#AHA21

Outcomes Of Adjunctive Left Atrial Appendage Ligation Utilizing The LARIAT Compared To Pulmonary Vein Antral Isolation Alone: The aMAZE Trial

David J. Wilber, MD, FAHA, FACC, FHRS| National Co-PI, Loyola University Chicago

DJ Lakkireddy, MD, MBBS, FACC | National Co-PI, Kansas City Heart Rhythm Institute

For the aMAZE Trial Investigators

American Heart Association.

Disclosures

- David Wilber MD: Abbott: Research Grant; AtriCure: Research Grant; Biosense Webster: Research Grant, Honoraria; Boston Scientific: Other (Executive Committee for Clinical Trial)
- DJ Lakkireddy MD, MBBS: Abbott: Research Grant; Atricure (Research Grant); Alta Thera (Research Grant); Biosense Webster (Research Grant); Biotronik (Research Grant); Boston Scientific (Research Grant); Medtronic (Research Grant)

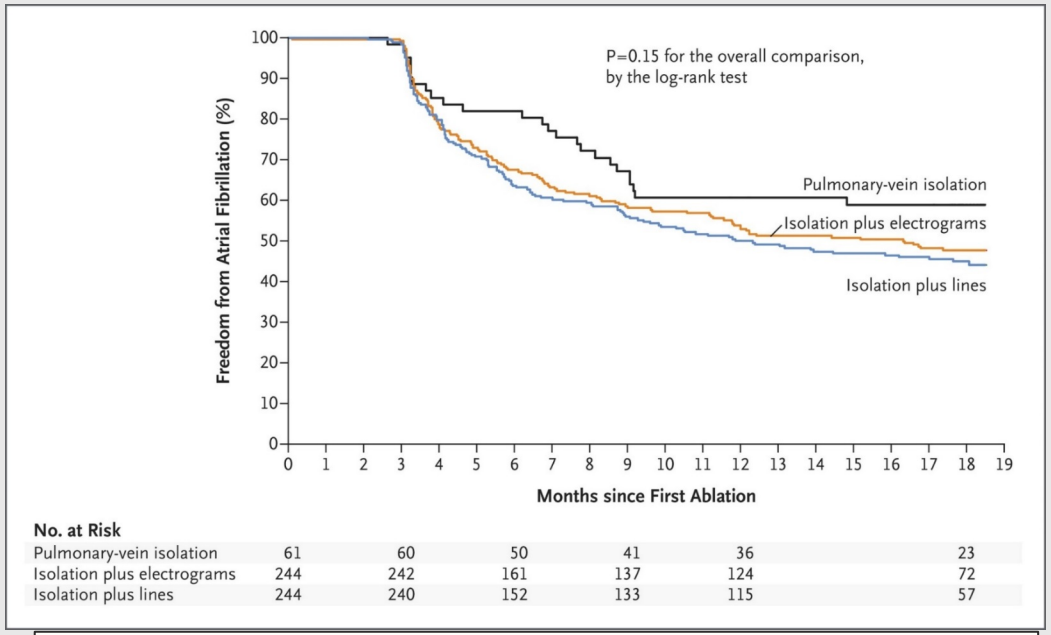
Disclaimer:

The aMAZE Trial was sponsored and funded by AtriCure, Inc.

The LARIAT LAA Exclusion System is 510(k) cleared for for use where soft tissue are being approximated and/or ligated with a pre-tied suture loop and was studied under the aMAZE Trial IDE G150107 to assess the safety and effectiveness of LAA ligation performed adjunctively to planned PVI catheter ablation in the treatment of subjects with symptomatic persistent or longstanding persistent AF. The following data and analyses have not been reviewed by the FDA.

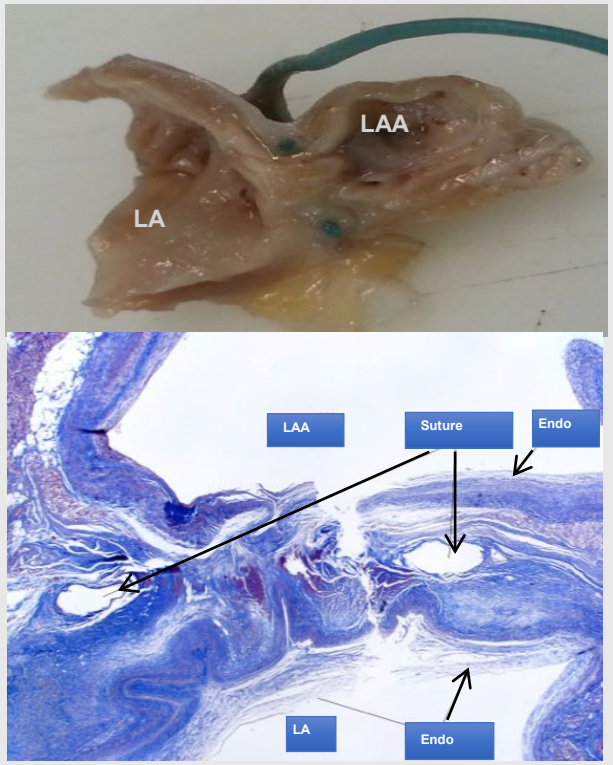
Background

- Outcomes for ablation of persistent atrial fibrillation (PersAF) by pulmonary vein antral isolation (PVAI) alone are historically suboptimal
- Adjunct strategies targeting sites outside the PV antra to improve outcomes, including foci and/or substrate in the left atrial appendage (LAA), have been the subject of recent intense investigation

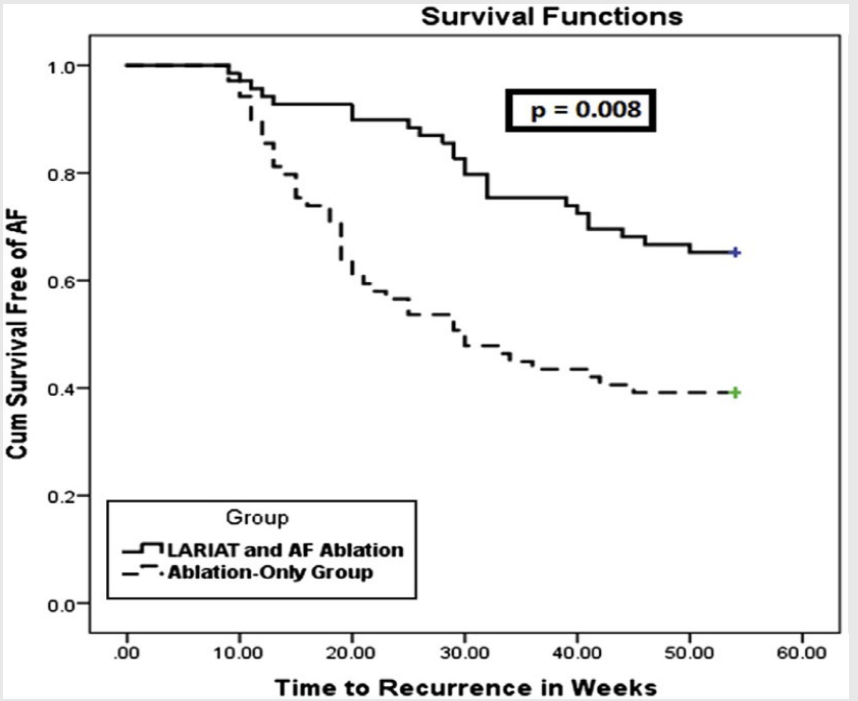


Freedom from documented atrial arrhythmia after one procedure, without antiarrhythmic drugs*	25 (41)	81 (33)	71 (29)	0.08

Verma et al, NEJM 2015



Bartus et al, Circ AE 2014

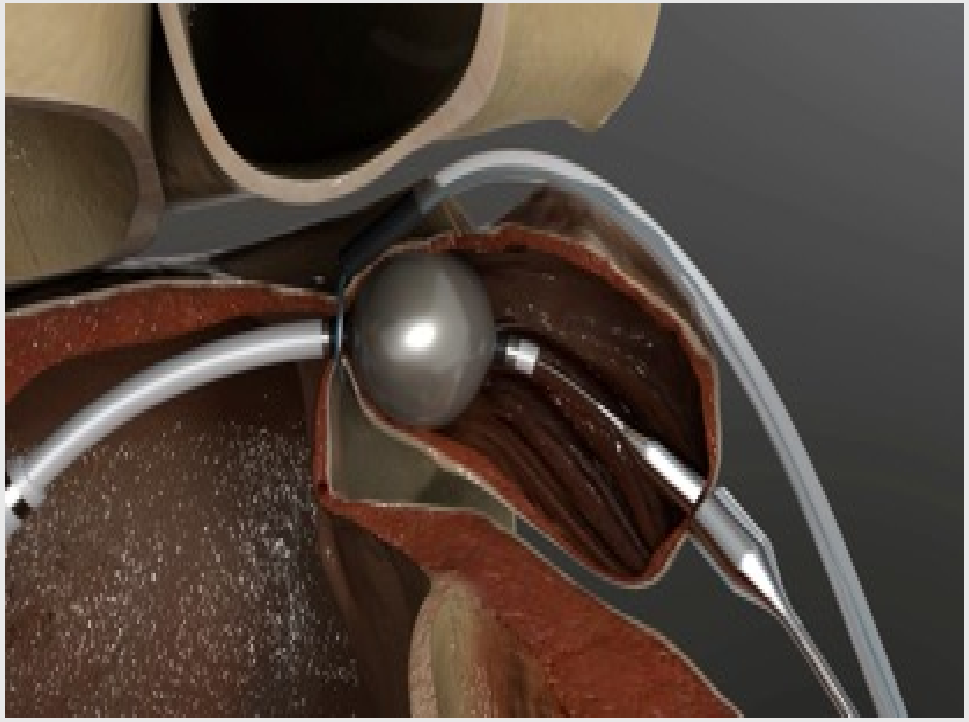


Lakkireddy et al, JACCEP 2015

Hypothesis and Trial Objectives

Hypothesis

- The LAA is a critical structure in the maintenance of persistent and longstanding persistent atrial fibrillation (AF)
- LAA ligation with the LARIAT System adjunctive to PVAI will decrease the recurrence of atrial arrythmia (AA) in patients with persistent AF



aMAZE Trial Objective

- Evaluate the additional efficacy of LARIAT LAA ligation as an adjunct to PVAI in decreasing the 12-month rate of recurrent AA following initial ablation therapy with an acceptable safety profile

Sponsor

- AtriCure, Inc. (Trial Lead: Pam Simons, VP Clinical Affairs)

Trial Design and Oversight

Design & Patient Population

Prospective, multicenter, randomized (2:1) controlled trial (NCT#02517397)

53 active U.S. sites
610 total randomized

Symptomatic persistent and longstanding persistent AF subjects (> 7 days and < 3 years continuous AF), failed AAD therapy, planned for initial catheter ablation

Bayesian Adaptive, Superiority Design (400 – 600 subjects)

Primary endpoint analyses performed in the modified intent to treat (mITT) population
mITT: randomized subjects who undergo an attempt at the assigned procedure (LARIAT or PVAI).

Endpoints

Primary Effectiveness Endpoint
Freedom from documented atrial arrythmias (AA) at 12M post PVAI with no new or increased dosage of Class I or III AAD

AA defined as atrial fibrillation, atrial flutter or atrial tachycardia lasting > 30 seconds

Rhythm evaluation: 24-hr Holter and symptomatic event monitoring

Primary Safety Endpoint
Composite of predefined 30-day post LARIAT serious adverse events compared to a performance goal (PG)

Technical Success
Successful LARIAT placement to achieve effective LAA ligation (≤1 ± 1mm diameter residual communication)

Trial design and endpoint definitions consistent with HRS 2012 Consensus Guidelines

Trial Oversight & Monitoring

National Co-Principal Investigators
David Wilber, MD
DJ Lakkireddy, MD

Executive Committee
Oversight of trial conduct

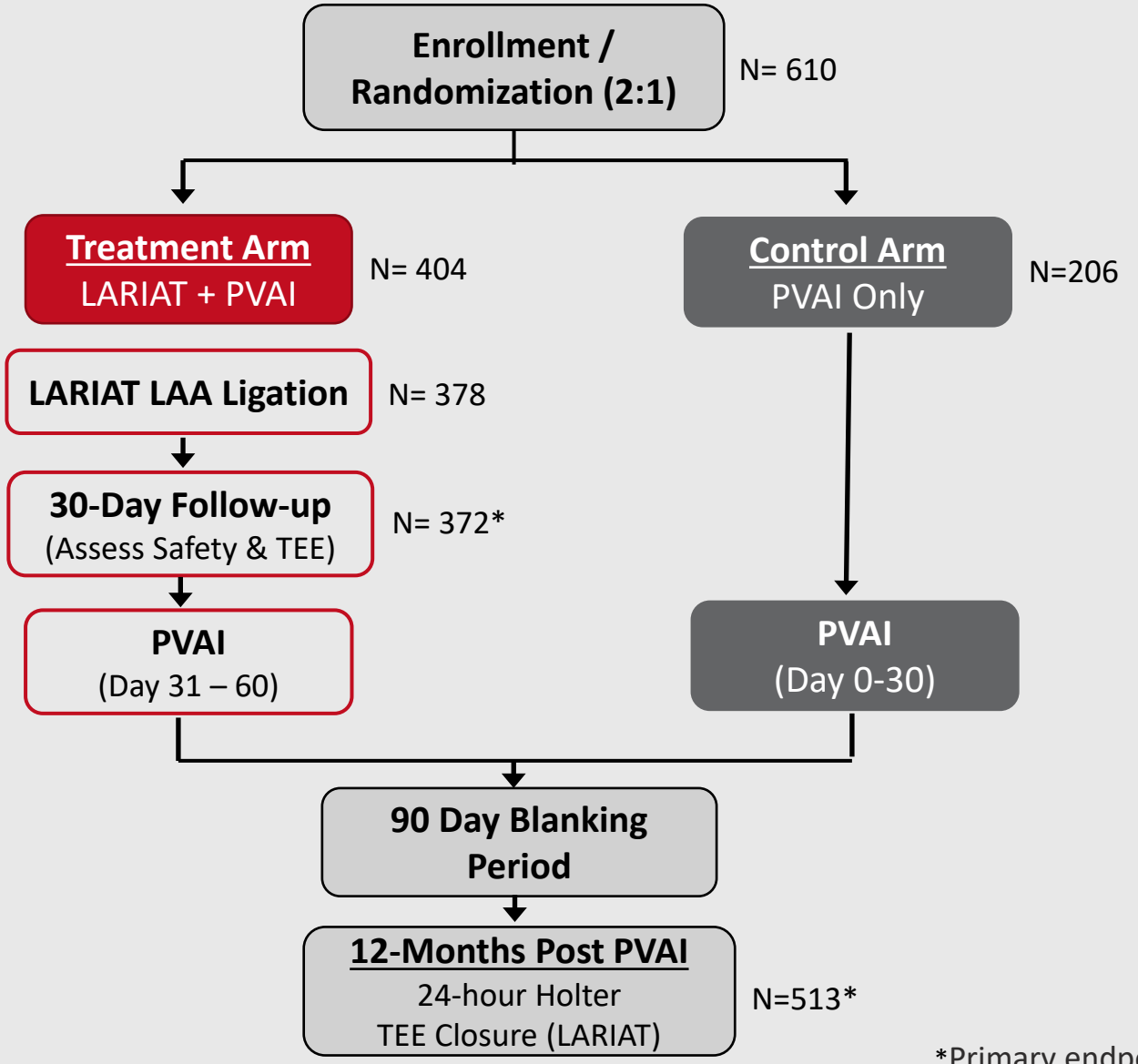
Independent Core Laboratories
Validated rhythm monitoring outcomes and CT/TEE imaging data
Cardiovascular Research Foundation
BioTel Research (Cardiocore)

Independent CEC and DMC
Adjudicated safety events, monitored safety, performance endpoints and integrity

Clinical Research Organization
Database, data analysis, CEC and DMC
Avania

Sponsor remained **blinded** to aggregate data and results throughout the trial

Treatment and Follow-Up



In both groups, PVAI performed by strict protocol:

- Use of radiofrequency, contact force sensing, irrigated tip commercially approved catheters
- After 20 min waiting period, validation of PV isolation by both entrance and exit block, and adenosine administration
- CTI line
- Additional LA lesions beyond PVAI considered protocol deviations; lesion set monitored and tracked on site

*Primary endpoint analyses performed in the mITT population with evaluable data

Key Baseline Characteristics

Characteristic	Overall (N=610)	LARIAT + PVAI (N=404)	PVAI Only (N=206)
Age (Mean ± SD)	66.6 ± 8.12	66.2 ± 8.42	67.4 ± 7.45
Female, n (%)	164 (27%)	116 (29%)	48 (23%)
BMI (kg/m^2) (Mean ± SD)	31.29 ± 4.55	30.98 ± 4.55	31.89 ± 4.51
NYHA Class II-III, n (%)	200 (33%)	137 (34%)	63 (31%)
AF Classification, n (%)*			
≥ 7 days - < 6 months	465 (79%)	306 (78.2%)	159 (81.5%)
≥ 6 months - < 12 months	54 (9%)	39 (10%)	15 (8%)
≥ 12 months - ≤ 3 years	67 (11%)	46 (12%)	21 (11%)
Left Atrial Volume (Mean ± SD)	137.55 ± 38.85	135.3 ± 38.35	141.9 ± 39.55
Hypertension, n (%)	506 (83%)	332 (82%)	174 (84.5%)
Diabetes, n (%)	123 (20%)	75 (19%)	48 (23%)

*Independently adjudicated duration in AF at time of eligibility confirmation

Primary Safety and Technical Success (LAA Closure)

- Primary safety endpoint rate at 30-days post LARIAT was 3.4% (<10% PG); 95% Bayesian CI: 2.0, 5.0]
- Primary safety endpoint was met with Bayesian posterior probability = 1 (>0.957)

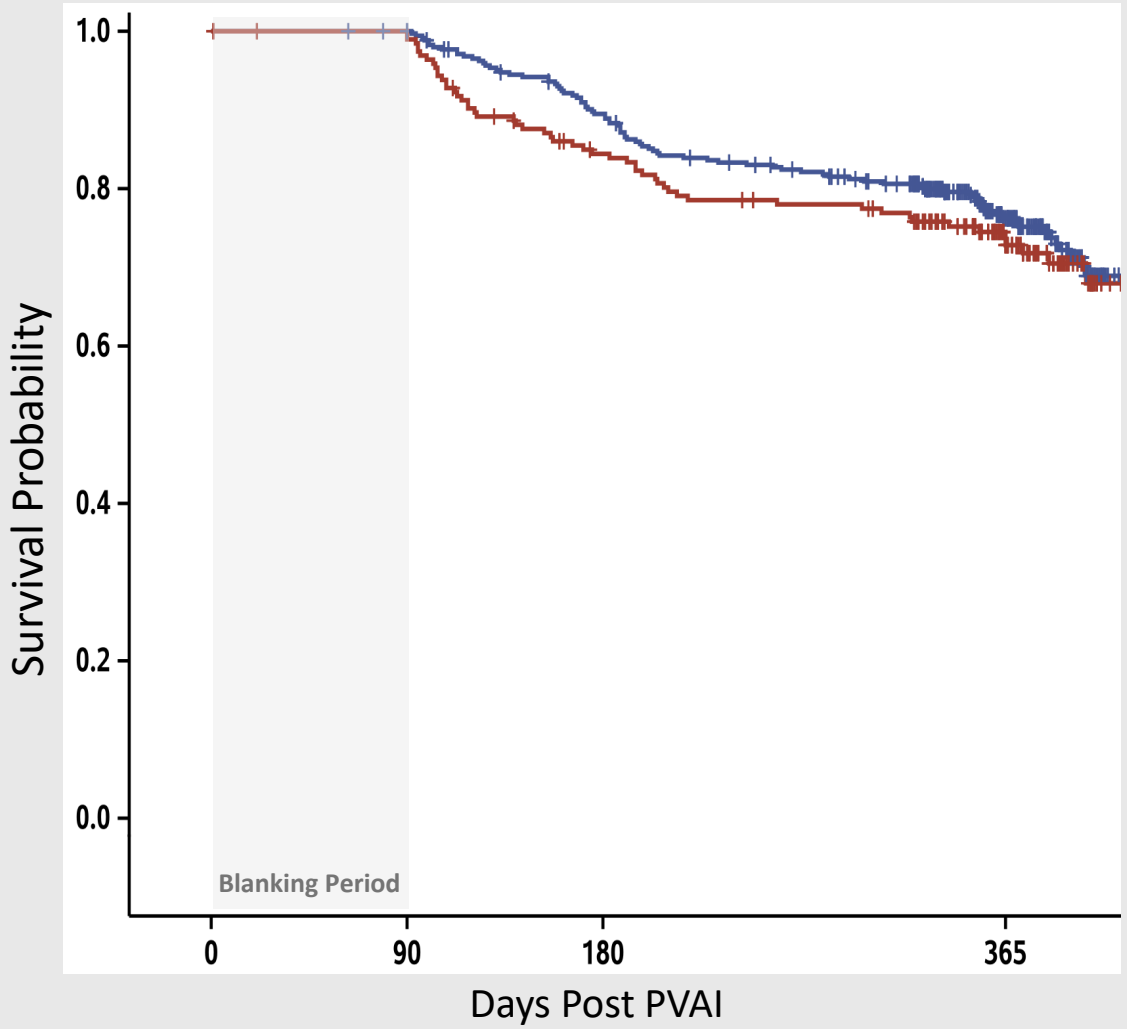
Event	% (N)
Serious Injury to cardiac/related structure requiring surgical intervention	0.8% (3)
Bleeding (≥ 2 PRBC in POD 1-2; organ structure/injury requiring intervention or fatal	2.2% (8)
Pericarditis requiring surgical intervention	0% (0)
Hemothorax requiring surgical intervention	0% (0)
Pneumothorax requiring surgical intervention	0% (0)
Vascular injury requiring surgical treatment, hospital admission or PRBC	0.3% (1)
Pseudoanerusym/Arteriovenous fistula	0% (0)
Pericardial Effusions requiring surgical intervention	0% (0)

- High LAA closure rates with LARIAT (85 – 99%) at 12 months post PVAI

Residual Communication (mm diameter) [1]	**Post LARIAT Ligation** [2]	**30-Days Post LARIAT**	**12-Months Post PVAI**
0 mm (100% Closure)	80%	75%	84%
≤ 1 ± 1 mm [3]	87%	81%	85%
≤ 3 mm	94%	89%	93%
≤ 5 mm	99%	99%	99%

[1] Assessed by TEE color Doppler, evaluated by echocardiography core laboratory (3D / 2D)
[2] During LARIAT Procedure, immediately post LAA ligation
[3] Technical Success definition per protocol

Primary Effectiveness



LARIAT+PVAI	349	347	305	159
PVAI Only	196	194	158	89

- Freedom from AA at 12-months post PVAI was **64.3%** in the LARIAT + PVAI group compared to **59.9%** for PVAI only
- Difference of 4.3%; [95% Bayesian CI: -4.2, 13.2]
- Criterion for superiority was not met; Bayesian posterior probability = 0.835
- >0.977 needed to declare primary effectiveness endpoint success

Subgroup Analyses

Prespecified subgroup analyses included primary effectiveness by baseline AF duration and LA volume

Subgroup Analysis: AF Duration

- ≥ 7 days to < 6 months (early persistent AF)
- ≥ 6 months to < 12 months (late persistent AF)
- ≥ 12 months to ≤ 3 years (longstanding persistent AF)

Duration of AF:	LARIAT + PVAI N=378 [% (n/N)]	PVAI only N=198 [% (n/N)]	Difference (%)	P-value
Early Persistent	66.0% (165/250)	58.5% (83/142)	7.5	0.084
Late Persistent	64.5% (20/31)	85.7% (12/14)	-21.2%	0.970
LS Persistent	52.4% (22/42)	61.1% (11/18)	-8.7%	0.817

Freedom from AA in the early persistent subgroup (79% of overall population):

- 66% with LARIAT + PVAI compared to 58.5%; difference of 7.5%
- P-value = 0.084 [95% Bayesian CI: -0.022, 0.174]; posterior probability = 0.931

Subgroup Analysis: Short persistent AF and LA volume

LA Volume < 133 cm^3 (median)			
LARIAT + PVAI N=186 % (n/N)	PVAI Only N=91 % (n/N)	Difference (%)	P-value
65.2% (86/132)	62.7% (42/67)	2.5	0.732

LA Volume ≥ 133 cm^3 (median)			
LARIAT + PVAI N=178 % (n/N)	PVAI Only N=101 % (n/N)	Difference (%)	P-value
65.8% (73/111)	53.4% (39/73)	12.4	0.093

Freedom from AA in the early persistent subgroup with increased LA volume (>133 cm^3) :

- 65.8% with LARIAT + PVAI compared to 53.4%; difference of 12.4%
- P-value = 0.093 [95% Bayesian CI: -0.021, 0.263]; posterior probability = 0.952

Summary Of Primary Results

- The LARIAT System appears to be safe, and successfully excludes the LAA in this first prospective, rigorous and independently monitored clinical trial evaluating LARIAT LAA ligation
- Adjunctive LAA ligation was not superior to PV antral isolation alone in reducing recurrent atrial arrhythmias in the overall persistent AF population undergoing initial AF ablation
- Exploratory analysis suggests that in the subgroup with early persistent AF and larger LA volumes, adjunctive LAA ligation may provide improved rhythm control.
- Further investigation is required to verify these exploratory observations.

We wish to extend our thanks to the aMAZE Trial Investigators and supporting study teams for their commitment and contribution to this important investigation.