PERCUTANEOUS LEFT ATRIAL APPENDAGE LIGATION FOR STROKE PREVENTION IN ATRIAL FIBRILLATION

Miguel Valderrábano, M.D. a, b; Matthew J. Price, M.D. b

aMethodist DeBakey Heart & Vascular Center, Houston Methodist Hospital, Houston, Texas; bScripps Clinic, La Jolla, California

Abstract
Prevention of thromboembolic complications in atrial fibrillation remains a tremendous clinical challenge. Knowledge that the left atrial appendage (LAA) is the most common anatomical origin of cardioembolic strokes1 has been the main motivation to develop clinical and procedural strategies to exclude the LAA from the circulation, either surgically or percutaneously. This review discusses the rationale behind these strategies, their relative merits, and future prospects for LAA exclusion strategies.

Left Atrial Appendage as a Source of Thromboembolism
Atrial fibrillation (AF) leads to loss of contractility in the fibrillating tissue. In the left atrial appendage (LAA), local stasis can lead to thrombus formation that may then embolize into the systemic circulation. Support for this premise derives from the finding that > 90% of thrombi found in patients with nonvalvular AF and stroke were found in the LAA.1 Other associated findings in line with the idea of LAA as a source of cardioembolism include low Doppler inflow velocities, spontaneous echocardiographic contrast, and the presence of thrombus in the LAA, all of which have been associated with high stroke risk in AF patients.2 Stroke risk is, however, influenced by a multiple other factors. It is important to recognize that not all strokes in AF can be prevented by LAA-targeted therapies, since up to 25% of strokes in AF patients can be linked to intrinsic cerebrovascular disease,3 and AF is often associated with other, LAA-independent risk factors for stroke. The CHADS2 or CHA2DS2-VASc scores4,5 can estimate the annual risk of thromboembolic events and select patients that benefit from anticoagulation,6 yet they do not include any parameters of LAA function or anatomy.

These facts are important when interpreting clinical trial results. Even a technically flawless, complication-free, perfect LAA exclusion cannot be expected to provide complete elimination of stroke risk in all AF patient populations since risk factors for stroke in AF include the risk of non-LAA-related stroke. Additionally, oral anticoagulation may provide stroke protection beyond its effects on LAA thrombi. With these caveats in mind, the LAA remains a worthwhile target to prevent strokes in patients with AF.

Exclusion of the LAA via Surgical Approaches
Surgical resection of the LAA to prevent arterial embolization in AF was proposed by Madden decades ago.7 While various forms of surgical ligation or excision have become routine, residual flow may lead to embolism recurrence. The pilot Left Atrial Appendage Occlusion Study (LAOOS) assessed closure efficacy after various LAA ligation strategies and found that 34% of patients had residual flow into the LAA after surgical exclusion,8 although it was least frequent with LAA excision.9 12 Correlations of surgical LAA closure with stroke reduction have provided conflicting results,13,14 and a large randomized trial is currently ongoing.14 The AtriClip® Left Atrial Appendage Exclusion System (AtriCure, Inc., West Chester, OH) is a surgically implanted clamp of the LAA.15 In the EXCLUDE study, complete LAA closure was achieved in 95% of patients who completed 3-month imaging follow-up, but stroke prevention data are lacking.16 Further evaluation using a stand-alone thoracoscopic17 implantation of the AtriClip are ongoing in the AtriCure Stroke Feasibility Study.

Percutaneous LAA Occlusion Devices
PLAATO
The percutaneous LAA occlusion (PLAATO) device was the first device designed for percutaneous LAA closure.18 It was made of a nitinol cage covered with a polytetrafluoroethylene membrane (Figure 1).18 In a multicenter registry of 64 high-risk patients with contraindications to warfarin,19 the procedure success was high (residual flow ≤ 3 mm in 98%); it also seemed to protect against stroke in that the annual incidence of stroke or transient ischemic attack was 3.8% compared with an expected rate of 6.6%, based on the CHADS2 score of the study population. This device was not evaluated further, but it provided proof-of-concept for device occlusion of the LAA for stroke prevention.

WATCHMAN
The WATCHMAN™ Left Atrial Appendage Closure Device (Boston Scientific, Natick, MA) consists of a self-expanding nitinol frame and a membrane cap (Figure 1) deployed in the LAA via a trans-septal puncture (Figure 2). The device has been evaluated in two randomized controlled clinical trials and one Continued Access Registry. The PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation)20 and PREVAIL (Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device In Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy)21 studies were noninferiority trials that compared the WATCHMAN device with warfarin anticoagulation in AF patients. Inclusion in PROTECT-AF required a CHADS2 score ≥ 1, while PREVAIL-AF required a CHADS2 score ≥ 2 or of 1 if additional stroke risk
Factors were present. Patients were randomized to either device implantation or warfarin in a 2:1 fashion. WATCHMAN-implanted patients were treated with warfarin and aspirin for 6 weeks, at which time a follow-up transesophageal echocardiography (TEE) was performed. If the TEE findings showed no thrombus or peridevice leak ≤ 5 mm, warfarin was discontinued and aspirin and clopidogrel prescribed for 4.5 more months followed by indefinite aspirin therapy.

In PROTECT-AF, the WATCHMAN was noninferior to warfarin for the primary endpoint of cardiovascular/unexplained death, any stroke, or systemic embolism at 1065 patient-years, 1588 patient-years, and 2621 patient-years of follow-up. At 2621 patient-years, the WATCHMAN device not only met superiority criteria but also demonstrated reduced all-cause mortality (HR 0.66; 95% CI, 0.45 to 0.98; frequentist \( P = 0.038 \)) and led to improved quality-of-life measures. There were important limitations of these analyses, including a greater rate of withdrawal in the warfarin arm, an unusually high rate of hemorrhagic stroke in the warfarin group, inclusion of patients with CHADS2 = 1 who may not require anticoagulation, and a large noninferiority margin.

In the smaller PREVAIL trial, the 18-month rates of the coprimary endpoint of cardiovascular death, any stroke, or systemic embolism were numerically similar between the WATCHMAN device and warfarin anticoagulation, but the device did not achieve noninferiority because the upper bound of the 95% credible interval for the 18-month rate ratio was not lower than the prespecified noninferiority margin (1.75). This finding should be interpreted in the context of a lower-than-expected event rate, particularly among the patients randomly assigned to warfarin, and the relatively short duration of follow-up.

The WATCHMAN device did not reduce ischemic stroke compared to warfarin in either trial. However, data provided support for the mechanistic hypothesis that LAA occlusion reduces thromboembolic risk in the absence of oral anticoagulation. Some strokes in WATCHMAN-treated patients were due to
air embolism. In PREVAIL, WATCHMAN implantation was noninferior to warfarin for the coprimary endpoint of ischemic stroke or systolic embolism occurring more than 7 days post randomization.

In PROTECT-AF, the rate of the major safety endpoint (excessive bleeding or a procedure-related complication) at 18 months was greater in the patients randomly assigned to the WATCHMAN compared with warfarin (RR 1.69; 95% CrI 1.01-3.19), determined by pericardial effusion requiring treatment and procedure-related ischemic stroke.20,26 Most safety events in the device arm occurred within the first 7 days of the procedure.26 However, over the longer-term, the difference in the cumulative safety events narrowed between treatment groups due to bleeding events in the warfarin arm, so that at 2621 patient-years of follow-up, there was no significant safety difference between the WATCHMAN and warfarin (RR 1.17, 95% CrI 0.78-1.96).24

In PREVAIL, safety events related to the procedure, including the incidence of serious pericardial effusions and procedural stroke, were significantly reduced compared with PROTECT-AF.21 This improved safety profile was consistent with the findings of the prospective Continued Access Registry that followed the PROTECT-AF trial.25

The ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) was an observational study of 150 AF patients who were ineligible for warfarin therapy27 predominantly due to prior bleeding. After WATCHMAN implantation, patients received clopidogrel for 6 months and aspirin indefinitely. At 14.4 ± 8.6 months, the observed rate of stroke or systemic embolism was 2.3% per year, significantly less than the expected rate of 7.3% per year based on CHADS\textsubscript{s} score.

**Amplatzer Cardiac Plug**

The AMPLATZER\textsuperscript{TM} Cardiac Plug (ACP) (St Jude Medical, Minneapolis, MN) is a self-expanding nitinol mesh that consists of a distal lobe and proximal disk, each with a sewn polyester patch, connected by a short central waist (Figure 1).28 The distal lobe acts as an anchor within the LAA, and the proximal disk covers the mouth of the LAA from the LA side, therefore the mechanism of LAA occlusion differs from that of the WATCHMAN, which occludes the LAA from within the appendage itself.

Clinical data with the ACP derive from several small observational studies, many of which are retrospective in design or involve a single center or operator.28-33 Most of the patients enrolled in these studies had intolerance or contraindications to oral anticoagulation and were treated with aspirin and clopidogrel during the postprocedural period. The most frequent safety events appear to be pericardial effusions and device embolization occurring at similar rates as the WATCHMAN experience. A randomized trial is necessary to robustly assess safety and efficacy in preventing thromboembolic events, as the mechanism of implantation and of closure differs from that of the WATCHMAN device. Moreover, most of the published studies of the ACP do not include patients who are candidates for oral anticoagulation. A large randomized clinical trial of the ACP compared with oral anticoagulation was recently halted, likely due to the presumed eminent U.S. Food and Drug Administration (FDA) approval of the WATCHMAN device, which would make patient enrollment in such a trial difficult.

**Lariat Procedure**

The LARIAT\textsuperscript{®} Suture Delivery Device (SentreHEART, Inc., Redwood City, CA) is designed to ligate the LAA through the delivery of a surgical suture via a combined trans-septal and subxiphoid approach (Figure 3).34,35 The system has FDA approval (510K) for “suture placement and knot-tying for use in surgical applications where soft tissue are (sic) being approximated.” However, its design is conceived for and clinically applied to LAA ligation. LAA anatomy has to be favorable as assessed by preprocedural cardiac computed tomography (CT); an LAA diameter > 40 mm, the presence of lobes behind the pulmonary artery, or a posteriorly-oriented appendage should all be avoided. A micropuncture or 17-G epidural needle is used to advance a guidewire and then a 14-Fr sheath into the pericardial space. A magnet-tipped guidewire is advanced into the anterior aspect of the LAA, and a second magnet-tipped guidewire is advanced into the pericardium toward the LAA. The magnets snap together to form a rail, over which the LARIAT snare is advanced and closed at the mouth of the LAA using TEE and fluoroscopic guidance. This snare contains a preloaded surgical knot (Figure 1D).

To date, the safety and efficacy of LAA closure with the LARIAT has been limited to small observational studies.36-39 The first reported series included 92 patients who were poor candidates or ineligible for warfarin therapy.36 Successful closure (residual leak < 1 mm) was achieved in 96% of cases. Significant pericardial effusions occurred in three patients, and pericarditis occurred in two patients. At 1-year follow-up, 55% of the patients remained on warfarin therapy and there were no thromboembolic events. Price et al.38 compiled retrospectively collected data from eight sites in the United States and a total of 154 unselected patients. In nine patients, the LARIAT device was not deployed due to access or delivery issues. Of the remaining 145, successful LAA ligation was achieved acutely in 92%, which was 86% of the attempted patients. Follow-up post-discharge imaging of the LAA was available in 63 patients, of whom 79% had persistent complete LAA ligation. Significant procedural complications occurred, including major bleeding (9%) as well as right and left ventricular perforations (3 total) that required surgery. On post-discharge follow-up, strokes occurred in two patients, and six pericardial and pleural effusions also occurred (three of each). A total of four deaths occurred following the procedure.
These data highlight that despite comparable rates of acute success with LAA ligation, the LARIAT device is associated with higher rates of complications than previously reported when applied to an unselected population of patients deemed to be at high risk of stroke and bleeding (the standard clinical indications). Of particular concern—in the absence of efficacy studies showing stroke protection—is the occurrence of LAA stump thrombosis (four cases) and the significant rate of incomplete LAA closure (up to 21%). Similar results were reported by Miller et al. in a series of 41 patients from four centers. Despite achieving an acute success (complete LAA closure) in 38 patients (93%), incomplete closure was detected on follow-up imaging in 24% of the patients. Two patients required surgical repair of an LAA perforation. One patient had a transient ischemic attack, and eight developed pericardial effusions requiring pericardiocentesis.

Similarly, despite the high acute technical success, the incidence of complications and significant LAA leaks raise concerns about its safety when applied to unselected populations. Thrombus at the LAA ligated stump has been reported. The real incidence remains unknown in the absence of prospective data collection sets.

In sum, from the small amount of data available, the LARIAT appears to provide high rates of acute anatomic closure, although procedural morbidity is not uncommon. Robust clinical efficacy data is absent.

Other Devices

Several other LAA closure devices are currently in development. The WaveCrest® LAA Occlusion System (Coherex Medical, Salt Lake City, UT) is unique in that device implantation is a two-step process: first, the proximal ePTFE (polytetrafluoroethylene) cap/occluder is positioned, and then the distal anchors are deployed. Incorporation of foam into the edges of the occluder could potentially enhance LAA sealing. This device currently has CE mark, and initiation of a pivotal trial within the United States is planned. The LAmbre™ LAA occluder (Lifetech Scientific Corp., Shenzhen, China) is a self-expanding nitinol device consisting of a distal hook-embedded umbrella and a proximal covering disk, both with sewn-in PET fabric. A short articulating central waist connects the umbrella and cover. The device is advanced through a relatively low-profile delivery sheath (8-10 Fr).

LAA Exclusion: Will it Ever Surpass Anticoagulation?

The role of LAA exclusion strategies in the therapeutic armamentarium for AF critically depends on their efficacy at stroke prevention and their procedural safety. Novel oral anticoagulants (NOACs) are noninferior or superior to warfarin for prevention of stroke and systemic embolism and do not require ongoing monitoring. However, inherent to OACs is a substantial ongoing hazard of major bleeding as well as noncompliance, side effects, and, in the case of the NOACs, lack of an available antidote. Currently, none of the LAA exclusion strategies has FDA approval for the indication of stroke prevention. Their final role will depend on their ability to demonstrate comparable clinical efficacy and safety to NOACs or acceptable outcomes when NOACs are contraindicated. Lariat is FDA approved for suture delivery and tissue approximation and its use for stroke prevention is considered “off-label”. Atriclip is FDA approved for surgical clipping of the left atrial appendage but not for stroke prevention. The Watchman device does not have FDA approval. At this point, compelling data are still absent.

References


