Repeat procedures after pulsed field ablation for atrial fibrillation: MANIFEST-REDO study

Daniel Scherr (b) 1*, Mohit K. Turagam (b) 2, Philippe Maury (b) 3,4, Yuri Blaauw⁵, Pepijn van der Voort (b) 6, Petr Neuzil (b) 7, Tobias Reichlin (b) 8, Andreas Metzner (b) 9, Johan Vijgen (b) 10, Josef Kautzner (b) 11, Serge Boveda (b) 12, Ante Anic (b) 13, Jim Hansen (b) 14, Martin Manninger (b) 1, Philipp Sommer (b) 15, Frederic Anselme (b) 16, Stephan Willems (b) 17, Thomas Deneke (b) 18, Roland Tilz (b) 19,20, Daniel Steven (b) 22, Reza Wakili^{23,24}, Pierre Jais (c) 25, Moritoshi Funasako (c) 7,26, Thomas Arentz (c) 27, Anne Rollin³, Bart A. Mulder (c) 5, Alexandre Ouss (c) 6, Jan Petru³, Thomas Kueffer (c) 8, Marc D. Lemoine (c) 9, Pieter Koopman (c) 10, Petr Peichl (c) 11, Raquel Adelino (c) 12, Zrinka Jurisic (c) 13, Martin Ruwald (c) 14, Anna-Sophie Eberl (c) 1, Christian Sohns (c) 15, Arnaud Savoure 16, Karin Nentwich (c) 17, Melanie Gunawardene (c) 18, Christian-Hendrik Heeger (c) 19,20,21†, Arian Sultan (c) 22, Jan-Eric Bohnen 28, Jana Kupusovic (c) 23,24, Nicolas Derval (c) 25, Heiko Lehrmann (c) 27, Emmanuel Ekanem (c) 2, and Vivek Y. Reddy (c) 2,7, for the MANIFEST-PF Cooperative

¹Division of Cardiology, Department of Internal Medicine, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria; ²Icahn School of Medicine at Mount Sinai, New York, NY, USA; ³Department of Cardiology, University Hospital Rangueil, Toulouse, France; ⁴I2MC, INSERM UMR 1297, Toulouse, France; ⁵Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; ⁶Catharina Hospital, Eindhoven, The Netherlands; ⁷Cardiology Department, Na Homolce Hospital, Homolka Hospital, Prague, Czech Republic; ⁸Inselspital—Bern University Hospital, University of Bern, Bern, Switzerland; ⁹University Heart & Vascular Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; ¹⁰Department of Cardiology, Jessa Hospitals, Hasselt, Belgium; ¹¹IKEM-Institute for Clinical and Experimental Medicine, Prague, Czech Republic; ¹²Heart Rhythm Department, Clinique Pasteur, Toulouse, France; ¹³Department for Cardiovascular Diseases, University Hospital Center Split, Split, Croatia; ¹⁴Department of Cardiology, Herlev-Gentofte University Hospital, Hellerup, Denmark; ¹⁵Clinic for Electrophysiology, Herz- und Diabeteszentrum NRW, Ruhr-University Bochum, Bad Oeynhausen, Germany; ¹⁶Department of Cardiology, Rouen Hospital, Rouen, France; ¹⁷Heart Center Bad Neustadt, Rhoen-Clinic Campus Bad Neustadt, Bad Neustadt an der Saale, Germany; ¹⁸Asklepios Hospital St. Georg, Hamburg, Germany; ¹⁹German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Lübeck, Germany; ²⁰University Heart Center Lübeck, Department of Rhythmology, University Hospital Schleswig-Holstein, Germany; ²¹Department of Rhythmology, Cardiology and Intensive Care Medicine, Asklepios Klinik Altona, Hamburg, Germany; ²²Department for Electrophysiology, Heart Center University Hospital of Cologne, Cologne, Germany; ²³Department of Medicine and Cardiology, Goethe University, Frankfurt, Germany; ²⁴German Center for Cardiovascular Research DZHK, Partn

Received 29 December 2024; accepted after revision 10 January 2025; online publish-ahead-of-print 17 January 2025

Aims

Initial clinical studies of pulsed field ablation (PFA) to treat atrial fibrillation (AF) indicated a >90% durability rate of pulmonary vein isolation (PVI). However, these studies were largely conducted in single centres and involved a limited number of operators. We aimed to describe the electrophysiological findings and outcomes in patients undergoing repeat ablation after an initial PF ablation for AF.

Methods and results

In the MANIFEST-REDO study, we investigated patients who underwent repeat ablation due to clinical recurrence—AF or atrial tachycardia (AT)—following first-ever PVI with a pentaspline PFA catheter (Farawave, Boston Scientific Inc.). At 22 centres, 427 patients (age 64 ± 11 years; 37% female) were included. Of note, the recurrent arrhythmia leading to the repeat ablation was paroxysmal AF (51%), persistent AF (30%), or AT (19%). At the repeat procedure, the PV reconnection rates were 30% (left superior pulmonary vein), 28% (left inferior pulmonary vein), 33% (right superior pulmonary vein), and 32% (right inferior

^{*} Corresponding author. Tel: +43 316 385 12544; fax: +43 316 385 13733. E-mail address: daniel.scherr@medunigraz.at

[†] Present address. Department of Rhythmology, Cardiology and Intensive Care Medicine, Asklepios Klinik Altona, Hamburg, Germany.

[©] The Author(s) 2025. Published by Oxford University Press on behalf of the European Society of Cardiology.

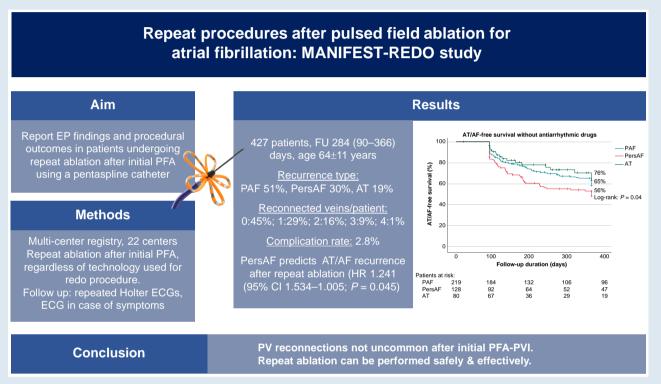
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

pulmonary vein). In 45% of patients, all PVs were durably isolated at the beginning of the repeat procedure, with the previous use of any imaging or mapping modality being univariately associated with durable PVI. After a post-redo follow-up period of 284 (90–366) days, the primary effectiveness endpoint (freedom from documented AF/AT lasting \geq 30 s after 3-month blanking without class I/III antiarrhythmic drugs or symptoms) was achieved in 65% of patients, with significant differences between groups (PAF 65% vs. PersAF 56% vs. AT 76%; P=0.04). Persistent AF as recurrent arrhythmia after the initial PFA ablation predicted AT/AF recurrence after repeat ablation [hazard ratio 1.241 (95% confidence interval 1.534–1.005); P=0.045]. The procedural complication rate was 2.8%

Conclusion

In repeat procedures for AF/AT performed after an index procedure with PFA for AF, PV reconnections are not uncommon. Repeat procedures can be performed safely and with an acceptable subsequent success rate.

Graphical Abstract



Keywords

Atrial fibrillation • Atrial tachycardia • Electroporation • Pulsed field ablation • Pulmonary vein isolation

What's new?

The present study MANIFEST-REDO is among the first to evaluate procedural findings and clinical outcome in patients undergoing repeat ablation after AF/AT recurrence after initial AF ablation with the pentaspline PFA catheter. It has several important findings:

- Lesion durability in repeat ablation patients after PFA is limited in a real-world setting and may contribute to AF/AT recurrence, with 45% of patients having durable PVI at the repeat procedure start, and the previous use of any imaging modality being associated with durable PVI in this cohort.
- Repeat ablations for AF/AT after an initial PFA ablation can be performed with acceptable safety and efficacy, with a 65% clinical success rate in the first year and a 2.8% procedural complication rate.
- Persistent AF as recurrent arrhythmia after the initial PFA ablation is a predictor of worse clinical outcome after a repeat ablation.

Introduction

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia worldwide, significantly contributing to morbidity, mortality, and rising healthcare costs. Catheter ablation has emerged as an important therapy for patients with symptomatic AF. Pulmonary vein isolation (PVI) serves as the procedural standard. However, the durability of PVI after the initial ablation procedure remains a key limitation, necessitating repeat procedures in a significant subset of patients due to AF recurrence. This limitation underscores the need for advancements in catheter design and ablation techniques, not only for PVI but also for targeting extra-PV substrates of AF. 1–3

Electroporation, also known as pulsed field ablation (PFA), is a new non-thermal ablation modality that employs high-voltage electrical pulses to selectively disrupt myocardial cell membranes.³ As opposed to thermal techniques, PFA minimizes the risk of collateral injury to

adjacent anatomical structures, such as the oesophagus or the phrenic nerve, while still achieving effective lesion formation.^{3–5} Recently, innovative catheter designs, such as the pentaspline catheter, a multielectrode catheter optimized for PFA, have demonstrated significant safety, efficiency, and efficacy in achieving PVI during AF ablation procedures.^{3–11}

The clinical utility of PFA has been demonstrated in multicentre studies. The MANIFEST-PF registry provides comprehensive data on the performance of PFA, highlighting its high procedural success rates and favourable safety profile. ^{12,13} Similarly, findings from the EU-PORIA registry emphasize the applicability of PFA in diverse patient populations, demonstrating its effectiveness in real-world settings. ¹⁴ Long-term studies have reinforced the durability of PFA-induced PVI, showing reduced AF recurrence rates over extended follow-up periods. Importantly, the capability to reapply PFA energy during repeat ablation procedures without compromising safety further underscores its versatility and clinical potential. ^{10,11} However, there is limited data on procedural findings and especially on outcomes in patients undergoing re-ablation for AF or atrial tachycardia (AT) recurrence after an initial PF ablation for AF. ^{15–20}

This multicentre study (MANIFEST-REDO) aims to evaluate the outcomes of catheter re-ablation in patients with AF/AT who previously underwent PF AF ablation using the pentaspline catheter. Specifically, procedural success, safety, and lesion durability findings during reablation, as well as factors contributing to AF/AT recurrence, are investigated.

Methods

Study design

MANIFEST-PF is an international, prospective, patient-level registry involving 24 European centres that initiated the post-approval clinical application of the pentaspline PFA catheter (Farawave, Boston Scientific Inc.) for AF ablation. 12,13,21,22 Patients (age ≥ 18 years) who underwent first-ever PFA for AF between October 2021 and January 2024 were included. Of note, most operators had no clinical experience with performing PFA prior to these patients, so the learning curve was incorporated into this registry. The *MANIFEST-PF* registry adhered to the principles of the Declaration of Helsinki, and the waiver of consent was approved by the Ethics Committee at Homolka Hospital.

Initial ablation procedure

The procedure methodology and post-procedural monitoring of patients included in the MANIFEST-PF registry have been detailed in previous publications. 12,13,21,22 In brief, the PFA procedure was conducted under deep sedation (without endotracheal intubation) or general anaesthesia with intubation. Procedures were typically performed with uninterrupted oral anticoagulation and systemic heparinization before transseptal puncture. Electroanatomic mapping and intracardiac echocardiography (ICE) imaging were used at operator discretion. Following transseptal puncture, the deflectable PFA sheath (Faradrive, Boston Scientific) was advanced into the left atrium (LA) using a 0.035 in super-stiff guidewire, and baseline electrical potentials were recorded from all pulmonary veins (PVs) using the pentaspline PFA catheter. Pulmonary vein isolation was performed with 2 applications per PV in both basket and flower configurations, and then the basket/ flower was rotated $\approx 36^{\circ}$ to change the spline orientation and another two applications were delivered (total of 8 per PV). Additional PFA applications were administered as deemed necessary by the operator. Confirmation of PVI typically relied on electrograms recorded from the pentaspline PFA catheter. Adjunctive ablation of the posterior wall, roof, mitral isthmus, cavo-tricuspid isthmus, and other sites was typically performed with PFA, though a commercially available radiofrequency (RF) ablation catheter may have been used per operator discretion. The use of post-procedure antiarrhythmic drugs (AADs) was at the discretion of the treating physician for a short duration, and oral anticoagulation was continued in accordance with AF guidelines.^{1,2}

Patients commonly attended follow-up visits at 3, 6, and 12 months post-procedure, during which evaluations were conducted to assess adverse events, AF-related symptoms, and recurrence of atrial arrhythmias with

either 12-lead electrocardiogram, 24-h Holter monitoring, or cardiac implantable electronic device interrogation, as determined by the physician's discretion

Repeat ablation procedures

If patients had a symptomatic AF/AT recurrence >3 months after the initial AF ablation procedure, they were deemed eligible for a repeat ablation procedure. With regard to sedation, anticoagulation, imaging, and mapping, repeat ablation procedures were performed under the same circumstances as the initial procedures.

For the repeat procedure, the ablation system was chosen at the operators' discretion. As for the ablation itself during the repeat procedure, the following energy forms were used in this study: RF ablation, cryoballoon ablation, PFA with the pentaspline catheter, focal PFA, and/or alcohol ablation of the vein of Marshall.

After transseptal puncture, confirmation of PVI typically relied on electrograms recorded from either the pentaspline PFA catheter or from a multipolar mapping catheter. If PVI or any lesion targeted during the initial procedure was incomplete, ablation of the PVs or the respective substrate was performed with the designated ablation system. Adjunctive ablations of the posterior wall, roof, mitral isthmus, cavo-tricuspid isthmus, and other LA sites were performed per operator discretion. The use of post-procedure AADs was at the discretion of the treating physician for a short duration and oral anticoagulation was continued in accordance with AF guidelines. 1,2 Patients' follow-up was conducted as described above. 12,13,21,22

Study endpoints

The primary effectiveness endpoint was freedom from documented AF/AT lasting ${\geq}30$ s (after 3-month blanking), without class I/III AADs or symptoms. The secondary effectiveness endpoint was freedom from AF/AT lasting ${\geq}30$ s (after 3-month blanking) with or without the necessity for class I/ III AADs.

The primary safety outcome encompassed a composite of acute events (occurring within 7 days post-procedure) and chronic major adverse events (occurring >7 days post-procedure). 12,13,21,22

Statistical analysis

Continuous variables were expressed as mean \pm SD or median (interquartile range) and compared nonparametric Kruskal–Wallis tests. All comparisons among groups were performed using the Student's t-test if the data were normally distributed or the Wilcoxon rank-sum test if the data were not normally distributed. Categorical variables were presented as counts/percentages and compared using χ^2 test or Fisher's exact test (expected cell count <5).

Kaplan-Meier survival curves were utilized for primary and secondary effectiveness outcomes, with treatment groups compared using the log-rank test. Cox proportional hazards modelling was conducted to generate hazard ratios (HRs) and corresponding 95% confidence intervals (Cls) for time-to-event analyses. Covariates included in the adjusted model were selected based on a clinically plausible association with AT/AF recurrence and PVI durability, and if a univariate association of P < 0.1 was present. Tested variables were time to repeat ablation, PVI durability, gender, body mass index (BMI) > 35, posterior wall isolation durability, persistent AF as initial arrhythmia, coronary artery disease, diabetes mellitus, hypertension, heart failure, LA diameter, left ventricular ejection fraction (LVEF), CHA₂DS₂-VASc score, size of pentaspline catheter, persistent AF as arrhythmia at repeat ablation, use of any imaging, or electroanatomic mapping modality used at initial procedure. All tests were two tailed, with P < 0.05considered statistically significant. SPSS software (version 29.0, IBM Corp.) was employed for all analyses.

Results

Patient characteristics

At 22 centres, 427 patients (age 64 ± 11 years; 37% female) who were scheduled for repeat ablation because of AF/AT recurrence after a previous PF ablation for AF with the pentaspline catheter were included. Table 1 shows the baseline characteristics of the patients grouped by

 Table 1
 Baseline characteristics of repeat ablation patients grouped by atrial tachyarrhythmia leading to the repeat ablation

	Paroxysmal AF (n = 219)	Persistent AF (n = 128)	Atrial tachycardia (n = 80)	P value
Age (years)	63 ± 11	63 ± 12	66 ± 11	0.080
Female gender [n (%)]	79 (36)	47 (37)	30 (38)	0.663
BMI (kg/m ²)	28 ± 5	28 ± 5	28 ± 5	0.524
CHA ₂ DS ₂ -VASc score	2.0 ± 1.4	2.2 ± 1.5	2.6 ± 1.5	0.014
CHF [n (%)]	17 (8)	19 (15)	18 (23)	0.002
Hypertension [n (%)]	109 (50)	73 (57)	52 (65)	0.051
Diabetes mellitus [n (%)]	32 (15)	18 (14)	17 (21)	0.320
Prior stroke/TIA [n (%)]	24 (11)	9 (7)	2 (3)	0.041
Sleep apnoea [n (%)]	14 (6)	11 (9)	7 (9)	0.674
Chronic obstructive pulmonary disease [n (%)]	11 (5)	6 (5)	6 (8)	0.644
CAD [n (%)]	26 (12)	21 (16)	16 (20)	0.170
LVEF (%)	58 ± 8	55 ± 11	57 ± 9	0.037
LA diameter (mm)	43 ± 7	46 ± 7	46 ± 7	0.009
Previous history of CTI-dependent flutter [n (%)]	24 (11)	26 (20)	20 (25)	0.005
Left common PV ostium [n (%)]	24 (11)	14 (11)	7 (9)	0.839
Paroxysmal AF at initial procedure [n (%)]	119 (54)	46 (36)	36 (45)	< 0.001
Class I/III AAD [n (%)]	76 (35)	34 (27)	38 (48)	0.023
Oral anticoagulation [n (%)]	212 (97)	122 (95)	77 (96)	0.451
Pentaspline catheter size at first procedure:				0.285
31 mm [n (%)]	161 (74)	101 (79)	56 (70)	
35 mm [n (%)]	58 (26)	27 (21)	24 (30)	
PVI at first procedure [n (%)]	219 (100)	128 (100)	80 (100)	1.00
Posterior wall ablation at first procedure [n (%)]	54 (25)	52 (41)	34 (43)	< 0.001
Other ablation at first procedure [n (%)]	28 (13)	22 (17)	26 (33)	<0.001

AAD, antiarrhythmic drug; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CTI, cavo-tricuspid isthmus; LA, left atrium; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; TIA, transient ischaemic attack.

their recurrent arrhythmia after their initial ablation that led to the repeat ablation. Of note, the recurrent arrhythmia was paroxysmal AF (PAF; 219 patients, 51%), persistent AF (PersAF; 128 patients, 30%), or AT (80 patients; 19%).

There was a difference between groups with regard to the CHA₂DS₂-VASc score (PAF 2.0 ± 1.4 vs. PersAF 2.2 ± 1.5 vs. AT 2.6 ± 1.5 ; P=0.014) and LA diameter (PAF 43 ± 7 mm vs. PersAF 46 ± 7 mm vs. AT 46 ± 7 mm; P=0.009). The proportion of patients who had undergone the initial ablation with the 35 mm pentaspline catheter was not different between groups. However, there was a significant difference in patients who had undergone posterior wall isolation and/or additional LA substrate ablation during the first procedure, with the proportion of patients being the highest in the AT group (Table 1). Furthermore, there was a difference in class I/III AAD use at the time of repeat ablation (PAF 35% vs. PersAF 27% vs. AT 48%; P=0.023).

Procedural characteristics and safety outcomes of repeat ablation

Patients underwent repeat ablation 279 ± 171 days after the initial PFA procedure. The procedural characteristics for the repeat ablation based on the recurrent arrhythmia after the initial procedure are shown in *Table 2*. Of note, in patients with AT, ICE imaging and electroanatomic mapping wer used in a higher proportion of patients than in patients presenting with PAF or PersAF. Furthermore, extra-PV targets were

ablated in a higher proportion of AT patients, leading to longer procedure and fluoroscopy duration. However, there was no difference between groups with regard to the energy form used (*Table 2*). The procedural complication rate was 2.8%: vascular complications (n = 5), pericardial effusion (n = 4), atrio-ventricular block (n = 1), stroke (n = 1), and LAA isolation (n = 1).

Pulmonary vein isolation and posterior wall isolation durability

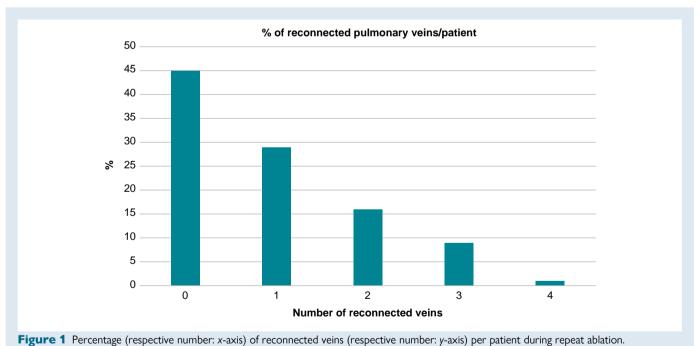
At the repeat procedure, the PV reconnection rates were 29% (left superior pulmonary vein, LSPV), 27% (left inferior pulmonary vein, LIPV), 32% (right superior pulmonary vein, RSPV), and 31% (right inferior pulmonary vein, RIPV). In 45% of patients, all PVs were durably isolated at the beginning of the repeat procedure (PAF 42%, PersAF 44%, AT 55%; P= ns). Patients had 0 (45%), 1 (29%), 2 (16%), 3 (9%), or 4 (1%) reconnected veins (*Figure 1*). Notably, of all univariate associations tested, there was no association between time from initial to repeat ablation and the freedom from PV reconnection (time from initial to repeat ablation and durable PVI rates: <90 days: 35%; 90 days to 6 months: 49%; 6–12 months: 39%; >12 months: 39%; P=0.454). However, the use of any form of (pre)procedural imaging (ICE, CT, electroanatomic mapping, rotational angiography) to guide the initial ablation was associated with a higher PVI durability rate (47% vs. 37%; P=0.036).

Of the 140 patients who underwent posterior wall ablation during the initial ablation procedure and underwent repeat procedure, 64 (46%)

Table 2 Procedural characteristics of repeat ablation patients

	Paroxysmal AF $(n = 219)$	Persistent AF (n = 128)	Atrial tachycardia/flutter (n = 80)	P value
General anaesthesia [n (%)]	25 (11)	28 (22)	20 (25)	0.003
ICE Imaging [n (%)]	78 (36)	26 (20)	36 (45)	< 0.001
Electroanatomic mapping [n (%)]	169 (77)	101 (79)	73 (90)	< 0.001
Energy form [n (%)]				0.714
Pentaspline PFA	72 (33)	40 (31)	27 (34)	
RF	122 (56)	71 (55)	45 (56)	
Cryo	4 (2)	0 (0)	0 (0)	
Focal PFA	16 (7)	10 (8)	5 (6)	
Vein of Marshall	5 (2)	7 (5)	3 (4)	
Durable PVI at procedure start [n (%)]	91 (42)	56 (44)	44 (55)	0.385
Ablation targets [n (%)]				
PVI	142 (65)	75 (59)	47 (59)	0.118
Posterior wall	65 (30)	66 (52)	32 (40)	< 0.001
Other LA substrate	114 (52)	69 (54)	63 (79)	0.012
Fluoroscopy time (min)	12 ± 9	15 ± 7	20 ± 12	< 0.001
Procedure time (min)	91 ± 27	103 ± 37	107 ± 40	< 0.001
Procedural complications [n (%)]	6 (3)	2 (2)	4 (5)	0.11

ICE, intracardiac echocardiography; LA, left atrium; PFA, pulsed field ablation; PVI, pulmonary vein isolation; RF, radiofrequency.



Telectriage (respective name) or reconnected term (respective name) per parent and green and gre

presented with complete posterior wall isolation, with a higher persistent isolation rate in patients who had undergone any form of (pre)procedural imaging to guide the initial ablation (50% vs. 42; P = 0.05).

Effectiveness outcome

After a follow-up period of 284 (90–366) days, the primary effectiveness endpoint (freedom from documented AF/AT lasting \geq 30 s after

3-month blanking without class I/III AADs or symptoms) was achieved in 65% of patients, with significant differences between groups (PAF 65% vs. PersAF 56% vs. AT 76%; P=0.04) (Figure 2). There was no association between time from initial to repeat ablation and the primary effectiveness endpoint (time from initial to repeat ablation and success rates: <90 days: 65%; 90 days to 6 months: 61%; 6–12 months: 61%; >12 months: 70%; P= ns). The secondary effectiveness endpoint (freedom from documented AF/AT lasting \geq 30 s after 3-month blanking

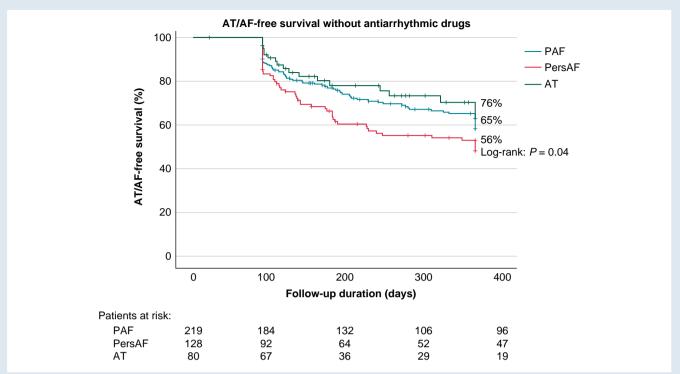


Figure 2 Kaplan–Meier estimate of primary effectiveness endpoint of freedom from documented AF/AT lasting ≥30 s (after 3-month blanking), without class I/III antiarrhythmic drugs or symptoms. AT, atrial tachycardia; PAF, paroxysmal AF; PersAF, persistent AF.

with or without class I/III AADs or symptoms) was achieved in 71% (PAF 74% vs. PersAF 61% vs. AT 80%; P = 0.007) (Figure 3).

In the subgroup of patients with persistent AF, there was borderline significance in secondary effectiveness with the use of posterior wall ablation (68% vs. 51%, P=0.07). In multivariate analysis [including the univariately associated diabetes mellitus (P=0.039), persistent AF as initial arrhythmia (P=0.04), and persistent AF as recurrent arrhythmia (P=0.067)], persistent AF as recurrent arrhythmia after the initial PFA ablation predicted AT/AF recurrence after repeat ablation [HR 1.241 (95% CI 1.534–1.005; P=0.045)] (*Table 3*).

Discussion

The present study MANIFEST-REDO is among the first to evaluate procedural findings and clinical outcome in patients undergoing repeat ablation after AF/AT recurrence after an initial PFA AF ablation with the pentaspline catheter. It has several important findings: (i) lesion durability in patients undergoing repeat ablation after initial PFA procedure is limited in a real-world setting and may contribute to AF/AT recurrence; (ii) repeat ablations for AF/AT after an initial PFA ablation can be performed with acceptable safety and efficacy; and (iii) persistent AF as recurrent arrhythmia is a predictor of worse clinical outcome after a repeat ablation.

Lesion durability and pulmonary vein reconnection rates

The durability of PVI is a critical determinant of successful AF ablation. Various studies have investigated PVI durability after PFA ablation with the pentaspline catheter and showed excellent results. ^{23,24} However, there is limited data on PVI durability in repeat ablation patients, bearing in mind that most studies, including ours, present PVI and posterior wall

isolation durability data only in patients with AF/AT recurrences, therefore underestimating the true durability rates. The early experience from Tohoku et al. 16 pointed to a PV reconnection rate of 9% in a limited patient cohort. On a per patient basis, persistent durable isolation of all four PVs was recorded in 19 (76%) patients. These single-centre findings, which in terms of PVI durability differ to the findings in our study as well as to the findings by Lemoine et al., 19 may be due to the limited patient number and the concentration in operator expertise possible in single-centre studies, as reported by Tohoku et al. In contrast, Lemoine et al. reported that of 82 initially isolated PVs after PFA-PVI, 31 (38%) were reconducting during repeat ablation and 73% of investigated patients showed at least one reconnected PV.¹⁹ Similarly, Maurhofer et al.²⁰ found that in patients undergoing repeat ablation with PFA, 60% of patients had at least one reconnected PV and Kueffer et al. 15 reported 62% in a sub-analysis of the EU-PORIA registry. Prior operator experience with cryoballoon ablation was associated with a higher PVI durability compared to operators with only point-by-point RF experience (76% vs. 60%; P < 0.001). Neither the operators' cumulative experience in AF ablation nor the size of the PFA device used (31 mm vs. 35 mm) had an impact on subsequent lesion durability. While the PVI durability rate in PF ablation has been reported to be excellent, especially with the pentaspline catheter, and even in repeat ablation patients higher in post PFA patients than in postcryoablation patients or post RF patients, 9 future developments in PFA technology should focus on improving PVI durability. Our limited data showed that in patients undergoing repeat ablation, the use of any form of imaging or mapping was associated with an increased PVI durability rate. As previously suggested, the use of ICE may be helpful for PVI, but the absence of randomization is an important confounder that limits confidence in this observation.²⁵ However, our study only investigated patients with clinical recurrence. Whether full integration of PFA technologies in 3D electroanatomic mapping systems or use of ICE will really improve PVI durability and therefore potentially clinical

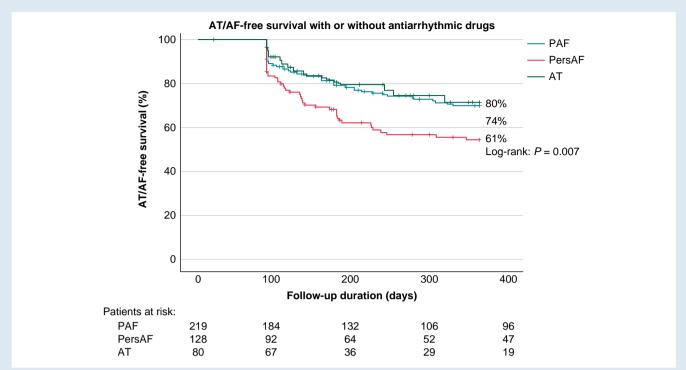


Figure 3 Kaplan–Meier estimate of secondary effectiveness endpoint of freedom from documented AF/AT lasting ≥30 s (after 3-month blanking), with or without class I/III antiarrhythmic drugs or symptoms. AT, atrial tachycardia; PAF, paroxysmal AF; PersAF, persistent AF.

Table 3 Multivariate predictors of AF/AT recurrence after repeat ablation

	HR	95% CI	P value
Persistent AF as recurrent arrhythmia	1.241	1.534–1.005	0.045
,	1.000	1.004–0.996	0.863
initial PFA ablation Absence of diabetes mellitus	0.745	1.106-0.502	0.144

AF, atrial fibrillation; AT, atrial tachycardia; CI, confidence interval; HR, hazard ratio.

outcomes remains to be investigated. Badertscher et al.²⁶ published their early experience on the impact of non-fully 3D integrated PF ablation and found that the use of a pentaspline PFA system with no mapping was associated with a significant decrease in procedural characteristics, while AF recurrence was not significantly different even if mapping was used. The routine use of mapping for PFA–PVI may be helpful. However, this needs to be investigated with fully integrated PF catheter systems that allow for contact assessment and lesion tracking.

Procedural efficacy and safety

The MANIFEST-PF registry provides robust evidence on procedural outcomes for PFA, including data on repeat ablations. ^{12,13,21,22} This registry underscored the consistent safety profile of the pentaspline catheter, reporting a complication rate of <3% even in patients undergoing re-ablation. The electroporation mechanism of PFA, which induces disruption of cardiomyocytes without thermal injury, emerges

as a key factor in minimizing risks such as oesophageal or phrenic nerve damage.²⁷ Several trials have validated the clinical efficacy of PFA ablation, which was shown to be at least equivalent to other energy modalities.²⁷

Furthermore, our study highlights that repeat ablation for AF/AT after an initial PF ablation leads to acceptable success rates, especially in patients with PAF or AT as a recurrent arrhythmia.

Despite promising results, several challenges persist in the context of repeat ablations following PFA. Variability in lesion durability remains a concern, influenced by patient-specific factors such as anatomical variability and comorbid conditions. While our study showed a near-significant effectiveness of posterior wall ablation in PersAF patients, this finding is at best hypothesis generating: this near-significant finding was achieved in patients undergoing repeat (not initial) ablation, with difference in subgroups in terms of baseline characteristics, lesion set during initial ablation, and ablation energy used during repeat ablation.

Limitations

This multicentre cohort study, involving 427 patients undergoing redo ablation of AF following a prior PFA ablation, has several limitations. Firstly, the absence of a control group restricts the ability to draw comparisons with other ablation techniques. The true PVI durability rate in the overall cohort of patients undergoing PFA cannot be concluded. Furthermore, the study does not provide direct evidence regarding the relative efficacy or safety of PFA in the redo ablation setting.

Secondly, the non-continuous nature of the follow-up could lead to an underestimation of arrhythmia recurrence, particularly in asymptomatic patients or those experiencing late PV reconnections. Continuous monitoring would provide a more accurate depiction of long-term outcomes.

Additionally, the multicentre design introduces heterogeneity in procedural techniques and operator experience across participating centres. This variability could influence the study results and limit their reproducibility. Future research with standardized protocols and continuous follow-up is essential to address all these limitations.

Conclusions

In repeat procedures for AF/AT performed after an index procedure with PFA for AF, PV reconnections are not uncommon. Repeat procedures can be performed safely and with an acceptable subsequent success rate. Persistent AF as the recurrent arrhythmia is a predictor of a lower success rate during follow-up.

Funding

Boston Scientific Corporation provided a grant to help fund data collection but was not otherwise involved with study design or analysis or had access to this manuscript prior to submission.

Conflict of interest: D.S. reports receiving consulting fees and speaker honoraria from Abbott. Biosense Webster. Biotronik, and Boston Scientific. M.K.T. reports receiving consulting fees from Biosense Webster, Boston Scientific, and AltaThera, and received speaker honoraria from Sanofi and Medtronic, Y.B. reports receiving research grant from Medtronic and AtriCure and consulting fees from Abbott, Biosense Webster, Boston Scientific, and member of the advisory board for Abbott, Biosense Webster, Boston Scientific, and Medtronic. P.N. reports receiving grant from the Ministry of Health, Czech Republic, DRO (NHH, 00023884). T.R. reports research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, and the sitem-insel support fund; speaker/consulting honoraria or travel support from Abbott/SJM, Bayer, Biosense Webster, Biotronik, Boston Scientific, Daiichi Sankyo, Medtronic, and Pfizer-BMS; and support for his institution's fellowship programme from Abbott/SJM, Biosense Webster, Biotronik, Boston Journal Pre-proof 21 Scientific, and Medtronic. A.M. reports research grant and fees from Farapulse. S.B. reports receiving consulting fees from Medtronic, Boston Scientific, Microport, Zoll, and BMS. A.A. reports receiving consultant fees from Farapulse Inc., Boston Scientific Inc., Galaxy Medical Inc., and Biosense Webster, and performs contracted research for Farapulse Inc., Boston Scientific Inc., Galaxy Medical Inc., and Biosense Webster. J.H. reports receiving speaker fees and grant support from Biosense Webster and Medtronic. M.M. reports receiving speaker fees from Bayer, Biosense Webster, Biotronik, Amomed, AOP Orphan, Boston Scientific, Daiichi Sankyo, and BMS/Pfizer and research grants from Biosense Webster and Abbott. P.S. is an advisory board member of Abbott, Boston Scientific, J&J MedTec, and Medtronic. F.A. reports receiving consulting fees from Boston Scientific, Medtronic, and Microport CRM. S.W. reports receiving grants and personal fees from Abbott, Boston Scientific, and Medtronic, and personal fees from Boehringer Ingelheim, Bristol Myers Squibb, Bayer Vital, Accutus, Daiichi, and Farapulse Inc. T.D. reports receiving speaker honoraria from Galaxy Medical, Abbott, and Biotronik, being a consultant to Farapulse, and serving on a Clinical Events Committee for Boston Scientific. R.T. reports receiving consulting fees from Boston Scientific, Abbott Medical, Biotronik, and Biosense Webster and speaker honorarium from Boston Scientific, Abbott Medical, Biotronik, and Biosense Webster. D.S. reports receiving speaking fees from Pfizer, Bayer, Abbott, Johnson & Johnson, and Medtronic; grant from Abbott, Johnson & Johnson, and Boston Scientific; and consulting fees from Boston Scientific and Johnson & Johnson. R.W. reports receiving honoraria for advisory board activities from Bayer, Boehringer Ingelheim, BMS, Pfizer, Daiichi Sankyo, Boston Scientific, and AtriCure; investigatorinitiated funding for research projects (initiated by him) from Abbott, Abiomed, Bristol Myers Squibb, Pfizer, and Boston Scientific; and speaking honoraria from Boston Scientific, Biotronik, Medtronic, Boehringer Ingelheim, Daiichi Sankyo, BMS, Pfizer, Abiomed, Zoll, and Novartis. P.J. reports receiving partial funding from IHU LIRYC ANR-10-IAHU-04 and receiving equity from Farapulse and consulting fees and grant from Boston Scientific. A.R. reports receiving research grant from Farapulse. M.D.L. reports receiving research grant from Farapulse. C.S. reports receiving modest honoraria from Medtronic. K.N. reports speaker's fees from Farapulse, Inc. M.G. reports grant from Farapulse Inc. and Abbott. A.S. reports receiving lecture and consulting honoraria from Medtronic, Abbott, and Bayer. J.K. reports personal fees from Bayer, Biosense Webster, Boehringer Ingelheim, Medtronic, and Abbott for participation in scientific advisory boards and has received speaker honoraria from Bayer, Biosense Webster, Biotronik, Boehringer Ingelheim, CathVision, Medtronic, Mylan, Pfizer, ProMed, and Abbott. C.-H.H. received travel grants and research grants by Boston Scientific, Lifetech, Biosense Webster, and CardioFocus and speaker's honoraria from Boston Scientific, Lifetech, Biosense Webster, Bayer, and CardioFocus. He is a consultant of Medtronic, Journal Pre-proof 22 Lifetech, Boston Scientific, Biosense Webster, and CardioFocus. N.D. reports receiving consulting fees from Boston Scientific. V.Y.R. reports receiving consulting fees (and equity—now divested) from Farapulse Inc. and is a consultant for Boston Scientific Inc.; unrelated to this manuscript, he also serves as a consultant for and has equity in Ablacon-Cortex, Acutus Medical, Affera-Medtronic, Anumana, Apama Medical-Boston Scientific, APN Health, Append Medical, Aquaheart, Atacor, Autonomix, Axon Therapies, Backbeat, BioSig, CardiaCare, CardioFocus, CardioNXT/AFTx, Circa Scientific, CoRISMA, Corvia Medical, Dinova-Hangzhou DiNovA EP Technology, East End Medical, EPD-Philips, EP Frontiers, Epix Therapeutics-Medtronic, Field Medical, Focused Therapeutics, Heartbeam, HRT, Intershunt, Javelin, Kardium, Laminar Medical, LuxMed, Medlumics, Nuvera-Biosense Webster, Oracle Health, Pulse Biosciences, Restore Medical, Sirona Medical, SoundCath, Volta Medical; unrelated to this work, V.Y.R. has served as a consultant for Abbott, Adagio Medical, AtriAN, Biosense Webster, BioTel Heart, Biotronik, Cairdac, Cardionomic, CoreMap, Fire1, Gore & Associates, Impulse Dynamics, Medtronic, Novartis, Novo Nordisk, Philips; and unrelated to this work, V.Y.R. has equity in Atraverse, DRS Vascular, Manual Surgical Sciences, Newpace, Nyra Medical, Soundcath, Surecor, and Vizaramed. All remaining authors declared no conflict of interest.

References

- Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns HJGM et al. 2024 ESC guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2024; 45:3314–414.
- Tzeis S, Gerstenfeld EP, Kalman J, Saad EB, Sepehri Shamloo A, Andrade JG 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.
- Chun KRJ, Miklavčič D, Vlachos K, Bordignon S, Scherr D, Jais P et al. State-of-the-art pulsed field ablation for cardiac arrhythmias: ongoing evolution and future perspective. Europace 2024;26:euae134.
- Koruth JS, Kuroki K, Iwasawa J, Enomoto J, Viswanathan R, Brose R et al. Preclinical evaluation of pulsed field ablation: electrophysiological and histological assessment of thoracic vein isolation. Circ Arrhythm Electrophysiol 2019;12:e007781.
- Vetta G, Della Rocca DG, Parlavecchio A, Magnocavallo M, Sorgente A, Pannone L et al. Multielectrode catheter-based pulsed electric field vs. cryoballoon for atrial fibrillation ablation: a systematic review and meta-analysis. Europace 2024;26:euae293.
- Reddy VY, Gerstenfeld EP, Natale A, Whang W, Cuoco FA, Patel C et al. Pulsed field or conventional thermal ablation for paroxysmal atrial fibrillation. N Engl J Med 2023;389: 1660–71.
- Erhard N, Frison E, Asselineau J, Aouar B, Boveda S, Cochet H et al. Comparing pulsed field electroporation and radiofrequency ablation for the treatment of paroxysmal atrial fibrillation: design and rationale of the BEAT PAROX-AF randomized clinical trial. Europace 2024;26:euae103.
- Urbanek L, Bordignon S, Schaack D, Chen S, Tohoku S, Efe TH et al. Pulsed field versus cryoballoon pulmonary vein isolation for atrial fibrillation: efficacy, safety, and long-term follow-up in a 400-patient cohort. Circ Arrhythm Electrophysiol 2023;16:389–98.
- Della Rocca DG, Marcon L, Magnocavallo M, Menè R, Pannone L, Mohanty S et al. Pulsed electric field, cryoballoon, and radiofrequency for paroxysmal atrial fibrillation ablation: a propensity score-matched comparison. Europace 2023;26:euae016.
- Metzner A, Fiala M, Vijgen J, Ouss A, Gunawardene M, Hansen J et al. Long-term outcomes of the pentaspline pulsed-field ablation catheter for the treatment of paroxysmal atrial fibrillation: results of the prospective, multicentre FARA-Freedom Study. Europace 2024;26:euae053.
- Schmidt B, Bordignon S, Tohoku S, Chen S, Bologna F, Urbanek L. 5S study: safe and simple single shot pulmonary vein isolation with pulsed field ablation using sedation. Circ Arrhythm Electrophysiol 2022;15:e010817.
- Ekanem E, Reddy VY, Schmidt B, Reichlin T, Neven K, Metzner A et al. Multi-national survey on the methods, efficacy, and safety on the post-approval clinical use of pulsed field ablation (MANIFEST-PF). Europace 2022;24:1256–66.
- Turagam MK, Neuzil P, Schmidt B, Reichlin T, Neven K, Metzner A 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.
- Schmidt B, Bordignon S, Neven K, Reichlin T, Blaauw Y, Hansen J et al. EUropean real-world outcomes with Pulsed field ablatiOn in patients with symptomatic atRIAI fibrillation: lessons from the multi-centre EU-PORIA registry. Europace 2023;25: euad185.

 Kueffer T, Bordignon S, Neven K, Blaauw Y, Hansen J, Adelino R et al. Durability of pulmonary vein isolation using pulsed-field ablation: results from the multicenter EU-PORIA registry. JACC Clin Electrophysiol 2024;10:698–708.

- Tohoku S, Chun KRJ, Bordignon S, Chen S, Schaack D, Urbanek L et al. Findings from repeat ablation using high-density mapping after pulmonary vein isolation with pulsed field ablation. Europace 2023;25:433–40.
- Magni FT, Scherr D, Manninger M, Sohns C, Sommer P, Hovakimyan T et al. Electrophysiological findings during re-do procedures after single-shot pulmonary vein isolation for atrial fibrillation with pulsed field ablation. J Interv Card Electrophysiol 2023;66:1729–37.
- Ruwald MH, Haugdal M, Worck R, Johannessen A, Hansen ML, Sørensen SK et al. Characterization of durability and reconnection patterns at time of repeat ablation after single-shot pulsed field pulmonary vein isolation. J Interv Card Electrophysiol 2024;67: 379–87.
- Lemoine MD, Obergassel J, Jaeckle S, Nies M, Taraba S, Mencke C et al. Pulsed-field-vs. cryoballoon-based pulmonary vein isolation: lessons from repeat procedures. Europace 2024:26:euae221.
- Maurhofer J, Tanner H, Kueffer T, Madaffari A, Thalmann G, Kozhuharov N et al. Pulsed-field ablation for repeat procedures after failed prior thermal ablation for atrial fibrillation. Heart Rhythm O2 2024;5:257–65.

Turagam MK, Neuzil P, Schmidt B, Reichlin T, Neven K, Metzner A, et al. Safety and
effectiveness of pulsed field ablation for atrial fibrillation in patients with heart failure:
a MANIFEST-PF sub-analysis. JACC Clin Electrophysiol 2024;24:S2405–500X.

- Ekanem E, Neuzil P, Reichlin T, Kautzner J, van der Voort P, Jais P et al. Safety of pulsed field ablation in more than 17,000 patients with atrial fibrillation in the MANIFEST-17K study. Nat Med 2024;30:2020–9.
- Reddy VY, Dukkipati SR, Neuzil P, Anic A, Petru J, Funasako M et al. Pulsed field ablation of paroxysmal atrial fibrillation: 1-year outcomes of IMPULSE, PEFCAT, and PEFCAT II. JACC Clin Electrophysiol 2021;7:614–27.
- 24. Kawamura I, Neuzil P, Shivamurthy P, Petru J, Funasako M, Minami K et al. Does pulsed field ablation regress over time? A quantitative temporal analysis of pulmonary vein isolation. Heart Rhythm 2021;**18**:878–84.
- Rauber M, Manninger M, Eberl AS, Scherr D. Zero-fluoroscopy ablation with multielectrode pulse field ablation system: case series. Pacing Clin Electrophysiol 2024;47:117–20.
- Badertscher P, Serban T, Isenegger C, Krisai P, Voellmin G, Osswald S et al. Role of 3D electro-anatomical mapping on procedural characteristics and outcomes in pulsed-field ablation for atrial fibrillation. Europace 2024;26:euae075.
- Boersma L, Andrade JG, Betts T, Duytschaever M, Pürerfellner H, Santoro F et al. Progress in atrial fibrillation ablation during 25 years of Europace journal. Europace 2023;25:euad244.