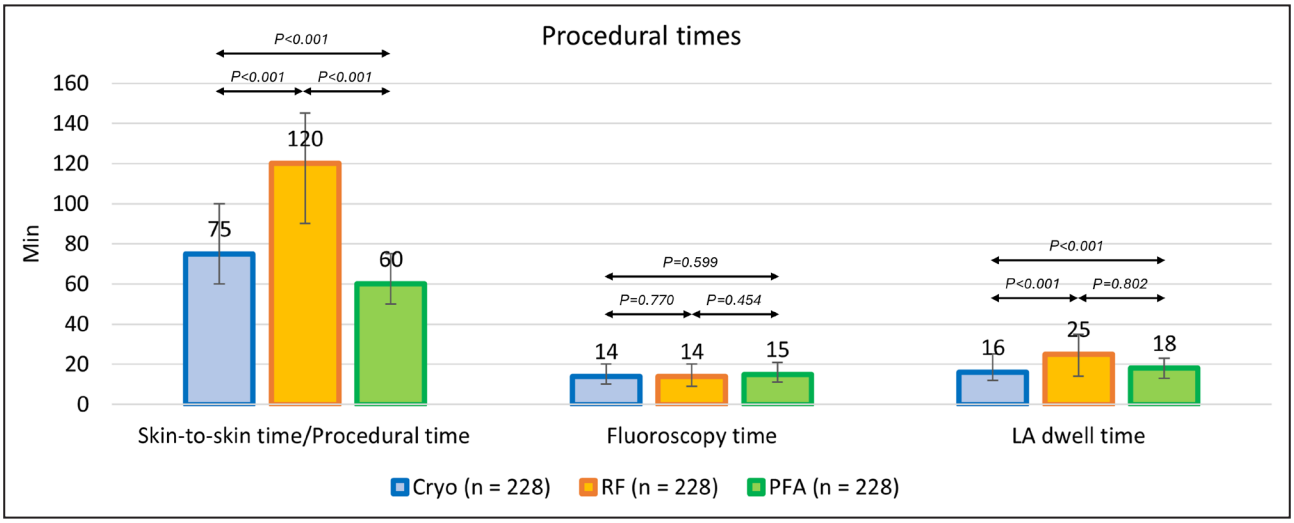

Figure 1. Procedural times among groups.
Skin-to-skin time, fluoroscopy time and left atrium dwell time were compared between matched cohort study groups (RF, Cryo and PFA). Cryo indicates cryoabalation; PFA, pulse-field ablation; and RF, radiofrequency.

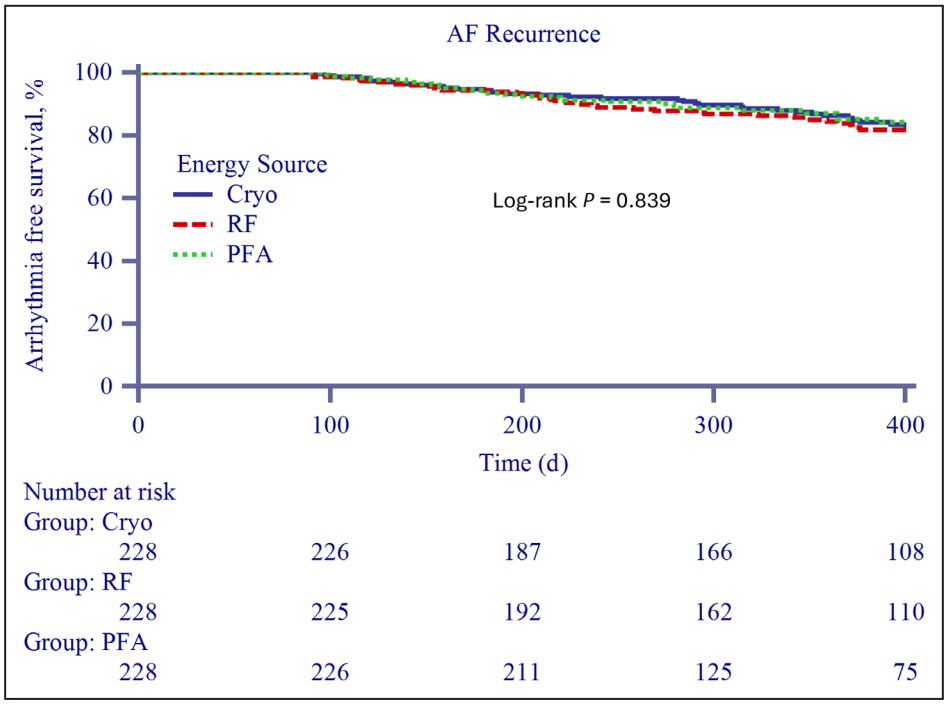

Figure 2. Kaplan–Meier estimated freedom from AF at 1-year follow-up.
Survival curve from AF recurrence during follow-up after the 90-day blanking period, according to energy source (RF, Cryo and PFA). AF indicates atrial fibrillation; Cryo, cryoabalation ; PFA, pulse-field ablation; and RF, radiofrequency.

and conventional thermal energy (cryoablation and radiofrequency) and among energy sources considering separately (Figure 2 and Figure S2 for the unmatched population): 86.8% with PFA versus 84% with thermal energy (log-rank *P* value: 0.642); 84.6% with cryoablation, and 83.3% with radiofrequency (overall log-rank *P* value: 0.839). Figure 3 shows the survival curve free from AF/AT/AFL (81.4%) during follow-up after the 90-day blanking period: 83.8% with PFA versus 80.3% with thermal energy (log-rank *P*value: 0.673); 81.6% with cryoablation, and 78.9% with radiofrequency (overall log-rank *P* value: 0.717) and Figure S3 for the unmatched population. Figure S4 shows the survival curve free from AT/AFL (93.9%) during follow-up after the 90-day blanking period: 96.1% with PFA versus 92.8% with thermal energy (log-rank *P* value: 0.185); 94.3% with cryoablation (OR, 0.68, 95%CI, 0.28–1.62, *P*=0.385 versus PFA), and 91.2% with radiofrequency (OR, 0.43, 95%CI, 0.19–0.98, *P*=0.039 versus PFA), overall log-rank *P* value: 0.182 with a trend in favor of PFA versus radiofrequency, log-rank *P*value: 0.082.At multivariate logistic analysis adjusted for baseline confounders (Tables S2 and S3), indexed left atrial volume emerged as the only parameter independently associated with AF recurrence (HR=1.03, 95%CI, 1.002–1.05, *P*=0.0328) and the combined endpoint of AF/AT/AFL recurrence (HR=1.03, 95%CI, 1.01–1.05, *P*=0.0132) during follow-up.

Periprocedural Complications

Overall complication rate was 3.4%, significantly higher in the thermal ablation (4.6%) than in the PFA group (0.9%, OR, 5.5, 95%CI, 1.3–23.5, *P*=0.0227). The rate of major complications was 0.9% consisting of 4 cardiac tamponades (0.6%, 3 in the radiofrequency group and 1 in the cryoablation group), one pericardial effusion with the need of hemodynamic support (0.1%, in the cryoablation group) and one stroke (0.1%, in the radiofrequency group). No esophageal complications, PV stenosis, persistent phrenic nerve injury or anesthesia-related complications were reported. Minor complications were reported in 17 patients (2.5%) after the procedure, predominantly related to vascular accesses or catheterization (n=5, 0.7%), pericardial effusion without intervention (n=5, 0.7%) or transient phrenic nerve palsy (n=4, 0.6%). Specifically, it was higher after radiofrequency ablation (5.3%) than PFA (*P*=0.012), it was not statistical different after radiofrequency and cryoablation (3.9%, *P*=0.656) procedures and we found a non-significant trend in favor of PFA than in cryoablation procedures (*P*=0.062). Details are reported in Table 3.

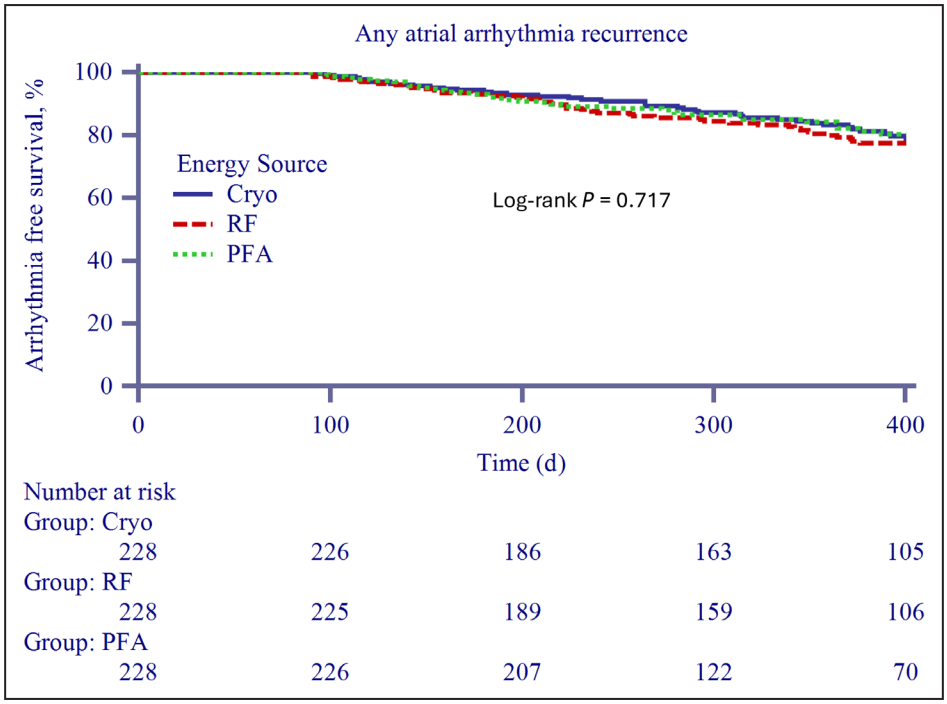

Figure 3. Kaplan–Meier estimated freedom from any atrial arrhythmia at 1-year follow-up. Survival curve from any atrial arrhythmia recurrence during follow-up after the 90-day blanking period, according to energy source (RF, Cryo and PFA). Cryo indicates cryoabalation; PFA, pulse-field ablation; and RF, radiofrequency.

DISCUSSION

Main Findings

This prospective, observational, multicenter analysis represents the first study to specifically evaluate acute efficacy, safety, and mid-term outcomes of de novo PVI for AF in female patients using the pentaspline PFA system compared to thermal-based ablation technologies.

The analysis revealed several significant findings:

Table 3. Periprocedural Complications of the Propensity Score-Matched Population With Major and Minor Periprocedural Complications Presented for the Entire Population and According to Matched Cohort Study Groups: Radiofrequency, Cryoablation, and PFA

Parameter	Overall population (n=684)	Cryoablation (n=228)	Radiofrequency (n=228)	PFA (n=228)
Major complications	6 (0.9)	2 (0.9)	4 (1.8)	0 (0.0)
Cardiac/Pericardial tamponade, n (%)	5 (0.7)	2 (0.3)	3 (0.6)	0 (0.0)
Stroke, n (%)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
TIA, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Phrenic nerve injury (persistent), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute kidney injury, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Minor complications	17 (2.5)	7 (3.1)	8 (3.5)	2 (0.9)
Phrenic nerve injury, n (%)	4 (0.6)	4 (1.8)	0 (0.0)	0 (0.0)
Pericardial effusion without intervention, n (%)	5 (0.7)	1 (0.4)	4 (1.8)	0 (0.0)
Vascular complication, n (%)	5 (0.7)	1 (0.4)	2 (0.9)	2 (0.9)
Carbonarcosis, n (%)	1 (0.1)	0 (0.0)	1 (0.4)	0 (0.0)
Hemoptysis with severe lung parenchyma, n (%)	1 (0.1)	1 (0.4)	0 (0.0)	0 (0.0)
Transient AV dissociation, n (%)	1 (0.1)	0 (0.0)	1 (0.4)	0 (0.0)
All complications, n (%)	23 (3.4)	9 (3.9)	12 (5.3)	2 (0.9)

PFA indicates pulsed-field ablation; and TIA, transient ischemic attack.

1. In female patients undergoing PVI for paroxysmal AF, PFA was associated with significantly shorter procedural times compared with conventional thermal ablation systems.
2. 12 months freedom from AF was high (>80% at 1 year), with comparable rates of arrhythmia-free survival across all ablation modalities during follow-up.
3. The overall complication rate was 3.4%, with significantly fewer complications observed following PFA compared with thermal ablation (0.9% versus 4.6%, *P*=0.0227).

Procedural Efficiency

Recent findings demonstrated that PFA was associated with shorter procedure times than thermal ablation but required a longer duration of fluoroscopy.[15,16] According to this, in our large female real clinical practice, we found that PFA was associated with shorter procedural time compared with both cryoablation and radiofrequency procedures. In addition to that, PFA also achieved a shorter left atrium dwell time (18 minutes), 7 minutes shorter than radiofrequency (25 minutes) and comparable to cryoablation (16 minutes). Differently from previous literature[15,16] fluoroscopy time, was similar in all groups. This lack of difference may be attributable by the multicenter nature of the study as well as by not having as a pre-determined focus in fluoroscopy exposition, particularly in procedures where a mapping system was used systematically (ie, radiofrequency procedures). However, operator experience has been shown to reduce fluoroscopy exposure during PFA[17] therefore, with the development of full integration between this system and EAM systems, the potential drawback of fluoroscopy dependency of PFA would be overcome.

The application of ionizing radiation in medical procedures carries notable health risks for both patients and healthcare providers. Emerging evidence suggests that women may be particularly vulnerable to radiation-induced injury during fluoroscopy-guided interventions, such as atrial fibrillation ablation. This increased susceptibility is attributable to several factors, including biological differences such as the heightened radiosensitivity of breast tissue and reproductive organs.[18]

In addition, the smaller average body size of women may result in increased radiation dose absorption relative to tissue volume. The reduced procedure time with PFA has significant clinical implications, particularly for women who, as reported in previous studies, often present with smaller left atria and increased procedural complexity.[19] In addition to this, female sex is known to relate to an increased risk of stroke/transient ischemic attack and major complications compared with male sex during AF ablation procedures,[20] independent of follow-up time. For all these reasons the hereby reported results on procedural tolerability may direct operator's preference to PFA within woman.

One-Year Outcome

Many studies indicate that women may experience poorer outcome, higher burden of AF-related comorbidities and treatment failure compared with men.[21–23]

Results from a recent cohort study on PFA-only procedures[9] suggest that after PFA for AF, there were no significant sex differences in clinical effectiveness or safety events. In our study of female patients only, mid-term efficacy results were comparable between PFA and thermal energy modalities. At one year, the Kaplan–Meier estimate of freedom from AF recurrence was 84.9%, with no significant differences between PFA (86.8%) and thermal energy (84%). Similarly, the combined endpoint of AF/AT/AFL recurrence showed no significant difference between energy source groups (81.4% for PFA versus 80.3% for thermal energy). These results are consistent with previous studies data suggesting equivalence of PFA and thermal energy in achieving durable pulmonary vein isolation in paroxysmal AF patients[24] and in line with the recent work of Turagam et al. which reported ≈80% of clinical effectiveness in the female group.[9]

In our analysis we found double AT/AFL recurrences in the radiofrequency (8.8%) compared with the PFA group (3.9%), and a trend of higher recurrences of AT/AFL in the cryoablation (5.7%) compared with PFA group (3.9%). This aspect could be determined by the different lesion modality between radiofrequency (ie, punctiform and possibly non-transmural lesions) and PFA (a homogeneous electroporation ablation through a basket/flower configuration of the pentaspline PFA catheter). Although not statistically significant in the temporal analysis given the sample size and the low overall recurrence rate, radiofrequency therefore seems more subject to AT/AFL recurrences (possible left AT and micro-reentrant tachycardias) compared with cryoablation or PFA. A comparative study specifically evaluating radiofrequency versus PFA and cryoablation versus PFA in female patients, powered to detect potential differences in AT/AFL recurrences, would be valuable to confirm these important findings and assess their potential healthcare expenditures related to ablation therapy.

Importantly, indexed left atrial volume emerged as the only independent predictor of AF recurrence, highlighting the role of atrial remodeling in ablation outcomes. Female patients demonstrated more advanced atrial remodeling and greater arrhythmia recurrence after AF ablation compared with male patients in terms of high-density electroanatomic mapping with lower atrial voltage, reduced conduction velocity, and greater proportion of complex fractionated signals.

These sex-related differences in atrial electrophysiology may contribute to worse long-term arrhythmia outcomes.[25] Future studies should investigate whether specific procedural strategies, such as adjunctive ablation beyond PVI or targeted substrate modification, could further improve outcomes in women with enlarged atria or persistent AF.

Safety Profile

The safety advantages of PFA over thermal energy were pronounced in this study. The overall complication rate was significantly lower with PFA (0.9%) compared with thermal ablation (4.6%), with a fivefold reduction in the odds of complications. The majority of major complications, including cardiac tamponade and stroke, occurred in the radiofrequency and cryoablation groups, with none reported in the PFA cohort. Procedural and dwelling time in the left atrium may, in fact, be critical in this respect. In addition, no esophageal injury, phrenic nerve palsies or pulmonary vein stenosis were observed in the PFA group, highlighting its safety profile.

The reduced risk of complications with PFA is likely due to its non-thermal mechanism, which spares adjacent tissues while delivering precise lesions. This is particularly relevant for women, who have been shown to face a higher risk of vascular complications and cardiac tamponade following AF ablation procedures.[20]

Clinical Perspective

This study highlights the importance of evaluating sex-specific outcomes in AF ablation. Women enrolled in AF randomized clinical trials were likely to have more comorbidities but less advanced AF, limiting the applicability of general results to women with AF.[26] Sex-specific differences in physiological, electrical and structural characteristics of the atria, which may result in higher AF recurrence in women than in men, include lower repolarizing ion currents, longer action potential duration in female atria, greater frequency of non-pulmonary triggered activity, inflammatory processes and more pronounced AF-associated fibrotic remodeling and AF progression.[27–29]

The comparable efficacy of PFA and its lower complication rates offer a promising solution to address these disparities. In addition, the streamlined procedural workflow of PFA may reduce access barriers for women, who are less likely than men to undergo ablation despite similar symptom burden. Despite these advantages, the comparable long-term efficacy of PFA and thermal ablation suggests that operator experience, patient selection, and procedural planning remain critical determinants of success. Further research is needed to assess the long-term impact of PFA on quality of life and symptom resolution in female patients, as well as to explore its role in challenging cases such as persistent AF or concomitant atrial flutter.

Limitations

The principal limitations of this analysis arise from its intrinsic non-randomized design. Nevertheless, both registries were conducted prospectively, adhering to the standard-of-care protocols at each participating center for AF ablation and patient management. Secondly, sinus rhythm maintenance was defined mainly on the basis of patients' symptoms, ECG and scheduled Holter monitoring, therefore some episodes of asymptomatic recurrence of atrial fibrillation may have been missed because continuous invasive monitoring was not used. Holter monitoring strategy was selected according to each center and operators maintained their usual clinical practice. However, considering that our evaluation methods is comparable to those used in most similar literature, it looks rather acceptable for the conclusion of the study. Atrial arrhythmias during the blanking period were not taken into account for analysis purposes. This analysis included female patients only, implying the absence of comparison to men. Although this may represent a limitation in terms of the extent of the analyses, it is exactly what is wanted, to report and highlight any differences in the use of different technologies in the female context only. Our findings may not be generalizable to women of other racial/ethnic groups. Due to the small number of safety outcome events, the study is unpowered to prove differences among the 3 groups. Lastly, no data on PV reconnections were available after the ablation procedures for all groups.

CONCLUSIONS

Our results demonstrate that in woman PVA offers comparable mid-term efficacy with significantly shorter procedure times and a more favorable safety profile than both radiofrequency and cryoablation procedures, underscoring its potential to address the challenges of AF ablation in female patients undergoing PVI of paroxysmal AF.

ARTICLE INFORMATION

Received February 18, 2025; accepted September 25, 2025.

Affiliations

Department of Clinical Electrophysiology & Cardiac Pacing, Monzino Cardiological Center, IRCCS, Milan, Italy (V.R., S.R., R.M., C.T.); Cardiology and Arrhythmology Clinic, Marche University Hospital, Ancona, Italy (A.D.R., P.C., Y.V.); Department of Biomedical Sciences and Public Health, Marche Polytechnic University, Ancona, Italy (A.D.R., F.S., P.C., Y.V., M.C.); Boston Scientific, Milan, Italy (M.M.); Center of Excellence in Cardiovascular Sciences, Ospedale Isola Tiberina - Gemelli Isola, Rome, Italy (S.B.); Montevergine Clinic, Mercogliano, AV, Italy (F.S.); Maria Cecilia Hospital, GVM Care &

Research, Cotignola, Italy (S.I., M.C.); S. Michele Clinic, Maddaloni, CE, Italy (A.D.S.); San Bortolo Hospital, Vicenza, Italy (A.R.); Istituto di Cardiologia Università Cattolica del Sacro Cuore, Rome, Italy (G.P.); Department of Cardiovascular Sciences, Arrhythmology Unit, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy (G.P.); Second Division of Cardiology, Cardiac-Thoracic-Vascular Department, New Santa Chiara Hospital, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy (G.Z.); Degli Infermi Hospital, Rivoli, TO, Italy (R.M.); San Filippo Neri Hospital, Rome, Italy (M.R.); Electrophysiology Unit, Cardiology Operating Unit, Fondazione Poliambulanza Hospital, Brescia, Italy (D.P.); Cardiology Unit, University of Ferrara, Sant'Anna University Hospital, Ferrara, Italy (M.B.); Clinical and Experimental Cardiology, Clinical and Interventional Cardiology, University Hospital, Sassari, Italy (S.B.); Cardiovascular Diseases and Electrophysiology Unit, S. Maria della Pietà Hospital, Nola, Naples, Italy (M.V.); IRCCS Ospedale Galeazzi - Sant'Ambrogio, Milan, Italy (V.D.S.); Division of Cardiology, Cardiovascular and Thoracic Department, "Città della Salute e della Scienza" Hospital, Torino, Italy (M.A.); Department of Medical Sciences, University of Torino, Torino, Italy (M.A.); Arrhythmia and Electrophysiology Unit, Division of Cardiology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (R.R.); S. Maria della Misericordia Hospital, Perugia, Italy (G.Z.); Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy (G.R.); Cardiology Department, Brotzu Hospital, Cagliari, Italy (E.A.); Dell'Angelo Hospital, Mestre, VE, Italy (S.T.); Department of Electrophysiology and Cardiac Pacing, ASST Spedali Civili, Brescia, Italy (G.M.); Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy (G.M.); Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy (C.T.); and Department of Clinical, Special, and Dental SciencesMarche Polytechnic University, Ancona, Italy (M.C.).

Sources of Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

M. M. is an employee of Boston Scientific. C. T. received speaker's and proctor's fees from Boston Scientific, Medtronic, Abbott and Biosense Webster. He serves in the Advisory Board of Medtronic, Boston Scientific. S. B. received teaching and proctor's fees and honoraria from Boston Scientific and Medtronic. G. Z. received contribution for travel and hotel accommodation by Boston Scientific, Biosense Webster, Medtronic and Abbott. The other authors have no conflicts of interest to declare that are relevant to the content of this article. M. A. is consultant for Johnson & Johnson and Boston Scientific, clinical proctor for Medtronic and has received educational grants from Abbott. A. D. R. is a consultant for Abbott Medical. M. C. has received speaker honoraria from Biosense Webster. The other authors have no conflicts of interest to declare that are relevant to the content of this article.

Supplemental Material

Tables S1–S3
Figures S1–S4

REFERENCES

1. Linde C, Bongiorni MG, Birgersdotter-Green U, Curtis AB, Deisenhofer I, Furokawa T, Gillis AM, Haugaa KH, Lip GYH, Van Gelder I, et al. Sex differences in cardiac arrhythmia: a consensus document of the European heart rhythm association, endorsed by the Heart Rhythm Society and Asia Pacific Heart Rhythm Society. *Europace*. 2018;20:1565–1565ao. doi: 10.1093/europace/euy067
2. Zörner CR, Tønnesen J, Riis-Vestergaard LD, Middelfart C, Hein R, Rasmussen PV, Ruwald MH, Gislason G, Hansen ML. Disparities in the access to atrial fibrillation ablation in Denmark: who gets ablated, who neglected? *Europace*. 2024;26:euae231. doi: 10.1093/europace/euae231
3. Russo AM, Zeitler EP, Giczewska A, Silverstein AP, Al-Khalidi HR, Cha YM, Monahan KH, Bahnson TD, Mark DB, Packer DL, et al. Association between sex and treatment outcomes of atrial fibrillation ablation versus drug therapy: results from the CABANA trial. *Circulation*. 2021;143:661–672. doi: 10.1161/CIRCULATIONAHA.120.051558
4. Cheung JW, Cheng EP, Wu X, Yeo I, Christos PJ, Kamel H, Markowitz SM, Liu CF, Thomas G, Ip JE, et al. Sex-based differences in outcomes, 30-day readmissions, and costs following catheter ablation of atrial fibrillation: the United States Nationwide readmissions database 2010-14. *Eur Heart J*. 2019;40:3035–3043. doi: 10.1093/eurheartj/ehz151
5. Zylla MM, Brachmann J, Lewalter T, Hoffmann E, Kuck KH, Andresen D, Willems S, Eckardt L, Tebbenjohanns J, Spitzer SG, et al. Sex-related outcome of atrial fibrillation ablation: insights from the German ablation registry. *Heart Rhythm*. 2016;13:1837–1844. doi: 10.1016/j.hrthm.2016.06.005
6. Kuck KH, Brugada J, Fürnkranz A, Chun KRJ, Metzner A, Ouyang F, Schlüter M, Elvan A, Braegelmann KM, Kueffer FJ, et al. Impact of female sex on clinical outcomes in the FIRE AND ICE trial of catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2018;11:e006204. doi: 10.1161/CIRCEP.118.006204
7. Tzeis S, Gerstenfeld EP, Kalman J, Saad EB, Sepehri Shamloo A, Andrade JG, Barbhaiya CR, Baykaner T, Boveda S, Calkins H, 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.
8. Turagam MK, Neuzil P, Schmidt B, Reichlin T, Neven K, Metzner A, Hansen J, Blaauw Y, Maury P, Arentz T, 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. doi: 10.1161/CIRCULATIONAHA.123.064959
9. Turagam MK, Neuzil P, Schmidt B, Reichlin T, Neven K, Metzner A, Hansen J, Blaauw Y, Maury P, Arentz T, et al. Clinical outcomes by sex after pulsed field ablation of atrial fibrillation. *JAMA Cardiol*. 2023;8:1142–1151. doi: 10.1001/jamacardio.2023.3752
10. Dello Russo A, Tondo C, Schillaci V, Casella M, Iacopino S, Bianchi S, Fassini G, Rossillo A, Compagnucci P, Schiavone M, et al. Intracardiac echocardiography–guided pulsed-field ablation for successful ablation of atrial fibrillation: a propensity-matched analysis from a large nationwide multicenter experience. *J Interv Card Electrophysiol*. 2024;65:1257–1266.
11. Schiavone M, Solimene F, Moltrasio M, Casella M, Bianchi S, Iacopino S, Rossillo A, Schillaci V, Fassini G, Compagnucci P, et al. Pulsed field ablation technology for pulmonary vein and left atrial posterior wall isolation in patients with persistent atrial fibrillation. *J Cardiovasc Electrophysiol*. 2024;35:1101–1111. doi: 10.1111/jce.16246
12. Bisignani A, Schiavone M, Solimene F, Dello Russo A, Filannino P, Magnocavallo M, Tondo C, Schillaci V, Casella M, Petretta A, et al. National workflow experience with pulsed field ablation for atrial fibrillation: learning curve, efficiency, and safety. *J Interv Card Electrophysiol*. 2024;67:2127–2136. doi: 10.1007/s10840-024-01835-6
13. Dello Russo A, Tondo C, Bianchi S, Schillaci V, Iacopino S, Casella M, Rossillo A, Maggio R, Themistoclakis S, Bertini M, et al. Does age impact safety and efficacy during pulse-field ablation for atrial fibrillation? *J Am Heart Assoc*. 2025;14:e037959. doi: 10.1161/JAHA.124.037959
14. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, 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.
15. Reddy VY, Gerstenfeld EP, Natale A, Whang W, Cuoco FA, Patel C, Mountantonakis SE, Gibson DN, Harding JD, Ellis CR, et al. Pulsed field or conventional thermal ablation for paroxysmal atrial fibrillation. *N Engl J Med*. 2023;389:1660–1671. doi: 10.1056/NEJMoa2307291
16. Della Rocca DG, Marcon L, Magnocavallo M, Menè R, Pannone L, Mohanty S, Sousonis V, Sorgente A, Almorad A, Bisignani A, et al. Pulsed electric field, cryoballoon, and radiofrequency for paroxysmal atrial fibrillation ablation: a propensity score-matched comparison. *Europace*. 2023;26:euae016. doi: 10.1093/europace/euae016
17. Ruwald MH, Johannessen A, Hansen ML, Haugdal M, Worck R, Hansen J. Pulsed field ablation in real-world atrial fibrillation patients: clinical recurrence, operator learning curve and re-do procedural findings. *J Interv Card Electrophysiol*. 2023;66:1837–1848.
18. International Network of Agencies for Health Technology Assessment (INAHTA). http://www.inahta.org/HTA.
19. Cheng X, Hu Q, Gao L, Liu J, Qin S, Zhang D. Sex-related differences in catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *Europace*. 2019;21:1509–1518. doi: 10.1093/europace/euz179

20. Fay Lavallaz J, Badertscher P, Ghannam M, Oral H, Jongnarangsin K, Boveda S, Madeira M, Gupta D, Ding WY, Providencia R, et al. Severe Periprocedural complications after ablation for atrial fibrillation: an international collaborative individual patient data registry. *JACC Clin Electrophysiol*. 2024;10:1353–1364.
21. Patel D, Mohanty P, Di Biase L, Sanchez JE, Shaheen MH, Burkhardt JD, Bassouni M, Cummings J, Wang Y, Lewis WR, et al. Outcomes and complications of catheter ablation for atrial fibrillation in females. *Heart Rhythm*. 2010;7:167–172. doi: 10.1016/j.hrthm.2009.10.025
22. Santangeli P, di Biase L, Pelargonio G, Natale A. Outcome of invasive electrophysiological procedures and gender: are males and females the same? *J Cardiovasc Electrophysiol*. 2011;22:605–612. doi: 10.1111/j.1540-8167.2010.01920.x
23. Boltze J, Jensen GB. Underrepresentation of women in trials of atrial fibrillation ablations: fact or thinking? *J Am Heart Assoc*. 2025;14(2):e039614.
24. Tenner ZM, Cottone MC, Chavez MR. Harnessing the open access version of ChatGPT for enhanced clinical opinions. *PLOS Digit Health*. 2024;3:e0000355. doi: 10.1371/journal.pdig.0000355
25. Wong GR, Nalliah CJ, Lee G, Voskoboinik A, Chieng D, Prabhu S, Parameswaran R, Sugumar H, Al-Kaisey A, McLellan A, et al. Sex-related differences in atrial remodeling in patients with atrial fibrillation: relationship to ablation outcomes. *Circ Arrhythm Electrophysiol*. 2022;15:e009925. doi: 10.1161/CIRCEP.121.009925
26. Khaing E, Aroudaky A, Dircks D, Almerstani M, Alziadin N, Frankel S, Hollenberg B, Limsiri P, Schleifer W, Easley A, et al. Representation of women in atrial fibrillation ablation randomized controlled trials: systematic review. *J Am Heart Assoc*. 2025;14:e035181. doi: 10.1161/JAHA.124.035181
27. Takigawa M, Takahashi A, Kuwahara T, Okubo K, Takahashi Y, Watari Y, Nakashima E, Nakajima J, Yamao K, Takagi K, et al. Long-term outcome after catheter ablation of paroxysmal atrial fibrillation: impact of different atrial fibrillation foci. *Int J Cardiol*. 2017;227:407–412. doi: 10.1016/j.ijcard.2016.11.028
28. Yu HT, Yang PS, Kim TH, Uhm JS, Kim JY, Joung B, Lee MH, Pak HN. Poor rhythm outcome of catheter ablation for early-onset atrial fibrillation in women - mechanistic insight. *Circulation*. 2018;82:2259–2268. doi: 10.1253/circj.CJ-17-1358
29. Jalife J, Kaur K. Atrial remodeling, fibrosis, and atrial fibrillation. *Trends Cardiovasc Med*. 2015;25:475–484. doi: 10.1016/j.tcm.2014.12.015