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THE LEFT ATRIAL APPENDAGE: TARGET FOR STROKE REDUCTION IN ATRIAL FIBRILLATION

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Abstract

A patient with atrial fibrillation (AF) has a greater than 5% annual risk of major stroke, a 5-fold increase compared to the general population. While anticoagulation remains the standard stroke prevention strategy, the nature of lifelong anticoagulation inevitably carries an increased risk of bleeding, increased stroke during periods of interruption, increased cost, and significant lifestyle modification. Many patients with atrial fibrillation have had their left atrial appendage (LAA) ligated or excised by surgeons during cardiac surgery, a decision based largely on intuition and with no clear evidence of efficacy in stroke risk reduction. The observation that 90% of the thrombi found in nonvalvular AF patients and 57% found in valvular AF are in the LAA, triggered significant interest in the LAA as a potential therapeutic target. Until recently, the results were inconsistent, and high rates of incomplete occlusions precluded the medical community from confirming a definite relationship between LAA and stroke. As a result, anticoagulation is still the recommended first-line stroke risk reduction in AF, and the American College of Cardiology/American Heart Association guidelines recommend LAA exclusion only with surgical ablation of AF or in the context of concomitant mitral valve surgery.

A handful of devices have been developed for LAA exclusion. This includes percutaneous options such as WATCHMAN™ Left Atrial Appendage Closure Device (Boston Scientific Corporation, Marlborough, MA), hybrid epicardial devices such as the LARIAT Suture Delivery Device (SentreHEART, Inc., Redwood City, CA), and epicardial surgical devices such as AtriClip® LAA Occlusion System (AtriCure, Inc., West Chester, OH). Studies of the Watchman device have shown noninferiority to Warfarin in stroke prevention and this device has recently gained approval from the U.S. Food and Drug Administration (FDA) following lengthy delays due to safety concerns. The Lariat device, which received 510K clearance by the FDA for tissue approximation but not LAA exclusion, has been the target of significant criticism due to serious procedural safety concerns and high incomplete closure rates. The surgical AtriClip has been FDA approved since 2009 and is currently the most widely used LAA exclusion device placed through an epicardial approach. Small studies have shown excellent reliability and success of complete LAA closure with the AtriClip device, which is implanted through an epicardial approach. Currently, we are conducting a multicenter trial to demonstrate the stroke prevention potential of this epicardial device through a short (45 minute), stand-alone, minimally invasive procedure in lieu of lifelong anticoagulation in patients at high risk of bleeding.

Introduction

A patient with atrial fibrillation (AF) has a 5% annual risk of stroke, a 5-fold increase compared to the general population.[1,2] Moreover, stroke and its debilitating consequences has been shown to be the most-feared complication, even higher than death, of patients undergoing surgery for AF.[1] These strokes are mostly embolic in nature, with the left atrium and LAA as the sources (Figure 1). For years and even still today, the gold standard strategy to reduce stroke risk is anticoagulation (AC) with warfarin to an international normalized ratio (INR) range of 2-3. However, due to numerous concerns with warfarin anticoagulation, alternatives have been explored. Novel anticoagulants including dabigatran, rivaroxaban, and apixaban seem to have comparable efficacy with potentially better safety profiles. Even so, the nature of anticoagulation inevitably carries an inherent risk of bleeding.

LAA Exclusion Data

The observation that 90% of the thrombi found in nonvalvular AF patients and 57% found in valvular AF are in the LAA triggered much interest.[3] As a result, many patients undergoing AF surgery have had LAA ligation or excision for reasons based largely on physician intuition but with no clear evidence of efficacy in stroke risk reduction. Until recently, the results were inconsistent, and high rates of incomplete occlusions hindered the medical community from drawing a definite relationship between LAA and stroke. As a result, anticoagulation continues to be the recommended first-line therapy to reduce stroke risk in AF, and the American College of Cardiology/American Heart Association guidelines recommend LAA exclusion only with surgical ablation of AF or in the context of mitral valve surgery.[4]

More recently, however, the PROTECT-AF randomized clinical trial (RCT) using the WATCHMAN percutaneous device demonstrated for the first time the noninferiority of LAA exclusion, and the follow-up publication showed superiority of LAA exclusion over warfarin therapy.[5,6] Despite this, concerns from the U.S. Food and Drug Administration (FDA) about device safety and increased complication rates have significantly delayed approval and commercial availability outside of a trial setting.

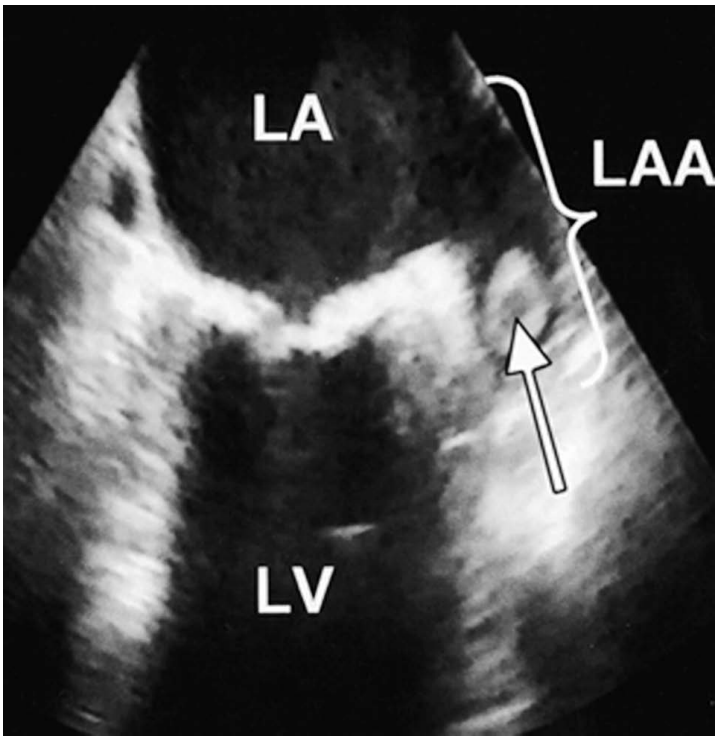

Figure 1. Left atrial appendage thrombi in a patient in atrial fibrillation. A small thrombus is present within the lumen of the appendage, and a larger one appears to be more fixed and is present at the orifice.

The WATCHMAN device, an umbrella-shaped plug, is placed into the LAA through a trans-septal approach requires at least 6 weeks of Warfarin anticoagulation therapy to allow some device endothelialization and avoid thrombus in the left atrium. This requirement may pose a problem in patients truly contra-indicated to anticoagulation. With a relationship established between LAA and stroke in AF patients, more devices and techniques are being developed for effective, complete, and reproducible LAA exclusion during surgery.

The LARIAT Suture Delivery Device (SentreHEART, Inc., Redwood City, CA) combines an epicardial and transcatheter endocardial approach. A magnet-tipped guidewire is delivered transseptally and attached to another guidewire that is epicardially inserted (Figure 2 B). A radio-opaque tie is guided down the wire and tightened at the base of the LAA. Although the suture delivery system is FDA-approved for "tissue-approximation," it is not approved specifically for LAA ligation. Bartus and colleagues reported their experience with 89 AF patients who were poor candidates for AC therapy.[7] The procedure seemed to be feasible with a complete LAA occlusion rate of 89% at 1 year. There were concerns, however, regarding dry pericardial access and included catheter-related myocardial puncture as well as subsequent severe pericardial effusion. These concerns were reproduced by two studies including 20 and 27 patients, respectively, that reported myocardial punctures requiring further procedures.[8,9] Each of the two studies also reported three patients who presented with severe postprocedural pericarditis, necessitating hospital stays and in one instance coronary angiography. Although the Lariat is a novel idea, we believe these events should raise questions about the safety of its use in this particular indication of LAA occlusion. Furthermore, the efficacy of LAA closure may be suboptimal, with up to 24% of patients showing persistent LAA flow at 3-month follow-up.

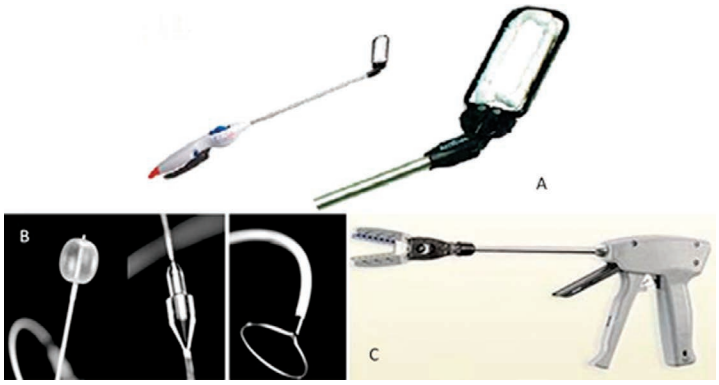

Figure 2. (A) The AtriClip; (B) the Lariat; and (C) the TigerPaw II.

The first RCT, published by Healey and colleagues, demonstrated no increase in morbidity with LAA excision during cardiac surgery.[10] Although the technique proved to be surgically safe, skepticism regarding its value in stroke reduction failed to convince surgeons to adopt LAA excision on a routine basis. A major problem was incomplete closure when using first-generation techniques such as simple suture ligation while the heart is flaccid on cardiopulmonary bypass, over-sewing with a running suture, or inadequate stapling devices designed for intestinal use. Results by Fernandez and colleagues confirmed this skepticism by demonstrating that incomplete LAA exclusion carries a 12-fold increase in the risk of stroke compared to no exclusion.[11] With LAA techniques yielding complete closure rates as low as 40%, as reported by Kasherian et al., this approach was considered to be problematic as recently as 2008.[12] Since then, complete occlusion rates have drastically improved, with more authors publishing encouraging data. Bakhtiary and colleagues reported 100% complete closure rates using a Derra clamp and a double level suture on an arrested heart.[13] The same rate was achieved by Ohtsuka and colleagues in lone AF patients through a minimally invasive thoracoscopic procedure.[14] No major complications were encountered, and the mean procedural time was reported to be only 32 minutes. These small series demonstrated the safety and feasibility of isolated, minimally invasive LAA exclusion.

Epicardial LAA exclusion devices are commercially available, have no foreign body-blood interface, and potentially have lower rates of thrombosis, infection, and embolization. The TigerPaw System II (Maquet Cardiovascular, Mahwah, NJ) was available for use during concomitant cardiac surgery until it was recently the subject of an FDA recall due to potential LAA tear and is no longer available on the market at this time. It is composed of a delivery tool and a fastener made of linearly spaced connectors overmolded with soft silicone (Figure 2 C). In a study by Slater et al., 54 patients followed up by transesophageal echocardiography (TEE) 3 months after surgery all had complete occlusions.[15] Both this device and the AtriClip (see below) can be used with other cardiac surgeries as well as lone procedures

The AtriClip® LAA Occlusion System (AtriCure, Inc., West Chester, OH) has become the preferred approach for safe and complete epicardial LAA exclusion in open cardiac surgery patients. The most widely used LAA exclusion device, the AtriClip has been FDA approved for LAA exclusion during open cardiac surgery since 2009 and is currently being studied for minimally invasive stand-alone procedures. It is a self-closing clip made of two parallel titanium tubes with elastic nitinol springs covered by knit braided polyester (Figure 2 A). The delivery

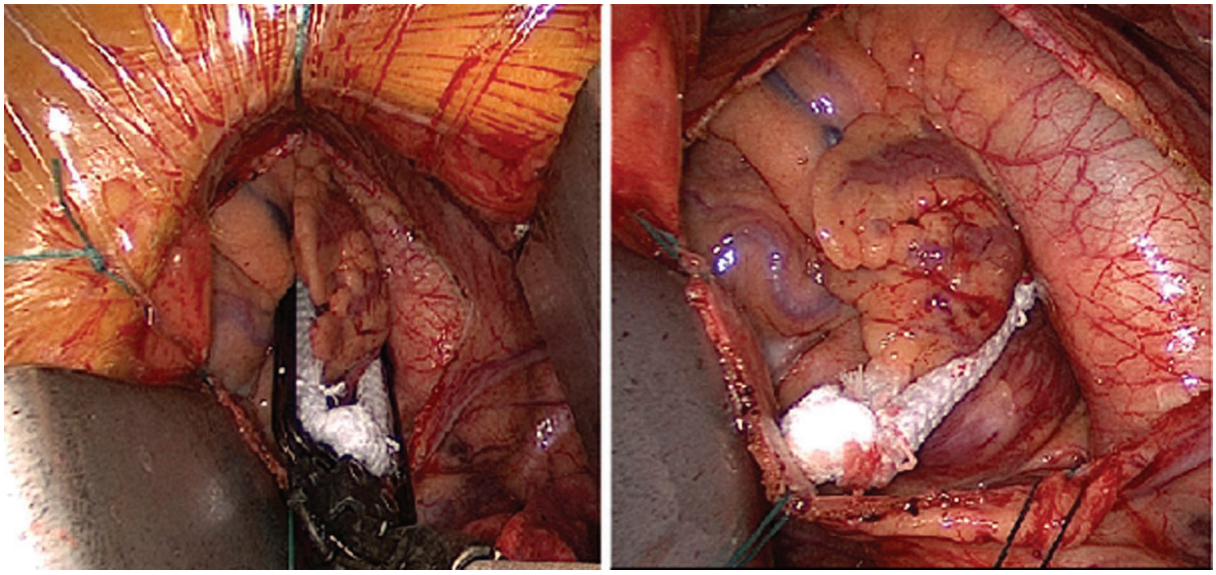

Figure 3. The AtriClip device is used to occlude the left atrial appendage at its base.

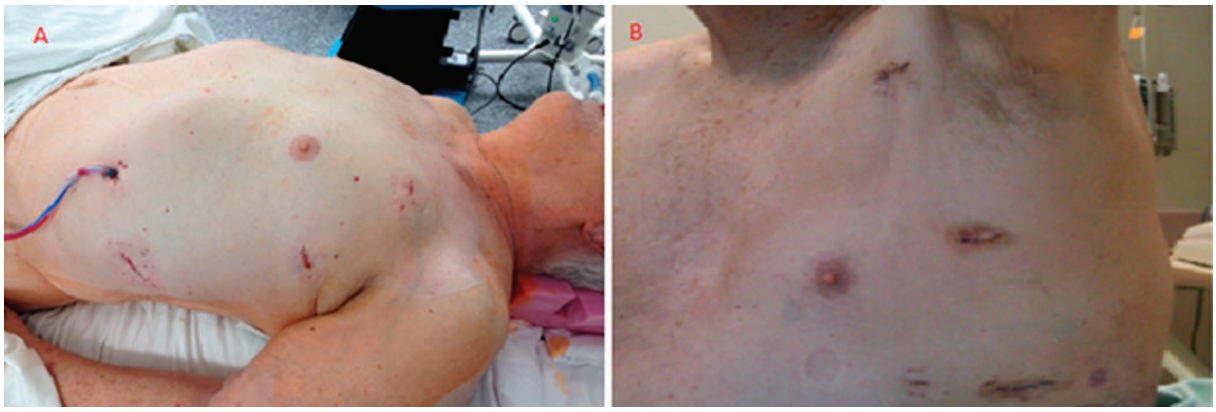

Figure 4. Intraoperative and postoperative (POD1) pictures of the patient following video-assisted thoracoscopic surgery for LAA exclusion with the AtriClip.

system allows for redeployment and repositioning to ensure optimal placement at the base (Figure.3). Two studies on 34 and 71 patients undergoing cardiac surgery reported complete occlusion rates of 100% and 98%, respectively, at 3 months with no reported adverse events.[16,17]

Our group at the Methodist DeBakey Heart & Vascular Center has deployed the AtriClip device using a short, safe, video-assisted thoracoscopic procedure that lasts approximately 30 to 45 minutes (Figure.4). Currently, a multicenter study for stand-alone LAA exclusion procedures using the AtriClip is recruiting patients with contraindications for AC and a $CHADS_2$ score ≥ 2. Even though it is still considered a "surgical" approach, this procedure has several potential advantages, including (1) procedure safety with minimal complications, (2) complete and consistent LAA exclusion with intraoperative TEE confirmation, (3) epicardial exclusion of LAA with no intracardiac foreign body, (4) Deployable on all vagaries of LAA morphology, (5) allows immediate cessation of anticoagulation medications, (6) direct visualization of LAA, (7) electrical and vascular isolation of LAA, (8) short procedure, (9) comparatively lower cost compared to other devices and long-term AC, (10) no atrial septal puncture, (11) no groin puncture, (12) no pericardial puncture, and (13) short hospital length of stay (1-3 days and potentially outpatient).

Well-powered comparisons of these LAA exclusion devices to anticoagulation are forthcoming. Longitudinal studies as well as well-powered RCTs comparing percutaneous LAA occluding devices to warfarin (i.e., WATCHMAN data) will help with data suggesting noninferiority of LAA exclusion to AC. Now that LAA exclusion is suggested to be at least a noninferior alternative to warfarin therapy in nonvalvular AF patients, studies should be questioning which device can achieve the most complete, reproducible closure through the safest and most cost-effective procedure. While newer anticoagulants address some of the disadvantages of warfarin, they have their own shortcomings and do not mitigate the fact that the patient is still committed to lifelong anticoagulation and its associated morbidities. We believe that patients with AF undergoing cardiac surgery should have a concomitant Maze including LAA exclusion/removal, and we expect future guidelines to allow for safe discontinuation of AC with TEE confirmation of complete LAA closure. Minimally invasive LAA exclusion using the AtriClip or other reliable devices can be performed safely and leads to effective and complete LAA closure. Ongoing studies will provide further evidence and confirm the role of LAA exclusion in patients at increased risk of bleeding.

Conclusion

With the availability of reliable occlusion devices, we recommend LAA exclusion in all AF patients undergoing cardiac surgery regardless of their suitability for anticoagulation therapy. For lone AF patients with an embolic risk that necessitates anticoagulation, we recommend LAA exclusion in those with failed

or with relative or absolute contraindications to anticoagulation. Characteristics of the ideal LAA exclusion include: (1) procedure is safe and minimally invasive, (2) procedure is complete and receives intraoperative TEE confirmation, (3) procedure is free of intracardiac foreign bodies, (4) procedure is applicable to all LAA morphologies, (5) procedure allows for immediate cessation of anticoagulation medications, and (6) cost is lower compared to other devices and long-term oral anticoagulation.

Conflict of Interest Disclosure: Dr. Ramlawi is the national principal investigator of the AtriClip Stroke Study and has industry relationships with AtriCure, Inc., Baxter, REPLICor Inc., and the Sorin Group, and Dr. Edgerton is on the speakers bureau for AtriCure, Inc.

Keywords: left atrial appendage, atrial fibrillation, LAA exclusion, stroke prevention

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