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Safety and Procedural Success of Left Atrial Appendage Exclusion With the Lariat Device

A Systematic Review of Published Reports and Analytic Review of the FDA MAUDE Database

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IMPORTANCE The Lariat device has received US Food and Drug Administration (FDA) 510(k) clearance for soft-tissue approximation and is being widely used off-label for left atrial appendage (LAA) exclusion. A comprehensive analysis of safety and effectiveness has not been reported.

OBJECTIVES To perform a systematic review of published literature to assess safety and procedural success, defined as successful closure of the LAA during the index procedure, of the Lariat device. We performed a formal analytic review of the FDA MAUDE (Manufacturer and User Facility Device Experience) database to compile adverse event reports from real-world practice with the Lariat.

DATA SOURCES For the systematic review, PubMed, EMBASE, CINAHL, and the Cochrane Library were searched from January 2007 through August 2014 to identify all studies reporting use of the Lariat device in 3 or more patients. The FDA MAUDE database was queried for adverse events reports related to Lariat use.

DATA EXTRACTIONS AND SYNTHESIS Data were abstracted in duplicate by 2 physician reviewers. Events from published literature were pooled using a generic inverse variance weighting with a random effects model. Cumulative and individual adverse events were also reported using the FDA MAUDE data set.

MAIN OUTCOMES AND MEASURES Procedural adverse events and procedural success.

RESULTS In the systematic review, 5 reports of Lariat device use in 309 participants were identified. Specific complications weighted for inverse of variance of individual studies were urgent need for cardiac surgery (2.3%; 7 of 309 procedures) and death (0.3%; 1 of 309 procedures). Procedural success was 90.3% (279 of 309 procedures). In the FDA MAUDE database, there were 35 unique reports of adverse events with use of the Lariat device. Among these, we identified 5 adverse event reports that noted pericardial effusion and death and an additional 23 reported urgent cardiac surgery without mention of death.

CONCLUSIONS AND RELEVANCE This review of published reports and case reports identified risks of adverse events with off-label use of the Lariat device for LAA exclusion. Formal, controlled investigations into the safety and efficacy of the device for this indication are warranted.

Invited Commentary
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Atrial fibrillation (AF) has an estimated prevalence of 2.7 to 6.1 million people in the United States.[1] Patients with AF have a 5-fold increased incidence of embolic stroke,[2] the risk of which has traditionally been managed with warfarin therapy.[3] However, warfarin elevates the risk of bleeding, has a narrow therapeutic range requiring regular monitoring of coagulation levels, and has high discontinuation rates.[4,5] Novel oral anticoagulants circumvent some of these issues but have led to new concerns including persistently elevated bleeding risk,[6] higher expense, and a current lack of readily available direct-acting antidotes.[7]

Ninety percent of thrombi causing AF-related strokes arise from the left atrial appendage (LAA).[8] Many of the limitations of oral anticoagulant use could theoretically be overcome with minimally invasive closure of the LAA, a strategy reportedly associated with risk reduction for strokes comparable to warfarin, without the concomitant increase in risk of bleeds.[9] In March 2015, the US Food and Drug Administration (FDA) approved the Watchman device (Boston Scientific Corp) for minimally invasive LAA closure after completion of two pivotal randomized clinical trials designed to demonstrate safety and efficacy of the device in comparison to warfarin therapy.[9,10] US trials are being planned for other devices that are mechanistically similar.[11-13]

A novel technique has been developed for LAA closure using the Lariat snare device (SentreHEART Inc), which has received FDA 510(k) clearance for the approximation of soft tissue.[14] This device has been adopted for transcatheter LAA exclusion in patients with atrial fibrillation through a unique epicardial approach. However, FDA 510(k) clearance does not require clinical testing of the Lariat device for the specific indication under consideration. Clearance was predicated on demonstration of "substantial equivalence" with existing devices used for suture placement during other types of surgery. We performed a systematic review of published reports of adverse events and procedural success seen with Lariat use and also queried the FDA Manufacturer and User Facility Device Experience (MAUDE) database to identify adverse events reported from real-world clinical practitioners using the Lariat device.

Methods

Systematic Review of Published Literature

Safety and efficacy data from published reports evaluating the Lariat device were compiled by 2 physician reviewers (S.C. and J.G.). The primary efficacy end point was defined as successful closure of the LAA during the index procedure with the Lariat device. Safety end points were initially defined as cardiac perforation, pericardial effusion, pericardial effusion requiring intervention, tamponade-hemodynamic instability, hypotension, emergent resuscitation, urgent pericardiocentesis, urgent cardiothoracic surgery, urgent need for cardiopulmonary bypass, left atrial laceration, stroke, and death. Published reports on safety were found by performing a keyword search without language restrictions in PubMed, EMBASE, CINAHL, and the Cochrane Library by using the keywords "Lariat," "FindrWIRZ," "EndoCATH," "SofTIP," "TenSURE," and "SureCUT" with, and without the phrases "suture," "snare," "left atrial appendage occlusion," "left atrial appendage exclusion," and "left atrial appendage closure," for the period January 2007 through August 2014, to identify all published literature reporting outcomes associated with the use of the Lariat device. "FindrWIRZ," "EndoCATH," "SofTIP," "TenSURE," and "SureCUT" are proprietary names for various devices needed to perform LAA exclusion with the Lariat snare. To include formal peer-reviewed research endeavors and avoid isolated case reports, we excluded reports of less than 3 cases and unpublished abstracts. We carefully evaluated studies for partial or complete patient overlap and included only studies with completely unique, nonoverlapping data sets. Given the lack of formal evaluations of the Lariat with prespecified end points, it was noted that reporting of many of the above end points was unreliable and nonstandardized between studies. Therefore, adverse events were grouped into 2 categories representing the most severe and reliably ascertainable complications of the procedure: in-hospital death and need for urgent cardiac surgery.

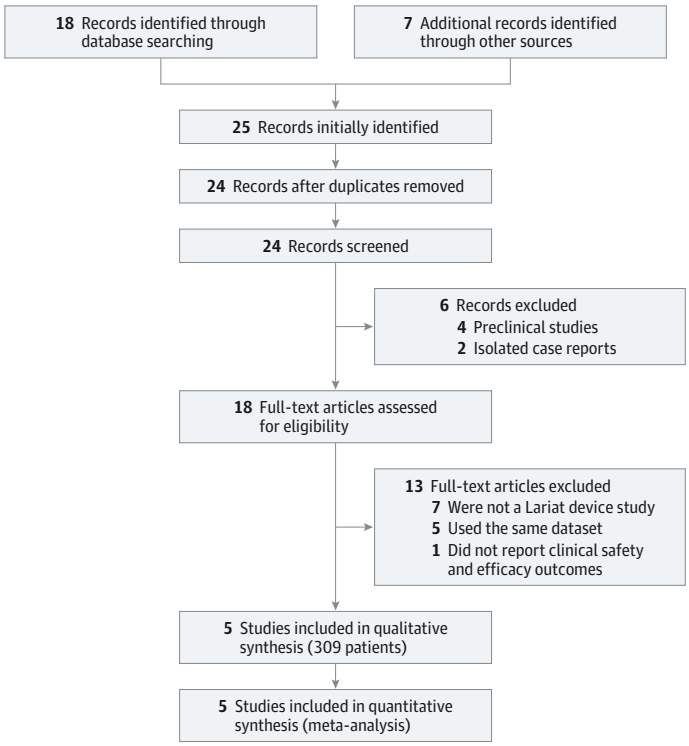
Rates of adverse events reported in each study were pooled by weighing each study by the inverse of the variance (1/standard error [SE]^2) and were combined with a generic variance approach using a random-effects model, as recommended in the Cochrane Handbook of Systematic Reviews,[15] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement.[16] Study quality was appraised with the validated Newcastle-Ottawa scale for observational studies.[17]

Query of the MAUDE Database

The MAUDE database is a searchable online database of medical device reports received by the FDA. Medical device reports are submitted by both mandatory (eg, manufacturers) and voluntary (eg, physicians) reporters. These MDRs serve as a passive surveillance tool to monitor device performance and potentially detect adverse events associated with device use. The information submitted by reporters has limitations, including the possibility of inaccurate or incomplete data. In addition, most reports are not verified through objective, independent assessment mechanisms. The prevalence and incidence of adverse events cannot be determined through the MAUDE database because events may be underreported and total number of devices used is not known.

We performed a review of complications associated with the Lariat device using the MAUDE database. In the online MAUDE database query form, the keywords "Lariat," "FindrWIRZ," "EndoCATH," "SofTIP," "TenSURE," and "SureCUT" were entered in the device field, and the keyword "SentreHeart" was entered into the manufacturer field. The date range of January 2007 through July 2014 was specified, and the search was last performed on August 12, 2014. This period was expected to include all Lariat device adverse events. All other query fields were left blank. When multiple complications were listed in the same report, each complication was tabulated separately in a standardized data collection spreadsheet.

Figure. Search Strategy and Study Selection as per PRISMA Checklist



Complications were initially separated into the aforementioned 11 prespecified categories but were then grouped into 2 categories matching those in the systematic review: in-hospital death and need for urgent cardiac surgery. We additionally classified each reported complication based on if it was attributable to the "FindrWIRZ," "Lariat," or "TenSURE" devices by the submitter of the MAUDE report. "FindrWIRZ" refers to the magnetic-tipped guidewires that are placed in the LAA and pericardial space serving as the rail for the Lariat snare device. The "TenSure" device is a mechanical suture tightener used to tighten the Lariat snare. Finally, we also determined whether the LAA was eventually closed successfully during the index procedure.

Statistical Analysis

Complications were identified as discrete events and were reported as absolute numbers. Procedural success was reported as the proportion of total reported procedures that resulted in successful LAA closure during the index procedure. Finally, rates of complications attributable to FindWIRZ and the Lariat device/suture tightener were expressed as proportions of total reported adverse events and compared using the χ^2 test. Per convention, $P<.05$ was deemed to be statistically significant.

Results

All reported instances of Lariat use in the medical literature were for the indication of LAA exclusion (**Figure**). We identified 5 reports of Lariat device use in human participants (n = 309) in the published literature[18-22] that included more than 3 patients, did not have any patient overlap, and reported safety and efficacy outcomes (**Table 1**). Procedural success, defined as successful closure of the LAA during the index procedure, was 90.3% (279 of 309 procedures). Specific complications weighted for inverse of variance of individual studies were need for urgent cardiac surgery (2.3%) (7 of 309 procedures) and in-hospital death (0.3%) (1 of 309 procedures). Formal statistical tests of heterogeneity, effect estimates, and statistical tests of significance were not performed noting the single-arm nature of the published reports. Assessment of quality identified the studies to be of good quality, apart from the absence of controls (**Table 2**).

A search of the MAUDE database returned 35 unique reports of adverse events with use of the Lariat device. We identified 1 adverse event report in 2009, 8 in 2012, 19 in 2013, and 7 from January through July 2014. Five adverse event reports noted pericardial effusion and in-hospital death, 22 reported pericardial effusion with the need for urgent cardiac surgery, and 1 reported the need for urgent cardiac surgery without mention of pericardial effusion. Seven additional reports noted urgent placement of a pericardial drain to address a pericardial effusion. Procedural success during these cases was noted to be 35.5% (11 of 31 procedures), with 4 cases unable to be characterized based on the report.

The majority of complications noted were similarly attributable to the FindWIRZ magnetic wires used for device deployment and the Lariat device/suture tightener (40.0% vs 54.3%; $P = .32$), while the remainder (5.7%) could not be clearly attributed to either or the reason for the complication was unknown.

Table 1. Baseline Characteristics of the Studies in the Systematic Review

Source	No. of Centers	Sample Size, No.	Mean Age (SD), y	Male, %	Paroxysmal AF, %	Persistent/ Permanent AF, %	Prior Stroke/ TIA, %	Mean CHADS2 Score	Mean HAS-BLED Score	Complications on Warfarin Therapy, %
Bartus et al,[21] 2013	1	89	62 (10)	57	34	66	25	1.9 (1.0)	2.4 (1.1)	13
Gafoor et al,[22] 2013	1	4	84 (4.3)	75	50	50	50	3.3 (1.)	NR	25
Massumi et al,[23] 2013	1	21	73.1 (7.9)	61.9	14	86	NR	3.2 (1.2)	3.5 (1.0)	71
Price et al,[24] 2014	8	154	72.1 (9.4)	62	NR	NR	38	2.8 (1.4)	3.2 (1.2)	NR
Miller et al,[25] 2014	4	41	75 (10)	46	34	66	54	3.0 (1.3)	4.4 (1.4)	68

Abbreviations: AF, atrial fibrillation; CHADS2, congestive heart failure, hypertension, age of 75 years or older, diabetes mellitus, and stroke (clinical prediction score for stroke in patients with AF); CHF, congestive heart failure; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), drugs/alcohol concomitantly (clinical prediction score for bleeding in patients with AF treated with warfarin); HTN, hypertension; NR, not reported; TIA, transient ischemic attack.

Table 2. Newcastle-Ottawa Scale of Bias Risk for Individual Studies

	Selection					Outcome Assessment		
Trial	ROS	SOC	AOE	DOI	Comparability	AOU	DOF	AFU
Bartus et al,[21]	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Gafoor et al,[22]	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Massumi et al,[23]	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Price et al,[24]	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Miller et al,[25]	Yes	No	Yes	Yes	No	Yes	Yes	Yes

Abbreviations: AFU, adequacy of follow-up of cohorts; AOE, ascertainment of exposure; AOU, assessment of outcome; DOF, degree of follow-up was long enough for outcomes to occur; DOI, demonstration that outcome of interest was not present at start of the study; ROS, representativeness of the exposed cohort; SOC, selection of nonexposed cohort.

Discussion

In our systematic review of the reported literature and analysis of the FDA MAUDE database regarding Lariat device use, we found no reports of the Lariat being used for any purpose other than LAA closure. Our systematic review revealed a procedural success rate of 90.3% but a potentially concerning safety profile with 1 in-hospital death and 7 cases requiring emergent cardiac surgery among the 309 uniquely reported cases. Our review of the FDA MAUDE database identified a total of 5 reported deaths and 23 additional instances of urgent cardiac surgery associated with the procedure.

The FDA classifies medical devices into 3 categories. Class III devices are those deemed to pose the greatest potential harm to patients, and full premarket approval is required prior to commercial marketing. Class I and II devices (low and intermediate risk, respectively) are cleared by the FDA under the 510(k) pathway, which requires demonstration of substantial equivalence with a similar legally marketed device. The 510(k) pathway does not necessarily require rigorous assessments of device safety and efficacy with evaluations by expert panels, as is the case for class III device premarket approval.

In June 2006, the Lariat device was granted FDA 510(k) class II clearance owing to stated substantial equivalence with the Ethicon Endosuture System (Ethicon US LLC), the Genzyme Saph-Loop Ligating Loop (Genzyme Corp), and the HysteRx Liga-Loop Suture Applicator (Hysterx Inc). These devices are preformed sutures used during laparoscopic surgery and vein harvesting.[23] Importantly, the Lariat device appears to have never been used for these indications, and US and global patent applications filed in 2008 specifically sought intellectual property rights for closing the LAA.[24,25] Because the Lariat device was classified based on different indications than what it is used for in clinical practice, it may carry an inappropriate class II designation of "intermediate risk" to patients, when its actual risk to patients based on its current utilization patterns may be greater.

One indication that the Lariat device may have had greater difficulty being approved by the FDA for its current use is that other minimally invasive LAA closure technologies with intracardiac approaches have faced substantial scrutiny from the FDA,[26-29] most notably the Watchman device (Boston Scientific Corp). Although the Watchman and Lariat devices accomplish closure of the LAA through different methods (the former is purely and intracardiac device, whereas the latter is a snare that cinches the LAA from the outside of the heart in the pericardial space), they share similar degrees of procedural complexity. Both are technically demanding procedures that involve general anesthesia, dual imaging modalities of transesophageal echocardiography and fluoroscopy, and atrial transseptal puncture. The initial premarket approval application for the Watchman in 2010 was based largely on results of the 800-patient PROTECT AF (Watchman Left Atrial Appendage System for Embolic PROTECTion in Patients With Atrial Fibrillation) trial,[9] which demonstrated noninferiority against warfarin

therapy. The FDA expressed specific concerns regarding a 9.1% rate of failed device implants, 5.3% rate of pericardial effusions requiring urgent intervention, and a 1.1% rate of periprocedural stroke.[9] However, there were no periprocedural deaths in PROTECT AF in contrast to the findings from our systematic review and FDA MAUDE analysis of the Lariat device.

In addition to the aforementioned issues related to safety of the Lariat device, its efficacy as a therapy for stroke prevention is also in question. This is because the assertion that minimally invasive LAA closure clearly reduces long-term stroke rates in patients with atrial fibrillation is contentious. There was initial enthusiasm for the efficacy of the Watchman for reducing stroke rates based on findings from the PROTECT AF trial and relatively short-term results from the PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial.[30] Although more recent analyses of the PREVAIL trial raised substantial concerns about the Watchman's effectiveness for long-term stroke prevention,[31] the FDA has approved the device. While it has been posited that the Lariat may be an ideal option for patients with atrial fibrillation truly intolerant of anticoagulation, this has never been tested, and there are theoretical concerns regarding ongoing significant stroke risk due to remnant LAA stumps after the procedure.[21] Persistent communication between the LAA and left atrium has been noted in 73% of patients undergoing open surgical suture-based exclusion of the LAA.[32]

Our analysis raises a broader issue regarding the FDA new device application 510(k) clearance protocol. The FDA needs a method for reassessing the safety of a device cleared for one purpose but used frequently for a different one, as is the case for the Lariat. In the 2002 document "Determination of Intended Use for 510(k) Devices," the FDA stated that substantial equivalence is predicated on intended use of the device under consideration.[33] The document stipulates a pathway for further assessment of potential off-label device use with a 510(k) submission if suspicion arises regarding intended use that is not specified within the application. FDA reviewers are instructed to consider "whether there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device" and "if such use could cause harm to the patient or consumer."[33(p2)] A protocol exists for internal FDA review of these matters, discussion with the submitting firm, and the possible issuance of a "substantial equivalence with limitations" letter that specifies labeling limitations for anticipated off-label uses of the device.[34]

Our present analysis suggests that the Lariat device meets the aforementioned 2 criteria as it is being used exclusively in an off-label fashion that is associated with harm in some circumstances. At the time of the initial 510(k) clearance in 2006, this may have been difficult for FDA reviewers to anticipate based on the application materials provided. However, the present analysis suggests that the 510(k) clearance pathway may not be nimble enough to readdress clearance of a product based on subsequent data including patent applications, actual usage patterns, and ongoing analysis of device-related harms.[35,36]

Our analysis has limitations. The studies reported in our systematic review are uncontrolled and arise from a limited number of centers. Reports to the FDA MAUDE database have not been independently verified, and the actual incidence of adverse events with the Lariat device in general practice cannot be calculated because the denominator of procedures performed remains unknown. We did not compare the Lariat device with other devices or procedures. We did not assess publication bias. We also did not control for operator-related or companion device-related factors. Because our analysis is based on published reports and case reports, we cannot say to what extent the Lariat device is being used for its cleared indications. However, to our knowledge, our study represents the most comprehensive analysis of acute procedural safety of the Lariat device to date.

Conclusions

On the basis of our review of the data reported in the literature and our analysis of the FDA MAUDE data set, high-quality randomized clinical trials examining the Lariat as a device for LAA exclusion should be obtained before its widespread use is adopted by the medical community.

ARTICLE INFORMATION

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Study concept and design: Wilensky, Hirshfeld, Kumbhani, Giri.
Acquisition, analysis, or interpretation of data: Chatterjee, Herrmann, McCormick, Frankel, Yeh, Armstrong, Kumbhani, Giri.
Drafting of the manuscript: Chatterjee, Herrmann, Giri.
Critical revision of the manuscript for important intellectual content: Herrmann, Wilensky, Hirshfeld, McCormick, Frankel, Yeh, Armstrong, Kumbhani, Giri.
Statistical analysis: Chatterjee, Giri.
Administrative, technical, or material support: Chatterjee, Herrmann, Armstrong, Giri.
Study supervision: Wilensky, McCormick, Frankel, Armstrong, Kumbhani, Giri.

Conflict of Interest Disclosures: Dr Yeh is on the advisory board for Abbott Vascular; is a consultant for Gilead Sciences; and receives research support and salary from Harvard Clinical Research Institute. Dr Armstrong is on the advisory board for Abbott Vascular and is a consultant for Angioscore. Dr Kumbhani is a consultant for the American College of Cardiology. Dr Herrmann has received research funding for the University of Pennsylvania from Edwards Lifesciences Inc, Medtronic Inc, and St Jude Medical Inc; is a consultant for and has received research funding from Siemens Medical Inc; and has equity in Microinterventional Devices Inc. Dr Wilensky reports that he is a member of the scientific advisor boards of Cardiostem, GenWay, Soteria, and Vascular Magnetics and has equity interest in Johnson & Johnson. Dr McCormick has received research grants from Abbott Vascular Corp, W. L. Gore, and Boston Scientific Corp. Dr Hirshfeld has served as a member of the FDA Circulatory Systems Device Advisory Panel. No other disclosures are reported.

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