Published in final edited form as:

Circ Arrhythm Electrophysiol. 2016 January ; 9(1): e003669. doi:10.1161/CIRCEP.115.003669.

Radiofrequency Ablation of Persistent Atrial Fibrillation:

Diagnosis-to-Ablation Time, Markers of Pathways of Atrial Remodeling, and Outcomes

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Abstract

Background—Various ablation strategies of persistent atrial fibrillation (PersAF) have had disappointing outcomes, despite concerted clinical and research efforts, which could reflect progressive atrial fibrillation–related atrial remodeling.

Methods and Results—Two-year outcomes were assessed in 1241 consecutive patients undergoing first-time ablation of PersAF (2005–2012). The time intervals between the first diagnosis of PersAF and the ablation procedures were determined. Patients had echocardiograms and measures of B-type natriuretic peptide and C-reactive protein before the procedures. The median diagnosis-to-ablation time was 3 years (25th–75th percentiles 1–6.5). With longer diagnosis-to-ablation time (based on quartiles), there was a significant increase in recurrence rates in addition to an increase in B-type natriuretic peptide levels ($P=0.01$), C-reactive protein levels ($P<0.0001$), and left atrial size ($P=0.03$). The arrhythmia recurrence rates over 2 years were 33.6%, 52.6%, 57.1%, and 54.6% in the first, second, third, and fourth quartiles, respectively ($P_{\text{categorical}}<0.0001$). In Cox Proportional Hazard analyses, B-type natriuretic peptide levels, C-reactive protein levels, and left atrial size were associated with arrhythmia recurrence. The diagnosis-to-ablation time had the strongest association with the ablation outcomes which persisted in multivariable Cox analyzes (hazard ratio for recurrence per +1Log diagnosis-to-ablation time 1.27, 95% confidence interval 1.14–1.43; $P<0.0001$; hazard ratio fourth versus first quartile 2.44, 95% confidence interval 1.68–3.65; $P_{\text{categorical}}<0.0001$).

Conclusions—In patients with PersAF undergoing ablation, the time interval between the first diagnosis of PersAF and the catheter ablation procedure had a strong association with the ablation

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Disclosures
None.

outcomes, such as shorter diagnosis-to-ablation times were associated with better outcomes and in direct association with markers of atrial remodeling.

Keywords

ablation; atrial fibrillation; catheter ablation; outcome; outcomes research

Atrial fibrillation (AF), the most common cardiac arrhythmia, is associated with increased morbidity and mortality. Catheter-based ablation targeting pulmonary vein isolation (PVI) has become a treatment of choice for drug-resistant paroxysmal AF.¹ However, in patients with persistent AF (PersAF), no optimal ablation strategies in addition to PVI have been defined to date. In fact, various ablation strategies of PersAF have had disappointing outcomes, despite concerted clinical and research efforts, and recurrences are still common and problematic.^{1–6}

The natural history of AF is characterized by progressive atrial remodeling,^{7–9} which eventually leads to persistence of the arrhythmia. This process involves the interaction of multiple complex pathways, which encompass among others AF-related hemodynamic strain, atrial dilatation, inflammation, cardiomyocyte injury, and alterations of collagen turnover, resulting in scarring and fibrosis.¹⁰

Given the progressive nature of atrial structural and functional remodeling in AF and the fact that advanced atrial remodeling significantly contributes to maintenance and persistence of the arrhythmia, we hypothesized that in patients with PersAF undergoing catheter ablation, longer diagnosis-to-ablation times are major determinants of the ablation outcomes and are in direct association with pathways of atrial remodeling. The study assessed the success rates of PersAF ablation as a function of the time interval between the very first diagnosis of PersAF and the ablation procedure, as well as the impact of multiple markers of AF-related remodeling and their relationship to chronicity of the arrhythmia.

Methods

Study Population

All consecutive patients undergoing radiofrequency ablation for recurrent symptomatic AF between January 2005 and December 2012 at our institution were enrolled in a prospectively maintained AF ablation data registry and screened for eligibility for the current study. Persistent AF was defined in concordance with the published guidelines¹ as continuous AF that is sustained beyond 7 days or as an episode of AF of >48 hours duration that required electrical or pharmacological cardioversion. Only patients with PersAF were eligible for inclusion and were identified by review of the data registry and medical records with clinical documentation of PersAF. The study excluded any patients with paroxysmal AF and those with a prior AF ablation procedure or cardiac surgery, as well as patients in whom it was not possible to determine the time of first diagnosis of PersAF (n=248). A total of 1241 consecutive patients met the inclusion criteria. In this group of patients, we investigated the arrhythmia recurrence rates as a function of the primary variable of interest which was the time interval between the very first PersAF diagnosis and the ablation procedure. The overall

duration of AF history was the time interval since the very first diagnosis of AF, and this was categorized into 2 components of time spent with paroxysmal AF diagnosis and the time spent with a diagnosis of PersAF. The latter was equal to the overall duration of AF history for patients in whom PersAF was the very first diagnosis ever of AF without a preceding diagnosis of paroxysmal AF. All patients were referred for ablation of symptomatic AF which had failed at least one antiarrhythmic medication. All patients gave written informed consent before the procedures. The Cleveland Clinic Foundation Institutional Review Board approved the study.

Radiofrequency Ablation Protocol

Our AF ablation protocol and periprocedural anticoagulation strategies were previously reported in detail.^{11–13} In general and when possible, antiarrhythmic medications were stopped 4 to 5 half-lives before ablation. All ablation procedures were performed without interruption of therapeutic anticoagulation.

A phased-array intravascular ultrasound catheter (Siemens AG Inc, Malvern, PA) was placed in the right atrium to assist with performing trans-septal punctures, guide catheter location and manipulation within the left atrium (LA), and monitor for complications during the procedure. A circular mapping catheter (Lasso) was used to guide PVI and LA ablations. In all cases, PVI was performed in addition to ablation at the posterior wall and septal to the right pulmonary veins. The decision whether to perform mapping and ablation in sinus rhythm after electrical cardioversion or in AF was left to the electrophysiologist performing the procedure. Additional ablation lesions targeting areas of complex rapid and fractionated electrograms, areas with continuous electrical activity, and areas with local gradients of activation representing potential local circuits were performed at the discretion of the ablating physicians. The superior vena cava was mapped in most patients, and potentials were ablated when there was no phrenic nerve stimulation.

The end point of the ablation procedure was complete isolation of the pulmonary veins (PVs) and superior vena cava (when feasible) and demonstration of absence of LA triggers in sinus rhythm. Successful isolation of the veins was defined as absence or dissociation of PV potentials along the antrum or inside the veins by use of the circular mapping catheter. In patients who remained in AF after PVI, electrical cardioversion to sinus rhythm was performed and followed by confirmation of PVI. For all patients with a history of typical atrial flutter (AFL), a cavotricuspid isthmus line was performed with confirmation of bidirectional block as an end point.

Preprocedural Data

All patients had trans-thoracic echocardiograms within 3 months before the ablation procedures to determine LA size and left ventricular function. On the day of ablation, blood samples were collected to allow measures of C-reactive protein (CRP) and B-type natriuretic peptide (BNP) levels. Plasma CRP concentrations were assayed by using the BNII analyzer protocol (Dade Behring, Deerfield, IL). The CRP levels were determined with a typical detection limit of 0.175 mg/l (ultrasensitive CRP). Plasma BNP levels were measured by

using the Triage Meter assay (Biosite Diagnostics, San Diego, CA). The assay reliably measures BNP concentrations ranging from 5 to 1300 pg/mL.

Clinical and Follow-Up Data

Clinical and follow-up data were collected before the procedure on the day of ablation and subsequent follow-up visits in all patients and continuously updated using electronic medical records. Patients had scheduled clinical visits and 12-lead ECG at 3, 6, and 12 months and on a yearly basis thereafter. More frequent follow-up visits were scheduled as needed for patients with arrhythmia recurrence and for those who had symptoms or required close management of their long-term anticoagulation. Holter monitor recordings were obtained at 3 and 6 months post ablation and every 6 months thereafter. Interrogation of implanted devices, whenever available, was also used to assess for recurrences. All patients wore rhythm transmitters for a minimum of 3 months after the procedure, and recorded their cardiac rhythm on a weekly basis and whenever symptomatic. Additional event recorder monitoring was obtained beyond the 3-month period for patients with documented arrhythmia and those who developed symptoms consistent with arrhythmia during the 3-month period. Atrial arrhythmias that occurred during the first 3 months after ablation were not counted as recurrences. This was considered a blanking period. Antiarrhythmic medications were generally continued during this 3-month period. An attempt at discontinuation of antiarrhythmics was considered in all patients during the third month after ablation, unless continuing recurrent arrhythmia indicated need for continued treatment.

All clinical documentation, including telephone encounters or other forms of communication with the patients or their referring physicians, such as letters, were documented electronically. The electronic records were maintained and regularly updated with clinical data collected before ablation, ablation procedure data, and data from subsequent follow-up visits in addition to all unscheduled visits, telephone encounters, and communication with referring physicians.

Arrhythmia recurrence was defined as electrocardiographic documentation of an atrial tachyarrhythmia, lasting 30 seconds, on a 12-lead electrocardiogram, event recording, or Holter monitor recording with or without symptoms. For recurrent arrhythmias, we sought to identify AF, AFL (thought to be reentrant, atrial rates >240 beats per minute) or atrial tachycardia (thought to be focal, atrial rates <240 beats per minute).

Statistical Analyses and Outcomes

All statistical analyses were performed by using the statistical software JMP pro version 10.0 (SAS, NC). A 2-sided P value <0.05 was considered statistically significant. The analysis of variance and Chi-square tests were used for comparison of means and proportions as appropriate. For non-normally distributed continuous variables, the nonparametric Wilcoxon rank-sum test was used.

The primary variable of interest which was the time interval between the very first PersAF diagnosis and the ablation procedure was analyzed both as a continuous log-transformed variable and categorized into quartiles. The proportional hazards assumption was met, and this was evaluated by plotting the log ($-\log(\text{survival})$) versus log of survival time. Cox

proportional hazards models were used to assess for factors associated with arrhythmia recurrence after ablation. Factors which were assessed in univariable analyses included in addition to the primary variable of interest age, sex, known coronary disease, diabetes mellitus, hypertension, left ventricular ejection fraction, and LA size by echocardiograms, BNP, and CRP levels (both log-transformed). All factors which were found to have a statistically significant relationship with the primary outcome of interest were included in multivariable Cox models. Hazard ratios (HR) and their 95% confidence intervals (CI) are reported from the proportional hazards models. For comparisons across quartiles of diagnosis-to-ablation time, we report the HRs for arrhythmia recurrences of the second, third, and fourth quartiles relative to the first quartile (reference) with a *P* value for the categorical variable with 3 degrees of freedom.

The primary endpoint was freedom of atrial arrhythmia recurrence over 2 years of follow-up after a single ablation procedure and of antiarrhythmic medications. All patients with documented arrhythmia and those maintained on antiarrhythmics for arrhythmia control beyond the blanking period were counted as recurrences. Patients without atrial arrhythmia recurrence were censored at the date of last follow-up.

Kaplan–Meier curves were used to present the primary outcome as a function of quartiles of the time interval between the first PersAF diagnosis and the ablation procedures. The log rank test was used for comparisons between these categories.

Results

The study sample included 1241 patients with persistent AF and no prior AF ablation or cardiac surgery who underwent AF ablation in our electrophysiology Labs between January 2005 and December 2012. The baseline characteristics and electrophysiological data from the index ablation procedures are summarized in Table 1. Patients were 61.0 ± 10.2 years of age, and 78.5% of them were men. Their comorbid conditions included coronary artery disease (20.1%), hypertension (38.5%), and diabetes mellitus (8.5%). By echocardiograms, the mean values for their left ventricular ejection fraction and LA size were $52.3 \pm 9.4\%$ and $26.7 \pm 6.3 \text{ cm}^2$, respectively. Preprocedural BNP and CRP levels were 117 pg/mL (25th–75th percentiles 66–191) and 1.8 mg/L (25th–75th percentiles 0.9–4.1), respectively.

The median time between the first PersAF diagnosis and ablation procedure was 3 years (25th–75th percentiles 1–6.5, mean 4.8 years). For 285 patients (23.0%), the diagnosis of PersAF was their first diagnosis ever of AF. A diagnosis of paroxysmal AF preceded the diagnosis of PersAF in the remaining 956 patients. Of those, the time interval between the 2 diagnoses could be determined for 822 patients, with a median approximate duration of paroxysmal AF (before PersAF diagnosis) of 1.7 years (25th–75th percentiles 1–3). Most patients ($n=1127$; 90.8%) presented in AF on the day of ablation. Of those, the time in continuous AF before the ablation procedure could be determined in 859 patients (median 13 weeks, 25th–75th percentiles 6–34, 168 with continuous AF >1 year).

Ablation Procedures and Outcomes

All patients had successful isolation of all 4 PVs (in most cases, this included the posterior wall and septal to the right PVs), and the superior vena cava was isolated in 69.6% of them. In addition to PVI and superior vena cava isolation, LA ablations (including complex fractionated electrograms) were performed in 65.6% of patients. The sets of ablation lesions around the contralateral PVs intersected at the roof or the posterior wall in 62.3% of patients.

Over the course of the 2-year follow-up period, 599 patients (48.3%) had arrhythmia recurrence. Recurrent arrhythmias were AF, AFL, AF/AFL, and atrial tachychardia in 60.4%, 13.6%, 20.7%, and 2.3%, respectively. Other combinations of these arrhythmias were observed in the remaining 3%.

Diagnosis-to-Ablation Time, Markers of Atrial Remodeling, and Outcomes

The study population was categorized into quartiles of the time interval between the very first diagnosis of PersAF and the ablation procedure (1, 1.1–3.0, 3.1–6.5, >6.5 years). The baseline characteristics of patients in each group are summarized in Table 1. At baseline, there were no differences between the quartiles in terms of age, sex, left ventricular ejection fraction, and the prevalence of coronary disease and diabetes mellitus (Table 1). With longer diagnosis-to-ablation times, patients were more likely to be hypertensive ($P<0.0001$) and, importantly, to have larger LA ($P=0.03$; Figure 1A), higher BNP levels ($P=0.01$; Figure 1B), and higher CRP levels ($P<0.0001$; Figure 1C).

The arrhythmia recurrence rates over the course of the 2 years of follow-up were 33.6%, 52.6%, 57.1%, and 54.6% in the first, second, third, and fourth quartiles, respectively ($P_{\text{categorical}}<0.0001$). The Kaplan–Meier curves for arrhythmia-free survival according to diagnosis-to-ablation time quartiles are shown in Figure 2 (log rank $P<0.0001$).

Cox Proportional Hazards Analyses

In univariable Cox proportional hazards analyses, factors found to have a significant association with arrhythmia recurrence were female sex (HR versus male sex 1.28, 95% CI 1.06–1.53; $P=0.01$), larger LA (HR per 1 cm² increase 1.02, 95% CI 1.01–1.04; $P=0.0002$), higher levels of BNP (HR per log increase 1.16, 95% CI 1.06–1.28; $P=0.001$), and CRP (HR per log increase 1.10, 95% CI 1.03–1.19; $P=0.008$). There was a significant association between the overall duration of history of AF and arrhythmia recurrences (HR per log increase 1.22, 95% CI 1.12–1.34; $P<0.0001$). However, the time spent with a paroxysmal AF diagnosis before the diagnosis of PersAF was not associated with the ablation outcomes (HR per log increase for arrhythmia recurrence 1.00, 95% CI 0.98–1.02; $P=0.9$). Similarly, the time spent in continuous AF before the ablation procedure was not associated with the ablation outcomes (HR per log increase for arrhythmia recurrence 1.01, 95% CI 0.99–1.04; $P=0.3$). In this group of patients with PersAF, patients with continuous AF of >12 months had similar recurrence rates when compared with those with continuous AF <12 months (HR 1.07, 95% CI 0.84–1.34; $P=0.6$).

Importantly, the diagnosis-to-ablation time interval was found to have a strong association with arrhythmia recurrence, regardless of whether it was treated as a continuous (HR per log increase 1.23, 95% CI 1.14–1.31; $P<0.0001$) or categorical variable (HR of fourth versus first quartile 1.94, 95% CI 1.54–2.44; $P_{\text{categorical}}<0.0001$; Table 2).

In multivariable Cox proportional hazards analyses adjusting for age, sex, and factors which were associated with arrhythmia recurrences in univariable analyses, the associations of markers of atrial remodeling with the primary outcome of interest were significantly attenuated with the exception of LA size (HR per 1 cm² increase 1.02, 95% CI 1.00–1.04; $P=0.01$; Table 2). Importantly, the diagnosis-to-ablation time interval continued to have a strong association with the primary outcome of interest in both continuous (HR per log increase 1.27, 95% CI 1.14–1.43; $P<0.0001$) and categorical analyses (HR of fourth versus first quartile 2.44, 95% CI 1.68–3.65; $P_{\text{categorical}}<0.0001$).

Repeat ablation procedures were performed in 362 patients (349 with 1 and 13 with 2 repeat ablations). The indications for repeat ablations were AF, AFL, AF/AFL, and atrial tachycardia in 53.5%, 13.4%, 26.4%, and 2.8%, respectively. The remaining 3.9% were performed for other combinations of these arrhythmias. The overall success rates at 2 years beyond the last procedure with 1 ablations and off antiarrhythmics were 67.7%, 57.1%, 58.8%, and 51.6% in the first, second, third, and fourth quartiles of diagnosis to index ablation time, respectively ($P_{\text{categorical}}=0.0003$).

Discussion

In this large sample of patients with PersAF diagnosis undergoing a first-time ablation procedure, the time interval between the very first diagnosis of PersAF and the ablation procedure appeared to have a strong association with the ablation outcomes. Importantly, the first diagnosis-to-ablation time had a stronger impact on outcomes than the time spent with a paroxysmal AF diagnosis, as well as the duration of continuous AF before the ablation procedure. The arrhythmia recurrence rates were significantly higher with longer diagnosis-to-ablation times in a graded relationship. With longer diagnosis-to-ablation times, there was evidence of a greater degree of atrial remodeling as reflected by atrial dilatation and higher levels of markers of inflammation and hemodynamic strain. These markers of pathways involved in AF-related remodeling were associated with arrhythmia recurrences in univariable analyses but were significantly attenuated in multivariable analyses, which accounted for the diagnosis-to-ablation times. Importantly, the diagnosis-to-ablation time remained significantly associated with recurrence rates in multivariable analyses when adjusted for age, sex, and risk factors for arrhythmia recurrence.

To our knowledge, this is the first study to assess PersAF ablation outcomes in relation to the very first diagnosis of PersAF. The progression from paroxysmal to persistent AF has been suggested to reflect the ongoing atrial structural remodeling process,^{7–9} which eventually leads to persistence of the arrhythmia. The first diagnosis of PersAF marks a critical stage in the natural history of AF and, hence, the importance of the current findings. This likely speaks for the atrial substrate and the ability of the arrhythmia to sustain itself. In the literature, multiple publications have reported on the association of continuous AF duration

and the procedural outcomes,⁶ but no studies have reported outcomes as a function of the critical time at which PersAF is first diagnosed.

Beside the important implications for clinical decisions in AF management, the findings suggest that AF, its chronicity and associated electro-anatomic remodeling, is a continuous disease spectrum, with patients at the extreme end of that spectrum having higher arrhythmia recurrence rates after catheter ablation, whereas patients with shorter diagnosis-to-ablation times having lower recurrence rates.

The novel findings add to the increasing body of knowledge about the importance of the atrial substrate in PersAF and emphasize the trigger-substrate model for arrhythmogenesis and persistence of the arrhythmia. It is well established that AF causes its self-perpetuation through progressive remodeling,^{7,8,10} which would be the pathophysiological basis of the current findings. This remodeling process involves multiple pathways, including inflammation, hemodynamic alterations, and atrial dilatation,¹⁰ which appear to be more prominent with longer diagnosis-to-ablation times as suggested by our findings.

These AF-related abnormalities result in changes of atrial electrical activation patterns, which manifest as areas with either decreased myocardial voltage or decreased effective refractory periods.^{7,14,15} The importance of the substrate in PersAF is further supported by observations of lower atrial voltages and longer LA total activation time in PersAF patients compared with those with paroxysmal AF.⁹ From arrhythmogenesis standpoint,^{14,15} these changes may serve as anisotropic barriers to normal propagation of electrical waves within the atrium favoring focal microentries and sustained rotors. The end result of anatomical, electrical, and contractile remodeling is, therefore, AF sustainability^{16–20} and most likely underlies the high recurrence rates with late interventions.

Study Limitations

The study has the inherent limitations of observational studies and was, therefore, limited by the absence of a comparative medical treatment arm which does not allow conclusions regarding timing of ablation. Residual confounding is another known limitation of observational studies. Despite the fact that the data presented in this article are derived from a prospectively maintained database, additional data pertaining to symptoms at the time of the very first diagnosis and the timing of diagnosis of PersAF were missing in a number of patients. These patients were excluded from the current analysis because of lack of information about the primary variable of interest that the study aimed to assess. Nonetheless, the overall outcomes in these patients were not different from the population of patients in this report. Similarly, although all patients in this study were designated as patients with PersAF in concordance with the published guidelines, this study was primarily based on clinical documentation in the medical records of PersAF diagnosis and information regarding whether this was based on a continuous AF episode >7 days versus >48 hours with a cardioversion could not be determined with precision. Although all patients were referred for ablation because of symptoms, information about symptoms at the time of very first diagnosis of AF or PersAF was lacking in a significant proportion of this population. More specifically, the proportion of patients who met the cardioversion within 7 days criterion could not be determined. The data on atrial size suggest no significant dilatation

and of those who presented in AF on the day of ablation, the median time in continuous AF was 13 weeks. As such, the population of patients in this study consisted primarily of patients with short-lasting PersAF without significant atrial dilatation, and the findings may not be generalizable to long-lasting AF or significant atrial dilatation. It is also possible that the inclusion of primarily short-lasting PersAF and the small proportion of patients with continuous AF of >1 year duration may underlie the observations of no association between continuous AF duration or long-standing PersAF and the ablation outcomes in this report as a result of the observational nature of this study. As far as the ablation strategy is concerned, the extent of extra-PV LA ablations could not be quantified, and it is possible that the extent of LA ablations may have affected the outcomes, but we note here that the proportion of patients who underwent LA ablations was similar across the quartiles of the primary variable of interest. Another limitation, which impacts most AF ablation outcome studies, is that the study may have missed asymptomatic recurrences, but this would have affected the groups equally. Importantly, in addition to novel and clinically important findings, the study has the strengths of a prospectively maintained data registry and large population size.

Conclusions

In a large population of patients with PersAF diagnosis undergoing first-time ablation procedure, the time interval between the very first diagnosis of PersAF and catheter ablation had a strong association with the ablation outcomes, such as shorter diagnosis-to-ablation times were associated with better outcomes and are in direct association with markers of atrial remodeling.

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WHAT IS KNOWN

- Various ablation strategies for persistent atrial fibrillation (PersAF) have had disappointing outcomes despite concerted clinical and research efforts.
- Chronicity of the arrhythmia is associated with progressive atrial remodeling.

WHAT THE STUDY ADDS

- The study shows that the time interval between the very first diagnosis of PersAF and catheter ablation is strongly associated with the ablation outcomes; shorter diagnosis-to-ablation times were associated with better outcomes.
- Longer diagnosis to ablation time for PersAF was associated with markers of atrial remodeling.

Figure 1.

Time interval between the first diagnosis of persistent atrial fibrillation and the ablation procedure and its association with left atrial size (A), plasma B-type natriuretic peptide levels (BNP; B), and C-reactive protein levels (CRP; C).

Figure 2. Kaplan–Meier curves presenting success of ablation of persistent atrial fibrillation as a function of the quartiles of the time interval between the very first diagnosis and the ablation procedure.

Baseline Characteristics of the Overall Study Population and Categorized Into Quintiles of the Time Interval Between the First Diagnosis of Persistent Atrial Fibrillation and the Ablation Procedure

Table 1

Variable	All Patients	First Diagnosis to Ablation Time Quintiles, y				P Value
		1	1.1–3.0	3.1–6.5	>6.5	
N	1241	382	287	268	304	
Continuous AF, weeks	13 (6–34)	12 (3–26)	13 (3–30)	11 (4–26)	11 (5–57)	0.0004
Continuous AF>12 months	17.3	5.2	19.6	19.9	28.2	<0.0001
Age, y	61.0±10.2	60.9±10.4	60.9±9.7	60.7±10.2	61.4±10.3	0.9
Male sex	78.5	78.3	77.0	75.8	82.6	0.2
Coronary disease	20.1	18.6	19.9	23.5	19.4	0.4
Hypertension	38.5	31.7	33.8	45.9	45.1	<0.0001
Diabetes mellitus	8.5	6.5	9.4	9.0	9.5	0.4
LVEF, %	52.3±9.4	52.4±9.1	52.1±9.5	52.3±9.3	52.3±9.8	0.9
Left atrial size, cm ²	26.7±6.3	25.5±5.3	26.8±7.7	26.9±6.0	27.4±6.0	0.03
hs-CRP, mg/L	1.8 (0.9–4.1)	1.5 (0.7–3.4)	1.8 (0.8–4)	2.3 (0.9–5.4)	2.1 (1.1–4.1)	<0.0001
BNP, pg/mL	117 (66–191)	104 (58–175)	122 (67–207)	116 (62–203)	126 (80–189)	0.01
Ablation						
PV isolation	100	100	100	100	100	1
Left atrial ablations	65.6	68.4	68.6	63.6	64.2	0.6
SVC isolation	69.6	53.0	64.1	72.3	83.2	<0.0001

Numbers are %, median (25th–75th percentile) or mean±SD. AF indicates atrial fibrillation; BNP, B-type natriuretic peptide; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; PV, pulmonary vein; and SVC, superior vena cava.

Table 2

Persistent Atrial Fibrillation (PersAF) Ablation Outcomes in Univariable and Multivariable Cox Proportional Hazards Analyses

	Univariable		Multivariable	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Age, +1 y	1.51 (0.85–2.72)	0.2	1.00 (0.98–1.01)	0.6
Sex, Female vs male	1.28 (1.06–1.53)	0.01	1.27 (0.95–1.67)	0.1
Year of ablation, +1 y	1.03 (0.99–1.06)	0.1		
Coronary disease	0.94 (0.77–1.15)	0.6		
Hypertension	1.06 (0.90–1.24)	0.5		
Diabetes mellitus	1.06 (0.79–1.39)	0.7		
LVEF, +1%	0.99 (0.99–1.00)	0.2		
LA size, +1cm ²	1.02 (1.01–1.04)	0.0002	1.02 (1.00–1.04)	0.01
BNP, +1 Log	1.16 (1.06–1.28)	0.001	1.12 (0.97–1.29)	0.1
CRP, +1 Log	1.10 (1.03–1.19)	0.008	0.98 (0.88–1.08)	0.2
Presenting rhythm, AF vs sinus	1.17 (0.98–1.40)	0.08		
Overall duration of AF, +1 Log	1.22 (1.12–1.34)	<0.0001	1.25 (1.08–1.45)	0.003 *
Time in PAF, +1 Log	1.00 (0.98–1.02)	0.9		
Time in continuous AF, +1 Log	1.01 (0.99–1.04)	0.3		
Continuous AF >1 y vs <1 y	1.07 (0.84–1.34)	0.6		
PersAF diagnosis-to-ablation time				
+1 Log	1.23 (1.14–1.31)	<0.0001	1.27 (1.14–1.43)	<0.0001
Quartiles (range)				
1 (1 y)	1 (reference)	<0.0001	1 (reference)	<0.0001
2 (1.1–3.0 y)	1.61 (1.27–2.04)		2.12 (1.43–3.20)	
3 (3.1–6.5 y)	1.95 (1.54–2.47)		2.32 (1.59–3.47)	
4 (>6.5 y)	1.94 (1.54–2.44)		2.44 (1.68–3.65)	

The hazard ratios are for arrhythmia recurrence over 2 years of follow-up after a single ablation procedure and off antiarrhythmics. AF indicates atrial fibrillation; BNP, B-type natriuretic peptide; CI, confidence interval; CRP, C-reactive protein; LA, left atrium; LVEF, left ventricular ejection fraction; Time in PAF, time with paroxysmal; AF diagnosis before the diagnosis of persistent AF.

* Separate multivariable model because of overlap with the primary variable of interest.