ATRIAL FIBRILLATION

REVIEW ARTICLE

The Left Atrial Appendage and Thromboembolic Stroke in Atrial Fibrillation: Rationale for Ligation by an Epicardial Approach: The AtriClip Stroke Trial

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Introduction

The connection between atrial fibrillation (AF) and left atrial appendage (LAA) thrombus is well documented, with >90% of left atrial thrombi residing in the LAA.1 It is estimated that 25% of all strokes are due to systemic thromboembolism arising from the LAA.2 In patients with known AF, 75% of all embolic events result from LAA thrombi,1 thus the LAA represents an attractive target for the prevention of AF-related embolic stroke. Oral anticoagulation (OAC) has proven an effective therapy for the prevention of systemic embolism in AF. While vitamin K antagonism with dose-adjusted warfarin was the only medical option for over 60 years, a cohort of novel drugs, referred to as novel or direct oral anticoagulants (NOACs or DOACs), have proven efficacious in large randomized trials.3–6 However, any oral anticoagulant is limited by patient compliance with dosing, dietary restrictions, drug–drug interactions, and variability in response based on renal or hepatic function. The inability to adhere to long-term anticoagulation due to major bleeding further reduces its true efficacy for stroke prevention. Several studies have shown that over half the AF population indicated for anticoagulation are not managed with any OAC. On warfarin, time in therapeutic range is typically 60–65% in well-monitored clinical trials, and significant, sometimes life-threatening bleeding occurs in at least 2–3% of patients annually. Additionally, systemic OAC does not prevent all embolic strokes.

Evidence for surgical LAA ligation

Non-pharmacologic strategies to limit LAA-associated thromboembolism have historically included surgical LAA exclusion as an adjunct for patients undergoing open heart surgery, such as valve surgery or coronary artery bypass grafting (CABG). Options have included suture ligation, surgical stapling, and excision with oversewing of the LAA. These have shown varying degrees
of success. In a 2008 study by Kanderian et al., the overall success rate for surgical exclusion of the LAA was only 40%. However, there was significant variability in surgical technique, and the success rates ranged from 0% for stapler exclusion, to 22% for suture ligation, and up to 73% for complete surgical excision of the LAA. Moreover, the failure rate for complete LAA surgical excision was driven primarily by the presence of a residual stump, with no appendiceal leak. The clinical relevance of a smooth-walled stump is unknown. In patients who underwent suture ligation or stapler exclusion, failed ligation resulted in persistent flow into the LAA body through small leaks between sutures or staples. Despite the occasional technical failure of LAA complete surgical excision, there were no documented LAA thrombi in this group, suggesting a residual stump is not relevant if all LAA trabeculations are removed. Conversely, in the suture ligation and stapler exclusion groups, the rates of subsequent LAA thrombosis were 32% and 42%, respectively. These data highlight the need for both efficacious and reproducible surgical LAA closure techniques.

Because primary surgical LAA exclusion has been used as an adjunct to open cardiac surgery, these interventions are not a viable stand-alone strategy, apart from the setting of an open Maze procedure. Additionally, patients receiving these interventions are commonly managed with anticoagulants regardless of LAA closure, because of indications such as mechanical valvular prosthesis; hence, this approach cannot reliably be used as an alternative to anticoagulation in the bleeding-prone patient.

Device-based LAA exclusion

In recent years, the focus on LAA exclusion has shifted to non-surgical, device-based occluders, and suture ligation by subxiphoid pericardial access techniques. Endocardial LAA occlusion devices include the WATCHMAN (Boston Scientific Inc, Marlborough, MA), which has recently been granted FDA approval in non-valvular AF. The WATCHMAN device is labeled for prevention of stroke and systemic embolism in patients who can tolerate warfarin, but in whom an alternative to long-term anticoagulation is warranted. The LARIAT (SentreHeart Inc, Redwood City, CA) suture ligation epicardial system is also being used labeled for soft tissue closure, though there are no prospective stroke prevention data. The LARIAT theoretically allows LAA ligation for patients who are completely contraindicated for OAC, though there are reports of post-ligation LAA thrombosis. This phenomenon is postulated to be due to acute endothelial injury, and experienced centers have moved to use dual antiplatelet therapy or OAC for 6 weeks after ligation until the transesophageal echocardiogram shows complete closure.

Excitement over interventional techniques for LAA ligation should be tempered. A recent study shows 13–25% persistent leak rates at the 12-month follow-up with either LARIAT or WATCHMAN techniques deployed by experienced operators.

AtriClip-Pro LAA ligation technique

The AtriClip-Pro LAA exclusion device (AtriCure Inc, Westchester, OH) is composed of two parallel titanium bars, which provide constant tension when deployed. The AtriClip is coated with polyester fabric, which promotes tissue in-growth and provides an atraumatic surface, preventing erosion into surrounding structures. The LAA is completely occluded immediately when placed; ischemic necrosis with complete electrical isolation of the LAA rapidly ensues. The short-term efficacy of the AtriClip was demonstrated in a 2011 report by Ailawadi et al., wherein the device was used as an adjunct to open heart surgery (primarily CABG or valve surgery). Acute intraprocedural closure of the LAA was achieved in 95% of patients, and at the 3-month follow-up, 98% of those imaged showed evidence of successful complete LAA exclusion. In the 12-month follow-up period, there were no cardioembolic events. In addition to the open surgical approach, the AtriClip-Pro can be deployed utilizing a totally thoracoscopic (TT) surgical technique (Figure 1). Patients must be able to tolerate a 45–60-min procedure under general anesthesia, with single lung ventilation. Prior sternotomy, left-sided thoracic surgery, chest wall irradiation, or severe pleural or pericardial disease are certainly exclusions. Most patients with left ventricular ejection fraction >30%, and forced expiratory volume in 1 s >0.7 l can safely undergo a stand-alone TT AtriClip-Pro placement. Major complications include pericardial or thoracic bleeding, pleurisy, phrenic nerve injury, and typical postoperative complications (wound infection, pneumonia, urinary tract infection). Complication rates for AtriClip placement at the time of epicardial ablation in the setting of 83 hybrid TT ablations at our center from 2009 to 2015 were low (<5%) (Figure 2), but total complications for stand-alone thoracoscopic surgical Atriclip-Pro placement will need to be determined in prospective clinical trials (Figure 3).

Secondary benefits of epicardial LAA exclusion

In addition to directly targeting the thromboembolic source in AF, LAA ligation or excision also carries potential hemodynamic and electrophysiologic benefits. The LAA is known to be a focal trigger for AF in 15–20% of patients, and is specifically targeted as part of the Maze procedure for this reason. There is evidence that epicardial ligation of the LAA also leads to electrical quiescence, and that AF burden is significantly reduced in patients undergoing LAA ligation via the LARIAT device. Additionally, epicardial LAA ligation leads to an up to 40% reduction in left atrial volume and surface area, which may derive a hemodynamic benefit and lower the risk of persistent AF.

LAA exclusion and clinical outcomes

It is important to acknowledge the distinction between acute technical success in LAA closure, the subsequent reduction in LAA thrombosis, and the long-term clinical outcome of stroke reduction. While the majority of available data focus on the feasibility of consistent LAA closure, there
is a relative paucity of long-term data demonstrating a reduction in embolic stroke, apart from the PROTECT-AF\textsuperscript{18} and PREVAIL\textsuperscript{19} trials. Single-operator retrospective surgical data suggest a low stroke rate after LAA excision in patients who otherwise had high predicted stroke rates.\textsuperscript{8} However, the lack of randomized surgical data on LAA occlusion still raises a critical question: Does ligation of the LAA alone prevent embolic stroke in AF?

**AtriClip-Pro Stroke Trial**

The trial that could best answer the above question is the AtriClip Stroke Trial. The rationale is that, to date, the best acute LAA closure data is from the EXCLUDE trial.\textsuperscript{14} In order to definitively test the theory that LAA occlusion will prevent AF-related stroke, a randomized trial of AtriClip-Pro versus placebo is necessary; enrollment of patients with CHA2DS2-VASc scores $\geq 2$ and contraindications to systemic anticoagulation, or a HAS-BLED score $\geq 3$, would be ideal. An unpublished feasibility trial of stand-alone TT LAA ligation for stroke prevention with the AtriClip-Pro in patients at risk for bleeding complications\textsuperscript{20} was slow to enroll. The FDA has agreed that a pivotal stroke trial with the AtriClip-Pro may proceed, given adequate safety and closure data from study data provided by AtriCure. Finalizing the

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**Figure 1:** Thoracoscopic port placement example during hybrid epicardial AF ablation. Stand alone Atriclep would be placed with left TT access only.
Figure 2: Hybrid thoracoscopic lesion set for epicardial ablation including placement of Atriclip on the base of the LAA.

Figure 3: Case example of large cauliflower LAA which could not be ligated with LARIAT. A 40mm Atriclip yielded successful closure.
stroke trial protocol has been a challenge, given the need for referral to a cardiac surgeon, and the recent FDA approval of the WATCHMAN device. The rate-limiting step in utilization of the Atriclip device is, of course, the availability of properly trained cardiac surgeons. An alternative population under consideration is the secondary prevention population: patients who have already suffered an AF-related stroke being referred mainly from stroke neurologists. This could enrich the event rate, thus lowering the estimated trial size; however, it may weaken enrollment from cardiac electrophysiologists. Additionally, a head-to-head trial of the WATCHMAN occluder versus the AtriClip-Pro would now be possible. The benefits to an epicardial LAA closure technique over an endovascular occluder device include electrical isolation of the LAA and reduction in LA volume. Regions of dense fragmentation in AF and sources of rotors anchored in the LAA may also help reduce atrial fibrillation burden in patients undergoing AtriClip ligation of the LAA. These sources of atrial arrhythmia would be unapproachable after placement of an endovascular LAA occluder device. The lack of persistent leaks into the remnant LAA after AtriClip closure also provides theoretically superior prevention of LAA-associated thromboembolic stroke. Owing to lack of any reported thrombus formation of significance, the AtriClip approach is uniquely suited to treat the truly “contraindicated” population, for whom there is no suitable alternative stroke prevention strategy available.

Conclusions

Left atrial appendage thrombi are responsible for the majority of non-valvular AF-related strokes. Recent advances in oral anticoagulation have provided clinicians more choices, but any anticoagulant-based stroke prevention strategy is imperfect. Occlusion of the LAA with the AtriClip-Pro device by a totally thoracoscopic approach has great appeal given its high acute closure rate, stable position, and lack of late persistent “leaks.” There have been no reported endocardial thrombi or late embolic strokes associated with the device. The benefit of closure that also electrically isolates the LAA may favor an epicardial approach when possible compared with endocardial LAA occluder devices. A randomized trial of totally transthoracic deployment of the AtriClip-Pro device, versus placebo or aspirin alone for stroke prevention in AF, has great promise to answer a critical question: Can complete occlusion of the LAA prevent embolic AF-related stroke?

References