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LARIAT Trial Updates

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Abstract

The thrombus formed within the LAA is responsible for the vast (about 90%) majority of strokes. Anticoagulation, although effective therapy for stroke prevention is not feasible in a significant minority of patients due to various reasons. Two percutaenous LAA exclusion techniques have been developed in an effort to decrease risk for stroke: endocardial closure/plugging of the LAA (Watchman, Amplatzer devices) and epicardial LAA ligation (LARIAT). The aim of this study is to review the trial data to date for the LARIAT device.

The LARIAT suture has been used in more than 4500 patients with high success of LAA complete closure (92-100%), mostly in the patients unable to take anticoagulation and in a small minority as antiarrhythmic option. The LARIAT technique has evolved with a change in pericardial access method that resulted in dramatic improvement of safety. LAA closure performance with LARIAT system seems to be similar to Watchman device, with small leaks during follow-up in 6-24% of the cases, which do not to correlate with thrombo-embolic events. LAA has been proven to play an important triggering role in patients with persistent atrial fibrillation. Small studies had shown that LAA ligation with LARIAT could terminate persistent atrial fibrillation and possible improve ablation success. Ongoing aMAZE randomized trial is studying if LAA ligaiton using LARIAT suture leads to improved atrial fibrillation ablation success.

Available data suggests that LAA closure using LARIAT epicardial suture is a good alternative for stroke risk reduction in patients who are unable to be on anticoagulation therapy. LARIAT system might improve success of AF ablation for patients with persistent and long persistent AF, pending the results of the ongoing a MAZE trial.

Introduction

The left atrial appendage (LAA) has been considered "the most fatal attachment" of the human body. In patients with non-valvular atrial fibrillation (AF) it is well accepted, based on surgical and transesophageal echocardiography (TEE) studies, that thrombus formed within the LAA is responsible for the vast (about 90%) majority of strokes[1]. The LAA anatomy, with different morphologies, presence of pectineate muscles, and blood flow characteristics predispose to blood stasis and thrombus formation in patients with AF[2,3]. Anticoagulation is the mainstay therapy, and has been proven in multiple randomized trials to be very effective for prevention and treatment of LAA thrombus and to decrease the incidence of stroke. However, this approach is not feasible in a significant minority of patients because they are either non-compliant with medications, are at elevated risk of bleeding, or have already experienced significant bleeding[4].

Surgical closure of the LAA as a standalone procedure or concomitant with cardiac surgery has historically been the only option for closure of the appendage. However surgical closure has a suboptimal success (persistence of flow in LAA reported to be persistent in 30-60%); incomplete closure has been shown to be associated with subsequent thrombo-embolic events[5]. Therefore, a lot of interest has developed in two percutaenous LAA exclusion techniques: endocardial closure/plugging of the LAA (Watchman, Amplatzer devices) and epicardial LAA ligation (LARIAT). The aim of this study is to review the trial data to date for the LARIAT device.

Key Words
Lariat, Appendage Ligation, LAA Ligation

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The LARIAT (SentreHeart, Redwood City, CA) was granted 510k class II clearance by the United States Federal Drug Administration (US FDA) in June 2006 for soft tissue approximation. The system has been used to percutaneously ligate the LAA. It requires guidewires with earth magnets at their tip placed epicardially and endocardially into the LAA following transseptal puncture to facilitate delivery of a suture that snares the LAA epicardially at its ostium. The system has been used as a stroke prevention as well as an antiarrhythmic strategy.

Feasibility of LAA closure using LARIAT suture

The initial canine experience demonstrated complete LAA exclusion in all cases, with progressive LAA atrophy and endothelialization of the LAA orifice[6]. This technique arose to fill an unmet need for reduction of risk for stroke in patients unable to take long term anticoagulation.

The first in human feasibility LARIAT system study was reported by Bartus et al in 2011. Thirteen patients were enrolled; 2 patients receiving the LARIAT during cardiac surgery, 10 patients underwent successful percutaneous ligation of the LAA, and in one patient the suture could not be delivered successfully[7]. The first clinical study was reported by the same investigators from Poland. They were able to successfully deploy the device in 85 (96%) of 89 patients who were unable to take anticoagulation. One patient developed a pericardial effusion during transseptal puncture and 2

had pericardial access complications (one effusion secondary to RV puncture and one superficial epigastric artery laceration requiring cauterization). During follow-up, there were 2 unexplained sudden cardiac deaths and 2 strokes; the latter were felt to be non-embolic. At 3 months and 1 year, 95% and 98% of patients respectively had complete LAA closure confirmed by TEE[8]. This study showed that LARIAT system is a viable option for stroke prevention in patients with contraindication to anticoagulation, with high success rate and acceptable risk for complications.

Success and safety of Lariat procedure

Since these initial studies, the LARIAT has been used in more than 4500 patients in the United States alone[9], mostly in patients with a contraindication to oral anticoagulation. In the process, multiple additional studies have emerged that report on the safety and efficacy of this procedure.

The investigators from the U.S. Transcatheter LAA Ligation Consortium[10] reported the results with LARIAT LAA ligation in 154 patients with a median of CHADS2 score of 3, who underwent a Lariat procedure at one of at 8 US centers. The overall procedural success was 86%; in 9 patients the suture could not be delivered due to either pericardial adhesions, challenging anatomy or need for emergent surgery due to right ventricular perforation. Among the 145 cases in which the suture was delivered, complete LAA closure was accomplished in 133 patients (92%). In the remaining 11 (7%) patients, although there was a residual leak, it was <5 mm in all patients. However, 15 (10%) patients experienced at least one major periprocedural complication; these included major bleeding (n=14, 9%), need for emergent cardiac surgery [n=3 (2%) - 2 for right ventricular perforation and one for LAA perforation], and an in-hospital death (n=1, 0.7%) 19 days after the procedure. During TEE follow-up, a leak < 5 mm was found in 14% of patients and >5 mm in 6% of patients. Finally, a thrombus was identified in 4 (6%) patients, all successfully treated with anticoagulation wihout any sequelae.

Another multicenter series by Miller and colleagues[11] reported 41 patients with a mean $CHADS_2$ score of 3 who underwent a Lariat procedure. Acute LAA closure was achieved in 38 (93%) patients; however, the procedure was complicated by LAA perforation in 4 (9%) patients, 2 of whom required urgent open surgical repair. Pericardial effusions requiring pericardiocentesis occurred in 8 (20%) patients. They also reported early pericarditis in 7 patients and late pericarditis in 5 patients; 2 of the patients with late pericarditis required percutaneous drainage for signs and symptoms of pericardial tamponade. A TEE or CT angio performed ~ 3 months post-procedure showed a residual leak > 1mm in 24% of patients; however, in all patients, the residual leak was < 5 mm. In this series, only one patient had a possible embolic complication, which manifest as amaurosis fugax.

In another multicenter international series, Sievert et al[12] reported a 99% acute closure with the Lariat system in 139 patients with a mean CHADS2 score of 2.4 who were ineligible for anticoagulation. Significant periprocedural complications occurred in 11.5%, which included 2 cardiac perforations and 1 death due to pulmonary embolism. Follow-up TEE, performed at least 1 month post-procedure, showed complete closure of LAA in 90% of patients; in the remaining, a 2-4 mm leak was observed. During a mean follow-up of 2.9 ± 1.1 years, stroke or systemic embolism was observed at a rate of 1% per year (n=4).

The results of these studies and an internal review of the MAUDE database resulted in the issuance of a safety communication by the US FDA on July 13, 2015. They described 45 adverse events reported in the database. Of concern, emergent cardiac surgery was needed in 75% of these patients with an adverse event and 6 patients died. In this communication, the FDA also reminded patients and providers that the safety and effectiveness of the Lariat procedure has not been fully established[13]. However, one of the major limitations of using the MAUDE database in drawing any form conclusions is the lack of a denominator; specifically, there is no way to know how many patients underwent the procedure during this period.

As is common with any new procedure or technique in any field, hurdles are overcome with increased experience, which impoves success and decreases complications. A high peri-procedural rate of complications observed in the initial experience with the Lariat procedure was primarily driven by inappropriate case selection, challenges obtaing epicardial access and uncertainties regarding optimal peri-procedural management. By learning through the initial experinces and making necessary modifications in technique and patient management, a dramatic improvement in safety has been observed,

Lakkireddy et al[14] reported in 2016 on a cohort of 712 patients, the largest study to date, who underwent a LARIAT LAA ligation procedure at one of 18 US centers. This study confirmed the significant improvement in procedural safety that has been observed with increased expertise. For example, a decrease in pericardial access complications occurred when a micropuncture needle replaced a large bore needle for pericardial access [Figure 1][14,15]. The use of colchicine, started prior to the procedure and continued for some time after the procedure, decreased the incidence of delayed pericarditis as well as pericardial and pleural effusions from 8.4% to 1.58%. The use of anti-inflammatory regimens is supported by the anatomic and histologic findings showing a significant inflammatory response in the LAA

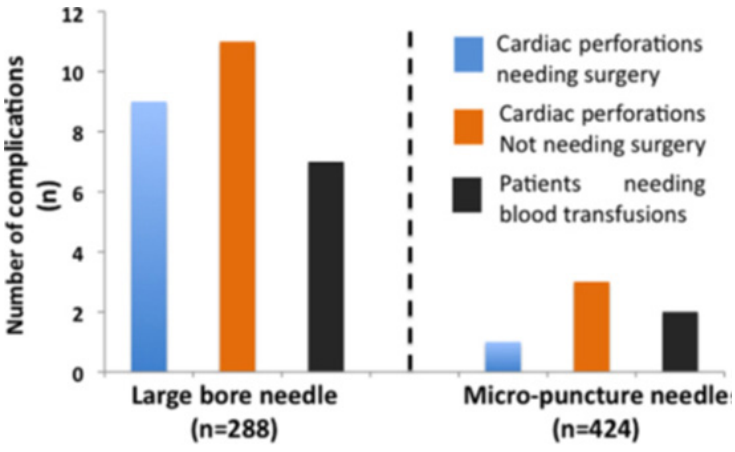

Figure 1: Difference in access site complications after the introduction of a micropuncture needle for pericardial access (Reproduced with permission from Heart Rhythm, Vol 13, No 5, May 2016)

Table 1: Acute procedural complications and the difference between the large bore (LB) Pajunk needle and the micropuncture (MP) needle during LARIAT deployment (Reproduced with permission from Heart Rhythm, Vol 13, No 5, May 2016)

Procedure variable	Total (N=712)	LB needle (n=288)	MP needle (n=424)	P
Procedure-related mortality	1	0	1	NA
Patientes needing open heart surgery	10	9	1	.002
Cardiac perforations without the need for cardiac surgery	14	11	3	.004
Patients needing transfusion	9	7	2	.02
Stroke in the periprocedural period	0	0	0	NA
Injury to superior epigastric, coronary, or internal mammary artery	4	2	2	.7
Total	38	29	9	.0001

Values are presented as counts unless otherwise indicated NA= not applicable

and the left atrium post ligation, that can possible trigger Dressler's syndrome[16]. The overall rate of acute complications decreased from 10.14% to 2.2% (p <1 0.0001, [Table 1]). The acute success of the Lariat procedure was > 95%, with a procedural mortality of only 0.14%.

Mid and long term efficacy of Lariat

Recent data have soght to compare the Lariat to a Watchman LAA closure device (Boston Scientific, Marlborough, MA) which is approved by the US FDA for as an alternative to warfarin for stroke prevention in atrial fibrillation patients at high-risk for stroke. Pillarisetti et al reported on 219 patients treated with a Watchman device and 259 patients treated with a LARIAT device[17]. Patients treated with a Watchman device were older, more likely to be male, had a lower mean CHADS2 score, were less likely to have had prior stroke or heart failure than patients treated with a Lariat device; in contrast, the Lariat patients had a larger left atrium and LAA. There were no deaths periprocedurally in either group. Significant complications included groin hematoma (n=1), pericardial effusion requiring drainage (n=2), and device embolization (n=1) in the Watchman group and cardiac tamponade requiring urgent surgical repair (n=4) in the Lariat group. Of note, all cardiac tamponades occurred in the early experience; none ocurred after switching to a micropuncture needle for pericardial access.

Post procedure, all Watchman patients received anticoagulation for at least the first 6 weeks followed by clopidogrel out to 6 months; in contrast, 30% of patients in the Lariat group received only antiplatelet drugs and only 31% of patients in Lariat group were treated with anticoagulation. Follow-up TEE at 30-90 days and 9-12 months showed that the Watchman group had a higher incidence and size of peri-device leak (21% vs 13% p = 0.019; 3.1 ± 1.1 mm vs. 2.15 ± 1.4 mm, respectively, [Figure 2]). This did not translate into differences in incidence of thrombus identification or TIA/stroke events between the groups [Table 2]. Furthermore, the neurologic events occurred in patients not on anticoagulation and did not correlate with presence of leaks or thrombus. This finding was debated in another series of 98 patients reported by Gianni et al.[18]. They report acute LAA closure in 95% of the patients with 20% leaks seen in follow-up on 3D TEE at one year (some of the leaks would have been missed on 2D TEE). There were 5 patients, all off anticoagulation, who suffered a TIA or stroke. In the 3 patients in whom TEE information was available, all had a small (<5 mm) leak; however no thrombus could be identified. Their conclusion was that incomplete occlusion of the LAA after LARIAT ligation is common [Table 3&4] and may be associated with thromboembolic events.

Table 2: Differences in the incidence of thrombus or transient ischemic attack (TIA)/stroke in patients with and without leaks in the Watchman and Lariat groups (Reproduced with permission from Pillarisetti et al., Heart Rhythm, Vol 12, No 7, July 2015)

	Watchman group (N=219)		Lariat group (N=259)	
If leak or not	Leak (n=46)	No Leak (n=173)	Leak (n=33)	No Leak n=(222)
Thrombus (n)	2	6	2	2
TIA/stroke (n)	1 (thrombus)	2	1 (no thrombus)	2
Noncerebral embolism	0	0	0	0

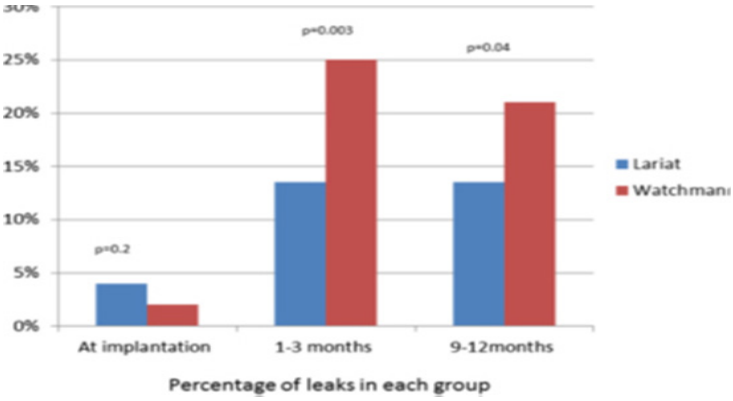

Figure 2: Comparison of prevalence of leaks in both groups at different follow-up times (Reproduced with permission from Pillarisetti et al., Heart Rhythm, Vol 12, No 7, July 2015)

In the LAA-LA AF registry an incomplete LAA ligation was found in 11 (12%) of the patients (1-3 mm in 7 patients and 4-5 mm in 4 patients) that occured in all LAA morphologies. Despite incomplete ligation, mean LAA size and volume, as measured by CT angio pre and one month post ligation, were significantly smaller beyond ligation, by 66% and 67% respectively, suggestive of LAA remodeling[19]. The remodeling of the LAA post ligation has been nicely demonstrated anatomically and histologically by Bartus K et al in 2 cases in whom the heart was explanted (one at autopsy and one after transplant) showing that LARIAT LAA ligation resulted in extensive LAA inflammation leading to fibrosis and scarring[16].

Table 3: Reported incidence of overall leaks rate after LAA ligation with the Lariat Device (Reproduced with permission from Gianni et al., JACC Interv, Vol 9, No 10, May 2016)

First Author (Year) (Ref.#)	n*	Follow-Up Imaging	Acute	Early (<6 months)	Late (6-12 months)
Bartus et al. (2013) (13)	85, 81, 65	2D TEE	4%	5%	2%
Massumi et al. (2013) (13)	20, 17, 17	2D TEE	0%	6%	6%
Stone et al. (2013) (13)	25, 22	2D TEE	0%	0%	NA
Miller et al. (2014) (25)	41, 41	2D TEE, CT	7%	24%	NA
Price et al. (2014) (26)	145, 63	2D TEE	8%	20%	NA
Pillarisetti et al.(2015) (27)	259, 259, 259	2D TEE	2%	13%	13%
This Study	98,96, 96	2D TEE, 3D TEE	5%	15%	20%

*Number of patients with fallow-up TEE across the 3 time points 2D=2-Dimentional; 3D=3-Diamentional; CT=Computer tomography; NA=not available; TEE=transesophageal echocardiography

Other potential applications of LARIAT suture

More recently it had been recognized the arrhythmogenic role of LAA in patients with AF, especially in those with persistent and long persistent AF. In a series of 987 patients, 71% non-paroxysmal AF, DiBiase et al.[20] reported impulses firing from LAA in 27% of the patients at re-do procedures. Interestingly enough, in 8.7% of the patients the LAA was the only source of arrhythmia with no pulmonary vein reconnection or other extra-pulmonary vein site triggers. Ablation and electrical isolation of the LAA showed significant decrease of AF recurrence in follow-up. This led to BELIEF trial[21] in which patients were randomized to undergo electrical LAA isolation in addition to extensive ablation vs. extensive ablation. Isolation of the LAA led to significantly increased percentage of recurrence free patients after single procedure (56% vs. 28%), and isolating the appendage in both groups at redo procedure resulted in a cumulative success in 76% vs. 56% at 24 months after an average of 1.3 procedures. However due to decrease LAA motility after electrical isolation there was an increased risk of thrombus formation and patients needed to be maintained long term on anticoagulation. With this knowledge LARIAT suture was seen as a possible therapeutic solution that could achieve both electrical isolation and stroke prevention. Closure of the LAA with LARIAT had shown acute decrease or complete elimination of LAA voltage[22]. Badhwar et al[23] reported in a series of 162 patients with persistent or long persistent AF who underwent Lariat LAA ligation that 13 patients (8%) spontaneously converted to sinus rhythm acutely or within 1-2 days and maintained sinus rhythm during a follow-up period of 15.8 ± 10.5 months (range 1-36 months), suggesting again the importance of LAA in triggering and maintaining AF. The impact of adding LARIAT closure of LAA to a conventional AF ablation procedure in patients with persistent AF was reported in a prospective observational series reported by Lakkireddy et al in LAALA-AF Registry[24].

The LARIAT cohort included 69 patients who underwent first LAA ligation using LARIAT suture followed by a conventional AF ablation procedure, mainly pulmonary vein isolation, at least 30 days afterwards. The results were compared to a sex and age matched cohort who underwent conventional ablation only during the same time frame. Freedom from atrial fibrillation or tachycardia at 12 months off antiarrhythmic therapy after 1 ablation procedure was 65% in the LARIAT group compared to 39% in the conventional group (p = 0.002) [Figure 3]. At the time of the AF ablation the LAA was electrically silent in all the patients with complete LAA ligation and in 73% of patients with incomplete LAA ligation. The patients with electrically active LAA underwent LAA isolation. Maintenance of sinus rhythm without antiarrhythmic drugs was similar in the group with leaks when compared with the group without leaks (64% vs 73%, p = 0.6)19.

Besides electrical isolation with elimination of the possible LAA triggers, there are other outcomes, unique to LAA ligation, that likely are contributing to success of AF management as revealed by DJ Lakkireddy et al in "The LAA HOMEOSTASIS STUDY"[25]. In this study blood concentrations of multiple hormones implicated in adrenergic, renin-angiotensin-aldosterone and metabolic systems, as well as natriuresis were evaluated immediately before the procedure

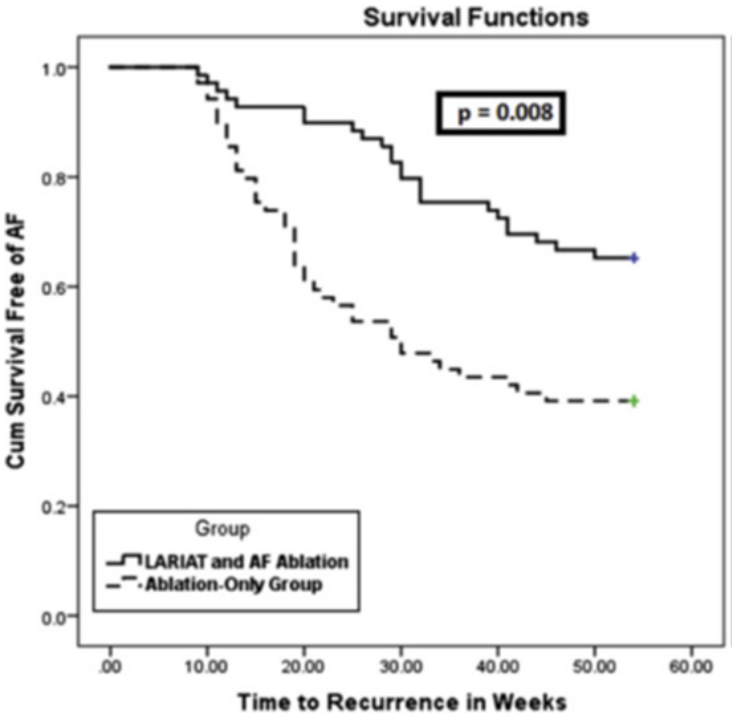

Figure 3: Survival analysis using Kaplan-Meier curve of the primary outcome in both groups (Reproduced with permission from Lakkireddy et al., JACC Clinical EP, Vol 1, No 3, 2015)

and after device deployment, at 24 h, and 3 months follow-up in 38 patients who underwent epicardial LAA ligation and 39 patients who underwent endocardial LAA occlusion. When compared with endocardial LAA closure the adrenaline, noradrenaline, aldosterone and renin were significantly lower at 24 h and 3 months. This was also associated with sustained lower blood pressure at 3 months in the epicardial ligation group (median [interquartile range] SBP 138.60 [20.10] to 117.90 [12.80] and DBP 81.90 [14.90] to 70.90 [14.95], p < 0.01 respectively), compared with no significant difference in the endocardial closure group 25. However the atrial and brain natriuretic peptide levels after initial variations were unchanged at 3 months, replicating the findings of Bartus et al in a study of 66 patients undergoing LARIAT LAA ligation[26].

Another potential benefit of LAA ligation has been shown by Badhwar et al.[27] in a small study of 22 patients which demonstrated the feasibility and safety of staged LAA ligation and pulmonary vein isolation for treatment of atrial fibrillation. In a subgroup of 10 patients whom were in sinus rhythm prior to LAA ligation there was a significant reduction of p wave duration and dispersion after LARIAT LAA ligation that persisted after pulmonary vein isolation (from 106 ± 16 msec to 97 ± 19 msec following LAA ligation and remained reduced (95 ± 12 msec following PVI). This likely demonstrates electrical remodeling, previously showing to be a predictor of ablation success[28].

These results made the basis for the ongoing aMAZE prospective trial in which the patients with persistent and long persistent AF are randomized to either LARIAT LAA ligation followed at least 30 days after by pulmonary vein isolation and cavo-tricuspid isthmus ablation or to pulmonary vein isolation and cavo-tricuspid isthmus

Table 4: Reported incidence of overall leaks rate after LAA ligation with the Lariat Device (Reproduced with permission from Gianni et al., JACC Interv, Vol 9, No 10, May 2016)

Stroke Prevention Studies	N	Procedural success	Complete occlusion < 1mm leak	Leak < 5mm	Peri-procedural complications					
					Total	Device related	Death	Cardiac tamponade	Emergent surgery	Pericardial effusion w/o intervention
Bartus K 2011	13	12/13(92%)	12/12 (100%)	0	1(8%)	1	0	0	0	0
Bartus K 2013	89	85/89(96%)	82/85(96%)	3(4%)	3(3.4%)	0	0	2	0	0
Massumi A 2013	21	20/20(100%)	19/20(95%)	1 (5%)	2(10%)	0	0	2	1	0
Price MJ 2014	154	145/154(94%)	133/145(92%)	11 (7%)	15(9.7%)	5	1	7	3	16
Miller M 2014	41	38/41(93%)	38/38(100%)	0	20/41(49%)	4	0	8	2	7
Lakkireddy DJ 2016	712	682/712(95.5%)	669/682(98%)	13(2%)	29/288(10.1%)	NR	0	11	9	0
Bartus K 2011	13	12/13(92%)	12/12 (100%)	0	1(8%)	1	0	0	0	0
					9/424(2.1%)	NR	1	3	1	0
Bartus K 2016	58	58/58(100%)	58/58(100%)	0	0	0	0	0	0	0
AF Reduction Studies										
Lakkireddy DJ2014	69	69/69(100%)	69/69(100%)	0	3/69(4%)	0	0	1	0	0
Afzal MR 2015	50	50/50(100%)	50/50(100%)	0	6/50(12%)	0	0	0	0	4

ablation alone[29]. The trial had finished the enrolment for the initial early stage of 175 patients and interim analysis by DSMC and FDA did not suggest any safety concerns or performance issues, allowing proceeding to the 2nd stage up to 600 patients. The results should be available in the next few years.

New and future developments

Currently the second generation of LARIAT system is available, LARIAT +, system that was developed from the experience and lessons learned with the initial system. The new system has a larger snare accommodating LAA diameters up to 45 mm and has now a steel braided shaft that provides increased columnar strength within the shaft allowing better torque-ability to overcome any influence of the epicardial sheath, and a platinum-iridium "L" marker has been placed in the distal tip of the LARIAT for easy detection of correct orientation under fluoroscopy. Initial experience with this new system has been reported by Bartus et al in 58 patients[30]. The acute success was high, all the patients having complete acute closure. There were no device or procedural related complications, only one late pericardial effusion at 30 days that required pericardiocentesis. In follow-up at 1 month and 3 months, TEE showed 96.3% and 92.3% LAA closure respectively, with no leaks greater than 3 mm. There were no strokes, embolic events or deaths after 12 months.

Future improvements of the system are either in evaluation or in conceptual phases including cutting of the snare prior to removal from the base of LAA and possible direct visualization of the ligation process.

Conclusion

LARIAT suture provides high success of LAA closure with long term results comparable to FDA approved Watchman device. Available data suggests that LAA closure using LARIAT epicardial suture is a good alternative for stroke risk reduction in patients who are unable to be on anticoagulation therapy. With experience and technique change safety of the procedure improved dramatically. LARIAT system might improve success of AF ablation for patients with persistent and long persistent AF, pending the results of the ongoing aMAZE trial.

Conflict of interest

None.

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