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# Predictors of recurrence of atrial fibrillation within the first 3 months after ablation

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## Aims

Freedom from atrial fibrillation (AF) at 1 year can be achieved in 50–70% of patients undergoing catheter ablation. Recurrent AF early after ablation most commonly terminates spontaneously without further interventional treatment but is associated with later recurrent AF. The aim of this investigation is to identify clinical and procedural factors associated with recurrence of AF early after ablation.

## Methods and results

We retrospectively analysed data for recurrence of AF within the first 3 months after catheter ablation from the randomized controlled AXAFA–AFNET 5 trial, which demonstrated that continuous anticoagulation with apixaban is as safe and as effective compared to vitamin K antagonists in 678 patients undergoing first AF ablation. The primary outcome of first recurrent AF within 90 days was observed in 163 (28%) patients, in which 78 (48%) patients experienced an event within the first 14 days post-ablation. After multivariable adjustment, a history of stroke/transient ischaemic attack [hazard ratio (HR) 1.54, 95% confidence interval (CI) 0.93–2.6;  $P=0.11$ ], coronary artery disease (HR 1.85, 95% CI 1.20–2.86;  $P=0.005$ ), cardioversion during ablation (HR 1.78, 95% CI 1.26–2.49;  $P=0.001$ ), and an age:sex interaction for older women (HR 1.01, 95% CI 1.00–1.01;  $P=0.04$ ) were associated with recurrent AF. The P-wave duration at follow-up was significantly longer for patients with AF recurrence ( $129 \pm 31$  ms vs.  $122 \pm 22$  ms in patients without AF,  $P=0.03$ ).

## Conclusion

Half of all early AF recurrences within the first 3 months post-ablation occurred within the first 14 days post-ablation. Vascular disease and cardioversion during the procedure are strong predictors of recurrent AF. P-wave duration at follow-up was longer in patients with recurrent AF.

## Trial registration

Clinicaltrials.gov identifier NCT02227550

## Keywords

Atrial fibrillation • Ablation • AXAFA • Early recurrence • Blanking period • Apixaban

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### What's new?

- In this retrospective analysis of the randomized control AXAFA-AFNET 5 trial, 28% of patients had recurrent atrial fibrillation (AF) within the first 3 months post-ablation. Half of all recurrences occurred within the first 14 days.
- Vascular disease and the need for cardioversion during ablation were strong predictors of recurrent AF.
- P-wave duration of patients with recurrent AF was longer at the 3 months of follow-up.

## Introduction

Catheter ablation has become an established rhythm control therapy in patients with symptomatic atrial fibrillation (AF).<sup>1,2</sup> Freedom from AF and maintenance of sinus rhythm at 1-year post-ablation can be achieved in 50–70% of patients undergoing catheter ablation. Thus, a substantial number of patients would require repeat ablation due to symptomatic recurrent AF.<sup>2</sup> Identification of patient groups at higher risk for developing recurrent AF can help in developing preventive strategies, and tailoring of rhythm control therapy post-ablation. Many AF recurrences occur early after AF ablation and terminate spontaneously without further interventional treatment.<sup>3</sup> While many patients with early recurrences of AF do not develop recurrent AF beyond the so-called 'blinking period', early recurrences have been shown to be associated with late and symptomatic recurrences of AF.<sup>3–9</sup>

Therefore, the aim of this study was to identify the clinical and procedural-related factors associated with the first recurrences of AF within the first 3 months following ablation in the multicenter AXAFA-AFNET 5 trial.<sup>3,10</sup> Because signs of advanced atrial remodelling such as dilated atria or prolonged P-wave duration have been associated with new-onset AF, we analysed the association of P-wave characteristics in a subset of patients for recurrence of AF.<sup>11</sup>

## Methods

### Study population

AXAFA was a prospective multicentre randomized parallel-group design, comparing apixaban to vitamin K antagonist (VKA) in a cohort of AF patients undergoing catheter ablation.<sup>12</sup> Participants were randomized 1:1 to VKA or apixaban therapy at baseline, stratified by investigation site and type of AF (paroxysmal vs. persistent/long-standing persistent). Additional drug treatment or procedural decisions (e.g. type of ablation technique) were at the discretion of the treating physician. All patients underwent 24-h Holter monitoring 3 months after ablation.

The trial was conducted by the steering committee in cooperation with Atrial Fibrillation NETWORK (AFNET e.V.), Münster, Germany ([www.kompetenznetz-vorhofflimmern.de](http://www.kompetenznetz-vorhofflimmern.de)) in accordance with the declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines (ICH-GCP), conducted in Europe and North America and approved by local ethic review boards (NCT02227550). The protocol of this analysis was approved by the steering committee and supported by AFNET. CONSORT statement and diagram are described in the original manuscript.<sup>10</sup>

### Study population and inclusion/exclusion criteria

In this study, we considered 678 patients in the AXAFA trial and excluded patients who were still in AF after ablation ( $N = 30$ ) and patients who had no complete 3 months of follow-up data including rhythm status or date of first recurrence of AF after ablation ( $N = 59$ , [Supplementary material online, Figure S1](#)). Excluded patients showed no difference in epidemiologic data, symptoms, or items of CHA<sub>2</sub>DS<sub>2</sub>-VASc score as compared to patients who were not excluded ([Supplementary material online, Table S1](#)). Participants with previous ablation or surgical therapy for AF were excluded by AXAFA inclusion and exclusion criteria.

All patients received pulmonary vein isolation. In a subset of patients, one or more additional techniques were performed: linear lesion ( $N = 11$ ), mitral isthmus line ( $N = 3$ ), left atrial roof lesion ( $N = 9$ ), coronary sinus ablation ( $N = 1$ ), ablation of complex fragmented atrial electrograms ( $N = 20$ ), and ablation left atrial appendage ( $N = 1$ ). This data were not considered for further statistical analysis due to low numbers. Treatment decisions, as energy type or ablation technique, was at discretion of the treating physician. In 19 patients, a cavotricuspid ablation was performed in addition to pulmonary vein isolation.

In a subset of patients with available electrocardiogram (ECG) recordings in sinus rhythm, we analysed the association of P-wave duration, inter-atrial block, and P-wave morphology at baseline ( $n = 383$ ), pre-ablation ( $n = 355$ ), and at 3 months of follow-up ( $n = 496$ ) with recurrent AF.

### Electrocardiogram analysis

Digital 12-lead ECGs recorded at baseline, at the index ablation, and follow-up after 3 months were analysed with GeoGebra 5.0<sup>®</sup> software. Digital calipers were used to measure P-wave duration, determined from the earliest to the last P-wave signal in any frontal lead. All measurements were performed by a blinded assessor and corroborated by a second expert observer when there was ambiguity.

P-wave morphology was assessed by observation of the inferior leads (II, III, and aVF).<sup>13,14</sup> Interatrial block (IAB) was defined as bimodal (positive/negative) P-wave morphology with an initial upward deviation from the baseline and a final downward deviation towards the baseline ([Supplementary material online, Figure S2](#)). Normal atrial conduction was considered as a P-wave duration of 120 ms regardless of morphology; partial IAB was defined as a P-wave  $\geq 120$  ms without bimodal morphology; and advanced IAB was defined as a P-wave  $\geq 120$  ms with bimodal morphology.<sup>15</sup>

### Statistical methods

The primary outcome, recurrence of AF within the first 3 months after ablation, was defined as any episode of AF (paroxysmal, persistent, long-lasting, or permanent AF) or atrial flutter, which lasted for at least 30 s, occurring within the 3 months blanking period according to the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement.<sup>1</sup> The date of first occurrence of primary outcome was determined by ECG or long-term ECG ( $N = 83$ ), AF symptoms ( $N = 74$ ), or by other ways ( $N = 6$ : implanted devices, self-measurement, unspecified). All patients with clinical recurrences of AF were included. Baseline characteristics of patients with and without recurrent AF within the first 3 months after ablation were assessed.

For statistical analysis, SPSS (SPSS Statistics version 25, IBM Corporation, USA) was used. Descriptive statistics for continuous variables were summarized as means (standard deviations) or medians (25th, 75th percentiles), and for categorical variables as counts (percentages), respectively. Continuous variables were compared using Student's *t*-test,

or Mann–Whitney  $U$  test, after checking for normality using the Kolmogorov–Smirnov test. Categorical variables were compared using Pearson's  $\chi^2$  test. Clinical, procedural, and therapy-related factors which may influence recurrence of AF were analysed using a univariate Cox model as well as multivariable Cox regression model analysis. Candidate variables were selected using forward selection (entry criterion  $P=0.05$ , removal  $P=0.1$ ). Variables considered were randomized treatment (VKA, apixaban), AF type (paroxysmal, persistent), sex (male, female), age (years), interaction of sex and age, height (cm), hypertension, diabetes mellitus, symptomatic heart failure, history of stroke/transient ischaemic attack (TIA), confirmed coronary artery disease, time since AF diagnosis (months), type of ablation technique (cryoballoon, radiofrequency, other), need for cardioversion during procedure, duration of procedure after transseptal puncture (minutes), antiarrhythmic drug usage of beta-blocker, Class IC, or Class III. Kaplan–Meier cumulative risk plots and the log-rank tests were used to estimate the proportion of patients free from AF after the initial procedure. A two-sided  $P$ -value of  $<0.05$  was considered statistically significant.

## Results

### Study population

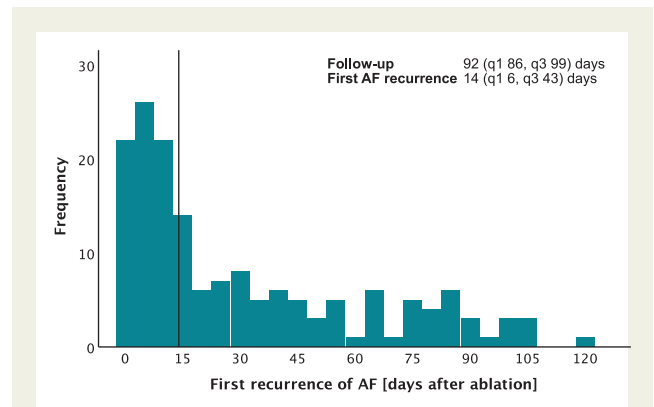
We analysed data from 589 patients with a median follow-up period of 92 [25th percentile (q1) 86, 75th percentile (q3) 99] days after ablation. Recurrent AF was observed in 163 (28%) patients with a median time to recurrence of 14 (q1 6, q3 43) days. Among the 163 patients with recurrent atrial arrhythmia, 91% ( $n=148$ ) had recurrent AF only, 5% ( $n=8$ ) had recurrent atrial tachycardia or atrial flutter only, and 4% ( $n=7$ ) had both. Overall, 48% of recurrences occurred within the first 14 days post-ablation ( $n=78$ ; Figure 1).

Compared to patients without AF recurrence, patients with recurrent AF were older, more likely to be female, had a history of stroke/TIA, coronary artery disease, had higher CHA<sub>2</sub>DS<sub>2</sub>-VASc scores, required electrical cardioversion during ablation more often and were less likely to have used sodium channel blocking antiarrhythmic drugs before ablation (Table 1). After ablation, patients with a recurrence of AF reported higher ( $n=16$ ), lower ( $n=97$ ), or unchanged ( $n=42$ ) EHRA score as compared to symptoms before ablation (missing,  $n=8$ ). In total, 56 patients with recurrence of AF had no AF-related symptoms after ablation (EHRA score = 1).

### Factors associated with recurrent atrial fibrillation

In univariate analyses (adjusted by site, Table 2), age per year [hazard ratio (HR) 1.02, 95% confidence interval (CI) 1.00–1.04;  $P=0.02$ ], history of stroke/TIA (HR 1.68, 95% CI 1.02–2.77;  $P=0.04$ ), coronary artery disease (HR 1.53, 95% CI 1.01–2.33;  $P<0.001$ ), the need for electrical cardioversion during ablation (HR 1.76, 95% CI 1.26–2.46;  $P<0.001$ ), longer duration of ablation after transseptal puncture (steps per minute, HR 1.01, 95% CI 1.00–1.01;  $P=0.005$ ) were associated with recurrent AF. Type of ablation technique (with cryoballoon as reference) did not show a significant association between use of radiofrequency ablation and recurrent AF (HR 2.85, 95% CI 0.35–23.48;  $P=0.33$ ).

The forward selection process in multivariate analyses identified three predictors associated with increased risk of recurrent AF within the first 3 months after ablation (Table 3): coronary artery



**Figure 1** Cumulative frequency of first AF recurrence after catheter ablation ( $n=163$ ). Vertical black line indicates Day 14. Follow-up and first AF recurrence are displayed as median and q1: 25th percentile; q3: 75th percentile. AF, atrial fibrillation.

disease (HR 1.85, 95% CI 1.20–2.86;  $P=0.005$ ), the need for cardioversion during the procedure (HR 1.77, 95% CI 1.26–2.49;  $P=0.001$ ), and an age:sex interaction (HR 1.01, 95% CI 1.00–1.01;  $P=0.04$ ) indicating higher risk of recurrent AF for young men and older women.

Kaplan–Meier cumulative risk curves indicated that the type of ablation technique did not influence AF recurrences (log-rank  $P=0.16$ , Figure 2A). Coronary artery disease (log-rank  $P=0.02$ , Figure 2B), history of stroke/TIA (log-rank  $P=0.01$ , Figure 2C), and the need for cardioversion during the ablation procedure (log-rank  $P<0.001$ , Figure 2D) were associated with recurrent AF.

### Interatrial block and P-wave duration

In patients who were in sinus rhythm at the time of ablation, the presence of advanced IAB or P-wave duration shorter of 90 ms in any available ECG (baseline, ablation, and follow-up) was not associated with recurrent AF (Supplementary material online, Table S2). There was no difference for IAB (partial or advanced) for recurrent AF at baseline, ablation and follow-up. When the ECG at the end of follow-up was analysed (i.e. including patients, who underwent AF ablation in AF), two parameters were associated with recurrent AF. Patients with recurrent AF showed a higher proportion of P-wave prolongation at follow-up compared to the day of ablation [no recurrence:  $n=108$  (42%) vs. AF recurrence:  $n=38$  (57%),  $P=0.03$ , Supplementary material online, Table S2], and a higher absolute P-wave duration compared to patients without recurrent AF (No recurrence:  $122 \pm 22$  ms vs. AF recurrence:  $129 \pm 31$  ms,  $P=0.03$ , Supplementary material online, Table S2).

## Discussion

### Main findings

This analysis of factors associated with recurrent AF in 589 AXAFA-AFNET 5 patients undergoing a first ablation of AF identified present vascular disease and the need for electrical cardioversion during the ablation procedure as strong predictors for

**Table 1** Characteristics of baseline, AF, ablation, AF recurrence, and follow-up data.

	No recurrence, N (%) / mean ± SD	AF recurrence, N (%) / mean ± SD	P-value
Patients	426 (72%)	163 (28%)	
Randomization apixaban group	212 (50%)	87 (53%)	0.43 <sup>b</sup>
Sex, male	294 (69%)	97 (60%)	0.03 <sup>a,b</sup>
Age (years)	63 ± 9	65 ± 9	0.04 <sup>a, c</sup>
Height (cm)	175 ± 10	175 ± 10	0.96 <sup>c</sup>
Weight (kg)	88 ± 17	89 ± 18	0.41 <sup>c</sup>
BMI (kg/m <sup>2</sup> )	28.72 ± 4.78	29.02 ± 5	0.47 <sup>c</sup>
RR systolic (mmHg)	135 ± 19	137 ± 19	0.37 <sup>c</sup>
RR diastolic (mmHg)	80 ± 12	81 ± 12	0.21 <sup>c</sup>
Atrial fibrillation, paroxysmal	267 (63%)	91 (56%)	0.13 <sup>b</sup>
AF diagnosis (months)	56 ± 67	58 ± 63	0.17 <sup>c</sup>
EHRA (baseline)			
IIa	119 (30%)	35 (23%)	0.14 <sup>b</sup>
IIb	141 (35%)	49 (32%)	
III	129 (32%)	64 (42%)	
IV	9 (2%)	5 (3%)	
NYHA			
No	295 (69%)	102 (63%)	0.12 <sup>b</sup>
I	44 (10%)	22 (14%)	
II	79 (19%)	31 (19%)	
III	8 (2%)	8 (5%)	
Prior cardioversion (pharmacological or electrical)	279 (66%)	114 (70%)	0.31 <sup>b</sup>
Age 65–74 years	150 (35%)	74 (45%)	0.02 <sup>a,b</sup>
Older than 74 years	36 (9%)	16 (10%)	0.6 <sup>b</sup>
History of stroke /TIA	26 (6%)	20 (12%)	0.01 <sup>a,b</sup>
Hypertension	385 (90%)	144 (88%)	0.47 <sup>b</sup>
Diabetes mellitus	43 (10%)	24 (15%)	0.11 <sup>b</sup>
Symptomatic heart failure	95 (22%)	38 (23%)	0.79 <sup>b</sup>
Coronary artery disease	44 (10%)	29 (18%)	0.01 <sup>a,b</sup>
Cardiomyopathy	51 (12%)	22 (13%)	0.62 <sup>b</sup>
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	1.4 ± 0.7	1.6 ± 0.8	0.03 <sup>a, c</sup>
Valvular disease	52 (12%)	13 (8%)	0.14 <sup>b</sup>
COPD	26 (6%)	10 (6%)	0.99 <sup>b</sup>
Heart rate (index) (/min)	68 ± 19	73 ± 23	0.1 <sup>c</sup>
QRS (ms)	97 ± 16	98 ± 19	0.88 <sup>c</sup>
PQ (ms)	177 ± 33	181 ± 36	0.3 <sup>c</sup>
QTc (ms)	435 ± 38	436 ± 47	0.93 <sup>c</sup>
Hospitalization (days)	2.3 ± 1.6	2.6 ± 2.9	0.31 <sup>c</sup>
Hospitalization after ablation (days)	1.6 ± 1.1	1.8 ± 2.1	0.43 <sup>c</sup>
Duration of ablation (min)	146 ± 57	147 ± 55	0.73 <sup>c</sup>
Duration after trans septal puncture (min)	120 ± 49	121 ± 51	0.96 <sup>c</sup>
Type of ablation technique			
Cryoballoon	126 (30%)	49 (30%)	0.11 <sup>b</sup>
Radiofrequency	263 (62%)	108 (66%)	
Other	37 (9%)	6 (4%)	
Fluoroscopy time (min)	14.9 ± 11.8	15.1 ± 11.6	0.69 <sup>c</sup>
Heparin total dose (IU)	12849 ± 5792	12004 ± 5588	0.1 <sup>c</sup>
Need for cardioversion during procedure	111 (26%)	68 (42%)	<0.001 <sup>a, b</sup>
Antihypertensive medication	250 (59%)	104 (64%)	0.26 <sup>b</sup>
Sodium channel blocker	105 (25%)	26 (16%)	0.02 <sup>a,b</sup>
Antiarrhythmic class III	98 (23%)	28 (17%)	0.12 <sup>b</sup>

Continued

**Table 1** Continued

	No recurrence, N (%) / mean $\pm$ SD	AF recurrence, N (%) / mean $\pm$ SD	P-value
Beta blockers	305 (72%)	113 (69%)	0.59 <sup>b</sup>
Diuretics	137 (32%)	61 (37%)	0.23 <sup>b</sup>
Statin	159 (37%)	55 (34%)	0.42 <sup>b</sup>
Total amount of drugs	4 $\pm$ 2.2	3.9 $\pm$ 2.1	0.45 <sup>c</sup>

CAD, history of coronary artery disease; CABG, coronary arterial bypass graft; FU, measurement at 3-month follow-up period; SD, standard deviation; TIA, transient ischaemic attack.

<sup>a</sup>P-value <0.05.

<sup>b</sup>Pearson's  $\chi^2$  test.

<sup>c</sup>Mann-Whitney *U* test.

**Table 2** Univariate analysis for recurrence of AF within the first 3 months after ablation

Reference category (unit)	Hazard ratio	95% CI	P-value
Randomization group, VKA	0.91	0.67–1.25	0.57
AF type, persistent	1.26	0.89–1.77	0.19
Age (years)	1.02	1.00–1.04	0.02 <sup>a</sup>
Sex, female	1.33	0.95–1.86	0.10
Age (years) $\times$ sex (female)	1.01	1.00–1.01	0.06
Height (cm)	0.98	0.97–1.00	0.08
Hypertension	1.13	0.67–1.90	0.65
Diabetes mellitus	1.35	0.86–2.11	0.19
Symptomatic heart failure	0.84	0.55–1.27	0.40
History of stroke/TIA	1.68	1.02–2.77	0.04 <sup>a</sup>
Coronary artery disease	1.53	1.01–2.33	<0.001 <sup>a</sup>
AF diagnosis (months)	1.00	0.99–1.00	0.65
Type of ablation technique			
Cryoballoon		–	0.009 <sup>a</sup>
Radiofrequency	2.85	0.35–23.48	0.33
Other	0.46	0.28–0.78	0.004 <sup>a</sup>
Need for eCV during procedure	1.762	1.26–2.46	<0.001 <sup>a</sup>
Duration of ablation after trans septal puncture (min)	1.01	1.00–1.01	0.005 <sup>a</sup>
Betablocker	0.97	0.68–1.37	0.85
Sodium channel blocker	0.77	0.48–1.23	0.27
Antiarrhythmic drug Class III	0.69	0.45–1.07	0.09

Hazard ratios were quantified for potential clinical and procedural factors associated with recurrence of AF. Data were adjusted for 'site' of ablation.

AF, atrial fibrillation; CI, confidence interval; eCV, electrical cardioversion; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

<sup>a</sup>Marks significant factors.

recurrence of AF after AF ablation. Notably, half of all observed AF recurrences occurred within the first 14 days after ablation. Although limited to analysis of P-wave duration at the end of follow-up, a longer P-wave duration appeared to be associated with recurrent AF after ablation.

## Baseline findings and timely course of atrial fibrillation

In our cohort of AF patients after first ablation with at least one risk factor for stroke, patients with recurrent AF were older, more often female, had more often coronary artery disease, a history of stroke/

TIA, a higher CHA<sub>2</sub>DS<sub>2</sub>-VASc score and more often underwent cardioversion during catheter ablation (Table 1).

Our finding that 28% of all patients had recurrent AF is in the range of reported recurrences in the first 3 months after ablation (19–56%).<sup>8,9,16</sup> The wide range can be explained due to varying AF definitions, observing intervals and efforts for AF diagnosis, and may include a temporal effect related to improved ablation techniques like pressure sensitive and irrigated ablation catheters or second-generation cryoballoon in our cohort. The improvement in AF-related symptoms in our cohort for patients with recurrence of AF is in line with previous reported improvement of symptoms<sup>17</sup> and quality of life.<sup>18</sup>

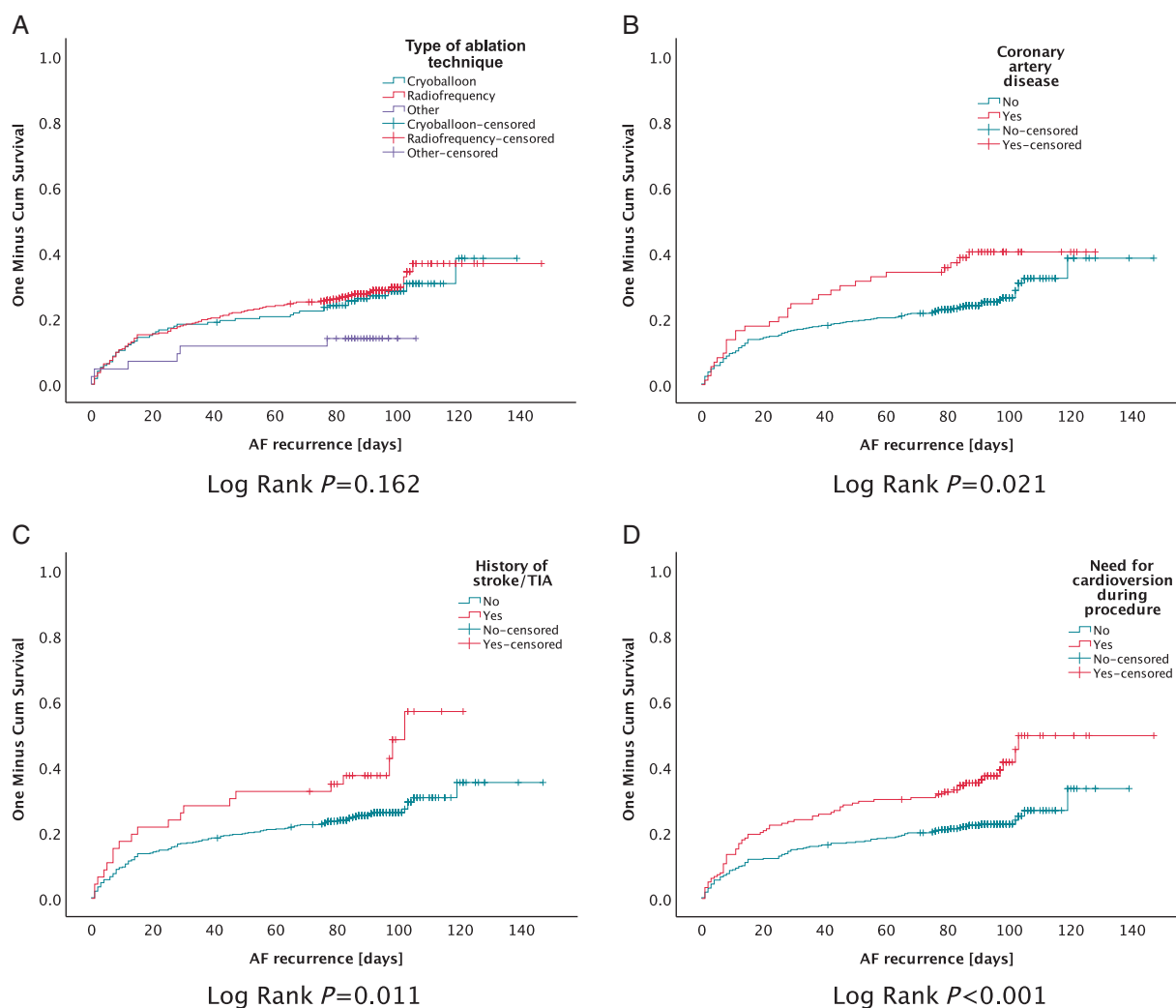
**Table 3** Multivariate analysis (Cox regression, adjusted for ‘site’ of ablation) for recurrence of AF within the first 3 months after ablation

	Hazard ratio	95% CI	P-value
History of stroke/TIA	1.54	0.93–2.56	0.1
Coronary artery disease	1.85	1.20–2.86	0.005 <sup>a</sup>
Need for cardioversion during procedure	1.77	1.26–2.49	0.001 <sup>a</sup>
Age (years) × sex (female)	1.01	1.00–1.01	0.04 <sup>a</sup>

Variables included in the forward selection are randomization (VKA, apixaban), AF type (paroxysmal, persistent), sex (female), age (steps per year), interaction of sex (female) and age (steps per year), height (steps in cm), hypertension, diabetes mellitus, symptomatic heart failure, history of stroke/TIA, confirmed coronary artery disease, AF knowledge (steps per months), type of ablation energy used (cryoballoon, radiofrequency, other), need for cardioversion during procedure, duration of procedure after transseptal puncture (steps in min), antiarrhythmic drug usage of betablocker, Class IC, or Class III.

AF, atrial fibrillation; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

<sup>a</sup>Marks significant factors.



**Figure 2** Kaplan–Meier cumulative risk plots of (A) type of ablation energy used, (B) coronary artery disease, (C) history of stroke/TIA, and (D) the need for cardioversion during procedure. AF, atrial fibrillation; TIA, transient ischaemic attack.

## Predictors of recurrence of atrial fibrillation

The interaction of higher age and female sex, history of stroke/TIA, coronary artery disease, and the need for cardioversion during procedure were predictors for recurrence of AF. Comparable risk factors were reported before for structural heart disease,<sup>7</sup> and cardioversion during procedure.<sup>6</sup> According to previous studies, several factors failed in prediction for recurrent AF in our cohort like hypertension,<sup>6</sup> AF type,<sup>7</sup> age, or the duration of ablation.<sup>16</sup> In addition to vascular disease as a marker for an atrial cardiomyopathy, the need for cardioversion during procedure may be considered as indication for an advanced substrate of maintaining AF.

Procedural effects like type of ablation technique used and duration of ablation showed no differences in comparison of the groups but an effect on rate of AF recurrence in univariate analysis while in multivariate analysis failed to do so. Similar findings for duration of ablation were reported before.<sup>3,19</sup> The fact that type of AF, type of ablation and procedural time showed no association to primary outcome, can be explained, as the treatment was at discretion of treating physicians. Thus, ablation was performed as needed for individual success. Therefore, it is not surprising that a well-chosen ablation strategy also leads to comparable outcome for recurrence of AF in advanced types of AF as with early stages of AF. Independently, the need for cardioversion shows a significant association to recurrence of AF. This could be a sign of more advanced atrial remodelling and probably more ablation is needed, because an AF trigger or a not ablated substrate still maintains the ongoing arrhythmia. The results for ablation technique used, is in line with the randomized trials comparing the two main energy sources (cryoballoon ablation and radiofrequency ablation)<sup>20</sup> and showed in the investigated cohort no significant difference. Notably, because used therapy was at the discretion of the treating physician this cohort consists of rarely used types of ablation techniques (PVAC  $N=3$ , Laser ablation  $N=42$ ). In Kaplan–Meier cumulative risk plot a lower dynamic of AF recurrences compared to cryoballoon and radiofrequency ablation was revealed for laser ablation technique.

## Potential clinical implications

Given the available data for recurrence of AF in comparable investigations with smaller cohorts, this investigation allows higher confidence in identified predictors for recurrent AF within the first 3 months after catheter ablation. While vascular disease was previously described as a risk factor for recurrent AF, our data identified as novel aspect the need for cardioversion during procedure as a potential and easily to assessable predictor for recurrent AF after a first AF ablation. Prolonged P-wave duration at the end of the blanking period in patients with recurrent AF might as well be considered as a marker of increased risk of recurrent AF. Recurrence of AF within the blanking period is a strong and independent predictor of long-term ablation success. Therefore, our finding that half of patients with early recurrent AF have their first recurrence within Day 1 to Day 14 after ablation, followed a robust recurrent AF frequency until 3 months after AF ablation, the blanking period of 3 months might be reconsidered.

## Electrocardiogram parameter

Atrial remodelling is independently associated with new-onset AF and higher number of AF recurrences after ablation and can be

measured by imaging techniques or 12-lead ECG. We analysed repeatedly recorded P-wave parameters and ECG sign for IAB as surrogate marker for atrial remodelling and its association to recurrence of AF. We found longer P-waves in patients with recurrent AF in our cohort. Due to the high number of patients undergoing the procedure in AF, this difference was only found when analyzing ECGs at the end of the 3 months of follow-up (Supplementary material online, Table S2). There is evidence for a change of P-wave indices due to surgical ablation procedure as effect of reverse electrical atrial remodelling.<sup>21</sup> However, prolonged P-wave duration and increased dispersion have been shown association with recurrent AF after AF ablation.<sup>22,23</sup> Furthermore, prolonged P-wave duration is known to be associated with enlarged atria,<sup>15</sup> atrial conduction disturbances and associated with AF development.<sup>11</sup> Based on our data, the presence of advanced IAB as a predictor for new-onset atrial fibrillation,<sup>11</sup> did not add to the prediction of recurrent AF within the first 3 months after ablation but should be seen as hypothesis generating. Upcoming investigation with primary outcome for AF recurrence in context of advanced IAB and extended follow-up period are warranted.

## Limitations

The data obtained from this multicentre study conducted in European and North America was collected in a structured and predefined way. Unfortunately, the data lack information on biomarkers and imaging data which might add more information for atrial structural remodelling. Continuous rhythm monitoring in this cohort was not provided after ablation, therefore reported rate of recurrence is related to clinical AF, because asymptomatic episodes could be missed by chance. Repeated ECG recording is available before and after the procedure, and in the follow-up period. Therefore, detailed 12-lead ECG analysis was performed as a surrogate marker for atrial electrical remodelling. There is little evidence for association of predictors of recurrent AF within the first 3 months with later recurrence. Future studies on predictors of early AF recurrences are therefore certainly warranted.

As because many patients presented in AF, the P-wave analysis and advanced IAB was not available in all patients. Although, P-wave analysis points towards an association of recurrent AF with advanced IAB the analysis is potentially biased by analyzing the healthier patients in our cohort and underestimates the association compared to existing evidence,<sup>11,13,14,24–26</sup> because in particular higher degree of atrial remodelling is probably associated with higher chance of presenting in AF at any time point. As a matter of fact, advanced IAB was a marker of AF much later than 3 months in previous investigations.<sup>11</sup>

Data of this study were obtained for a comparison of Apixaban vs. VKA, thus the primary objective and hypothesis of this retrospective analysis was not defined a priori and no placebo control was included; therefore, our results should be considered as descriptive and not as a confirmatory investigation. Because no 1-year follow-up data is available, a comparison of long-term ablation success, linked to recurrence within the blanking period is not possible.

## Conclusion

Half of all early AF recurrences occurred within the first 14 days after first ablation. Ablation technique source, duration of ablation,



hypertension, type of AF, diabetes mellitus, or antiarrhythmic drug usage showed no effect on recurrence of AF within the blanking period. Present vascular disease (coronary artery disease or stroke/TIA) and the need for cardioversion during the procedure are strong predictors for recurrent AF within the blanking period. P-wave duration at follow-up was longer in patients with recurrent AF in the first 3 months after ablation.

## Supplementary material

Supplementary material is available at *Europace* online.

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## Data availability

Access to data (raw and derived) is regulated by the AXAFA steering committee. For a reasonable request please contact the corresponding author.

## References

- Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L et al.; Document Reviewers. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* 2018;**20**:e1–160.
- Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–78.
- Andrade JG, Khairy P, Verma A, Guerra PG, Dubuc M, Rivard L et al. Early recurrence of atrial tachyarrhythmias following radiofrequency catheter ablation of atrial fibrillation. *Pacing Clin Electrophysiol* 2012;**35**:106–16.
- Nalliah CJ, Lim TW, Kizana E, Qian P, Kovoor P, Thiagalingam A et al. Clinical significance of early atrial arrhythmia type and timing after single ring isolation of the pulmonary veins. *Europace* 2015;**17**:1038–44.

- Andrade JG, Khairy P, Macle L, Packer DL, Lehmann JW, Holcomb RG et al. Incidence and significance of early recurrences of atrial fibrillation after cryoballoon ablation: insights from the multicenter Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) trial. *Circ Arrhythm Electrophysiol* 2014;**7**:69–75.
- Themistoclakis S, Schweikert RA, Saliba WJ, Bonso A, Rossillo A, Bader G et al. Clinical predictors and relationship between early and late atrial tachyarrhythmias after pulmonary vein antrum isolation. *Heart Rhythm* 2008;**5**:679–85.
- Bertaglia E, Stabile G, Senatore G, Zoppo F, Turco P, Amellone C et al. Predictive value of early atrial tachyarrhythmias recurrence after circumferential anatomical pulmonary vein ablation. *Pacing Clin Electrophysiol* 2005;**28**:366–71.
- Takayama K, Hachiya H, Iesaka Y, Hirao K, Isobe M. Early recurrence after long-standing persistent atrial fibrillation ablation. *Int Heart J* 2018;**59**:321–7.
- Oral H, Knight BP, Ozaydin M, Tada H, Chugh A, Hassan S et al. Clinical significance of early recurrences of atrial fibrillation after pulmonary vein isolation. *J Am Coll Cardiol* 2002;**40**:100–4.
- Kirchhof P, Haessler KG, Blank B, De Bono J, Callans D, Elvan A et al. Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation. *Eur Heart J* 2018; doi:10.1093/eurheartj/ehy176.
- Enriquez A, Sarrías A, Villuendas R, Ali FS, Conde D, Hopman WM et al. New-onset atrial fibrillation after cavotricuspid isthmus ablation: identification of advanced interatrial block is key. *Europace* 2015;**17**:1289–93.
- Di Biase L, Callans D, Haessler KG, Hindricks G, Al-Khalidi H, Mont L et al. Rationale and design of AXAFA-AFNET 5: an investigator-initiated, randomized, open, blinded outcome assessment, multi-centre trial to comparing continuous apixaban to vitamin K antagonists in patients undergoing atrial fibrillation catheter ablation. *Europace* 2017;**19**:132–8.
- Wu JT, Zhao DQ, Li FF, Wu R, Fan XW, Hu GL et al. Advanced interatrial block predicts recurrence of atrial fibrillation after accessory pathway ablation in patients with Wolff-Parkinson-White syndrome. *Clin Cardiol* 2019;**42**:806–11.
- Bayes de Luna A, Escobar-Robledo LA, Aristizabal D, Weir Restrepo D, Mendieta G, Masso van Roessel A et al. Atypical advanced interatrial blocks: definition and electrocardiographic recognition. *J Electrocardiol* 2018;**51**:1091–3.
- Bayes de Luna A, Platonov P, Cosio FG, Cygankiewicz I, Pastore C, Baranowski R et al. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. *J Electrocardiol* 2012;**45**:445–51.
- Chang SL, Tsao HM, Lin YJ, Lo LW, Hu YF, Tuan TC et al. Characteristics and significance of very early recurrence of atrial fibrillation after catheter ablation. *J Cardiovasc Electrophysiol* 2011;**22**:1193–8.
- Bjorkenheim A, Brandes A, Magnuson A, Chemnitz A, Svedberg L, Edvardsson N et al. Assessment of atrial fibrillation-specific symptoms before and 2 years after atrial fibrillation ablation: do patients and physicians differ in their perception of symptom relief? *JACC Clin Electrophysiol* 2017;**3**:1168–76.
- Kuck KH, Furnkranz A, Chun KR, Metzner A, Ouyang F, Schluter M et al. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. *Eur Heart J* 2016;**37**:2858–65.
- Budzianowski J, Hiczkiewicz J, Burchardt P, Pieszko K, Rzeźniczak J, Budzianowski P et al. Predictors of atrial fibrillation early recurrence following cryoballoon ablation of pulmonary veins using statistical assessment and machine learning algorithms. *Heart Vessels* 2019;**34**:352–9.
- Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med* 2016;**374**:2235–45.
- Nassif M, Krul SP, Driessen AH, Deneke T, Wilde AA, de Bakker JM et al. Electrocardiographic P wave changes after thoracoscopic pulmonary vein isolation for atrial fibrillation. *J Interv Card Electrophysiol* 2013;**37**:275–82.
- Jiang H, Lu Z, Lei H, Zhao D, Yang B, Huang C. Predictors of early recurrence and delayed cure after segmental pulmonary vein isolation for paroxysmal atrial fibrillation without structural heart disease. *J Interv Card Electrophysiol* 2006;**15**:157–63.
- O'Donnell D, Furniss SS, Dunuwille A, Bourke JP. Delayed cure despite early recurrence after pulmonary vein isolation for atrial fibrillation. *Am J Cardiol* 2003;**91**:83–5.
- Wu JT, Long DY, Dong JZ, Wang SL, Fan XW, Yang HT et al. Advanced interatrial block predicts clinical recurrence of atrial fibrillation after catheter ablation. *J Cardiol* 2016;**68**:352–6.
- Escobar-Robledo LA, Bayes-de-Luna A, Lupon J, Baranchuk A, Moliner P, Martinez-Selles M et al. Advanced interatrial block predicts new-onset atrial fibrillation and ischemic stroke in patients with heart failure: the “Bayes’ Syndrome-HF” study. *Int J Cardiol* 2018;**271**:174–80.
- Baranchuk A, Yeung C. Advanced interatrial block predicts atrial fibrillation recurrence across different populations: learning Bayes syndrome. *Int J Cardiol* 2018;**272**:221–2.