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CLINICAL RESEARCH

Impact of atrial fibrillation phenotype and left atrial volume on outcome after pulmonary vein isolation

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Aims Pulmonary vein isolation (PVI) is increasingly performed in patients with atrial fibrillation (AF). Both AF phenotype and left atrial (LA) volume have been shown to influence ablation outcome. The inter-relationship of the two is incompletely understood. We aimed to investigate the impact of AF phenotype vs. LA volume on outcome after PVI.

Methods and results In a retrospective analysis of a prospective registry of patients undergoing a first PVI, the association of AF phenotype and LA volume index (LAVI) was assessed as well as their impact on AF recurrence during follow-up. Overall, 476 patients were enrolled (median age 63 years, 29% females, 65.8% paroxysmal AF). Obesity, hypertension, chronic kidney disease, and heart failure were all significantly more frequent in persistent AF. After 1 year, single-procedure, freedom from arrhythmia recurrence was 61.5%. Patients with paroxysmal AF had better outcomes compared with patients with persistent AF (65.6 vs. 52.7%, $P = 0.003$), as had patients with no/mild vs. moderate/severe LA dilation (LAVI <42 mL/m^2 67.1% vs. LAVI ≥ 42 mL/m^2 53%, $P < 0.001$). The combination of both parameters refined prediction of 1-year recurrence ($P < 0.001$). After adjustment for additional clinical risk factors in multivariable Cox proportional hazard analysis, both AF phenotype and LAVI ≥ 42 mL/m^2 contributed significantly towards the prediction of 1-year recurrence.

Conclusion Atrial fibrillation phenotype and LA volume are independent predictors of outcome after PVI. Persistent AF with no/mild LA dilation has a similar risk of recurrence as paroxysmal AF with a moderate/severe LA dilation and should be given similar priority for ablation.

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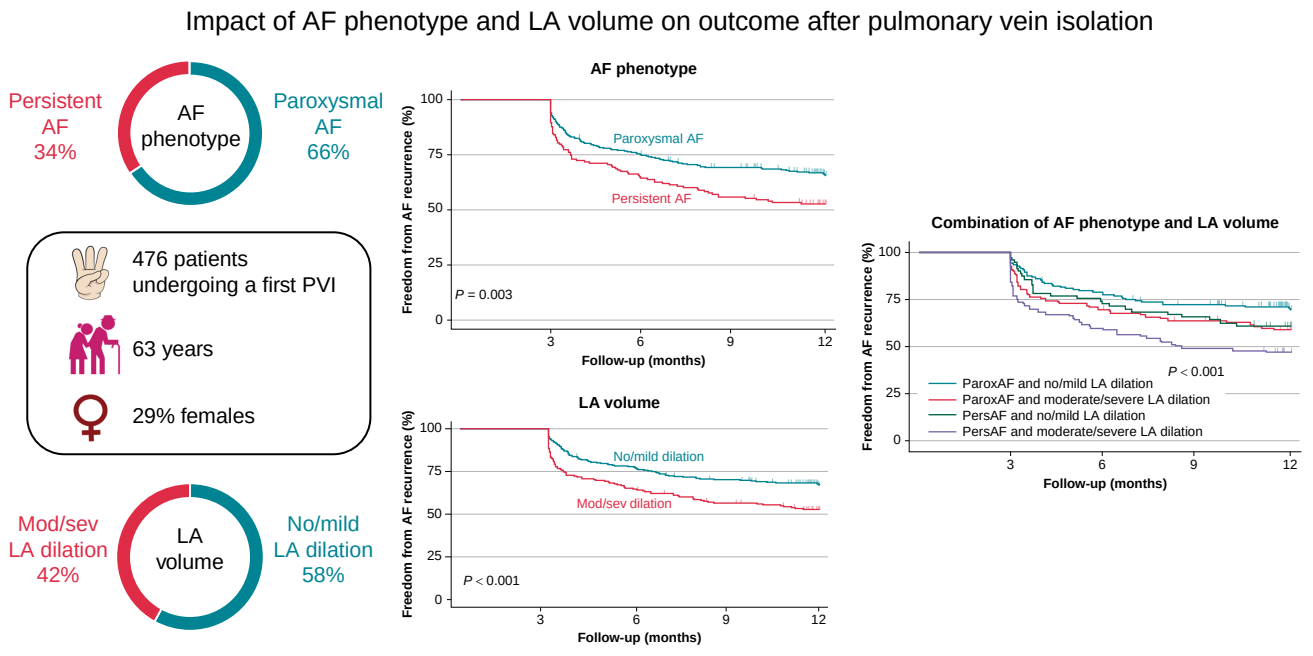
Graphical Abstract



Keywords Atrial fibrillation (AF) • Pulmonary vein isolation (PVI) • Left atrial volume (LAV) • Left atrial volume index (LAVI)

What's new?

- Combination of atrial fibrillation (AF) phenotype and left atrial (LA) volume index has prognostic value for AF recurrence after pulmonary vein isolation.
- Patients with persistent AF and no/mild LA dilation have outcomes comparable with patients with paroxysmal AF and moderate/severe LA dilation.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in adults and responsible for significant morbidity including recurrent hospitalizations. The current prevalence is 2–4% in the general population.[1] Pulmonary vein isolation (PVI) is superior to antiarrhythmic drugs with regard to both symptom control and prevention of arrhythmia recurrence.[2,3] However, despite improved technologies, recurrence rates after PVI remain high.[4,5]

Several risk factors for AF recurrence after PVI have been identified including AF phenotype, left atrial (LA) dilation, AF duration, age, sleep apnoea, obesity, renal dysfunction, and advanced atrial cardiomyopathy on magnetic resonance imaging (MRI). Among those, an increased LA volume is one of the best predictors for both progression from paroxysmal AF (paroxAF) to persistent AF (persAF) and for worse outcomes after PVI. While PVI is recommended as a first-line therapy in patients with paroxAF in the current guidelines, the role of PVI in patients with persAF is less well established due to worse outcomes compared with patients with paroxAF.[1,6,7]

In clinical practice, patients may present with persAF and a non-dilated LA and have good ablation outcomes after PVI. Conversely, patients with paroxAF and a severely dilated LA may show poor outcomes after PVI. Accordingly, focusing on AF phenotype as the primary criterion for patient selection for catheter ablation of AF may be inadequate. The inclusion of LA volume in clinical decision-making for AF ablation may improve patient selection.[1,8,9]

This study therefore aimed to investigate the inter-relationship of AF phenotype and LA volume on outcomes after PVI in ablation naïve patients.

Methods

Study sample

This retrospective analysis of a prospective registry was conducted in a tertiary care ablation centre in Switzerland (Inselspital University Hospital Bern). Patients undergoing a first PVI between January 2017 and April 2020 were enrolled. Patients without a pre-procedural echocardiography enabling measurement of LA volume index (LAVI) and patients with LA lesion sets beyond PVI were excluded from the study. This study was approved by the local Ethics Committee and complies with the principles of the Declaration of Helsinki. The authors vouch for data integrity.

Baseline evaluation

Each patient underwent a pre-procedural evaluation, including detailed assessment of clinical status, and standard blood tests. Patients were classified as paroxysmal if the duration of AF was <7 days and as persistent if AF lasted >7 days.[1] A two-dimensional transthoracic echocardiography (TTE) was performed, with acquisition of images in parasternal and apical views according to the guidelines from the American Society of Echocardiography.[10] The LA volume was measured from the temporal frame just prior to mitral valve opening on the four-chamber view and the two-chamber view. The resulting LA volume was calculated by the disk summation method of Simpson and adjusted for the patient's body surface to calculate the LAVI.[10]

Peri-procedural examination, sedation, and left atrial access

Before the procedure, patients underwent transoesophageal echocardiography and/or computed tomography (CT) to exclude intra-cardiac thrombi

and to obtain a detailed understanding of the left trial anatomy. Deep conscious sedation using midazolam, fentanyl, and propofol was used, guided by a physician-led, nurse-administered protocol.[11] A small subset of patients with a high risk of sedation complications underwent general anaesthesia. Left atrial access was obtained by fluoroscopy-guided transseptal puncture using a standard transseptal sheath. Heparin was administered to maintain an activated clotting time above 350 s during the procedure.

Protocol for cryoballoon ablation

Cryoablation procedures were performed with a 28 mm cryoballoon catheter (Arctic Front Advance), a 20 mm circular mapping catheter (Achieve Advance), and a steerable sheath (FlexCath Advance; all Medtronic, Minneapolis, MN, USA). In case of an effective freeze (judged by the disappearance of all local pulmonary vein (PV) signals before 60s or reaching a temperature of −40°C), cryoablation was continued for 2 additional minutes after effect ('time-to-effect plus 2 min strategy').[12] In case of an ineffective freeze, the ablation was stopped and the balloon repositioned, aiming for better occlusion of the PV. Pulmonary vein isolation was verified at the end of the procedure with the assessment of Entrance- and Exit-Block in all PVs using the circular mapping catheter.

Protocol for radiofrequency ablation

Radiofrequency procedures were performed using a three-dimensional (3D) mapping system (CARTO3, Biosense Webster, Irvine, CA, USA) in combination with a contact force-sensing ablation catheter (Smarttouch SF, Biosense Webster) and a high-density multipolar mapping catheter (Pentaray, Biosense Webster). A steerable sheath was used (Destino Reach, Oscor, Palm Harbor, FL, USA). Ablation was performed by adhering to the CLOSE protocol.[13] Pulmonary vein isolation was verified by 3D mapping at the end of the procedure.

Follow-up

Patients were followed with 7-day Holter electrocardiograms after 3, 6, and 12 months. Cessation of anti-arrhythmic therapy was either recommend immediately after the procedure or the latest by 3 months after the procedure. The primary endpoint was the first recurrence of any atrial tachyarrhythmia (AF, atrial flutter, or atrial tachycardia) lasting longer than 30 s after a blanking period of 3 months.[1] Repeat ablation during the blanking period was considered to be a primary endpoint event.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or as median and inter-quartile range (IQR) and as count and percentages, as appropriate. Comparisons between groups were made using the χ^2 test (categorical variables) and Wilcoxon rank-sum test (continuous variables).

Univariate Cox regression analysis was used to identify hazard ratios (HRs) for individual predictors of arrhythmia-free survival. Multivariable Cox proportional hazards models were used to identify independent predictors of AF recurrence during 1 year of follow-up. Variables were included based on clinical relevance and literature review. Kaplan–Meier analyses were used to assess AF recurrence over a period of 365 days, across strata of AF phenotype, LA size, and the combination of AF phenotype and LA size. The log-rank and stratified log-rank test was used to assess the significant differences across strata. A *P*-value cut-off of <0.05 was used to indicate statistical significance. The statistical analyses were conducted using STATA 18 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX, USA: StataCorp LLC).

Results

Patient and procedural characteristics

Between 2017 and 2019, 597 patients underwent a first PVI for AF in our centre. Eighteen patients were excluded from the analysis due to prior ablation in an external hospital, 24 patients for LA substrate ablation in addition to PVI, and 76 patients due to insufficient TTE image quality not allowing LAVI measurement (see Supplementary material online, *Figure S1*). Three patients were lost to follow-up, leaving 476 patients for analysis.

Baseline and procedural characteristics according to AF phenotype are summarized in *Tables 1* and *2*. The majority of patients had paroxAF (n = 313, 65.7%). The median age was 63 years (IQR 56–70), and 138 (29%) were female. When compared with patients with persAF, patients with paroxAF had lower body mass index and were less likely to have heart failure, chronic kidney disease, and previous cardioversion. They were more likely to have a left ventricular ejection fraction >50%. The CHA_2DS_2-VASc score, AF symptom severity, and symptom status graded by the European Heart Rhythm Association symptom scale were also different between the two groups ($P < 0.001$ and $P = 0.04$, respectively). Overall 64% of the patients underwent radiofrequency ablation and 36% underwent cryoablation.

Association of atrial fibrillation phenotype and left atrial dimensions

Overall, the median LAVI was 38 mL/m^2 (IQR 29–49 mL/m^2), and the median LA diameter was 44 mm (IQR 39–48 mm). Patients with persAF had higher LAVI [median 44 (32–55) vs. median 35 (28–46), $P < 0.001$] and higher LA diameter [median 47 (42–52) vs. median 43 (37–47), $P < 0.001$] compared with paroxAF patients. There was however a relevant overlap between the two groups (*Figure 1*).

Overall, 41% of patients had a normal LAVI (<35 mL/m^2), 17% a mildly dilated LAVI (35–41 mL/m^2), 16% a moderately dilated LAVI (42–48 mL/m^2), and 26% a severely dilated LAVI (>48 mL/m^2). In patients with paroxAF, the distribution was 47, 19, 14, and 20%. In patients with persAF, the distribution was 29, 13, 20, and 37%.

Impact of atrial fibrillation phenotype vs. left atrial volume on outcome after pulmonary vein isolation

In Kaplan–Meier analysis, freedom from AF recurrence 1 year after ablation was 61.5%. Freedom from AF recurrence was higher in patients with parox AF compared with persAF (65.6 vs. 52.7%, $P = 0.003$, *Figure 2*).

Freedom from AF recurrence according to the degree of LA dilation is shown in *Figure 3A*. Importantly, freedom from AF recurrence was higher in patients with no/mild LA dilation compared with patients with moderate/severe LA dilation (67.1 vs. 53%, $P < 0.001$, *Figure 3B*).

The combination of AF phenotype (paroxAF or persAF) and AF volume (no/mild vs. moderate/severe LA dilation) further refined the prediction of outcomes after PVI ($P < 0.001$, *Figure 4*). Freedom from AF after 1 year was highest in patients with paroxAF and no/mild LA dilation (69.1%) and lowest in patients with persAF and moderate/severe LA dilation (47%). No difference was found between patients with paroxAF and moderate/severe LA dilation and those with persAF and no/mild LA dilation (58.4 vs. 61%, $P = 0.67$).

A sensitivity analysis for the subgroups of patients undergoing cryoablation and radiofrequency ablation was performed. In both subgroups, a similar pattern of the impact of AF phenotype and LA volume was found (see Supplementary material online, *Figures S2–S4*).

Predictors of atrial fibrillation recurrence in multivariable analysis

Univariable Cox regression analysis showed persAF, moderate/severe LA dilation (LAVI ≥42 mL/m^2), presence of coronary artery disease (CAD), and CHA_2DS_2-VASc score to be predictors of AF recurrence at 1 year (*Table 2*). In multivariable Cox proportional regression analysis, persAF [HR 1.39, 95% confidence interval (CI) 1.03–1.8, $P = 0.03$] and moderate/severe LA dilation (LAVI ≥42 mL/m^2; HR 1.7, 95% CI 1.08–1.99, $P = 0.01$) remained independent predictors of AF recurrence (*Table 2*) after adjusting for age, sex, and CAD.

Table 1 Baseline characteristics of the patients overall and according to AF phenotype

	All patients $N = 476$	Paroxysmal AF $N = 313$	Persistent AF $N = 163$	*P*-value
Age (years)	63 (56–70)	62 (55–69)	64 (57–71)	0.1
Female gender	138 (29)	94 (30.0)	44 (27)	0.48
BMI (kg/m^2)	27 (25–31)	27 (24–30)	29 (25–32)	<0.001
Hypertension	290 (61)	179 (57)	111 (68)	0.02
Coronary artery disease	60 (13)	34 (10)	26 (15)	0.11
Heart failure	97 (20)	29 (09)	68 (41)	<0.001
Diabetes	37 (8)	21 (7)	16 (10)	0.22
GFR < 60 mL/min	82 (17)	40 (13)	42 (26)	<0.001
CHA_2DS_2-VASc score	2 (1–3)	2 (1–3)	2 (1–3)	<0.001
EHRA score	2 (2–3)	2 (2–3)	2 (2–3)	0.04
AF duration (months)	16.5 (5–48)	17 (4–49)	16 (6–42)	0.8
Previous cardioversion	158 (33)	52 (16)	106 (65)	<0.001
Left ventricular EF (%)	60 (50–60)	60 (55–65)	55 (43–60)	<0.001
Left ventricular EF <50%	86 (18)	28 (32)	58 (67)	<0.001
Left atrial diameter (mm)	44 (39–48)	43 (37–47)	47 (42–52)	<0.001
Left atrial volume index (mL/m^2)	38 (29–49)	35 (28–46)	44 (32–55)	<0.001
Moderate/severe LA dilation	199 (42)	105 (34)	94 (58)	<0.001
Radiofrequency ablation	307 (64)	214 (68.3)	93 (57.0)	0.014
Cryoballoon ablation	169 (35)	99 (31.6)	70 (42.9)	0.014
Number of patients with a complete 12 months follow-up, *n* (%)	420 (88.3)	269 (86)	151 (92)	0.03

Values are presented as median (IQR) or *n* (%). Moderate/severe LA dilatation if LAVI ≥42 mL/m^2.
AF, atrial fibrillation; BMI, body mass index; EF, ejection fraction; EHRA, European Heart Rhythm Association; GFR, glomerular filtration rate; IQR, inter-quartile range; LA, left atrial; LAVI, LA volume index.

Table 2 Cox regression analysis to predict recurrence during 1 year of follow-up

	Univariable		Multivariable	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Persistent AF	1.53 (1.1–2.0)	0.004	1.39 (1.03–1.88)	0.03
Age (years)	1.10 (0.9–1.0)	0.21	1.00 (0.98–1.01)	0.7
Female gender	1.17 (0.9–1.6)	0.30	1.20 (0.87–1.66)	0.24
BMI (≥30 kg/m^2)	1.26 (0.9–1.7)	0.14		
Hypertension	1.24 (0.9–1.7)	0.15		
Coronary artery disease	1.51 (1.03–2.2)	0.03	1.39 (0.94–2.06)	0.09
Chronic kidney disease	1.29 (0.9–1.8)	0.16		
Heart failure	1.00 (0.7–1.5)	0.95		
Diabetes	1.16 (0.7–1.9)	0.56		
CHA_2DS_2-VASc score ≥2	1.1 (1.0–1.2)	0.04		
AF duration (months)	1.00 (0.99–1.00)	0.06		
LVEF <50%	1.08 (0.7–1.6)	0.66		
Moderate/severe LA dilation	1.82 (1.25–2.65)	0.002	1.47 (1.08–1.99)	0.01

Values are presented as median (IQR) or *n* (%). Moderate/severe LA dilatation if LAVI ≥42 mL/m^2.
AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; HR, hazard ratio; IQR, inter-quartile range; LVEF, left ventricular ejection fraction; LA, left atrial; LAVI, LA volume index.

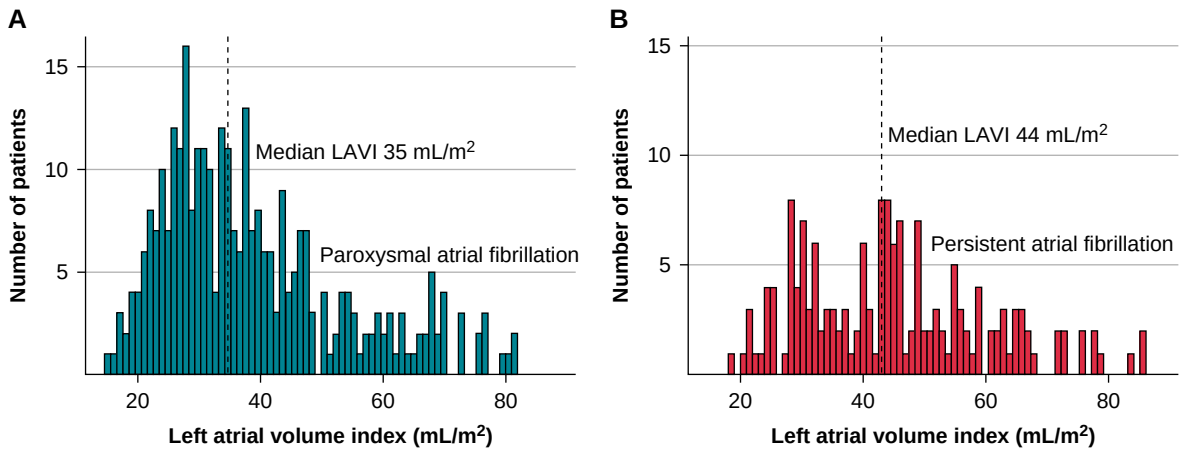


Figure 1 Medians for paroxysmal and persistent AF individually: (*A*) paroxysmal AF and (*B*) persistent AF. The dotted lines indicate the median LAVI values for paroxysmal and persistent AF. AF, atrial fibrillation; LAVI, left atrial volume index.

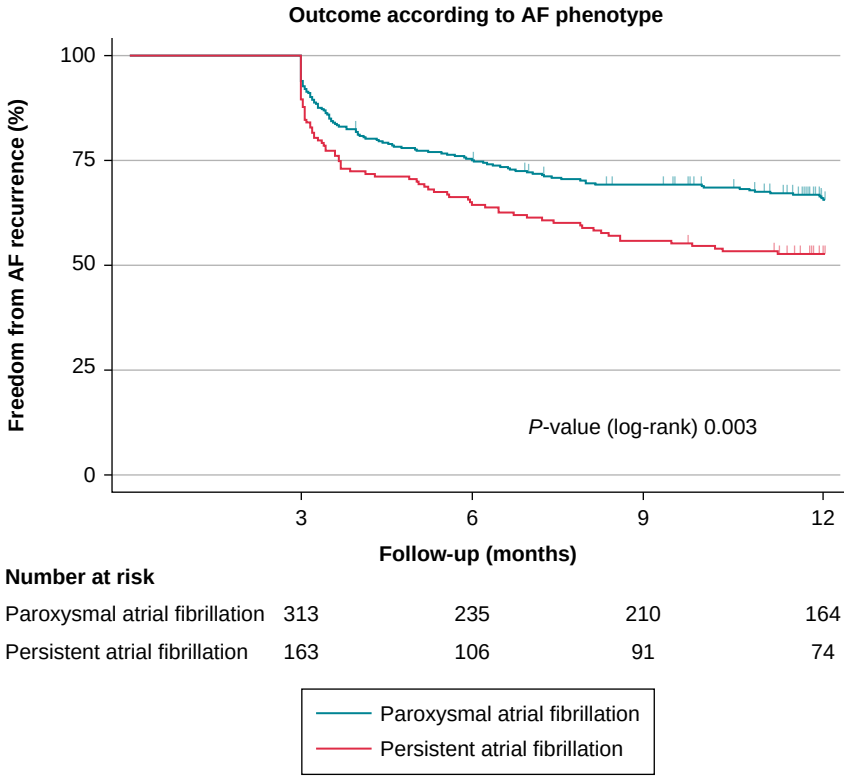


Figure 2 Freedom from AF recurrence after PVI according to AF phenotype. Kaplan–Meier estimates showing the recurrence of AF after PVI in patients with paroxysmal AF and persistent AF. Numbers at risk are indicated below the Kaplan–Meier curves. AF, atrial fibrillation; PVI, pulmonary vein isolation.

Discussion

Our study aimed to assess the interplay of AF phenotype and LA volume on outcomes after PVI. We report the following major findings.

First, the median LA volume was higher in patients with persAF compared with paroxAF, linking AF volume with AF progression. There was however a significant overlap in LA volume between the two groups. Second, we found a better 1-year freedom from arrhythmia recurrence in patients with paroxAF as opposed to persAF (65.6 vs. 52.7%, $P = 0.003$) as well as in patients with no/mild vs. moderate/severe dilated left atria (67.1 vs. 53%, $P < 0.001$). Third, the combination of both parameters refined prediction of 1-year recurrence ($P < 0.001$). Last, both

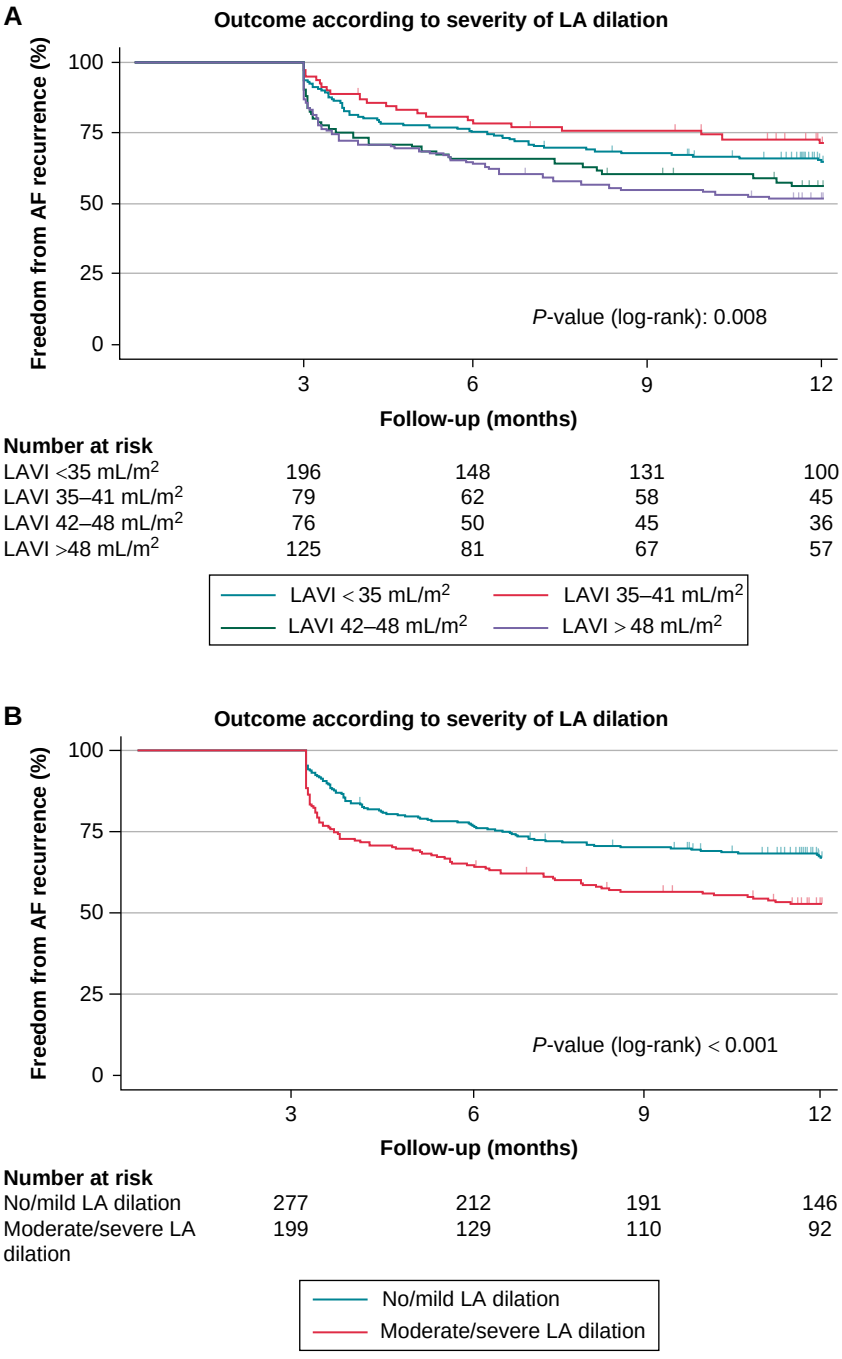


Figure 3 Freedom from AF recurrence after PVI according to LA volume. (*A*) Outcomes according to the degree of LA dilation and (*B*) outcomes comparing no/mild LA dilation with moderate/severe LA dilation. (*A*) Kaplan–Meier estimates showing the recurrence of AF after PVI in patients with normal left atrial volume (LAVI <35 mL/m^2), mild LA dilation (LAVI 35–41 mL/m^2), moderate LA dilation (LAVI 42–48 mL/m^2), and severe LA dilation (LAVI >48 mL/m^2). Numbers at risk are indicated below the Kaplan–Meier curves. AF, atrial fibrillation; LA, left atrial; LAVI, LA volume index; PVI, pulmonary vein isolation.

AF phenotype and dilated LA remained independent predictors of 1-year recurrence after adjustment for additional clinical risk factors in multivariable Cox proportional hazard analysis.

Our study corroborates and extends previous studies that have shown the impact of LA volume as predictors for AF recurrence. In a recent meta-analysis of 21 studies including 3822 subjects, significant group differences in LA volumes were found between patients with and without recurrence after PVI.[14] These studies however did not assess the interplay between LA volume and AF phenotype. In this regard, Costa *et al.*[15] showed that relapse rates in patients with paroxAF and dilated LA volume were higher compared with patients with non-paroxAF and small LA volume. In their analysis, LA volume

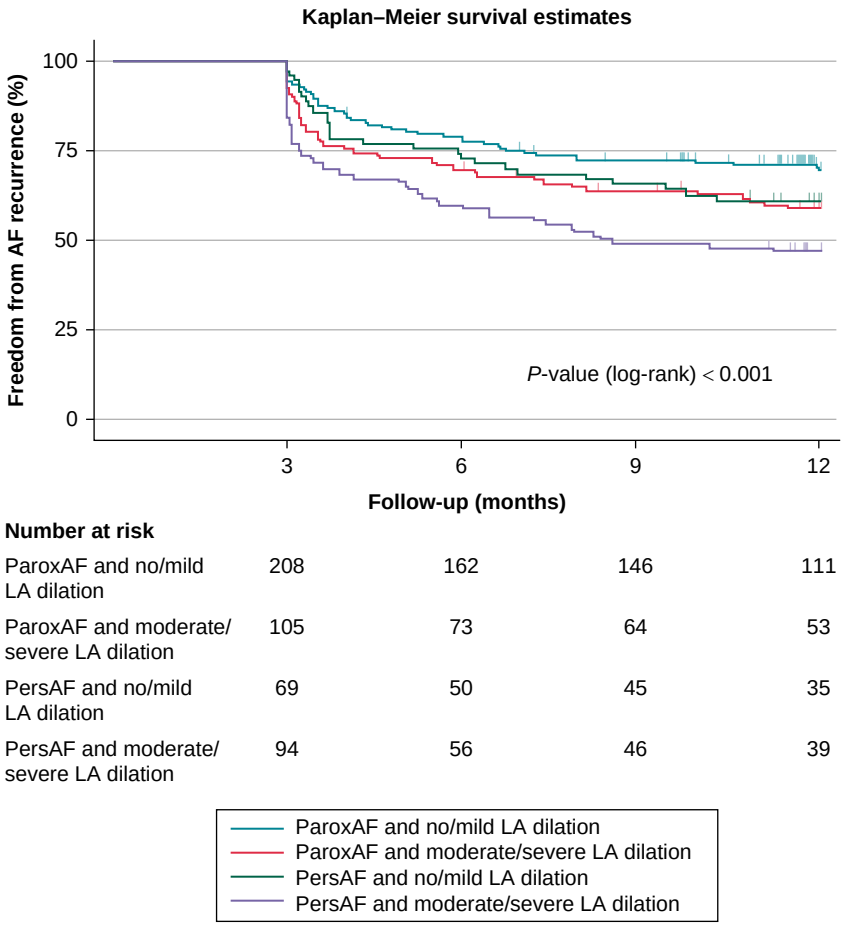


Figure 4 Freedom from AF recurrence after PVI according to the combination of AF phenotype and LA volume. Kaplan–Meier estimates showing the recurrence of AF after PVI in patients with paroxysmal AF and no/mild left atrial dilation, paroxysmal AF and moderate/severe LA dilation, persistent AF and no/mild LA dilation, and persistent AF and moderate/severe LA dilation. Numbers at risk are indicated below the Kaplan–Meier curves. AF, atrial fibrillation; LA, left atrial; PVI, pulmonary vein isolation.

emerged as an independent predictor of recurrence. They however used cardiac CT to assess LA volumes, which is more expensive than echocardiography and exposes patients to ionizing radiation. Our study used echocardiography, which is widely available, is less expensive, and does not expose patients to ionizing radiation. Despite the higher inter-observer variability in estimating LAVI from echocardiography than from CT, studies have shown good correlation to measurements by CT scan and consider it an independent risk factor for recurrence.[7,14,16,17] In our study, LAVI was a predictor of AF recurrence independent from AF phenotype. Hence, our study expands the literature and may aid to better emphasize the role of LA dimensions in clinical decision-making and patient selection in ablation naïve patients.[14,15] While current guidelines suggest PVI as a first-line treatment in patients with paroxAF but not persAF, our data indicate that patients with persAF and normal LA dimensions might also be good candidates for early AF ablation.[1]

Previous studies have evaluated clinical predictors for arrhythmia recurrence after PVI, both in isolation and in the aggregation of scores such as the CHA_2DS_2-VASc score or the APPLE score.[18–23] Studies have also shown association between diabetes, hypertension, renal disease, heart failure, and obesity with LA sizes and that increased LA sizes predict recurrence after PVI.[24–30] Most of these factors are linked to advanced atrial cardiomyopathy. Our data however indicate that the LA dimensions likely integrate many of these individual factors, making it an excellent single-parameter surrogate for AF substrate. This is reflected by its value in the Cox proportional hazard regression analysis, where the individual factors were non-significant.

A more comprehensive approach to phenotyping atrial remodelling in the future should incorporate advanced atrial parameters from MRI, CT, and echocardiography. It is imperative to move beyond the conventional reliance on 'AP LA diameter' as the primary metric, as it serves merely as a surrogate for structural changes and does not fully reflect the atrial volume and function. A more refined approach to assess atrial remodelling would entail the evaluation of true 3D volumes of the atria by CT or MRI. In addition to volumetric analysis, incorporating strain measurements from MRI or echocardiography would allow for the detailed assessment of deformation and contraction properties of the atrial walls. Magnetic resonance imaging, in particular, offers the advantage of evaluating tissue characteristics such as late gadolinium enhancement, enabling the direct visualization of atrial fibrosis. Incorporating these measurements into future studies and correlating them with outcomes will provide a deeper insight into atrial mechanics and structural alterations, thereby improving risk-stratifying patients.[31–37]

Our study also confirmed the well-known worse outcome of PVI in patients with persAF compared with patients with paroxAF. Randomized studies to date have failed to demonstrate that substrate

modification beyond PVI is better than PVI alone in patients with persAF.[38,39] We therefore excluded patients with LA substrate ablation beyond PVI from the current analysis. Recent observational studies using pulsed field ablation for substrate modification beyond PVI in patients with persAF have shown favourable early results.[40,41] It seems worth to test substrate modification concepts that previously failed with radiofrequency ablation again in randomized studies using pulsed field ablation. Until those results are available, PVI should remain the standard for clinical routine in patients with persAF, and for this approach, our study results are valid.

Study limitations

Potential limitations of this study should be taken into consideration. First, this was a retrospective analysis of a prospective registry. Second, echocardiography rather than CT or MRI was used for estimation of the LAVI in our study. Left atrial volume index measurements from CT were available only in a small minority of patients. Accordingly, we were not able to compare the value of LAVI estimated from echocardiography vs. CT. Third, echocardiography recordings from the clinical routine were used in our study. Accordingly, we do not have additional LA markers such as LA ejection fraction or LA strain parameters, which might also reflect AF substrate and might be of value to predict AF recurrence.[42,43] Another potential limitation of our study is that 3D electroanatomical mapping was not used in patients undergoing cryoablation. Accordingly, we cannot correlate LA voltage abnormalities with AF phenotype, LA volume, and outcomes after ablation. Lastly, while we derived our results from a relatively large sample size, larger multi-centre studies are needed to confirm our findings from a single-centre study.

Conclusions

Atrial fibrillation phenotype and LA volume are complementary in the prediction of outcome after PVI. Persistent AF with no/mild LA dilation has a similar risk of recurrence as paroxAF with a moderate/severe LA dilation and should be given similar priority for ablation.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: T.R. has received research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the Sitem Insel Support Fund, Biotronik, Boston Scientific, and Medtronic, all for work outside the submitted study. He has received speaker/consulting honoraria or travel support from Abbott/SJM, Biosense Webster, Biotronik, Boston Scientific, and Medtronic. He has received support for his institution's fellowship programme from Abbott/SJM, Biosense Webster, Biotronik, Boston Scientific, and Medtronic. L.R. has received research grants from Medtronic, the Swiss National Foundation, the Swiss Heart Foundation, the Immanuel and Ilse Straub Foundation, and the Sitem Insel Support Fund, all for work outside the submitted study. He has received speaker/consulting honoraria from Abbott and Medtronic. A.H.: travel fees/educational grants from Medtronic, Biotronik, Abbott, and Philips/Spectranetics without impact on his personal remuneration. He serves as a proctor for Medtronic. He has received research grants from the Swiss National Science Foundation, the Swiss Innovation Agency Innosuisse, the Swiss Heart Foundation, the University of Bern, the University Hospital Bern, the Velux Foundation, the Hasler Foundation, the Swiss Heart Rhythm Foundation, and the Novartis Research Foundation. He is the co-founder and CEO of Act-Inno AG. All other authors have no relationships relevant to the contents of this paper to disclose.

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Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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