Extensive left atrial low-voltage area during initial ablation is associated with a poor clinical outcome even following multiple procedures.

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March 11, 2021

Abstract

Introduction Some patients fail to respond to persistent atrial fibrillation (PeAF) catheter ablation in spite of multiple procedures and ablation strategies, including low voltage area (LVA)-guided, linear, and complex fractionated atrial electrogram (CFAE)-guided ablation procedures. We hypothesized that LVA extent could predict non-response to PeAF catheter ablation in spite of multiple procedures. Methods This study included 510 patients undergoing initial ablation procedures for PeAF. LVAs were defined as regions with bipolar peak-to-peak voltages of <0.50 mV after PVI during sinus rhythm. Patients were categorized by LVA size into groups A (0-5 cm2), B (5-20 cm2), and C (over 20 cm2). The primary endpoint was AF-free survival after the last procedure. Results During a median follow-up of 25 (17, 36) months, AF recurrence was observed in 101 (20%) patients after 1.4±0.6 ablation procedures (maximum 4). A Kaplan-Meier analysis showed the AF-free survival rate significantly differed by LVA size. Conclusion Extensive LVA after initial PVI was associated with a poor clinical outcome even following multiple procedures.

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Methods

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Results

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Conclusion

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KEYWORDS: Atrial fibrillation, Catheter ablation, Low voltage area, multiple procedures

Introduction

Although catheter ablation has been established as an important treatment for atrial fibrillation (AF), the outcomes of PVI alone for persistent AF (PeAF) are unsatisfactory. [1-3] Substrate modification to improve outcomes has been performed, and favorable outcomes have been reported for low voltage area (LVA)-guided, linear, and CFAE ablation. [4,5] Nevertheless, some patients remain as non-responders to PeAF catheter ablation in spite of multiple procedures and various ablation strategies. The prevalence of left atrial low-voltage areas (LVAs) is strongly associated with the recurrence of atrial tachyarrhythmias following catheter ablation.[6-11] We considered that LVA extent could predict non-responders to PeAF catheter ablation in spite of multiple procedures.

Methods

Study subjects

From October 2014 to December 2018, 518 consecutive patients undergoing initial ablation for persistent AF using Carto 3 (Biosense Webster, Inc., Diamond Bar CA, USA), Ensite NavX (St. Jude Medical, Inc., St. Paul MN, USA) or Rhythmia (Boston Scientific, Boston MA, USA) at our hospital were retrospectively enrolled. Patients who could not undergo voltage mapping were excluded. Other exclusion criteria were age < 20 years, left atrial thrombus, and prior catheter ablation of AF. This study complied with the Declaration of Helsinki. Written informed consent for ablation and the use of data in this study was obtained from all patients, and the protocol was approved by our institutional review board.

Catheter ablation procedure

We discontinued all antiarrhythmic drugs (AADs) [?] 3 days before ablation, except for amiodarone, which was stopped [?] 1 month before. Patients underwent transesophageal echocardiography (TEE) the day before the procedure to exclude the presence of thrombi.

Electrophysiological studies and catheter ablation were performed under intravenous sedation with dexmedetomidine or propofol, with the latter performed by one of four experienced operators (M.M, T.K, A.S, and Y.M). Most of the patients underwent radiofrequency catheter ablation. Cryoballoon ablation was performed for persistent AF of short standing. Patients with common PVs or a large PV diameter underwent radiofrequency catheter ablation.

In cryoballoon ablation, an Arctic Front Advance cryoballoon catheter with a 28-mm balloon size (Medtronic, Inc., Minneapolis MN, USA) was passed into each PV under guidance by fluoroscopy and the 3-D mapping system. After confirming PV occlusion by pulmonary venography, cryoablation commenced and continued for 180 s, during which individual PVs were isolated. If LA–PV conduction persisted after cryoballoon ablation, an additional touch-up ablation was performed using an open-irrigated Thermocool SmartTouch (Biosense Webster) or FlexAbility (St. Jude Medical) linear ablation catheter with a 3.5-mm tip.

In radiofrequency catheter ablation, circumferential ablation around both ipsilateral PVs was performed using an open-irrigated Thermocool SmartTouch (Biosense Webster) or FlexAbility (St. Jude Medical) linear ablation catheter via an Agilis or Swartz Braided SL0 Transseptal Guiding Introducer Sheath (St. Jude Medical). Radiofrequency energy was applied for 30 s at each site using a maximum temperature of 42°C, maximum power of 35 W, and flow rate of 17 mL/min. PV isolation was considered complete when the 20-pole circular catheter no longer recorded any PV potentials.

We allowed additional ablation procedures in this study as recommended by the guidelines at the discretion of the operator, such as focal ablation for reproducible non-PV triggers; ablation of linear lesions, complex

fractionated atrial electrograms (CFAE), and LVA homogenization; superior vena cava (SVC) isolation; and cavotricuspid isthmus linear ablation if patients had clinical or induced typical atrial flutter.

Voltage mapping

Following PV isolation, detailed voltage mapping was performed using a bipolar 3.5-mm tip catheter or multi-electrode mapping catheter during sinus rhythm or with pacing from the right atrium. Voltage mapping was not completed due to unstable cardiac rhythm in 8 of the total patients. (Figure 1) Mapping points were acquired to fill all color gaps on the voltage map using the electroanatomical mapping system. Respective fill and color interpolation thresholds were 15 mm and 23 mm using Carto 3 (Biosense Webster) and 20 mm and 7 mm using Ensite NavX (St. Jude Medical). Using Rhythmia (Boston Scientific), interpolation threshold was 5 mm.

Sites at which LVAs were recorded were then evaluated by high-density mapping to precisely delineate their extent, using the confidence module with the Carto 3 system and Ensite Automap with Ensite NavX. Adequate endocardial contact was confirmed by distance to the geometry surface and stable electrograms. Each acquired point was classified according to the peak-to-peak electrogram as follows: >0.5 mV, healthy; and <0.5 mV, LVAs, with the band pass filter set at 30 to 500 Hz. The target number of mapping points was [?]100 with the 3.5-mm tip catheter and [?]1000 with the multi-electrode mapping catheter throughout the left atrium. Patients were categorized by LVA size into 3 groups. Patients in Group A had none or small LVAs less than 5 cm^2; those in Group B had mildly or moderately damaged LA which contained LVAs less than 20 cm^2; and those in Group C had severely damaged LA which contained LVAs of more than 20 cm^2 (Figure 2).

Patient follow-up

If their clinical status was stable, patients were discharged two days after ablation. After a 3-month blanking period, they attended outpatient clinic visits and underwent 12-lead ECG monitoring at 1, 3, 6 and 12 months, and 24 h-Holter ECG monitoring every 6 months. Additional Holter monitoring was performed if arrhythmic symptoms occurred.

Repeat ablation was allowed for patients with recurrence of AF but was avoided during the blanking period. Repeat ablation during this period was counted as a recurrence just after the blanking period. Use of anti-arrhythmic drugs during the blanking period was allowed, but discontinuation after the blanking period was strongly recommended.

Study endpoints

The primary endpoint was AF-free survival after the last procedure. Either of two events was considered an AF/AT recurrence: (1) atrial tachyarrhythmia recorded on routine or symptom-triggered ECG during an outpatient visit, or (2) at least 30 s of atrial tachyarrhythmia during ambulatory ECG monitoring.

Statistics

Categorical variables are expressed as counts (percentages) and compared with the chi-squared test or Fisher's exact test. Continuous variables are expressed as mean (standard deviation) or median [interquartile range] and compared using Student's t-test and Mann–Whitney U test, respectively. Event-free survival rates were estimated by the Kaplan–Meier method. Univariate and multivariate logistic regression analyses were used to determine clinical factors associated with AF recurrence after the final procedure and extent of LVAs, wherein variables with a P value < 0.05 in the univariate models were included in the multivariate analysis. All analyses were performed using SPSS 26.0 (IBM Corporation, Armonk, NY). P values of less than 0.05 were considered statistically significant.

Results

Study subjects

This study enrolled 518 patients. After excluding 8 patient whose voltage mapping was not completed due to unstable cardiac rhythm, a total of 510 patients were stratified according to LVA area into 3 groups. 374 patients had no LVA (group A). The remaining 136 patients had LVAs after PVI and were allocated to groups B (n=96) and C (n=40) according to the size of their LVAs (Figure 1). Patient characteristics are shown in Table 1. Patients in group B and C were older than those in groups A, more female, had lower BMI, more diabetes, higher CHA_2DS_2VASc scores, higher BNP or NT-BNP levels, lower eGFR, larger LAD, and higher E/e'.. On comparison of groups B and C, patients in group C had a significantly lower BMI and a larger LAD.

Ablation procedure

PVI was successfully completed in all patients, using Carto 3 in 479 (94%), Rhythmia in 20 (4%) and Ensite NavX in 11 (2%). The majority of cases underwent radiofrequency catheter ablation. Cryoballoon ablation was performed in 23 cases (5%).

Details of the initial and additional procedures are listed in Table 2. In the initial procedure, BOX isolation and LVA ablation were more frequently performed in group B and C. With the additional treatments, a higher percentage of PVI was completed in group C and there was more LVA ablation in groups B and C. In group A, SVC isolation was performed more frequently. There was no difference in the number of times ABL was performed among the three groups.

Ablation outcomes

AF recurrence was observed in 101 (20%) patients after 1.4±0.6 ablation procedures (maximum 4). On analysis of AF recurrence at 1 year after the first ablation (Figure 3A), group A performed significantly better than the other groups, but there was no difference between groups B and C. Comparison of clinical outcomes after multiple procedures in the three groups showed that the results depended on the extent of LVA (Figure 3B). Namely, the group without LVA (group A) had an extremely high success rate despite persistent AF. In contrast, more than half of the patients with extensive LVAs (group C) developed recurrence within a few years, even after multiple treatments. The poor prognosis of patients with extensive LVAs was also seen in the analysis of patients who were retreated (Figure 3C).

Multivariate analysis of AF-free survival after the last procedure showed that LVAs > 20 cm^2 and longer AF duration were independent factors associated with AF recurrence (Table 2).

Predictors of extensive LVAs

Because the extent of LVA spreading after initial PVI might contribute significantly to clinical outcomes, we performed additional analyses of factors that predict extensive LVAs. Univariate analysis revealed that advanced age, female, lower BMI, longer AF duration, higher CHA_2DS_2-VASC score, lower renal function, and large LAD were significant predictors for extensive LVAs (Table 3). After multivariate analysis, female, low BMI, and large LAD were considered to be independent factors associated with extensive LVAs (Table 4).

Discussion

In this study, we found that the extent of LVAs was an independent predictor for recurrence even after multiple procedures. The efficacy of catheter ablation was limited in patients with extensive LVAs. In patients with extensive LVAs, the indications and strategies for additional treatment should be carefully considered. In addition, female, lower BMI, and larger LAD were shown to be predictors of extensive LVAs. These findings suggest that the results of voltage mapping after initial PVI can predict the clinical course of second and subsequent treatments.

Efficacy of AF ablation in patients with no or limited LVAs

In this study, group A patients without LVA had a good prognosis up to the late phase after multiple sessions. This result is consistent with previous studies of LVA-guided therapy [12-14]. Considering the implications

of LVAs on AF development, LVAs reflect atrial fibrosis[15,16] and fibrotic remodeling tissue leads to slow conduction and short action potential duration, which facilitates reentry [17,18]. In group A patients who did not have these arrhythmic substrates, many non-PV procedures such as SVC isolation were performed at the time of additional procedures, suggesting that if the AF initiator could be treated, the results might be comparable to those of paroxysmal patients.

Efficacy of ablation in patients with LVAs

As described above, although clinical outcomes were worse in patients without LVAs after initial PVI than in the group with LVA after multiple sessions, when patients with LVAs were compared with each other, a significant difference in clinical outcomes was seen after additional procedures, depending on the extent of the LVA.

Although PV reconnection is still considered a major cause of AF recurrence after initial ABL[19], this factor seems to have diminished in terms of post-retreatment outcomes. At repeat procedures, the operator used his or her own discretion to determine treatment strategy for non-pulmonary veins, and most of the ablation targeted the LVA. This result suggests that LVA ablation, linear ablation, and CFAE are effective beyond PVI. [4,5]

It has been reported that LVA is associated with fibrosis of the left atrium. Extensive LVAs were associated with more residual fibrosis.[20] Development and progression of atrial fibrosis, which plays an important role in AF maintenance, is the hallmark of structural remodeling in AF. The presence of extensive LVAs can lead to multiple or complex areas of arrhythmogenicity. Extensive LVAs could have increased the area that could not be treated by ablation therapy, which might have resulted in poor clinical outcomes.

On the other hand, it must also be considered that fibrosis may simply be the final step of a remodeling cascade which includes myocyte architectural changes, ion channel dysfunction, connexin disarray and disruption of fiber orientation, all of which might precede scarring but not be seen on voltage mapping or imaging. [20] Based on this concept, the extent of an LVA might indicate the progression of fibrosis throughout the atrium. This might in turn suggest that patients with extensive LVAs are more likely to develop new arrhythmogenic features in the future.

The results of our study suggest that the benefit of beyond PVI therapy applies to patients with moderately advanced remodeling, such as those in group B. Table 2 and Figure 3 show that group C, with extensive LVAs, had a high recurrence rate even when PVI was complete. This suggests that clinical outcomes in patients with extensive LVAs are not yet sufficient, even with additional treatment of PVIs with high durability. Ablation therapy can also create new iatrogenic LVAs, which may limit the effectiveness of treatment in cases that already have extensive LVAs. These cases may require concomitant use of appropriate anti-arrhythmic drugs, in addition to ablation therapy.

Clinical factors associated with extensive LVAs

Although several methods for preoperative prediction of the presence of LVAs have been reported [21-23], the present study showed that widespread LVAs worsen the clinical prognosis. We identified the following as independent predictors of extensive LVAs: female, low BMI, and large LAD (Table 4). These factors have been reported to be related to LVAs in the past, and we discuss them here with reference to these reports.

These previous reports identified mechanisms underlying the sex differences in atrial fibrosis. [24] On histological analysis of atrial tissue, females showed stronger expression of CX40 than males, which indicates remodeling-induced change in connexins.[25] In addition, fibrosis-related genes were upregulated in postmenopausal woman with AF. [26]Clinically, females reportedly experience AF recurrence more frequently than males during long-term follow-up after AF ablation, likely due to non-PV arrhythmogenicity. [27]

The reason why low BMI and large LAD are associated with extensive LVAs may be that they both reflect wall stress on the LA. As reported previously, LVA is a result of the progression of remodeling. LA remodeling in AF patients is suggested to be associated with continuous internally generated stretch and wall

stress.[9,28-30] Anatomical contact with external structures surrounding the LA provokes the perpetuation of AF by arrhythmogenic substrates in patients with persistent AF. [31,32] In patients with low BMI, the distance between the LA and external structures such as the vertebral bodies may be close enough to trigger the development of LVA.

Clinical implications

It has become widely known that LVA predicts the outcome of the first treatment. [10,12,21,33] Our present results indicate that evaluating the extent of LVA can predict the clinical course of the second and subsequent treatments.

Limitations

Several limitations of our study warrant mention. The main limitation is the study's retrospective design, which meant that procedures were not standardized but rather at the discretion of the operator. Although prospective studies are necessary to solve these problems, standardization of procedures and long-term observation in an era of constantly improving strategies is not easy. Second, our follow up did not include routine continuous monitoring with implanted devices or transtelephonic electrocardiographic monitoring, and our AF-recurrence-free rate might therefore be underestimated. Third, since we performed voltage mapping using either bipolar 3.5-mm tip catheters or multi-electrode mapping catheters, the distribution of LVAs might have changed, given that multielectrode catheters produce smaller LVA measurements than ablation catheters. [34] Fourth, our conduct of voltage mapping after the completion of PV isolation and in the left atrium only might have influenced the prevalence of LVAs. Fifth, patients with the worst prognosis, namely those in whom a voltage map could not be obtained after the first PVI, were excluded. Sixth, the cut-off values (5 cm^2 and 20 cm^2) used for grouping were arbitrary. Finally, statistical analyses were limited by the relatively small size of the study population.

Conclusion

Extensive LVA after initial PVI was associated with poor clinical outcomes in spite of multiple procedures. Female, lower BMI, and larger LAD predicted extensive LVAs.

Figure Legends

Figure 1. Patient flow chart

Among 518 patients in whom voltage mapping was attempted, 374 patients had no LVA (group A). The remaining 136 patients had LVAs after PVI and were allocated to group B or C according to the size of the LVA. Voltage mapping was not completed in 8 patients (group D) due to unstable heart rhythm.

Figure 2. Example of LVA ablation in addition to PVI

Patients were categorized by LVA size into 3 groups. Patients in group A had no or small LVAs of less than 5 cm^2. Patients in group B had mildly or moderately damaged LA which contained LVA of less than 10 cm^2. Patients in group C had severely damaged LA which contained LVAs of less than 20 cm^2.

Figure 3. AF recurrence-free survival rates

Kaplan-Meier curves for AF-recurrence-free survival are shown. Figure 3A shows the analysis of AF recurrence at 1 year after the first ablation. Figure 3B indicates that clinical outcomes after multiple procedures depended on the extent of LVAs. Figure 3C shows the results of the post-reintervention analysis by extracting the reintervention group only.

Blue line, patients in group A); red line, patients allocated to group B; green line, patients allocated to group C. In Figures 3B and 3C, patients in group A demonstrated excellent rhythm outcomes. In contrast, those with extensive LVAs (group C) had a significantly lower AF-recurrence-free survival rate.

Table 1. Patient characteristics

	Group A (0-5 cm^2) n=374	Group B (5-20 cm^2) n=96	Group
Age, years	65±10	72±8	71±8
Female, n (%)	67 (18)	47 (49)	21 (53
Body mass index, kg/m^2	24.7±3.8	24.1±4.6	22.4±3
AF duration, months	4 (2, 11)	6 (3, 11)	4 (2, 1
Hypertension, n (%)	207 (56)	47 (49)	24 (60
Diabetes mellitus, n (%)	57 (15)	24 (25)	10 (25
Heart failure, n (%)	92 (25)	31 (32)	10 (25
CHA_2DS_2-VASc score	2.2±1.4	3.1±1.3	3.4±1.
BNP [?] 100 pg/ml or NT-proBNP [?] 400 pg/ml, n (%)	297 (79)	88 (92)	36 (90
eGFR, ml/min	63±17	55±17	55±22
Echocardiographic parameters			
Left atrial diameter, mm	43±6	43±6	47±7
Ejection fraction, %	58±13	57±13	60±14
Left ventricular mass, g	194±57	184±66	194±6
E/e'	10.4±3.8	12.4±6.5	12.4±5

Abbreviations: NT-proBNP, N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate;

E, diastolic early transmitral flow velocity; e', diastolic early mitral annular velocity

Table 2. Procedural background

	Group A (0-5 cm^2) n=374	Group B (5-20 cm^2) n=96	Group C(>20 cm^2) n=40	*P value*
Number of procedures	1.4±0.3	1.4±0.6	1.6±0.3	0.304
Initial procedure	n=374	n=96	n=40	
PVI, n (%)	374 (100)	96 (100)	40 (100)	1.000
Mitral isthmus, n (%)	31 (8)	12 (13)	3 (8)	0.339
BOX isolation, n (%)	4 (1)	2 (2)	3 (8)	0.048
Roof line, n (%)	34 (10)	11 (11)	3 (8)	0.361
CFAE, n (%)	20 (5)	0 (0)	2 (5)	0.155
LVA ablation, n (%)	12 (3)	31 (32)	10 (25)	<0.001
Non PV foci, n (%)	2 (1)	1 (1)	2 (5)	0.090
SVC isolation, n (%)	2 (1)	0 (0)	1 (3)	0.793
CTI, n (%)	65 (17)	13 (14)	10 (25)	0.255
Additional procedure	n=102	n=35	n=23	
Redo PVI, n (%)	66 (65)	25 (71)	7 (30)	0.234
Mitral isthmus, n (%)	8 (8)	6 (17)	3 (13)	0.048
BOX isolation, n (%)	5 (5)	2 (6)	5 (22)	0.756
Roof line, n (%)	10 (10)	5 (14)	3 (13)	0.195
CFAE, n (%)	7 (7)	1 (3)	1 (4)	0.142
LVA ablation, n (%)	15 (15)	25 (71)	20 (50)	<0.001
Non PV foci, n (%)	31 (30)	15 (43)	8 (43)	0.215
SVC isolation, n (%)	27 (26)	1 (3)	1 (3)	0.002
CTI, n (%)	39 (38)	8 (23)	7 (23)	0.351

Abbreviations: PV, pulmonary vein; PVI, pulmonary vein isolation; CFAE, complex fractionated atrial electrogram; LVA, low voltage area; SVC, superior vena cava; CTI, cavo tricuspid isthmus

Table 3. Factors associated with AF recurrence after the final procedure

	Recurrence	**Recurrence**	**Univariate**	**Univariate**	**Univariate**	**Multivariate**	**Multivariate**	**Multiv**
	With n = 101	*Without n =409*	*HR*	*95% CI*	*P value*	*HR*	*95% CI*	*P value*
Age, years	68±9	67±10	1.02	0.999-1.05	0.055	1.02	0.98-1.07	0.389
Female, n (%)	26 (33)	109 (25)	1.38	0.86-2.22	0.186			
Body mass index	24.6±5.0	24.4±3.8	0.99	0.94-1.05	0.825			
AF period, months	5 (2, 37)	4 (2, 10)	1.007	1.001-1.01	0.026	1.01	1.001-1.014	0.024
Heart failure, n (%)	19 (24)	114 (27)	0.92	0.56-1.52	0.917			
CHA_2DS_2-VASc score	2.8±1.6	2.4±1.5	1.15	0.998-1.33	0.054	1.01	0.76-1.33	0.975
Estimated GFR, pg/ml	59±17	61±18	0.99	0.98-1.006	0.993			
Left atrial diameter, mm	44.5±6.7	42.8±6.1	1.04	1.01-1.08	0.027	1.02	0.977-1.067	0.353
Ejection fraction, %	58.0±14.4	58.0±12.5	1.001	0.98-1.02	0.872			
LVAs > 20 cm^2, n (%)	16 (20)	240 (6)	5.39	2.77-10.48	<0.001	7.94	2.91-21.67	<0.001

Factors with p <0.10 in the univariate analysis were incorporated in the multivariate analysis.

HR, hazard ratio; CI, confidence interval, AF, atrial fibrillation; GFR, glomerular filtration rate; LVA, low-voltage area.

Table 4. Factors associated with extensive LVAs (>20 cm^2)

	Extensive LVAs (> 20 cm^2)	**Extensive LVAs (> 20 cm^2)**	**Univariate**	**Univariate**	**Univariate**	**Multivariate**	**Multivariate**	**Multiv**
	With (n = 40)	Without (n = 470)	*HR*	*95% CI*	*P value*	*HR*	*95% CI*	*P value*

	Extensive LVAs (> 20 cm^2)	Extensive LVAs (> 20 cm^2)	Univariate	Univariate	Univariate	Multivariate	Multivariate	Multiv
Age, years	71±8	67±10	1.06	1.02-1.10	0.004	1.04	0.97-1.12	0.275
Female, n (%)	21 (53)	114 (24)	3.45	1.79-6.65	<0.001	3.86	1.40-10.64	0.009
Body mass index	22.4±3.4	24.6±4.0	0.84	0.76-0.93	0.001	0.82	0.70-0.95	0.010
AF period, months	4 (2,17)	4 (2,11)	1.007	1.001-1.01	0.026	1.004	0.99-1.02	0.498
Heart failure, n (%)	10 (25)	122 (26)	0.94	0.45-1.98	0.871			
CHA_2DS_2-VASc score	3.3±1.7	2.3±1.4	1.59	1.28-1.97	<0.001			
Estimated GFR, pg/ml	55.2±21.8	61.2±17.0	0.98	0.97-0.999	0.037	0.99	0.96-1.01	0.355
BNP [?] 100 pg/ml or NT-proBNP [?] 400 pg/ml, n (%)	36 (90)	385 (82)	1.85	0.64-5.35	0.257			
Left atrial diameter, mm	47±6	43±6	1.10	1.04-1.15	<0.001	1.09	1.01-1.18	0.020
Ejection fraction, %	60±14	58±13	1.01	0.99-1.04	0.383			
E/e'	11.6±4.7	10.8±4.6	1.06	0.996-1.13	0.065			

Factors with p <0.05 in the univariate analysis were incorporated in the multivariate analysis.

HR, hazard ratio; CI, confidence interval, AF, atrial fibrillation; GFR, glomerular filtration rate; LVA, low-voltage area

BNP, Brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide

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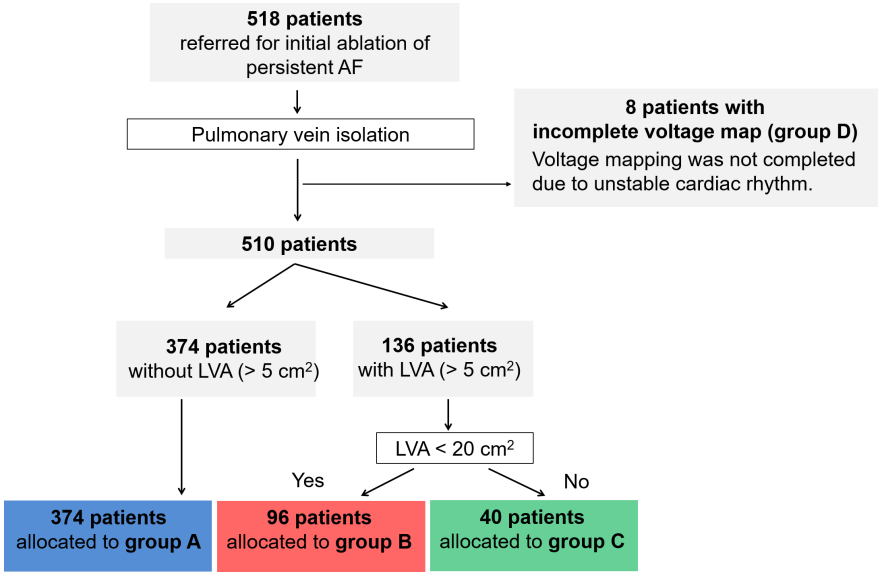
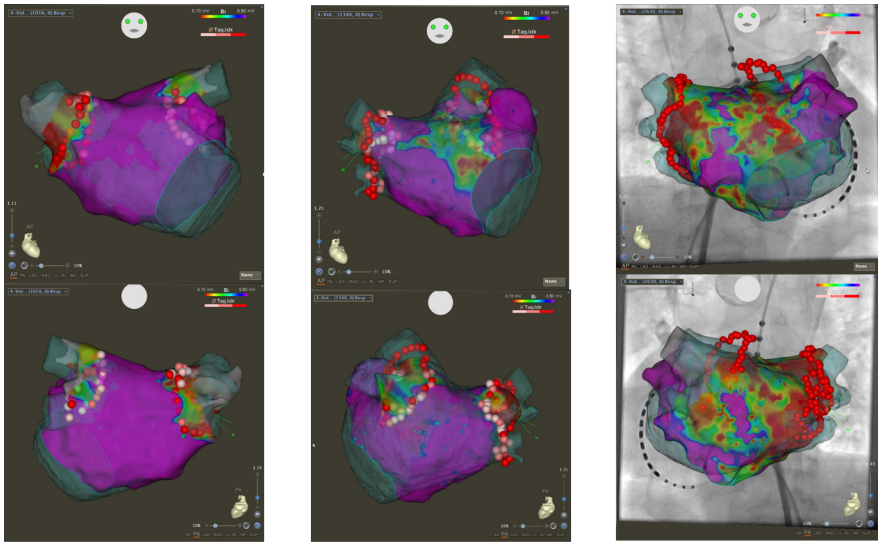
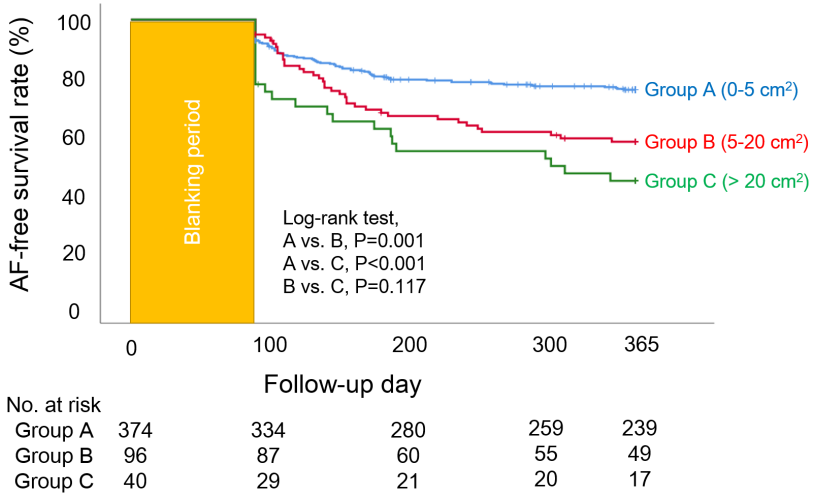




Group A (0-5 cm^2) Group B (5-20 cm^2) Group C (> 20 cm^2)

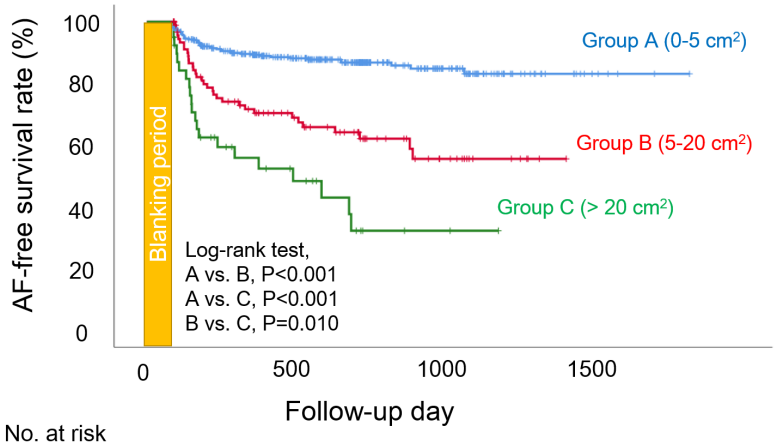
Figure 3A



No. at risk

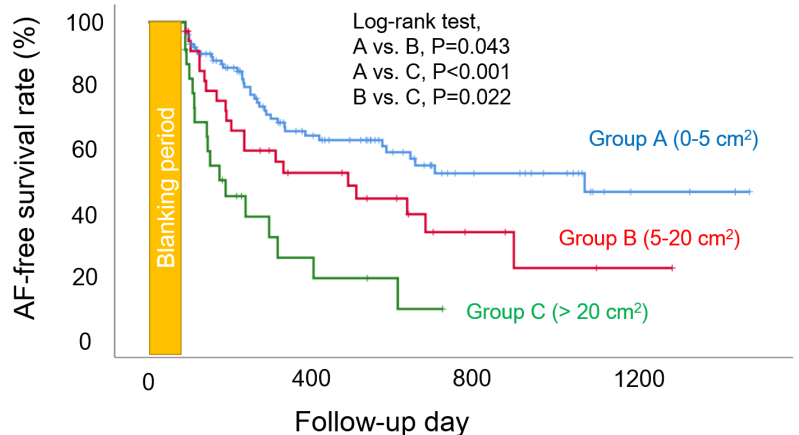
Group A	374	334	280	259	239
Group B	96	87	60	55	49
Group C	40	29	21	20	17

Figure 3B



No. at risk				
Group A	374	228	61	6
Group B	96	45	13	0
Group C	40	12	2	0

Figure 3C



No. at risk				
Group A	102	46	17	4
Group B	35	14	4	0
Group C	23	4	0	0