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Pulmonary Vein Isolation With or Without Left Atrial Appendage Ligation in Atrial Fibrillation
The aMAZE Randomized Clinical Trial

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IMPORTANCE Left atrial appendage elimination may improve catheter ablation outcomes for atrial fibrillation.

OBJECTIVE To assess the safety and effectiveness of percutaneous left atrial appendage ligation adjunctive to catheter pulmonary vein isolation for nonparoxysmal atrial fibrillation.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, prospective, open-label, randomized clinical trial evaluated the safety and effectiveness of percutaneous left atrial appendage ligation adjunctive to planned pulmonary vein isolation for nonparoxysmal atrial fibrillation present for less than 3 years. Eligible patients were randomized in a 2:1 ratio to undergo left atrial appendage ligation and pulmonary vein isolation or pulmonary vein isolation alone. Use of a 2:1 randomization ratio was intended to provide more device experience and safety data. Patients were enrolled from October 2015 to December 2019 at 53 US sites, with the final follow-up visit on April 21, 2021.

INTERVENTIONS Left atrial appendage ligation plus pulmonary vein isolation compared with pulmonary vein isolation alone.

MAIN OUTCOMES AND MEASURES A bayesian adaptive analysis was used for primary end points. Primary effectiveness was freedom from documented atrial arrythmias of greater than 30 seconds duration 12 months after undergoing pulmonary vein isolation. Rhythm was assessed by Holter monitoring at 6 and 12 months after pulmonary vein isolation, symptomatic event monitoring, or any electrocardiographic tracing obtained through 12 months after pulmonary vein isolation. Primary safety was a composite of predefined serious adverse events compared with a prespecified 10% performance goal 30 days after the procedure. Left atrial appendage closure was evaluated through 12 months after pulmonary vein isolation.

RESULTS Overall, 404 patients were randomized to undergo left atrial appendage ligation plus pulmonary vein isolation and 206 were randomized to undergo pulmonary vein isolation alone. Primary effectiveness was 64.3% with left atrial appendage ligation and pulmonary vein isolation and 59.9% with pulmonary vein isolation only (difference, 4.3% [bayesian 95% credible interval, −4.2% to 13.2%]; posterior superiority probability, 0.835), which did not meet the statistical criterion to establish superiority (0.977). Primary safety was met, with a 30-day serious adverse event rate of 3.4% (bayesian 95% credible interval, 2.0% to 5.0%; posterior probability, 1.0) which was less than the prespecified threshold of 10%. At 12 months after pulmonary vein isolation, complete left atrial appendage closure (0 mm residual communication) was observed in 84% of patients and less than or equal to 5 mm residual communication was observed in 99% of patients.

CONCLUSIONS AND RELEVANCE Percutaneous left atrial appendage ligation adjunctive to pulmonary vein isolation did not meet prespecified efficacy criteria for freedom from atrial arrhythmias at 12 months compared with pulmonary vein isolation alone for patients with nonparoxysmal atrial fibrillation, but met prespecified safety criteria and demonstrated high rates of closure at 12 months.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02513797

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Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A complete list of investigators in the aMAZE trial appears in Supplement 4.

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Atrial fibrillation is evolving as a global public health concern with clinical, social, and economic implications.[1] Catheter ablation has changed the atrial fibrillation therapeutic paradigm.[2] Although there is consistent success treating paroxysmal atrial fibrillation using pulmonary vein isolation, outcomes for nonparoxysmal atrial fibrillation are suboptimal.[2,3] This observation may be related to adverse atrial remodeling (including increased left atrial volume and scar) associated with nonparoxysmal forms. Adjunctive ablation targeting sites outside the pulmonary veins (complex fractionated electrograms, rotors, left atrial scar, ganglionated plexi, and empirical anatomic block lines) have had variable success and are not superior to pulmonary vein isolation alone.[2,4,5]

The LARIAT left atrial appendage exclusion system is a novel percutaneous device that places an epicardial suture at the left atrial appendage neck, resulting in left atrial appendage necrosis and resorption.[2,6-8] Initial experience with the device suggested that left atrial appendage elimination could produce both electrical isolation of the left atrial appendage and a reduction in left atrial volume.[9,10] A nonrandomized observational study suggested a favorable effect of ligation relative to pulmonary vein isolation alone on the recurrence of atrial fibrillation after ablation.[10] To test the hypothesis that left atrial appendage exclusion is a viable adjunctive strategy to increase efficacy of pulmonary vein isolation in maintaining sinus rhythm in patients with nonparoxysmal atrial fibrillation, this trial assessed effectiveness and safety of left atrial appendage ligation plus pulmonary vein isolation for nonparoxysmal atrial fibrillation treatment.

Key Points

Question Does left atrial appendage ligation improve catheter ablation treatment of nonparoxysmal atrial fibrillation?

Findings In this randomized clinical trial of 610 adults, primary effectiveness was based on freedom from atrial arrhythmias at 12 months and was not statistically different between those receiving percutaneous left atrial appendage ligation adjunctive to pulmonary vein isolation and pulmonary vein isolation alone (64.3% vs 59.9%; difference, 4.3% [bayesian 95% credible interval, −4.2% to 13.2%]). Primary safety was met, with a 30-day serious adverse event rate of 3.4%. At 12 months after pulmonary vein isolation, there was complete closure in 84% of patients who underwent left atrial appendage, and 99% had less than or equal to 5 mm of residual communication with the left atrium.

Meaning Percutaneous left atrial appendage ligation adjunctive to pulmonary vein isolation met prespecified safety criteria, but did not meet prespecified efficacy criteria for freedom from atrial arrhythmias at 12 months compared with pulmonary vein isolation alone.

Methods

Trial Design and Oversight

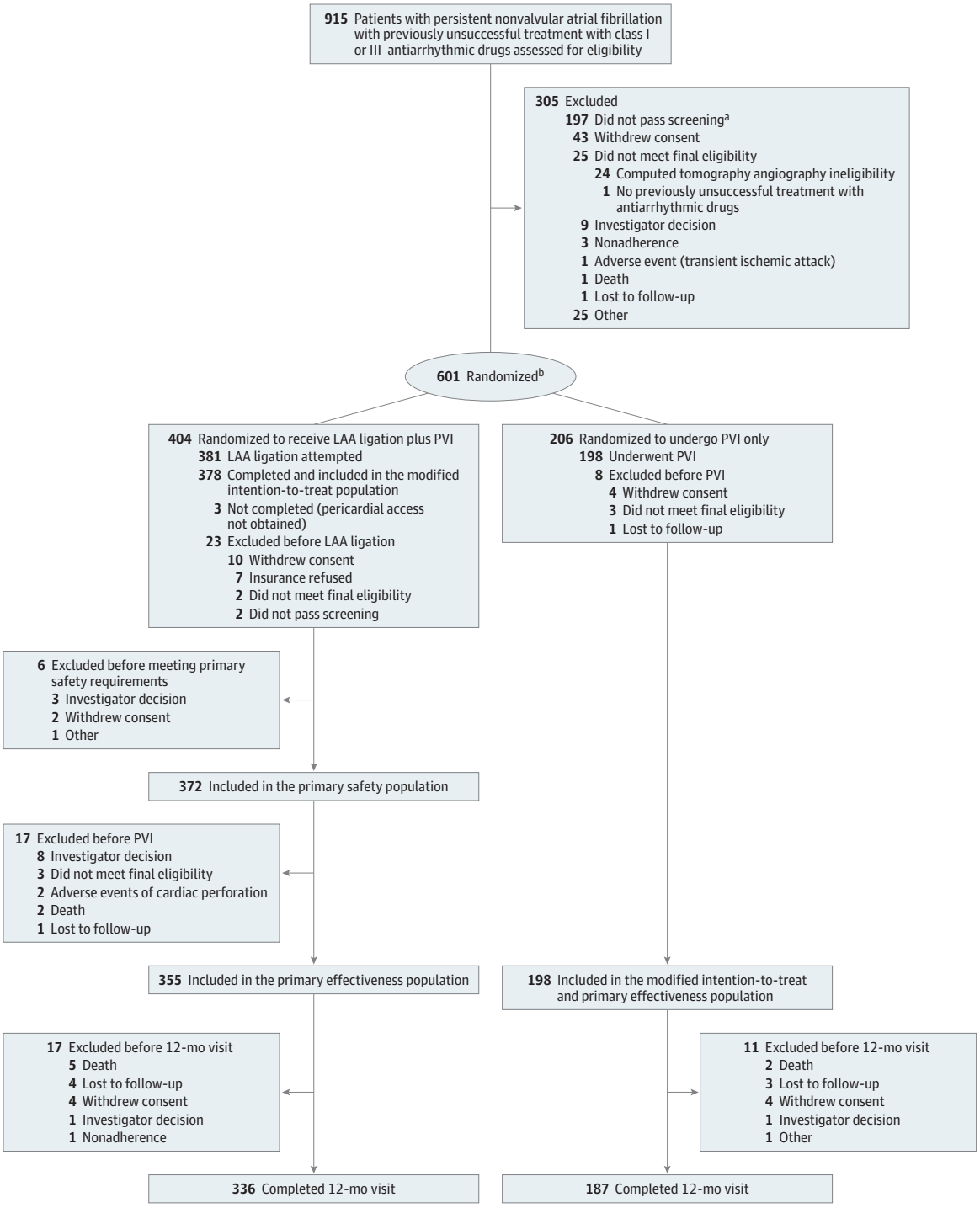
The aMAZE trial was a prospective, multicenter, open-label, randomized clinical trial of LARIAT (AtriCure, Inc) left atrial appendage ligation adjunctive to pulmonary vein isolation in patients with nonparoxysmal atrial fibrillation undergoing initial catheter ablation (NCT02513797). The device is US Food and Drug Administration 510(k)-cleared to facilitate suture placement and knot tying for use in surgical applications in which soft tissue are being approximated and/or ligated with a pretied suture loop and was investigational in the current trial for its use to percutaneously ligate the left atrial appendage as an adjunct to planned pulmonary vein isolation catheter ablation in the treatment of patients with symptomatic persistent or long-standing persistent atrial fibrillation. It is a 1-piece single-use device that delivers a pretied size "0" polyester suture loop to the epicardial heart surface for left atrial appendage ligation using a percutaneous approach. Investigators underwent comprehensive training to use the device safely. Trial rationale, design, and protocol have been published.[11] Participants had documented symptomatic nonparoxysmal atrial fibrillation (7 days to 3 years of continuous atrial fibrillation), unsuccessful treatment with at least 1 class I/III antiarrhythmic drug, and were eligible and planned to undergo catheter ablation. Key exclusion criteria included left atrial diameter greater than 6 cm, New York Heart Association class IV heart failure, body mass index greater than 40, prior opening/entry into the pericardial space, and documented thromboembolic event, myocardial infarction, or unstable angina within 3 months of enrollment. Inclusion and exclusion criteria are shown in in eTable 1 in Supplement 1.

After final eligibility adjudication, patients were randomized in a 2:1 ratio to undergo left atrial appendage ligation with pulmonary vein isolation or pulmonary vein isolation alone (control) with stratification by site and atrial fibrillation duration (**Figure 1**). The 2:1 randomization ratio was intended to provide more device experience and safety data and help boost enrollment. The randomization schedule was masked to patients, site personnel, and the study sponsor.[11] The study statistician or designee used a computerized random number generator to generate randomization schedules for all strata in advance considering center, persistent vs long-standing persistent atrial fibrillation, and left atrial volume index greater or less than 32 mL/m^2. Reasons for not passing screening are described in eTable 2 in Supplement 1.

The study was conducted at 53 US academic and nonacademic sites (eTable 3 in Supplement 1) and was overseen by the co-principal investigators and executive committee. Independent core laboratories validated rhythm monitoring outcomes and computed tomographic/transesophageal echocardiography imaging. An independent clinical events committee and data and safety monitoring committee adjudicated safety events and monitored safety and performance end points and study integrity. An external clinical research organization (Avania, Inc) managed the database, performed data analysis, and coordinated clinical events committee and data and safety monitoring committee activities. The sponsor (AtriCure, Inc) remained blinded to the aggregate data and results throughout the trial.

The trial was approved by all centers' ethics committees or institutional review boards. Written informed patient consent was obtained. Because of published differences in atrial fibrillation management and outcomes in patients of racial and

Figure 1. Flow of Participants in a Study of Pulmonary Vein Isolation (PVI) With or Without Left Atrial Appendage (LAA) Ligation in Atrial Fibrillation



At 30- and 90-day follow-up, the following assessments were used: medication review, physical examination, electrocardiogram, Atrial Fibrillation Effect on Quality of Life questionnaire, international normalized ratio, CHA_2DS_2-VASc score (30-day only), and adverse event/serious adverse event assessment. At 180- and 365-day follow-up, the following assessments were used: medication review, physical examination, 24-h Holter monitoring, electrocardiogram, transesophageal echocardiogram (365-day only), Atrial Fibrillation Effect on Quality of Life questionnaire, international normalized ratio, CHA_2DS_2-VASc score, and adverse event/serious adverse event assessment.

[a] See eTable 2 in Supplement 1 for more information.

[b] Randomized in a 2:1 ratio. Enrollment was completed on December 13, 2019. Participants who consented prior to receipt of the official enrollment closure notification were allowed to continue to be screened, randomized, and treated per protocol.

ethnic minority groups, self-classified race and ethnicity data from fixed categories were collected during consent.

End Points

There were 2 co-primary end points. The primary effectiveness end point was freedom from episodes of atrial fibrillation 12 months after pulmonary vein isolation. This was defined as no evidence of any episode of atrial arrhythmia (atrial fibrillation, tachycardia, or flutter) greater than 30 seconds in duration documented by Holter or event monitor anytime after the 90-day blanking period after index pulmonary vein isolation through 12 months as assessed by the core laboratory, no additional catheter ablation procedures after index pulmonary vein isolation for treatment of atrial arrhythmia (except right-sided atrial flutter ablation), and no requirement for new or increased dose of previously unsuccessful class I or III antiarrhythmic drug prescribed to treat atrial fibrillation after the 90-day blanking period.[12] Rhythm was assessed by Holter monitoring at 6 and 12 months after pulmonary vein isolation, symptomatic event monitoring, or any electrocardiogram tracing throughout follow-up. All patients were provided event recorders at the 90-day postblanking follow-up visit for as-needed monitoring should symptoms occur. On occurrence of symptoms, patients were instructed to contact the site coordinator and apply and wear the monitor for 7 to 30 days.

The primary safety end point was a composite of predefined serious adverse events 30 days after left atrial appendage ligation plus pulmonary vein isolation compared with a prespecified performance goal of 10%. This was based on a weighted mean of published studies of LARIAT safety experience at the time of the trial (eAppendix 14.4 in the trial protocol in Supplement 2), yielding a 6% event rate; a 4% margin was added per best clinical judgement to this observed rate to account for more rigorous monitoring and adjudication inherent to a randomized clinical trial. Primary serious adverse events were defined as serious injury to cardiac or related structure requiring surgical intervention; significant bleeding, defined as 2 or more units of packed red blood cells administered on postoperative day 1 or 2; organ/structure injury requiring intervention or fatality; pericarditis requiring surgical treatment; hemothorax requiring surgical treatment; pneumothorax requiring surgical treatment; vascular injury requiring surgical treatment, hospital admission, or packed red blood cell transfusion; pseudoaneurysm or arteriovenous fistula on imaging or direct visualization; and pericardial effusion requiring surgical intervention. Primary safety end points were consistent with contemporary left atrial appendage closure devices.

Per the trial protocol, both primary effectiveness and safety end point analyses were performed in the modified intention-to-treat population, ie, randomized patients who underwent an attempt at left atrial appendage ligation plus pulmonary vein isolation or pulmonary vein isolation and had evaluable data. Secondary end points included technical success of left atrial appendage ligation plus pulmonary vein isolation, defined as less than 1 (±1) mm diameter residual communication between the left atrium and left atrial appendage assessed by transesophageal echocardiography immediately after the procedure, at 30 days after left atrial appendage ligation plus pulmonary vein isolation, and at 1 year after pulmonary vein isolation. All secondary end points are shown in eTable 4 in Supplement 1.

Interventions

Patients randomized to receive left atrial appendage ligation plus pulmonary vein isolation underwent left atrial appendage ligation within 30 days via a percutaneous subxiphoid approach.[11,13] This requires a "dry" pericardiocentesis and transseptal catheterization to allow connection of the endocardial magnet-tipped guidewire placed in the left atrial appendage apex with the epicardial magnet-tipped guidewire for left atrial appendage stabilization. The snare is passed over the epicardial magnet-tipped guidewire to allow left atrial appendage capture with release of the pretied suture for ligation. Periprocedural anticoagulation guidelines and risk mitigations for bleeding, postprocedure inflammation, and patient discomfort are summarized in eTable 5 in Supplement 1. Patients had a 30-day follow-up visit for clinical assessment and transesophageal echocardiography. Patients underwent pulmonary vein isolation within the next 30 days.

The pulmonary vein isolation alone (control) group underwent pulmonary vein isolation within 30 days of randomization. For pulmonary vein isolation in both groups, left and right pulmonary vein antra were encircled, employing radiofrequency ablation with commercially approved contact force sensing irrigated catheters guided by electroanatomical mapping. Pulmonary vein isolation entrance and exit block were validated and adenosine was administered to exclude dormant conduction. Additional left atrial lesions were protocol deviations, but ablation of ongoing atrial tachycardia or flutter or suppression of recurrent spontaneous triggered atrial fibrillation when foci could be identified by mapping were allowed. Isoproterenol administration or burst pacing were not permitted.

Follow-Up

Follow-up visits were at 3, 6, and 12 months after pulmonary vein isolation in all patients. Antiarrhythmic drugs to suppress early recurrences were allowed but were to be discontinued after 90 days. Anticoagulation was continued throughout the trial per Heart Rhythm Society recommendations.[12,14]

Adaptive Sample Size

Uncertainty existed regarding primary end point rates and treatment effect magnitude, making it difficult to determine the sample size required for sufficient statistical power. Thus, a bayesian adaptive sample size strategy was used to allow observed data to determine the appropriate sample size and minimize risk of too large or small of a sample, in which multiple interim analyses were performed for sample size estimation, with the following 3 potential decisions: (1) stop the study for futility, (2) stop patient accrual due to predicted success then follow up all patients to 12-month out-

comes, or (3) continue enrollment.[15,16] Bayesian predictive probabilities of trial success were used for making interim sample size decisions. These predictive probability calculations accounted for observed data (effectiveness, safety, and missing data patterns), number of patients without primary end point outcomes, and number of future patients not yet enrolled. The predictive probability calculations incorporated bayesian multiple imputation using 6-month outcome data for patients lacking 12-month outcome data to better estimate probability of trial success. Interim analyses were performed after 100 patients were enrolled and 67 patients undergoing left atrial appendage ligation plus pulmonary vein isolation had complete safety data (futility stopping only based on safety end point) and then after a total of 400, 450, 500, and 550 patients were enrolled. Enrollment continued to the predetermined maximum sample size of 600 patients; 10 additional patients were randomized but did not undergo procedures before enrollment stopped.

Statistical Analysis

The primary effectiveness analysis was conducted 12 months after the last patient completed pulmonary vein isolation. Bayesian primary effectiveness and safety analyses have been published.[11,17] A bayesian analysis was conducted on the primary effectiveness end point. The total number of patients without atrial fibrillation was modeled with a binominal distribution, with a rate from a uniform beta prior distribution, resulting in a beta posterior distribution for each treatment group (see the statistical analysis plan in Supplement 3). These distributions accounted for missing data through bayesian multiple imputation, in which 6-month atrial fibrillation–free data were used to impute 12-month atrial fibrillation–free data for those with missing data. A bayesian posterior probability was obtained for the probability that the atrial fibrillation–free rate was greater in the treatment group compared with the control group. The superiority criterion would be considered met for efficacy if this probability exceeded 0.977 and the lower boundary of the 95% bayesian posterior credible interval was greater than or equal to 0.20. Per the statistical analysis plan, the study had 2 randomized stages: the limited early stage (n = 163) followed by the pivotal stage. Data from all patients enrolled and treated in both stages were included for primary analysis. Per the study protocol, an interim assessment of safety and performance data from the first 100 consecutively enrolled patients with follow-up data complete through 30-day postindex procedure was reviewed by the data and safety monitoring committee, which confirmed progression to stage 2 per criterion specified in the statistical analysis plan (Supplement 3).

The primary safety end point was modeled with a binomial distribution with a rate based on a beta distribution, resulting in beta posterior distribution. If the probability that the serious adverse events rate was less than 10% exceeded 0.957, the safety end point would be considered met. Efficacy and safety posterior threshold criterion (0.977 and 0.957, respectively) were prespecified to control the adaptive design type I error as demonstrated via extensive design simulations.

Results

Patient Characteristics

Between October 2015 and December 2019 (final follow-up visit on April 21, 2021), a total of 610 patients were enrolled and randomized to receive left atrial appendage ligation plus pulmonary vein isolation (404 patients) or pulmonary vein isolation alone (206 patients) (Figure 1). The mean (SD) duration of atrial fibrillation was 4.7 (7.7) months and 465 of 586 patients (79%) had persistent atrial fibrillation for less than 6 months. Patients undergoing pulmonary vein isolation alone were a mean of 1 year older than those receiving left atrial appendage ligation plus pulmonary vein isolation, but baseline characteristics were balanced (**Table 1**).

Treatment and Follow-Up

Of patients randomized to undergo left atrial appendage ligation plus pulmonary vein isolation, left atrial appendage ligation was attempted among 378 patients (93.6%). After pulmonary vein isolation, entrance and exit block confirmed pulmonary vein isolation in 335 of 355 patients (94%) assigned to receive left atrial appendage ligation plus pulmonary vein isolation and 185 of 196 (94%) assigned to pulmonary vein isolation alone. Additional non–pulmonary vein left atrial ablation was performed in 28 of 355 patients (7.9%) assigned to receive left atrial appendage ligation plus pulmonary vein isolation and 13 of 196 (6.7%) assigned to receive pulmonary vein isolation alone. Final follow-up was completed in April 2021.

Effectiveness

Of 610 patients randomized, 57 patients exited the study due to withdrawn consent, loss to follow-up, inability to complete the procedure, or death. Of 553 patients assessed for primary effectiveness, 523 patients (336 in the left atrial appendage ligation plus pulmonary vein isolation group and 187 in the pulmonary vein isolation alone group) had evaluable data at 365 days after pulmonary vein isolation due to withdrawn consent, loss to follow-up, or death (Figure 1). At 12 months, absolute freedom from atrial arrhythmias was 63.7% (211/331) for left atrial appendage ligation plus pulmonary vein isolation compared with 59.3% (108/182) for pulmonary vein isolation alone. The bayesian primary analysis model estimated 12-month effectiveness to be 64.3% for left atrial appendage ligation plus pulmonary vein isolation and 59.9% for pulmonary vein isolation alone, a difference of 4.3% (95% bayesian credible interval, −4.2% to 13.2%; posterior probability, 0.835) (**Table 2**, **Figure 2**). The bayesian probability did not meet the 0.977 criterion to demonstrate superiority of left atrial appendage ligation plus pulmonary vein isolation vs pulmonary vein isolation alone.

Incomplete left atrial appendage closure was not associated with efficacy. In patients with successful pulmonary vein isolation, baseline class I or III antiarrhythmic drugs were maintained at the same or reduced dose or discontinued in 69% of patients in the left atrial appendage ligation plus pulmonary vein isolation group compared with 64% of patients in the pul-

Table 1. Baseline Patient Characteristics and Medical History

Variable	LAA ligation plus PVI (n = 404)	PVI (n = 206)
Age, mean (SD), y	66.2 (8.42)	67.4 (7.45)
Median (range)	68.0 (29-80)	68.0 (40-80)
Sex, No. (%)		
Male	288 (71)	158 (77)
Female	116 (29)	48 (23)
Ethnicity, No. (%)[a]		
Not Hispanic or Latino	376 (93)	198 (96)
Hispanic or Latino	17 (4)	5 (2)
Unknown	11 (3)	3 (1)
Race, No. (%)[a]		
American Indian or Alaska Native	2 (<1)	0 (0)
Asian	8 (2)	1 (<1)
Black or African American	13 (3)	4 (2)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (<1)
White	375 (93)	200 (97)
Other	1 (<1)	0
Unknown	8 (2)	2 (<1)
Body mass index, mean (SD)	30.98 (4.546)	31.89 (4.514)
Median (range)	31.00 (19.2-42.6)	31.70 (20.7-41.0)
Prior cardioversion, No. (%)	327 (81)	83 (172)
Medical history, No. (%)[b]		
Hypertension (current or past)	332 (82)	174 (84.5)
Hyperlipidemia (current or previously resolved)	242 (59.9)	122 (59.2)
Diabetes (current or past)	75 (18.6)	48 (23.3)
Stroke (previously resolved)	26 (6.4)	14 (6.8)
Transient ischemic attack or suspected neurological event (previously resolved)	20 (5.0)	16 (7.8)
Thromboembolism (previously resolved)	17 (4.2)	7 (3.4)
Peripheral artery disease (current or previously resolved)	15 (3.7)	5 (2.4)
Smoking (current or former)	185 (46)	86 (42)
AF diagnosis, No. (%)[c]		
Persistent	365 (88)	180 (87)
Long-standing persistent	48 (12)	26 (13)
Duration of AF, mo	n = 255	n = 135
Mean (SD)	4.8 (8.3)	4.6 (6.4)
Median (range)	0.17 (0.0-8.0)	0.17 (0.0-3.0)
Duration of AF, No. (%)	n = 391	n = 195
≥7 d to <6 mo	306 (78)	159 (82)
≥6 mo to <12 mo	39 (10)	15 (8)
≥12 mo	46 (12)	21 (11)
History of AAD use, No. (%)[d]		
Class IB	2 (<1)	0
Class IC	144 (36)	74 (36)
Class III	301 (75)	154 (75)
CHA_2DS_2-VASc score		
Mean (SD)	1.6 (1.10)	1.6 (1.17)
Median (range)	1.0 (0-5)	1.0 (0-6)
NYHA classification, No. (%)[e]	n = 400	n = 205
I	59 (15)	38 (18)
II	106 (26)	45 (22)
III	31 (8)	18 (9)
No history of heart failure	204 (50)	104 (50)
Left atrium diameter, mm	n = 390	n = 200
Mean (SD)	44.11 (6.00)	45.38 (6.85)
Median (range)	44.10 (25.7-59.7)	45.60 (5.7-58.8)
Left atrial volume, mL	n = 388	n = 199
Mean (SD)	135.31 (38.35)	141.92 (39.55)
Median (range)	131.75 (45.6-283.0)	137.90 (65.2-258.0)
Left atrial volume index, mL/m^2		
Mean (SD)	63.86 (18.10)	64.94 (18.03)
Median (range)	62.94 (21.49-137.96)	63.04 (25.50-120.94)

Abbreviations: LAA, left atrial appendage; PVI, pulmonary vein isolation.

[a] The case report forms had closed categories for race and ethnicity; unknown was a selectable category on the case report form for race and ethnicity.

[b] Medical history was assessed by authorized staff at participating sites using a case report form.

[c] Persistent atrial fibrillation (AF) is defined as AF sustained for ≥7 days and ≤1 year; long-standing persistent AF is defined as continuous AF for >1 year duration.

[d] No patients had a history of class IA antiarrhythmic drug (AAD) use.

[e] New York Heart Association (NYHA) heart failure classes range from I to IV. Class I is defined as no limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, or shortness of breath. Class II is defined as slight limitation of physical activity; comfortable at rest; ordinary physical activity results in fatigue, palpitation, shortness of breath. Class III is defined as marked limitation of physical activity; comfortable at rest; less than ordinary activity causes fatigue, palpitation, shortness of breath. The exhibition of NYHA IV symptoms was an exclusion criterium for the study (unable to carry on any physical activity without discomfort; symptoms of heart failure at rest; any physical activity causes further discomfort).

monary vein isolation alone group 12 months after pulmonary vein isolation. This variable was not associated with efficacy (eTable 6 in Supplement 1). There were no significant treatment effect differences across prespecified baseline variables (eFigure in Supplement 1).

Baseline implantable rhythm monitoring devices were present in 61 of 576 patients (10.6%); mean (SD) atrial fibrillation burden rate was 59.6% (41.7%) and the median (IQGR) rate was 71% (IQR 4-100), range 0%-100%. Atrial fibrillation burden decreased in both groups after pulmonary vein isolation with no significant difference between groups at 6 or 12 months (eTable 7 in Supplement 1).

Safety

Twelve patients (3.2%) experienced primary safety events within 30 days of left atrial appendage ligation (Table 2). The bayesian safety estimate was 3.4% (bayesian 95% credible interval, 2.0% to 5.0%; posterior probability, 1.0), which met the probability criterion of 0.957 for safety compared with the performance goal of less than or equal to 10%.

Table 2. Primary Outcomes[a]

Outcome	LAA ligation plus PVI (n = 378)[b]	PVI (n = 198)[b]	Difference (bayesian 95% credible interval)	Posterior probability
Bayesian-estimated primary effectiveness through 365 d, %[c]	64.3	59.9	4.3 (−4.2 to 13.2)	0.835
Primary effectiveness rate, No./total No. (%)	211/331 (63.7)	108/182 (59.3)		
Bayesian-estimated primary safety at 30 d, %[d]	3.4		(2.0 to 5.0)	1
Primary safety, No./total No. (%)[e]	12/372 (3.2)			
Bleeding	8 (2.2)			
Serious injury to cardiac/related structure requiring surgical intervention	3 (0.8)			
Vascular injury requiring surgical treatment, hospital admission, or PRBC transfusion	1 (0.3)			

[a] Quality of life outcomes are presented in eTable 12 in Supplement 1.

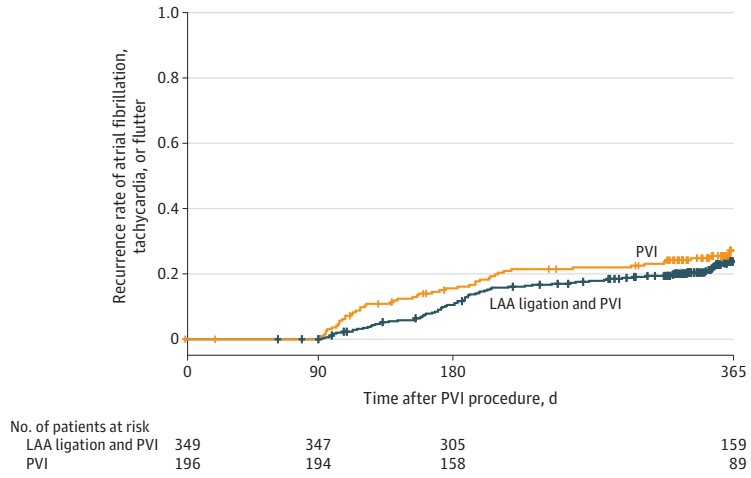
[b] Modified intention-to-treat population.

[c] Primary effectiveness outcome was freedom from episodes of atrial fibrillation >30 seconds at 12 months after pulmonary vein isolation, defined as no evidence of any episode of atrial fibrillation/atrial flutter/atrial tachycardia >30 seconds duration, as documented by Holter monitoring or event monitor at any time following the 90-day blanking period after index pulmonary vein isolation through 12 months; no additional catheter ablation procedures after index pulmonary vein isolation for treatment of atrial fibrillation/atrial flutter/atrial tachycardia (aside from ablation for right-sided atrial flutter); and no requirement for new or increased dose of previously failed Class I or III antiarrhythmic drugs prescribed to treat atrial fibrillation following the 90-day blanking period.

[d] Primary safety outcome was the incidence of significant device- or procedure-related serious adverse events at 30 days after left atrial appendage ligation. The protocol-specified primary safety events were serious injury to cardiac/related structure requiring surgical intervention; bleeding (2 or more units PRBC administered on postoperative day 1 or 2, organ/ structure injury requiring intervention, or fatal); pericarditis requiring surgical treatment; hemothorax requiring surgical treatment; pneumothorax requiring surgical treatment; vascular injury requiring surgical treatment/hospital admission or packed red blood cell (PRBC) transfusion; pseudoaneurysm/arteriovenous fistula on imaging or direct visualization; and pericardial effusions requiring surgical intervention.

[e] No patients experienced the following safety outcomes: pericarditis requiring surgical intervention, hemothorax requiring surgical intervention, pneumothorax requiring surgical intervention, pseudoaneurysm/ arteriovenous fistula, or pericardial effusion requiring surgical intervention.

Figure 2. Freedom From Recurrent Atrial Arrhythmias by Treatment Group After Ablation



Number of patients at risk was counted from the actual day after pulmonary vein isolation (PVI) and thus the Kaplan-Meier curve is not truncated at day 365. Of note, there were 7 patients across treatment groups whose final end point assessment visits were performed beyond the 365-day visit window due to various factors (including the COVID-19 pandemic). Recurrences in the initial 90-day blanking period were excluded from analysis. (This was a post hoc analysis and not prespecified per the statistical analysis plan.)

A sensitivity analysis assessed total procedural risk of left atrial appendage ligation plus pulmonary vein isolation. The rate of left atrial appendage ligation plus pulmonary vein isolation procedure-related events through 30 days after pulmonary vein isolation was 7% (26/372). The pulmonary vein isolation alone procedure-related event rate through 30 days after pulmonary vein isolation was 3.5% (7/198) (eTables 8 and 9 in Supplement 1). Two pericardial access-related adverse events occurred. Eight bleeding adverse events were due to presumed left atrial appendage perforations with pericardial effusions not requiring additional interventions. There were no significant differences between procedure-related events with left atrial appendage ligation plus pulmonary vein isolation compared with pulmonary vein isolation alone (eTable 9 in Supplement 1).

Secondary End Points

At 12 months after pulmonary vein isolation, the per-protocol (≤1 [±1] mm residual communication) closure rate was 85% (258/302); complete closure (0 mm residual communication) was 84% (253/302), closure with less than 3 mm residual communication was 93% (278/299), and closure with less than or equal to 5 mm residual communication was 99% (295/299) (**Table 3**). Two patients had thrombi after left atrial appendage ligation on 30-day transesophageal echocardiography, which resolved and were undetectable on 12-month

Table 3. Secondary Outcome of Technical Success of Left Atrial Appendage (LAA) Ligation

	Diameter residual communication, No./total No. (%)[a,b]			
Assessment point	0 mm (100% Closure)[c]	≤1 (±1) mm[d]	≤3 mm	≤5 mm
After LAA ligation plus PVI[e]	250/314 (80)	274/314 (87)	292/310 (94)	307/310 (99)
30 d after LAA ligation plus PVI	246/328 (75)	267/328 (81)	288/324 (89)	321/324 (99)
12 mo after PVI	253/302 (84)	258/302 (85)	278/299 (93)	295/299 (99)

[a] Assessed by transesophageal echocardiography color Doppler and evaluated by core laboratory (3D/2D).

[b] Data measurement categories are not mutually exclusive.

[c] Some patients (4 patients after LAA ligation, 4 patients 30 days after LAA ligation, and 3 patients 12 months after pulmonary vein isolation [PVI]) had residual leak reported, but maximum width was not captured. These patients are included in the 0 mm and ≤1 (±1) mm rows because leak was identified, but were omitted from ≤3 mm and ≤5 mm rows because width was not determined.

[d] Technical success definition per protocol.

[e] During LAA ligation plus PVI procedure, immediately after LAA ligation.

transesophageal echocardiography. There were no apparent correlations to leaks or stump greater than 10 mm; however, this incidence is too low to draw conclusions. The device-related thrombus rate was 0.5%, which is lower than the rate for endocardial closure devices (3%-4.5%).[18-20]

Secondary effectiveness analyses, including freedom from atrial arrhythmia recurrence after the 90-day blanking period through 12 months after pulmonary vein isolation based on Kaplan-Meier analysis (Figure 2), cardiac hospitalizations through 12 months after pulmonary vein isolation, and quality of life assessment, demonstrated no significant differences between groups (eTables 10, 11, and 12 in Supplement 1).

Secondary safety analyses, including the composite of all-cause stroke, systemic embolism, or all-cause death through 12 months after index pulmonary vein isolation, found no significant differences between treatment groups (eTable 9 in Supplement 1). Although there was an imbalance of deaths in the left atrial appendage ligation plus pulmonary vein isolation group, only 1 death was attributed to the left atrial appendage ligation procedure (eTable 13 in Supplement 1). The data and safety monitoring committee completed a comprehensive interim review of mortality events, concluding that there were no safety signals related to this imbalance and therefore the observed events did not present any concerns for patient risk in the left atrial appendage ligation plus pulmonary vein isolation group.

Discussion

In this multicenter randomized clinical trial of patients with nonparoxysmal atrial fibrillation, percutaneous left atrial appendage ligation adjunctive to pulmonary vein isolation did not meet prespecified efficacy criteria for freedom from atrial arrhythmias at 12 months compared with pulmonary vein isolation alone. However, percutaneous left atrial appendage ligation adjunctive to pulmonary vein isolation met prespecified safety criteria and demonstrated high rates of closure at 12 months.

This trial was based on the premise that left atrial appendage ligation creates left atrial appendage ischemic necrosis, atrophy, and resorption leading to left atrial appendage electrical isolation and a reduction of left atrial appendage tissue.[10,21] The unique pathophysiology of left atrial appendage ligation differentiates this form of left atrial appendage closure from devices that occlude the left atrial appendage, which do not lead to left atrial appendage necrosis and have been evaluated for stroke prevention rather than reduction in atrial fibrillation. The results do not support adjunctive left atrial appendage ligation plus pulmonary vein isolation in the overall nonparoxysmal atrial fibrillation population undergoing initial atrial fibrillation ablation. Discrepancies between catheter ablation–based left atrial appendage electrical isolation results and the primary efficacy outcome may lie in the population of the trial studied and differences in the approach to electrically isolate the left atrial appendage. Catheter ablation strategies target the atrial fibrillation triggers at the left atrial appendage base (ostium), which can be as high as 30% in those who do not respond to pulmonary vein isolation and are not eliminated with left atrial appendage ligation at the neck.[22,23] Study participants predominantly had early persistent atrial fibrillation, whereas prior catheter-based left atrial appendage electrical isolation trials consisted of patients with late persistent and long-standing persistent atrial fibrillation and included non–pulmonary vein substrate ablation.[9,22] Additionally, left atrial appendage ligation decreases left atrial volume, resulting in decreased left atrial critical mass, which may be beneficial with pulmonary vein isolation only in patients with nonparoxysmal atrial fibrillation with left atrial enlargement.[10]

The adverse event rate in this study is similar to procedural and 7-day complication rates from randomized trials of endocardial occlusion.[18-20] A specific adverse event inherent to LARIAT left atrial appendage ligation is related to the "dry" pericardiocentesis. The 2 pericardial access–related adverse events in the current study are similar to access-related complications for epicardial arrhythmia ablation (4%-7%, with 1%-2% requiring intervention),[24-26] but would not occur with left atrial appendage implantation or pulmonary vein isolation alone. The combined procedural adverse event rate of left atrial appendage ligation plus pulmonary vein isolation of 7% was numerically higher but not statistically different than pulmonary vein isolation alone. Adverse events were similar to reported pulmonary vein isolation adverse events[14] and were deemed by the data and safety monitoring committee to be typical of this patient population, without any clinical trends or relation to treatment device.

The 84% complete closure rate at 1 year demonstrates LARIAT left atrial appendage closure durability, which is favorable compared with left atrial appendage occlusion devices.[18] The conventional less than or equal to 5 mm residual communication was achieved in more than 99% of patients who underwent left atrial appendage ligation plus pulmonary vein isolation. The rate of leaks greater than 3 mm and less than 5 mm was 7% and unrelated to device-related thrombus or embolic events. Stroke prevention was not a study end point, but future studies for this outcome are warranted because the device appears to be effective for left atrial appendage exclusion and the safety performance goal of the trial was met.

Limitations

This study has limitations. First, neither left atrial appendage electrical isolation nor its relationship to closure were measured, although leaks were not associated with efficacy outcomes. Second, 23 of 378 patients who received left atrial appendage ligation exited the study prior to the 30-day post–left atrial appendage ligation transesophageal echocardiography. Lack of protocol-specified transesophageal echocardiography imaging planes or color Doppler imaging were study deviations. Missing transesophageal echocardiography could have affected closure rates, but likely not dramatically, because 85% of patients had evaluable transesophageal echocardiography. The primary efficacy end point of atrial arrhythmia freedom was dependent on the left atrial appendage ligation procedure, not closure success. Third, patients were unevenly distributed between 3 nonparoxysmal atrial fibrillation classifications, with most having early persistent atrial fibrillation. Investigators bias to target non-pulmonary vein substrate in late persistent and long-standing persistent atrial fibrillation may have reduced enrollment of those patients for whom left atrial appendage ligation benefit may be expected to be more prominent, thus diluting overall treatment effect.

Conclusions

There was no significant difference in freedom from atrial arrhythmias at 12 months between patients receiving left atrial appendage ligation and pulmonary vein isolation compared with pulmonary vein isolation alone. Although adjunctive left atrial appendage ligation does not provide significant benefit to pulmonary vein isolation in reducing recurrent atrial arrhythmias in the overall nonparoxysmal atrial fibrillation population undergoing initial atrial fibrillation ablation, it demonstrates durable long-term closure and primary safety events were significantly lower than the prespecified goal.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Lakkireddy reported consulting for Abbott, Acutus, AltaThera, AtriCure, Inc, Biotronik, Boston Scientific, Biosense Webster, Lifetech, Medtronic, Philips, and Sanofi Consultant during the conduct of the study. Dr Wilber reported grants from AtriCure, Inc and Sentre Heart Research for conduct of aMAZE trial to institution during the conduct of the study and grants from Biosense Webster, Abbott, and Boston Scientific and personal fees from Biosense Webster and Medtronic outside the submitted work. Dr Ellis reported receiving consulting fees from Atricure Inc. Dr Calkins reported receiving personal fees from Atricure, Inc outside the submitted work. Dr Saville reported receiving consulting fees for the statistical design and analysis of the randomized clinical trial from SentreHeart and Berry Consultants (employer) during the conduct of the study. Dr Lee reported having a patent for devices and methods for left atrial appendage closure (patent #10,258,408) issued with rights owned by University of California, San Francisco. No other disclosures were reported.

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REFERENCES

1. Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. *Int J Cardiol*. 2013;167(5):1807-1824. doi:10.1016/j.ijcard.2012.12.093

2. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149(1):1-156. doi:10.1161/CIR.0000000000001193

3. Clarnette JA, Brooks AG, Mahajan R, et al. Outcomes of persistent and long-standing persistent atrial fibrillation ablation: a systematic review and meta-analysis. *Europace*. 2018;20(FI_3):f366-f376. doi:10.1093/europace/eux297

4. Verma A, Jiang CY, Betts TR, et al; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med*. 2015;372(19):1812-1822. doi:10.1056/NEJMoa1408288

5. Cheniti G, Vlachos K, Pambrun T, et al. Atrial fibrillation mechanisms and implications for catheter ablation. *Front Physiol*. 2018;9:1458. doi:10.3389/fphys.2018.01458

6. Bartus K, Morelli RL, Szczepanski W, Kapelak B, Sadowski J, Lee RJ. Anatomic analysis of the left atrial appendage after closure with the LARIAT device. *Circ Arrhythm Electrophysiol*. 2014;7(4):764-767. doi:10.1161/CIRCEP.113.001084

7. Ellis CR, Byrd JM, Scalf SL. Ischemic necrosis of the left atrial appendage at autopsy 4 weeks following epicardial suture ligation via a sub-xiphoid approach (LARIAT). *J Interv Card Electrophysiol*. 2015;43(1):99-100. doi:10.1007/s10840-015-9993-4

8. Lee RJ, Bartus K, Yakubov SJ. Catheter-based left atrial appendage (LAA) ligation for the prevention of embolic events arising from the LAA: initial experience in a canine model. *Circ Cardiovasc Interv*. 2010;3(3):224-229. doi:10.1161/CIRCINTERVENTIONS.109.914978

9. Di Biase L, Burkhardt JD, Mohanty P, et al. Left atrial appendage isolation in patients with longstanding persistent AF undergoing catheter ablation: BELIEF trial. *J Am Coll Cardiol*. 2016;68(18):1929-1940. doi:10.1016/j.jacc.2016.07.770

10. Lakkireddy D, Sridhar Mahankali A, Kanmanthareddy A, et al. Left Atrial Appendage Ligation and Ablation for Persistent Atrial Fibrillation: The LAALA-AF Registry. *JACC Clin Electrophysiol*. 2015;1(3):153-160. doi:10.1016/j.jacep.2015.04.006

11. Lee RJ, Lakkireddy D, Mittal S, et al. Percutaneous alternative to the Maze procedure for the treatment of persistent or long-standing persistent atrial fibrillation (aMAZE trial): rationale and design. *Am Heart J*. 2015;170(6):1184-1194. doi:10.1016/j.ahj.2015.09.019

12. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace*. 2012;14(4):528-606. doi:10.1093/europace/eus027

13. Bartus K, Han FT, Bednarek J, et al. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. *J Am Coll Cardiol*. 2013;62(2):108-118. doi:10.1016/j.jacc.2012.06.046

14. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. 2017;14(10):e275-e444. doi:10.1016/j.hrthm.2017.05.012

15. Broglio KR, Connor JT, Berry SM. Not too big, not too small: a goldilocks approach to sample size selection. *J Biopharm Stat*. 2014;24(3):685-705. doi:10.1080/10543406.2014.888569

16. Saville BR, Connor JT, Ayers GD, Alvarez J. The utility of Bayesian predictive probabilities for interim monitoring of clinical trials. *Clin Trials*. 2014;11(4):485-493. doi:10.1177/1740774514531352

17. Reddy VY, Lehmann JW, Gerstenfeld EP, et al. A randomized controlled trial of pulsed field ablation versus standard-of-care ablation for paroxysmal atrial fibrillation: the ADVENT trial rationale and design. *Heart Rhythm O2*. 2023;4(5):317-328. doi:10.1016/j.hroo.2023.03.001

18. Lakkireddy D, Thaler D, Ellis CR, et al. Amplatzer amulet left atrial appendage occluder versus watchman device for stroke prophylaxis (Amulet IDE): a randomized, controlled trial. *Circulation*. 2021;144(19):1543-1552. doi:10.1161/CIRCULATIONAHA.121.057063

19. Holmes DR, Reddy VY, Turi ZG, et al; PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. 2009;374(9689):534-542. doi:10.1016/S0140-6736(09)61343-X

20. Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol*. 2014;64(1):1-12. doi:10.1016/j.jacc.2014.04.029

21. Han FT, Bartus K, Lakkireddy D, et al. The effects of LAA ligation on LAA electrical activity. *Heart Rhythm*. 2014;11(5):864-870. doi:10.1016/j.hrthm.2014.01.019

22. Di Biase L, Burkhardt JD, Mohanty P, et al. Left atrial appendage: an underrecognized trigger site of atrial fibrillation. *Circulation*. 2010;122(2):109-118. doi:10.1161/CIRCULATIONAHA.109.928903

23. Liu CF, Daian F, Goyal R, et al. The left atrial appendage ostium: hotspots for localized re-entry. *JACC Clin Electrophysiol*. 2021;7(3):333-342. doi:10.1016/j.jacep.2020.09.002

24. Della Bella P, Brugada J, Zeppenfeld K, et al. Epicardial ablation for ventricular tachycardia: a European multicenter study. *Circ Arrhythm Electrophysiol*. 2011;4(5):653-659. doi:10.1161/CIRCEP.111.962217

25. Tung R, Michowitz Y, Yu R, et al. Epicardial ablation of ventricular tachycardia: an institutional experience of safety and efficacy. *Heart Rhythm*. 2013;10(4):490-498. doi:10.1016/j.hrthm.2012.12.013

26. Baldinger SH, Kumar S, Barbhaiya CR, et al. Epicardial radiofrequency ablation failure during ablation procedures for ventricular arrhythmias: reasons and implications for outcomes. *Circ Arrhythm Electrophysiol*. 2015;8(6):1422-1432. doi:10.1161/CIRCEP.115.003202