Prognostic Value of Left Atrial Calcification After Catheter Ablation for Atrial Fibrillation

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ORIGINAL RESEARCH

CATHETER ABLATION OF AF- PROGNOSTIC INDICATORS

Prognostic Value of Left Atrial Calcification After Catheter Ablation for Atrial Fibrillation

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ABSTRACT

BACKGROUND Left atrial calcification (LAC) has occasionally been observed in patients who underwent catheter ablation for atrial fibrillation (AF) by chest computed tomography (CT). However, the evidence regarding the clinical impact of LAC in patients with AF is lacking.

OBJECTIVES This study aims to investigate the prevalence of LAC in AF patients and evaluate its clinical significance after AF ablation.

METHODS This observational registry included AF patients who received computed tomography and serial transthoracic echocardiography between January 2010 and November 2017. The primary composite outcome included cardiovascular death, hospitalization for worsening heart failure, and ischemic stroke.

RESULTS Among 534 patients (age 72 ± 13 years, 62.5% men) who met the inclusion criteria, 31 (5.8%) had LAC. In multivariable analysis, AF ablation was associated with an 11.8-fold (OR: 11.8; 95% CI: 2.03-227.65) increased risk of the development of LAC in AF patients. Among 218 patients with AF ablation, LAC was detected in 30 (13.8%) patients. Prior stroke (HR: 2.73; 95% CI: 1.08-6.93) and multiple ablation procedures (HR: 4.21; 95% CI: 1.63-10.87) were independently associated with the development of LAC in AF-ablation patients. During a median follow-up of 5.8 years, the primary composite outcome occurred in 11 patients in the LAC group (39.8 per 1,000 person-years) and 10 patients in the non-LAC group (8.9 per 1,000 person-years). The adjusted HR for the primary composite outcome in the LAC group, as compared with the non-LAC group, was 2.81 (95% CI: 1.16-6.84; $P = 0.02$).

CONCLUSIONS The presence of LAC was a significant and independent prognostic factor for identifying major adverse cardiovascular events after AF ablation. (J Am Coll Cardiol EP 2023;9:1108-1117) © 2023 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia and confers an increased risk of cardiovascular events, including heart failure and ischemic stroke.[1] Catheter ablation for AF is superior to pharmacological treatment in restoring and maintaining sinus rhythm.[2] The restoration and maintenance of sinus rhythm by AF ablation led to the reverse remodeling of the left

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atrium (LA) and improvement of left ventricular diastolic and systolic function.[3,4] However, AF ablation can cause injury to the LA myocardium by its mechanism, resulting in necrosis, which ultimately leads to LA scarring and structural remodeling.[5,6]

Left atrial calcification (LAC) is a rare incidental finding on chest radiograph or computed tomography (CT), often associated with rheumatic valvular disease, postoperative valvular disease, and end-stage renal disease.[7] We previously reported that LAC associated with stiff LA physiology was observed after AF ablation.[8] However, little is known about the frequency and clinical significance of LAC after catheter ablation.

The present study aims to investigate the incidence and clinical predictors of LAC and determine the clinical impact of LAC after catheter ablation.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ATA = atrial tachyarrhythmia

CT = computed tomography

LAC = left atrial calcification

PV = pulmonary vein

RVSP = right ventricular systolic pressure

TTE = transthoracic echocardiography

METHODS

STUDY DESIGN. Patients with AF admitted to our department from January 2010 to November 2017 who underwent chest CT scans and serial transthoracic echocardiography (TTE) examination were included in this study. The purpose of the CT scan included the assessment of LA and pulmonary vein (PV) anatomy before catheter ablation; the evaluation of pulmonary, cardiac, coronary artery, or aortic disease; and the preoperative examination. All the patients scheduled to undergo AF ablation received CT for anatomical assessment of the LA and PV. In patients who underwent AF ablation, postablation CT images at least 1 year after the AF ablation were adopted. The exclusion criteria included patients with rheumatic valve disease, valve replacement, or those receiving dialysis. Of 1,450 patients with AF, 534 patients met the inclusion criteria. Among the 534 patients, 218 underwent AF ablation according to the Japanese guidelines for AF ablation. This retrospective study protocol conformed to the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board (Approval number: 21C150). Informed consent was obtained from all the patients.

COMPUTED TOMOGRAPHY. All scans were obtained using a 64-multidetector CT Aquilion 64 (Toshiba, Japan). Image acquisition was performed with the following parameters: tube voltage, 120 kVp; automatic tube current modulation; beam pitch, 0.8-1.0; collimation, 0.5 millimeters. The acquired CT images were reconstructed with a slice thickness of 1.0 millimeter at the pulmonary window and 5.0 millimeters at the mediastinal window. The LA endocardial contours were identified by manually tracing the LA cavity on transverse CT images without contrast agents. LAC was defined according to the definition of coronary artery calcification.[9,10] In brief, sequential lesions with a density of >130 HU and >3 pixels were defined as showing LAC using more than 1,280 × 1,024 resolution viewer and the workstation system (Synapse Vincent, Fujifilm Co). The calcified lesions of the mitral valve annulus were excluded for LAC. To analyze the spatial distribution of LAC, the LA wall was segmented into 8 regions: PV antrum, anterior wall, septum, inferior wall, posterior wall, lateral wall, and LA appendage. The location of LAC was determined by comparing the ablation points on 3-dimensional electroanatomical mapping (CARTO 3 system, Biosense Webster). Concomitant locations were allocated to each segment when present. **Figure 1** shows example images of LAC distributions in the LA. The acquired CT scans were independently analyzed by 2 cardiologists (D.Y., Y.F.). Any discordance in findings between the 2 reviewers was referred to a third cardiologist (M.A.). Incidental findings during CT reading were also described. PV stenosis was defined as a reduction of >75% in the cross-sectional area.

ECHOCARDIOGRAPHY. All AF patients underwent TTE at the diagnosis of AF. TTEs were routinely conducted in AF patients who underwent AF ablation within 3 months before the ablation and at the annual follow-up after the procedure. The LA diameter left ventricular ejection fraction, transmitral flow velocity (early [E] filling wave), and tissue Doppler echocardiography of the early diastolic mitral annular velocity (E') were obtained according to the American Society of Echocardiography guideline.[11] LA anterior-posterior diameter was indexed by dividing LA diameter by body surface area. E' was calculated as an average septal and lateral side E'. Pulmonary artery systolic pressure was estimated using right ventricular systolic pressure (RVSP) on TTE. Using the modified Bernoulli's equation, RVSP was calculated from the peak tricuspid regurgitant jet velocity. Stiff LA physiology was defined as a >10 mm Hg increase in RVSP postablation compared to pre-ablation and a postablation RVSP >35 mm Hg.[12]

ABLATION PROCEDURES. The study included cases that underwent catheter ablation between 2009 and 2017 by a single operator. PV isolation was performed in all patients using an irrigated ablation catheter (Navistar ThermoCool, ThermoCool SF, or ThermoCool Smarttouch SF, Biosense Webster, Inc) and a 3-dimensional mapping system (CARTO 3). The

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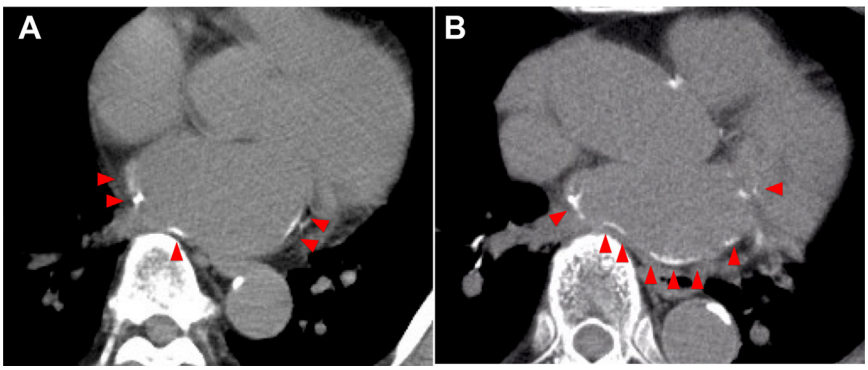
FIGURE 1 Representative Computed Tomography Images of Left Atrial Calcifications



(A) A plain computed tomography (CT) scan of the heart shows calcifications around the right inferior pulmonary vein and lateral wall of the left atrium **(red arrowheads). (B)** A plain CT of the heart shows calcifications around bilateral pulmonary veins and the posterior wall of the left atrium **(red arrowheads).**

ablation generator output was 30 W, reduced to 20 to 25 W near the esophagus. As an extra-PV ablation, additional procedures such as superior vena cava isolation, cavotricuspid isthmus ablation, linear ablation in LA (including roof line, floor line, and mitral isthmus line), and complex fractionated atrial electrograms ablation were performed in patients with persistent AF or inducible AF after pulmonary vein isolation (PVI) at the discretion of the operator. Repeat PVI was performed if reconnection of PVs was observed at the time of redo ablation, and additional ablation procedures were also performed.

FOLLOW-UP. The patients were scheduled for follow-up visits in the outpatient clinic at 1, 3, 6, and 12 months, and thereafter every 12 months. Electrocardiogram and 24-hour Holter monitoring were conducted at 3, 6, and 12 months, and thereafter every 12 months according to the 2017 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society/Asia Pacific Heart Rhythm Society/Latin American Society of Electrophysiology and Cardiac Stimulation expert consensus statement.[13] Additional Holter monitor or event monitor recordings were used to detect the recurrence of atrial tachyarrhythmia (ATA) when patients reported palpitations. A blanking period of 3 months was applied.[13] Recurrence of ATA was defined as any electrocardiographic documentation of ATA following 3 months blanking period.

CLINICAL OUTCOMES. The primary clinical outcome was a composite of cardiovascular death or hospitalization due to worsening heart failure or ischemic stroke. Patients without events were censored at the time of their last clinical follow-up.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD or median (IQR). Categorical variables are presented as numbers (percentages). The clinical and procedural characteristics of the 2 groups were compared using the Student *t*-test or Mann-Whitney *U* test for continuous variables and Fisher exact test for categorical variables. The multivariable logistic regression model was used to examine the predictors of LAC formation among patients with AF. The multivariable Cox proportional hazards model was used to examine independent risk factors for LAC formation after AF ablation, and the proportional hazards assumption was tested using Schoenfeld residuals. All model covariates were preselected based on clinical importance with reference to previous literature or results of univariate analyses with outcomes. Factors confounding the variables were not incorporated into the multivariable analysis. From the final multivariable model, a point-based score was derived in which each factor corresponds to its coefficient in the model (ie, log[HR]) multiplied by 10. The total score for a patient is the sum of all risk factors present in that patient. Because the development of LAC varied over time, Cox proportional hazards regression model with time-dependent covariates was used to estimate the association of the LAC formation with the primary composite outcome. For patients with non-LAC, time zero corresponded to the time at which each patient received AF ablation. The patients with LAC were

TABLE 1 Baseline Characteristics, Echocardiographical Findings, and Therapies in AF Patients Who Underwent Catheter Ablation (N = 218)

Age, y	63.3 ± 9.8
Male	160 (73.4)
BMI, kg/m^2	24.7 ± 3.5
AF type	
Paroxysmal	135 (61.9)
Persistent	65 (29.8)
Longstanding	18 (8.3)
CHA_2DS_2 -VAS_C score	2.0 ± 1.3
CHF	30 (13.8)
CAD	7 (3.2)
Hypertension	129 (59.2)
Dyslipidemia	167 (76.6)
Diabetes	25 (11.5)
Prior stroke	21 (9.6)
Radiation therapy	1 (0.5)
Medication	
Calcium channel blocker	62 (28.4)
Warfarin	99 (45.4)
Direct oral anticoagulant	119 (54.6)
Statin	47 (21.6)
Calcium supplement	7 (3.2)
LVEF, %	65.8 ± 8.6
LADI, mm/m^2	24.2 ± 4.4
No. ablation procedures	275
1	171 (78.4)
2	37 (17.0)
3	10 (4.6)
PVI	218 (100.0)
Extra PV LA ablation	39 (17.9)
Linear ablation	38 (17.4)
LA posterior wall isolation	16 (7.3)
Mitral isthmus ablation	8 (3.7)
Other linear ablation	27 (12.4)
CFAE ablation	11 (5.0)

Values are mean ± SD or n (%).

AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; CFAE = complex fractionated atrial electrograms; CHA_2DS_2 -VAS_C = congestive heart failure, hypertension, age, diabetes, previous stroke/transient ischemic attack, vascular disease, female sex; CHF = congestive heart failure; LA = left atrium; LADI = left atrial diameter index; LVEF = left ventricular ejection fraction; PV = pulmonary vein; PVI = pulmonary vein isolation.

counted as the non-LAC group until LAC was detected on CT images, after which they were moved to the LAC group. For patients with LAC, time zero corresponded to the time at which the CT detected LAC. Paired t-test was used to evaluate changes in echocardiographic parameters before and after ablation. All statistical analyses were 2-tailed, and $P < 0.05$ was considered statistically significant. R statistical software, version 4.2.1 (R foundation), was used for univariate and multivariable survival analyses with time-dependent covariates. All other analyses were conducted by JMP 14 software (SAS Institute Inc).

RESULTS

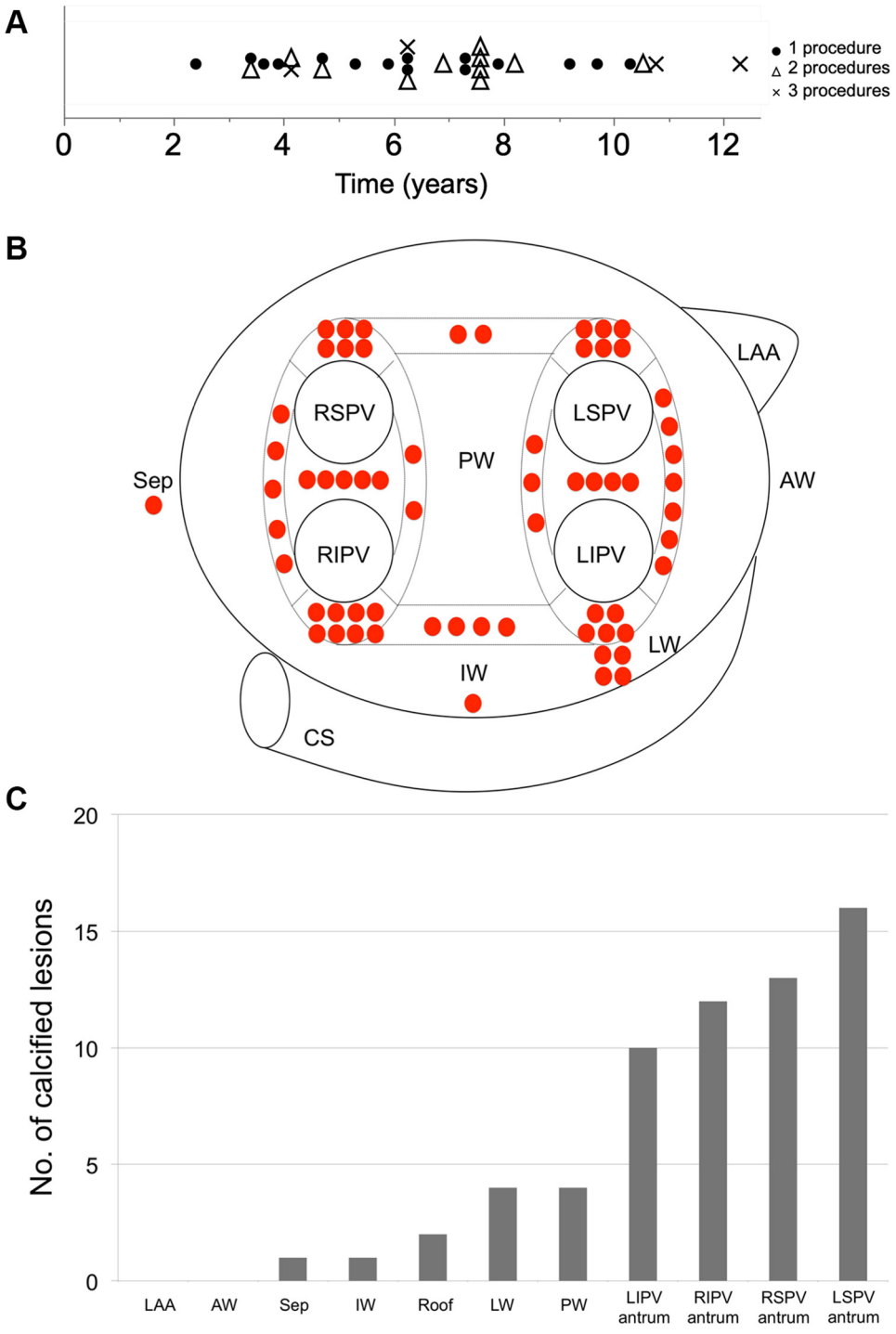
INCIDENCE OF LAC IN AF PATIENTS. A total of 534 patients (age 71.6 ± 12.5 years, 62.5% men) met the inclusion criteria. This cohort's demographic and clinical characteristics were presented in Supplemental Table 1. Of the 534 patients, 292 (54.7%) presented with paroxysmal AF, which was more common than persistent AF (n = 129, 24.2%) and long-standing persistent AF (n = 113, 21.2%). For the cohort, LAC was detected in 31 (5.8%) patients. In the multivariable logistic model, AF ablation (odds ratio: 11.8; 95% CI: 2.03-227.65) was independently associated with the development of LAC in AF patients (Supplemental Table 2). Demographic and clinical characteristics of this cohort with and without AF ablation were presented in Supplemental Table 3.

CHARACTERISTICS OF LAC IN PATIENTS WHO UNDERWENT AF ABLATION. In total, 218 patients (age 63.3 ± 9.8 years, 73.4% male, 61.9% paroxysmal AF) underwent AF ablation, chest CT, and echocardiography at the selected time intervals. The baseline characteristics of this cohort are presented in **Table 1**. No cases of LAC were detected before the initial ablation. There were 275 AF ablations performed, including 47 (21.6%) repeat procedures for recurrent AF (Supplemental Table 4). After a median follow-up of 6.6 years (IQR: 4.6-8.0 years) after the initial ablation, LAC was detected in 30 (13.8%) patients. Among the 30 patients, 15 (50.0%) presented with paroxysmal AF at baseline. LAC was observed in 15 (8.8%), 11 (29.7%), and 4 (40.0%) patients who underwent 1-, 2-, and 3-time procedures, respectively (**Figure 2A**).

To determine the spatial distribution of LAC, the location of LAC in 8 LA regions was examined. The most common LAC regions were located at the PV antra (51 of 63 [81%]) in 23 patients, and all were observed around ablation sites (**Figures 2B and 2C**). The posterior or lateral wall (4 of 63 [6%]) had the second most common region. All the patients with lateral wall LAC underwent mitral isthmus ablation.

To explore the development of LAC after AF ablation, patients who underwent ablation were divided into 2 groups based on the presence of LAC (Supplemental Table 5). Compared to patients without LAC formation, those with LAC formation tended to have hypertension, a history of stroke, larger LA size before ablation, multiple ablation procedures, and extra PV LA ablation, and be taking calcium channel blocker or warfarin (**Table 2**). No correlation was found between LAC and PV stenosis, coronary calcifications, or LA dwell time. After adjusting for potential risk

FIGURE 2 Detection Period, Spatial Distribution, and Dominant Location of Left Atrial Calcification in Patients After Atrial Fibrillation Ablation



(A) Time of left atrial calcification (LAC) detection after the initial atrial fibrillation (AF) ablation in patients classified by the number of ablations. **(B)** Left atrium depicting the distribution of LAC. **Red dots** indicate calcified lesions. **(C)** The graph shows the incidence of LAC in each left atrial segment. AW = anterior wall; CS = coronary sinus; IW = inferior wall; LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; LW = lateral wall; PW = posterior wall; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; Sep = septum.

factors, prior stroke (HR: 2.74; 95% CI: 1.08-6.93) and multiple ablation procedures (HR: 4.21; 95% CI: 1.63-10.87) were independently associated with the development of LAC in AF-ablation patients. Kaplan-Meier curves showing the LAC formation according to the presence and absence of the identified risk factors were shown in Supplemental Figure 1. These 2 predictive factors were incorporated into a risk score model and assigned scores based on the predictive power of each variable (Supplemental Table 6). The total score obtained from this risk score model can be converted to a 7-year predicted risk of LAC formation (Supplemental Table 7).

ASSOCIATION BETWEEN LAC AND THE PRIMARY CLINICAL OUTCOMES AFTER AF ABLATION. To determine the role of LAC and its consequence in cardiovascular diseases, we investigated the clinical outcomes in patients with or without LAC. During 5.8 years (IQR: 4.3-8.8 years) of follow-up, 21 (9.6%) patients experienced the primary composite endpoint: 1 cardiovascular death, 12 hospitalization due to worsening heart failure, and 8 ischemic stroke. Seven of 8 patients who had strokes took anticoagulants (3 direct oral anticoagulants and 4 warfarin). Six were in sinus rhythm at the onset, and 2 were in AF. The primary composite outcome occurred in 11 LAC patients (39.8 cases per 1,000 person-years) and 10 non-LAC patients (8.9 cases per 1,000 person-years). The adjusted HR for the primary composite outcome in the LAC group, as compared with the non-LAC group, was 2.81 (95% CI: 1.16-6.84; $P = 0.02$) among AF-ablation patients (**Table 3**). The cumulative risk curves are shown in **Figure 3** and Supplemental Figure 2.

ECHOCARDIOGRAPHIC PARAMETERS BEFORE AND AFTER ABLATION. **Figure 4** presents the changes in echocardiographic parameters before and after AF ablation in patients with and without LAC. LA dimension was significantly decreased after ablation in both groups. Although E/E' ratio was significantly reduced in the non-LAC group, it was significantly increased in the LAC group. RVSP did not change in the non-LAC group. In contrast with the non-LAC group, RVSP was considerably increased in the LAC group. Of 218 patients, 36 (16.5%) had stiff LA physiology. There was a substantially larger percentage of patients with stiff LA physiology at postablation echocardiography in the LAC group compared with the non-LAC group (40.0% vs 12.8%, $P = 0.0007$).

TABLE 2 Cox Proportional Hazards Analysis for the Predictors of LAC Formation After Ablation

	Univariate		Multivariable	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y	1.00 (0.96-1.04)	0.90		
Male	2.01 (0.77-5.26)	0.20		
BMI, kg/m^2	1.04 (0.93-1.15)	0.40		
Non-PAF	1.55 (0.76-3.18)	0.20		
CHA_2DS_2-VAS_C score	1.18 (0.89-1.57)	0.20		
CHF	1.22 (0.46-3.21)	0.70		
CAD	1.98 (0.47-8.34)	0.30		
Hypertension	2.55 (1.03-6.29)	0.04	2.19 (0.86-5.56)	0.10
Diabetes	1.78 (0.67-4.67)	0.20		
Dyslipidemia	2.84 (0.86-9.36)	0.09		
Prior stroke	3.24 (1.39-7.57)	0.006	2.74 (1.08-6.93)	0.03
Calcium-channel blocker	2.36 (1.15-4.84)	0.02		
Warfarin	2.35 (1.09-5.01)	0.02		
Statin	1.98 (0.92-4.24)	0.08		
Calcium supplement	0.99 (0.13-7.26)	1.00		
LVEF, %	1.02 (0.65-1.02)	0.40		
LADI	1.08 (1.00-1.16)	0.04	1.08 (0.98-1.19)	0.10
Creatinine	0.83 (0.17-1.33)	0.70		
LA dwell time at first ablation	1.01 (0.99-1.02)	0.20		
Multiple procedures	3.70 (1.81-7.57)	0.0003	4.21 (1.63-10.87)	0.003
Extra PV LA ablation	3.97 (1.69-9.14)	0.002		
Coronary calcification	2.46 (0.85-7.06)	0.09		
Valvular calcification	0.59 (0.08-4.36)	0.60		
PV stenosis after ablation	2.47 (0.34-18.20)	0.20		

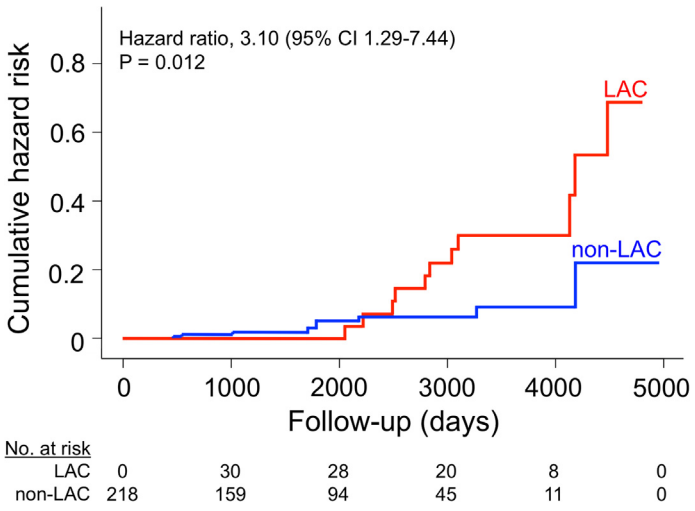
LA = left atrium; LAC = left atrial calcification; PAF = paroxysmal atrial fibrillation; other abbreviations as in Table 1.

TABLE 3 Association Between Primary Composite Endpoint and Clinical Variables

	Univariate		Multivariable	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y	0.99 (0.95-1.05)	0.90		
Male	0.71 (0.28-1.77)	0.50		
BMI, kg/m^2	1.08 (0.95-1.20)	0.20		
Non-PAF	1.39 (0.58-3.31)	0.50		
CHA_2DS_2-VAS_C score	1.09 (0.81-1.48)	0.50		
CHF	2.40 (0.86-6.71)	0.09		
CAD	0.78 (0.10-6.00)	0.80		
Hypertension	0.64 (0.25-1.60)	0.30		
Diabetes	0.86 (0.19-3.79)	0.80		
Dyslipidemia	0.86 (0.31-2.34)	0.80		
Prior stroke	1.66 (0.57-4.81)	0.30	1.24 (0.42-3.65)	0.70
LVEF	1.08 (1.03-1.12)	0.002	1.07 (1.03-1.12)	0.001
LADI	1.06 (0.96-1.16)	0.20	1.05 (0.95-1.15)	0.30
Multiple procedures	1.52 (0.63-3.69)	0.40		
LAC	3.10 (1.29-7.44)	0.01	2.81 (1.16-6.84)	0.02

Abbreviations as in Tables 1 and 2.

FIGURE 3 Cumulative Hazard Risk of the Primary Composite Outcome According to the LAC Development



The cumulative risk of the composite outcomes of death from cardiovascular causes, hospitalization for worsening heart failure, and ischemic stroke with and without LAC development. Abbreviation as in Figure 2.

DISCUSSION

The significant findings of this study are as follows. 1) The development of LAC was significantly associated with AF ablation in AF patients. 2) LAC occurred in 13.8% of patients after AF ablation with a median follow-up of 6.6 years. 3) Regions with high LAC frequency were PV antra. 4) Repeat ablation procedures and a history of stroke were associated with a greater risk of LAC formation. 5) The presence of LAC was predictive of adverse cardiovascular events after AF ablation (**Central Illustration**). 6) The patients with LAC significantly increased estimated pulmonary pressure.

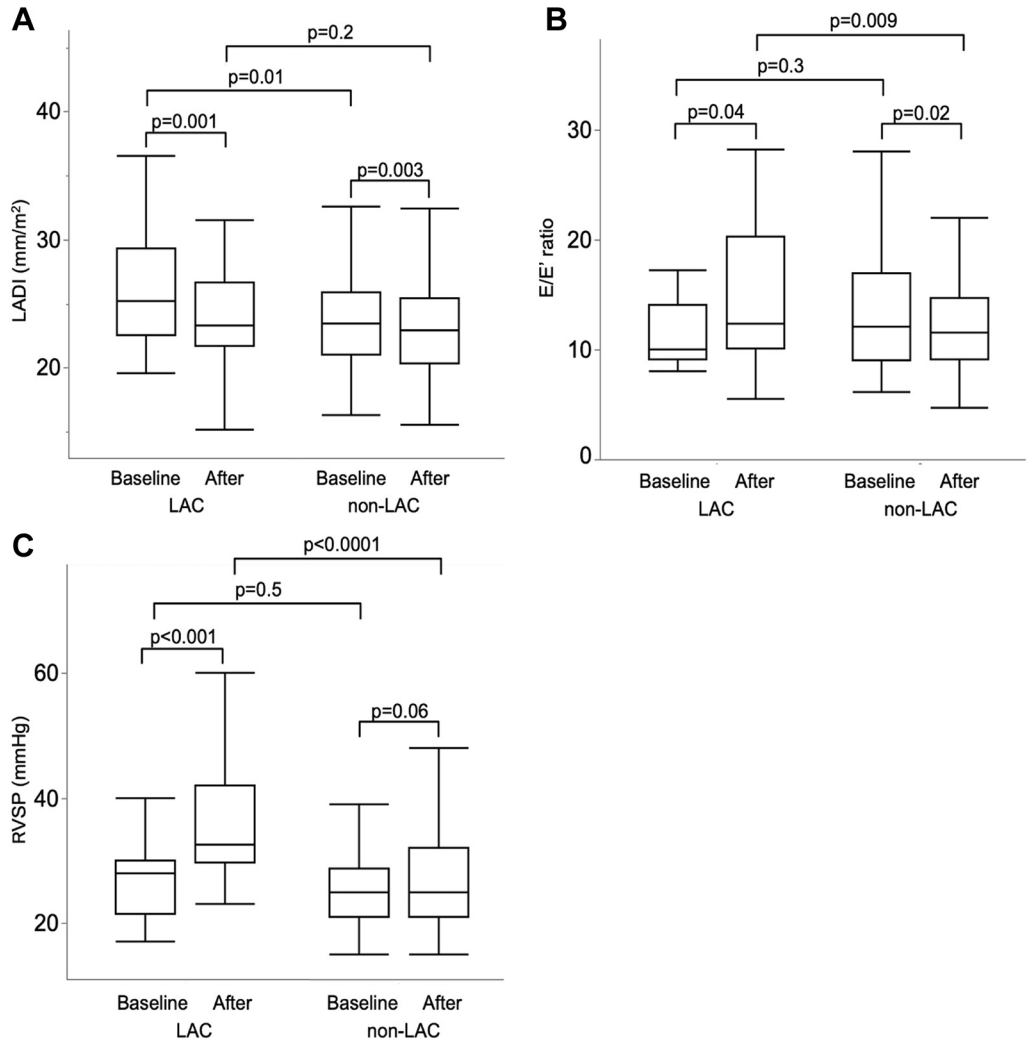
LAC has been most commonly described in long-standing rheumatic heart disease with a previous mitral valve surgery and presumably developed as a consequence of rheumatic and surgical inflammation.[7] Patients predisposed to LAC include those with end-stage renal failure and postradiotherapy, but it has been rarely described in other conditions. Indeed, the present AF cohort showed that only 1 (0.2%) patient who suffered AF for 30 years exhibited nonablation-related LAC localized at the LA posterior wall in the vicinity of the vertebra. Long-standing inflammation in AF and mechanical pressure or friction with the vertebra might contribute to the LAC formation in this case.[14]

In this study, LAC presented diverse image findings from focal deposits to diffuse myocardial involvement in patients after catheter ablation. LAC was most observed around the ostia of the PVs, and they reflected the most frequent ablation site.[8] The PV ostia had consistently high wall stress, which might contribute to the development of LAC.[15] We have shown that the multiple ablation procedures were independent predictors of LAC formation. Catheter ablation, by its nature, injures the atrial myocardium, and cardiomyocyte damage may eventually lead to calcium deposition.[16,17] The calcification continued to evolve after only 1 ablation (Supplemental Figure 3).

Dystrophic calcification represents a localized deposition of calcium phosphate crystals in degenerated or necrotic tissues, often associated with injury.[18] A prior experimental animal study has shown that radiofrequency catheter ablation caused inflammation, coagulation necrosis, and interstitial hemorrhage in the acute phase, followed by tissue calcification in the chronic phase.[19] The underlying causes of calcium deposition after ablation are unknown; however, the resultant subendocardial edema and hemorrhage may lead to focal changes favoring calcium deposition and culminate into the deposition of calcium crystals.[20,21] Several mechanisms, including inflammatory signals, the release of cytokines such as bone morphogenic protein 2, and transdifferentiation of mesenchymal stem cells, might be implicated in the development of calcification.[22,23] Although a repeat ablation is effective for recurrent AF, the accessional burden of myocardial injury may be vulnerable to calcium precipitation. We showed that the prior stroke was significantly associated with LAC formation. Earlier studies reported a considerably higher LA fibrosis in patients with previous stroke.[24] Future studies are needed to unravel whether fibrotic tissue is prone to calcium precipitation by catheter ablation.

This study shows that LAC formation correlates with increased adverse cardiovascular events after AF ablation. A crossing of the cumulative risk curves was observed, possibly reflecting that LAC was detected at a median of 6.6 years after the initial AF ablation. The prognostic value may be explained by the pathophysiological consequences of myocardial calcification, in which the development of secondary atrial remodeling and subsequent LA dysfunction leads to worsening heart failure. Echocardiographic data show that the calcium deposition in the LA subendocardium is associated with increased LA stiffness, as indicated by elevated RVSP after ablation.

FIGURE 4 **Changes in Echocardiographic Parameters Before and After AF ablation According to the Presence or Absence of LAC**

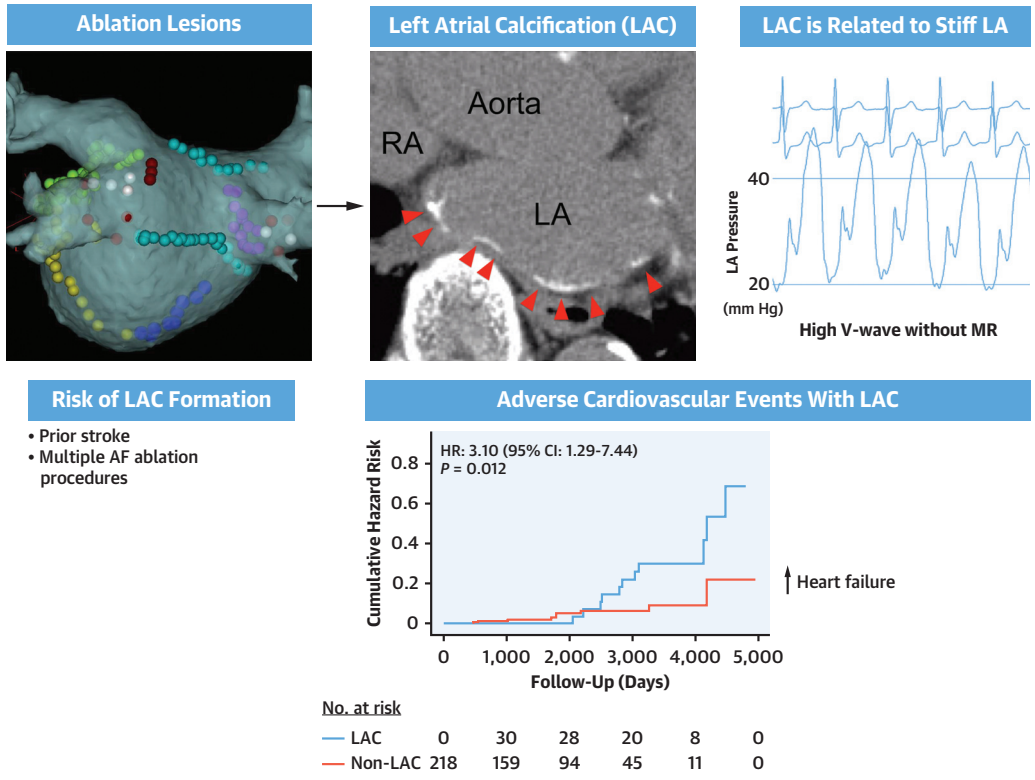


(A) Left atrial diameter index (LADI). **(B)** The ratio of the peak mitral flow velocity of the early rapid filling to the early diastolic velocity of the mitral annulus (E/E'). **(C)** RVSP. Abbreviations as in Figure 2.

The enhanced LA stiffness caused by LAC may result in impaired LA filling and elevated LA pressure, which ultimately leads to heart failure or pulmonary hypertension.[25]

STUDY LIMITATIONS. There were several limitations in this study. A retrospective observational study from a single center included highly selected patients who underwent AF ablation and had a relatively small population. The timing of CT and echocardiograms was not uniform in each patient. Patients who had a deficiency of appropriate echocardiographical data were excluded. Consequently, the incidences of LAC were likely underestimated or overestimated. When assessing the LA size, measuring LA volume instead of LA diameter is recommended. In the early 2010s, LA volume was not routinely measured; hence, it is not eligible for statistical analysis. Data allowed us to adjust for several key variables; however, the possibility of residual confounding remains. This study included cases treated with older catheters without contact-force function. Therefore, the results may not apply to cases treated with current ablation techniques, such as index-guided ablation with

CENTRAL ILLUSTRATION **The Development of Left Atrial Calcification Was Significantly Associated With Adverse Events After Atrial Fibrillation Ablation**



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AF = atrial fibrillation; LA = left atrium; MR = mitral regurgitation; RA = right atrium.

contact-force catheters and various types of balloon ablation.

CONCLUSIONS

LAC was not rare among patients who underwent AF ablation, especially after multiple ablation procedures. The development of LAC might raise additional concerns about long-term clinical outcomes following AF ablation. These findings underscore the importance of understanding the clinical presentation of patients scheduled for AF ablation and the significance of careful follow-up after ablation. A better ablation strategy would be expected to improve clinical outcomes while reducing potential complications.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our study shows that multiple ablation procedures were associated with a greater risk of LAC formation. Therefore, it is desirable to develop a method to establish durable PV isolation and prevent AF recurrence in a single procedure, which may lead to a reduction in cardiovascular adverse events.

TRANSLATIONAL OUTLOOK: Although this study included radiofrequency ablation cases, various new ablation techniques have been introduced in real practice; it is desirable to establish methods to reduce AF recurrence and minimize LAC formation.

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KEY WORDS atrial fibrillation, catheter ablation, left atrial calcification, left atrial remodeling, stiff left atrial physiology

APPENDIX For supplemental tables, please see the online version of this paper.

Supplemental Appendix

Supplemental Table 1. Demographic and clinical characteristics of patients with and without LAC

	All (n=534)	LAC (n=31)	No LAC (n=503)	P
Age, years	71.6 ± 12.5	64.2 ± 8.4	72.1 ± 12.5	0.0006
Male	334 (62.5)	25 (80.6)	309 (61.4)	0.04
BMI, kg/m^2	23.6 ± 3.6	24.1 ± 3.2	23.6 ± 3.8	0.9
AF type				0.01
paroxysmal	292 (54.7)	15 (48.4)	277 (55.1)	
persistent	129 (24.2)	15 (48.4)	114 (22.7)	
longstanding	113 (21.2)	1 (3.2)	112 (22.3)	
CHA_2DS_2–VAS_C score	3.7 ± 2.0	2.3 ± 1.4	3.7 ± 2.0	0.0003
CHF	72 (13.5)	5 (17.2)	67 (13.4)	0.6
CAD	92 (17.2)	2 (6.5)	90 (17.9)	0.1
Hypertension	384 (72.5)	23 (79.3)	361 (72.1)	0.5
Dyslipidemia	393 (73.6)	27 (87.1)	366 (72.8)	0.09
Diabetes	150 (28.3)	6 (20.7)	144 (28.7)	0.4
Prior stroke	81 (15.2)	7 (22.6)	74 (14.7)	0.3
Radiation therapy	5 (0.9)	0 (0.0)	5 (1.0)	1
Medication				
β blocker	307 (57.5)	21 (67.7)	286 (56.9)	0.3
ACEI/ARB	278 (52.1)	20 (64.5)	258 (51.3)	0.2
Calcium channel blocker	171 (32.0)	14 (45.2)	157 (31.2)	0.1
Antiarrhythmic drug	226 (42.3)	22 (71.0)	204 (40.6)	0.001
Warfarin	214 (40.1)	21 (67.7)	193 (38.4)	0.002
Direct oral anticoagulant	287 (53.8)	10 (32.3)	277 (55.1)	0.016
Statin	127 (23.8)	10 (32.3)	117 (23.3)	0.3
Calcium supplement	24 (4.5)	1 (3.2)	23 (4.6)	1
LVEF, %	64.3 ± 8.5	63.4 ± 9.7	64.4 ± 9.8	0.6
LADI, mm/m^2	25.7 ± 5.7	26.3 ± 4.9	25.6 ± 5.8	0.5
Laboratory data				
Creatinine, mg/dL	1.1 ± 1.2	0.8 ± 0.7	1.2 ± 1.3	0.5
BNP, pg/mL	128 ± 187	113 ± 123	130 ± 194	0.6
CT findings				

Coronary calcification	78 (14.6)	5 (16.1)	73 (14.5)	0.8
Valvular calcification	58 (10.9)	1 (3.2)	57 (11.3)	0.2
Cather ablation	218 (40.8)	30 (96.8)	188 (37.4)	<0.0001

Data are mean ± SD or n (%) unless otherwise specified. LAC indicates left atrial calcification, AF; atrial fibrillation; BMI, body mass index; CHF, congestive heart failure; CAD, coronary artery disease; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CT, computed tomography; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LADI, left atrial diameter index.

Supplemental Table 2. Predictors of LAC formation among AF patients

	Univariate		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	0.95 (0.93-0.98)	0.0007	1.01 (0.96-1.05)	0.7
Male	2.61 (1.12-7.14)	0.02	1.73 (0.70-4.95)	0.2
Non-PAF	1.28 (0.62-2.68)	0.5		
CHA_2DS_2–VAS_C score	0.68 (0.55-0.84)	0.0002		
CHF	1.34 (0.44-3.39)	0.6		
CAD	0.32 (0.05-1.07)	0.07		
Hypertension	1.48 (0.63-4.09)	0.4		
Diabetes	0.64 (0.23-1.52)	0.3		
Dyslipidemia	2.52 (0.96-8.66)	0.06		
Prior stroke	1.69 (0.65-3.87)	0.3		
β blocker	1.59 (0.73-3.45)	0.2		
ACEI/ARB	1.73 (0.82-3.80)	0.1		
Calcium channel blocker	1.81 (0.86-3.77)	0.1		
Antiarrhythmic drug	3.58 (1.66-8.35)	0.0009		
Warfarin	3.37 (1.59-7.62)	0.001		
Statin	1.57 (0.69-3.35)	0.3		
Calcium supplement	0.22 (0.04-3.48)	0.7		
Creatinine	0.22 (0.04-0.76)	0.04		
BNP	1.00 (0.99-1.00)	0.7		
LVEF	1.00 (0.96-1.03)	0.8		
LADI	1.02 (0.95-1.08)	0.5		
Coronary calcification	1.13 (0.37-2.82)	0.8		
Valvular calcification	0.26 (0.01-1.25)	0.1		
Cather ablation	50.3 (10.64-898.34)	<0.0001	11.80 (2.03-227.65)	0.003

LAC indicates left atrial calcification; AF, atrial fibrillation; OR, odds ratio; CI, per 1 unit change of continuous variable; PAF, paroxysmal atrial fibrillation. The other abbreviations as in Supplemental Table 1.

Supplemental Table 3. Demographic and clinical characteristics of patients with and without AF ablation

	All (n=534)	AF ablation (n=218)	No ablation (n=316)	P
Age, years	71.6 ± 12.5	63.3 ± 9.8	77.4 ± 10.4	<0.0001
Male	334 (62.5)	160 (73.4)	174 (55.1)	<0.0001
BMI, kg/m^2	23.6 ± 3.6	24.7 ± 3.5	22.9 ± 3.8	<0.0001
AF type				<0.0001
paroxysmal	292 (54.7)	135 (61.9)	157 (49.7)	
persistent	129 (24.2)	65 (29.8)	64 (20.3)	
longstanding	113 (21.2)	18 (8.3)	95 (30.1)	
CHA_2DS_2–VAS_C score	3.7 ± 2.0	2.0 ± 1.3	4.7 ± 1.6	<0.0001
CHF	72 (13.5)	30 (13.8)	42 (13.3)	0.9
CAD	92 (17.2)	7 (3.2)	85 (26.9)	<0.0001
Hypertension	384 (72.5)	129 (59.2)	255 (80.7)	<0.0001
Dyslipidemia	393 (73.6)	167 (76.6)	226 (71.5)	0.2
Diabetes	150 (28.3)	25 (11.5)	125 (39.6)	<0.0001
Prior stroke	81 (15.2)	21 (9.6)	60 (18.9)	0.003
Radiation therapy	5 (0.9)	1 (0.5)	4 (1.3)	0.3
Medication				
β blocker	307 (57.5)	139 (63.8)	168 (53.2)	0.01
ACEI/ARB	278 (52.1)	109 (50.0)	169 (53.5)	0.4
Calcium channel blocker	171 (32.0)	62 (28.4)	109 (34.5)	0.1
Antiarrhythmic drug	226 (42.3)	175 (80.3)	51 (16.1)	<0.0001
Warfarin	214 (40.1)	99 (45.4)	115 (36.4)	0.04
Direct oral anticoagulant	287 (53.8)	119 (54.6)	168 (53.2)	0.7
Statin	127 (23.8)	47 (21.6)	80 (25.3)	0.3
Calcium supplement	24 (4.5)	7 (3.2)	17 (5.4)	0.2
LVEF, %	64.3 ± 8.5	65.8 ± 8.6	58.9 ± 14.5	<0.0001
LADI, mm/m^2	25.7 ± 5.7	24.2 ± 4.4	28.9 ± 6.9	<0.0001
Laboratory data				
Creatinine, mg/dL	1.1 ± 1.2	0.9 ± 0.7	1.3 ± 1.5	<0.0001
BNP, pg/mL	128 ± 187	101 ± 155	298 ± 274	<0.0001
CT findings				

Coronary calcification	78 (14.6)	13 (6.0)	65 (20.6)	<0.0001
Valvular calcification	58 (10.9)	11 (5.0)	47 (14.9)	0.0003

Data are mean ± SD or n (%) unless otherwise specified. The other abbreviations as in Supplemental Table 1.

Supplemental Table 4. Additional procedures other than PV isolation.

	1st procedure (n=171)	2nd procedure (n=37)	3rd procedure (n=10)
Linear ablation	24 (14.0)	10 (27.0)	4 (40.0)
LA posterior wall isolation	9 (5.3)	4 (10.8)	3 (30.0)
Mitral isthmus	2 (1.2)	3 (8.1)	3 (30.0)
Other	16 (9.4)	8 (21.6)	3 (30.0)
CFAE ablation	5 (2.9)	5 (13.5)	1 (10.0)

Data are n (%). PV indicated pulmonary vein; LA, left atrium; CFAE, complex fractionated atrial electrogram.

Supplemental Table 5. Demographic and clinical characteristics of AF patients who underwent catheter ablation with and without LAC

	All (n=218)	LAC (n=30)	No LAC (n=188)	P
Age, years	63.3 ± 9.8	63.7 ± 8.0	63.3 ± 10.1	0.8
Male	160 (73.4)	25 (83.3)	135 (71.8)	0.3
BMI, kg/m^2	24.7 ± 3.5	25.3 ± 3.2	24.7 ± 3.5	0.4
AF type				0.2
paroxysmal	135 (61.9)	15 (50.0)	120 (63.8)	0.004
persistent	65 (29.8)	15 (50.0)	45 (23.9)	
longstanding	18 (8.3)	0 (0.0)	23 (12.2)	
CHA_2DS_2 –VAS_C score	2.0 ± 1.3	2.3 ± 1.2	1.9 ± 1.3	0.2
CHF	30 (13.8)	5 (17.9)	25 (13.4)	0.6
CAD	7 (3.2)	2 (6.7)	5 (2.7)	0.2
Hypertension	129 (59.2)	22 (78.6)	107 (57.5)	0.04
Dyslipidemia	167 (76.6)	27 (90.0)	140 (74.5)	0.07
Diabetes	25 (11.5)	5 (17.9)	20 (10.8)	0.3
Prior stroke	21 (9.6)	7 (23.3)	14 (7.5)	0.01
Radiation therapy	1 (0.5)	0 (0.0)	1 (0.5)	1
Medication				
β blocker	139 (63.8)	21 (70.0)	118 (62.8)	0.5
ACEI/ARB	109 (50.0)	19 (63.3)	90 (47.9)	0.2
Calcium channel blocker	62 (28.4)	14 (46.7)	48 (25.5)	0.03
Antiarrhythmic drug	175 (80.3)	22 (73.3)	153 (81.4)	0.3
Warfarin	99 (45.4)	20 (66.7)	79 (42.0)	0.02
Direct oral anticoagulant	119 (54.6)	10 (33.3)	109 (58.0)	0.02
Statin	47 (21.6)	10 (33.3)	37 (19.7)	0.1
Calcium supplement	7 (3.2)	1 (3.3)	6 (3.2)	1
LVEF, %	65.8 ± 8.6	64.3 ± 8.5	66.0 ± 8.6	0.3
LADI, mm/m^2	24.2 ± 4.4	25.9 ± 4.6	24.0 ± 4.4	0.03
Laboratory data				
Creatinine, mg/dL	0.9 ± 0.7	0.8 ± 0.6	0.9 ± 0.7	0.7
BNP, pg/mL	101 ± 155	113 ± 123	99 ± 159	0.7
Ablation procedures	275	49	226	0.0002

1 procedure	171 (78.4)	15 (50.0)	156 (83.0)	
2 procedures	37 (17.0)	11 (36.7)	26 (13.8)	
3 procedures	10 (4.6)	4 (13.3)	6 (3.2)	
PVI	218 (100.0)	30 (100.0)	188 (100.0)	1
Extra PV LA ablation	39 (17.9)	12 (40.0)	27 (14.4)	0.002
Linear ablation	38 (17.4)	12 (40.0)	26 (13.8)	0.001
LA posterior wall isolation	16 (7.3)	6 (20.0)	10 (5.3)	0.01
Mitral isthmus ablation	8 (3.7)	3 (10.0)	5 (2.7)	0.08
Other linear ablation	27 (12.4)	10 (33.3)	17 (9.0)	0.0009
CFAE ablation	11 (5.0)	3 (10.0)	8 (4.3)	0.2
LA dwell time at 1st ablation, minutes	153 ± 50	174 ± 23	152 ± 51	0.2
CT findings after ablation				
Coronary calcification	13 (6.0)	4 (13.3)	9 (4.8)	0.09
Valvular calcification	11 (5.0)	1 (3.3)	10 (5.3)	1
PV stenosis	3 (1.4)	1 (3.3)	2 (1.1)	0.4

Data are mean ± SD or n (%) unless otherwise specified. LAC indicates left atrial calcification, BMI, body mass index; AF; atrial fibrillation; CHF, congestive heart failure; CAD, coronary artery disease; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; LVEF, left ventricular ejection fraction; LADI, left atrial diameter index; BNP, brain natriuretic peptide; PVI, pulmonary vein isolation; LA, left atrium; CFAE, complex fractionated atrial electrograms; CT, computed tomography.

Supplemental Table 6. Hazards ratio from Cox proportional hazards analysis for the predictors of LAC formation and assigned risk scores

	Multivariable			
	HR (95% CI)	P value	Log (HR)	Score
Hypertension	2.19 (0.86-5.56)	0.1		
Prior stroke	2.74 (1.08-6.93)	0.03	1.00	10
Left atrial diameter index	1.08 (0.98-1.19)	0.1		
Multiple procedures	4.21 (1.63-10.87)	0.003	1.16	12

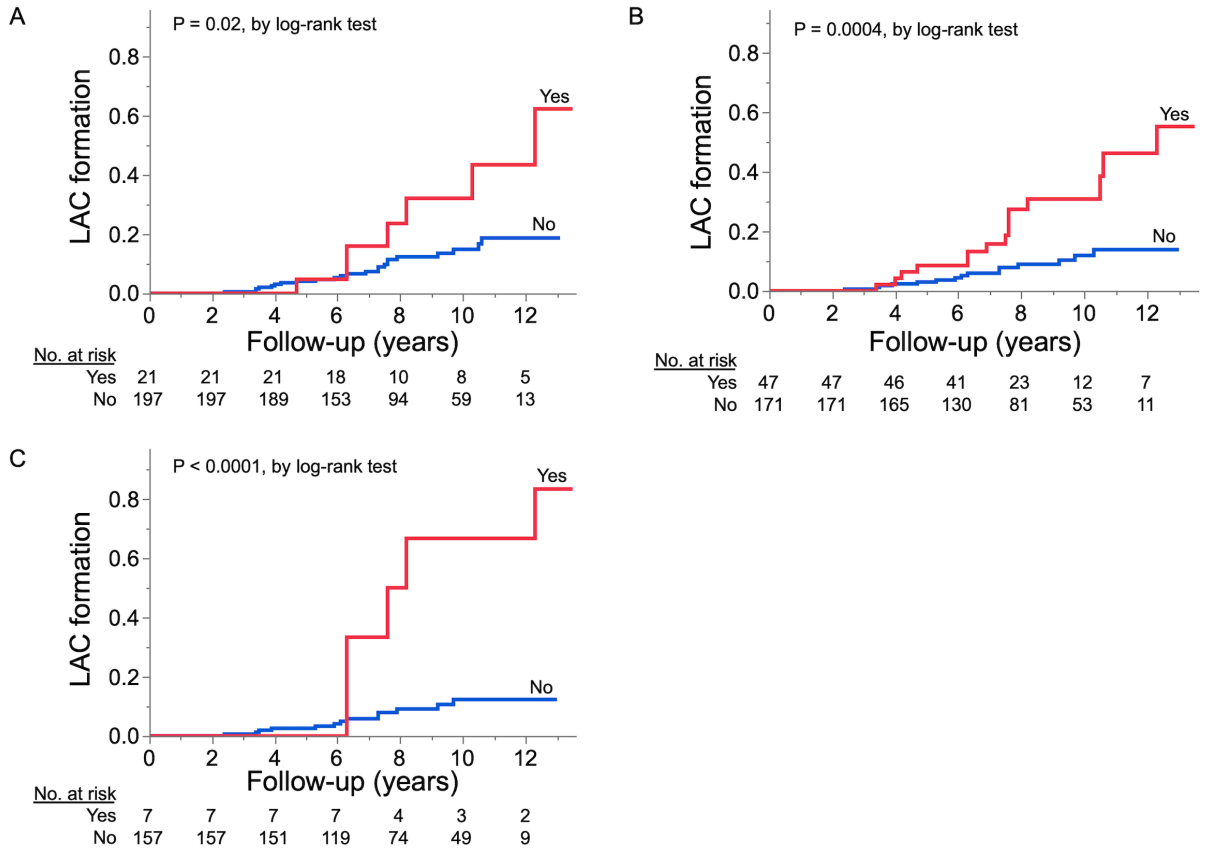
LAC indicates left atrial calcification; HR, hazards ratio; CI, per 1 unit change of continuous variable.

Supplemental Table 7. Risk factors, scores, and 7-year predicted risks of LAC development

Prior stroke	Multiple procedures	Score	Risk of LAC development (%)
0	0	0	5.8
1	0	10	7.1
0	1	12	13.0
1	1	22	33.3

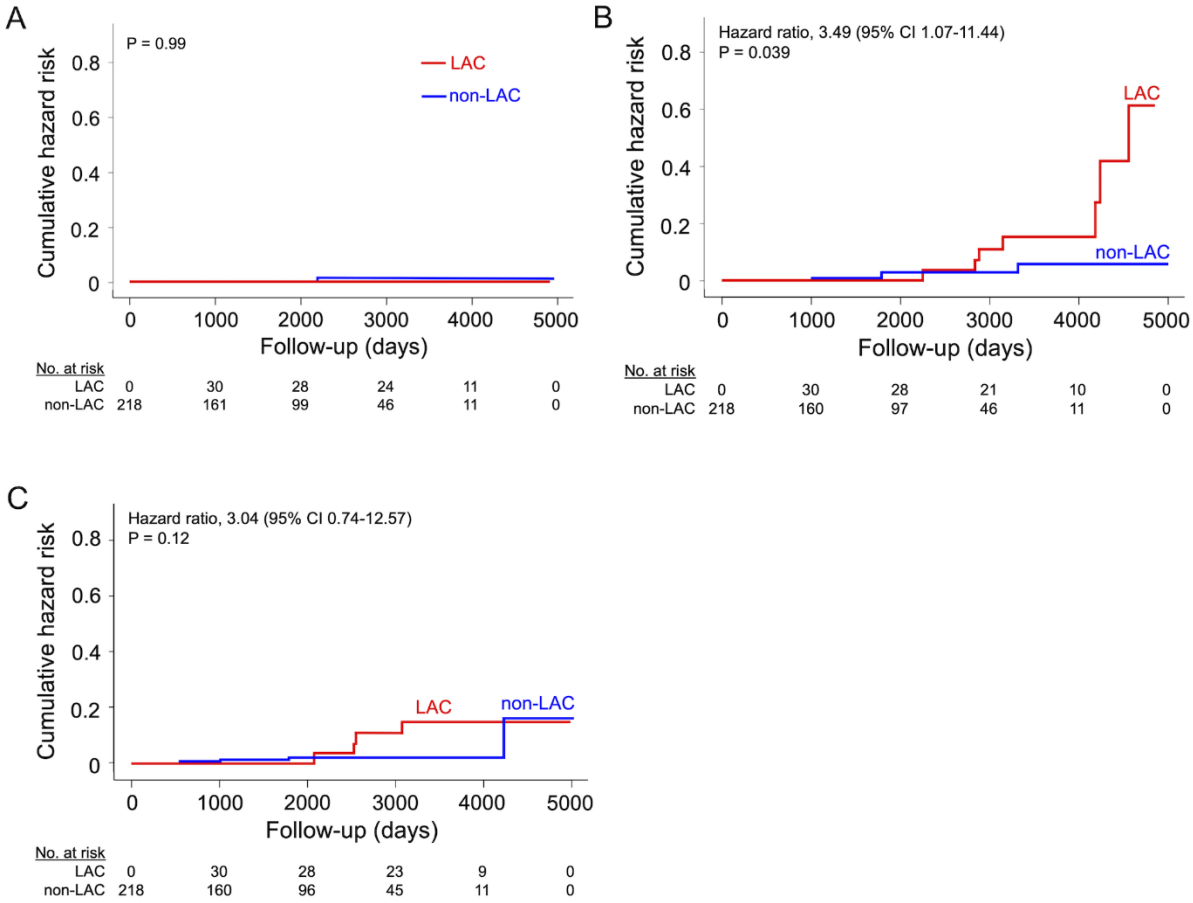
LAC indicates left atrial calcification.

Supplemental Figure 1.



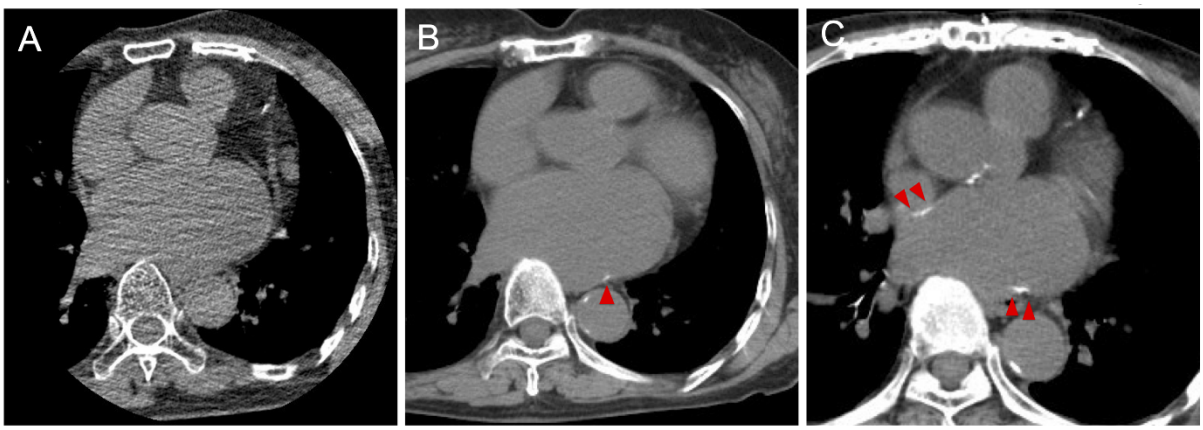
Supplemental Figure 1. Kaplan-Meier curves showing the left atrial calcification (LAC) formation in AF patients after AF ablation when comparing the presence and absence of the two independent risk factors. (A) With and without prior stroke; (B) multiple ablation procedures (yes) and single ablation procedure (no); (C) cases that meet both prior stroke and multiple ablation procedures (yes) and cases that satisfy neither prior stroke nor multiple ablation procedures (no).

Supplemental Figure 2.



Supplemental Figure 2. Cumulative risk of the clinical outcomes. Cumulative risk of cardiovascular death (A), hospitalization for heart failure (B), ischemic stroke (C) in patients after AF ablation with and without left atrial calcification (LAC).

Supplemental Figure 3.



Supplemental Figure 3. A case with increased LAC over time. The patient was undergoing regular CT scans for follow-up after the lung cancer treatment. (A) Plain computed tomography of the heart shows no calcification before catheter ablation. (B) LAC around the left inferior pulmonary vein at the posterior wall (red arrowhead) was observed 4 years after AF ablation. (C) The increased LAC was observed around the left inferior pulmonary vein at the posterior wall (red arrowheads), and newly developed LAC was also seen around the right upper pulmonary vein (red arrowheads) 7 years after AF ablation.