

# Personalized pulmonary vein antrum isolation guided by left atrial wall thickness for persistent atrial fibrillation

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## Aims

Pulmonary vein (PV) antrum isolation proved to be effective for treating persistent atrial fibrillation (PeAF). We sought to investigate the results of a personalized approach aimed at adapting the ablation index (AI) to the local left atrial wall thickness (LAWT) in a cohort of consecutive patients with PeAF.

## Methods and results

Consecutive patients referred for PeAF first ablation were prospectively enrolled. The LAWY three-dimensional maps were obtained from pre-procedure multidetector computed tomography and integrated into the navigation system. Ablation index was titrated according to the local LAWY, and the ablation line was personalized to avoid the thickest regions while encircling the PV antrum. A total of 121 patients (69.4% male, age  $64.5 \pm 9.5$  years) were included. Procedure time was 57 min (IQR 50–67), fluoroscopy time was 43 s (IQR 20–71), and radiofrequency (RF) time was 16.5 min (IQR 14.3–18.4). The median AI tailored to the local LAWY was 387 (IQR 360–410) for the anterior wall and 335 (IQR 300–375) for the posterior wall. First-pass PV antrum isolation was obtained in 103 (85%) of the right PVs and 103 (85%) of the left PVs. Median LAWY values were higher for PVs without first-pass isolation as compared to the whole cohort ( $P = 0.02$  for left PVs and  $P = 0.03$  for right PVs). Recurrence-free survival was 79% at 12 month follow-up.

## Conclusion

In this prospective study, LAWY-guided PV antrum isolation for PeAF was effective and efficient, requiring low procedure, fluoroscopy, and RF time. A randomized trial comparing the LAWY-guided ablation with the standard of practice is in progress (ClinicalTrials.gov, NCT05396534).

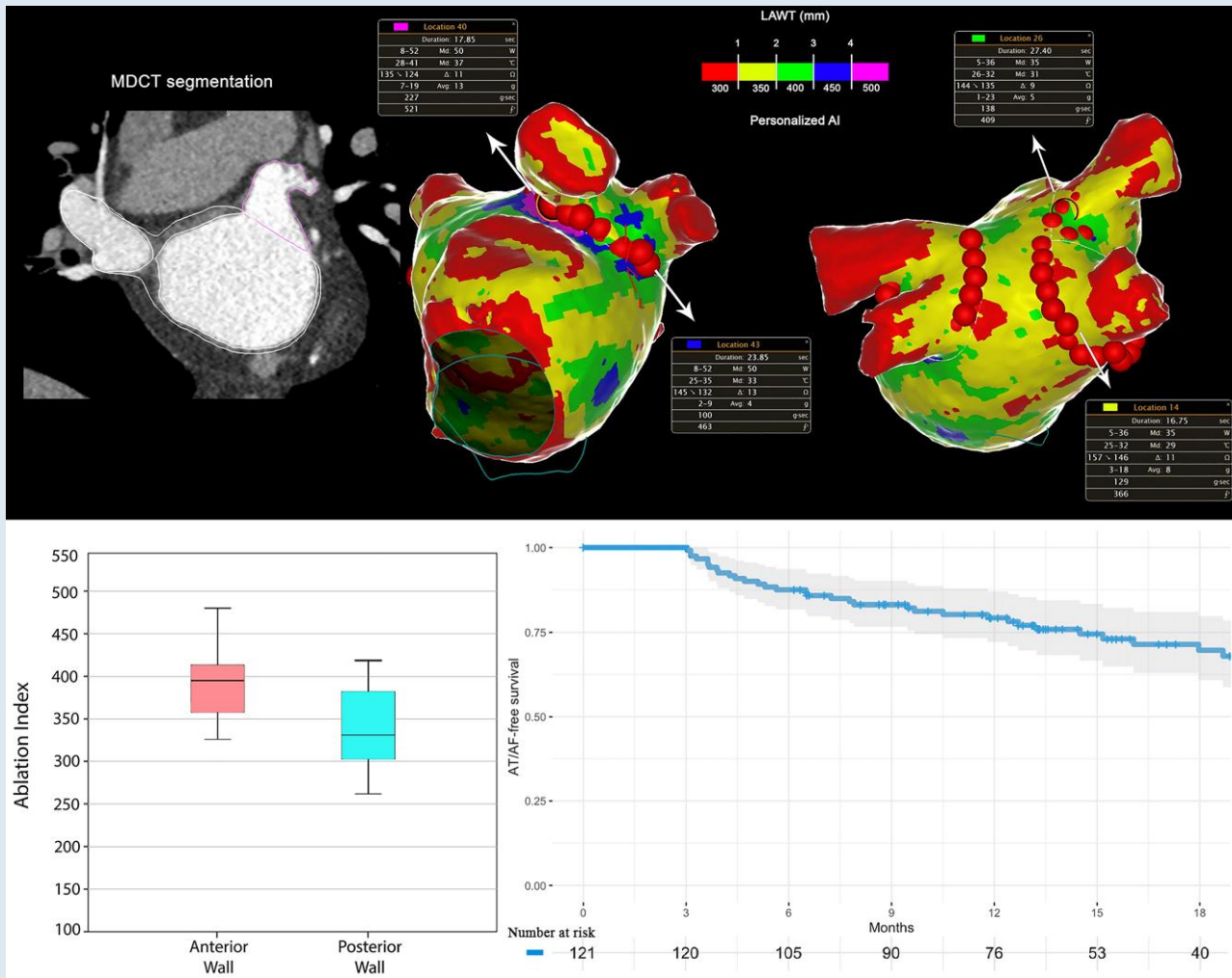
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## Graphical Abstract



## Keywords

Persistent atrial fibrillation • Left atrial wall thickness • Catheter ablation • Pulmonary vein isolation • Multidetector cardiac tomography

## What's new?

- The present study is the first reporting the feasibility of a pulmonary vein antrum isolation-only approach using a local left atrial wall thickness-guided titration of ablation index for persistent atrial fibrillation ablation.
- This approach permits to avoid the thickest left atrial regions and to titrate radiofrequency delivery by increasing ablation index in the thicker segments and avoiding unnecessary high amounts of radiofrequency delivery in the thinnest ones, lowering procedural requirements in terms of radiofrequency delivery, fluoroscopy, and procedure time, while maintaining a recurrence-free survival comparable to that reported in literature.
- Absence of first-pass during first procedure and reconnection sites found at redo procedure were mostly located in the thickest antral regions.

## Introduction

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia in adults<sup>1</sup> and is associated with significant morbidity and overall mortality.<sup>2-5</sup> Radiofrequency (RF) catheter ablation is an established and widely adopted strategy for rhythm control.<sup>6-8</sup> Pulmonary vein isolation (PVI) is the cornerstone of catheter-based strategies for AF ablation<sup>9</sup> and has proven to be effective in treating persistent atrial fibrillation (PeAF), although long-term outcomes have been significantly less favourable than in paroxysmal AF. In a recent meta-analysis,<sup>10</sup> PVI for PeAF ablation achieved an arrhythmia-free survival rate of 66.7% at 12 months. Ablation strategies combining PVI with additional substrate ablation, such as either linear ablation, complex fractionated atrial electrogram ablation, or MRI-guided fibrosis ablation, failed to demonstrate better outcomes than PVI-only approach.<sup>11-13</sup> Pulmonary vein (PV) reconnection after AF ablation is the main cause of AF recurrence and results from non-contiguous or non-transmural RF lesions. The latter are

**Table 1** Protocol for ablation parameters adapted to left atrial wall thickness and for high-frequency low-tidal volume ventilation  
**Table 1a** Protocol for ablation parameters adapted to left atrial wall thickness

LAWT	Colour code	Ablation index		RF energy (Watts)	
		Anterior	Posterior	Anterior	Posterior
< 1mm	Red	300	300	40	35
1–2 mm	Yellow	350	350	40	35
2–3 mm	Green	400	400	50	35
3–4 mm	Blue	450	450	50	35
> 4 mm	Purple	500	500	50	35

**Table 1b** Protocol for standard high-frequency low-tidal volume ventilation

Parameter	Value
FiO <sub>2</sub> (%)	60
Ventilation rate (breath/min)	45–50
Inspiration/expiration ratio	1–2
Tidal volume (mL/kg)	3.5–4

FiO<sub>2</sub>, fraction of inspired oxygen; LAWT, left atrial wall thickness; RF, radiofrequency.

often the consequence of insufficient RF delivery in the thickest myocardial areas.<sup>14</sup> On the other hand, excessive RF delivery in thin regions of the left atrial (LA) wall is associated to increased complication rate.<sup>15</sup>

Advances in technology and innovative ablation protocols resulted in a remarkable improvement in the outcomes after PVI. Indeed, contact force-sensing catheters, novel indices for the estimation of lesion size, and ensuring  $\leq 6$  mm inter-lesion distance have markedly improved the arrhythmia-free survival after PVI.<sup>16,17</sup>

Recently, a personalized PVI approach using ablation index (AI) titration according to the local left atrial wall thickness (LAWT) as assessed with multidetector cardiac tomography (MDCT)-data postprocessing<sup>18</sup> demonstrated to achieve a high arrhythmia-free survival rate at 12 months in paroxysmal AF. This approach reported high efficiency, while maintaining good outcomes at long-term follow-up.

The present study sought to investigate the feasibility, safety, and efficacy of a personalized PVI approach based on LAWT-guided titration of the AI in a cohort of consecutive patients with PeAF.

## Methods

### Patient sample

We conducted a single-centre, experimental, and prospective study. Consecutive patients who underwent first PeAF ablation were prospectively enrolled between April 2019 and June 2021. All patients had documented symptomatic PeAF, non-response or intolerance to  $\geq 1$  antiarrhythmic drug (AAD) (Class I or III), and indication for first ablation in accordance with the ESC guidelines.<sup>19</sup> The PeAF was defined in the presence of at least one AF episode that was continuously sustained beyond 7 days, including episodes terminated by cardioversion after  $> 7$  days; long-standing PeAF was defined as continuous AF of  $> 12$  months duration when a rhythm control strategy was adopted. In all patients, a MDCT study was obtained prior to the ablation procedure, and post-processing aimed for the reconstruction of MDCT-derived maps with LAWT information was performed, as

previously described.<sup>18</sup> Exclusion criteria were age  $< 18$ , impossibility to perform a MDCT and any clinical condition contraindicating general anaesthesia or high-frequency low-tidal volume (HFLTV) ventilation.

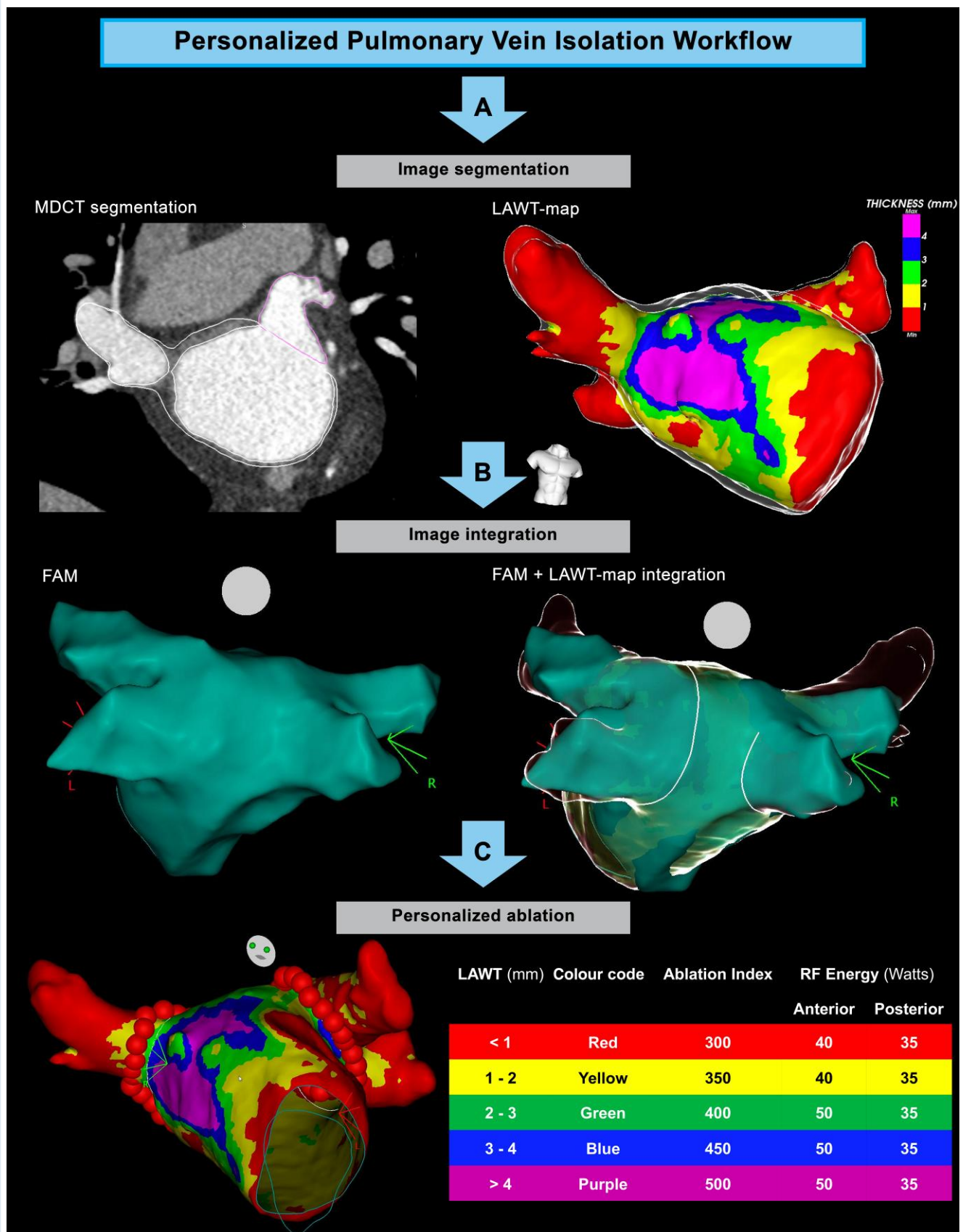
Written informed consent was obtained from all patients. The study complied with the Declaration of Helsinki and was approved by the Institutional Ethics Committee.

### Pre-procedural cardiac multidetector computed tomography and image post-processing

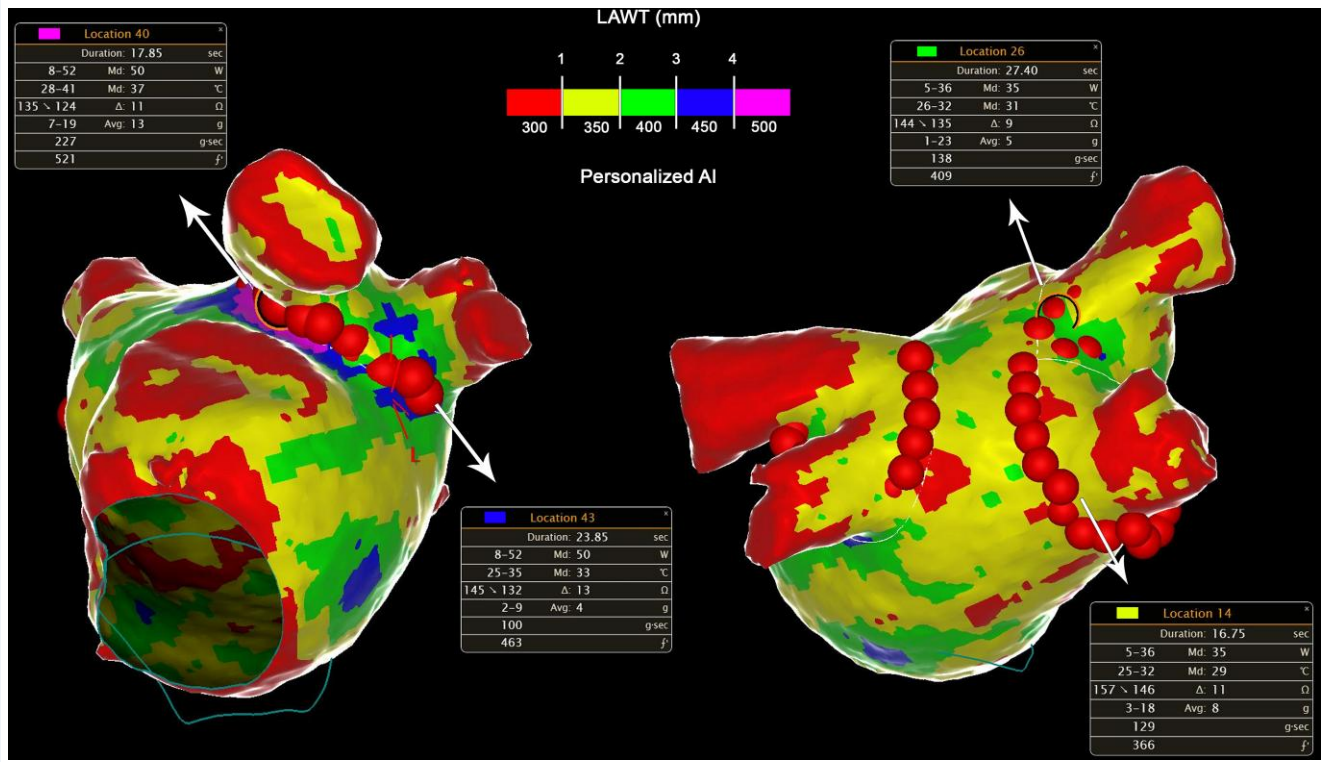
A pre-procedural cardiac MDCT was obtained with a Revolution<sup>TM</sup> CT scanner (General Electric Healthcare). The images were acquired during an inspiratory breath-hold using retrospective ECG-gating technique with tube current modulation set between 50% and 100% of the cardiac cycle. The MDCT images were analysed with ADAS 3D<sup>TM</sup> software (ADAS3D Medical, Barcelona, Spain) to obtain 3D LAWT maps. To compute the LAWT, a three-step algorithm was applied: the endocardial layer was delineated by means of a semi-automatic segmentation based on pixel signal intensity thresholds; the epicardial layer was defined manually; finally, LAWT was automatically computed at each point as the distance between each endocardial point and its projection to the epicardial shell. The resulting 3D LAWT map was then imported into the CARTO navigation system (Biosense Webster Inc., Irvine, CA, USA). The LAWT maps were colour-coded as follows: red  $< 1$  mm, 1 mm  $\leq$  yellow  $< 2$  mm, 2 mm  $\leq$  green  $< 3$  mm, 3 mm  $\leq$  blue  $< 4$  mm, and purple  $\geq 4$  mm.<sup>18</sup> Data on the reproducibility of the segmentation method have been reported previously.<sup>20</sup> The reproducibility agreement of LAWT maps derived by the described semi-automatic threshold-based segmentation was also recently analysed.<sup>21</sup> Results of the analysis reported a colour agreement between LAWT maps of 95.5% and 92.9% intra- and inter-observer, respectively; the titration of the AI showed an average difference lower than 25 units in all cases. For all analyses, the concordance increased with user experience. These results suggest that LAWT measurements are reproducible; moreover, variability has a negligible impact in the target AI. The distance between the epicardial LA posterior wall and the oesophagus was also computed, and an oesophageal isodistance colour-coded map was created and imported into CARTO.<sup>22</sup> This information was used to personalize the ablation line and avoid, as far as possible, RF application on the posterior atrial wall region closest to the oesophagus.

### Left atrial wall thickness-guided pulmonary vein isolation

All procedures were performed using CARTO3 mapping system (Biosense Webster, Johnson & Johnson Medical S.p.A., CA, USA). All procedures were performed under general anaesthesia and utilizing HFLTV ventilation protocol.<sup>23,24</sup> Transseptal puncture was guided by transoesophageal echocardiography (TOE), performed by cardiologists experienced in cardiac imaging.<sup>25</sup> All procedures were performed with single catheter technique,<sup>26</sup> using a contact force-sensing irrigated ablation catheter (Thermocool Smarttouch, Biosense Webster Inc., CA, USA). A fast-anatomical map



**Figure 1** Workflow of left atrial wall thickness-guided persistent atrial fibrillation ablation. (A) The first step is multidetector computed tomography-derived image segmentation and 3D left atrial wall thickness-map rendering. (B) Image integration in the navigation system after performing left atrial fast anatomical map. (C) Pulmonary vein isolation with the AI targets adapted to left atrial wall thickness-information.



**Figure 2** Personalized persistent atrial fibrillation ablation with ablation index adapted to left atrial wall thickness.

(FAM) of the entire LA anatomy and the PVs was acquired and then merged with the imported 3D LAWТ map within the spatial reference coordinates of the CARTO system. Before starting ablation, a multi-thermocouple temperature probe (SensiTherm, St Jude Medical, Inc., St Paul, MN, USA) was always advanced into the oesophagus under fluoroscopic guidance to monitor the oesophageal temperature rises. Endocardial voltage mapping data were acquired in sinus rhythm. Low-voltage areas were defined as areas of endocardial bipolar voltage  $< 0.5$  mV. The PVI was performed with point-by-point RF lesion pattern with a maximal inter-lesion distance of 6 mm.<sup>17</sup> The personalized ablation line was depicted on the merged 3D LAWТ map around the PV antrum according to a wide antral circumferential ablation (WACA) pattern  $> 10$  mm outside the PV ostia, where the local electrograms did not show near-field PV signals. The line was moved in or moved out with respect to the strict PV antrum to avoid the thickest LAWТ areas; moreover, the line is also personalized according to the oesophageal isodistance colour-coded map in order to avoid, as far as possible, RF application on the LA posterior wall where the MDCT-derived atrio-oesophageal distance is the shortest ( $< 1$  mm, red area of the colour-coded isodistance map). The AI targets were defined by the local LAWТ on the thickness colour-coded map, as previously described<sup>18</sup> (Table 1). The power output was set at 35 W for the posterior wall, 40 W for anterior wall at zones with LAWТ between  $< 1$  and 2 mm (red-yellow zones on thickness map), and 50 W anterior wall at zones with LAWТ  $\geq 2$  mm (green, blue, and purple zones on thickness map) (Table 1). If the AI target was not reached at a given point for any reason, another lesion reaching the target was applied. A carina line was mandatory for the right pulmonary veins (RPVs), except if a common trunk was found, as RPVs intervenous carina is a common site for both acute and late reconnections.<sup>27</sup> Regardless of the local thickness of the 3D LAWТ map, AI was down-titrated to 300 whenever the RF point was at  $< 1$  mm distance from the oesophagus footprint on the posterior LA wall.<sup>22</sup>

Acute PVI was confirmed by demonstrating bidirectional block: entry block was demonstrated by the absence of PV potentials inside the vein with the ablation catheter placed sequentially in each segment inside the circumferential PV line and exit block by proving absence of electric capture of

the atrium during high-output pacing from inside the circumferential PV line, at each segment sequentially. In case of ongoing AF at the end of the RF applications, electrical cardioversion was performed to demonstrate bidirectional block during sinus rhythm.<sup>26</sup> Additional ablation was delivered at connected sites until PVI was achieved. The procedure was not terminated until confirming the absence of visual gaps between VisiTags.<sup>17</sup>

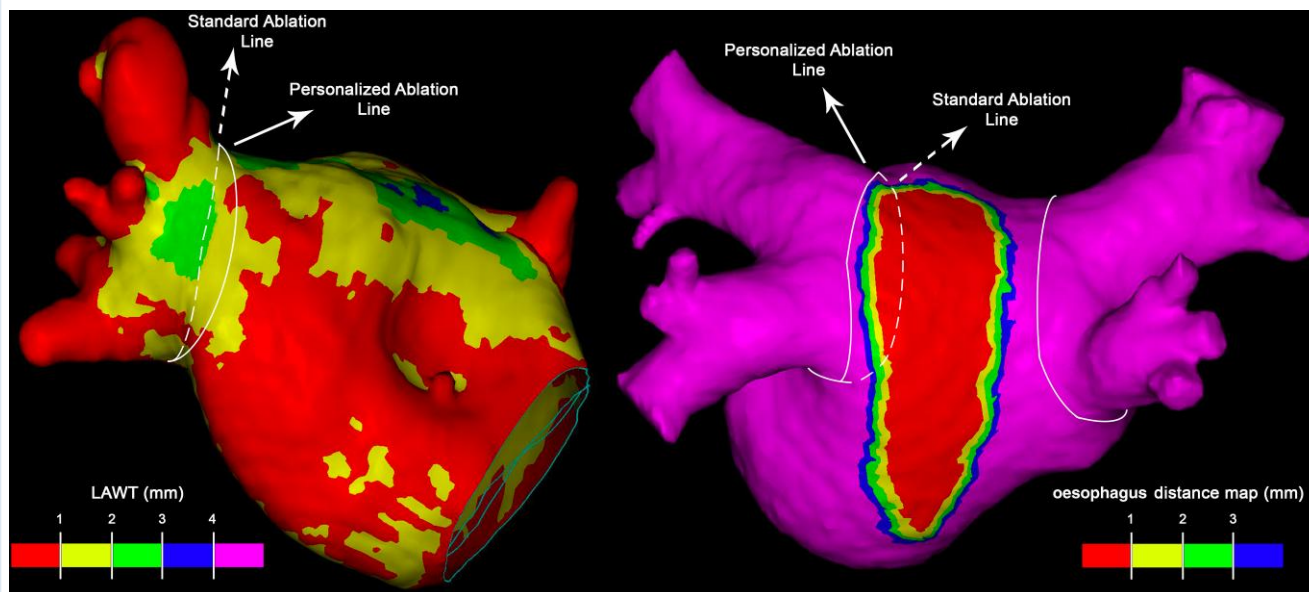
The procedural workflow of LAWТ-guided PeAF ablation is represented in Figure 1, Figure 2, and Figure 3.

## Follow-up

Patients were scheduled for follow-up at the outpatient clinic at 1, 3, 6, 12, and every 12 months thereafter, or in case of symptoms. Each evaluation included an ECG and 24 h Holter ECG monitoring. The primary outcome was freedom from recurrence after a blanking period of 3 months. Recurrence was defined as any documented AF, atrial flutter, or atrial tachycardia (AT) episode lasting more than 30 s, regardless of symptoms.<sup>28</sup> In the absence of other indications, all AADs were stopped at the end of the blanking period; however, the final decision on whether to withdraw all AADs was left to medical choice. Patients with recurrence were also scheduled for a redo ablation, according to the decision of the treating physician; there was no blanking period after a second procedure.

## Statistical analysis

Continuous variables were presented as mean  $\pm$  standard deviation or median (interquartile range) as appropriate. Categorical variables were presented as total number (percentage). The Student's *t*-test or Wilcoxon test were used to compare continuous variables, as appropriate;  $\chi^2$  or Fisher's exact test were used to compare categorical variables, as appropriate. Kaplan–Meier curves and the log-rank test were used to assess cumulative AF/AT-free survival. Logistic regression models were performed to identify predictors of AF/AT recurrence during the follow-up, while Youden index analysis was used to calculate the optimal cut-off value. A level of  $P < 0.05$  was considered for statistical significance. Data were



**Figure 3** Personalized ablation lines in order to avoid antral thickest regions and left atrial posterior wall segments closest to the oesophagus.

analysed with R version 3.6.2 software (R Foundation for Statistical Computing, Vienna, Austria) and Matlab statistics toolbox (Matlab R2010a, The Mathworks, Inc., Natick, MA, USA).

## Results

### Baseline population

Between April 2019 and June 2021, a total of 125 consecutive patients meeting the inclusion criteria underwent PeAF ablation. Four patients had a minimum follow-up of less than 6 months and were excluded for analysis. The remaining 121 patients were included in the analysis. Baseline clinical characteristics are summarized in *Table 2* and *Table 3*. Mean age was  $64.5 \pm 9.5$  years, 69.4% were male, and 34 patients (28.1%) had a diagnosis of long-standing PeAF. The 37.2% of the population had a diagnosis of prior structural heart disease, being hypertensive cardiomyopathy the most prevalent entity (15.7%). Mean LA diameter was greater in patients with long-standing PeAF diagnosis ( $42.5 \pm 6.0$  mm vs.  $46.1 \pm 4.5$  mm,  $P = 0.005$ ). The LV function was impaired in 26 patients (21.5%).

The mean time between MDCT acquisition and the procedure was  $24 \pm 12$  h.

### Procedural characteristics

Procedural characteristics are summarized in *Table 4*.

At the time of ablation, 43 (35.5%) of patients were in spontaneous AF rhythm.

The mean ventilation rate was  $48 \pm 7$  rpm with a mean tidal volume of  $263 \pm 47$  mL. The median total procedure skin-to-skin time was 57 min (IQR 50–67), and the FAM acquisition time was 12 min (IQR 11–14). The fluoroscopy time was 43 s (IQR 20–71), and the fluoroscopy dose was 4.2 mGy (IQR 1.3–8.4). The proportion of patients with low-voltage area  $>1$  cm<sup>2</sup> during sinus rhythm mapping was higher in long-standing PeAF patients (19.5% vs. 38.2%,  $P = 0.04$ ). The median number of VisiTags was 28 (IQR 24–33) for the left pulmonary veins (LPVs) and 31 (IQR 28–39) for the RPVs, including the right carina. The median RF time was 7.7 min (IQR 6.5–8.6) for the LPVs and

8.8 min (IQR 7.7–10.0) for the RPVs. Acute PVI was achieved in all procedures. First-pass PVI was obtained in 103 (85%) of the RPVs and 103 (85%) of the LPVs, with an overall rate of complete first-pass of 73.6%. Acute reconnections were observed in 3 out of 250 (1.2%) LPVs and in 4 out of 250 (1.6%) RPVs. Complications occurred in four patients: two patients had intraprocedural severe pericardial effusion related to the transeptal puncture and required pericardiocentesis; two patients experienced pseudoaneurysm at inguinal access requiring percutaneous treatment. No patients undergoing personalized PeAF ablation experienced pericarditis. No neurological complications were observed. No patient died peri-procedurally nor during the follow-up.

### Left atrial wall thickness and ablation index

The wall thickness (WT) of the circumferential PV line was thicker in the LPVs as compared to the RPVs [1.64 mm (1.5–1.81) vs. 1.31 mm (1.16–1.57),  $P < 0.01$ ]. More specifically, anterior wall segments were thicker in the LPVs as compared to the RPVs [2.1 mm (1.9–2.4) vs. 1.4 mm (1.1–1.9),  $P < 0.01$ ], while posterior wall segments had similar WT in LPVs and RPVs [1.1 mm (0.9–1.3) vs. 1.0 mm (0.7–1.2),  $P = \text{NS}$ ]. Median WT values were higher for PVs with no first-pass during RF ablation with respect to the whole cohort [1.73 mm (1.57–1.98) vs. 1.64 mm (1.50–1.81)  $P = 0.02$  for LPVs; 1.46 mm (1.21–1.65) vs. 1.29 mm (1.16–1.57)  $P = 0.03$ , for RPVs]. No statistically significant differences in the WT of the PVs were found between PeAF and long-standing PeAF patients. Ladybug and histogram plots of the WT values for each PV segment are represented in *Figure 4*.

The median AI applied was 387 (IQR 360–410) for the anterior wall and 335 (IQR 300–375) for the posterior wall. More specifically, for the LPVs, the median AI applied was 405 (IQR 380–430) for the anterior wall and 345 (IQR 320–375) for the posterior wall, while for the RPVs was 380 (IQR 355–397) for the anterior wall and 341 (IQR 320–360) for the posterior wall.

### Clinical outcomes

All patients were maintained on AADs during the blanking period (3 months); 26 patients (21%) continued taking AADs after the end of

**Table 2** Patients' baseline characteristics according to persistent atrial fibrillation classification

	PeAF (n = 87)	Long-standing PeAF (n = 34)	Total patients (n = 121)	P-value
Age (years)	64.1 ± 9.7	65.5 ± 9.1	64.5 ± 9.5	0.52
Male	58 (66.7)	26 (76.5)	84 (69.4)	0.38
BMI (kg/m <sup>2</sup> )	29.1 ± 6.4	30.6 ± 5.1	29.6 ± 6.0	0.06
Hypertension	46 (52.8)	24 (70.6)	70 (57.8)	0.10
Dyslipidaemia	25 (28.7)	14 (41.2)	39 (32.2)	0.28
Smoke history	5 (5.71)	1 (2.9)	6 (5.0)	0.67
Type 2 diabetes	13 (14.9)	8 (23.5)	21 (17.3)	0.28
LVEF > 55%	66 (75.9)	29 (85.3)	95 (78.5)	0.33
LA diameter (mm)	42.5 ± 6.0	46.1 ± 4.5	43.5 ± 5.8	<b>&lt;0.01</b>
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.88
HAS-BLED score	1.0 (0.0–2.0)	1.0 (0.2–1.0)	1.0 (0.0–2.0)	0.35
Longest AF episode (months)	2.0 (1.0–2.0)	16.0 (14.2–17.0)	2.0 (1.0–13.0)	<b>&lt;0.01</b>
Time since diagnosis (months)	8.0 (7.0–9.0)	22.0 (21.0–24.0)	9.0 (8.0–20.0)	<b>&lt;0.01</b>
Baseline Medications				
Beta-blocker	31 (38.3)	14 (43.8)	45 (37.2)	0.67
Flecainide	15 (17.2)	6 (17.6)	21 (17.4)	0.99
Propafenone	2 (2.3)	1 (2.9)	3 (2.5)	0.99
Amiodarone	42 (48.3)	22 (64.7)	64 (52.9)	0.11
Underlying cardiomyopathy				
None	55 (63.2)	21 (61.8)	76 (62.8)	0.64
Hypertensive	15 (17.6)	4 (11.8)	19 (15.7)	
Ischaemic	4 (4.7)	3 (8.8)	7 (5.8)	
Valvular	2 (2.4)	2 (5.9)	4 (3.3)	
Hypertrophic	1 (1.2)	1 (2.9)	2 (1.7)	
Other	9 (10.6)	3 (8.8)	12 (9.9)	

Results are reported as n (%) for categorical variables and median (interquartile range) or mean ± standard deviation for continuous variables. Statistically significant differences between the two groups are shown in bold ( $P < 0.05$ ).

BMI, body mass index; LA, left atrium; LVEF, left ventricle ejection fraction; PeAF, persistent atrial fibrillation; PVs, pulmonary veins.

the blanking period. At 12-month follow-up, primary outcome has been reached in the 79% of patients. At the median follow-up of 16 months (IQR 8–21), primary outcome has been reached in the 73% (95% IC: 65–82) of patients. The primary outcome rate was significantly higher in patients with PeAF with respect to those with long-standing PeAF diagnosis ( $P = 0.044$ ). The primary outcome rate was significantly higher in patients presenting sinus rhythm at the beginning of the ablation procedure with respect to those presenting spontaneous AF ( $P < 0.05$ ). The presence of low-voltage area  $>1 \text{ cm}^2$  during sinus rhythm mapping was more frequent in patients reporting AF/AT recurrence during the follow-up (20% vs. 41%,  $P = 0.03$ ). Moreover, at logistic regression analysis, the presence of low-voltage area  $>1 \text{ cm}^2$  during sinus rhythm mapping resulted an independent predictor of AF/AT recurrence during the follow-up (OR = 2.9, 95%CI 1.2–7.2,  $P = 0.02$ ). There was no significant difference in AF/AT recurrence between the group of patients who discontinued AADs at the end of blanking period and the group with prolonged AADs intake ( $P = 0.32$ ). Left PVs WT values were significantly higher in patients with AF/AT recurrence during the follow-up with respect to the patient group without recurrences ( $1.80 \pm 0.17 \text{ mm}$  vs.  $1.63 \pm 0.27 \text{ mm}$ ;  $P = 0.01$ ). More specifically, a significant difference of WT values was reported for the left anterior carina ( $2.40 \pm 0.28 \text{ mm}$  vs.  $2.22 \pm 0.25 \text{ mm}$ ;  $P = 0.01$ ), while a trend towards higher values of WT was reported for left roof ( $P = 0.07$ )

and anterior left superior ( $P = 0.09$ ) segments (Table 5). At the logistic regression analysis, left PVs WT  $>1.75 \text{ mm}$  resulted an independent predictor of AF/AT recurrence during the follow-up (OR = 12.2, 95% CI 1.9–96.4,  $P = 0.01$ ). Patients' baseline characteristics according to LPVs WT are reported in Table 6. At the median follow-up, a second ablation was performed in 18 (62%) out of 29 patients with AF/AT recurrence. Specifically, 10 (56%) out of 18 patients presented reconnections in both RPVs and LPVs, only 3 patients in RPVs, and only 1 patient in LPVs, while 4 (22%) out of 18 patients undergoing redo procedure presented isolated PVs. Median WT values were higher for PVs with reconnection found in the redo procedures as compared to the median WT of the corresponding PVs of the whole cohort [1.77 mm (1.65–2.14) vs. 1.64 mm (1.50–1.81)  $P = 0.01$  for LPVs; 1.43 mm (1.25–1.61) vs. 1.29 mm (1.16–1.57)  $P = 0.05$ , for RPVs].

Kaplan–Meier curves for primary outcome are shown in Figure 5.

## Discussion

### Main findings

To our knowledge, this is the first study reporting the feasibility, the efficacy, and the efficiency of a PVI-only approach using a

**Table 3** Patients' baseline characteristics according to atrial arrhythmia recurrence during the follow-up

	No recurrence (n = 92)	Arrhythmia recurrence (n = 29)	Total patients (n = 121)	P-value
Age (years)	64.0 ± 9.4	66.0 ± 10.0	64.5 ± 9.5	0.37
Male	64 (69.6)	20 (69.0)	84 (69.4)	0.99
BMI (kg/m <sup>2</sup> )	29.8 ± 6.1	29.1 ± 5.5	29.6 ± 6.0	0.62
Hypertension	52 (56.5)	18 (62.1)	70 (57.8)	0.66
Dyslipidaemia	29 (31.5)	10 (34.5)	39 (32.2)	0.64
Smoke history	5 (5.4)	1 (3.4)	6 (5.0)	0.99
Type 2 diabetes	15 (16.3)	6 (20.7)	21 (17.3)	0.56
LVEF >55%	70 (76.1)	25 (86.2)	95 (78.5)	0.31
LA diameter (mm)	42.9 ± 6.0	45.4 ± 4.7	43.5 ± 5.8	<b>0.02</b>
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.32
HAS-BLED score	1.0 (0.0–2.0)	1.0 (0.0–1.0)	1.0 (0.0–2.0)	0.85
Longest AF episode (months)	2.0 (1.0–13.0)	3.0 (2.0–15.0)	2.0 (1.0–13.0)	0.14
Time since diagnosis (months)	9.0 (8.0–18.2)	10.0 (8.0–21.0)	9.0 (8.0–20.0)	0.32
Baseline medications				
Beta-blocker	32 (34.8)	13 (44.8)	45 (37.2)	0.17
Flecainide	13 (14.1)	8 (27.6)	21 (17.4)	0.16
Propafenone	3 (3.3)	0 (0.0)	3 (2.5)	0.99
Amiodarone	52 (56.5)	12 (41.4)	64 (52.9)	0.20
Underlying cardiomyopathy				
None	58 (63.0)	18 (62.1)	76 (62.8)	0.68
Hypertensive	14 (15.2)	5 (17.2)	19 (15.7)	
Ischaemic	5 (5.4)	2 (6.9)	7 (5.8)	
Valvular	3 (3.3)	1 (3.4)	4 (3.3)	
Hypertrophic	1 (1.1)	1 (3.4)	2 (1.7)	
Other	11 (11.9)	1 (3.4)	12 (9.9)	

Results are reported as n (%) for categorical variables and median (interquartile range) or mean ± standard deviation for continuous variables. Statistically significant differences between the two groups are shown in bold ( $P < 0.05$ ).

BMI, body mass index; LA, left atrium; LVEF, left ventricle ejection fraction; PeAF, persistent atrial fibrillation; PVs, pulmonary veins.

personalized local LAWV-guided titration of AI for PeAF ablation. The main findings of the study are the following: (i) local LAWV-guided ablation is a feasible approach for PeAF ablation leading to a high first-pass rate of PVI; (ii) the presented approach is safe and reported no RF-related adverse events; (iii) the procedure is efficient, reporting low procedural requirements in terms of procedure, fluoroscopy, and RF time; (iv) LAWV-guided PVI-only strategy for PeAF ablation was associated with a high recurrence-free survival at a median follow-up of 16 months, probably due to durable lesions; (v) no first-pass during the first procedure and reconnection sites at redo ablation are mostly encountered in PVs with the thickest antral regions. Our study is the first proof-of-concept demonstration that a LAWV-guided ablation approach is feasible, safe, and effective also in patients with PeAF, who differ from paroxysmal AF patients, being characterized by an increased LA remodelling and a higher prevalence of comorbidities such as hypertension, diabetes, and left ventricular dysfunction.<sup>29</sup> Moreover, the reported single-centre prospective study is an initial experience of a novel approach, and its results support the study design and the patient sample calculation of the ongoing multicentre randomized PeAF-by-LAWV trial (NCT05396534) which have a control arm (AI-guided PVI approach according to the CLOSE protocol) and could allow to compare the results of the two procedural approaches.

## LAWV-guided pulmonary vein isolation approach

Non-transmural ablation is considered a major determinant of post-ablation arrhythmia recurrence; El Haddad et al.<sup>30</sup> showed that PV reconnection could be due to an insufficient lesion depth. Several studies demonstrated that AI accurately predicts the depth of the ablation lesions; therefore, AI has been proposed as a novel marker of ablation lesion quality. Previous analysis has also identified that minimum AI values of 540 and 380 were predictive of freedom from acute reconnection in the anterior/roof and the posterior/inferior segments of PVs antrum, respectively.<sup>17</sup> However, growing evidence support the complex anatomical reality of the LA and encompasses the intra- and inter-patient regional variability of LAWV distribution for both anterior and posterior segments of PV–LA junction.<sup>31,32</sup> In the present study, LAWV ranged from 0.51 to 2.21 mm in the posterior wall and from 0.86 to 4.43 mm in the anterior wall. Therefore, fixed AI targets and a dichotomized anterior/posterior ablation approach could be an oversimplification and may not fully reflect this variability, leading to non-transmural lesions in the thickest LA regions and, on the other hand, to excessive RF applications in the thinnest ones.

The MDCT-derived LAWV measurements have been reliably validated on a porcine model,<sup>31</sup> and integrating 3D LAWV maps into the



**Table 4** Acute procedural data according to persistent atrial fibrillation classification

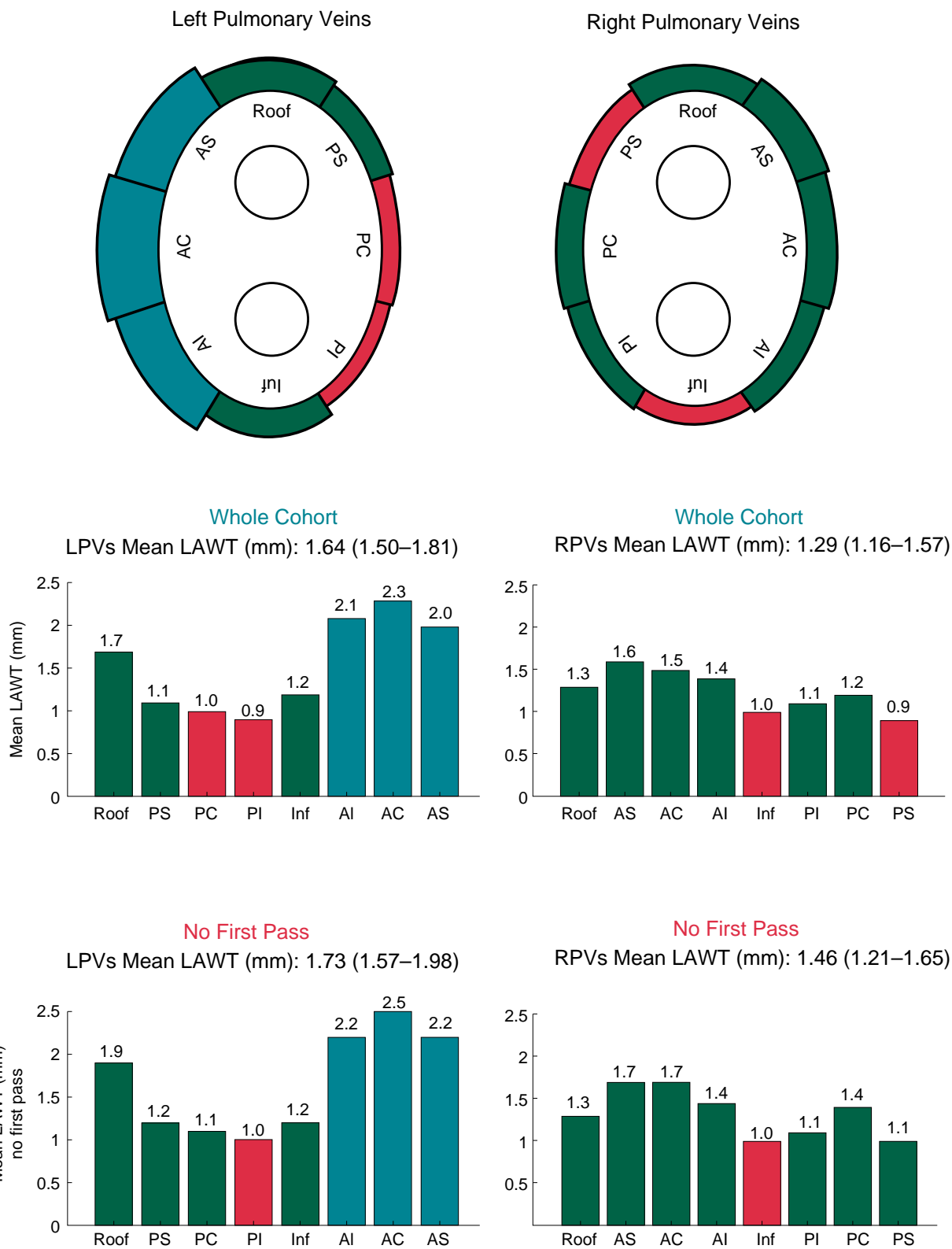
	PeAF (n = 87)	Long-standing PeAF (n = 34)	Total patients (n = 121)	P-value
AF at the beginning of the procedure	30 (34.4)	13 (38.2)	43 (35.5)	0.99
Procedure time skin-to-skin (min)	57.0 (50.0–65.5)	60.0 (52.5–71.0)	57.0 (50.0–67.0)	0.15
FAM time (min)	12.0 (11.0–14.0)	12.5 (11.0–14.0)	12.0 (11.0–14.0)	0.42
Fluoroscopy time (s)	40.0 (18.0–68.0)	52.5 (33.0–71.2)	43.0 (20.0–71.0)	0.07
Fluoroscopy dose (mGy)	3.5 (1.2–7.5)	4.7 (3.2–10.2)	4.2 (1.3– 8.4)	0.17
<0.5 mV points during SR (%)	6.0 (1.0–11.0)	16.0 (13.0–20.0)	7.0 (2.0–14.0)	<b>&lt;0.01</b>
Low-voltage area > 1cm <sup>2</sup> during SR	17 (19.5)	13 (38.2)	30 (24.8)	<b>0.04</b>
Total RF time (min)	15.8 (14.1–18.4)	16.7 (15.5–18.9)	16.5 (14.3–18.4)	0.17
Total VisiTags	59 (53–69)	64 (58–71)	60 (54–70)	0.14
Mean anterior AI	390 (365–408)	380 (360–405)	387 (360–410)	0.40
Mean posterior AI	337 (310–375)	330 (305–370)	335 (300–375)	0.45
<b>Right pulmonary veins</b>				
RF time (min)	8.6 (7.6–9.7)	9.0 (8.0–10.9)	8.8 (7.7–10.0)	0.12
VisiTags	31 (27–38)	33 (31–41)	31 (28–39)	0.10
Mean VisiTag time (s)	14.9 (13.0–18.9)	14.8 (12.7–18.1)	14.9(12.8–18.5)	0.22
Mean anterior AI	382 (357–398)	379 (354–396)	380 (355–397)	0.41
Mean posterior AI	343 (325–361)	339 (320–350)	341 (320–360)	0.39
First-pass isolation	75 (86.2)	28 (82.4)	103 (85.1)	0.58
Acute reconnection	2 (2.3)	2 (5.9)	4 (3.3)	0.19
Anterior right PVs antrum WT (mm)	1.5 (1.3–1.9)	1.4 (1.1–1.9)	1.4 (1.1–1.9)	0.40
Posterior right PVs antrum WT (mm)	1.1 (0.9–1.2)	0.98 (0.8–1.2)	1.0 (0.7–1.2)	0.37
<b>Left pulmonary veins</b>				
RF time (min)	7.5 (6.5–8.6)	7.7 (6.5–9.1)	7.7 (6.5–8.6)	0.42
VisiTags	28 (23–33)	31 (27–33)	28 (24–33)	0.40
Mean VisiTag time (s)	15.0 (13.0–19.0)	14.8 (12.7–18.2)	15.0 (12.7–19.0)	0.22
Mean anterior AI	408 (382–431)	403 (379–428)	405 (380–430)	0.36
Mean posterior AI	348 (330–376)	342 (320–370)	345 (320–375)	0.29
First-pass isolation	73 (83.9)	30 (88.2)	103 (85.1)	0.78
Acute reconnection	2 (2.3)	1 (2.9)	3 (2.5)	0.99
Anterior left PVs antrum WT (mm)	2.04 (2.0–2.4)	1.98 (1.8–2.2)	2.1 (1.9–2.4)	0.45
Posterior left PVs antrum WT (mm)	1.13 (1.0–1.3)	0.99 (0.8–1.1)	1.1 (0.9–1.3)	0.31
Overall acute first-pass	65 (74.7)	24 (70.6)	89 (73.6)	0.65
Overall acute reconnection	3 (3.4)	3 (8.8)	6 (5.0)	0.13
Acute procedural complication	2 (2.3)	2 (5.9)	4 (3.3)	0.45

Results are reported as n (%) for categorical variables and median (interquartile range) or mean ± standard deviation for continuous variables. Statistically significant differences between the two groups are shown in bold ( $P < 0.05$ ).

AI, ablation index; FAM, fast anatomical map; RF, radiofrequency; SR, sinus rhythm; WT, wall thickness.

navigation system allows to be aware of the real-time local LAWT in contact with the ablation catheter tip during the procedure. The use of this tool has been already described by our group in order to aid paroxysmal AF ablation<sup>18</sup> and AF reablation procedures.<sup>20</sup> The aim of the proposed personalized ablation is that modifying the ablation line to avoid the thickest atrial areas and rising the AI targets in the thickest segments may likely improve the lesion transmural and consequently the PVI durability. Conversely, lowering the AI targets in the thinnest segments may reduce the procedure duration and improve the safety by avoiding unnecessary RF application. In the recent large non-randomized Surpoint trial,<sup>33</sup> Di Biase *et al.* reported the excellent safety and

effectiveness outcomes of a standardized AI-guided ablation protocol for paroxysmal AF ablation; the LAWT-guided approach may add complexity to the procedure in terms of pre-procedural scanning, segmentation, and map integration, but the potential benefits of a personalized approach may outweigh these challenges, particularly in terms of minimizing the procedure and the RF times, in order to maximize the procedural efficiency. Moreover, the small increase in overall complexity due to LA segmentation will be further reduced in the near future because of the progressive increase in the use of artificial intelligence that could enable a full-automatic segmentation process, thereby reducing complexity and enabling a more streamlined approach to a personalized AF ablation.



**Figure 4** Ladybug and histogram plots of the wall thickness values for each pulmonary vein segment in the whole cohort and in the no first-pass subgroup.

**Table 5** Left atrial wall thickness values in the total cohort of patients and according to AF/AT recurrence during the follow-up

	<b>No recurrence (n = 92)</b>	<b>Arrhythmia recurrence (n = 29)</b>	<b>Total patients (n = 121)</b>	<b>P-value</b>
<b>PVs antrum</b>	1.65 ± 0.17	1.72 ± 0.29	1.66 ± 0.19	0.44
<b>Left PVs antrum</b>	1.63 ± 0.27	1.80 ± 0.17	1.66 ± 0.25	<b>0.01</b>
Left roof	1.68 ± 0.31	1.76 ± 0.32	1.71 ± 0.29	0.07
Anterior left superior	1.95 ± 0.28	2.11 ± 0.35	2.02 ± 0.31	0.09
Posterior left superior	1.09 ± 0.27	1.13 ± 0.33	1.10 ± 0.27	0.22
Anterior left carina	2.22 ± 0.25	2.40 ± 0.28	2.31 ± 0.25	<b>0.01</b>
Posterior left carina	0.98 ± 0.32	1.01 ± 0.25	1.00 ± 0.26	0.36
Anterior left inferior	2.08 ± 0.26	2.11 ± 0.41	2.09 ± 0.29	0.31
Posterior left inferior	0.90 ± 0.18	0.92 ± 0.28	0.91 ± 0.24	0.45
Left floor	1.19 ± 0.21	1.20 ± 0.33	1.20 ± 0.22	0.55
<b>Right PVs antrum</b>	1.31 ± 0.29	1.36 ± 0.35	1.32 ± 0.30	0.42
Right roof	1.30 ± 0.28	1.34 ± 0.34	1.33 ± 0.23	0.25
Anterior right superior	1.61 ± 0.31	1.65 ± 0.40	1.62 ± 0.35	0.15
Posterior right superior	0.90 ± 0.19	0.91 ± 0.27	0.91 ± 0.23	0.56
Anterior right carina	1.51 ± 0.25	1.57 ± 0.29	1.54 ± 0.27	0.35
Posterior right carina	1.22 ± 0.26	1.21 ± 0.28	1.22 ± 0.27	0.55
Anterior right inferior	1.40 ± 0.24	1.41 ± 0.32	1.41 ± 0.28	0.62
Posterior right inferior	1.10 ± 0.21	1.08 ± 0.22	1.10 ± 0.20	0.35
Right floor	1.00 ± 0.22	1.01 ± 0.25	1.01 ± 0.23	0.39

Results are reported as mean ± standard deviation for continuous variables. Statistically significant differences between the two groups are shown in bold ( $P < 0.05$ ). PV, pulmonary vein.

## Long-term clinical outcomes

The presented results are in line with the long-term clinical outcomes reported in literature about PeAF patients undergoing PVI-only ablation strategy. In the recent PRAISE trial,<sup>14</sup> clinical recurrence was documented in the 20% of patients at the end of the 12-month follow-up. The STAR AF II trial<sup>11</sup> reported a recurrence-free survival of 59% at the 18-month follow-up within the PVI-only ablation arm. In the present study, we reported a recurrence-free survival rate of 79% at the 12-month follow-up and of 73% at the median 16-month follow-up. In line with the previous findings,<sup>9</sup> long-term outcomes in the case of long-standing PeAF were significantly worse than those of patients with PeAF episodes lasting less than 1 year.

Berruzo *et al.*<sup>34</sup> showed that hypertension and LA diameter are independent pre-procedural predictors of AF recurrence after PVI to treat AF. A meta-analysis published by D'Ascenzo *et al.*<sup>35</sup> has shown that a PVI-only approach for PeAF patients might present a more favourable long-term outcome in case of LA diameter < 50 mm and non-valvular AF. In addition, it has been shown that the absence of early recurrence during the classical 3-month blanking period is associated with a higher rate of recurrence-free survival at long-term follow-up.<sup>10</sup>

Moreover, McCready *et al.*<sup>36</sup> reported that in a population of mainly long-standing PeAF, LA size was the major determinant of recurrence after ablation. In line with these previous findings, the presented study reported higher values of LA diameter in patients with arrhythmia recurrence during the follow-up ( $P = 0.02$ ). Furthermore, in our PeAF cohort, patients with large low-voltage areas demonstrated a higher recurrence rate after PVI-only ablation.<sup>37–39</sup>

## Safety outcomes

Overdosing may contribute to increase the risk of serious complications such as atrial perforation and atriopharyngeal fistula<sup>9</sup>; for this reason, the experts recommend the use of lower energy when RF is applied in thinnest areas and in the posterior aspect of LA.<sup>9</sup> An imaging modality that allows to localize the areas of decreased wall thickness more accurately may facilitate a safer RF energy delivery. Notably, we reported no RF-related adverse events, such as deaths, strokes, atriopharyngeal fistulas, or cases of symptomatic PV stenosis.

Moreover, MDCT images post-processing permits to obtain the oesophageal fingerprinted isodistance map and to integrate it into the navigation system<sup>22</sup>: this information permits to personalize the

**Table 6** Patients' baseline characteristics according to the left pulmonary veins wall thickness

	Left PVs LAWT ≤ 1.75 mm (n = 76)	Left PVs LAWT > 1.75 mm (n = 45)	Total patients (n = 121)	P-value
Age (years)	65.1 ± 9.9	63.4 ± 8.8	64.5 ± 9.5	0.34
Male	46 (60.5)	38 (84.4)	84 (69.4)	<b>0.01</b>
BMI (kg/m <sup>2</sup> )	29.2 ± 6.1	30.6 ± 5.7	29.6 ± 6.0	0.25
Hypertension	42 (55.2)	28 (62.2)	70 (57.8)	0.24
Dyslipidaemia	26 (34.2)	13 (28.9)	39 (32.2)	0.54
Smoke history	4 (5.3)	2 (4.4)	6 (5.0)	0.99
Type 2 diabetes	13 (17.1)	8 (17.8)	21 (17.3)	0.80
LVEF >55%	61 (80.3)	34 (75.6)	95 (78.5)	0.65
LA diameter (mm)	43.2 ± 5.8	44.2 ± 5.9	43.5 ± 5.8	0.47
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.74
HAS-BLED score	1.0 (0.0–1.2)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.56
Longest AF episode (months)	2.0 (2.0–14.0)	2.0 (1.0–8.0)	2.0 (1.0–13.0)	0.13
Time since diagnosis (months)	9.0 (8.0–20.2)	9.0 (8.0–14.0)	9.0 (8.0–20.0)	0.25
Baseline medications				
Beta-blocker	28 (36.8)	17 (37.8)	45 (37.2)	0.69
Flecainide	11 (14.5)	10 (22.2)	21 (17.4)	0.32
Propafenone	2 (2.6)	1 (2.2)	3 (2.5)	0.99
Amiodarone	43 (56.6)	21 (46.7)	64 (52.9)	0.35
Underlying cardiomyopathy				
None	52 (68.4)	24 (53.3)	76 (62.8)	0.31
Hypertensive	8 (10.5)	11 (24.4)	19 (15.7)	
Ischaemic	4 (5.3)	3 (6.7)	7 (5.8)	
Valvular	3 (3.9)	1 (2.2)	4 (3.3)	
Hypertrophic	1 (1.3)	1 (2.2)	2 (1.7)	
Other	8 (10.5)	4 (8.9)	12 (9.9)	

Results are reported as n (%) for categorical variables and median (interquartile range) or mean ± standard deviation for continuous variables. Statistically significant differences between the two groups are shown in bold ( $P < 0.05$ ).

BMI, body mass index; LA, left atrium; LAWT, left atrial wall thickness; LVEF, left ventricle ejection fraction; PeAF, persistent atrial fibrillation; PVs, pulmonary veins.

ablation line moving it away from the areas of the LA posterior wall where the atrioesophageal distance is the shortest and to reduce AI delivery when ablation through these areas is unavoidable. This information combined with the use of the oesophageal temperature probe may reduce the possibility of oesophageal heating, therefore increasing procedural safety.<sup>22</sup>

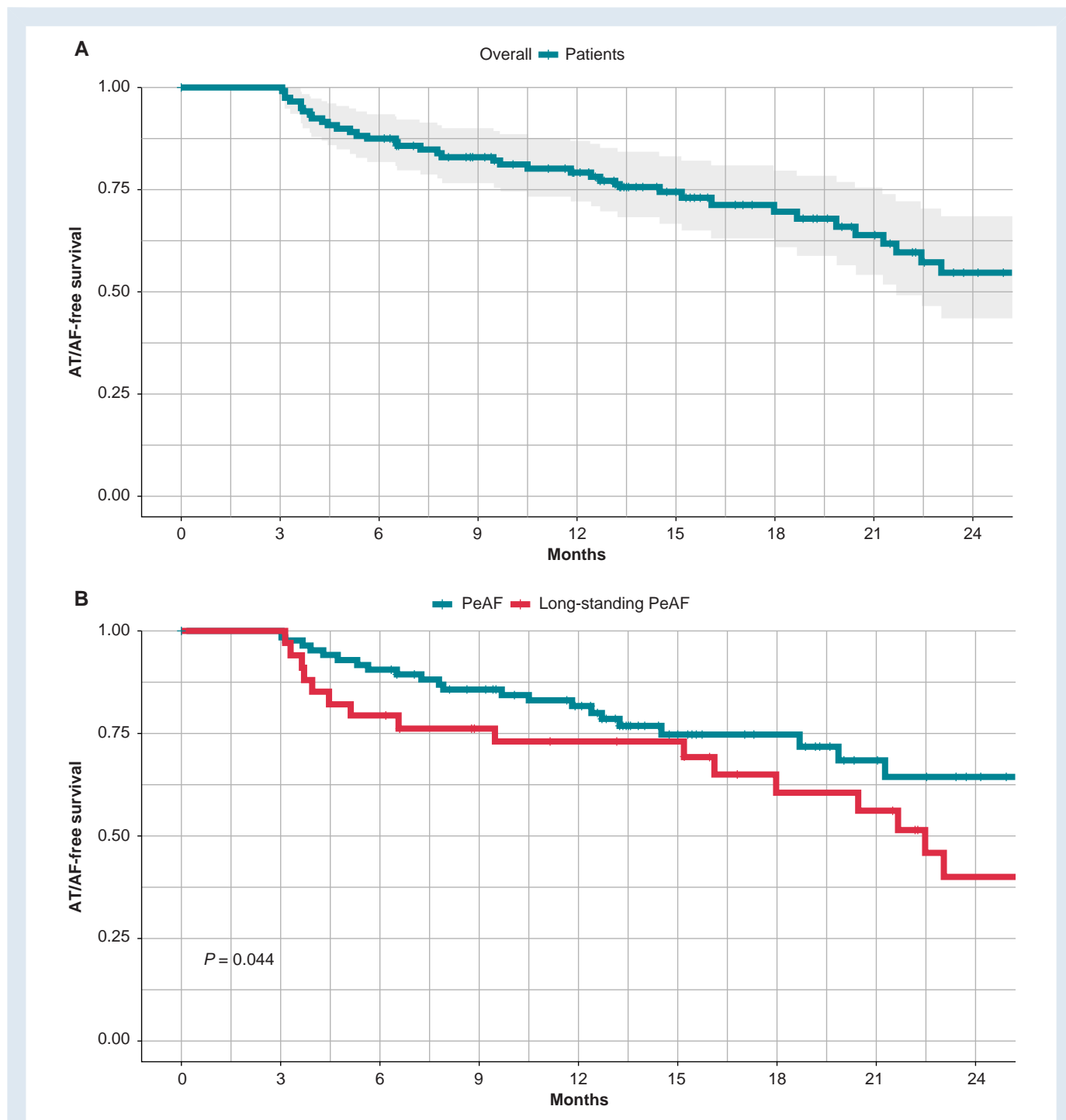
## Procedural efficiency

The goal of PVI is to deliver enough energy to prevent PV reconnection and, on the other hand, to avoid unnecessary and potentially harmful excess of RF. In the PRAISE trial,<sup>14</sup> PeAF patients were treated with PVI-only RF ablation according to the CLOSE protocol; they reported a procedure time of 158 ± 34 min, a RF time of 36 ± 9 min, and a fluoroscopy time of 12 min. In the PVI-only subgroup of the STAR AF II trial,<sup>11</sup> procedural outcomes showed a procedure time of 167 ± 55 min and a fluoroscopy time of 29 ± 16 min. In the present study, low procedural requirements and low median AI values for both posterior and anterior walls of PV antrum were reported. This was due to the LAWT-guided AI titration and to the personalized ablation line aiming to avoid the thickest LA regions whenever possible. The use of a standardized stepwise near zero-fluoroscopy approach with TOE guidance<sup>25</sup> and the use of the pre-procedural imaging integration

may explain the low fluoroscopy requirements. As reported by Marrouche *et al.*,<sup>12</sup> procedure duration is an important issue, especially keeping in mind that a higher rate of complications has been generally observed in ablations requiring longer procedural times, regardless of the strategy used.

## LAWT information

In line with the literature,<sup>40</sup> mean LAWT values encountered in the presented cohort of PeAF patients are higher with respect to those of a previous published study reporting the outcomes of LAWT-guided ablation in patients with paroxysmal AF. Notably, direct measurements of LA on human myocardial specimens performed by Hall *et al.*<sup>41</sup> showed mean thickness values (1.86 mm for anterior and 1.4 mm for posterior segments) comparable to that reported by our group. Moreover, in keeping with previous findings,<sup>42</sup> our data showed a trend towards thinner values of LAWT in the long-standing PeAF subgroup. The present study agrees with the data by Inoue *et al.*,<sup>43</sup> that reported a higher AF recurrences rate in patients with higher LAWT values ( $P < 0.001$ ) and that reconnection segments were found at the thickest antral regions ( $P = 0.038$ ). Moreover, Mulder *et al.*<sup>44</sup> reported that AI, force-time integral, and impedance drop did not correlate with PV reconnection, whereas AI adjusted to wall thickness had predictive



**Figure 5** Atrial arrhythmia-free survival Kaplan–Meier curves. Overall curve (4a) and according to persistent atrial fibrillation classification (4b).

value for PV reconnection. These issues further support that having a real-time local myocardial thickness information available during the ablation may aid to create transmural ablation lesions and prevent PV reconnection after PVI.

### Limitations

This is a proof-of-concept single-centre pilot study. The main limitations of the study are the single-centre design and the lack of a control group, so that we cannot draw definitive conclusions or compare the presented approach to a standard AI-guided PVI ablation: a randomized

multicentre trial is ongoing to overcome these limitations. Secondly, the AI targets for each LAWTT range were based on data already used in two studies<sup>18,20</sup>; further research is needed to evaluate the optimal parameters of AI titration according to the LAWTT. Thirdly, despite the low complication rate, the study size is too small to provide a definitive safety assessment of personalized LAWTT-guided ablation strategy for PeAF. Fourthly, all procedures were performed under general anaesthesia, using mechanical ventilation with HFLTV, and with CARTO3 mapping system; thus, the present study results could not

be the same if other procedural settings are used. Fifthly, antiarrhythmic therapy was not systematically withdrawn after the blanking period and may have improved clinical success; however, the percentage of patients taking AADs is comparable to that of studies in the literature.<sup>17</sup> Sixthly, we adopted the classical 3-month blanking period, but we cannot exclude that a shorter blanking period might be preferable.<sup>45,46</sup> Seventhly, slightly different LAWV values have been reported by other groups; this could partly depend on different MDCT acquisition protocols and on differences between segmentation tools and LAWV rendering. Finally, in the absence of continuous ECG monitoring or periodic single-lead ECG monitoring by wearable devices,<sup>47–49</sup> it is possible that brief asymptomatic episodes were missed, thereby overestimating the success rates.

## Conclusions

The real-time intraprocedural knowledge of the local LAWV could guide PeAF ablation permitting to move away the ablation line from the thickest LA regions and to titrate RF delivery by increasing AI in the thickest segments of the PV antrum; at the same time, this novel approach allow to avoid unnecessary high amounts of RF energy delivery in the thinnest part of the PV antrum, improving procedural efficiency while maintaining a recurrence-free survival comparable to that reported in literature. No first-pass during the first procedure and reconnection sites at redo ablation are mostly encountered in PVs with the thickest antral regions. A multicentre randomized trial comparing the LAWV-guided and the standard AI-guided PVI for PeAF ablation is in progress (ClinicalTrials.gov, NCT05396534). Patient recruitment started on June 2022 and the enrolment completion is estimated by April 2023.

## Author's contributions

G.F.: study concept and design, manuscript drafting, critical revision. D.P.: study concept and design, manuscript drafting, critical revision. D.S.-I.: study concept and design, manuscript drafting, critical revision. P.F.: manuscript drafting, critical revision. C.T.: manuscript drafting, critical revision. A.S.: contributed to major revision answers, critical revision. B.J.: manuscript drafting, critical revision. D.V.: manuscript drafting, critical revision. A.B.: manuscript drafting, critical revision. J.A.: manuscript drafting, critical revision. J.M.-S.: manuscript drafting, critical revision. P.F.: manuscript drafting, critical revision. C.G.: manuscript drafting, critical revision. A.C.: manuscript drafting, critical revision. J.M.C.: manuscript drafting, critical revision. R.S.: manuscript drafting, critical revision. A.O.: manuscript drafting, critical revision. M.H.: manuscript drafting, critical revision. O.C.: manuscript drafting, critical revision. J.-T.O.-P.: manuscript drafting, critical revision. J.M.A.: manuscript drafting, critical revision. A.B.: study concept and design, manuscript drafting, critical revision.

**Conflict of interest:** A.B. is a stockholder of Galgo Medical. D.S.-I. is an employee of Biosense Webster. All remaining authors have declared no conflicts of interest.

## Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local ethics committee.

## Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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