Prospective Clinical Study of a Novel Left Atrial Appendage Occlusion Device

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Purpose. **This Food and Drug Administration–approved investigational device exempt trial assessed the safety and efficacy of a novel device for external left atrial appendage (LAA) exclusion.**

Description. **Delivery tool and implant consisting of connectors imbedded in a compliant, soft silicone applied to the base of the LAA flush with the external wall was assessed.**

Evaluation. **Patients in this prospective, multicenter trial were undergoing elective, nonendoscopic cardiac operations. A core laboratory independently assessed all intraprocedural and 90-day transesophageal echocardiograms. Sixty patients (37 men), aged 33 to 86 years, enrolled. The mean LAA application time was 27 seconds. Transesophageal echocardiograms at 90 days were available in 54 patients, and no leaks were detected. The residual LAA cavity exceeded 6 mm in 5 patients. One delivery device failed to close, and an adjunctive suture was required to complete LAA exclusion. One patient required adjunct sutures at a small tear site related to manual manipulation after fastener application.**

Conclusions. **The study demonstrated safety and efficacy of this LAA exclusion device, offering an alternative to manual suturing or staples with or without reinforcement.**

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Atrial fibrillation is a common cardiac arrhythmia affecting approximately 2.5 million people in the United States [1]. Atrial fibrillation markedly increases the risk of stroke [2]. With loss of atrial contraction, thrombus can develop in the left atrium (LA); more than 90% of atrial clots in nonrheumatic atrial fibrillation form in the left atrial appendage (LAA) [3].

Studies have shown that anticoagulation with warfarin or dabigatran will decrease the incidence of stroke in patients with atrial fibrillation, but both are associated with the risk of hemorrhage and warfarin is often not prescribed in patients at risk [4]. These findings suggest LAA exclusion may decrease the risk of stroke in patients. Thus, a safe and simple method for complete occlusion of the LAA has been sought with a variety of techniques and devices.

Percutaneous devices, as well as suture techniques and staples, have resulted in appendage injuries and bleeding or incomplete occlusion of the LAA with residual flow to the appendage and residual thrombus [5]. This Food and Drug Administration–approved prospective, multicenter trial assessed the safety and efficacy of a novel device (TigerPaw System, LAAx Inc, Livermore, CA) for external LAA exclusion as a concomitant procedure to open cardiac surgical procedures.

Technology

Patient Selection and Study Design

Patients aged 18 years or older scheduled to undergo nonemergency, nonendoscopic heart operations, having a CHADS score (Congestive heart failure, Hypertension, Age, Diabetes mellitus, prior Stroke or transient ischemic attack) of 1 or higher were eligible for the study. Patients who met the eligibility criteria were invited to participate

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in the research study, signed informed consent, and were treated at 1 of 4 medical centers between August 20, 2009, and March 19, 2010.

Intraoperative transesophageal echocardiography (TEE) was used to rule out the presence of thrombus in the LAA. The TigerPaw System was used to occlude the LAA of enrolled patients. Perioperative confirmation of successful LAA occlusion was achieved through visual and TEE examination after the device had been placed at the base of the LAA by the operating surgeon.

Patients were assessed at 30 to 45 days and then at 90 days for safety and effectiveness. TEEs were examined and graded by an independent core laboratory for leaks and residual LAA cavity, which was graded as more than 6 mm or 6 mm or less from the ostial interface. All operative and postoperative device-related complications were recorded, including bleeding, tissue tears, and device malfunctions.

This study was conducted using practices that ensured adherence to good clinical practice and protection of the patients. Investigational Review Board approval was obtained at all sites, and the trial was registered with http://www.clintrials.gov. An independent Clinical Research Organization managed all data collection and verification.

Device

The TigerPaw System consists of a delivery tool and an implantable fastener (Fig 1). The fastener portion of the device is designed around the concept of interrupted, mattress sutures. The fastener consists of a series of evenly spaced individual connectors embedded in a soft, compliant silicone housing. The silicone housing has a U-shaped connector at one end of the connector series that is positioned on the proximal end of the delivery jaws and allows target tissue to be captured and fully seated in the fastener. The silicone housing has zero porosity, thus eliminating the possibility of LA wall attachment. It seals the puncture site of the barb and conforms to the varying shape and wall thickness variations of the LAA os (Fig 2).

Technique

One series of connectors has a male titanium needle barb fixed in the center, and the opposing series of connectors has a female receptor mechanism that catches and holds the end of the needle barb. The needle barb of the male connector is conical-shaped to act as a tissue dilator and has no cutting edges. When connected, the male and female connector bases are parallel to each other and the central single needle barb is perpendicular to both opposing surfaces, thus creating the effect of a buttressed, interrupted, mattress suture.

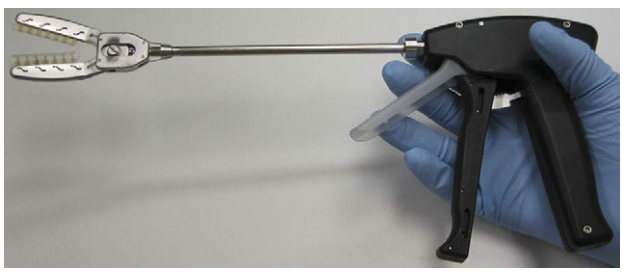

Fig 1. Photograph shows the TigerPaw device for external exclusion of the left atrial appendage.

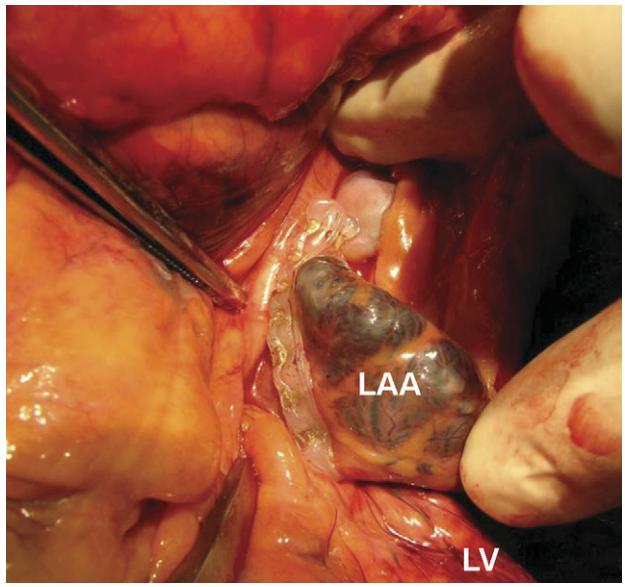

Fig 2. Intraoperative photograph shows the TigerPaw device implanted for external exclusion of the left atrial appendage (LAA). (LV = left ventricle.)

The delivery tool is a jaw applicator with a shaft and pistol grip actuator. A 15-degree angle between the jaws holding the fastener and the shaft of the delivery tool aids in placing the fastener at the base of the LAA ostium. The delivery tool also has a wide opening for easy capturing of the base of the LAA ostium and can be adjusted by the surgeon, based on anatomy.

Clinical Experience

Sixty-one patients were successfully screened and consented at 4 clinical sites. One patient presented intraoperatively with an LAA anatomic anomaly (LAA tip attached to pulmonary vein) and was excluded; thus, 60 patients (37 men), aged 33 to 86 years, were enrolled. Demographics, including the cardiac surgical procedures performed, are listed in Table 1.

There were no unanticipated adverse events and only one (1 of 60) device-related adverse event (minor tissue tear), which occurred with manipulation of the appendage after fastener placement. One device malfunction occurred (failure to close properly due to fracture of the trigger pivot point) requiring a single suture closure to achieve complete LAA occlusion. The trigger pivot design was revised and reapproved by the Food and Drug Administration with no further malfunctions.

Table 1. Demographics and Reason for Operation

Variable	Frequency No. (%) or Median (range)
Patients	60
Sex	
Male	37 (62)
Female	23 (38)
Age at procedure, years	65.9 (32.1–84.8)
Body mass index, kg/m^2	31.9 (18.5–48.6)
Heart disease/reason for operation	
CABG	47 (78)
AVR	2 (3)
MVR	2 (3)
MVR/TVR	1 (2)
AV replacement	1 (2)
CABG/MVR	1 (2)
CABG/AVR	5 (8)
MVR/AVR/Maze/CABG	1 (2)

AV = aortic valve; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MVR = mitral valve repair; TVR = tricuspid valve repair.

Complete occlusion of the LAA with the TigerPaw System was visually confirmed in 59 of 60 the patients, and 56 of 60 were confirmed by the TEE assessment. Four operative TEEs were not properly completed. There were no incidences of bleeding or leakage from the area of the device footprint.

Fifty-eight patients successfully completed postprocedural follow-up at 30 to 45 days, and 54 successfully completed the 90-day follow-up. Six patients failed to complete follow-up: 1 patient died of respiratory failure unrelated to the device, 2 patients withdrew consent, 2 refused complete follow-up, and the TEE for 1 patient was improperly performed at 90 days.

In all cases where the required color Doppler flow videos were available (56 intraoperative and 54 at the 90-day follow-up), the core laboratory determined absence of any leaks or communicating flow between the left atrium and the LAA.

Four TEE videos were not properly completed at the time of the procedure. TEE examinations were successfully completed in these 4 patients at 90 days, with no leak and a LAA residual cavity of 6 mm or less. The intraoperative TEEs for the patients whose 90-day TEE was not completed showed no leaks and no residual LAA cavities.

A residual LAA cavity exceeding 6 mm was identified in 5 patients at 90 days and in 6 patients at the intraoperative examination.

There were no circumflex coronary artery injuries and no strokes. Other complications, as expected for patients receiving coronary artery bypass grafting or valve operations, or both, were unrelated to the device and are listed in Table 2.

Comment

A variety of techniques and devices for ligation, excision, or exclusion of the LAA, both as adjuncts to the cardiac operation and as a sole therapy have been described, and at least one study demonstrated that exclusion of the LAA reduced the risk of subsequent stroke in patients after mitral valve operations [6]. Surgical epicardial occlusion of the LAA was evaluated in the Left Atrial Appendage Occlusion Study (LAAOS) trial [7] in patients undergoing coronary

Table 2. Adverse Events

Event	Study Patients No. (%)
Cardiovascular complications	
Chest pain	4 (5)
Congestive heart failure	3 (5)
Arterial stenosis	1 (2)
Thrombus (aortic arch)	1 (2)
Arrhythmias	
Atrial fibrillation	23 (38)
Supraventricular	1 (2)
Ventricular	2 (3)
Conduction disturbances	5 (8)
Neurologic complications	
Cerebrovascular event	1 (2)
Stroke	0
Central nervous system	1 (2)
Peripheral nervous system	1 (2)
Neurologic changes (encephalopathy)	1 (2)
Pulmonary	
Embolism (pulmonary or other)	1 (2)
Pneumonia	3 (5)
Adult respiratory distress	2 (3)
Hypoxia/hypoxemia	10 (17)
Lung and airway complications	11 (18)
Prolonged ventilation	2 (3)
Death from respiratory infection	1 (2)
Renal failure	4 (7)
Gastrointestinal tract complications	4 (7)
Bleeding complications	
Cardiac tamponade/pericardial effusion	1 (2)
Reoperation for bleeding	3 (5)
Bleeding requiring transfusion	2 (3)
Gastrointestinal bleeding	0
Acute bleeding, no intervention needed	1 (2)
Leukocytosis (thrombocytopenia)	6 (10)
Anemia and anemia requiring transfusion	24 (40)
Wounds and infection	
Sternal wound dehiscence or infection	5 (8)
Infections at graft and/or catheter site	4 (7)
Nonrelated infections (viral/fungal/etc)	8 (13)
Myocardial infarction/cardiac arrest	1 (2)
Death from cardiac cause	0
Tissue tear	1 (2)

artery bypass grafting with an increased risk of stroke (CHADS score > 2) and reported a 12% rate of LAA injury requiring further suture repair. Complete appendage closure rates were only 45% using sutures and 75% using staples on predischarge studies [7]. Incomplete closure has been associated with an increased rate of thromboembolic events [8].

In a retrospective study of patients with exclusion or excision of the LAA, complete closure of the LAA was only successful in 40% of patients. Successful closure occurred more often with excision of the LAA (73%) vs suture exclusion (23%) or stapler exclusion (0%). Of the patients in whom exclusion was unsuccessful, persistent flow into the appendage was found in 100% of the stapled exclusions and in 50% of the suture exclusions. The prevalence of thrombus in the appendages with persistent flow was high: 46% in suture exclusion and 67% in stapled exclusion [9].

Percutaneous endocardial devices have been evaluated and suggest decreased stroke rates compared with historical controls. However, strokes were not completely eliminated, and echocardiographic studies have shown residual flow into the appendage in some cases [9]. There have been episodes of device dislodgement [8], and the device represents a foreign body in contact with blood and requires oral anticoagulation medications.

External application of a flexible band has been shown to be effective in LAA exclusion in experimental studies [9], and a titanium and nitinol clip covered with knitted Dacron (DuPont, Wilmington, DE) was effective in a clinical trial of 34 patients with no evidence of leak or hemodynamic consequence [10]. These previous studies, as well as ours, demonstrate that an externally placed device is adaptable to the variable anatomy of the LAA.

The silicone housing of this device provides a soft, flexible compression surface to ensure complete apposition of the LAA surfaces for 100% occlusion at closure. The median procedure time was 27 seconds and was reported as easy to use by all surgeons with no prior clinical experience with the device.

Because of the ease of application, minimal morbidity, and high level of effective occlusion of the LAA, placement of an external occlusion device may become a standard part of elective cardiac operations to prevent LAA thrombus, particularly as our population ages and the incidence of atrial fibrillation increases.

In conclusion, our study demonstrated the safety and efficacy of this novel LAA exclusion device, with rapid closure times and reduced rates of bleeding and tissue tear. Results suggest that the TigerPaw System is a superior alternative to manual mattress suture or staples with or without reinforcement.

Disclosures and Freedom of Investigation

The study was funded by LAAx, Inc (Livermore, CA). The authors were free from outside interests in controlling the design of the study, acquisition of data, collection, analysis and interpretation of data and have freedom to fully disclose all results. The devices were provided at no charge.

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Disclaimer

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DISCUSSION

DR V. SEENU REDDY (San Antonio, TX): I would like to thank the program committee and the Society for the privilege of discussing this novel paper and the authors for their most timely transmittal of the full manuscript for review. The authors present a single-arm, prospective, multicenter feasibility study of a novel system for left atrial appendage exclusion, which is presumed to be a major source of intracardiac emboli, particularly for those patients in atrial fibrillation. They were able to enroll 60 patients in a

6-month period at 4 clinical sites, and they describe 45-day and 90-day follow-up with completeness in the 90% range. The authors clearly report a few cases of incomplete transesophageal echocardiography (TEE) follow-up, but overall had excellent technical success and no major complications. Longer-term data were not included on device stability, failure of appendage exclusion, or late stroke.

I have a few questions for the authors: First, why was the dialysis status, renal failure, or elevated creatinine an exclusion criterion for this device?

Next, what do you think the anticipated cost would be of this device?

What is its theoretical or actual superiority over currently available devices such as the AtriClip (AtriCure, West Chester, OH) that are on the market today?

How do you propose this device would be used in the setting of direct access to intracardiac oversewing of the left atrial appendage as is often performed during open or minimally invasive mitral surgery?

Finally, in your paper you mentioned patients who had a residual 6-mm cavity. Do you relegate those patients to anticoagulation? As you note in your paper, some of those patients are at elevated risk for late stroke. What is the anticoagulation strategy, in general, for patients treated with this device? Thank you very much.

DR SLATER: I really don't know the reason why the patients with renal insufficiency were excluded. I suspect that it relates to coagulation effects that may be associated with renal disease that may have influenced the study.

The cost of the device I think is around $1,900.

You mentioned the other clip that is commercially available at this time. I have no experience with this clip. I do have experience with another device that uses the elastic rubber band approach. I think that what the study suggests is that an externally applied fastener or device such as this is effective. Whether it is more effective than some of the other products that are being introduced to the market, I can't comment on that.

There are studies that have shown that oversewing the left atrial appendage will result in a certain percentage of leaks and continued communication between the left atrium and the left atrial appendage and that those patients are at risk for stroke, and therefore, we believe that that is an inferior technique for atrial appendage exclusion.

In the patients with the 6-mm os, when you look at the internal surface of the atrium after you apply this clip and then open the atrium, there is a smooth line. The experimental studies with this fastener prior to the clinical study showed that over time the atrial surface heals to a completely smooth endocardial surface, and we have not used anticoagulation in any of the patients that had a greater than 6-mm os and know of no adverse effect from that practice.

DR RICHARD LEE (Chicago, IL): I appreciate this, and I agree these results are much better than historical reports. I have a couple of questions for you.

Number one, did you have any problems getting down to the base? For example, we learned from our experience, we have an atraumatic grasper that we use to elevate the appendage so we can really get down to the base, because it is quite challenging to get flush down fully from an epicardial approach. In addition, at times the first application of the device will fail. Is there a bailout option?

The second question is really somewhat of a comment. We have also learned from our experience that we got much better doing this because we started paying attention and we do a better job. So prior to making your claim and your second conclusion (that this is a superior alternative to other devices or other approaches), do you think you need a randomized study to fully support that conclusion?

DR SLATER: Well, I would say this is not a comparative study. We based our assumption that this was better based on historical information of leaks and communications that have occurred with suturing and staple techniques. So our comparison is based on those historical data.

The way the device is constructed with the offset angle, we had really no trouble placing it at the base of the appendage. It required very little handling of the appendage. You do have to hold the tip of the appendage to make sure that you place it flush against the atrial wall. But it was reported as easy by all the surgeons who used it.

DR KEVIN D. ACCOLA (Orlando, FL): It would have been nice to show a brief video how this works intraoperatively. We are all using smaller incisions, and this still seems somewhat of a cumbersome device to utilize a linear object and try to occlude somewhat of a curvilinear left atrial appendage. Also, you did have some areas of the appendage that were still open. This is a novel idea, but yet it still seems very cumbersome to use, as well as I would be concerned about the expense of adding a device like this to a regular procedure.

DR SLATER: The fastener is designed of a very soft plastic material that does sort of bend and conform to the shape of the appendage, and it does give some flexibility in the situation that you describe.

DR SUBHASIS CHATTERJEE (Evanston, IL): I have two questions. First, and building on the previous question, is whether this has been tried through a left minithoracotomy approach to consider it for thoracoscopic stand-alone atrial fibrillation surgery?

Second, I would like you to speculate a little bit. When you look at the transcatheter trial Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO), Amplatzer, the Watchman trial, they have excellent efficacy with 95% to 99% left atrial appendage occlusion. But, it is interesting that their stroke reduction benefits are more modest, in the 50% to 60% range. Do you think ultimately that surgical results with a device like this are going to be comparable or do you think we might be able to see better results because the appendage is completely removed? Your thoughts.

DR SLATER: Our speculation is that these will be better results because there is no communication of this device with the circulation, whereas the PLAATO device remains in contact with blood surface. I don't know the answer to that. This study only addressed safety and efficacy, so I can't really comment on reduction of stroke related to this device.

In answer to your second question, the company is investigating use of this device through other incisions. This was a study done on patients having sternotomies, and as I say, it was quite easy to use through a sternotomy. Whether it would be that easy to use through a ministernotomy or a minithoracotomy, I can't comment on that.

DR ANDREA J. CARPENTER (San Antonio, TX): This is an efficacy study where we are looking at reduction in stroke rate

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and you include in your population patients with a CHADS (congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or transient ischemic attack) score of 1. These patients have no indication for anticoagulation and are at low risk of stroke. Can you comment on what percentage of your study population had a low CHADS score of only 1 and whether it might have been better to have looked only at patients with higher CHADS scores?

DR SLATER: I really don't know what percentage of the patients had a CHADS score of 1 or what percentage was higher. I can't answer that question.