MANIFEST-US Multicenter Registry

Multicenter study on the safety of pulsed field ablation in over 40,000 patients (MANIFEST-US)[1]

OBJECTIVE

- To evaluate the real-world use and safety profile of the FARAPULSE™ Pulsed Field Ablation System across clinical practices in the United States.

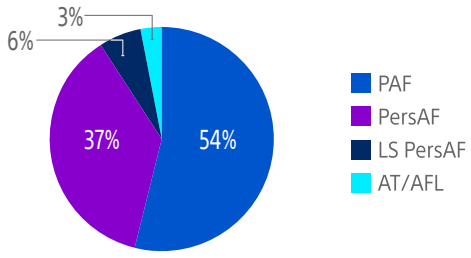
MANIFEST-US REGISTRY DESIGN

- Retrospective observational study of the real-world commercial use of the FARAPULSE™ Pulsed Field Ablation System (PFA) in the US.
- Center level data was collected on patient demographics, procedural details and adverse events from 102 centers and more than 500 operators with an average time in practice of 8.1 years (range 4-32).
- This registry included 41,968 patients. Each center treated a median of 412 patients (range 26-1961).
- The results from MANIFEST-US reflect FARAWAVE™ PFA Catheter use from February 2024 – July 2025.
- *This was an independent investigator sponsored study, not funded by Boston Scientific.*

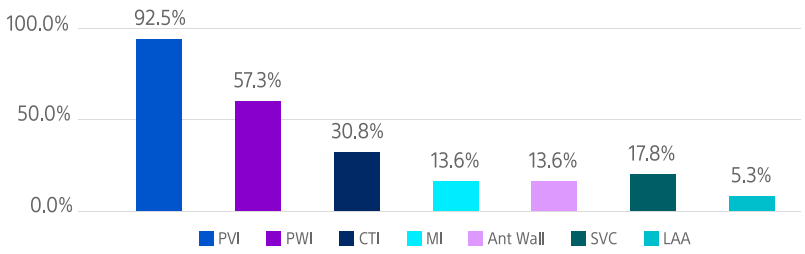
Data from 41,968 patients treated with FARAWAVE from February 2024 - July 2025

PROCEDURE CHARACTERISTICS

- Most patients were de novo AF patients, undergoing ablation for PAF (54.0%) or persAF (37.0%).



- PVI was performed in 93.0% of patients with additional lesion sets shown below.



- Electroanatomical mapping was utilized in 88.0% of cases. ICE was also used in 88.2% of cases. General anesthesia with endotracheal intubation was administered in 97.2% patients and 72.0% of patients were discharged the same day. Adjunctive use of thermal ablation was only done in 2.3% of patients.

SAFETY

- *Definition: Major complications were categorized as atrio-esophageal fistula, pulmonary vein stenosis, persistent phrenic nerve injury, pericardial tamponade, stroke within 7 days, vascular complications requiring intervention, coronary artery spasm, acute renal failure requiring dialysis, myocardial infarction within 30 days, or death within 30 days.*

MAJOR ADVERSE EVENTS*

- The major adverse event rate was 0.63%, with the majority of events being vascular access complications or pericardial tamponade.
- There were no reports of esophageal fistula, pulmonary vein stenosis or persistent phrenic nerve injury.
- Other major complications were rare and included stroke (0.1%), TIA (0.08%), hemolysis requiring hemodialysis (0.02%), coronary spasm (0.1%) and vascular access complications requiring intervention (0.18%).
- Safety event rates were consistent with the prior MANIFEST-17K[2] cohort with a slight improvement in major and minor adverse event rates in MANIFEST-US. Importantly, the registry included over twice the patient population and reinforced the favorable safety profile.

FARAPULSE is indicated for ablation of PV in patients with paroxysmal or persistent AF (Including PW). Safety and effectiveness has not been established outside of PV and PW.

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MAJOR ADVERSE EVENTS*

	MANIFEST-US (n=41,968)	MANIFEST-17K[2] (n= 17,642)
Major Adverse Events	261 (0.63%)	173 (0.98%)
Minor Adverse Events	859 (2.1%)	567 (3.21%)
Death	16 (0.04%)	5 (0.03%)
Stroke	40 (0.1%)	22 (0.12%)
Esophageal Fistula	0 (0)	0 (0)
Pulmonary Vein Stenosis	0 (0)	0 (0)
Persistent Phrenic Nerve Injury	0 (0)	0 (0)
Pericardial Tamponade	65 (0.16%)	63 (0.36%)
Vascular Complication (w/Intervention)	73 (0.18%)	53 (0.30%)
Coronary Artery Spasm	40 (0.1%)	25 (0.14%)
Hemolysis – Renal Failure	7 (0.02%) (dialysis)	5 (0.03%) (hospitalization)

0.63%
major adverse event rate in nearly **42,000** patients

* Due to the retrospective nature of the registry, the adverse event rate was not reported at a pre-specified timepoint.

MINOR ADVERSE EVENTS*

▶ The minor complication rate was 2.1% with a majority of events being vascular complications (0.96%) or pericarditis (0.52%).

	MANIFEST-US (n=41,968)
Minor Adverse Events	859 (2.1%)
Transient Ischemic Attack (within 7 days)	36 (0.08%)
Phrenic Nerve Palsy (Transient) †	5 (0.01%)
Pericardial Effusion (no intervention)	51 (0.12%)
Pericarditis	220 (0.52%)
Esophageal/Gastric Dysmotility	16 (0.04%)
Air Embolism	16 (0.04%)
Vascular Complication (No Intervention)	405 (0.96%)
Hematoma	293 (0.69%)
Pseudoaneurysm	68 (0.16%)
AV Fistula	8 (0.02%)
Other	36 (0.08%)
Other Complications	110 (0.26%)

2.1%
minor complication event rate

†Persistent injury is defined as being present beyond hospital discharge while transient injury has recovered before discharge.
*Due to the retrospective nature of the registry, the adverse event rate was not reported at a pre-specified timepoint.

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ADDITIONAL SAFETY ANALYSIS

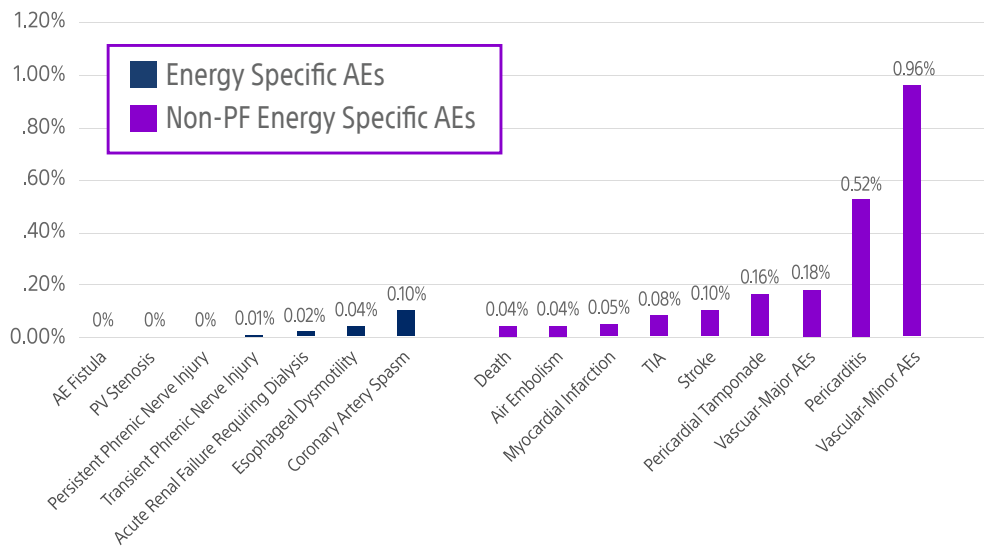
Sensitivity Analysis

- To evaluate potential response bias due to participation from only 23.4% of centers, a sensitivity analysis was conducted to estimate the national AE rate. This analysis assumed that non-responding centers observed a twofold higher AE rate compared to responding centers. Based on the estimated total of 178,981 patients treated across 405 centers, the resulting AE rates were 1.11% (major) and 3.71% (minor).

Adverse Event Relationship to Energy Source

- Adverse events were characterized by the relation or specificity to the PF energy source (PF energy-specific AEs) vs general ablation procedure complications (non-PF energy specific AEs).

Complication Rates by Relationship to Pulsed Field Energy



LOW RATE

PFA Energy Specific Complications

PFA Energy Specific Complications	
Phrenic Nerve Injury	• No persistent phrenic nerve injury was reported • At 3 centers, transient PN paresis was noted in 5 patients after SVC (n=3) or high right atrial ablation (n=1) • 4/5 resolved in 10 mins and the other within 24 hours without intervention
Acute Renal Failure Requiring Dialysis	• Observed in 7 male patients • Mean number of PFA applications was 67 ± 14 • 4 patients recovered and 3 died in the hospital secondary to stroke, tamponade or cardiogenic shock
Esophageal Complications	• No atrio-esophageal fistulas were reported • Esophageal or gastric dysmotility (muscular dysfunction – reported as heartburn, bloating, vomiting, dyspepsia) was reported in 16 patients (0.04%) • Transient in all patients, 14/16 reported at a single center • It is **NOT** the same as or indicative of atrio-esophageal fistula
Coronary Spasm	• Occurred in 40 patients **Proximity Related (PFA more susceptible, managed with prophylactic NTG)** • 30/40 (75.0%) were proximity related, 26/30 were CTI, 4 were MI • NTG was administered in 22/30 (200 mcg-3 mg) • 4/5 pts who received 2 or 3 mg had coronary artery disease • Clinical sequelae occurred in 5/30 (16.6%) pts

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ADDITIONAL SAFETY ANALYSIS

PFA Energy Specific Complications	
Coronary Spasm	**Generalized (not PFA specific)** • Suspected in the remaining 10 pts, 8 had ECG changes during the procedure and 2 occurred ~10 and ~45 min post-procedure • Clinical sequelae occurred in 7/10 (70.0%) pts, 4 of these pts were treated at a single center and were 1st generation immigrants of Marshallese descent

Non-PFA Specific Complications	
Mortality	• The 30-day mortality rate was 0.04% (n=16) • ½ of the deaths were explainable: 2 ischemic strokes, 2 hemorrhagic strokes and 1 tamponade, 1 sepsis, 1 retroperitoneal bleed and 1 cardiogenic shocked related to renal failure • ½ were unexplained sudden death or cardiac arrests occurring between 2-18 days post-ablation. The hypothesis is that these would be delayed generalized spasm (not PFA specific) • This rate compares favorably to thermal AF ablation studies (surveys, prospective registries and retrospective claims databases) with a median mortality rate of 0.13%

Stroke	• Occurred in 40 patients
	• Root cause analysis of 36 pts
	  • Interruption of anticoagulation was the most common cause (n=6)
	  • Air embolism related to sheath management (n=4)
	  • LAA isolation (n=2)
	  • No factor identified (n=22)

Other	• Occurred in 110 (0.26%) of patients • Most common was transient vagal mediated bradycardia/asystole (n=15) • No other unusual complications were reported

CONCLUSIONS

- This data strengthens the evidence supporting the strong safety profile of the FARAWAVE PFA Catheter by establishing a benchmark for large-scale transparent post-approval surveillance with nearly 60K patients in the MANIFEST-US and MANIFEST-17K registries.
- There was a low major adverse event rate (0.63%) driven mostly by non-PFA specific events.
- There were zero reported AE fistulas, PV stenosis or persistent phrenic nerve injury.
- Stroke (0.1%), TIA (0.08%), coronary spasm (0.1%) and hemolysis requiring hemodialysis (0.02%) were rare.
- The mortality rate was low and classified as a non-PFA specific AE, consistent with rates reported in existing cardiac ablation literature and the general population.
- Esophageal/gastric dysmotility occurred infrequently (0.04%), was transient in all patients, and primarily reported from a single center.
- The favorable safety profile demonstrated with FARAPULSE system in this, and other real-world registries are specific to this technology and should not be generalized to other PFA systems.

FARAPULSE™ Pulsed Field Ablation System
Indications, Safety, and Warnings

https://www.bostonscientific.com/en-US/products/catheters--ablation/farapulse/farapulse-indications.html

1. Turagam, Mohit K., et al. "Multicenter Study on the Safety of Pulsed Field Ablation in Over 40,000 Patients: MANIFEST-US." *JACC* (2025).
2. Ekanem, Emmanuel, et al. "Safety of pulsed field ablation in more than 17,000 patients with atrial fibrillation in the MANIFEST-17K study." *Nature medicine* 30.7 (2024): 2020-2029.

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Cardiology
300 Boston Scientific Way
Marlborough, MA 01752-1234
bostonscientific.com

Medical Professionals:
1.800.CARDIAC (227.3422)
Customer Service:
1.888.272.1001