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Left Atrial Appendage Ligation and Ablation for Persistent Atrial Fibrillation

The LAALA-AF Registry

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ABSTRACT

OBJECTIVES This study was intended to evaluate the impact of adding the left atrial appendage (LAA) closure system (LARIAT) procedure to conventional atrial fibrillation (AF) ablation in patients with persistent AF.

BACKGROUND Percutaneous endoepicardial LARIAT may result in both mechanical and electrical exclusion of the LAA and aid in improving the outcomes of catheter ablation by eradicating the LAA triggers and altering the substrate.

METHODS We performed a prospective observational study of patients with persistent AF referred for AF ablation. Patients underwent LAA ligation with LARIAT procedure before undergoing AF ablation (LARIAT group). Age- and sex-matched persistent AF patients undergoing AF ablation during the same time frame were included in the control group (ablation-only group).

RESULTS A total of 138 patients were included in the study, with 69 patients in the LARIAT group. The mean age of the population was 67 ± 10 years, with 96 (70%) men. Left atrial (LA) size, $CHADS_2$, CHADSVasc, and HAS-BLED scores were higher in the LARIAT group when compared with the ablation-only group. There were no differences in the type of lesions during AF ablation between the groups. The primary outcome of freedom from AF at 1 year off antiarrhythmic therapy after 1 ablation procedure was higher in the LARIAT group (45 [65%] vs. 27 [39%]; $p = 0.002$). More patients in the ablation-only group underwent repeat ablation because of AF recurrence (11 [16%] vs. 23 [33%]; $p = 0.018$).

CONCLUSIONS In patients with persistent AF, addition of LAA ligation with the LARIAT device to conventional ablation appears to improve the success rate of AF ablation. (J Am Coll Cardiol EP 2015;1:153–60) © 2015 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice (1,2). Management of AF primarily involves control of symptoms and prevention of stroke. Catheter ablation of AF is the standard of care in the management of drug-refractory symptomatic AF (3). However, the success rates of AF ablation are less than ideal, especially in patients with persistent AF. The left atrial appendage (LAA) has been shown to play a role in the initiation and maintenance of atrial arrhythmias (4,5). Addition of electrical isolation of LAA to conventional AF ablation has shown to improve

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ABBREVIATIONS AND ACRONYMS

AAD = anti-arrhythmic drugs
AF = atrial fibrillation
AT = atrial tachycardia
GP = ganglionated plexi
LA = left atrium/atrial
LAA = left atrial appendage
PV = pulmonary vein
TEE = transesophageal echocardiography/ echocardiogram

outcomes of persistent AF ablation (4). However, electrical isolation of LAA during catheter ablation can be challenging and may potentially result in increased risk of thrombogenesis in the LAA, especially if the mechanical function of the LAA is persistently impaired post-ablation.

The LAA is the most common source of thrombus formation in patients with AF-related thromboembolism (1). Anticoagulation is considered to be the gold standard for preventing thromboembolic complications in AF; however, many patients are intolerant of anticoagulants. Recent studies have shown the feasibility and noninferiority of LAA exclusion in preventing thromboembolic complications (6,7). Device-based endocardial LAA excluders, such as Watchman (Boston Scientific, Natick, Massachusetts) and Amplatzer Cardiac Plug (St. Jude Medical, Minneapolis, Minnesota), can result in mechanical occlusion of the LAA. LAA exclusion with endoepicardial system (LARIAT) and surgical epicardial ligation can result in both mechanical and electrical isolation of the LAA as a result of LAA infarction. Moreover, soon after the LAA occlusion with the LARIAT, there is a significant decrease in voltage (8).

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Because the LAA has an "electrical role" in persistent AF and the LARIAT procedure can result in "electrical exclusion" of LAA, we proposed that addition of LAA exclusion with the LARIAT to conventional AF ablation in patients with persistent AF may improve the success rate of the ablation procedure (9–13).

METHODS

PATIENT POPULATION. We performed a prospective, multicenter, observational study of patients who were referred for ablation of persistent AF. The protocol was approved by all the participating institutions' institutional review boards. After evaluating the following inclusion and exclusion criteria, patients referred for persistent AF ablation (with or without prior ablation) were considered for the LARIAT procedure for LAA exclusion as an adjunct to AF ablation.

Patients for the LARIAT procedure were screened using the following inclusion criteria: 1) age 18 years or older; 2) persistent nonvalvular AF; 3) at least 1 risk factor of embolic stroke ($CHADS_2$ $\geq$1); and 4) a life expectancy of at least 1 year. Patients were excluded from the study if they met any of the following exclusion criteria: 1) history of cardiac surgery; 2) unfavorable chest anatomy (pectus excavatum); 3) recent myocardial infarction (within 3 months); 4) embolic event within the past 30 days; 5) New York Heart Association functional class IV heart failure symptoms; and 6) history of thoracic radiation. Patients who gave informed consent had their computed tomography scan of the heart evaluated for suitability for LARIAT procedure. Exclusion criteria based on LAA anatomy included: 1) a LAA width >40 mm; 2) a superiorly oriented LAA with the LAA apex directed behind the pulmonary trunk; 3) bilobed LAA or multilobed LAA in which lobes were oriented in different planes exceeding 40 mm; and 4) a posteriorly rotated heart.

After excluding patients (n = 18) who were not candidates for LARIAT, a total of 69 patients successfully underwent a protocol-driven LARIAT procedure (LARIAT group) from January 2012 through December 2013. All of these patients then underwent a conventional AF ablation procedure at least 30 days later, primarily involving pulmonary vein antral isolation. We prospectively included an equal number of age- and sex-matched patients with persistent AF undergoing AF ablation during the same time frame as a control group of the study (ablation-only group).

PERCUTANEOUS SUTURE EXCLUSION OF THE LAA USING THE LARIAT DEVICE. LAA exclusion was performed using the standard protocol for LARIAT device implantation as previously described (6). In brief, patients underwent the procedure under general anesthesia. Pericardial access and transseptal puncture for left atrial (LA) access was performed. The standard LARIAT endocardial and epicardial sheaths were used, and under transesophageal echocardiography (TEE) and angiography guidance, the LARIAT device was deployed and LAA occlusion was confirmed. Patients were followed routinely with 1-month and 3-month TEE.

AF ABLATION. AF ablation in both the LARIAT and ablation-only group patients consisted of pulmonary vein isolation using a roving lasso technique using double transseptal puncture. Additional ablation was performed at the discretion of the operator and included linear LA ablation, right atrial flutter line, and complex fractionated atrial electrogram ablation. LAA isolation was attempted only in patients with an identifiable trigger during the procedure. Other non-pulmonary vein triggers were mapped and ablated, if present.

CLINICAL FOLLOW-UP. Patients were followed for a minimum of 1 year. They were seen in the clinic at 2, 6, and 12 months post-procedure. Additional clinic visits occurred when patients developed symptoms. Clinic visits included history and physical

examination, 12-lead electrocardiogram, and interrogation of cardiac implantable electrical devices where available. All patients underwent 2-month nonlooping event monitoring starting 2 weeks after the procedure and a 7-day monitor at the 6- and 12-month visits, or in between visits if they developed symptoms. The updated medication list was obtained at every visit to ensure the stability of antiarrhythmic drug (AAD) therapy. Patients were offered redo ablation if they had recurrence beyond 2 months postprocedure (blanking period).

STATISTICAL ANALYSIS. Normally distributed continuous variables are expressed as mean ± SD. A Student *t* test was used to test for differences of the means. Categorical variables are expressed as percentages and compared using chi-square tests or Fisher exact test when needed. The Mann-Whitney *U* test was performed for comparing non-normally distributed samples. The primary outcome evaluated was freedom from atrial tachycardia (AT) or AF during the first 1 year off AADs (after the first 2 months of the post-ablation blanking period). A multivariate regression analysis was performed to identify the independent predictors of AF recurrence with and without including the "participating center" as a variable. A p value of <0.05 was considered significant. All statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, New York).

RESULTS

BASELINE DATA. A total of 138 patients were included in the study, with 69 in each group. Baseline characteristics are described in Table 1. Mean age of the population was 67 ± 10 years, with 96 (70%) men, with no difference between the groups, as per design. All patients had persistent AF, and the mean duration of AF was 52 months, with no difference between the groups. Patients in the LARIAT group had a higher $CHADS_2$ score (2.46 ± 1.30 vs. 2.02 ± 1.19; p = 0.040), higher CHADSVASc score (3.68 ± 1.64 vs. 3.09 ± 1.33; p = 0.022) and HAS-BLED score (2.91 ± 1.25 vs. 2.33 ± 1.20; p = 0.006), and greater LA size (5.0 ± 0.52 vs. 4.8 ± 0.6). The mean ejection fraction was 53 ± 11, with no difference between the groups. A total of 36 (26%) patients underwent a prior AF ablation procedure with no significant difference between the groups (21 [30%] vs. 15 [22%]; p = 0.266).

TABLE 1 Baseline Characteristics

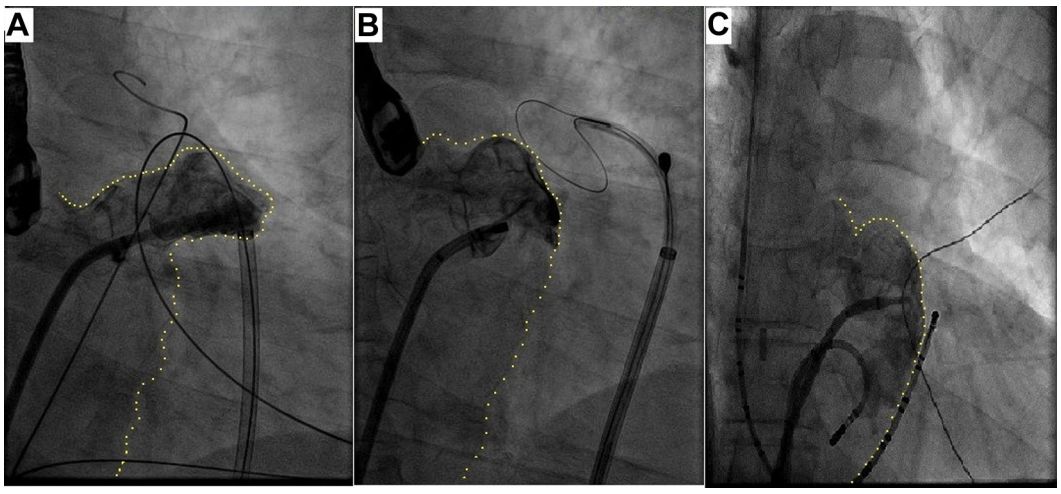
	LARIAT Group (n = 69)	Ablation-Only Group (n = 69)	Total (N = 138)	p Value
Age, yrs	67 ± 10	67 ± 10	67 ± 10	1.00
Men	48 (70)	48 (70)	96 (70)	1.00
Caucasian race	62 (90)	64 (93)	126 (91)	0.545
Coronary artery disease	20 (29)	12 (17)	32 (23)	0.107
Hypertension	51 (74)	54 (78)	105 (76)	0.549
Diabetes mellitus	20 (29)	18 (26)	38 (28)	0.703
Heart failure	12 (17)	10 (15)	22 (16)	0.551
Cardiomyopathy	15 (22)	13 (19)	28 (20)	0.672
Obstructive sleep apnea	20 (29)	27 (39)	47 (34)	0.295
Prior stroke/TIA	23 (33)	11 (16)	34 (25)	0.018
Gastrointestinal bleed	22 (32)	14 (20)	36 (26)	0.121
Renal insufficiency	5 (7)	10 (15)	15 (11)	0.171
Sinus node dysfunction	18 (26)	12 (17)	30 (22)	0.216
Prior cardiac device	17 (25)	12 (17)	29 (21)	0.296
$CHADS_2$ score	2.46 ± 1.30	2.02 ± 1.19	2.25 ± 1.26	0.040
CHADSVASc score	3.68 ± 1.64	3.09 ± 1.33	3.38 ± 1.52	0.022
HAS-BLED	2.91 ± 1.25	2.33 ± 1.20	2.62 ± 1.26	0.007
LA size	5.0 ± 0.52	4.8 ± 0.6	4.9 ± 0.6	0.006
Left ventricular ejection fraction	53 ± 11	53 ± 11	53 ± 11	0.921
Baseline LA volume	168 ± 35	166 ± 29	167 ± 33	0.721
Post-procedure LA volume	129 ± 32	149 ± 30	139 ± 32	<0.001
AADs	69 (100)	69 (100)	138 (100)	1.00
Class I	33 (48)	26 (38)	59 (43)	
Dofetilide	15 (22)	17 (25)	32 (23)	
Sotalol	11 (16)	13 (19)	24 (17)	
Amiodarone	4 (6)	5 (7)	9 (7)	
Dronedarone	6 (9)	8 (12)	14 (10)	
Beta-blockers	51 (74)	50 (73)	101 (73)	0.848
Calcium-channel blockers	17 (25)	20 (29)	37 (27)	0.564
Anticoagulation				0.153
Warfarin	41 (59)	49 (71)	90 (65)	
Rivaroxaban	28 (41)	20 (29)	48 (35)	

Values are mean ± SD or n (%).
AAD = antiarrhythmic drug; LA = left atrial; TIA = transient ischemic attack.

LARIAT PROCEDURE. Among patients undergoing the LARIAT procedure, the mean LAA length was 52.0 mm, with a neck width of 34.2 mm. Exclusion success was defined as the successful closure of the LAA with the absence of a contrast leak on LA angiogram and ≤1-mm jet as visualized by color Doppler on TEE. All the patients in the study group achieved an immediate success of the LAA exclusion (Figure 1). Mean procedural time for the LARIAT procedure was 67.3 min, with a mean of 21.7 min of fluoroscopy time (Table 2). At 3 months TEE, 7 (10%) patients had a leak with a size ranging from 1 to 5 mm. Major complications occurred in 3 (5%) patients. One patient suffered a right ventricular perforation, which was conservatively managed; 1 patient had a pleural effusion needing thoracentesis; and 1 patient developed a groin hematoma, which did not require surgery.

AF ABLATION. Mean procedural time, fluoroscopy time, and ablation times were 228 ± 47 min, 48 ± 15 min, and 50 ± 21 min, respectively. The majority of the patients (103 [74%]) had at least moderate LA scar identified on the electroanatomic mapping, and

FIGURE 1 Serial Fluoroscopic Image of the LA Angiogram in Patients Who Underwent LARIAT and Subsequent AF Ablation



(A) Visualization of left atrial (LA) appendage (LAA) before the LARIAT placement; **(B)** exclusion of the LAA immediately after LARIAT placement; **(C)** persistent exclusion of LAA as seen during subsequent atrial fibrillation (AF) ablation. The **dotted yellow line** indicates the limits of the left atrium and left atrial appendage.

it was not different between the groups (Figure 2). Ablation beyond the pulmonary veins were performed in 66 (48%) patients, with no difference between the groups. Only 1 patient in the ablation-only group underwent LAA isolation for LAA trigger. Major complications occurred in 4 (3%) patients: 2 in each group. Complications included: pericardial effusion (1 patient in the LARIAT group requiring a tap), groin hematoma (2 patients requiring blood transfusion: 1 in each group), and atrioventricular fistula (1 patient in the ablation-only group requiring surgical repair).

TABLE 2 Procedural Characteristics and Outcomes

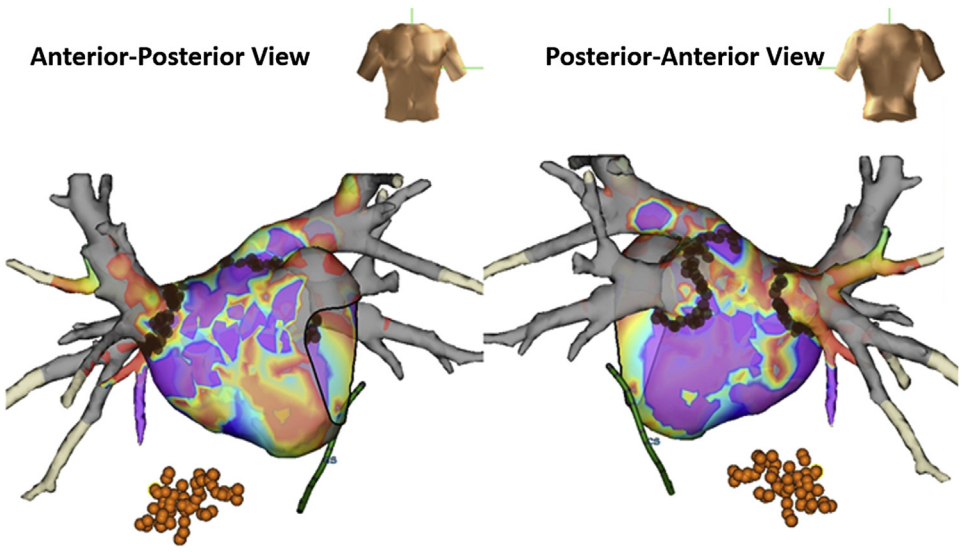
	LARIAT Group (n = 69)	Ablation-Only Group (n = 69)	Total (N = 138)	p Value
AF ablation procedure time, min	238 ± 30	218 ± 57	228 ± 47	0.011
Fluoroscopy time, min	42 ± 9	50 ± 18	48 ± 15	<0.001
Ablation time, min	49 ± 28	52 ± 16	51 ± 21	0.440
Moderate-to-severe LA scar	51 (74)	52 (75)	103 (75)	0.841
Extra-pulmonary vein ablation	31 (45)	36 (52)	66 (48)	0.394
Freedom from AF/AT at 12 months off AADs after 1 ablation procedure	45 (65)	27 (39)	72 (52)	0.002
Median time to recurrence, weeks	27 (12–37)	19 (11–25)	21 (11–28)	0.030
Repeat ablation in 12 months	11 (16)	23 (33)	34 (25)	0.018
Patients on AADs at 12-month follow-up	9 (13)	15 (22)	24 (17)	0.177
Freedom from AF/AT at 12 months off AADs after >1 ablation procedure	53 (77)	40 (58)	93 (67)	0.018

Values are mean ± SD, n (%), or median (interquartile range).
AF = atrial fibrillation; AT = atrial tachycardia; other abbreviations as in Table 1.

OUTCOMES. All 138 patients completed a 12-month follow-up after AF ablation. The primary outcome evaluated was freedom from AT/AF off AADs at 12 months after first ablation (excluding the blanking period). All attempts were made to discontinue AADs after the first 2 months of the blanking period. A total of 66 (48%) patients had AF or AT recurrence at 1 year, post-blanking period, off AADs. Patients in the LARIAT group were much more likely to have freedom from AT/AF at 12 months post-ablation compared with the ablation-only group (45 [65%] vs. 27 [39%]; p = 0.002) (Figure 3). We evaluated the primary outcome after excluding patients who had a history of AF ablation (AF ablation before enrolling in the study). More patients in the LARIAT group had freedom from AT/AF off AADs at 12 months after excluding the 36 (26%) patients who had a previous AF ablation (30 of 48 [62%] vs. 22 of 54 [41%]; p = 0.028). Repeat ablation was performed in 34 (25%) patients (11 [16%] in the LARIAT group vs. 23 [33%] in the ablation-only group; p = 0.018). LARIAT patients were also more likely to have freedom from AT/AF at 12 months off AADs after >1 ablation procedure compared with ablation-only patients: (53 [77%] vs. 40 [58%]; p = 0.018).

The median time to recurrence was shorter for the ablation-only group (19 weeks: interquartile range 11 to 25 vs. 27 weeks: interquartile range 20 to 40 weeks; p = 0.030). We performed a multivariate regression analysis to predict the independent

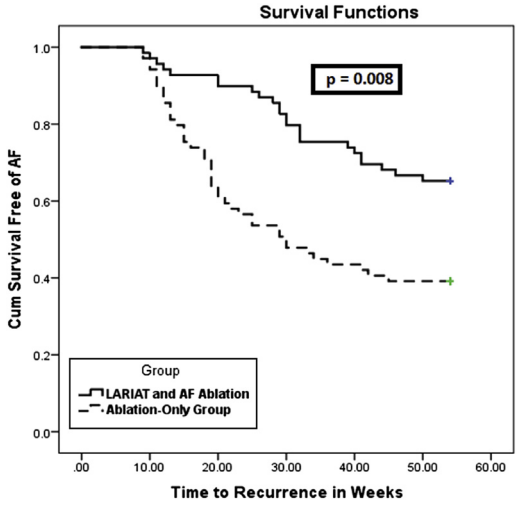
FIGURE 2 Three-Dimensional Electroanatomic Map



Three-dimensional electroanatomic map showing left atrial voltage and the lesion set in a patient who had undergone a previous LARIAT procedure.

predictors of AT/AF recurrence. Variables including in the multivariate model were age, sex, CHADSVASc score, previous AF ablation, AF duration, baseline LA volume, and LARIAT procedure. Advanced age (odds ratio [OR]: 1.043/year; p = 0.037), higher baseline LA volume (OR: 1.021/ml; p = 0.003), and not undergoing LARIAT procedure (OR: 3.343; p = 0.004) were the only independent predictors of AT/AF recurrence at 12 months.

FIGURE 3 Survival Analysis Using a Kaplan-Meier Curve of the Primary Outcome in Both Groups

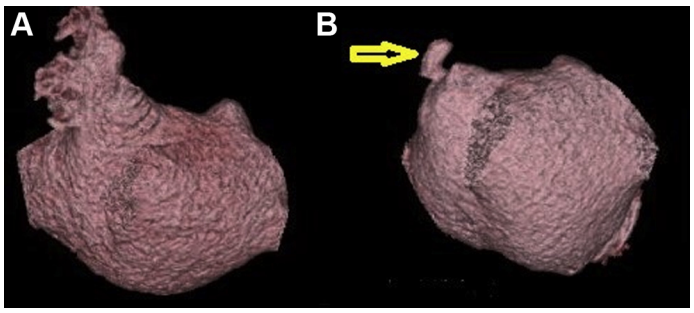


AF = atrial fibrillation; Cum = cumulative.

Incomplete exclusion (leak size range 1 to 5 mm) of the LAA was seen in about 7 (10%) patients. There was no significant difference in the recurrence rates between the patients who had a leak versus those who did not (2 of 7 [29%] vs. 22 of 62 [35%]; p = 1.0). In patients (n = 4) with a leak between 1 and 3 mm, there was a significant reduction in the size of the LAA beyond the ligation site on the follow-up computed tomography scan, suggestive of possible ischemic remodeling of the LAA despite the small leak at the ligation site (Figure 4). One of these patients needed a redo ablation. At the time of the redo procedure, the stump/ostium of the LAA was electrically silent. One of the 3 patients with a leak >3 mm had recurrence of AF and underwent a redo ablation. There was no triggered activity from the LAA, but there was electrical conduction into the LAA that could be easily isolated.

More patients underwent discontinuation of anticoagulation at 6 months after AF ablation in the LARIAT group when compared with those in the ablation-only group (40 [56%] vs. 19 [28%]; p < 0.001). Baseline LA volumes were comparable between the groups. Post-procedural LA volume was much less in the LARIAT group compared with the ablation-only group (129 ± 32 ml vs. 149 ± 30 ml; p < 0.001) (Figure 5).

FIGURE 4 A Patient With a 2-mm Leak Post-LARIAT



(A) LA appendage pre-LARIAT ligation. **(B)** LA appendage post-LARIAT ligation with a residual stump. Patient had a residual stump with severely atrophied left atrial appendage **(yellow arrow)**. At the time of redo procedure, the stump was not electrically active.

Two (3%) patients had a transient ischemic attack in the ablation-only group after discontinuing anticoagulation from recurrent silent AF.

DISCUSSION

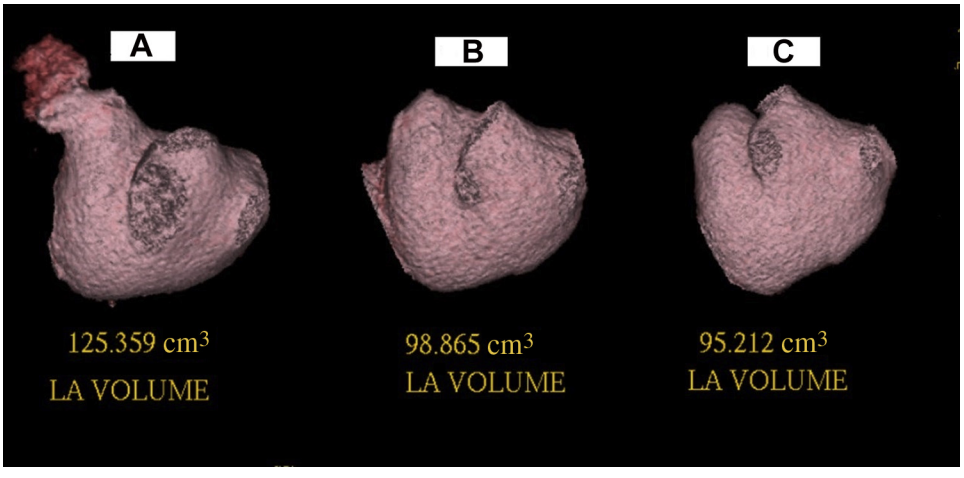
In our prospective multicenter study, we found that addition of the LARIAT procedure to catheter ablation for patients in persistent AF was associated with a significant decrease in the recurrence of AF.

ROLE OF LAA IN ARRHYTHMOGENESIS. The role of LAA in the initiation and maintenance of AF and AT has been described in several recent studies. Two studies (5,12) of AT originating from the LAA proposed that the underlying mechanism is increased automaticity. Epicardial exclusion of the appendage with a minimally invasive occlusion device (Atriclip, AtriCure, West Chester, Ohio) implanted from outside the heart through a thoracoscopic approach has been shown to be successful in achieving electrical isolation and thus elimination of focal AT (11). In a series of 10 consecutive patients undergoing coronary bypass surgery, epicardial LAA clip occlusion led to the complete electrical isolation of the LAA. Thus, LAA ligation resulted not only in the elimination of an important source of systemic thromboembolism but also in the electrical exclusion of potential triggers of AF (14).

Di Biase et al. (4) reported that 266 (27%) of 987 patients undergoing redo catheter ablation for paroxysmal and persistent AF showed firing from the LAA, and in 86 patients (8.7%), the LAA was found to be the only source of arrhythmia without any evidence of pulmonary venous or extra-pulmonary sources. The role of the LAA in organized atrial arrhythmias arising in the context of AF ablation was systematically studied in the study by Hocini et al. (13). The study described a cohort of patients with localized re-entrant AT harbored within the LAA after persistent AF ablation, suggesting that the LAA may directly contribute to the maintenance of AF.

Studies with power spectral analysis and mapping to localize dominant frequency sites of activation have shown that pulmonary veins (PVs) harbor the highest-frequency sites in patients with paroxysmal

FIGURE 5 LA Volume After LAA Exclusion Using LARIAT



A significant reduction in LA volume after LAA exclusion using LARIAT is shown. **(A)** LA volume before LARIAT; **(B)** LA volume after LARIAT; **(C)** LA volume post-ablation. Abbreviations as in Figure 1.

AF, and AF can be terminated successfully by targeting radiofrequency ablation to those sites in up to 87% of patients. However, the recent data in persistent AF patients provide compelling evidence that the sources are likely re-entrant and located outside of the PVs. However, in patients with long-standing persistent AF, it is rare to find dominant frequency sites at the PV region, and this agrees well with the relatively poor success rate of PV isolation in such patients. The data suggest that in patients with persistent AF, atrial remodeling somehow augments the number of AF drivers and shifts their location away from the PV region (1). On the basis of these observations, it is speculated that the LAA might harbor some of the triggers.

The intrinsic cardiac autonomic nervous system includes clusters of ganglia, known as autonomic ganglionated plexi (GP). Stimulating the GP produces repetitive short bursts of rapid, irregular firing in the adjacent PV, initiating sustained AF. Similarly, there are GP along the groove between the left superior PV and the LAA. These GP, in addition to the poorly defined autonomic plexi in the fat pad around the LAA, play a role in arrhythmogenesis and could be affected during LAA ligation.

One of the last structures of the LA to develop a scar in patients with persistent AF is the LAA. It is likely that the electrically active LAA in these patients contributes to the substrate for AF maintenance. Typically, there is a 10% to 40% reduction in the LA volume after LAA exclusion, which essentially decreases the available LA substrate for AF propagation and perpetuation. This role of LAA in AF is in addition to it being a source of AF triggers. LAA ligation using LARIAT may eliminate this substrate and also the triggers. These 2 factors can translate into an AF reduction benefit. LAA ligation using the suture or a clip causes an acute infarct of the tissue and result in significant voltage reduction (8). Over a period of time, the LAA tissue becomes atretic and becomes a fibrotic cord. This will result in complete mechanical and electrical isolation of the LAA from the rest of the LA.

The LAA is an important site for AF initiation and maintenance, and its exclusion using a LARIAT device as an adjunct to conventional AF ablation appears to decrease the recurrence of AF in patients with persistent AF.

STUDY LIMITATIONS. The greatest limitation is the nonrandomized nature of the study. The patient characteristics were different between the groups. However, with the sicker substrate in the LARIAT group, the results are even more impressive. Furthermore, it is a relatively small study. Patients in the LARIAT group may be less likely to choose repeat ablation if there is a recurrence compared with the ablation-only group, which could have resulted in the differential redo ablation rates. These observations need to be reproduced in a larger randomized controlled study.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The LAAA has a recognized role in the initiation and maintenance of AF. Addition of LAA ligation to conventional AF ablation can improve the efficacy outcomes in patients with persistent AF and decrease the need of anticoagulation post-ablation.

TRANSLATIONAL OUTLOOK: The role of the LAA in arrhythmogenesis and thrombogenesis in AF should be discussed with patients while formulating their management plans. The impact of LAA ligation on left atrial remodeling with alterations in the reservoir and homeostatic functions needs to be further evaluated in well-designed studies.

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