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Safety and Effectiveness of Pulsed Field Ablation to Treat Atrial Fibrillation: One-Year Outcomes From the MANIFEST-PF Registry

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BACKGROUND: Pulsed field ablation is a novel nonthermal cardiac ablation modality using ultra-rapid electrical pulses to cause cell death by a mechanism of irreversible electroporation. Unlike the traditional ablation energy sources, pulsed field ablation has demonstrated significant preferentiality to myocardial tissue ablation, and thus avoids certain thermally mediated complications. However, its safety and effectiveness remain unknown in usual clinical care.

METHODS: MANIFEST-PF (Multi-National Survey on the Methods, Efficacy, and Safety on the Post-Approval Clinical Use of Pulsed Field Ablation) is a retrospective, multinational, patient-level registry wherein patients at each center were prospectively included in their respective center registries. The registry included all patients undergoing postapproval treatment with a multielectrode 5-spline pulsed field ablation catheter to treat atrial fibrillation (AF) between March 1, 2021, and May 30, 2022. The primary effectiveness outcome was freedom from clinical documented atrial arrhythmia (AF/atrial flutter/atrial tachycardia) of ≥30 seconds on the basis of electrocardiographic data after a 3-month blanking period (on or off antiarrhythmic drugs). Safety outcomes included the composite of acute (<7 days postprocedure) and latent (>7 days) major adverse events.

RESULTS: At 24 European centers (77 operators) pulsed field ablation was performed in 1568 patients with AF: age 64.5±11.5 years, female 35%, paroxysmal/persistent AF 65%/32%, CHA_2DS_2-VASc 2.2±1.6, median left ventricular ejection fraction 60%, and left atrial diameter 42 mm. Pulmonary vein isolation was achieved in 99.2% of patients. After a median (interquartile range) follow-up of 367 (289–421) days, the 1-year Kaplan-Meier estimate for freedom from atrial arrhythmia was 78.1% (95% CI, 76.0%–80.0%); clinical effectiveness was more common in patients with paroxysmal AF versus persistent AF (81.6% versus 71.5%; *P*=0.001). Acute major adverse events occurred in 1.9% of patients.

CONCLUSIONS: In this large observational registry of the postapproval clinical use of pulsed field technology to treat AF, catheter ablation using pulsed field energy was clinically effective in 78% of patients with AF.

Key Words: atrial fibrillation ■ catheter ablation ■ irreversible electroporation therapy ■ treatment outcome

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Clinical Perspective

What Is New?

- Pulsed field ablation using irreversible electroporation is a novel method of cardiac ablation for atrial fibrillation that has revealed promising safety and effectiveness in first-in-human clinical trials.
- In this multinational registry of the postapproval clinical use of pulsed field ablation to treat atrial fibrillation, freedom from clinically documented recurrent arrhythmia was 78.1%.
- The registry also demonstrated a low rate of major complications at 1.9% with no instances of esophageal injury or pulmonary vein stenosis.

What Are the Clinical Implications?

- MANIFEST-PF demonstrated that catheter ablation of atrial fibrillation using pulsed field ablation appears to be safe and effective in routine clinical practice.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AF/AFL/AT	atrial fibrillation/atrial flutter/atrial tachycardia
LA	left atrium
PFA	pulsed field ablation
PV	pulmonary vein
PVI	pulmonary vein isolation

Pulsed field ablation (PFA) is a novel, nonthermal method of cardiac ablation that rapidly delivers lesions through a mechanism of irreversible electroporation. During PFA, ultra-rapid electrical pulses are applied to cause dielectric breakdown of the cardiac cell membranes, culminating in tissue necrosis and cell death.[1,2] The propensity of cell membrane breakdown varies between tissues (eg, esophagus, nerves, blood vessels), and the electric waveforms can be optimized to provide an important degree of preferentiality to myocardial tissue ablation.[1–11] Preclinical studies have demonstrated that PFA is not associated with any pulmonary vein (PV) stenosis, or even PV narrowing, that there is minimal to no phrenic nerve injury, and, most importantly, there is no esophageal injury.

In the first-in-human trials of the first clinical PFA system, a multielectrode catheter, the safety of these potential energy-specific complications was indeed borne out: there was no PV stenosis, phrenic nerve palsy, or evidence of esophageal injury.[12–15] The latter was further corroborated by direct MRI of the esophagus post-PFA, as opposed to post–thermal ablation.[16] And most recently, after the initial postapproval introduction of the PFA catheter into European clinical practice, the safety of the system was again corroborated in the center-level MANIFEST-PF survey (Multi-National Survey on the Methods, Efficacy, and Safety on the Post-Approval Clinical Use of Pulsed Field Ablation) of all PFA cases evaluated at the 24 centers that commenced use of this technology. This 1758-patient analysis identified no energy-specific complications, such as esophageal damage, PV stenosis, or phrenic nerve palsy, although there was a 0.46% rate of transient phrenic nerve paresis.[17]

Beyond the favorable safety profile, the first-in-human PFA trials demonstrated good effectiveness: the 1-year freedom from recurrent atrial arrhythmias was 84.5% in the 121-patient IMPULSE (A Safety and Feasibility Study of the IOWA Approach Endocardial Ablation System to Treat Atrial Fibrillation)/PEFCAT (A Safety and Feasibility Study of the FARAPULSE Endocardial Ablation System to Treat Paroxysmal Atrial Fibrillation)/PEFCAT2 (Expanded Safety and Feasibility Study of the FARAPULSE Endocardial Multi Ablation System to Treat Paroxysmal Atrial Fibrillation) trials of paroxysmal atrial fibrillation (AF), and 92% in the smaller 25-patient PersAFOne trial (Feasibility Study of the FARAPULSE Pulsed Field Ablation System Plus–PerAF in the Treatment of Persistent Atrial Fibrillation) of persistent AF.[14,18] However, the validity of these effectiveness data to general clinical practice is limited by: (1) the fact that these trials were designed to assess lesion durability so the majority of patients underwent 2- to 3-month remapping studies, during which any reconnected PVs were reablated, so the 1-year clinical success does not represent single-procedure success; (2) the relatively small numbers of patients; and (3) the modest number of operators (n=5) operators.

Accordingly, we conducted the multicenter patient-level MANIFEST-PF Registry of consecutive patients who underwent a first-ever AF ablation procedure using a pentaspline PFA catheter after regulatory approval in Europe. Because all postapproval patients are included, each operator's learning curve is encapsulated in this registry. In addition to patient-level data on long-term safety of PFA, the registry also collected data on effectiveness, specifically, 1-year freedom from atrial arrhythmia recurrence.

METHODS

Study Design

The data that support the findings of this study are available from the corresponding author on reasonable request. An invitation to participate in MANIFEST-PF Registry was sent to all 24 European centers that had been performing PFA procedures since commercialization and had participated in the MANIFEST-PF survey. This retrospective patient-level registry includes consecutive patients who received a first-ever PFA

(Farawave, Boston Scientific Inc) for paroxysmal AF, persistent AF, or long-standing persistent AF after regulatory approval between March 1, 2021, and May 30,2022. Informed consent was obtained from all subjects. Although this was a retrospective analysis, all data presented were prospectively recorded at each center. Patient data were de-identified in each individual registry at the respective centers. Institutional review board approval was obtained from each respective institution. This registry was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee at Homolka Hospital.

Study Population

The study included all patients aged ≥18 years who received catheter ablation for paroxysmal AF, persistent AF, or long-standing persistent AF. persistent AF was defined as AF duration ≥7 days but <1 year and long-standing persistent AF was defined as continuous AF duration >1 year, as per guidelines.[19] Patients were excluded if they had previous left atrial ablation. No echocardiographic exclusion criteria were applied.

PFA System

The components of the PFA system (Boston Scientific) were previously described in detail (Figure 1).[13] In brief, these components include: (1) the PFA generator that delivers high-voltage microsecond pulses at 1.8 to 2 kV, (2) a controller for signal acquisition and processing, (3) a 13.8F deflectable sheath (Faradrive; Boston Scientific Inc.), and (4) a 12F over-the-wire multielectrode PFA catheter (Farawave; Boston Scientific Inc.) that consists of 5 splines with 4 electrodes each. The PFA catheter can be configured to various poses from a baseline linear to either a basket or flower petal configuration. Two catheter sizes were available: 31 or 35 mm at full deployment. The PFA catheter is advanced over a guidewire to achieve circumferential contact/proximity of the splines with the left atrial-PV junction, and pulsed field energy is delivered from all electrodes.

Catheter Ablation Procedure

Procedures were typically performed with uninterrupted oral anticoagulation. The left atrial appendage was assessed for thrombus by either preprocedure CT, transesophageal echocardiogram, or intracardiac echocardiography on the basis of each individual center's standard practice preferences. Procedures were performed either under intravenous moderate sedation or general anesthesia with endotracheal intubation. Luminal esophageal temperature monitoring was rarely performed during the initial few procedures at a few centers but deferred in the vast majority of cases.

After femoral venous access, patients were heparinized, aiming for an activated clotting time of 300 to 350 seconds. The deflectable sheath is introduced into the left atrium (LA) after a single transseptal puncture. The ablation catheter is introduced into the LA and sequentially positioned at the ostium of each PV to deliver a series of lesions in basket and flower orientation to achieve electrical pulmonary vein isolation (PVI), and if persistent AF, this was followed by a series of applications along the posterior LA wall (Figure 1). Additional ablation including roof, mitral isthmus, cavotricuspid isthmus, and other ablation was performed either with PFA or a conventional radiofrequency ablation catheter as per operator discretion.

The PV ablation protocol consisted of pairs of energy applications: at each PV, 1 pair of applications was performed in a basket configuration, then the basket was rotated ≈36° to change spline orientation before another pair of PFA applications was delivered. The same algorithm was repeated using

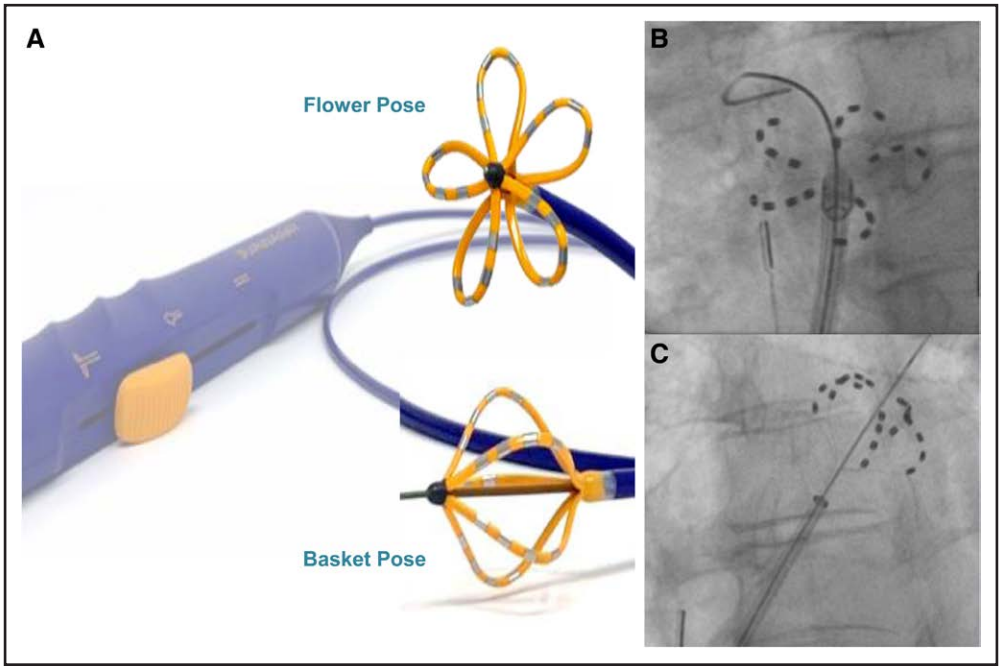

Figure 1. Pulsed field ablation catheter.
A, Pulsed field ablation catheter in flower (**top**) and basket (**bottom**) configurations. **B**, Fluoroscopic images of the pulsed field ablation catheter over a guidewire at the left superior pulmonary vein. **C**, Fluoroscopic images of the pulsed field ablation catheter over a guidewire at the right superior pulmonary vein.

the flower configuration to proximally extend the level of isolation. In the instance of left common PVs, operators typically adhere to the same workflow with 4 pairs of pulses delivered to both subbranches.

Energy applications are delivered at 1.8 to 2 kV as biphasic microsecond-scale waveforms, unsynchronized to cardiac rhythm.[13] Each waveform consists of a complex train of 5 consecutive pulses delivered over 2.5 seconds. Device size selection (31 versus 35 mm) was at the discretion of the operator. PVI is defined by entrance block, as confirmed by the absence of electrograms. Patients were discharged home the same day or monitored overnight, depending on the center's practice pattern. Therapeutic anticoagulation is typically resumed the evening after the procedure. Antiarrhythmic drugs are continued as per physician discretion. Total procedure time was the time between obtaining vascular access until removal of catheters from the patient.

Follow-Up

Follow-up was per each center's standard practice. Patients typically seen in outpatient clinics at 3, 6, and 12 months postprocedure, with assessments for AF-related symptoms, adverse events, and ECG or 24-hour Holter monitoring to document any atrial arrhythmia recurrence, as per physician discretion.

Clinical Outcomes

The primary effectiveness outcome was freedom from documented atrial arrhythmia (atrial fibrillation/atrial flutter/atrial tachycardia [AF/AFL/AT]) episodes of ≥30 seconds duration on the basis of electrocardiographic data after a 3-month blanking period, on or off antiarrhythmic drugs. This outcome was chosen because it represents the gold standard definition of recurrence on the basis of the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society recommendations for reporting outcomes in AF ablation trials.[20–22] The secondary effectiveness outcome was freedom from atrial arrhythmia episodes of ≥30 seconds after a 3-month blanking period, plus freedom from class I or III antiarrhythmic drugs or reablation. Safety outcomes included the composite of acute (<7 days postprocedure) and latent (>7 days postprocedure) major adverse events, including esophageal complications such as atrioesophageal fistula, symptomatic PV stenosis, cardiac tamponade/perforation requiring intervention or surgery, stroke or systemic thromboembolism, persistent phrenic nerve injury, vascular access complications requiring surgery, coronary artery spasm, and death.

Statistical Analysis

Continuous variables were reported as mean±SD or median (25th and 75th percentile, minimum and maximum) values if not normally distributed and were compared by a Student *t* test or Mann-Whitney *U* test. Categorical variables were reported as counts (percentage) and compared by a Pearson χ^2 test or Fisher exact test. The primary effectiveness outcome was evaluated with Kaplan-Meier analysis and the log-rank test. Time 0 was defined as the date of ablation, and data were censored at the patient's 400-day follow-up or exit from the registry. The start date for assessing atrial arrhythmia was 91 days after time 0.

To identify risk factors associated with primary effectiveness failure, multivariable Cox regression analysis was used, and results presented as hazard ratio with 95% CIs. Multiple imputation was used to account for missing data. All significance tests were 2-tailed, and *P* values <0.05 indicated statistical significance. Statistical analyses were performed using SPSS software (version 29.0; IBM Corp).

RESULTS

Patient Characteristics

The cohort included 1568 consecutive patients from 24 European centers (77 operators) who underwent first-ever catheter ablation for paroxysmal or persistent AF using the approved PFA catheter between March 2021 and May 2022 (Figure S1). The mean age was 64.5 years (range, 19–92) with a mean body mass index of 28.1 (range, 14–58), and 35% were female (Table 1). The mean CHA_2DS_2-VASc score was 2.2 (range, 0–9) and the mean LA diameter was 42 mm (interquartile range, 39–46). The AF type was paroxysmal (65%), persistent (32%), or long-standing persistent (3%). The mean left ventricular ejection fraction was 57.3±9.6 (range, 15–80), with 6.4% of patients having a left ventricular ejection fraction <40%. A class I or III antiarrhythmic drug had failed in 39.7% of patients before PFA.

Procedural Characteristics

As shown in Table 2, most procedures were performed under deep sedation without endotracheal intubation (80%), and 6.4% of patients were discharged on the same day as the procedure. PVI was achieved in 99.2% (1556/1568 patients). The median procedure time was 61 minutes (range, 15–362), inclusive of pre- or postablation electroanatomical mapping, or both, in 29% of patients. The median fluoroscopy time was 12 minutes (range, 3–114). Intraprocedural imaging was used in all patients, with fluoroscopy in 100% of patients and intracardiac echocardiography in 33% of patients. Additional non-PVI lesion sets were performed in a subset of patients (22.8%); when used, the most common such additional lesions were LA posterior wall "box" isolation in 11% (173/1568 patients) followed by cavotricuspid isthmus ablation in 5.4% (84/1568 patients). Of the 173 patients (11%) who received posterior LA ablation, 76% (131/173) had persistent/long-standing persistent AF, whereas 24% (42/173 patients) had paroxysmal AF.

Effectiveness Outcomes

Follow-Up

As demonstrated in Table 3, the median number (interquartile range) of follow-up visits and 24-hour Holter monitors were 2 (1–3) and 3 (2–3), respectively. During follow-up, 66% (1043/1568) underwent ≥2 24-hour

Table 1. Baseline Characteristics

Characteristics	Patients with available data	Value
Age, n (%)/ mean±SD	1568 (100)	64.5±11.5
Female, n (%)	1568 (100)	553 (35)
Atrial fibrillation type, n (%)		
Paroxysmal	1568 (100)	1021 (65)
Persistent	1568 (100)	498 (32)
Long-standing persistent	1568 (100)	49 (3)
CHA_2DS_2-VASc, n (%)/mean±SD	1568 (100)	2.2±1.6
Medical history		
Body mass index, n (%)/mean±SD	1554 (99.1)	28±5
Atrial flutter, n (%)	1235 (78.8)	158 (12.8)
Coronary artery disease, n (%)	1235 (78.3)	167 (13.5)
Diabetes, n (%)	1568 (100)	196 (12.5)
Hypertension, n (%)	1568 (100)	959 (61.1)
Heart failure, n (%)	1568 (100)	226 (14.4)
Sleep apnea, n (%)	1104 (70.4)	102 (9.2)
Prior stroke/transient ischemic attack, n (%)	1568 (100)	97 (6.2)
Chronic obstructive pulmonary disease, n (%)	992 (63.3)	50 (5)
Echocardiographic parameters		
Left ventricular ejection fraction, n (%)/median (interquartile range)	1381 (88.1)	60 (55–64)
Left atrium diameter (mm), n (%)/median (interquartile range)	1220 (77.8)	42 (39–46)
Antiarrhythmic medications, n (%)		
Class I antiarrhythmic drugs	1566 (99.9)	343 (21.9)
Class III antiarrhythmic drugs	1567 (99.9)	279 (17.8)

Holter monitoring, whereas 21% (336/1043) received one 24-hour Holter monitoring.

Primary Effectiveness Outcome

After a median (interquartile range) follow-up of 367 (289–421) days, the 1-year Kaplan-Meier estimate for freedom from AF/AFL/AT after a single procedure was 78.1% (95% CI, 76.0%–80.0%; Table 3; Figure 2A). The clinical effectiveness was more common in paroxysmal AF versus patients with persistent AF (81.6% versus 71.5%; P=0.001; Figure 2B). The effectiveness of freedom from arrhythmia in patients with persistent AF was not significantly different than those with long-standing persistent AF (71.3% versus 73.5%, P=0.15; Figure S2).

A subgroup analysis revealed that freedom from AF/AFL/AT was lower with age ≥65 years compared with age <65 years, but similar between men and women (Table S1).

Risk Factors Associated With Primary Effectiveness Outcome

Multivariable Cox regression modeling was performed to identify potential risk factors associated with primary effectiveness failure. The hazard ratio of primary effectiveness failure for subjects with age >65 years was 1.57 (95% CI, 1.41–1.76; P<0.001), with LA diameter of >45 mm the hazard ratio of primary effectiveness failure was 1.33 (95% CI, 1.21–1.46; P<0.001), with procedure time >60 minutes it was 1.30 (95% CI, 1.18–1.42; P<0.001), with a left ventricular ejection fraction >50% it was 0.78 (95% CI, 0.68–0.90; P<0.001), and with persistent AF it was 1.39 (95% CI, 1.26–1.53; P<0.001; Figure 3).

Secondary Effectiveness Outcome

The Kaplan-Meier estimate of freedom from AF/AFL/AT *off* antiarrhythmic drugs or redo ablation was 70.8% (95% CI, 68.4%–73%); again, clinical effectiveness was more common in the paroxysmal AF versus persistent AF/long-standing persistent AF cohort (73.8% versus 65.1%, P=0.001; Table 3, Figures S3 and S4).

Outcomes by Procedure Volume

The freedom from AF/AFL/AT was analyzed by center to assess the effect of different practices/operators on outcomes. The centers were stratified into 3 groups on the basis of the number of procedures performed: (1) group 1: >100 procedures (n=4 centers); (2) group 2: 50 to 100 procedures (n=5 centers); and (3) group 3: <50 procedures (n=15 centers). As shown in Figure S5, there was no significant center variation in outcomes; the 12-month freedom from atrial arrhythmia ranged between 76% and 79% across the low- to high-volume centers (P=0.11; Figure S5).

Outcomes by PVI Durability

Redo ablation procedures were performed in 9.3% (147/1568) of patients, of which 59.2% (n=87) had paroxysmal AF, 37.2% (n=55) had persistent AF, and 3.4% (n=5) had long-standing persistent AF. In these patients presenting for redo ablation procedures, durable PVI was observed in 72.6% of PVs (427/588 PVs). On a per-patient basis, this translated to 45.5% of patients (67/147) with all PVs durably isolated.

In a post hoc analysis, we determined whether clinical outcomes varied on the basis of PVI durability. After excluding centers that performed <5 redo procedures (n=15 centers), outcomes were determined from the remaining centers segregated by PVI durability. As shown in Figure 4, patients from those centers (n=3) with a per-patient PVI durability >50% in the redo cases demonstrated a higher 1-year freedom from AF/AFL/AT compared with those centers (n=6) with per-patient PVI durability <50% (81% versus 71%, P<0.001). These differences by PVI durability remained consistent when the cohort was separated into either paroxysmal AF (82.5% versus 79.0%, P=0.04) or persistent AF (76.4% versus 56.2%, P<0.001) subgroups (Figure S6).

Table 2. Procedural Characteristics

Procedure characteristics	Patients with available data	Value
Intubation, n (%)	1568 (100)	317 (20)
Mapping, n (%)	1568 (100)	457 (29)
Intracardiac echocardiography imaging, n (%)	1234 (79)	407 (33)
Ablation lesion sets, n (%)		
Acute pulmonary vein isolation	1568 (100)	1568 (100)
Acute success	1568 (100)	1556 (99.2)
Additional non–pulmonary vein ablation	1568 (100)	359 (22.8)
Posterior wall ablation	1568 (100)	173 (11)
Mitral line	1568 (100)	37 (2.4)
Cavotricuspid isthmus line	1568 (100)	84 (5.4)
Roof line	1568 (100)	21 (1.3)
Other ablation	1568 (100)	44 (2.8)
Type of energy used to perform additional ablation		
Pulse field energy	359 (100)	305 (85)
Radiofrequency	359 (100)	54 (15)
Fluoroscopy time, min, n (%)/median (interquartile range)	1521 (97.0)	12 (7–19)
Procedure time, min, n (%)/median (interquartile range)	1540 (98.2)	61 (40–90)
Same day discharge, n (%)	1234 (78.7)	101 (6.4)

Safety Outcomes

As shown in Table 4, the major complication rate was 1.9% (30/1568 patients). These major complications were primarily cardiac tamponades and, to a lesser extent, stroke and vascular complications. Mortality was rare, occurring in 1 patient (0.06%) who had sustained a stroke. The minor complication rate was 4% (63/1568 patients), largely driven by vascular complications (2.6%), followed by transient phrenic nerve injury in 0.4% and transient ischemic attacks in 0.1%.

Table 3. Effectiveness Outcomes

Effectiveness outcomes	N=1568
Primary effectiveness outcome	
Freedom from AF/AFL/AT, n (%)	1224 (78.1)*
Secondary effectiveness outcome	
Freedom from atrial arrhythmia off antiarrhythmic drugs or redo ablation, n (%)	1110 (70.8)*
Follow-up duration, days, median (IQR)	367 (289–421)
No. of follow-up 24-hour Holter monitors, median (IQR)	2 (1–3)
No. of follow-up visits, median (IQR)	3 (2–3)
Time to AF/AFL recurrence, days, median (IQR)	180 (129–266)
Redo ablation, n (%)	147 (9.3)

AF/AFL/AT indicates atrial fibrillation/atrial flutter/atrial tachycardia; and IQR, interquartile range.

* Based on a Kaplan-Meier analysis.

PFA-Specific Adverse Events

There were no post-PFA esophageal complications, including no instances of atrioesophageal fistula, esophageal ulcerations, or esophageal dysmotility disorders. There were also no instances of symptomatic PV stenosis.

Persistent phrenic nerve injury occurred in 1 patient (0.06%). The phrenic nerve injury was not initially noted at the time of the procedure but was subsequently detected due to ongoing symptoms and a persistently elevated right hemidiaphragm by chest radiography during follow up. (Figure S7). In addition, transient phrenic nerve injury occurred in 0.4% (n=6) of patients, with near-immediate recovery within a few minutes and complete recovery before hospital discharge.

Coronary arterial spasm occurred in 2 patients (0.1%). One patient had coronary spasm with associated ST-segment elevation while the operators were performing ablation along the posterior mitral isthmus; this resolved with the administration of intracoronary nitroglycerin. In a second patient, remote coronary spasm occurred while the operator(s) were performing PVI, coronary angiography revealed diffuse coronary spasm, which promptly resolved with intracoronary nitroglycerine.

Non–PFA-Specific Adverse Events

Cardiac tamponade occurred in 1.1% (18/1568) of patients. Most of these (0.8%) were managed with percutaneous drainage, but surgical treatment was required in 0.1%. Stroke occurred in 0.4% (6/1568) of patients, with one culminating in death (0.06%).

As shown in Table 4, the most frequent complications overall were of a vascular pathogenesis. The majority of these (2.6%) were minor complications treated conservatively, most commonly, hematomas (2.1%) followed by arteriovenous fistula in 0.3%, but there also were some major vascular complications requiring surgical repair (0.1%).

DISCUSSION

The MANIFEST-PF Registry is a multinational patient-level registry including the cohort of 1568 consecutive patients with AF from the 24 European sites that commenced AF ablation using the PFA catheter in 2021 after regulatory approval. The major findings are: (1) PVI was achieved in 99.2%; (2) 1-year freedom from atrial arrhythmias (AF/AFL/AT) was 78.1%, with clinical effectiveness being more common with paroxysmal AF versus persistent AF (81.6% versus 71.5%, *P*=0.001); (3) clinical effectiveness was greater in those centers that demonstrated a higher PVI durability rate in clinical redo procedures; (4) the rate of major adverse events was low (1.9%), with no occurrences of esophageal complications or symptomatic PV stenosis; and (5) the overall procedure-related mortality was <1 in 1000 patients (0.06%; Figure S8).

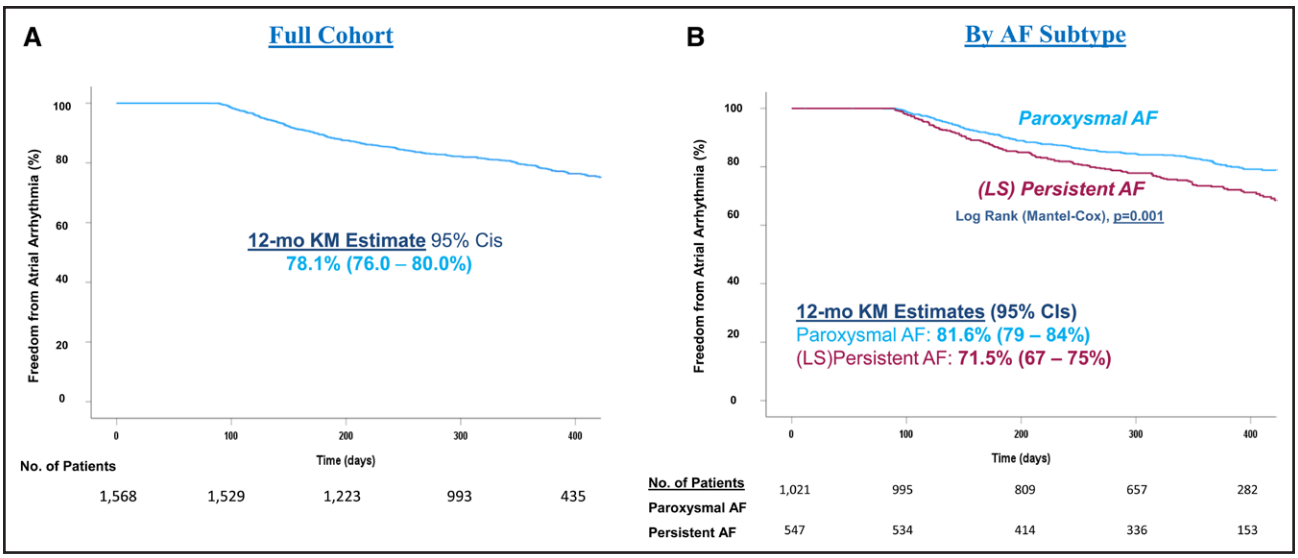

Figure 2. Primary effectiveness outcome.
Kaplan-Meier analysis demonstrating 1-year freedom from arrhythmia in either the full cohort (**A**) or by AF subtype: paroxysmal AF vs (long-standing) persistent AF (**B**). AF indicates atrial fibrillation; KM, Kaplan-Meier; and LS, long-standing.

Clinical Effectiveness

Even in the hands of multiple operators (n=77), PVI was achieved in a large number of patients (99.2%). But most importantly, the primary effectiveness outcome of freedom from AF/AFL/AT recurrence >30 seconds postblanking was 78.1% after a single ablation procedure at 12 months follow-up, with the more effectiveness in the paroxysmal AF cohort (81.6%) than the (long-standing) persistent AF cohort (71.5%). These effectiveness rates compare favorably with the first-in-human trials using this PFA catheter.[14,15,23] The other clinical effectiveness data published with PFA were from the recently published inspIRE study (A Study for Treatment of Paroxysmal Atrial Fibrillation [PAF] by Pulsed Field Ablation [PFA] System with Irreversible Electroporation) using a different circular PFA catheter system: 186 patients with paroxysmal

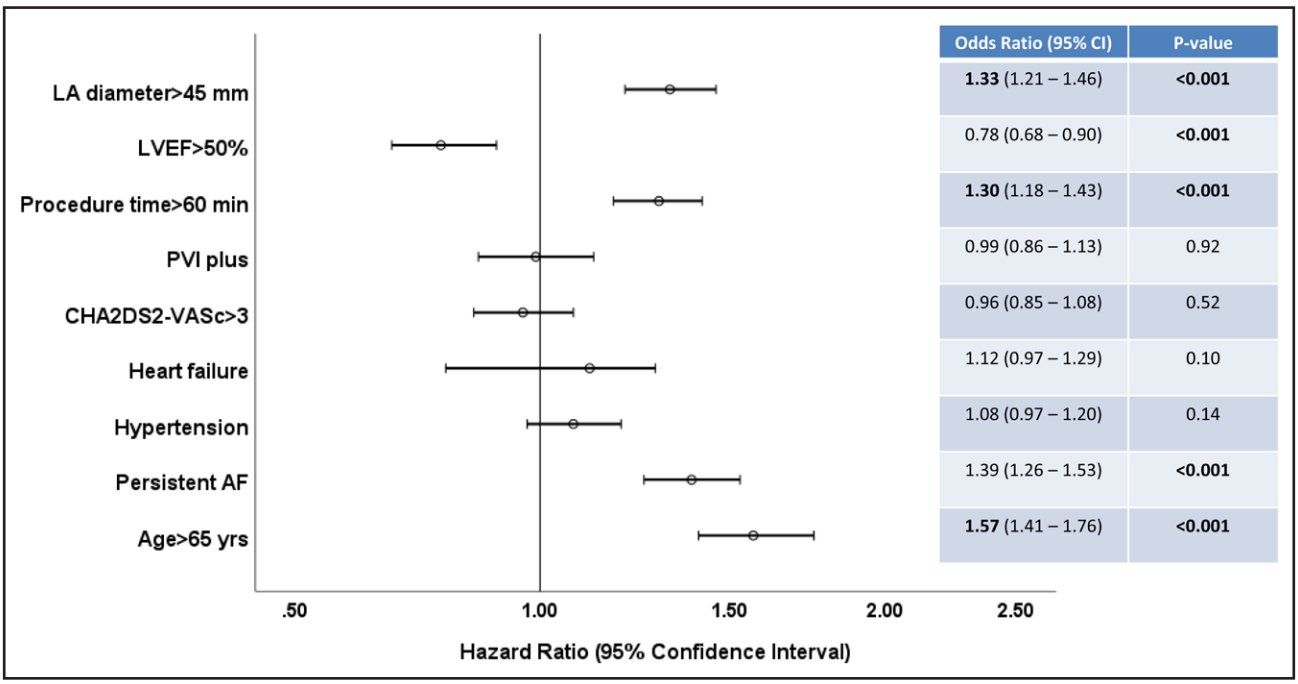

Figure 3. Multivariable Cox regression: risk factors for primary effectiveness failure.
The risk factors that predict post–pulsed field ablation recurrence are elderly age (>65 years), enlarged LA, persistent AF, and prolonged procedure time. AF indicates atrial fibrillation; LA, left atrium; LVEF, left ventricular ejection fraction; and PVI, pulmonary vein isolation.

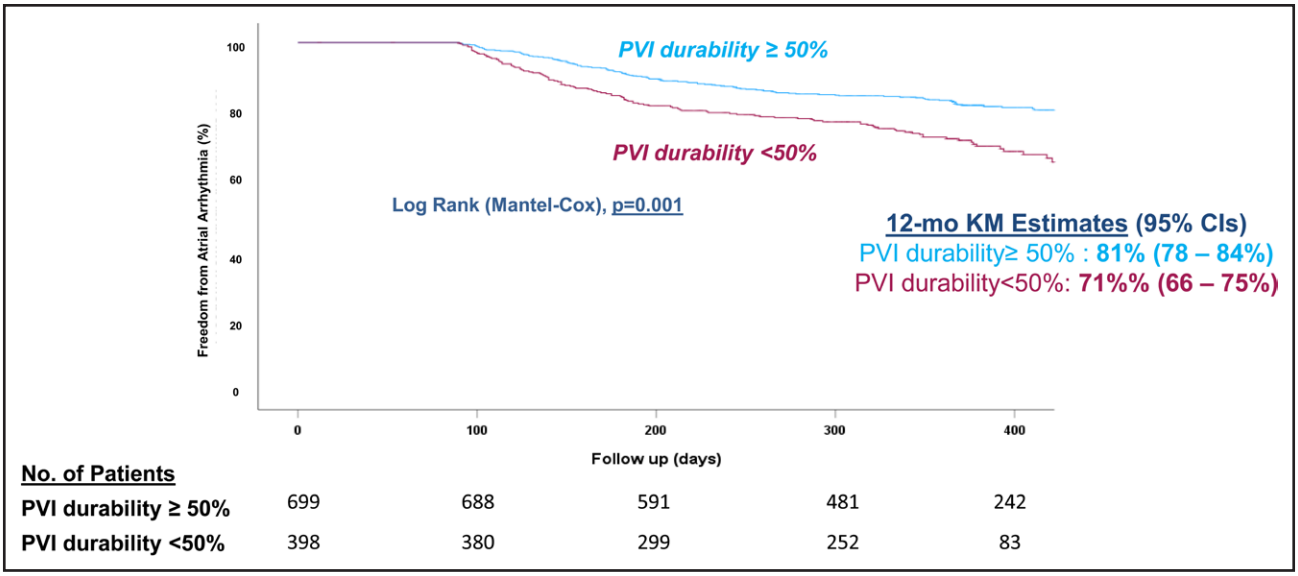

Figure 4. Primary effectiveness outcome by center-level PVI durability at redo ablation.
Among sites that performed at least 5 redo procedures for clinical recurrence, they were dichotomized into those with a per-patient durability of >50% vs <50%. Shown is the Kaplan-Meier analysis of 1-year freedom from arrhythmia on the basis of PVI durability at redo ablation. KM indicates Kaplan-Meier; and PVI, pulmonary vein isolation.

AF underwent PFA at 13 centers, and the 1-year Kaplan-Meier estimate of freedom from AF/AFL/AT was 70.9%.[24] Also reported recently, the 1-year clinical effectiveness in the PULSED AF study (Pulsed Field Ablation to Irreversibly Electroporate Tissue and Treat AF) using yet another circular PFA catheter system was 66.2% and 55.1% for paroxysmal and persistent AF, respectively.[23] In comparing these various studies, one should be cognizant that the observed higher freedom from atrial tachyarrhythmia recurrence in MANIFEST-PF may reflect differences in monitoring intensity. On the other hand, it is possible that symptomatic AF (the most relevant in clinical practice) was adequately captured through 12-lead ECGs and intentional 24-hour Holter monitoring.

Because some of these patients underwent reisolation of reconnected PVs (28%) at the time of redo ablation procedures, we also analyzed per-patient PVI durability by center. That is, for centers doing at least 5 redo procedures, we dichotomized them into 2 groups: >50% versus <50% PVI durability on a per-patient basis: freedom from AF/AFL/AT was 81% with the former versus 71% with the latter, respectively ($P<0.001$). These differences by PVI durability remained consistent when the cohort was separated into either paroxysmal AF (82.5% versus 79.0%, $P=0.04$) or (long-standing) persistent AF (76.4% versus 56.2%, $P<0.001$). This is comparable to results of previous studies with mandatory PVI reassessment procedures; for example, in the RACE-AF trial (Radiofrequency vs Cryoballoon Ablation for Atrial Fibrillation Assessed by Implantable Cardiac Monitor) that studied both radiofrequency and cryoballoon ablation and included both implantation of implantable loop recorders in all patients and mandatory remapping procedures, postablation AF burden was strongly predicted by the number of durably isolated PVs ($P<0.01$).[25]

In this large observational registry, the favorable clinical outcomes were achieved with overall procedure (61 minutes [range, 15–362]) and fluoroscopy times (12 minutes [range, 3–114]) similar to those observed in the first-in-human PFA trials.[14,15] It is expected that, as observed with past devices, learning curves usually improve rapidly over time, and outcomes such as procedural efficiencies and effectiveness may further improve when the catheter is more widely used in routine clinical practice.

Safety

The rate of major complications was 1.9% and primarily consisted of cardiac tamponade (1.1%) and stroke (0.4%), with the only procedural mortality (0.06%) being related to one of these strokes. In this large registry, the preferentiality of myocardial tissue susceptibility to PFA was evidenced by no identified instances of atrioesophageal fistula or symptomatic PV stenosis. This is consistent with previous preclinical and clinical studies, including the center-level MANIFEST-PF survey.[7,12–15,26–28]

Stroke

In our series, we observed 6 patients (0.4%) with stroke. Although the source of embolization remains unclear, stroke was attributed to improper sheath handling, especially during catheter exchanges through the 13F deflectable sheath in 3 cases. Prolonged procedure duration and procedure complexity were attributed to stroke in 2 patients. Stroke in 1 patient was due to interruption of non-vitamin K antagonist oral

Table 4. Major and Minor Adverse Events

Safety outcomes	N=1568 (%)
Acute major adverse events, n (%)	30 (1.9)
Esophageal fistula	0
Symptomatic pulmonary vein stenosis	0
Cardiac tamponade	18 (1.1)
Percutaneous drainage	14 (0.8)
Surgical drainage	2 (0.1)
Stroke	6 (0.4)
Coronary spasm	2 (0.1)
Phrenic nerve injury (persistent)	1 (0.06)
Death	1 (0.06)
Vascular complications requiring surgery	2 (0.1)
Acute minor adverse events, n (%)	63 (4.0)
Pericardial effusion without intervention	4 (0.3%)
Pericarditis	1 (0.06)
Air embolism	4 (0.3)
Transient ischemic attack	2 (0.1)
Phrenic nerve injury, transient	6 (0.4)
Vascular access complications	41 (2.6)
Hematoma	33 (2.1)
Arteriovenous fistula	5 (0.3)
Pseudoaneurysm	2 (0.1)
Deep vein thrombosis	1 (0.06)
Respiratory related	4 (0.3)
Latent major adverse events	0 (0.00)

anticoagulants in the setting of underlying active malignancy. There were no instances of left atrial appendage thrombus in any of the patients.

Phrenic Nerve

Transient phrenic nerve injury/stunning did occur in 0.4% of patients, all regaining normal function by the next day after the procedure. On the other hand, the current registry identified 1 patient (0.06%) who had symptomatic phrenic nerve injury after PVI that was reconfirmed weeks after the procedure with only partial remission at 1 year (note that this was not initially identified at the time of the procedure, and thus excluded from the previously published MANIFEST-PF survey).[29]

There are limited available data characterizing the effects of PFA on the phrenic nerve: stunning or injury. Whether this represents electrical hyperpolarization or axonal necrosis is unknown; however, due to its transient nature and rapid recovery, the former mechanism might be more likely. A recent preclinical study revealed that both the proximity of the catheter to the phrenic nerve and the PFA dose level (voltage amplitude) were critical for phrenic nerve injury.[11] However, in this experiment, despite any acute phrenic nerve impairment, all phrenic nerve functionality reversed to normal, with no grossly visible or histopathological changes suggestive of latent or persistent injury. In another acute porcine model, supraclinical PFA doses administered through a focal catheter from the right atrium transiently reduced or abrogated diaphragmatic contractions for 5 minutes before returning to baseline, again without histological changes.[9] As a result, the finding of this patient with phrenic nerve injury in the present large MANIFEST-PF Registry requires further attention, in particular, in mechanically ventilated patients because phrenic nerve injury can go unnoticed. In any event, it seems prudent to avoid positioning the PFA catheter deep within the right superior PV and to routinely monitor phrenic nerve capture before and after pulse field energy delivery.

Coronary Arterial Spasm

As previously reported, 2 patients (0.1%) developed coronary vasospasm with associated ST-segment elevations: (1) an instance of proximity-related vasospasm during mitral isthmus ablation as previously reported,[25] and (2) an instance of remote vasospasm during conventional PVI.[30,31] Regarding the former, among the 37 patients in this registry (2.4% of the full MANIFEST-PF cohort) who received mitral isthmus ablation, regional clinically evident coronary vasospasm was observed in 1 patient (2.7%). This phenomenon of proximity-related transient coronary spasm has been reported previously in preclinical and clinical studies and appears to be related to the distance between the PFA catheter and the coronary arteries.[30,32] Coronary arterial vasospasm may also occur with radiofrequency ablation at the mitral isthmus, again typically resolving with intracoronary nitroglycerin.[33] Likewise, we have previously demonstrated that subclinical right coronary artery vasospasm almost universally occurs during PFA with the PFA catheter at the cavotricuspid isthmus, a process attenuated by treatment with intracoronary/intravenous nitroglycerin before treatment. As a result, it seems prudent to consider administering parenteral nitroglycerin before delivering pulsed field energy near a coronary artery.

The second patient with coronary spasm had so-called remote vasospasm; that is, vasospasm during ablation of the PVs that are remote from the location of the coronary arteries. As we previously published, this generalized diffuse coronary vasospastic phenomenon appears to be an autonomically/sympathetically driven one.[30] In a prospective study of systematic coronary angiography in 25 patients undergoing PFA, there were no instances of remote/generalized spasm.[30] In a recent meta-analysis of conventional thermal ablation, the rates of remote generalized vasospasm with radiofrequency or cryoballoon ablation were 0.04% and 0.23%, respectively.[34] The rate of remote generalized vasospasm with PFA in the current MANIFEST-PF Registry (1/1568 patients, 0.06%) is well within this range, suggesting no unique susceptibility to pulsed electrical fields. But of course, just as with

thermal ablation, physicians clearly must be cognizant of this rare phenomenon that can even be life-threatening in some instances.[35] If diffuse ST elevation is observed during PVI, particularly with coincident hemodynamic collapse, immediate coronary angiography is necessary, also with a plan to administer intracoronary nitroglycerin.[30]

Limitations

First, this is a retrospective, observational, and nonrandomized study with no control group. Second, the study is reliant on the accuracy of individual prospective centers to ensure inclusion of consecutive patients who received PFA for AF. Third, there is a potential bias in patient selection and clinical management. However, the large sample size including numerous operators should mitigate this bias. Last, missed rhythm monitoring and the use of intermittent rather than continuous monitoring may have resulted in an overestimation of treatment success. However, this should not affect the relative differences in comparisons between groups (eg, paroxysmal AF versus persistent AF, outcome by center PVI durability). Furthermore, until the results of randomized control trials comparing PFA versus radiofrequency/cryoablation are available, this observational analysis is the largest multicenter experience to date of PFA for paroxysmal or persistent AF.

ARTICLE INFORMATION

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Supplemental Material

Expanded Methods

Figures S1–S8

Tables S1–S3

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