Impact of Left Atrial Posterior Wall Ablation During Pulsed Field Ablation for Persistent Atrial Fibrillation: A *MANIFEST-PF* Registry Sub-Study

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ABSTRACT

Background: Pulmonary vein isolation (PVI) alone is insufficient to treat many patients with persistent atrial fibrillation (PerAF). Adjunctive left atrial posterior wall (LAPW) ablation with thermal technologies has revealed mixed results, perhaps limited by the difficulty in achieving lesion durability amid concerns of esophageal injury.

Objective: To compare the safety and effectiveness of PVI+ LAPW ablation *versus* PVI in patients with PerAF using pulsed-field ablation (PFA).

Methods: In a retrospective analysis of the *MANIFEST-PF* registry, we studied consecutive PerAF patients undergoing post-approval treatment with a pentaspline PFA catheter. The primary effectiveness outcome was freedom from any atrial arrhythmia of ≥30 seconds. Safety outcomes included the composite of acute and chronic major adverse events (MAE).

Results: Of the 547 PerAF patients who underwent PFA, 131 (24%) received adjunctive LAPW ablation. Compared to PVI-alone, patients receiving adjunctive LAPW ablation were younger (65 *vs* 67 years, p=0.08), had a lower CHA_2DS_2-VASc score (2.3±1.6 *vs* 2.6±1.6, p=0.08), more likely to receive electroanatomical mapping (48.1% *vs* 39.0%, p=0.07) and ICE imaging (46.1% *vs* 17.1%, p<0.001). The 1-year Kaplan-Meier estimate for freedom from atrial arrhythmias was similar between groups (PVI+LAPW: 66.4% [95% CI 57.6-74.4%] *vs* PVI: 73.1% [95% CI, 68.5-77.2%], p=0.68). This 1-year effectiveness remained similar between groups after propensity matching of clinical characteristics (PVI+LAPW: 71.7% *vs.* PVI: 68.5%, p=0.34). There was also no significant difference in MAE between the groups (2.2% *vs.* 1.4%, respectively, p=0.51).

Conclusions: In PerAF patients undergoing PFA, as compared to PVI-alone, adjunctive LAPW ablation resulted in similar effectiveness without increasing complications.

Key Words: Atrial fibrillation; pulsed field ablation; posterior wall ablation; pulmonary vein isolation

CONDENSCEND ABSTRACT

In a retrospective analysis of the *MANIFEST-PF* registry including PerAF (n=547) patients who underwent PFA, 131 (24%) received adjunctive LAPW ablation while 416 underwent PVI-alone. The 1-year Kaplan-Meier estimate for freedom from atrial arrhythmias was similar between groups (PVI+LAPW: 66.4% [95% CI 57.6-74.4%] vs PVI: 73.1% [95% CI, 68.5-77.2%], p=0.68). This 1-year effectiveness remained similar between groups after propensity matching of clinical characteristics (PVI+LAPW: 71.7% vs. PVI: 68.5%, p=0.34). There was also no significant difference in MAE between the groups (2.2% vs. 1.4%, respectively, p=0.51).

INTRODUCTION

Pulmonary vein isolation (PVI) is the cornerstone of catheter ablation therapy for atrial fibrillation (AF).(1) While the PVI-only approach to ablation for paroxysmal AF (PAF) has improved in the last decade, the clinical success rates in patients with persistent AF (PerAF) have remained suboptimal, with single-procedure success ranging from 43% to 67%.(2,3) In an attempt to improve outcomes, adjunctive strategies targeting AF sources (e.g., non–pulmonary vein triggers) and empiric atrial substrate modification have been pursued – including ablation of the left atrial posterior wall (LAPW), mitral isthmus, left atrial appendage, low voltage areas and complex fractionated atrial electrograms (CFAE).(4-8)

The LAPW has been postulated to be a potential source of AF triggers and a vulnerable substrate allowing arrhythmia maintenance due to its embryological origins from the pulmonary veins, complex architecture, and propensity for fibrosis-related conduction delay.(9,10) However, studies evaluating adjunctive LAPW ablation for persistent AF using thermal ablation technologies have shown mixed results. However, these studies are confounded by the inability to ensure lesion durability given epicardial connections and concerns of damage to the esophagus within close proximity.(5,11-21)

Pulsed field ablation (PFA) is a novel, largely nonthermal energy source with an important degree of preferentiality to myocardium ablation. During PFA, ultra-rapid electrical pulses cause a breakdown of the cardiac sarcolemma, resulting in cell death through irreversible electroporation.(22,23) Importantly, in first-in-human clinical trials and real-world registries, PFA has demonstrated an excellent safety profile, with no reported instances of pulmonary vein stenosis or esophageal injury.(24-33) In *PersAFOne*, a two-center single-arm prospective study of PFA using a multielectrode PFA catheter in patients with PersAF, safe and durable PVI and

LAPW ablation was observed in 96% (82 of 85) of PVs and 100% (21 of 21) of LAPWs upon invasive remapping at 3 months.(26) Whether additional LAPW ablation with PFA translates to better outcomes remains unknown.

After European regulatory approval of the pentaspline PFA catheter in March 2021, there were a total of 24 centers that commenced use of this catheter in clinical practice that year. The *MANIFEST-PF* registry was an observational study of all 1,568 patients at these sites that underwent first-time PFA to treat atrial fibrillation. (30) Herein, the present *MANIFEST-PF* sub-study investigates the safety and effectiveness of PVI alone *versus* PVI plus adjunctive LAPW ablation in the cohort of patients with PerAF.

METHODS

Study Design

In this retrospective analysis of the *MANIFEST-PF* registry, the primary hypothesis to test was that the addition of LAPW ablation to PVI in patients with PerAF or long-standing PerAF (LS-PerAF) will decrease the recurrence of atrial arrhythmias, compared with PVI alone. As previously described, the *MANIFEST-PF* registry was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee at Homolka Hospital, and the ethics committee granted a waiver of consent.

Study Patients

As previously reported, *MANIFEST-PF* is a multinational, prospective patient-level registry from 24 European centers, including consecutive patients who received a first-ever PFA

with a pentaspline catheter (Farawave, Boston Scientific Inc.) for paroxysmal (PAF), PersAF, or LS-PersAF after *Conformité Européene*-mark approval. The procedures were performed between March 2021 and May 2022.(30) Patients were categorized by those who received PVI and additional LAPW *vs.* PVI alone for PersAF or LS-PerAF, and clinical outcomes were evaluated – including freedom from atrial arrhythmias and adverse events. PersAF was defined as AF duration ≥7 days but <1 year, and LS-PersAF was defined as continuous AF duration greater than 1 year, as per the guidelines.(34) Patients who received PFA for paroxysmal AF were excluded from this sub-analysis.

Pulsed Field Ablation

Details of the PFA procedure and follow-up in the *MANIFEST-PF* registry have been previously reported.(30) Briefly, PFA was performed under moderate sedation or general anesthesia. Procedures were typically performed on uninterrupted oral anticoagulation with systemic heparinization prior to transseptal puncture. Electroanatomical mapping and intracardiac echocardiography (ICE) imaging were performed at the discretion of the operator. After transseptal puncture, the 13-Fr deflectable PFA sheath (Faradrive, Boston Scientific) was inserted into the left atrium and baseline electrical potentials were recorded from all PVs using the pentaspline PFA catheter. PVI was performed as previously described, with two paired applications (four total) per PV in both basket and flower configurations.(30) Additional PFA applications were delivered at operator discretion. PVI was typically confirmed based on electrograms recorded from the pentaspline PFA catheter.

LAPW ablation was performed in some patients with PerAF or LS-PerAF, at operator discretion. Using a pentaspline catheter in flower configuration, empirical PFA was performed

along the posterior wall in an overlapping fashion between the most inferior margins of the inferior pulmonary veins and the superior aspect of the superior pulmonary veins. LAPW ablation was performed under either fluoroscopy or guidance using a standard electroanatomical mapping system. LAPW isolation was confirmed by the absence of electrograms recorded on the pentaspline PFA catheter. Isoproterenol and adenosine were administered, per physician discretion. A dedicated post-ablation voltage map was created, per operator discretion. According to operator discretion, ancillary ablation lesions included roof-line-only, mitral isthmus, cavo-tricuspid isthmus, and other ablations performed with either the pentaspline PFA catheter, or a commercially available radiofrequency ablation catheter.

Oral anticoagulation was resumed in the evening following the procedure and continued in accordance with AF guidelines. Antiarrhythmic drugs (AADs) were typically continued for a short duration and then discontinued, according to operator discretion.

Follow-Up

Typically, patients had follow-up visits at 3-, 6- and 12-months post-procedure, with assessments for AF-related symptoms, adverse events, and 12-lead ECG or 24-Holter monitoring to document any atrial arrhythmia recurrence, per physician discretion.

Clinical Outcomes

Effectiveness Outcomes

The primary effectiveness outcome was freedom from any atrial arrhythmia (i.e., AF/atrial flutter/atrial tachycardia) of ≥30 seconds documented on a cardiac rhythm recording,

after a 3-month blanking period, irrespective of symptoms or AAD use. The secondary effectiveness outcome was freedom from any atrial arrhythmia of ≥30 s documented on a cardiac rhythm recording after a 3 month-blanking period, *plus* freedom from class I or III AADs or re-ablation.

Safety Outcomes

Safety outcomes included the composite of acute (<7 days post-procedure) and chronic (>7 days post-procedure) major adverse events, including atrioesophageal fistula, PV stenosis, cardiac tamponade/perforation requiring intervention, stroke or systemic thromboembolism, vascular access complications requiring surgery, persistent phrenic nerve injury, coronary artery spasm, and death.

Statistical Analysis

Continuous variables were reported as mean ± SD or median (interquartile range) and were compared using Student's *t*-test or Mann-Whitney *U* test. Categorical variables were expressed as percentages and compared using Pearson's $\chi 2$ test or Fisher's exact test. A 1:1 propensity score–matched analysis was performed using baseline characteristics, such as age, sex, CAD, hypertension, CHA_2DS_2-VASc score, LA diameter, and LVEF. The primary and secondary effectiveness outcomes were analyzed using Kaplan–Meier survival curves, and the treatment groups were compared using the log-rank test.

To identify risk factors associated with the recurrence of atrial arrhythmia, multivariable Cox regression analysis was used, and results were presented as hazard ratios (HR) with 95% confidence intervals (CI). All variables with $p<0.10$ in the univariate analysis were included in

the Cox regression model. Multiple imputations were used to account for missing data. A p-value < .05 (2-sided) was considered statistically significant. Statistical analyses were performed using the SPSS software (version 29.0; IBM Corp).

Results

Patient Characteristics

The *MANIFEST-PF* registry included 547 patients who underwent PFA for PersAF or LS-PersAF, of whom 131 (24%) patients received PVI + LAPW ablation and 416 (76%) patients received PVI alone. On average, patients who received LAPW ablation were younger (mean age, 65 *vs.* 67 years, p=0.08) with a lower CHA_2DS_2-VASc score (2.3±1.6 *vs* 2.6±1.6, p=0.08) and were less likely to have coronary artery disease (12.5% *vs.* 20.4%, p=0.055) than the PVI-alone cohort. The prevalence of hypertension, diabetes, heart failure, sleep apnea, chronic obstructive pulmonary disease, and previous stroke/transient ischemic attack was similar between groups. The median LA diameter (45 *vs* 44 mm, p=0.04) was larger in patients who underwent PVI + LAPW ablation than in those receiving PVI alone, but there was no difference in the median LVEF (60 vs 55 %, p=0.31) between the two groups (**Table 1**).

Procedural Characteristics

As shown in **Table 2**, a similar proportion of patients underwent PFA with endotracheal intubation in both groups (PVI+LAPW: 20.6% *vs* PVI: 23.4%, p=0.55). Patients who received LAPW ablation were more likely to receive electroanatomical mapping (48.1% *vs* 39.0%, p=0.07) and ICE imaging (46.1% *vs* 17.1%, p<0.001) than patients receiving PVI alone. There

were no significant differences in the use of adjunctive lesion sets (other than LAPW ablation) between groups (PVI+LAPW: 16.8% vs PVI: 11.8%, p=0.14). The LAPW ablation group was more likely to undergo additional mitral isthmus ablation than the PVI group (12.2% *vs* 2.2%, p<0.001).

The median fluoroscopy (14 *vs* 12.4 min, p=0.19) times were similar, but the procedure (80 *vs* 61 min, p<0.001) times were longer in patients who received adjunctive LAPW ablation. The likelihood of undergoing repeat ablation did not differ between groups (PVI + LAPW: 13.7% *vs* PVI: 10.1%, p=0.26; **Table 3**). The time from the initial ablation procedure to a repeat procedure also did not differ between groups (median 220 days in the PVI + LAPW group *vs* 202 days in the PVI group; p=0.92).

Effectiveness Outcomes

The primary effectiveness outcome of the 1-year Kaplan-Meier estimate for freedom from atrial arrhythmias after a single procedure was similar between groups (PVI + LAPW group: 66.4% [95% CI 57.6-74.4%] *vs* PVI-group: 73.1% [95% CI, 68.5-77.2%], p=0.68; **Table 3**, **Figure 1A**). The median time to first AF recurrence in the PVI + LAPW group was 207 days compared with 178 days in the PVI group (p=0.68). The secondary effectiveness outcome of the 1-year Kaplan-Meier estimate for freedom from atrial arrhythmias *off* AADs or redo-ablation was also similar between groups (PVI + LAPW group: 59.5% [95% CI, 50.6–68%] *vs* PVI-group: 66.8% [95% CI, 62.1 – 71.3%], p=0.77; **Figure 1B**).

Primary clinical effectiveness was also similar in the subgroup of LS-PersAF patients (PVI + LAPW group: 73.6% [95% CI 48.4 – 90.8%] vs PVI group: 73.3% [95% CI 54.1 – 87.7%], p=0.87; **Figure 2**). A subgroup analysis in the PVI + LAPW group (N=131) revealed

that patients with higher CHA_2DS_2-VASc scores (2.8 *vs* 2.1, p=0.01) were more likely to have atrial arrhythmia recurrence (AF/AFL/AT; **Supplementary Table S1**).

Risk Factors Associated with Primary Effectiveness Failure

Multivariable Cox-regression modeling was performed to identify potential risk factors associated with primary effectiveness failure (recurrence of atrial arrhythmia). The hazard ratio (HR) of primary effectiveness failure for subjects aged > 65 years was 1.45 (95% CI, 1.16 – 1.81, p<0.001), female sex was 1.25 (95% CI 1.02 – 1.53, p=0.03), history of heart failure was 1.59 (95% CI 1.28 – 1.97, p<0.001), LA diameter of >45 mm was 1.74 (95% CI 1.46 – 2.08, p<0.001), additional ablation was HR 0.64 (95% CI 0.48 – 0.84, p=0.002), and procedure time >60 min was 1.45 (95% CI, 1.16 – 1.79, p<0.001; **Figure 3**).

Propensity Score-Matched Population

The propensity-matched cohort included 184 patients (PVI + LAPW group, 92 patients; PVI group, 92) with age 64.3±10.1 years, BMI 29.0±5.2 kg/m^2, and CHA_2DS_2-VASc score 2.2±1.6. After propensity matching for risk factors, including age, sex, CAD, hypertension, CHA_2DS_2-VASc score, LA diameter and LVEF, the baseline characteristics, echocardiographic parameters, and use of AADs were similar between the groups. (**Supplementary Table S2**).

The procedural characteristics of the two groups of the propensity-matched cohort were overall similar (**Supplementary Table S3**). However, ICE imaging was more frequently used in in the PVI + LAPW group (60.9% *vs* 27.2%, p<0.001) than patients receiving PVI alone, and median fluoroscopy time was longer in the PVI group (12.7 *vs* 16.0 min, p=0.01).

In this propensity-matched cohort, there was again no difference in the primary effectiveness outcomes of AF recurrence between the two groups (PVI + LAPW group 71.7% *vs* PVI group 68.5%, p=0.34; **Figure 4**). A multivariate Cox-regression analysis demonstrated that LA diameter (HR 1.82, 95% CI, 1.03 – 3.23; p=0.04) was the only risk factor associated with recurrence of atrial arrhythmia.

Adverse Events

As shown in **Table 4**, the overall rate of adverse events was low, with major adverse events occurring in 2.2% (3 of 131) of the PVI + LAPW group *vs* 1.4% of the PVI group (6 of 416; p=0.51). There were no instances of PFA-related esophageal complications, including no atrio-esophageal fistula, esophageal ulcerations, or esophageal dysmotility in any of the patients. Similarly, there were no instances of symptomatic PV stenosis or persistent phrenic nerve injury in either group of patients. Transient phrenic nerve injury occurred in 0.2% of patients in the PVI group (1 of 416) and none in the LAPW ablation group (p=1.00). Coronary spasm was rare, occurring in 0.8% of patients in the PVI + LAPW group and none in the PVI group.

Complications related to catheter manipulation, such as cardiac tamponade, occurred in 0.8% (1 of 131) in the PVI + LAPW-group and 1.2% (5 of 416) of PVI group (p=1.00). Stroke rates were similar between groups, occurring in 0.8% (1 of 131) of the PVI + LAPW group and 0.2% (1 of 416) of the PVI group. No deaths occurred in either group.

There was also no significant difference between groups in the incidence of acute minor adverse events (PVI+LAPW group, 6.8% *vs* PVI group, 3.6%; p=0.13).

DISCUSSION

This report constitutes the largest comparative analysis of adjunctive LAPW ablation with PVI using PFA in patients with Pers-AF or LS-PersAF. In patients undergoing first-time PFA for PersAF and LS-PersAF, empirical addition of LAPW ablation to PVI did not improve freedom from atrial arrhythmia at 1 year compared to PVI – this was true in both the full (66.4% *vs* 73.1%, p=0.68) and propensity-score matched cohorts (71.7% *vs* 68.5%, p=0.34). (***Central Illustration***) The secondary arrhythmic recurrence outcomes *off* AADs or redo-ablation were also not significantly different between the two ablation approaches. The addition of LAPW ablation to PVI resulted in longer procedural times, but without an increase in complication rates. Importantly, there were no PFA-related primary safety events, such as esophageal complications, permanent phrenic nerve palsy, or PV stenosis, in either group.

Clinical Effectiveness

MANIFEST-PF demonstrated no difference in clinical outcomes between PVI and PVI + LAPW ablation with PFA for Pers/LS-PersAF. The primary effectiveness outcome of freedom from atrial arrhythmia recurrence was 73.1% with PVI and 66.4% with PVI+LAPW ablation at 12 months follow-up. These effectiveness rates were lower than the first-in-human clinical experience with this pentaspline PFA catheter in persistent AF patients: *PersAFOne* was a single-arm, observational study of 25 PerAF patients who underwent both PVI and LAPW ablation, and demonstrated a a 1-year Kaplan-Meier estimate of freedom from any atrial arrhythmia of 92.5±5.4%.(26,28,35) This variance in outcomes may be related to the small number of patients included in *PersAFOne*, the small number of centers and operators in *PersAFOne* (2 centers and 2 operators) *vs*. *MANIFEST-PF* (24 centers and 77 operators), and/or perhaps the extra scrutiny expected in the first-in-human study, as opposed to the "real world"

observational nature of the *MANIFEST-PF* registry. The *PersAFOne* study included a protocol-mandated invasive remapping procedure at ~3 months after the index procedure; this revealed durable isolation in 96% (82 of 85) of PVs and 100% (21 of 21) of LAPWs. In contrast, for those patients in the *MANIFEST-PF* cohort that presented for redo procedures, the durable PV isolation rates was approximately 70%. (30) PULSED-AF (Pulsed Field Ablation to Irreversibly Electroporate Tissue and Treat AF) study using a different circular PFA catheter (Medtronic Inc.) in 150 patients with Pers-AF showed that the 1-year clinical effectiveness was 55.1% [95% CI, 46.7 to 62.7].(28) The observed differences from atrial tachyarrhythmia in *MANIFEST-PF* may reflect variation in the intensity of cardiac monitoring and adjunctive ablation performed.

Previous studies using conventional thermal ablation technologies such as radiofrequency or cryo-ablation showed mixed results in the ablation effectiveness of empirical LAPW ablation compared to PVI-alone. (5,14,15,18-20) On one hand, two recent RCTs using cryoballoon ablation reported lower recurrence of AF with additional LAPW ablation. (14,18) On the other hand, two other RCTs using RFA concluded that there was no difference in outcomes with additional LAPW ablation to PVI. (5,15) However, a meta-analysis including 26 studies and 3,287 patients reported a significantly lower risk of atrial arrhythmia recurrence (risk ratio, 0.74 [95% CI, 0.62-0.90]; P < .001) with adjunctive LAPW ablation in patients with persistent AF.(19) Furthermore, the CONVERGE (Convergence of Epicardial And Endocardial Radiofrequency Ablation For The Treatment Of Symptomatic Persistent AF) trial, which compared hybrid surgical epicardial and catheter-based endocardial ablation (PVI and additional LAPW ablation) demonstrated that at 12 months, freedom from atrial arrhythmias was achieved in 67.7% with the hybrid convergent procedure and 50.0% with catheter ablation (p=0.03). (36)

Overall, these studies were limited by a relatively small sample size and lack of assessment of durable LAPW ablation.

Clinical Safety

There are several challenges to achieving durable LAPW isolation using thermal ablation technologies. The roof, which serves as the uppermost line of the LAPW, is relatively thick because of the Bachmann's bundle and is surrounded by epicardial fat, making it difficult to achieve transmural lesions. Important electrical connections from the epicardium in the form of a septopulmonary bundle course over the superior aspect of the LAPW may not be completely ablated endocardially. High-force and extensive ablation in this region may result in inadvertent complications, such as cardiac perforation and pericardial tamponade. The ablation lesion set along the inferior margins of the LAPW is in close proximity to the esophagus and may result in esophageal injury, including a risk of catastrophic atrioesophageal fistula formation. (37) Hence, it is not uncommon to find areas of reconnection on the LAPW during a redo procedure. (17)

In the *MANIFEST-PF* registry, the rate of major procedure-related adverse events (PVI, 1.4% *vs.* PVI + LAPW, 2.2%) was lower with PFA than with other prior studies using thermal ablation techniques for LAPW ablation. (5,14,15,18,36). Importantly, there were no instances of esophageal injury, including ulceration or atrioesophageal fistulas, in either group. It is important to note that the pentaspline catheter was maneuvered over the entire LAPW, and PFA was performed directly adjacent to the esophagus in a flower configuration. These safety data are similar to those observed in prior preclinical and first-in-man clinical studies using pentaspline PFA catheters. (25,26,38,39) Similarly, there were no instances of permanent phrenic nerve injury, PV stenosis, or coronary spasm in any of the patients. In addition, the lack of a significant

difference in stroke and pericardial tamponade is important given that multiple PFA applications were delivered to the LAPW.

Future Studies on Posterior Wall Ablation with PFA

ADVANTAGE AF (A Prospective Single Arm Open Label Study of the Farapulse Pulsed Field Ablation System in Subjects With Persistent Atrial Fibrillation) is a prospective, non-randomized study (NCT05443594) including ~417 participants for the treatment of drug-resistant Pers-AF is currently ongoing. The primary outcomes included acute and chronic safety and effectiveness at one year, and the estimated completion date was August 2024.

Study Limitations

First, this study was a non-randomized analysis of consecutive patients with Pers-AF who underwent PVI or PVI + LAPW ablation with PFA. Despite extensive adjustments, we cannot rule out the possibility of unknown confounders in either treatment group, which could potentially affect the outcomes. Second, we could not assess the impact of durable LAPW ablation on clinical outcomes because we did not have data on its durability in patients who underwent repeat procedures. Third, the completion of the LAPW ablation was determined by the absence of electrograms on the pentaspline PFA catheter. High-density voltage mapping following PFA was performed in only 41% of the patients. Fourth, there was slight variation in the extent of adjunctive ablation performed among the sites and operators. Finally, interval ambulatory cardiac monitoring may fail to detect the recurrence of asymptomatic AF and overestimate the treatment success.

CONCLUSION

In this large observational registry of the first post-approval clinical use of PFA to treat persistent AF, the addition of LAPW ablation to PVI did not improve freedom from atrial arrhythmia at 12 months compared with PVI. Large-scale multicenter randomized trials are required to further examine the role of empirical LAPW ablation in persistent AF.

Clinical Perspective

Core Clinical Competencies: Beyond pulmonary vein isolation, adjunctive left atrial posterior wall ablation with thermal technologies has revealed mixed results in patients with persistent atrial fibrillation. Pulsed field ablation is a novel cardiac ablation method with a reduced risk for esophageal damage – raising the possibility of improved efficacy of left atrial posterior wall ablation.

Translational Outlook: In the multi-national *MANIFEST-PF* registry, as compared with pulmonary vein isolation alone, adjunctive left atrial posterior wall ablation achieved by pulsed field energy resulted in similar effectiveness without increasing complications in patients with persistent atrial fibrillation. Large-scale multicenter randomized trials are required to further examine the role of empirical LAPW ablation in persistent AF.

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Author Disclosures

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Figure Legends

Figure 1: Primary and Secondary Effectiveness Outcomes. Shown are the Kaplan-Meier analyses for both (A) the primary endpoint of 1-year freedom from atrial arrhythmia, and (B) the secondary endpoint of 1-year freedom from arrhythmia off AADs or re-ablation, as compared between the PVI + LAPW and PVI alone groups.

Figure 2: Primary Effectiveness Outcome in the LS-Persistent AF Cohort. Shown is the Kaplan-Meier analysis for the primary endpoint of 1-year freedom from all atrial arrhythmia in the cohort of patients with LS-Persistent AF.

Figure 3: Multivariate Cox regression: Risk Factors for Primary Effectiveness Failure.

Figure 4: Primary Effectiveness Outcome in the Propensity-Matched Cohort. Shown is the Kaplan-Meier analysis for the primary endpoint of 1-year freedom from all atrial arrhythmia in a propensity-matched cohort of patients.

Figure 5: Central Illustration

Table 1: Baseline Characteristics

Characteristics	No. of Patients w/ Available Data	Entire Cohort (n=547)	PVI + LAPW ablation (n=131)	PVI (n=416)	P-Value
Age (mean ± SD)	547 (100%)	66.3 ±2.6	64.8 ± 10.4	66.7 ± 10.8	0.08
Female (%)	547 (100%)	165 (30.2%)	36 (27.5%)	129 (31.0%)	0.51
CHA_2DS_2-VASc (mean ± SD)	547 (100%)	2.5 ± 1.6	2.3 ± 1.6	2.6 ± 1.6	0.08
Past Medical History					
Body Mass Index (mean ± SD)	544 (99.1%)	28.9±5.2	28.9±4.5	28.9±5.4	0.96
Atrial flutter (%)	427 (78.0%)	66 (15.5%)	22 (17.2%)	44 (14.7%)	0.56
Coronary artery disease (%)	427 (78.0%)	77 (18.0%)	16 (12.5%)	61 (20.4%)	0.055
Diabetes (%)	547 (100%)	97 (17.7%)	29 (22.1%)	68 (16.3%)	0.15
Hypertension (%)	547 (100%)	377 (68.9%)	90 (68.7%)	287 (69.0%)	1.00
Heart failure (%)	547 (100%)	139 (25.4%)	35 (26.7%)	104 (25.0%)	0.73
Sleep apnea (%)	413 (75.5%)	48 (11.6%)	13 (11.0%)	35 (11.9%)	0.86
Prior stroke/TIA (%)	547 (100%)	38 (7.0%)	7 (5.4%)	31 (7.5%)	0.55
COPD (%)	365 (66.7%)	29 (7.9%)	10 (9.4%)	19 (7.3%)	0.52
Echocardiographic Parameters					
LVEF (%) (median, IQR)	486 (88.8%)	57 (50 – 60)	60 (50 – 60)	55 (50 – 60)	0.31
LA diameter (mm) (median, IQR)	429 (78.4%)	44 (40 – 48)	45 (42 – 48)	44 (40 – 48)	**0.04**
Antiarrhythmic Medications					
Class I AADs (%)	545 (99.6%)	74 (13.6%)	24 (18.3%)	50 (12.1%)	0.08
Class III AADs (%)	546 (99.6%)	137 (25.1%)	30 (22.9%)	107 (25.8%)	0.56

TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; LA, left atrium; AADs, anti-arrhythmic drugs

Table 2: Procedural Characteristics

Procedure Characteristics	No. of Patients w/ Available data	Entire Cohort (n=547)	PVI + LAPW ablation (n=131)	PVI (n=416)	P-Value
Intubation (%)	547 (100%)	124 (22.7%)	27 (20.6%)	97 (23.4%)	0.55
Mapping (%)	547 (100%)	225 (41.2%)	63 (48.1%)	162 (39.0%)	0.07
ICE imaging (%)	426 (77.8%)	110 (25.8%)	59 (46.1%)	51 (17.1%)	**<0.001**
Additional ablation lesion sets (%)	547 (100%)	71 (12.9%)	22 (16.8%)	49 (11.8%)	0.14
Mitral line (%)	547 (100%)	25 (4.6%)	16 (12.2%)	9 (2.2%)	**<0.001**
CTI line (%)	547 (100%)	32 (5.9%)	5 (3.8%)	27 (6.5%)	0.29
Roof line (%)	547 (100%)	14 (2.6%)	5 (3.8%)	9 (2.2%)	0.34
Other ablation (%)	547 (100%)	21 (3.8%)	6 (4.6%)	15 (3.6%)	0.60
Type of Energy used for additional ablation					
Pulsed-field energy	71 (100%)	53 (9.6%)	21 (16.0%)	32 (7.6%)	**0.01**
Radiofrequency	71 (100%)	18 (3.3%)	1 (0.7%)	17 (4.1%)	0.07
Fluoroscopy time (min; median, IQR)	527 (96.3%)	13.0 (7.0 – 20.5)	14 (9.3 – 20.3)	12.4 (6.7 – 20.8)	0.19
Procedure time (min) (median, IQR)	536 (97.9%)	68.0 (45.0 _ 100.0)	80 (61 – 114)	61 (40 – 95)	**<0.001**
Same day discharge (%)	426 (77.8%)	29 (6.8%)	3 (2.3%)	26 (8.7%)	**0.02**

Table 3: Effectiveness Outcomes

Effectiveness Outcomes	Entire Cohort (n=547)	PVI + LAPW ablation (n=131)	PVI (n=416)	P-Value
Primary Effectiveness Outcome				
Freedom from AF/AFL/AT*	391 (71.5%)	87 (66.4%)	304 (73.1%)	0.68
Secondary Effectiveness Outcome				
Freedom from AF/AFL/AT *off* AADs or redo-ablation*	356 (65.1%)	78 (59.5%)	278 (66.8%)	0.77
Follow up duration, days (median, IQR)	365 (278 – 420)	390 (347 – 445)	363 (249 – 408)	**<0.001**
No. of follow up 24-hour Holter monitors (median, IQR)	2 (1 – 3)	2 (1- 3)	2 (1- 3)	0.20
No. of follow up visits (median, IQR)	3 (2 – 3)	3 (2 – 4)	2 (2 – 3)	**<0.001**
Time to AF/AFL recurrence, days (median, IQR)	182 (127 – 292)	207 (130 – 314)	178 (125 – 290)	0.68
Redo-ablation (%)	60 (11.0%)	18 (13.7%)	42 (10.1%)	0.26

*KM estimate at 1-year

Table 4: Major and Minor Adverse Events

Safety Outcomes	Entire Cohort (n=547)	PVI + LAPW ablation (n=131)	PVI (n=416)	P-Value
Acute major adverse events (%)	9 (1.6%)	3 (2.2%)	6 (1.4%)	0.51
Esophageal fistula	0	0	0	-
Symptomatic PV stenosis	0	0	0	-
Cardiac tamponade	6 (1.1%)	1 (0.8%)	5 (1.2)	1.00
Percutaneous drainage	5 (1.2%)	1 (0.8%)	4 (1.3%)	1.00
Surgical drainage	0	0	0	-
Stroke	2 (0.4%)	1 (0.8%)	1 (0.2%)	0.42
Coronary spasm	1 (0.2%)	1 (0.8%)	0	0.24
Phrenic nerve injury (persistent)	0	0	0	-
Death	0	0	0	-
Vascular complications requiring surgery	0	0	0	0
Acute minor adverse events (%)	24 (4.4%)	9 (6.8%)	15 (3.6%)	0.13
Pericardial effusion w/o intervention	2 (0.5%)	2 (1.6%)	0	0.09
Pericarditis	1 (0.2%)	0	1 (0.3%)	1.00
Air embolism	3 (0.5%)	1 (0.8%)	2 (0.5%)	0.56
TIA	2 (0.4%)	0	2 (0.5%)	1.00
Phrenic nerve injury, transient	1 (0.2%)	0	1 (0.2%)	1.00
Vascular access complications	13 (2.3%)	4 (3.0%)	9 (2.1%)	0.56
Hematoma	11 (2.0%)	4 (3.1%)	7 (1.7%)	0.30
A-V fistula	1 (0.2%)	0	1 (0.2%)	1.00
Pseudoaneurysm	1 (0.2%)	0	1 (0.2%)	1.00
DVT	0	0	0	-
Respiratory-related	2 (0.4%)	2 (1.5%)	0	0.06
Chronic major adverse events	0	0	0	-

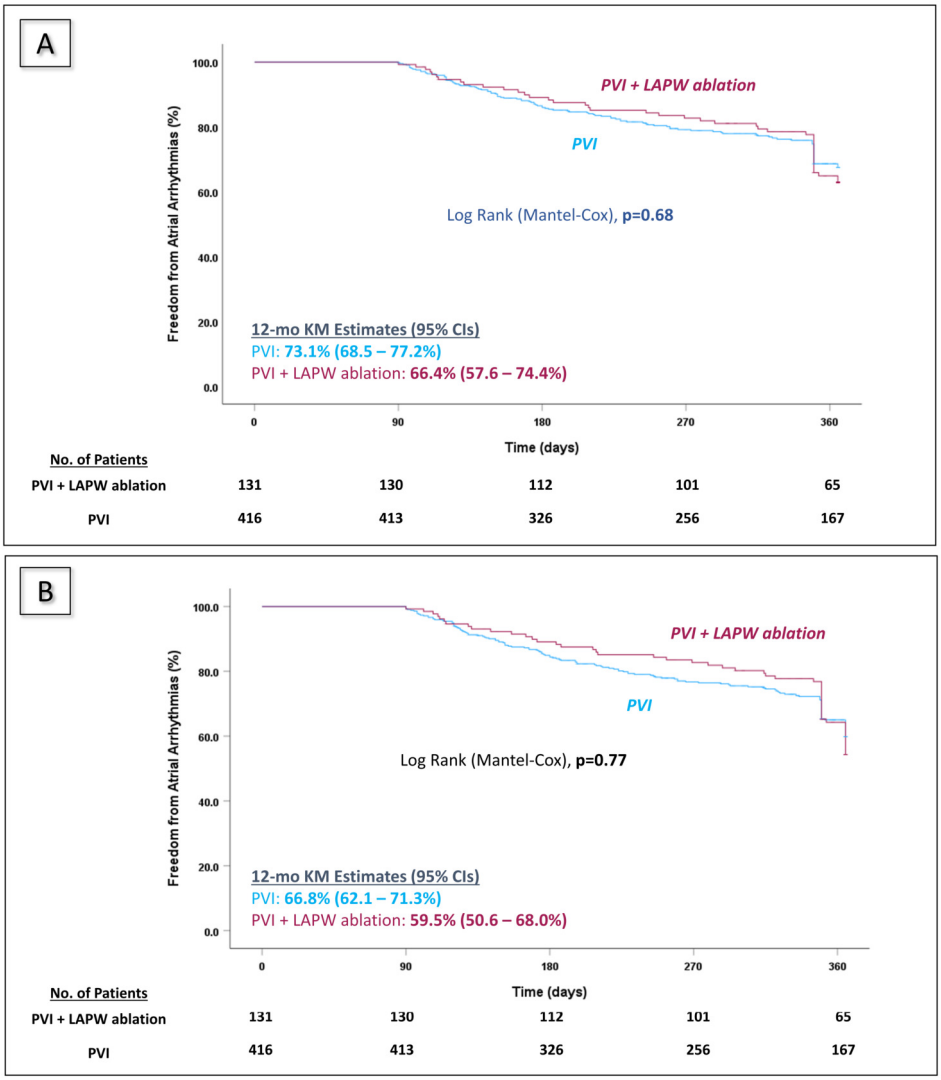
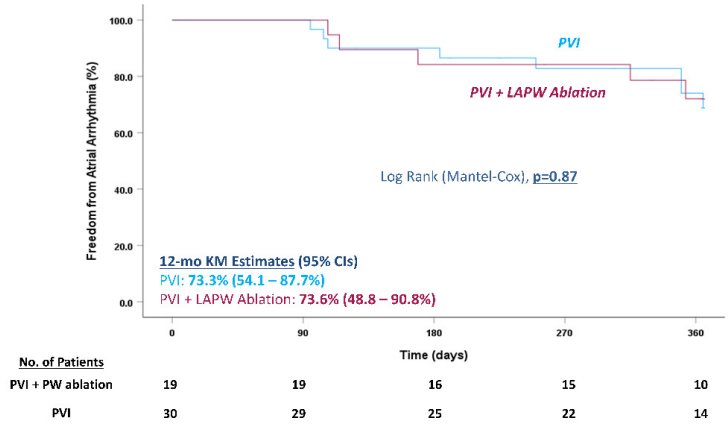


Figure 1: Primary and Secondary Effectiveness Outcomes. Shown are the Kaplan-Meier analyses for both (A) the primary endpoint of 1-year freedom from atrial arrhythmia, and (B) the secondary endpoint of 1-year freedom from arrhythmia off AADs or re-ablation, as compared between the PVI + LAPW and PVI alone groups.



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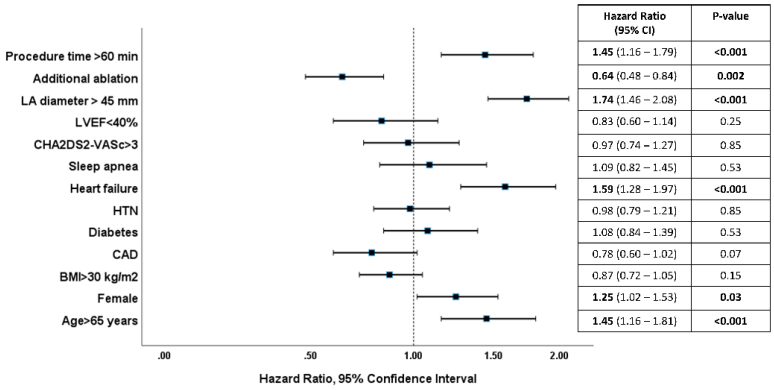

Hazard Ratio (95% CI)	P-value
1.45 (1.16 – 1.79)	**<0.001**
0.64 (0.48 – 0.84)	**0.002**
1.74 (1.46 – 2.08)	**<0.001**
0.83 (0.60 – 1.14)	0.25
0.97 (0.74 – 1.27)	0.85
1.09 (0.82 – 1.45)	0.53
1.59 (1.28 – 1.97)	**<0.001**
0.98 (0.79 – 1.21)	0.85
1.08 (0.84 – 1.39)	0.53
0.78 (0.60 – 1.02)	0.07
0.87 (0.72 – 1.05)	0.15
1.25 (1.02 – 1.53)	**0.03**
1.45 (1.16 – 1.81)	**<0.001**

Figure 3: Figure 3: Multivariate Cox regression: Risk Factors for Primary Effectiveness Failure.

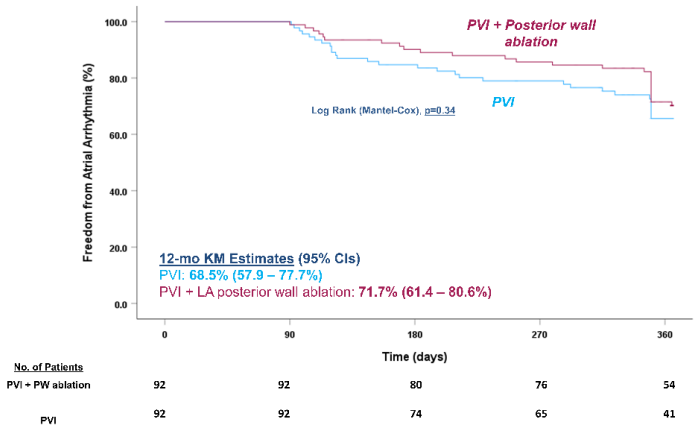

Figure 4: Primary Effectiveness Outcome in the Propensity-Matched Cohort. Shown is the Kaplan-Meier analysis for the primary endpoint of 1-year freedom from all atrial arrhythmia in a propensity-matched cohort of patients.

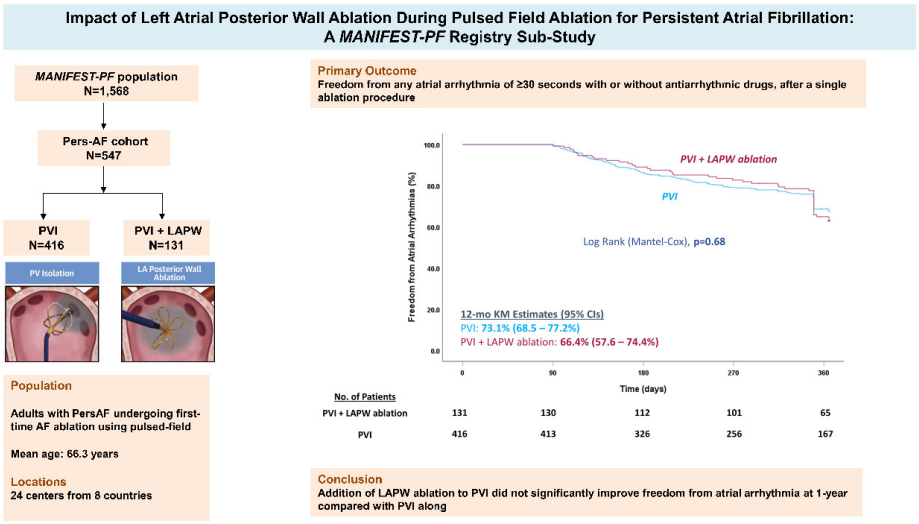

Figure 5: Central Illustration