

Safety of pulsed field ablation in more than 17,000 patients with atrial fibrillation in the MANIFEST-17K study

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Pulsed field ablation (PFA) is an emerging technology for the treatment of atrial fibrillation (AF), for which pre-clinical and early-stage clinical data are suggestive of some degree of preferentiality to myocardial tissue ablation without damage to adjacent structures. Here in the MANIFEST-17K study we assessed the safety of PFA by studying the post-approval use of this treatment modality. Of the 116 centers performing post-approval PFA with a pentaspline catheter, data were received from 106 centers (91.4% participation) regarding 17,642 patients undergoing PFA (mean age 64, 34.7% female, 57.8% paroxysmal AF and 35.2% persistent AF). No esophageal complications, pulmonary vein stenosis or persistent phrenic palsy was reported (transient palsy was reported in 0.06% of patients; 11 of 17,642). Major complications, reported for ~1% of patients (173 of 17,642), were pericardial tamponade (0.36%; 63 of 17,642) and vascular events (0.30%; 53 of 17,642). Stroke was rare (0.12%; 22 of 17,642) and death was even rarer (0.03%; 5 of 17,642). Unexpected complications of PFA were coronary arterial spasm in 0.14% of patients (25 of 17,642) and hemolysis-related acute renal failure necessitating hemodialysis in 0.03% of patients (5 of 17,642). Taken together, these data indicate that PFA demonstrates a favorable safety profile by avoiding much of the collateral damage seen with conventional thermal ablation. PFA has the potential to be transformative for the management of patients with AF.

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder, with notable impact on quality of life, morbidity and mortality^{1–4}. Catheter ablation using thermal energy is an effective means to treat AF, even as a first-line therapy to improve quality of life and morbidity and even to prevent mortality in heart failure patients^{5–7}. Technological evolution in catheter design, mapping and optimization across the spectrum of thermal ablation modalities (radiofrequency/laser/heat or cryotherapy/cold) have made positive strides in improving its safety and efficacy.

However, inherent to thermal ablation is the indiscriminate nature of tissue destruction, which can have deleterious consequences on the myocardium and pericardiac structures. While the overall complication

rates during thermal ablation have improved over time, there remain residual safety considerations including the risk for pulmonary vein (PV) stenosis, stroke, phrenic nerve palsy and the deadliest complication, atrio-esophageal fistula, which even today has a mortality of ~50% (refs. 8–10).

Pulsed field ablation (PFA) is an emerging AF ablation modality with an important degree of preferentiality to myocardial tissue damage. By delivering ultrarapid (microsecond to nanosecond) electrical pulses to generate strong electrical fields, PFA can produce irreversible nanoscale pore formation culminating in cellular death^{11,12}. Pre-clinical studies demonstrated no (or little) damage to peri-atrial tissue such as the esophagus and phrenic nerve, and no PV stenosis^{13–16}. The first

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and most extensively investigated PFA catheter is a multi-electrode pentaspline catheter, studied in first-in-human trials for treating either paroxysmal or persistent AF patients in IMPULSE/PEFCAT/PEFCAT2 and PersAFOne, respectively^{17–19}. These trials demonstrated the feasibility and safety of PFA for AF ablation in a relatively small cohort of patients (<150) and few operators. Though promising, concerns remained around the safety of this novel ablation modality, particularly in a ‘real-world’ setting with a large volume of patients and operators.

After European regulatory approval (CE mark certification) of the pentaspline PFA catheter in March 2021, the MANIFEST-PF Survey of all AF patients receiving PFA in year 2021 ($n = 1,758$ patients at 24 centers) revealed no esophageal damage or PV stenosis and rare phrenic palsy (<1 in 1,000) with good clinical effectiveness^{20–22}. These findings were consistent with the safety observed in the EU-PORIA registry ($n = 1,233$ patients at 7 centers). Additionally, the recently published ADVENT randomized clinical trial demonstrated noninferiority of PFA to conventional thermal ablation (cryothermal or radiofrequency) for efficacy and safety in a cohort of 707 paroxysmal AF patients²³.

While encouraging, it is important to recognize that: (1) when cryoballoon ablation was first introduced approximately two decades ago, atrio-esophageal fistula formation was observed only after a few thousand patients were treated, and (2) unforeseen PFA-related adverse events (AEs) may only manifest after several thousands of procedures are performed^{24–26}. Accordingly, the retrospective MANIFEST-17K study assessed the safety of PFA in the very large cohort of >17,000 patients.

Results

MANIFEST-17K is a retrospective observational study of centers performing PFA after regulatory approval of the pentaspline PFA catheter (Farawave, Farapulse-Boston Scientific Inc.) with the goal of collecting comprehensive data on the methods and safety of the post-approval clinical use of PFA. An invitation to participate in MANIFEST-17K was sent to all 116 centers performing post-approval clinical cases with this PFA catheter. Institution-level data were obtained on center characteristics, limited patient baseline characteristics, limited procedure parameters, and all AEs. We excluded from this analysis the initial 1,758 patients treated in 2021 by the initial 24 centers (herein referred to as the ‘initial MANIFEST-PF sites’) and previously reported in the MANIFEST-PF survey (the ‘MANIFEST-PF cohort’)^{20,21}.

Baseline characteristics

Clinical site characteristics. Out of 116 centers contacted for participation, a total of 106 centers agreed (91.4% response), including the 24 initial MANIFEST-PF sites, plus 82 of the expanded MANIFEST-17K sites (Fig. 1). Clinical centers were located in 20 countries, 19 in Europe and 1 in Israel. All data forms were considered complete. Of the ten nonparticipating centers, five were not reachable, three declined participation owing to the time required for either local ethics approval or insufficient research staff, and two could not provide the data within the specified time frame.

As shown in Extended Data Table 1, most centers (61.3%) self-classified as academic, 21.7% were hybrid and 17% were private practice. The mean number of operators per center was 3.9 (range 1–11), with an average of 13.6 years in practice (range 3–25 years). The average number of AF ablations performed annually was 590 (range 80–2,000). The date of the first PFA case performed ranged from March 2021 to March 2023, with each site performing an average of 166 PFA cases (range 17–1,277). The average follow-up time was 15 months (range 3–25 months).

As compared to the initial MANIFEST-PF sites ($n = 24$), the expanded MANIFEST-17K sites ($n = 82$) similarly classified themselves as private (18.3% versus 12.5%, respectively, $P = 0.506$) or hybrid (20.7% versus 25%, respectively, $P = 0.655$). The initial MANIFEST-PF sites were higher volume centers for total AF ablation (801 (200–2,000) versus 436 (80–1,200), $P < 0.001$), and for PFA cases (328 (54–1,277) versus

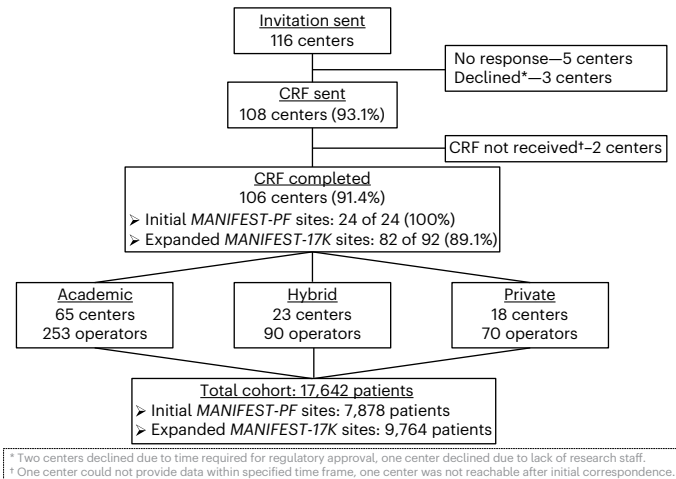


Fig. 1 | Study center, operator and patient numbers. Shown are the invited and participating centers, along with the number of operators and the number of patients included in the study. CRF, case report form.

119 (17–472), $P < 0.001$) and, as expected, had earlier exposure to PFA (average first case—June 2021 versus June 2022; Extended Data Table 1).

Patient characteristics. The study population included a total of 17,642 patients who underwent PFA between early 2022 to, for most centers, June 2023. The mean age was 64 years (range 11–96 years), of which 34.7% were female (Table 1). The type of AF treated was paroxysmal (57.8%), persistent (35.2%), long-standing persistent AF (5.6%) or, infrequently, atrial flutter/atrial tachycardia (1.4%). The procedures were performed under deep sedation without intubation in 53.1% of the patients.

AEs overview

As shown in Table 2 and Fig. 2a, in the 17,642 patient cohort, the major complication rate was 0.98%. The most common of these major complications were of vascular origin (0.30%) and pericardial tamponade (0.36%), with the majority of the latter being treated percutaneously (56 of 63, 88.9%) instead of surgically (7 of 63, 11.1%). The remaining major complications included stroke (0.12%) and coronary spasm (0.14%), with mortality being rare at 0.03% ($n = 5$).

The minor complication rate was 3.21%, composed primarily of vascular complications (2.2%) and, to a lesser extent, pericardial effusion not requiring intervention (0.33%). Other minor complications included transient ischemic attack (0.12%), pericarditis (0.17%) and transient phrenic injury (0.06%)—the last defined as phrenic palsy that recovered before hospital discharge.

PFA energy-specific AEs

There were no post-PFA esophageal complications, including no reported instances of atrio-esophageal fistula formation or dysmotility disorders (Table 2). There were also no instances of pulmonary vein stenosis.

Phrenic nerve. Persistent phrenic nerve injury was not reported. However, transient phrenic paresis was reported in 11 patients (0.06%), with patients recovering diaphragmatic function by the next day.

Coronary spasm. There was evidence of coronary arterial spasm in 25 patients (0.14%). The majority of these cases were proximity-related spasm (22 of 25, 88%), and the remaining were instances of generalized/remote spasm (Table 3). Electrocardiogram (EKG) changes were observed in most patients (23 of 25; 92%), hypotension was observed in 5 cases (20%) and intravenous or intracoronary nitroglycerin was

Table 1 | Baseline patient characteristics

	Full MANIFEST-17K cohort (N=17,642)
Demographic	
Age (years), mean (minimum–maximum)	64 (11–96)
Female (%)	34.7
Indication for ablation	
Paroxysmal atrial fibrillation (%)	57.8
Persistent atrial fibrillation (%)	35.2
Long-standing persistent atrial fibrillation (%)	5.6
Atrial flutter/atrial tachycardia (%)	1.4
Sedation	
General anesthesia (%)	46.9
Deep sedation/no intubation (%)	53.1

administered in 21 cases (84%). Clinical sequelae were reported in four cases (16%): (1) one patient developed atrioventricular block and ventricular fibrillation during PFA of the cavotricuspid isthmus (CTI), prompting resuscitation and defibrillation²⁷, (2) two patients developed chest pain in the post-procedure recovery area, with both promptly resolved with nitroglycerin, and (3) one patient developed anterior ST elevation, polymorphic premature ventricular contractions and subsequent ventricular fibrillation after PFA at the right inferior PV—prompting resuscitation, defibrillation and intravenous nitroglycerin administration.

Hemolysis-related renal failure. Hemolysis with resultant acute renal failure occurred in five patients (0.03%). The creatinine level increased by 100% by the next post-procedure day in all patients, with a peak creatinine of 6.5 mg dl⁻¹ in one patient (Extended Data Fig. 1). Symptomatology included hemoglobinuria, nausea and oliguria, beginning either immediately post-procedure or the next day. Three patients had normal creatinine levels at baseline, while two patients had baseline elevation (1.2 and 1.5 mg dl⁻¹). For all patients, transient hemodialysis significantly improved renal function by the time of hospital discharge.

All five patients had received PFA for persistent AF, with a complex lesion set including pulmonary vein isolation (PVI), posterior wall ablation, mitral isthmus and CTI lines. Importantly, an extensive number of PF applications (143 ± 27 per procedure) had been placed (patient details in Extended Data Table 2).

Hemolysis. One other patient was reported as having hemolysis, but without kidney injury (Table 2). In addition, there were several patients at one other center reported to have ‘dark urine or hemoglobinuria’ in either the immediate post-procedure setting or the next day. However, there was no reported kidney injury or drop in the red cell count.

Non-PFA energy-specific AEs

Pericardial tamponade. Pericardial tamponade occurred in 63 patients (0.36%), with the majority ($n = 56$, 0.32%; or 56 of 63, 88.9%) managed with percutaneous pericardiocentesis. Surgery was required in the remaining seven patients (0.04%), of which details were available for four: (1) right atrial appendage injury related to the guidewire for transeptal puncture, (2) laceration of the left atrium (LA) and right inferior pulmonary vein, (3) left ventricular perforation with the PFA catheter while trying to probe the left inferior pulmonary vein, and (4) perforation/tamponade with emergent sternotomy and repair but irreversible brain damage culminating in death (see below).

Table 2 | Major and minor complications

	Full patient cohort from all 106 MANIFEST-17K sites ^a (N=17,642)
Major AEs	173 (0.98%)
Death ^b	5 (0.03%)
Stroke	22 (0.12%)
Esophageal fistula or dysmotility	0 (0%)
Pulmonary vein stenosis	0 (0%)
Phrenic nerve injury (persistent) ^c	0 (0%)
Pericardial tamponade ^b	63 (0.36%)
Percutaneous intervention	56 (0.32%)
Surgical intervention ^b	7 (0.04%)
Vascular complication (with intervention)	53 (0.30%)
Coronary artery spasm	25 (0.14%)
Myocardial infarction	0 (0.0%)
Hemolysis renal failure (hospitalization)	5 (0.03%)
Other (thrombosis)	1 (0.006%)
Minor AEs	567 (3.21%)
Transient ischemic attack	21 (0.12%)
Phrenic nerve injury (transient) ^c	11 (0.06%)
Pericardial effusion (no intervention)	59 (0.33%)
Pericarditis	30 (0.17%)
Vascular complications (no intervention)	388 (2.20%)
Hemolysis renal failure (no hospitalization)	1 (0.006%)
Other complications	57 (0.32%)

^aThe initial 1,758 patients treated in 2021 (and previously reported in the MANIFEST-PF survey) are excluded from this analysis. ^bOne patient requiring surgical intervention for tamponade subsequently died and is thus counted in both categories. ^cPersistent injury is defined as being present after hospital discharge, while transient injury is defined as having recovered by the time of discharge. Overall major and minor event rates have been highlighted in bold.

Stroke. Stroke occurred in 22 patients (0.12%). In a root cause analysis including 16 of these patients, the most common putative cause was catheter exchanges/sheath management in 4 cases (Extended Data Table 3). Other putative contributory causes were an activated clotting time (ACT) <300 and interruption of anticoagulation in each of two patients, and uncontrolled hypertension in one patient. No definitive cause was identified in seven cases. None of these strokes culminated in death.

In a subset of the MANIFEST-17K cohort, 96 patients at eight clinical sites underwent routine post-procedural brain magnetic resonance imaging (MRI) to assess for asymptomatic lesions. Such asymptomatic MRI abnormalities were observed in nine patients (9.4%).

Vascular complications. Vascular complications occurred in 2.5% of patients, with most being minor complications (2.2%) not requiring intervention (Table 2). As shown in Extended Data Table 4, the most commonly observed vascular complications were hematomas (1.84%). The cohort was stratified by centers that did versus did not routinely use ultrasound guidance for vascular access: 55 sites versus 48 sites, respectively (data on ultrasound usage were not reported by 3 sites). The sites routinely using ultrasound were more likely to be classified as academic (70.9% versus 52.1%, $P = 0.037$) and less likely to be private (5.5% versus 29.2%, $P = 0.0014$). The clinical site characteristics and baseline patient characteristics were similar between both groups,

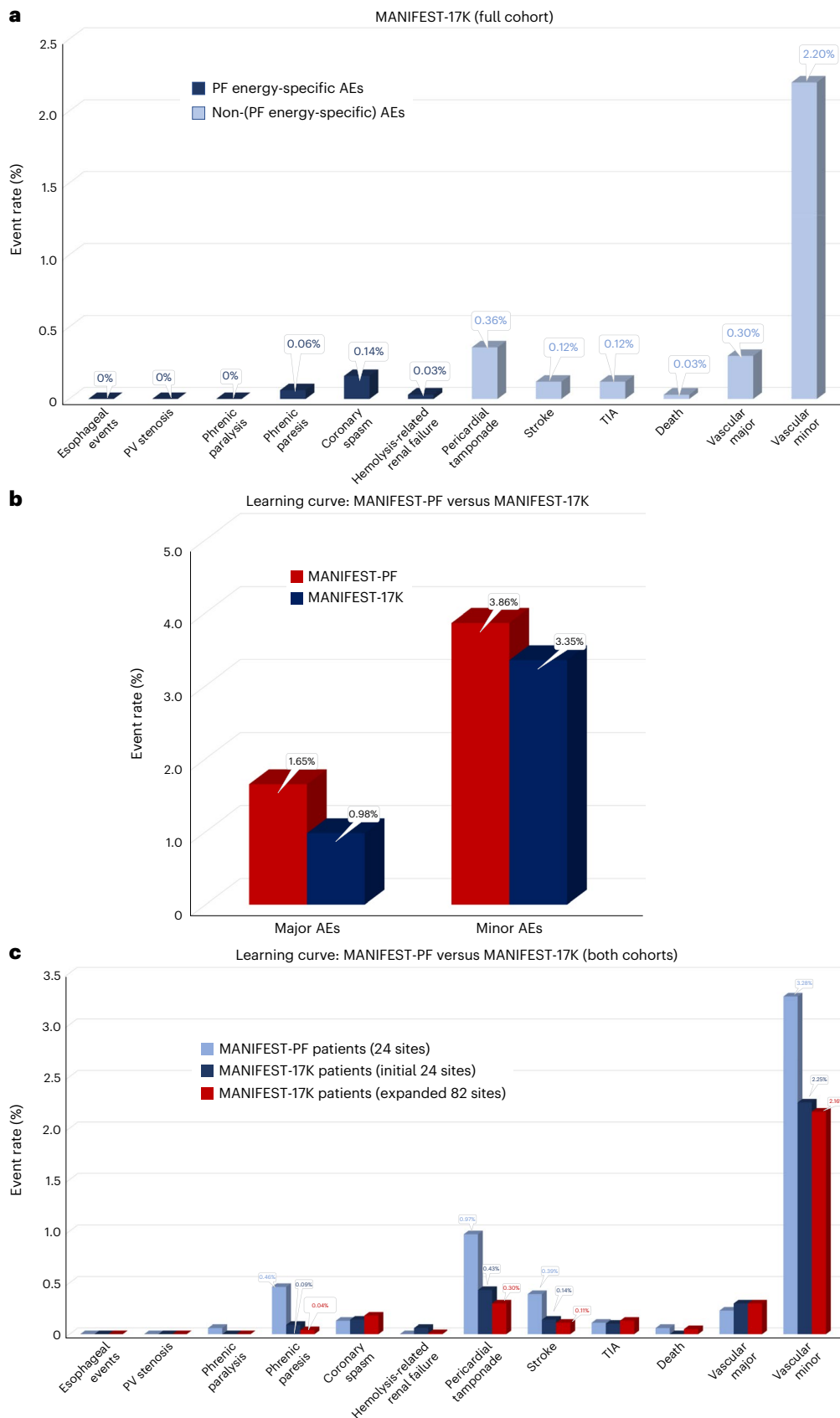


Fig. 2 | Complication rates. **a**, Shown are the rates of complications, partitioned by relationship to pulsed field energy. Dark blue, complications with some degree of specificity to the energy source; light blue, complications that are more general to catheter ablation procedures. **b**, Shown are aggregated major and minor AE rates as initially reported in the MANIFEST-PF cohort ($n = 1,758$ patients;

red bars) and observed in the currently studied MANIFEST-17K cohort ($n = 17,642$ patients; blue bars). **c**, Shown is a comparison of complication rates between those observed in the MANIFEST-PF cohort (light blue) as compared to both subcohorts of MANIFEST-17K. TIA, transient ischemic attack.

Table 3 | Coronary artery spasm

	Coronary spasm (N=25)
Type of spasm:	
Proximity-related spasm ^a	22 (88%)
Generalized spasm ^b	3 (12%)
EKG changes	23 (92%)
Hypotension	5 (20%)
Clinical sequelae	4 (16%)
Chest pain	2 (8%)
Ventricular fibrillation	2 (8%)
Intravenous nitroglycerin administered	21 (84%)

^aSpasm occurring during PFA adjacent to a coronary artery, either during mitral isthmus or CTI ablation. ^bSpasm occurring during conventional PV application remote from the location of a coronary artery.

including the number of PFA cases per site (182 (range 17–707) versus 151 (18–1,277), $P = 0.393$). However, the rate of major vascular complications was significantly higher in the group not routinely using ultrasound guidance (0.50% versus 0.17%, $P = 0.046$; Extended Data Table 4).

Mortality. The mortality rate was 0.03% ($n = 5$) in the MANIFEST-17K cohort. The available relevant details for each patient are listed in Extended Data Table 5. Briefly, two deaths were clearly procedure-related—a cardiac tamponade prompting emergent surgical repair but resulting in irreversible neurological damage and post-procedure cardiogenic shock in a patient with cardiomyopathy and decompensated heart failure. The remaining three deaths occurred at 3, 9 and 30 days post-ablation—two were sudden deaths that were unexplained or in the setting of severe coronary artery disease, respectively, and the last was a noncardiovascular death secondary to a brain hemorrhage.

Other complications. Complications categorized as ‘other’ occurred in 57 patients—0.32% of the full cohort. As shown in Table 4, the most common of these was the need for pacemaker implantation, occurring in 0.07% ($n = 12$), with lead dislocation or malfunction in another 0.02% ($n = 3$). Air emboli without clinical sequelae occurred in 0.06% ($n = 10$). Hemoptysis was noted in 0.02% ($n = 3$). Other notable unusual complications included individual cases of Takotsubo, Bell’s palsy and electrical isolation of the left atrial appendage (Extended Data Table 6).

Learning curve

The initial 24 sites included in the previously published MANIFEST-PF study were the first sites/operators to utilize PFA for AF ablation after regulatory approval in Europe. There was an overall decrease in the rate of AEs when comparing outcomes from the 1,758 patients from MANIFEST-PF versus these same sites’ experience with the subset of 7,878 patients treated by these sites in MANIFEST-17K. There were trends for reduced rates of both major (1.65% versus 0.98%, $P = 0.193$) and minor (3.86% versus 3.35%, $P = 0.266$) AEs (Fig. 2b). As shown in Fig. 2c and Extended Data Table 6, there were numerical reductions in the rates of cardiac tamponade (0.97% versus 0.43%, $P = 0.093$) and minor vascular complications (3.28% versus 2.25%, $P = 0.326$). There were also numerical reductions in the rates of stroke (0.39% versus 0.14%, $P = 0.387$), transient phrenic nerve paresis (0.46% versus 0.09%, $P = 0.344$) and mortality (0.06% versus 0%, $P = 0.323$), although these did not reach statistical significance. The rate of major vascular complications was not different (0.23% versus 0.30%, $P = 0.592$).

In addition to the site-level learning observed at these 24 sites, there was also evidence of community-level global learning: when the AE rates of the initial MANIFEST-PF sites were compared to the

Table 4 | Other complications

	Other complications N=57 (0.32%)
Pacemaker implant	12 (0.07%)
Air emboli	10 (0.06%)
Lead malfunction/dislocation	3 (0.02%)
Atrioventricular block	3 (0.02%)
Migraine	3 (0.02%)
Hemoptysis	3 (0.02%)
Anesthesia-related hypotension	2 (0.01%)
Heart failure	2 (0.01%)
Pneumonia	2 (0.01%)
Gastritis	2 (0.01%)
Miscellaneous	15 (0.09%)

expanded MANIFEST-17K sites, there was no significant difference in complication rates (Extended Data Fig. 2). Interestingly, all five deaths in this study occurred in the expanded MANIFEST-17K cohort, while all five cases of hemolysis with renal failure occurred in the initial MANIFEST-PF cohort.

Discussion

The MANIFEST-17K registry is a multicenter multinational study including 17,642 consecutive unselected AF patients undergoing post-approval PFA with a pentaspline catheter in routine clinical practice. Patients were treated at 106 clinical sites—representing >90% of all centers employing this PFA catheter. The major findings are: (1) there were no esophageal complications, symptomatic PV stenoses or persistent phrenic nerve injury, demonstrating the tissue preferentiality of PFA; (2) the overall rate of non-PFA energy-specific AEs was low, including a major complication rate of 0.98%—primarily pericardial tamponade and vascular complications—and a minor complication rate of 3.21%—primarily of vascular etiology; (3) coronary spasm occurred in 0.14%, primarily proximity-related vasospasm (0.12%), and to a lesser extent, generalized vasospasm (0.02%) during PVI; (4) there was an unexpected finding of hemolysis with associated acute renal failure requiring temporary hemodialysis in five patients (0.03%), although all patients recovered without sequelae; (5) the overall mortality rate was low at 0.03%; and (6) there was evidence of both center-level and global community-level learning with reduced rates of key AEs in the MANIFEST-17K cohort as compared to the previously published MANIFEST-PF cohort.

PFA is being utilized across the spectrum of AF, mostly paroxysmal AF (57.8%), but also persistent AF (35.2%). This is unsurprising given the success of PVI alone in many patients with persistent AF, and especially since posterior wall ablation is relatively easy to perform with PFA. PFA utilization spanned all practice settings, mostly academic centers (61.3%). Patient demographics, average age of 64 (11–96) and 34% female were consistent with routine clinical practice.

For procedural workflow, it is interesting that the use of deep sedation without endotracheal intubation and general anesthesia with intubation was relatively evenly split, slightly in favor of the former: 56.1% versus 43.9%, respectively. In the initial MANIFEST-PF survey, the majority of cases (82.1%) were performed without endotracheal intubation. The reason for this variance is unclear, but perhaps related to better access to anesthesia services, or a desire to minimize diaphragmatic stimulation and cough.

The cohort enrolled in this study, namely 17,642 patients, represents the largest PFA study so far. In this real-world cohort, preferentiality to tissue ablation was demonstrated for PFA, including no esophageal complications, PV stenosis or persistent phrenic nerve

injury. This is consistent with prior pre-clinical, observational and randomized clinical studies.

Pre-clinical studies demonstrated the esophageal sparing properties of PFA. In an open chest porcine model, PFA application (200 J) directly atop the esophagus resulted in only intraepithelial vesicles being noted in the esophageal adventitia on day 2, with complete normalization by day 7 (ref. 13). In another porcine model, which better approximated the clinical situation, the esophagus was mechanically apposed against the inferior vena cava, from which either radiofrequency ablation (RFA) or PFA was performed. PFA revealed no chronic histopathological esophageal changes, while RFA demonstrated the full spectrum of esophageal injury including deep ulcers, abscesses and fistula formation¹⁵.

The initial clinical experience, including the initial MANIFEST-PF survey of >1,700 patients, also revealed no esophageal complications. Although promising, cryoballoon ablation was also initially thought to not result in esophageal complications; however, this was proven untrue after a few thousand patients were treated^{24–26}. In the POTTER-AF worldwide survey including 553,729 procedures, the incidence of esophageal fistula was 0.025% (RFA, 0.038% (1 in 2,600) and cryoablation, 0.0015% (1 in 66,000)), with an associated mortality rate of 65.8% (ref. 8). In this context, it is striking that in the present MANIFEST-17K cohort of >17,000 patients, with no esophageal management strategy employed during procedures, no esophageal complications were observed. These data are entirely consistent with a post-ablation chest MRI study of patients undergoing either PFA ($n = 18$) or thermal ablation ($n = 23$; radiofrequency or cryoballoon) for AF; acute esophageal lesions were observed in 43% of thermal cases, but none with PFA¹⁶.

Interestingly, at one center, routine post-procedural esophago-gastroduodenoscopy was performed in all patients ($n = 29$) undergoing PFA ablation. Imaging identified four cases of esophageal wall edema. However, there was no evidence of ulceration or gastric dysmotility, and no clinical symptoms were reported.

In pre-clinical studies of phrenic nerve injury, only transient (recovering in 30 min) phrenic nerve palsy was observed^{14,28,29}. There were no histological changes suggestive of nerve injury. In the MANIFEST-PF registry of 1,568 patients, only 1 patient (0.06%) sustained phrenic nerve injury persisting beyond 1 year²¹. In the randomized ADVENT trial, persistent phrenic nerve injury was observed in 2 of 302 thermal ablation patients (0.7%), as opposed to 0 of 305 PFA patients.

In the present MANIFEST-17K cohort of >17,000 patients, there were no instances of persistent phrenic nerve injury and only 11 cases (0.06%) of transient phrenic nerve injury recovering within a few minutes or by the next day, with the latter nominally less frequently observed than in the initial MANIFEST-PF study (0.46%; $P = 0.29$). It has been postulated that transient phrenic nerve paresis may represent electrical hyperpolarization due to its rapid recovery. Nonetheless, care should be taken to limit excessive PFA in proximity to the phrenic nerve, and routine monitoring of post-PFA diaphragmatic function should be considered.

There were no reported cases of PV stenosis in this MANIFEST-17K cohort. Importantly, this is in the context of a large number of operators ($n = 413$) with varying experience (average 13.6 years, range 3–25 years). Notably, this potential complication was not prospectively defined and routine post-ablation PV imaging was not performed. However, these findings are in line with prior pre-clinical and clinical studies, including a nonrandomized comparison of RFA to PFA: neither PV stenosis nor even PV narrowing was present with PFA, whereas PV stenosis/narrowing was present in 32.5% of patients with RFA³⁰. In the randomized ADVENT trial, there was a significant average decrease in the change in PV cross-sectional area 3 months post-ablation with thermal ablation (12.0%) versus no significant decrease with PFA (0.9%; posterior probability of superiority of PFA >99.9%)²³.

There were 25 cases (0.14%) of coronary spasm: (1) most were proximity-related ($n = 23$, 88%), that is, occurring during PFA adjacent

to a coronary artery during mitral isthmus or CTI ablation, and (2) the remaining ($n = 3$, 12%) were generalized spasm. The latter represent the Prinzmetal's type of spasm occurring after ablation anywhere within the LA. Three cases of proximity-related spasm occurred while intending to perform PFA of the left inferior PV, but fluoroscopy review revealed inadvertent anterior positioning of the pentaspine catheter in flower pose toward the mitral isthmus. Of the 25 cases of spasm, 2 (8%) culminated in ventricular fibrillation; both patients required resuscitation and nitroglycerin administration; however, both patients recovered.

Coronary spasm during AF ablation, although rare, has even been reported with RFA in proximity to the coronary arteries^{31,32}. The increased depth of the electric field generated during PFA may increase this likelihood. Indeed, upon routine post-PFA coronary angiography, PFA at the CTI or mitral isthmus results in frequent subclinical coronary vasospasm^{33,34}. And there have been case reports of patients manifesting clinical spasm^{35,36}. Importantly, spasm is attenuated by pre-administration of intracoronary or intravenous nitroglycerin^{33,34}. The possibility of ventricular fibrillation, although infrequent, suggests that nitroglycerin should be considered before PFA in proximity to coronary arteries.

Most intriguing are the cases of generalized spasm following PFA at locations remote from the coronary arteries. This appears to be a sympathetic/autonomic response to energy delivery, and is not unique to PFA. Indeed, in a meta-analysis of >22,000 Japanese patients, generalized coronary vasospasm during PVI occurred with both cryoablation (0.27%) and RFA (0.04%) at rates similar to that presently observed with PFA (0.017%; 3 of 17,640)³⁷. Proceduralists must be aware of this rare complication as timely intervention is crucial in this circumstance.

An unexpected finding was hemolysis-related renal failure, which occurred in five patients (0.03%). Symptoms were reported either immediately post-procedure or by the next day, with rapid progression of oliguria or anuria, requiring dialysis for normalization in renal function. One or more factors additional to the higher number of PFA applications may have contributed, including dehydration, relative hypotension due to general anesthesia, contrast computed tomography on the day of procedure and some degree of pre-existing kidney disease. With thermal ablation, hemolysis-related renal failure is an extremely rare finding. In the surgical literature, an increased risk of acute kidney injury with concomitant surgical AF ablation has been reported, but the pathophysiology may not be the same²⁷.

The mechanism of hemolysis is probably related to the electroporative effects on erythrocytes. Foundational experiments had demonstrated voltage-induced pore formation in human erythrocytes during therapeutic PFA applications³⁸. Using clinical defibrillators, when a homogeneous electrical field (field strength of 1,700 V cm⁻¹ as single or double monopolar or bipolar pulses) was applied to a human erythrocyte suspension, hemolysis occurred in a dose-dependent fashion³⁹, and of course, the renal toxic effect of sudden high concentrations of globular hemoproteins is well appreciated (for example, myoglobinuria from rhabdomyolysis after traumatic crush injury to an extremity). In fact, there are probably more instances of under-recognized hemolysis not resulting in renal failure.

Given this putative mechanism, it is not surprising that all five patients received more complex lesion sets than simple PVI, with a mean of 143 PFA applications per patient; indeed two patients received 159 PFA applications. For context, in the PFA for persistent AF ablation (PersAFOne) trial, wherein patients underwent PVI, posterior wall isolation and CTI, an average of 46 PF lesions were applied per patient¹⁹. In a real-world retrospective analysis of 45 patients undergoing PVI, posterior wall ablation and mitral isthmus ablation, a total of 85 ± 23 PFA applications/patient were employed⁴⁰. It seems likely that the risk of hemolysis is dose-dependent. Accordingly, it is prudent to moderate the number of PFA applications, and when a large number

of PFA applications is necessary, one should consider applying simple mitigation strategies such as saline hydration.

The major complication rate was low at ~1% and primarily consisted of pericardial tamponade (0.36%), stroke (0.12%), and vascular complications (0.30%), with a procedural mortality rate of only 0.03%. Considering the novelty of the technology, diversity of operators, and the first utilization by most operators, these rates are consistent with an excellent safety profile. For comparison, in a large US registry of AF ablation between 2000 and 2010 including >90,000 patients, the rate of pericardial complications was 1.52%, stroke was 1.02% and mortality was 0.42% (refs. 10,41). Furthermore, all 24 sites who treated the initial 1,758 patients in the MANIFEST-PF safety study were also in MANIFEST-17K, and there was a striking learning curve observed with >50% reductions in arguably the two most important complications, namely pericardial tamponade (0.97% reduced to 0.43%) and stroke (0.39% reduced to 0.14%). Interestingly, these low complication rates were also observed in the remaining 82 expanded MANIFEST-17K sites, namely pericardial tamponade (0.30%) and stroke (0.11%); this is indicative that the learnings from the initial MANIFEST-PF experience (in other words, careful catheter manipulation with utilization of a J-tip guidewire and careful sheath management with diligent saline flushing) were successfully elaborated to the full community. This bodes well for future sites commencing utilization of PFA.

Finally, it is notable that, in a small subset of the MANIFEST-17K cohort who underwent routine post-procedural brain MRI, asymptomatic abnormalities were observed in only 9 of 96 patients (9.4%). Their clinical significance remains unclear, as asymptomatic MRI-detected brain lesions are commonly seen after conventional AF ablation and other interventional cardiac procedures and more recently with another PFA ablation catheter^{42–44}. Indeed, this incidence compares favorably with the 26.1% rate of silent cerebral ischemic events observed during routine brain MRI in 321 patients undergoing RF or cryoballoon ablation in the prospective multicenter AXAFA-AFNET5 trial (anticoagulation using the direct factor Xa inhibitor apixaban during atrial fibrillation catheter ablation: comparison to vitamin K antagonist therapy)⁴⁵

MANIFEST-17K is limited by being a retrospective observational study of center-level data without prospectively defined safety outcomes. However, most centers maintained a PFA registry from which the data were extracted, and the near-universal engagement of the centers for data acquisition (91.4% overall participation), the breadth of AEs reported and the sheer scale of PFA cases included (representing almost all post approval PFA cases for AF) extends credibility to the study. Second, it is possible that additional patients may have sustained subclinical events; examples include esophageal lesions that healed without symptomatology, asymptomatic PV stenosis, asymptomatic cerebral lesions, subclinical coronary spasm, hemolysis causing mild reversible renal dysfunction, and so on. Third, in the cases of suspected vasospasm, actual spasm was not always observed, probably because of both prompt nitroglycerin administration and the time delay to angiography; thus, clinical determination of spasm was based on a number of factors (for example, proximity of PFA location to a coronary artery, distribution of ST elevation, temporal response to nitroglycerin and so on). Fourth, while MANIFEST-17K included >400 operators at 106 sites, of which 38.7% were private practice and hybrid institutions, it is possible that this cohort of operators is enriched for greater expertise; accordingly, the favorable safety profile may not directly translate to all other centers. Finally, this study is focused on the pentaspline PFA catheter; because of potential variability between PFA technologies, the safety observed in this study should not be assumed for other PFA catheters.

In conclusion, this is the largest registry of the safety of the post-approval use of a PFA catheter for the treatment of AF. In a 'real-world' setting of an unselected AF patient population, PFA demonstrated a safety profile consistent with an important degree of preferentiality to myocardial tissue ablation, with no evidence of

esophageal complications, and with a low rate of major complications. Hemolysis-related renal failure requiring hemodialysis did occur, albeit rarely. Finally, the low incidence of coronary arterial spasm belies its potentially serious implications and warrants further study and guidance.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-024-03114-3>.

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Methods

Survey overview

The MANIFEST-17K study is a retrospective observational study of centers performing PFA after regulatory approval of the pentaspline PFA catheter (Farawe, Farapulse-Boston Scientific Inc). The data form was developed by two of the authors (E.E. and V.R.) with the goal of collecting comprehensive data on the methods and safety of the post-approval clinical use of PFA (Online Supplement, case report form pages 7–9). MANIFEST-17K was approved by the Homolka hospital ethical committee (6.4.2022/18). The requirement of informed consent was waived by the ethical committee given the retrospective nature of the study.

An invitation to participate in the MANIFEST-17K study was sent to all 116 centers performing clinical cases with this PFA catheter since commercialization. All centers who accepted the invitation were sent the comprehensive data form. Institution-level data were obtained on center characteristics, limited patient baseline characteristics, limited procedure parameters and all AEs. Additional root cause analysis data were obtained for specific AEs. Data were typically collected from each center's institution-level ablation database when available. All data forms were provided with the condition of anonymity of the identity of the physicians and institutions. Of note, we excluded from this analysis the initial 1,758 patients treated in 2021 by the initial 24 centers (herein referred to as the 'initial MANIFEST-PF sites') and previously reported in the MANIFEST-PF survey (the 'MANIFEST-PF cohort'). Thus, the patients included in this study include those patients treated after 2021 from the initial MANIFEST-PF sites plus all patients treated by newer sites not initially participating in MANIFEST-PF (the 'expanded MANIFEST-17K sites').

The PFA procedure

The PFA system has been previously described; per manufacturer protocol, physicians were trained to employ a standard protocol^{17–19}. Briefly, the 12F over-the-wire pentaspline PFA catheter (Farawe) is advanced through a 13F steerable sheath (Faradrive; Farapulse-Boston Scientific) into the LA. After positioning either a straight- or J-tip 0.035 guidewire into each target PV, the PFA catheter is positioned at the ostium of each PV and a total of eight PF lesions are applied per vein: four each in 'basket' and 'flower' configurations, with rotation between each pair of lesions. For posterior LA wall ablation, the catheter was placed into a flower configuration and positioned along the posterior LA to deliver overlapping sets of pulses at each location. The PF voltage amplitude could range between 1.8 and 2.0 kV, but 2.0 kV was typically employed. Unlike thermal ablation where one typically employs esophageal mitigation strategies (such as reduced ablation energy application along the posterior LA, esophageal temperature monitoring, esophageal cooling or mechanical esophageal deviation), no esophageal management strategy was employed during the PFA procedures.

Study data specifics

The data form was composed of questions covering the following areas: geographic region, clinical site characteristics, baseline patient characteristics, procedural parameters and AEs (Online Supplement, case report form pages 7–9). Major complications were defined as death, stroke, esophageal fistula or dysmotility, PV stenosis, phrenic nerve injury (persistent), pericardial tamponade, vascular complications requiring intervention, coronary spasm, myocardial infarction, hemolysis with resultant renal failure requiring hospitalization/dialysis, and thrombosis. If a major AE was identified (specifically stroke and coronary spasm) a root cause analysis form or AE detail form, respectively, was sent to the clinical site. The root cause analysis collected information on the event details, the physician's hypothesis as to the most likely etiology and recommendations to prevent future complications. Minor complications were defined as transient ischemic attack,

phrenic nerve injury (transient), pericardial effusion (no intervention), vascular complications (no intervention), hemolysis not requiring hospitalization and others.

Data analysis

The survey data form was considered complete if at least 80% of the questions were answered. In actuality, >95% of the forms were 100% completed. Importantly, the missing data were limited to the baseline patient demographics; there was no missingness in the reported safety outcomes.

Descriptive statistics were employed to analyze outcomes. Continuous variables were presented as means with minimum and maximum values provided. Continuous variables were compared using either the unpaired Student's *t*-test (normal distribution) or Mann–Whitney *U* test (skewed distribution). Categorical variables were presented as counts or percentages and comparative analysis performed using the chi-squared or Fisher exact test. A two-tailed *P* value <0.05 was considered statistically significant. All analyses were performed using SPSS software (IBM Corp) version 29.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Data can be made available upon reasonable request as part of a scientific collaboration with adherence to standards of good scientific practice. Restrictions may apply due to privacy reasons, scale of contributors and ongoing research projects. Requests should be sent to the corresponding author, and a period of 90 days should be expected for a response.

Author contributions

E.E. and V.Y.R. designed, conducted and analyzed the study, and prepared the manuscript. All authors were study investigators and contributed to data acquisition and interpretation, review, revisions and final approval of the manuscript.

Competing interests

E.E. received speaker honorarium from Boston Scientific and travel grants from Abbott and Biotronik. V.Y.R. has served as a consultant to Boston Scientific and formerly owned stock options in Farapulse (now divested); unrelated to this manuscript, he serves as a consultant for and has equity in Ablacon, Acutus Medical, Affera-Medtronic, Apama Medical-Boston Scientific, Anumana, APN Health, Aquaheart, Atacor, Autonomix, Axon Therapies, Backbeat, BioSig, CardiaCare, CardioNXT/AFTx, Circa Scientific, CoRISMA, Corvia Medical, Dinova-Hangzhou DiNova EP Technology, East End Medical, EPD-Philips, EP Frontiers, Epix Therapeutics-Medtronic, EpiEP, Eximo, Field Medical, Focused Therapeutics, HRT, Intershunt, Javelin, Kardium, Keystone Heart, LuxMed, Medlumics, Middlepeak, Neutrace, Nuvera-Biosense Webster, Oracle Health, Restore Medical, Sirona Medical, SoundCath, Valcare; unrelated to this work, has served as a consultant for Abbott, AtriAN, Biosense Webster, BioTel Heart, Biotronik, Cairdac, Cardiofocus, Cardionomic, CoreMap, Fire1, Gore and Associates, Impulse Dynamics, Medtronic, Novartis, Philips, Pulse Biosciences; and has equity in DRS Vascular, Manual Surgical Sciences, Newpace, Nyra Medical, Surecor and Vizarmed. T.R. has received research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the sitem insel support funds, Boston-Scientific, Medtronic and Biotronik. He has received speaker/consulting honoraria or travel support from Abbott/SJM, Biosense Webster, Biotronik, Boston-Scientific and Medtronic, and support for the institution's fellowship program from Abbott/SJM, Biosense Webster, Biotronik, Boston-Scientific and Medtronic.

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Additional information

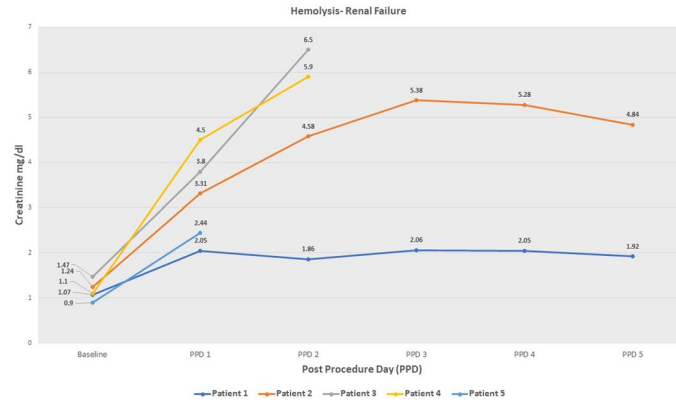
Extended data is available for this paper at <https://doi.org/10.1038/s41591-024-03114-3>.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41591-024-03114-3>.

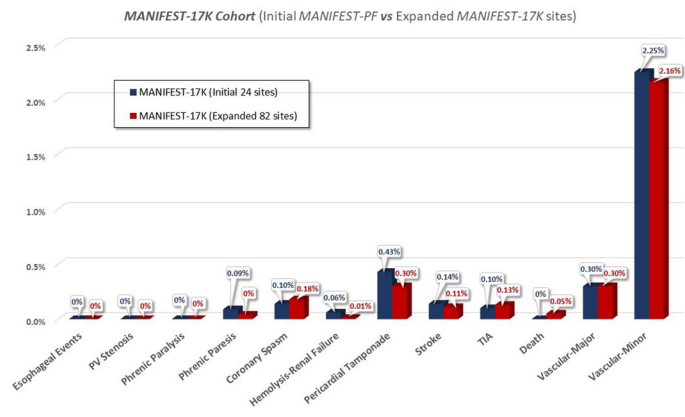
Correspondence and requests for materials should be addressed to Vivek Y. Reddy.

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Extended Data Fig. 1 | Hemolysis-Renal Failure. Shown are the creatinine trends for the five patients with hemolysis related renal failure.



Extended Data Fig. 2 | MANIFEST-17K Cohort (Initial MANIFEST-PF vs Expanded MANIFEST-17K sites).

Extended Data Table 1 | Clinical Site Characteristics

	Full Patient Cohort from All <i>MANIFEST-17K</i> Sites* 106 Sites (N=17,642)	Patients from Initial <i>MANIFEST-PF</i> Sites* 24 Sites (N=7,878)	Patients from Expanded <i>MANIFEST-17K</i> Sites* 82 Sites (N=9,764)
Practice type			
Academic (%)	61.3	62.5	61
Private (%)	17	12.5	18.3
Hybrid (%)	21.7	25	20.7
No. of operators, mean (min-max)	3.9 (1-11)	5 (2-10)	3.6 (1-11)
Years in practice, mean (min-max)	13.6 (3-25)	12.2 (5-25)	14 (3-25)
Annual no. of AF ablations, mean (min-max)	519 (80-2000)	801 (200-2000)	436 (80-1200)
Date of first PFA case, (earliest-latest)	5/2022 (3/2021-3/2023)	6/2021 (3/2021-12/2021)	8/2022 (11/2021-3/2023)
No. of PFA cases performed, mean (min-max)	166 (17-1277)	328 (54-1277)	119 (17-472)

PFA, Pulsed field ablation

Extended Data Table 2 | Hemolysis-Related Acute Renal Failure: Patient Details

	Baseline Creatinine	Narrative Summary
Patient #1	Cr 1.07 mg/dl	Patient is a 59-year-old male with history of persistent AF with prior radiofrequency ablation who underwent repeat ablation. The lesion set performed included pulmonary vein isolation, posterior wall isolation and mitral isthmus line. A total of 159 PFA applications were delivered. Nausea, vomiting and hematuria were noted post procedure. Creatinine increased to 2.05 mg/dl by PPD 1 requiring hemodialysis. He was discharged PPD 5 with a creatinine level of 1.92 mg/dl.
Patient #2	Cr 1.24 mg/dl	Patient is a 73-year-old male with a history of persistent AF and prior ablation who underwent repeat ablation. The lesion set performed included pulmonary vein isolation, posterior wall isolation, mitral isthmus line and cavotricuspid isthmus line. A total of 159 PFA applications were delivered. He reported nausea and hematuria was noted PPD 1. Creatinine increased to 3.31 mg/dl by PPD1 and peaked at 5.38 mg/dl requiring hemodialysis. He was discharged PPD 7 with a creatine level of 3.89 mg/dl
Patient #3	Cr 1.47 mg/dl	Patient is a 79-year-old female with known renal dysfunction (proteinuria and erythrocyturia), heart failure with preserved ejection fraction, persistent AF who underwent ablation. A total of 158 PFA applications were delivered (lesion sets not detailed). She was noted to have hematuria and oliguria on the same day of the procedure. Creatinine increased to 3.8 mg/dl on PPD 1 and peaked at 6.5 mg/dl before hemodialysis (2 sessions) was instituted. Renal function eventually normalized prior to discharge.
Patient #4	Cr 1.1 mg/dl	Patient is a 65-year-old male with history of hypertension, diabetes mellitus, peripheral artery disease, cirrhosis, persistent AF who underwent ablation. The lesion set performed included pulmonary vein isolation, posterior wall isolation, and mitral isthmus line. A total of 96 PFA applications were delivered. He was noted to have hematuria and anuria on the day of the procedure. Creatinine increased to 4.5 mg/dl on PPD 1 and peaked at 5.9 mg/dl before hemodialysis (3 sessions) was instituted. Renal function eventually normalized prior to discharge.
Patient #5	Cr 0.9 mg/dl	Patient is a 69-year-old female with a history of tachycardia induced cardiomyopathy (EF 35-50%), hepatopathy, persistent AF who underwent ablation. The lesion set performed included pulmonary vein isolation, posterior wall isolation and mitral isthmus line. A total of 144 PFA applications were delivered. She was noted to have hematuria and anuria on the day of the procedure. Creatinine increased to 2.44 mg/dl on PPD 1 and peaked at 2.44 mg/dl before hemodialysis (2 sessions) was instituted. Renal function normalized prior to discharge and remained stable at 6-month follow up with normalization of left ventricular function.

Extended Data Table 3 | Root Cause Analysis of Stroke Events

	Root Cause Analysis - Stroke N = 16
No definitive cause	7
Catheter exchanges/Sheath management	4
ACT < 300	2
Interruption of anticoagulation	2
Uncontrolled Hypertension	1

Extended Data Table 4 | Vascular Complications as a Function of Routine Vascular Ultrasound Usage

	Full Cohort* 106 Sites (N=17,642)	Routine Ultrasound Use 55 Sites (N=10,029)	Not Routine Ultrasound Use 48 sites (7,177)
Baseline Patient characteristics			
Age (years), Mean (min-max)	64.1 (11-96)	64.5 (11-96)	63.4 (20-96)
Female (%)	34.6	34.1	35.4
Total vascular complications			
Hematoma	441 (2.50)	246 (2.45)	195 (2.72)
Pseudoaneurysm	324 (1.84)	193 (1.92)	131 (1.83)
AV fistula	58 (0.33)	28 (0.28)	30 (0.42)
Other	46 (0.26)	19 (0.19)	27 (0.38)
Major (requiring intervention)	13 (0.07)	6 (0.06)	7 (0.10)
Minor (no intervention)	53 (0.30)	17 (0.17) *	36 (0.50) *
	388 (2.20)	229 (2.28)	159 (2.22)
Clinical Site Characteristics			
Practice type			
Academic (%)	61.4	70.9	52.1
Private (%)	17.8	5.5	29.2
Hybrid (%)	20.8	23.6	18.8
No. of operators, mean (min-max)	3.8 (1-11)	4 (1-11)	3.5 (1-9)
Years in practice, mean (min-max)	13.5 (3-25)	12.7 (3-25)	14.6 (5.2-25)
Annual no. of AF ablations, mean (min-max)	528 (80-2000)	546 (80-1400)	516 (100-2000)
No. of PFA cases performed, mean (min-max)	167 (17-1277)	182 (17-707)	151 (18-1277)

*Statistically significant (p value = 0.046, 95% CI 0.0000497 – 0.0057194, Two tailed independent T test)

Extended Data Table 5 | Details of Patient Deaths

	Timing of Death Post-Ablation	Cause of Death	Narrative Summary
Patient #1	9 days	Unexplained Sudden Death	Unremarkable ablation procedure, but followed by unexplained death 9 days post-procedure. Autopsy failed to reveal any specific cause of death.
Patient #2	1 week	Cardiac Tamponade	75-year-old man with ablation complicated by perforation and cardiac tamponade. Pericardiocentesis was unsuccessful, and thus requiring emergent surgical sternotomy. However, patient suffered irreversible brain damage and died 1 week later.
Patient #3	8 hours	Decompensated Heart Failure	84-year-old man with tachycardia induced cardiomyopathy and admission 1 week pre-ablation for decompensated heart failure. After 2 failed cardioversions, patient underwent PFA: pulmonary vein isolation and mitral isthmus line. Procedure was unremarkable – only transient intra-procedural hypotension. But, cardiogenic shock ensued 2 hours post-procedure necessitating mechanical circulatory support. There was no pericardial effusion, other bleeding, or acute coronary syndrome. Mechanical circulatory support was eventually discontinued, and patient died. Autopsy findings were unremarkable, and death was attributed to severe LV failure.
Patient #4	3 days	Cardiac Arrest (in setting of severe CAD)	62-year-old man with chronic kidney disease and multivessel coronary artery disease (prior stent), and preserved LV function. PFA unremarkable, and patient was discharged home. Two days later, patient developed chest pain and dizziness at home and collapsed. ACLS instituted by emergency personnel within 6 min of symptoms – initial rhythm was asystole, but spontaneous circulation returned. Upon arrival to hospital, ventricular fibrillation occurred, prompting ACLS measures. Extracorporeal membrane oxygenation was instituted. Coronary angiography revealed no acute lesions. Pulmonary angiography revealed no pulmonary embolism, and no pericardial effusion by echocardiography. He had continued hemodynamic instability, poor neurological recovery and died 24 hours later.
Patient #5	30 days	Cerebellar Hemorrhage	60-year-old man underwent an uncomplicated ablation procedure, but he developed headache 8 days post-procedure and rapidly became unconscious. He died 30 days after ablation. Autopsy revealed massive cerebellar hemorrhage.

Extended Data Table 6 | Complications in Both Cohorts – Initial *MANIFEST-PF* Sites vs Expanded *MANIFEST-17K* Sites

	Full Patient Cohort from All <i>MANIFEST-17K</i> Sites * 106 Sites (N=17,642)	Patients from Initial <i>MANIFEST-PF</i> Sites * 24 Sites (N=7,878)	Patients from Expanded <i>MANIFEST-17K</i> Sites * 82 Sites (N=9,764)
Major Adverse Events	173 (0.98%)	82 (1.04%)	91 (0.93%)
Death	5 (0.03) †	0 (0)	5 (0.05) †
Stroke	22 (0.12)	11 (0.14)	11 (0.11)
Esophageal fistula or dysmotility	0 (0)	0 (0)	0 (0)
Pulmonary vein stenosis	0 (0)	0 (0)	0 (0)
Phrenic nerve injury (persistent)	0 (0) ‡	0 (0) ‡	0 (0) ‡
Pericardial tamponade	63 (0.36) †	34 (0.43)	29 (0.30) †
Percutaneous intervention	56 (0.32)	30 (0.38)	26 (0.27)
Surgical intervention	7 (0.04) †	4 (0.05)	3 (0.03) †
Vascular complication (with intervention)	53 (0.30)	24 (0.30)	29 (0.30)
Coronary artery spasm	25 (0.14)	8 (0.10)	17 (0.17)
Myocardial Infarction	0 (0)	0 (0)	0 (0)
Hemolysis-Renal Failure (hospitalization)	5 (0.03)	5 (0.06)	0 (0)
Other (thrombosis)	1 (0.006)	0 (0)	1 (0.01)
Minor Adverse Events	567 (3.21%)	264 (3.35%)	303 (3.10%)
Transient Ischemic Attack	21 (0.12)	8 (0.10)	13 (0.13)
Phrenic nerve injury (transient)	11 (0.06) ‡	7 (0.09) ‡	4 (0.04) ‡
Pericardial effusion (no intervention)	59 (0.33)	24 (0.30)	35 (0.36)
Pericarditis	30 (0.17)	12 (0.15)	18 (0.18)
Vascular complications (no intervention)	388 (2.20)	177 (2.25)	211 (2.16)
Hemolysis-Renal Failure (no hospitalization)	1 (0.006)	0 (0)	1 (0.01)
Other complications	57 (0.32)	36 (0.46)	21 (0.21)

* The initial 1,758 patients treated in 2021 (and previously reported in the *MANIFEST-PF* survey) are excluded from this analysis.
† One patient requiring surgical intervention for tamponade subsequently died and is thus counted in both categories.
‡ Persistent injury is defined as being present after hospital discharge, while transient injury is defined as having recovered at the

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Reporting on sex and gender	Data on sex and gender was self reported prospectively and in accordance to Nature's guidelines
Reporting on race, ethnicity, or other socially relevant groupings	Data on race or ethnicity was not collected as part of this study
Population characteristics	There were a total of 17,642 patients, average age of 64 (range 11-96) and 34.7% female
Recruitment	This was a observational study of center level data. An invitation document was sent to each participating center via email.
Ethics oversight	This study was approved by the Ethical Committee at Homolka Hospital

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Life sciences study design

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Sample size	This was a retrospective observational study design and sample size calculation was not performed
Data exclusions	All data reported by participating centers was utilized
Replication	There was no data replication as this was a new study on a unique patient population not previously evaluated
Randomization	Given the retrospective nature of the study, prospective randomization was not performed
Blinding	Given the retrospective nature of the study studying the same intervention and no placebo, blinding was not deemed to be necessary for the study

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern
<input checked="" type="checkbox"/>	<input type="checkbox"/> Plants

Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.