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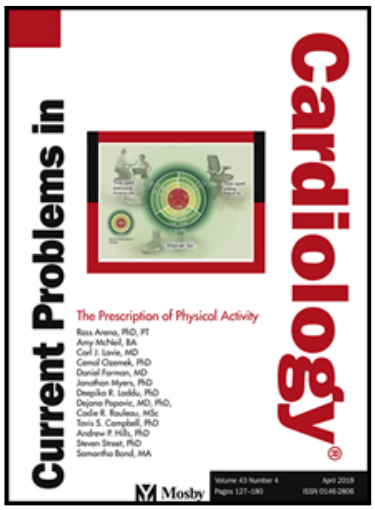

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Clinical Phenotypes and Atrial Fibrillation Recurrences after Catheter Ablation: An Unsupervised Cluster Analysis

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Abstract:

Catheter ablation (CA) is a well-established treatment of atrial fibrillation (AF). Data-driven cluster analysis is able to better distinguish prognostically-relevant phenotype clusters among patients with AF. We performed a hierarchical cluster analysis in a cohort of AF patients undergoing a first CA and evaluate associations between identified clusters and recurrences of arrhythmia following ablation. The study included 209 AF patients treated with CA. 3 clusters with distinct characteristics were identified. Recurrences at one year occurred in 27.2% in Cluster 1, 43.2% in Cluster 2 and 60.9% in Cluster 3 ($p<0.0001$). Cluster classification was independently associated with arrhythmia recurrences (HR 1.58, 95% CI 1.01–2.49, $p=0.046$) after adjustment for age, CHA_2DS_2-VASc score, left atrial volume, type of atrial fibrillation and ejection fraction. To concluded, cluster analysis identified three statistically-driven groups among AF patients treated with CA with different risks for arrhythmia recurrences.

Key words: Atrial fibrillation, Cluster analysis, Outcomes, Machine learning.

List of abbreviations:

AADs: Antiarrhythmic drugs

ACEi: Angiotensin-converting enzyme inhibitors

AF: Atrial fibrillation

ARBs: angiotensin receptor blockers

BNP: brain natriuretic peptide

CFAEs: Complex fractionated atrial electrograms

CI: Confidence interval

CRP: C reactive protein

CT-scan: Computed tomography scan

a/HR: adjusted Hazard ratio

LA: Left atrium

ML: Machine learning

MRI: Magnetic resonance imaging

PVI: Pulmonary vein isolation

SD: Standard deviation

1. Introduction

Over the last decades, catheter ablation has become a well-established therapy for rhythm control in patients with symptomatic atrial fibrillation (AF) [1-2]. The latter has moved from a therapy of last resort for highly symptomatic patients with drug-refractory AF to an accepted first-line option for patients across the spectrum of AF type and severity. However, freedom from arrhythmia and maintenance of sinus rhythm at 1-year post-ablation is variable and the rate of recurrences ranges from 60 to almost 90% depending on many factors [3-7]. Identification of patient groups at higher risk for recurrent AF may help in developing preventive strategies and tailoring of rhythm control therapy post-ablation. A number of risk-prediction scores have been evaluated but with only modest predictive performance [8-11]. Of note, recurrence of AF after catheter ablation is driven by complex interactions of various factors and might not be optimally characterized with simplified risk scores. Rather than occurrence in isolation or a binary manner (eg. diabetes yes/no), clinical risk factors(s) often occur concurrently leading to potentially 'clinically complex' phenotype clusters.

Unsupervised cluster analysis is a machine learning method that categorizes complex entities without investigators' supervision by segregating samples into homogenous groups based on each cluster's dissimilarities [12]. This data-driven approach helps unveil meaningful phenotypes within a disease that has been previously considered as homogenous. Thus, cluster analysis may be invaluable in phenotyping several cardiovascular diseases and exploring the clinical complexity of cardiovascular patients.

Hence, this study aimed to explore for the first time whether unsupervised cluster analysis can identify clinically relevant groups among AF patients treated with catheter ablation and second, to evaluate whether these cluster phenotypes are associated with different rates of arrhythmia recurrence.

2. Methods

2.1. Study population

Consecutive patients with symptomatic AF referred to the Cardiology Department of the University Hospital of Tours (France) for AF ablation between February 2013 and May 2014 were included in this study. Patients with a prior ablation for AF were excluded. Collected clinical data included symptoms (EHRA classification) and history of arrhythmia, presence of thrombo-embolic risk factors (CHA_2DS_2-VASc score (**Supplemental table 1**)), and past and current medications. Trans-thoracic echocardiography and cardiac magnetic resonance imaging (MRI) or computed tomography scan (CT-scan) were performed to assess left ventricular function and left atrial (LA) diameter and volume before ablation.

Procedures were performed under general anaesthesia. A 4-millimeter irrigated-tip catheter was used in all patients to deliver radiofrequency energy (Thermocool SF, Biosense Webster; Flexability, St Jude Medical). A circular lasso catheter (Biosense Webster, St Jude Medical) was used for mapping. After transseptal puncture, antral pulmonary vein isolation (PVI) was performed in all patients. A bidirectional block was systematically obtained in all veins. In patients with persistent AF and remaining arrhythmia at that stage a stepwise approach was performed: sequentially, anterior roof and mitral isthmus lines were obtained (endocardially, and epicardially through the coronary sinus, when necessary), complex fractionated atrial electrograms (CFAEs) within LA (LA appendage, inferior-posterior wall, interatrial septum), coronary sinus, and right atrium (crista terminalis, superior venacava, cavotricuspid isthmus), were mapped and defragmented when necessary. Stable atrial tachycardias were systematically mapped and ablated. When return to sinus rhythm was obtained, either with ablation, or with electrical cardioversion at the end of procedure, bidirectional block was confirmed on all performed lines.

2.2. Follow-Up and Outcomes

Recurrence was defined as ≥1 documented sustained episode (≥30 seconds) of any atrial arrhythmia, symptomatic or not, on any ECG or Holter monitoring strip (scheduled or additional), after a single ablation procedure, after a 3-month blanking period.

During the blanking period, antiarrhythmic drugs (AADs) were continued in most of the patients, and a cardioversion was performed in the event of persistent recurrence. At the end of the blanking period, AADs were systematically discontinued in all patients. All patients were rigorously followed for 12 months. A 24-hour Holter monitoring was performed at 3 and 6 months along with a clinical examination and a resting ECG. A 7-day Holter recording was systematically performed at 12 months (Spiderview, Sorin Group, Le Plessis-Robinson, France).

2.3. Cluster analysis

The whole cohort was used for analysis. Variables with missing data rate for any variables above 30% were excluded and variables with missing rate under 30% were imputed using Multivariate Imputation By Chained Equations algorithm [13]. 33 Baseline clinical and procedural variables were therefore used for the analysis (**Supplemental table 2**).

The hierarchical clustering method (using Ward's linkage criterion) was used to identify homogenous phenotypic subgroups of AF patients without prior knowledge of the outcomes. The algorithm begins with each element (i.e., patient) as a separate cluster and then proceeds with a "bottom-up" approach grouping each cluster with the most similar one until all clusters become one.

A dendrogram is provided to display the distance obtained at each inter-action of the clustering process (**Figure 1**). Small values of the distance indicate that the merged clusters were similar, and large values indicate the combination of 2 dissimilar (heterogeneous) clusters. The determination of

the numbers of clusters was not prespecified. Examination of the dendrogram indicated that the groupings became more heterogeneous after being expanded to 3 clusters. Both 3-cluster and 4-cluster models were examined. The 3-cluster model formed much clearer patterns of patient groups than a 4-cluster model. Therefore the 3-cluster model was used in this study. Cluster models were implemented in Python using open-source packages: Scikit-learn version 1.1.1. Once clusters were identified, we assessed the association between clusters and clinical characteristics and outcomes.

2.4. Statistical analysis

Qualitative variables were described using counts and percentages, and continuous quantitative variables were described as mean ± standard deviation (SD) or median [interquartile range]. Comparisons were made using parametric or nonparametric tests, as appropriate: The Wilcoxon signed rank and Kruskal Wallis tests were used for comparing values between 2 independent groups, and the Chi^2 test was used to compare categorical data. Unadjusted and multivariate-adjusted Cox analyses were used and results were expressed as hazard ratio (HR) and 95% confidence intervals (95%CI). Analyses were performed using Python version 3.09 and STATA version 16.0 (Stata Corp, College Station, TX). All statistical significance levels were two-sided, and significant differences were expressed as $p < 0.05$.

2.5. Ethics approval

All methods, including the ablation procedure, were carried out in accordance with the guidelines effective at the time of the study. The ethics committee for human research of the University Hospital Centre of Tours (France) approved the study protocol. All patients signed informed consent before inclusion.

3. Results

A total of 209 patients were included in the study, of whom 103 had paroxysmal AF (49%). Patients were predominantly men (69%), with a mean age of 62 ± 10 years (median 63 [56-69]). Hypertension was found in 49% of patients, and diabetes in 19% and 13% had a CHA_2DS_2-VASc score >2. Mean ejection fraction was 53 ± 11%, LA volume 133 ± 41 mL and brain natriuretic peptide (BNP) 169 ± 284 ng/mL. The analysis identified three patient clusters as shown in the dendrogram (**Figure 1**). **Figure 2** displays the projection of the classification according to the three phenogroups identified after reduction of dimension using principal component analysis. Baseline clinical characteristics and procedural characteristics according to the three clusters were compared and are reported in **Tables 1 and 2**.

3.1. Clusters

3.1.1. Cluster 1

Cluster 1 was composed of 103 patients, representing 49.3% of the cohort. These patients had a mean age of 61±10 years, were mostly males (63%) and had few comorbidities as reflected by a mean CHA_2DS_2-VASc score of 1.7±1.41. The phenotype of these patients was characterized by a higher prevalence of paroxysmal AF (90%), higher rate of sinus rhythm at admission (95%) and lower LA volume (116±32mL) than for other clusters (all p-values<0.05). Procedure, fluoroscopy and total ablation time were significantly shorter than for other clusters (all p-values<0.05) and PVI only was the ablation strategy performed in 76.5% of patients.

3.1.2. Cluster 2

Cluster 2 was composed of 37 (18%) patients. This intermediate cluster included patients of a similar age to Cluster 1 (60±8 years) but with slightly lower rates of comorbidities and fewer symptoms but without reaching statistical significance. However, more patients had persistent AF than in Cluster 1, and had more dilated LA (p<0.005). When considering procedural characteristics, anatomy comprised a lower rate of left common pulmonary vein (2.7%) (p<0.05) than in other

clusters and 51.6% of the patients received PVI associated with lines and CFAEs ablation ($p<0.005$).

3.1.3. Cluster 3

Cluster 3 was composed of 69 (33%) patients and was characterized by older patients (mean age: 65.93±9.96 years, $p<0.005$) and highest mean CHA_2DS_2-VASc scores (2.81±1.54, $p<0.05$) reflecting a higher burden of cardiovascular comorbidities than the other clusters. These patients had more often persistent AF, higher weight, more comorbidities such as hypertension and heart failure, more dilated LA, higher level of BNP, galectine-3 and C reactive protein (CRP) and lower estimated glomerular filtration rate (eGFR) than in other clusters ($p<0.05$). Class I AADs and betablockers were less prescribed ($p<0.05$) and these patients underwent more complex procedures including PVI associated with lines and CFAEs ablation in 75.8% of cases ($p<0.0001$).

3.2. Associations with Clinical Outcomes

Table 3 compares the crude rates of recurrence among clusters. Recurrence rate at one year was 27.2% for Cluster 1, 43.2% for Cluster 2 and 60.9% for Cluster 3 ($p=0.09$ for Cluster 1 *versus* 2, $p=0.1$ for Cluster 2 *versus* 3 and $p<0.0001$ for Cluster 1 *versus* 3). The type of arrhythmia recurrence was also different among clusters with paroxysmal AF in 78.6% and persistent AF in 10.7% of patients with recurrences in Cluster 1 and persistent AF in 64.3% and atrial flutter in 64.3% for Cluster 3 ($p<0.0001$). Time to first recurrence was the lowest for Cluster 3 and the longest for Cluster 1 ($p<0.0001$). Patients among Cluster 3 experienced more redo procedures.

Figure 3 displays Kaplan-Meier curves of AF recurrences within the year following AF ablation. In the unadjusted Cox regression analysis (**Table 4)**, when compared with Cluster 1, Cluster 2 and Cluster 3 had a significantly higher risk of arrhythmia recurrence. After the adjustments on age, AF type, CHA_2DS_2-VASc score, ejection fraction and left atrial volume, patients included in Cluster 3 remained at higher risk of recurrence than patients included in Cluster 1 (aHR 0.29, 95% CI 0.01-0.84, $p=0.023$).

4. Discussion

To our knowledge, this is the first exploratory study using cluster analysis on a population of AF patients treated with catheter ablation. The major findings of this study are as follows: (i) cluster analysis led to the identification of three statistically-driven groups of AF patients with distinct phenotype characteristics; (ii) clusters significantly varied among the measures of demographic characteristics, blood testing, cardiac imaging, concomitant treatment and procedural characteristics; and (iii) these distinct clusters were independently associated with different probability of arrhythmia recurrences.

Our analysis identified three main clinical phenotypes. The first cluster was characterized by young patients with mostly paroxysmal AF, low rate of associated comorbidities and non-dilated LA. These patients were treated more frequently with class I AADs and experienced shorter AF ablation procedures mostly composed of PVI alone. This cluster had the best prognosis with the lower rate of arrhythmia recurrence. These recurrences occurred latter than in the other clusters and were mainly composed of paroxysmal AF. The second cluster was composed of patients similar to those in Cluster 1 in terms of comorbidities. Even though Cluster 2 appeared like a subset of borderline patients of Cluster 1 at first glance, these patients were distinguishable by a higher proportion of persistent AF, a higher proportion of men, more dilated LA, and a low rate of left common pulmonary vein anatomy. These patients had an intermediate risk profile for arrhythmia recurrences after AF ablation mainly composed of persistent AF and atrial flutter. For the third cluster, patients were older, had more frequently persistent AF, more comorbidities and more dilated LA than the other clusters. Biomarkers (BNP, CRP and galectine-3) associated with AF recurrences after ablation were also higher [14-18]. These patients were treated with longer and more complex procedures. The prognosis of patients included in this cluster was worse with more frequent and earlier recurrences mainly comprised of persistent AF and atrial flutter.

Although it is well known as a risk factor of recurrences after ablation, diagnosis to ablation time was not significantly different among the three clusters [3,19,20]. Moreover, there was a trend towards shorter duration in Cluster 2 and 3. This highlights the fact that, when considering the natural history of AF, the progression of the disease and symptoms may matter more than only the duration since its onset. This contradicts the rule that "the sooner the better" and underlines the importance of not recusing patients from ablation just because of a long history of AF without assessing the whole clinical complexity.

AF type (i.e., paroxysmal, persistent or long standing) is also described as a strong predictor of post-ablation AF recurrences [20-23]. However, the risk of recurrence is the result of more complex and varied phenomena that cannot be summarized only by the type of AF. This simple classification often overlooks the variety of underlying conditions that are commonly associated with AF and that play an important role in recurrences. Comorbidities such as hypertension, diabetes, obesity, structural heart disease and mitral regurgitation are described as important risk factors contributing to the development of LA dilatation, atrial fibrosis and then atrial cardiomyopathy translating into poorer outcomes with rhythm control strategies [23-29]. Applying cluster analysis helps consider the great heterogeneity of AF ablated patient phenotypes (so-called "clinical complexity"), which is strongly involved in the progressive nature of atrial remodelling, and leads to a new relevant classification. This novel statistical approach defined phenogroups 1 and 3 which were independently associated with AF recurrence even after adjustment on strong and well described predictors such as age, AF type, CHA_2DS_2-VASc score, ejection fraction and LA volume [3,8,9,30-35].

Interestingly, cluster analysis can elucidate differences in practice patterns across a population. Indeed, patients included in Cluster 2 and 3 were more often treated with complex ablation procedure including lines and CFAEs ablation probably due to the higher rate of persistent AF. It has since been shown that the choice of such aggressive strategy is ineffective for the treatment of persistent AF when compared to PVI alone [5].

4.1. Clinical implications and perspectives

These findings reveal a previously unrecognized heterogeneity of clinical phenotypes and outcomes among AF patients treated with catheter ablation, which may have important clinical implications. There is an important need for more sophisticated risk stratification tools using clinical factors, diverse imaging parameters, biomarkers and procedural information to identify individuals at risk of recurrence. Different therapeutic strategies, optimal timing of intervention and surveillance might be needed for each cluster, as a step toward precision-medicine in AF. Specifically, a tailored and comprehensive management focusing on higher risk of recurrence clusters with more aggressive modifiable risk factor reduction could improve time to first recurrence, rather than aggressive procedural ablation (including additional lines and CFAEs) as it is often the case [5,36]. In a way, stop the progression of the substrate rather than make it worse.

Cluster analysis is a powerful hypothesis generating approach giving new insights on clinical complexity. This avenue of research should be investigated. Further studies clarifying the interaction between clusters and treatment, such as ablation strategy or lifestyle modification could substantially enhance the clinical implications of phenotype cluster analysis in daily practice and improve outcomes.

5. Limitations

First, clustering algorithm results are dependent on the underlying population and associated patterns of care in the community. Caution should be taken when generalizing these results from a single centre study. Second, as cluster analysis depends on available data, the incorporation of other variables such as LA substrate might yield different results. Since cluster analysis necessitates complete data on individual patients, we chose to drop variables with a greater than 30% missing data rate to insure the quality of the data. Another caveat is the limited sample size which is likely to result in a lack of statistical power, especially when comparing Cluster 2 to other clusters. This

has also been a limitation to the incorporation of a larger number of clusters. Finally, patients were included from 2013 to 2014, and treatment strategies and clinical practice have changed over time (ie, new energy delivery tools such as cryoballoon or pulsed field ablation), partly limiting the generalization of the results to current clinical practice. Nonetheless, our aim was to provide first exploratory data on clusters analysis in patients treated with AF ablation.

6. Conclusion

Unsupervised cluster analysis led to the identification of statistically-driven phenogroups of AF patients treated with catheter ablation. These results provide new insight into the clinical complexity of AF ablated patients and its influence on outcomes. These data suggest a more holistic and tailored management approach to treat existing comorbidities alongside AF to improve outcomes. Further studies based on high-dimensional databases with large sample size are necessary to confirm these findings and potential future implications in clinical practice.

Data Statement:

The data that support the findings of this study are available from the corresponding author, upon reasonable request, and after approval of all other co-investigators.

Conflicts of interest:

Bisson has been a consultant or speaker for Astra-Zeneca, Bayer, BMS/Pfizer, Medtronic, Vitorpharma and Alnylam. Clementy has been a consultant or speaker for Abbott, Medtronic and Microport. Angoulvant has been a consultant or speaker for Amgen, Astra-Zeneca, Bayer, BMS/Pfizer, MSD, Novartis, Novo Nordisk, Sanofi, Servier. Lip has been a consultant or speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally**.** LF reports consulting fees for AstraZeneca, Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, Novo Nordisk and Novartis and lecture fees for AstraZeneca, Bayer, BMS/Pfizer, Boehringer Ingelheim and Zoll. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Figure legends

Figure 1. Dendrogram generated by hierarchical clustering showing three main clusters. The dendrogram represents the relative degree of similarity between individual patients. The greater the height of the branch points (distance), the greater the differences are between the branches and the more dissimilarity exist between clusters. The red line indicates the stopping location.

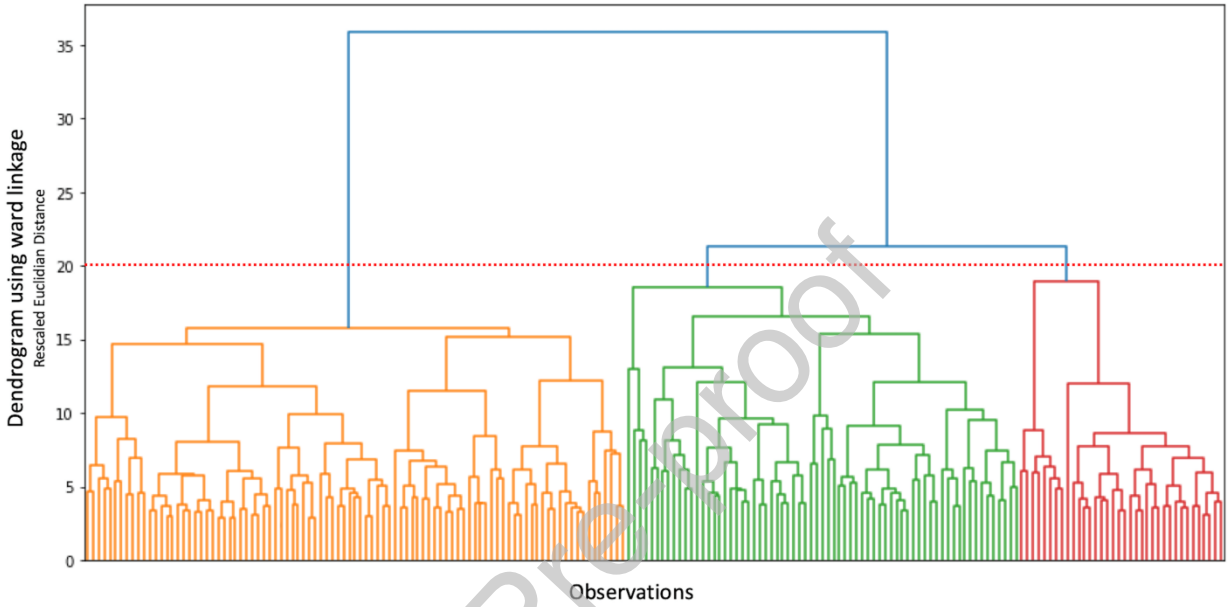


Figure 2. 2D projection of the classification according to the 3 clusters after reduction of dimension using principal component analysis.

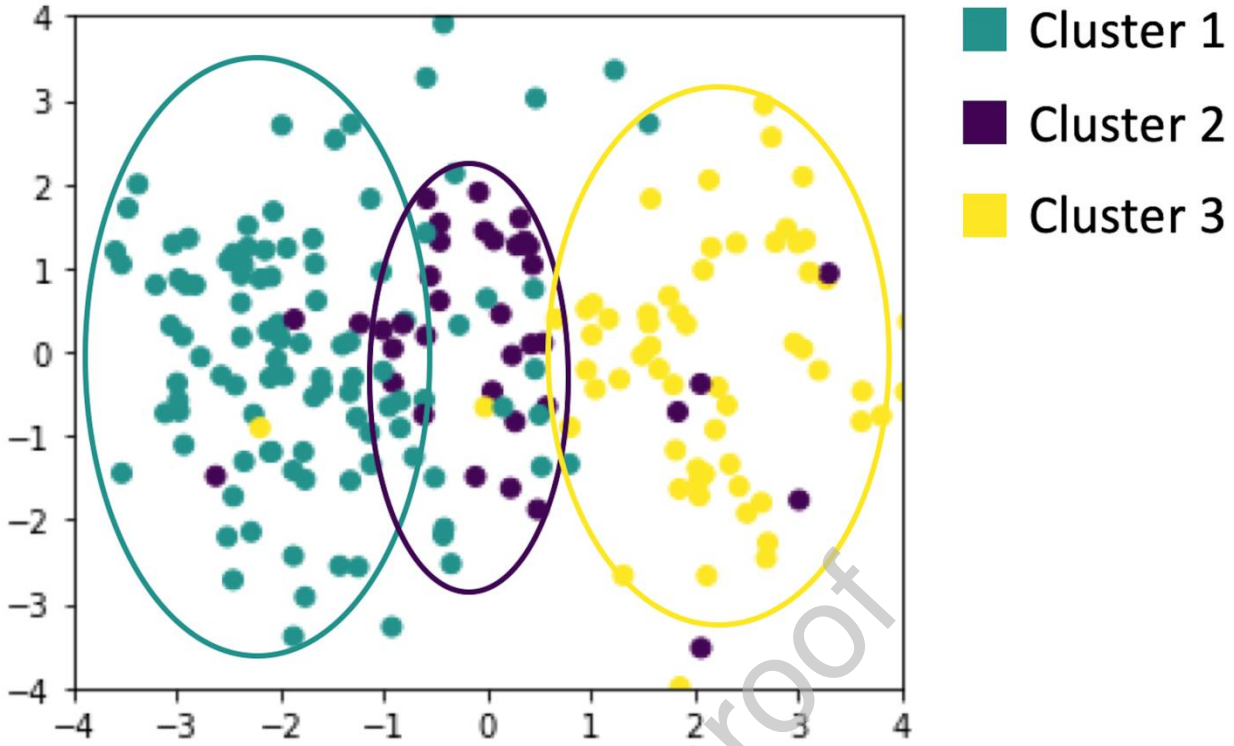
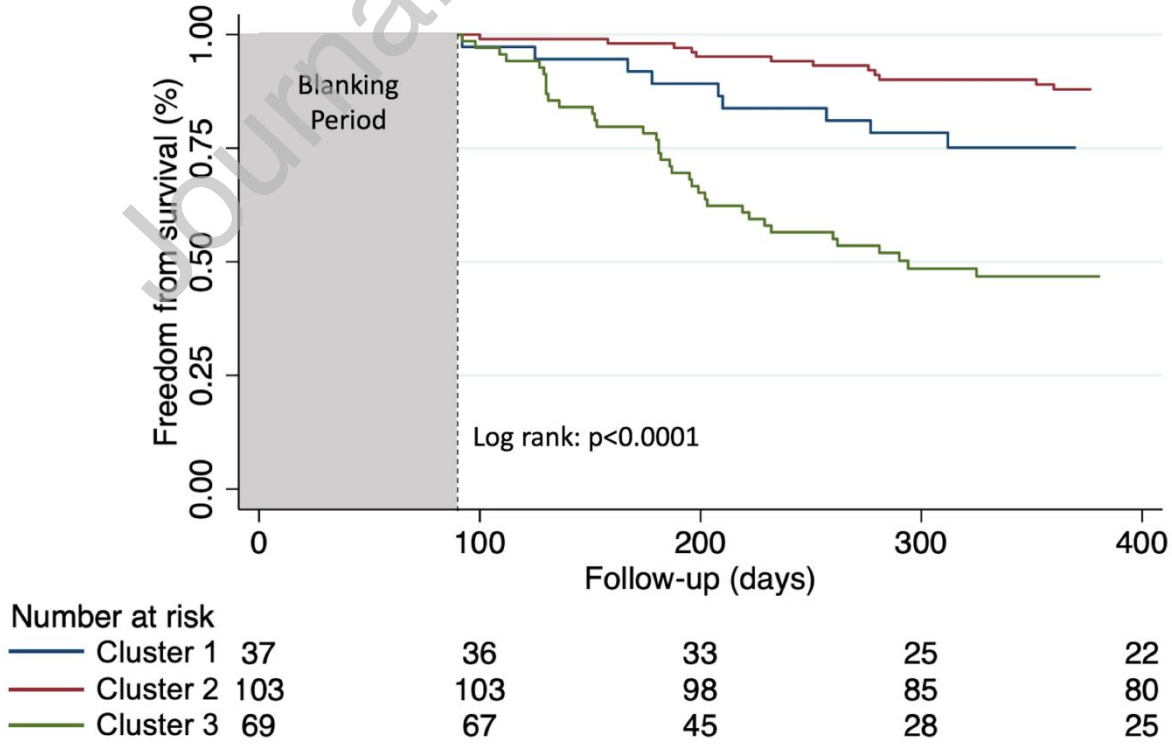


Figure 3. Kaplan-Meier curves for atrial fibrillation recurrences after catheter ablation.



Tables

Table 1. Baseline characteristics of patients stratified by clusters.

	Cluster 1 (n=103)	**Cluster 2** (n=37)	**Cluster 3** (n=69)	**p 1 vs 2**	**p 2 vs 3**	**p 1 vs 3**
Age, y	60.88±9.85	60.16±8.42	65.93±9.96	0.69	0.003	0.001
Female sex	38 (36.9)	6 (16.2)	20 (29)	0.02	0.16	0.28
CHA_2DS_2-VASc score	1.7±1.41	1.41±1.14	2.81±1.54	0.26	<0.0001	<0.0001
Paroxysmal AF	93(90.3)	7(18.9)	3(4.4)	<0.0001	<0.0001	0.03
EHRA class	2.90±0.65	2.68±0.63	3.04±0.65	0.07	0.006	0.17
Diagnosis to ablation time, d	2179±2090	2028±1959	1725±2902	0.71	0.58	0.24
Weight, kg	81.6±18.8	81.6±14.1	91.8±22.7	0.99	0.02	0.002
BMI, kg/m2	27.8±5.5	27.1±3.9	30.9±6.6	0.53	0.003	0.001
Hypertension	49 (47.6)	13 (35.1)	41 (59.4)	0.19	0.02	0.13
Diabetes mellitus	14 (13.6)	5 (13.5)	21 (30.4)	0.99	0.06	0.01
Cardiomyopathy	17 (16.5)	2 (5.4)	38 (55.1)	0.09	<0.0001	<0.0001
Heart failure	9 (8.7)	7 (18.9)	39 (56.5)	0.1	0.0002	<0.0001

Mitral regurgitation	44(42.7)	22(59.5)	43(62.3)	0.09	0.84	0.013
Vascular disease	9 (8.7)	2 (5.4)	8 (11.6)	0.52	0.49	0.54
Stroke	8 (7.8)	6 (16.2)	6 (8.7)	0.32	0.42	0.88
SR at admission	98(95.2)	9(24.3)	5(7.3)	<0.0001	0.02	<0.0001
Ejection Fraction, %	57±7	56±7	44±12	0.38	<0.0001	<0.0001
CT/MRI LA Vol., mL	116±32	133±36	159±43	0.01	0.003	<0.0001
eGFR, mL/min/1.73 m^2	76.5±15.7	78.8±23	65.9±24	0.51	0.01	0.001
BNP, ng/mL	81.4±91.7	108.5±87.5	328.6±434.1	0.13	0.003	<0.0001
Galectin-3, ng/mL	13.3±4.2	12.9±3.2	19.9±12.1	0.54	0.001	<0.0001
CRP, mg/L	3.5±3.7	3.1±3.31	6.8±7.5	0.55	0.005	0.0002
Class I AADs	68 (66)	20 (54.1)	17 (24.6)	0.2	0.005	<0.0001
Class III AADs	60 (58.3)	31 (83.8)	58 (84.1)	0.005	1	0.0003
Betablockers	45 (43.7)	10 (27)	13 (18.8)	0.08	0.34	0.001
DOAC *versus* VKA	23 (22.3)	9 (24.3)	16 (23.2)	0.81	1	0.9
ACEi or ARBs	22 (21.4)	5 (13.5)	14 (20.3)	0.3	0.44	0.87

Values are n (%) or mean±SD. AADs: Antiarrhythmic drugs; ACEi: angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; BMI: Body mass index; BNP: Brain natriuretic peptide**;** CRP: C reactive protein; CT: Computed tomography; DOAC: Direct oral anticoagulant; eGFR: Estimated glomerular filtration rate; EHRA: European Heart Rhythm association; LA Vol.: Left atrium volume; MRI: Magnetic resonance imaging; SR: Sinus rhythm; VKA: Vitamin K antagonist.

Table 2. Characteristics of procedures stratified by clusters.

	Cluster 1 (n=103)	**Cluster 2** (n=37)	**Cluster 3** (n=69)	**p 1 vs 2**	**p 2 vs 3**	**p 1 vs 3**
Left common PV	27(26.2)	1(2.7)	14(20.3)	0.001	0.02	0.47
Procedure duration, min	119.1±45.9	178.1± 67.6	180.2± 47.9	<0.0001	0.87	<0.0001
Fluoroscopy time, min	20.9±10.1	36.6±25.8	33.4±12.2	<0.0001	0.41	<0.0001

Total ablation duration, min	46.1±24.1	64.3±25.3	69.5±19.2	0.003	0.34	<0.0001
Time to LPVs disconnection, min	31.8±18.1	31.2±15.9	26.8±18.4	0.86	0.24	0.09
Time to RPVs disconnection, min	26±15	23.8±12.5	21.7±12.6	0.45	0.44	0.06
Ablation strategy (n=174)*	(n=81)	(n=31)	(n=62)			
-PVI alone	62(76.5)	5(16.1)	2(3.2)	<0.0001	0.04	<0.0001
-PVI + lines	16(19.8)	10(32.3)	13(21)	0.21	0.31	1
-PVI + lines + CFAEs	3(3.7)	16(51.6)	47(75.8)	<0.0001	0.03	<0.0001

Values are n (%) or mean±SD.

*Data available for 174 patients.

CFAEs: Complex fractionated atrial electrograms; PVI: Pulmonary vein isolation; L/R/PVs: Left/right/pulmonary vein.

Table 3. Arrhythmia recurrence according to clusters.

	Cluster 1 (n=103)	**Cluster 2** (n=37)	**Cluster 3** (n=69)	**p 1 vs 2**	**p 2 vs 3**	**p 1 vs 3**
Recurrence at 12 months	28(27.2)	16(43.2)	42(60.9)	0.09	0.1	<0.0001
-Paroxysmal AF*	22(78.6)	3(18.8)	2(4.8)	<0.0001	0.12	<0.0001
-Persistent AF*	3(10.7)	7(43.8)	27(64.3)	0.02	0.23	<0.0001
-Atrial flutter*	2(7.1)	5(31.3)	13(31)	0.08	0.12	<0.0001
-Atrial tachycardia*	1(3.6)	1(6.3)	0(0)	1	0.28	0.4
Time to recurrence, day	340±211	241±164	144±139	0.11	0.03	<0.0001
Redo procedures	18(64.3)	10(62.5)	32(76.2)	1	0.34	0.29

Values are n (%) or mean±SD. * (%) are among patients with recurrence.

AF: Atrial fibrillation.

Table 4. Unadjusted and adjusted Cox regression analysis for arrhythmia recurrence.

	Unadjusted Analysis			Multivariate Analysis		
	HR	**95% CI**	**p**	**aHR***	**95% CI**	**p**
Arrhythmia recurrence						
Cluster 1 *vs.* 2	0.48	0.26-0.90	0.022	0.78	0.34-1.81	0.57
Cluster 1 *vs.* 3	0.29	0.18- 0.47	<0.0001	0.29	0.01-0.84	0.023
Cluster 2 *vs.* 3	0.55	0.31-0.98	0.043	0.67	0.30- 1.49	0.32

*Adjusted HR for age, paroxysmal atrial fibrillation, CHA_2DS_2-VASc score, ejection fraction and left atrial volume.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Bisson has been a consultant or speaker for Astra-Zeneca, Bayer, BMS/Pfizer, Medtronic, Vitorpharma and Alnylam. Clementy has been a consultant or speaker for Abbott, Medtronic and Microport. Angoulvant has been a consultant or speaker for Amgen, Astra-Zeneca, Bayer, BMS/Pfizer, MSD, Novartis, Novo Nordisk, Sanofi, Servier. Lip has been a consultant or speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally**.** LF reports consulting fees for AstraZeneca, Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, Novo Nordisk and Novartis and lecture fees for AstraZeneca, Bayer, BMS/Pfizer, Boehringer Ingelheim and Zoll. All other authors have reported that they have no relationships relevant to the

Graphical abstract.

AF: Atrial fibrillation; CV: Cardiovascular; EF: Ejection fraction; LA vol: Left atrial volume.