Catheter-Based Left Atrial Appendage (LAA) Ligation for the Prevention of Embolic Events Arising From the LAA
Initial Experience in a Canine Model

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Background—Surgical ligation of the left atrial appendage (LAA) has been shown to be an effective alternative to warfarin therapy in patients with atrial fibrillation. A novel catheter-based approach for LAA ligation was evaluated for safety and effectiveness in a canine model.

Methods and Results—A total of 26 healthy mongrel dogs underwent ligation of the LAA through a catheter-based approach. Intracardiac echocardiography and contrast fluoroscopy were used to position a marker balloon at the origin of the LAA. An over-the-wire approach was used to guide the LARIAT snare device over the LAA to enable ligation of the LAA. Sixteen dogs were euthanized acutely. The LAA was examined to assess the placement and completeness of the ligation. The remaining 10 dogs were used for long-term follow-up. The snare delivery device was able to completely capture, advance, and close the anatomic base of the LAA in all cases. In all animals, complete LAA exclusion through this closed-chest approach was achieved without complications. Chronic follow-up revealed healthy active dogs. Examination of the LAA at 7 days, 1 month, and 3 months demonstrated completely endothelialized orifice of the LAA.

Conclusions—Using a closed-chest approach in the canine model, the catheter-based snare delivery device achieved safe and reliable ligation of the entire LAA. The clinical application of this novel approach may provide an alternative to warfarin or to permanent device implants in patients with nonvalvular atrial fibrillation for the prevention of embolic events originating from the LAA. (Circ Cardiovasc Interv. 2010;3:224-229.)

Key Words: fibrillation • catheter • stroke • left atrial appendage • left atrial appendage exclusion

More than 6 million people worldwide suffer from atrial fibrillation (AF), a cardiac disorder that results in systemic emboli.1 Patients with AF are 5 times more likely to have a stroke compared with those without AF.2 It has been suggested that 90% of thromboemboli responsible for stroke in patients with AF originate in the left atrial appendage (LAA).3 Because of the association of AF with advanced age, the stroke risk increases dramatically with age. AF may be the most common cause of stroke worldwide. The efficacy of anticoagulation with warfarin in stroke risk reduction in patients with AF is well understood, yet still understudied in clinical practice because of difficulty in administration and compliance as well as risk of bleeding.4

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Since the 1940s, cardiac surgeons have used a variety of techniques to exclude the LAA.5,6 Suture ligation from the endocardial surface of the left atrium requires the use of cardiopulmonary bypass and may be associated with bleeding or injury to the circumflex coronary artery. In addition, endocardial suture ligation is incomplete in 10% to 36% of patients; the incomplete exclusion may predispose the patient to thromboembolic events.7,8 A potential reason for this high rate of incomplete exclusion is that the closure is performed while the heart is in a flaccid state on cardiopulmonary bypass. No method is available to adequately confirm or correct the completeness of closure until the heart is volume replete.

In contrast, external ligation or excision can be performed without opening the left atrium and without cardiopulmonary bypass. Such approaches may include suture ligation or use of cutting or noncutting surgical staplers.9,10 These techniques can cause troublesome bleeding if friable tissue tears.11 Despite surgical access, it is difficult to identify the anatomic origin of the appendage on the epicardial surface while the heart is beating because of its posterior location within the heart. This often leads to closure of the appendage distal from the origin of the appendage, resulting in a remnant diverticulum that may be a nidus for future thrombus formation. Furthermore, epicardial application of a purse-string suture or loop on a beating heart involves grasping the friable LAA.12 This may result in tearing of the LAA or failure to completely exclude the LAA.13
More recently, percutaneous approaches to LAA exclusion have been introduced. Several reports of preclinical data and human feasibility trials document successful endocardial application of implants and the possibility of stroke prevention.\textsuperscript{14,15} In the first prospective, randomized trial of its type, the Embolic Protection in Patients with Atrial Fibrillation study showed that in patients with AF who were candidates for warfarin therapy, device closure of the LAA was associated with a reduction in hemorrhagic stroke risk compared with warfarin. All-cause stroke and all-cause mortality outcomes were noninferior to warfarin.\textsuperscript{16} Of the patients receiving the device, 87% were able to stop warfarin therapy, leading to the conclusion that device closure of the LAA is an effective alternative to warfarin. However, safety events, particularly pericardial effusion, in the implant device group were significantly higher compared with that of warfarin. Additional risks associated with the implanted device include air embolism, device migration, pseudoaneurysm, infection, and device thrombus formation, which may limit broad adoption of the technology.\textsuperscript{17}

A percutaneous approach for the exclusion of the LAA would be more desirable than surgical LAA exclusion and may be an alternative to an LAA occlusion device. The purpose of this study was to determine the efficacy and safety of a catheter-based approach for LAA ligation.

### Methods

#### Animal Preparation

A total of 26 healthy mongrel dogs weighing 22 to 34 kg were used in the present study. Sixteen dogs underwent acute studies, whereas 10 were chronically treated. The study was approved by the LyChron Animal Research Committee (Mountain View, Calif), and all animals received humane care in compliance with the Guide for the Care and Use of Laboratory Animals.\textsuperscript{18}

The dogs underwent general anesthesia in the supine position. A 6F introducer sheath was placed in the left femoral vein to accommodate the intracardiac echocardiography (ICE) catheter. Measurements of the canine LAA were acquired using ICE to determine the maximum width of the LAA for suitability of the LARIAT device’s 40-mm loop. No dogs were excluded. The pericardium was in all animals with a 17-gauge Tuohy needle using a standard technique described in the literature for access to a healthy pericardium.\textsuperscript{19,20} A stiff Amplatz 0.035-inch guide wire with a floppy tip was placed into the pericardium, and the access was sequentially dilated to 14F. Transseptal access was gained using a standard technique for placement of the 8.5F SL1 guide catheter into the left atrium and was successful in all animals. A heparin bolus (2000 to 3000 U) was administered once transseptal access was achieved.

#### Device Components for a Catheter-Based Approach for LAA Ligation

The products used for LAA ligation consist of 3 components: (1) a 20-mm-compliant occlusion balloon, (2) 0.025-inch and 0.035-inch magnet-tipped guide wires, and (3) a 12F suture delivery device. The occlusion balloon is a unique, low profile, 20-mm occlusion balloon (EndoCATH) with echogenic properties that enables identification and landmarking of the true anatomic base of the LAA and acts as a template for LAA exclusion without the need for contrast. The EndoCATH is a highly compliant, nonlatex balloon material that is inflated to the appropriate size of the LAA apex and the 0.035-inch FindrWIRE into the pericardial space overlying the LAA apex, a 3D impression of the LAA is obtained. The magnet wires, which establish contact easily, align the endocardial and epicardial aspect of the LAA under fluoroscopy. This can be appreciated by tactile feel. Furthermore, the ability to stabilize the LAA during the procedure with the FindrWIRE eliminates the need for placing traction on or grasping of the highly friable LAA.

The third component is the snare device (LARIAT). The catheter has a 12F profile that delivers a 40-mm diameter, pretied suture loop contained on a closure snare composed of size 0 Teflon-coated braided polyester suture. There are several unique and advantageous design features of the LARIAT catheter for percutaneous LAA exclusion that provide ease-of-use, imaging compatibility, and repeatable outcomes. These include radiopaque identification of the pretied suture that allows the operator to know where the suture is at all times during delivery and deployment. The LARIAT also can be opened and closed as desired for ideal positioning without risk of suture deployment. Furthermore, the operator may preconfirm the completeness and quality of exclusion of the LAA before deployment or removal of the device. Finally, the unique method for suture release eliminates the risk of tearing or bleeding at the LAA base, adjacent structures, or vessels such as the left circumflex artery.

#### LAO Ligation Procedure

After preparation to evacuate all air, the EndoCATH occlusion balloon and FindrWIRE system consisting of a 0.025-inch guide wire were advanced together through the 8.5F SL1 transseptal catheter under fluoroscopic guidance in the anteroposterior view. The SL1 catheter enabled direct placement of the EndoCATH/FindrWIRE combination into the LAA consistently and repeatedly. Once in position, an appendagram could be performed through the guide wire lumen of the EndoCATH with the 0.025-inch FindrWIRE remaining in place because of distal side holes that allow for contrast delivery (Figure 1A). This procedure was typically performed in the anteroposterior or 30° right anterior oblique views for optimal visualization of the relevant anatomy. The purpose of this step was to confirm that the distal tip of the 0.025-inch FindrWIRE was placed into the apical region of the LAA. Once in position, the FindrWIRE was secured by closure of the rotating hemostasis valve.

The Amplatz guide wire was removed from the pericardium. The 0.035-inch epicardial FindrWIRE was back-loaded into a suture delivery device (LARIAT), and both were advanced through a 14F soft-tipped epicardial guidewire cannula. The distal tip of the LARIAT device and the FindrWIRE were advanced under fluoroscopic guidance until the magnet located on the endocardial and epicardial FindrWIRE attract and attach to each other to stabilize the LAA (Figure 1B).

The radiopaque snare of the LARIAT that contains the pretied suture was fully opened and advanced over the appendage (Figures 1C and 2A). A radiopaque marker on the distal tip of the LARIAT was aligned with the proximal marker of the EndoCATH occlusion balloon that had been positioned at the origin of the LAA. This was the initial placement for closure of the LAA.

With the snare still open around the LAA, the EndoCATH was inflated to the appropriate size of the LAA ostium and visualized using ICE and fluoroscopy. Ideal positioning of the EndoCATH was at the anatomic ostium of the LAA where the snare would be closed (Figures 1D and 2B). Because of the innovative design of the LARIAT device, suture closure without the release of the suture allows the operator to preconfirm the exclusion location and result by echocardiography (ICE), angiography, or both as well as allows for reopening and repositioning if necessary. With the snare closed, a left atriumogram was performed to confirm closure at the ostium of the LAA (Figure 1E).

On confirmation of LAA capture and closure in the desired location, the EndoCATH was reinflated before suture release. The inflated occlusion balloon acts as a template for the suture release position and ensures that slippage off of the LAA cannot happen during tightening. This procedure replaces the need for grasping or placing traction on the LAA, which has a propensity for tearing and bleeding when handled. The suture was then tightened around the LAA by retracting the suture-release actuator. Because of the closed
position of the snare during release, an atraumatic method of LAA closure occurs. Because the suture was closed with the snare around the LAA during tightening, the operator was actually removing the slack suture through the 1-way knot until release from the snare when all slack is removed, thus eliminating the risks of sawing or shearing of tissue during tightening. By using tactile feel and imaging verification, all exclusions of the LAA were successfully completed without any instances of tearing or bleeding of the LAA or any surrounding anatomic structures such as the circumflex artery.

After initial tightening of the suture, the EndoCATH was deflated and a follow-up appendagram was performed through the guide wire lumen of the EndoCATH to confirm primary closure. The EndoCATH and 0.025” FindrWIRE were removed from the LAA as a single component and withdrawn from the transseptal guide catheter. Additional tightening of the suture was performed, and the final result was confirmed with left atriagram and color duplex ICE (Figures 1F and 2C). Initially, a left atriagram was performed through the transseptal guide catheter but was later discontinued as ICE confirmation was found to be accurate, thereby reducing the use of contrast and device manipulation within the left atrium. If residual flow was observed, additional suture tightening was performed until eliminated. The LARIAT device and 0.035” FindrWIRE were then removed from the pericardium. The remote suture cutter designed for use with the system was easily advanced over the remnant suture and activated to remove the excess suture tail.

**Chronic Follow-Up Study**

Ten dogs were chronically treated with LAA ligation as described earlier for the acute evaluation. Follow-up studies were scheduled for 7 days (n=3 dogs), 1 month (n=3 dogs), and 3 months (n=4 dogs). On the day of euthanization, transseptal catheterization under fluoroscopic guidance was performed to allow for atrial pressure

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**Figure 1.** LAA ligation. A contrast dye injection through the EndoCATH balloon catheter demonstrates the position of the endocardial magnet wire at the apex of the LAA (A). End-to-end connection of the endocardial and epicardial magnet wires (B) allows advancement of the snare over the LAA (C). The balloon is positioned at the orifice of the LAA (C), assuring the closure of the snare (1 day) will result in complete ligation of the LAA (E). A left atriagram at the completion of the procedure demonstrates a smooth surface at the closure site of the ostium of the LAA (F).

**Figure 2.** ICE demonstration of the LAA. The use of ICE allows for left atrial and LAA imaging (A), placement of the balloon at the orifice of the LAA (B), and documentation with color flow Doppler that the LAA is completely ligated (C). LA indicates left atrium.
Left atrial pressures measured through transseptal catheter-
Assessment of LAA exclusion was performed at 7 days, 1 month, and 3-month follow-up animals. After completion of the echocardiography, the animals were euthanized, and a sternotomy was performed to examine the pericardium, LAA, and epicardial surface of the heart. Hearts were harvested and formalin fixed for histological examination.

Results

LARIAT LAA Exclusion
In all animals, exclusion of the LAA with the LARIAT system was accomplished without complications. Connection of the FindrWIRZ was easily achieved in all animals and ranged from 1 to 240 seconds for proper attachment. After the origin of the LAA was identified and landmarked using the occlusion balloon method described, the LARIAT was able to capture and exclude the desired target site in all cases without slippage or migration. By using the method described earlier, the LAA was captured in a single attempt in 23 of 26 animals (88%) and within 2 attempts 100% of the time. LA angiogram confirmed complete exclusion in all animals. Three animals demonstrated a diverticulum of ≤3 mm. Duplex echocardiographic imaging was not available in 1 case (animal 12), and assessment was completed by angiographic confirmation only. ICE imaging revealed complete LAA exclusion in 22 of 25 animals. A median sternotomy was performed acutely on 16 animals for post hoc assessment of results. No trauma to or bleeding of the LAA or the epicardial surface was observed. To correlate angiographic and echocardiographic exclusion findings, excision of the distal apex of the LAA was performed in all animals to observe for residual flow or incomplete exclusion (Figure 3A). No remnant flow was observed in all animals after a 10-minute verification. The animals were then euthanized and the heart removed to macroscopically examine the epicardial surface for trauma and adhesions and to access the left atrial dome to assess the endocardial exclusion results. No trauma was observed at the LAA or epicardial surface in either the 7-day or 1-month animals. It was noted that during macroscopic observation of the LAA closure (preeuthanization), the LAAs were dark in color. On removal of the LAA tip, it appeared that organized thrombus was present. Thin, hair-like adhesions from the LAA to the epicardium were observed on each of the 7-day animals. Macroscopic examination of the 7-day animals confirmed a diverticulum of ≤3 mm in 1 of the 7-day animals and complete LAA exclusion in all of the 1-month and 3-month animals. The diverticulum found in the 7-day animal also was seen with left atrial angiogram. Coronary angiograms in the 1-month and 3-month animals revealed normal coronary arteries. The animals were then euthanized and the heart removed to macroscopically examine the epicardial surface for trauma and adhesions and to access the left atrial dome to assess the endocardial exclusion results. No trauma was observed at the LAA or epicardial surface in either the 7-day or 1-month animals. It was noted that during macroscopic observation of the LAA closure (pre euthanization), the LAAs were dark in color. On removal of the LAA tip, it appeared that organized thrombus was present. Thin, hair-like adhesions from the LAA to the epicardium were observed on each of the 7-day animals. Macroscopic examination of the 7-day animals confirmed a diverticulum of ≤3 mm in the same animal identified to have a diverticulum by ICE and left atrial angiogram. Histological examination of the 7-day animals revealed endothelization at the closure site with no necrosis or inflammatory response. Macroscopic observations of the LAA closure in the 1-month animals demonstrated that all LAAs had experienced atrophy pink coloration and had begun to fuse to the left atrial wall. The 1-month animals revealed a smooth contiguous endocardial surface uniformly (Figure 4A). Histological examination of the 1-month specimens revealed completely endothelialized orifices of the LAA (Figure 4B). Macroscopic examination of the LAA closure in the 3-month animals demonstrated a continuation of the atrophic changes observed at the 7-day and 1-month time points. The LAA was almost completely incorporated into the visceral pericardium. Histological examination of the 3-month animals revealed completely endothelialized orifices of the LAA similar to the 1-month animals. There was complete absence of inflammatory reaction and a smooth epicardial covering.

Discussion
This study demonstrates the feasibility, efficacy, and safety of a novel, catheter-based LAA ligation device for the exclusion of the LAA in an animal model. The use of the magnet wires to align and stabilize the LAA allows for the snare to be
positioned at the base of the LAA, whereas positioning the balloon catheter at the orifice of the LAA enables complete ligation of the LAA. The ability of the device to completely exclude the LAA without a significant diverticulum compares favorably with surgical approaches.

With present surgical methods, achieving complete LAA exclusion requires careful attention to technique and is variable from operator to operator. A previous study of endocardial closure of the LAA at the time of mitral valve surgery, using double-row Prolene sutures, reported only a 64% rate of successful ligation. More recently, the 90% rate of successful exclusion reported by Garcia-Fernandez et al was attributed to the endocardial closure technique, which used both a purse-string and a running suture. Neither study commented about the amount of residual LAA remaining proximal to their sutures. Dominno et al reported that thrombus formation was found in the proximal portion of the LAA despite successful ligation of the distal segment. Thus, ligation at the distal portion of the LAA leaves a small basal portion of the appendage intact, which may be a nidus for thrombus formation. This finding highlights the importance of establishing a method or technique that allows reliable complete exclusion of the LAA at the ostium. Clearly to be useful for stroke prevention, a high rate of complete LAA exclusion is required. Identification of the true anatomic origin (base) of the LAA through the surgical technique can be difficult and may explain occasional incomplete LAA exclusion by the surgical approach. The catheter-based LAA ligation procedure does not use an endocardial closure technique by which it is often difficult to intraoperatively assess the true geometry of the LAA because of the decompressed status of the heart. Furthermore, there are several methods of preconfirming the result before finalization of closure with the LARIAT snare device, which has the potential to reduce incomplete exclusions. It is also believed that operator variability may be reduced by providing a prescribed method of LAA exclusion that includes a template for accurate placement. In this study, the true anatomic base of the LAA could be identified, landmarked, and excluded in all cases using the EndoCATH occlusion balloon to guide optimal suture placement.

Surgical exclusion of the LAA has long been believed to be a potential alternative to anticoagulation therapy because thrombi are known to originate in the LAA of patients with AF. Results from the prospective, randomized Watchman trial of 800 patients with 2-year follow-up demonstrated noninferiority of percutaneous occlusion of the LAA compared with warfarin treatment for patients with AF. An evaluation of both ischemic and hemorrhagic stroke reveals a lower rate (n = 15, 3.2%) in the device arm than in the control arm (n = 11, 4.5%) of this trial. Additionally, the 5-year results of the use of the percutaneous LAA occlusion device revealed an annual stroke/transient ischemic attack rate of 3.8%, which is less than the annual stroke rate of 6.6% predicted by the CHADS2 scoring system. The combination of the surgical literature and recent results of LAA occlusion devices may support the exclusion of the LAA as a viable alternative or adjunct to warfarin therapy.

Complications anticipated with placement of an implant in the friable tissue of the LAA have been reported that include the occurrence of pericardial effusions (6.6%) and thrombus formation (3.8%). In addition, residual flow around the implant was demonstrated in 7%. Furthermore, in 42% (188 of 449) of the procedures, capture, removal, and replacement of the initial device with another device were required at least once, and in ~4% (17 of 449), recapture was necessary ≥4 times. Because of the fixation of the equipment to the appendage and ability to landmark it reliably, LARIAT may overcome these technical difficulties with less propensity for injury complicated by pericardial hemorrhage. If device repositioning is necessary, it does not require additional catheter-exchange manipulations within the left atrium and appendage. Moreover, LARIAT eliminates the risk of thrombus formation and infection associated with any permanent foreign intracardiac device. Finally, Su et al reported that the orifice of the LAA is not circular, but oval, which may lead to incomplete exclusion with currently available implanted devices, suggesting that an epicardial approach to exclusion of the LAA may offer geometric advantages to an implant that occludes the LAA.

Limitations of the use of the LAA ligation device in humans may include patients with existing thromboemboli, pericardial adhesions, superior-oriented LAA, or LAA that are >40 mm. The LARIAT loop was designed to expand to 40 mm to be able to be placed over a dilated LAA. The size of the LARIAT loop was determined by review of the literature that had sized the LAA appendage in patients with chronic AF and was designed to potentially treat 90% of patients at risk for embolic events originating from the LAA.

Conclusions
The catheter-based LAA ligation procedure for percutaneous LAA exclusion using the LARIAT is safe, effective, and
compatible with present techniques and imaging used in cardiology. The catheter-based LAA ligation procedure provides a reliable means of identification, landmarking, and exclusion of the true anatomic origin of the LAA. It may provide an effective percutaneous approach for protecting patients with AF against strokes, thereby potentially eliminating the need for chronic warfarin therapy.

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References

CLINICAL PERSPECTIVE
Stroke prevention in patients with atrial fibrillation is a significant challenge. Anticoagulation with warfarin is the mainstay of therapy for most of these patients, despite the difficulty of maintaining patients in a correct therapeutic range. Anticoagulation management of these patients is particularly difficult because of bleeding risk, which usually is high in the age group characteristically at risk of atrial fibrillation. Alternative therapies that lessen the necessity of warfarin are highly desirable. Because most thromboembolic events (>90%) in atrial fibrillation originate from thrombus that develops in the left atrial appendage (LAA), exclusion of the LAA using minimally invasive percutaneous procedures may lessen the risk of stroke. Open heart surgical procedures to exclude the LAA are common; however, recurrence of LAA patency also is common. Implanted devices (Watchman, Amplatz LAA plug) are under clinical investigation. We evaluated a technique of suture closure by using percutaneous pericardial and transseptal access, magnet wires, and an alignment balloon. This approach avoids problems associated with permanent intracardiac device implantation (migration, thrombus formation, and cardiac tamponade). In the future, percutaneous LAA exclusion may prove to be a therapeutic option for patients with atrial fibrillation.
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