Minimally Invasive Closure of the Left Atrial Appendage: A Non-Pharmacologic Approach to Prevention of Stroke in Patients with Atrial Fibrillation

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ABSTRACT

Atrial Fibrillation's (AF) role in the pathogenesis of thromboembolic stroke has been well established, with estimates from trials of approximately 15-20% of all strokes in the U.S. Research shows more than 90% of atrial thrombi originate from the left atrial appendage (LAA). Traditionally, oral anticoagulants (OACs) have been the keystone of management for AF in reducing the risk of thromboembolic stroke. However, OACs also pose a non-negligible risk of bleeding with between 30-50% of eligible patients not receiving OACs due to absolute contraindications or perceived increased bleeding risk. New technologies aimed at isolating the LAA through ligation, exclusion, or occlusion are attempting to mitigate the embolic risk posed by LAA thrombi while simultaneously reducing the bleeding risk associated with OAC. In this review, we discuss the safety, efficacy, and clinical utility of these technologies as alternatives to OACs.

KEYWORDS: Atrial fibrillation, Lariat, Left atrial appendage closure, stroke, Watchman

INTRODUCTION

Atrial Fibrillation's (AF) role in the pathogenesis of thromboembolic stroke has been well established. Currently, in the United States, stroke ranks as the fifth leading cause of death. There are approximately 795,000 strokes annually with one occurring every 40 seconds (1). Estimates from numerous trials, including the local Framingham trial, attribute approximately 15-20% of all strokes to AF (2-3). The mere presence of AF carries with it a five-fold increased risk for embolic stroke (4). Research has shown that more than 90% of atrial thrombi originate from the left atrial appendage (LAA). Strokes originating from the LAA tend to be more severe with a 70% chance of death or permanent disability (5). Traditionally, oral anticoagulants (OACs) have been the keystone of management for AF and embolic strokes, with relative overall success. In fact, a meta-analysis in 2014, showed a 64% embolic stroke reduction with a 26% mortality reduction with OAC use (6,7). While OACs have demonstrated an ability to reduce embolic stroke, they also are associated with a non-negligible risk of bleeding. Unfortunately, between 30-50% of eligible patients do not receive OACs due to absolute contraindications or perceived increased bleeding risk (8). Bleeding risk takes several forms, from increased risk of spontaneous intraparenchymal hemorrhage to the complications of surgical procedures. Hence, current clinical guidelines for OAC balance the risk of stroke using risk assessment tools such as the CHA2DS2-VASc score against the patient's native bleeding risk via HAS-BLED score. New technologies aimed at isolating the LAA through ligation, exclusion, or occlusion are attempting to mitigate the embolic risk posed by LAA thrombi while simultaneously reducing the bleeding risk associated with OAC. As with most percutaneous procedures in modern cardiology, these LAA occluder technologies have evolved from cardiothoracic surgical techniques traditionally used to isolate the LAA from the systemic circulation.

DEVICES FOR CLOSURE OF THE LAA

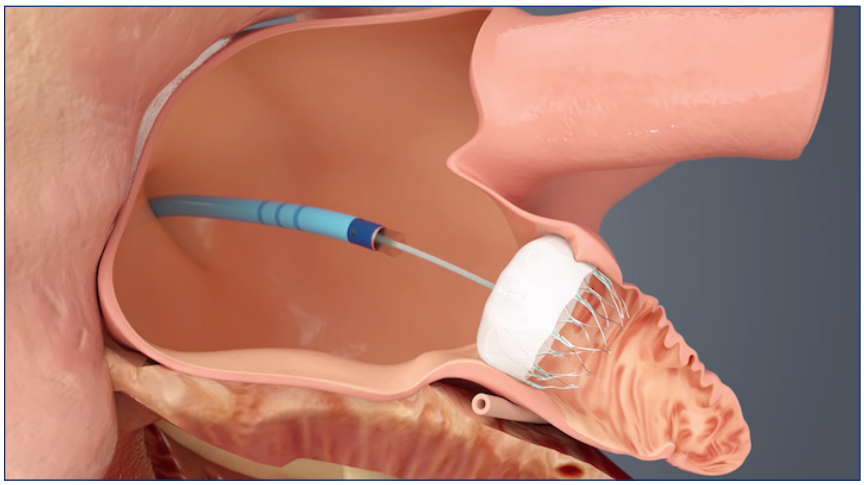
Broadly the devices used for closure of the LAA can be classified into two primary categories, epicardial and endocardial. The epicardial devices include the LARIAT suture delivery device (SentreHEART, Palo Alto, CA, USA) and the BELIEF trial. The LARIAT physically isolates the LAA by ligation through a combination of pericardial and transseptal access. Individuals with a history of pericarditis, cardiac surgery, recent myocardial infarction, or pectus excavatum are not candidates for the LARIAT (9) approach. The BELIEF trial utilized radiofrequency ablation to isolate the pulmonary veins while rendering the LAA inert, adding rhythm control to LAA exclusion. The BELIEF trial showed the possible benefit of radiofrequency isolation of the LAA in maintaining consistent rhythm control (10). The obvious advantage of both of these epicardial techniques is that there are no retained endovascular devices. The endocardial devices currently available include Amplatzer Amulet (St. Jude Medical, St. Paul, MN, USA) and the Watchman device (Boston Scientific, Plymouth, MN, USA). Both of these devices are percutaneously delivered occluders which remain with the LA. Of all the percutaneous devices available for LAA occlusion, the Watchman has been the most thoroughly investigated with extensive trials and follow-up registry data. **See Figures 1 & 2**.

PERCUTANEOUS LAA OCCLUSION

Percutaneous left atrial appendage occlusion (LAAO) via the Watchman device has been extensively studied. The Percutaneous Closure of the Left Atrial Appendage Versus Warfarin

Figure 1. WATCHMAN Left Atrial Appendage Occluder Device.

Figure 2. Deployment of the WATCHMAN Left Atrial Appendage Occluder Device via a transeptal catheter.



Therapy for the Prevention of Stroke in Patients with Atrial Fibrillation (PROTECT-AF) trial was a large, non-blinded, randomized trial utilizing the Watchman device in a non-inferiority comparison to standard warfarin therapy (11). It was a multi-center, open-label trial involving 707 patients with non-valvular AF randomly assigned in a 2:1 ratio to either Watchman implantation or long-term warfarin (INR 2.0-3.0). Patients in the device group were given warfarin for 45 days to facilitate device endothelialization, a timeline chosen from canine experience. After 45 days, warfarin was discontinued and a follow-up transesophageal echocardiogram (TEE) showed either an acceptable residual per-device flow with a jet <5mm or complete LAAO. After discontinuation of warfarin, clopidogrel and aspirin were given for 6 months, followed by aspirin alone. The control arm received warfarin with a target INR between 2.0–3.0, which was only accomplished two-thirds of the time despite close INR monitoring. Implant success rate was 91%. Primary outcomes of stroke, systemic embolism, and cardiovascular death were measured at 18 months and the event rate was similar in both arms (3.0 vs. 4.9 events per 100 patient-years). The PROTECT-AF study successfully demonstrated non-inferiority of the Watchman device compared to standard warfarin therapy. Subsequently, several subset analyses were conducted, and while being constrained by the limitations inherent to subset analysis, some notable findings were discovered. One analysis of the PROTECT-AF trial assessed quality-of-life parameters in a subset of 547 patients (361 device and 186 control) (12). This demonstrated that patients with AF at risk for stroke who underwent LAAO had favorable quality-of-life changes at 12 months compared to patient treated with warfarin. At face value this makes sense; warfarin patients require frequent blood-test monitoring, which places a burden on a patient's time. A post-hoc analysis of the PROTECT-AF and its long-term monitoring registry, the Continuous Access Protocol, assessed the net clinical benefit (NCB) of LAAO. They looked for rates of thromboembolism, intracranial hemorrhage, major adverse events, and death while objectively comparing Watchman implantation to warfarin. This study showed that the NCB of LAAO was highest for those at highest risk for stroke, but also reported that this benefit increased over time. As with most device trials, the NCB favored the control arm in the initial 6-month period; however, by 6–9 months, the NCB changed favorably toward the intervention arm. In the early phase, those receiving the device had procedural-related complications to deal with such as cardiac tamponade or procedure-related stroke. Additionally, this study showed that operator experience might have some bearing on the procedural complication rate.

The ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology (ASAP) Registry demonstrated that all-cause stroke and systemic embolization risk was 2.3% per year. Also, the observed ischemic stroke rate was 77% lower than expected by the CHA2DS2-VASc predictive model (13). In 2014, the long-term follow-up data from the PROTECT-AF trial were published (14). With a mean follow-up of 3.8 years, the primary efficacy rate (combined end-point consisting of strokes, cardiovascular death or unexplained death, and systemic embolism) was lower in the Watchman group (2.3%) than in the control arm (3.8%), reflecting a 40% relative risk (RR) reduction, and a 96% probability of superiority. In 2016, the results from the Registry on WATCHMAN Outcomes in Real-Life Utilization (EWOLUTION) were released. In this large, prospective, multicenter registry a total of 1025 subjects from 47 centers in 13 countries were enrolled. Interestingly, their CHA2DS2-VASc risk scores were 4.5 +/- 1.6 with almost half the subjects having either a history of TIA (10.7%), ischemic stroke (19.7%), or hemorrhagic stroke (15.0%), classifying this population as high-risk. Additionally, 62% of patients were deemed unsuitable for OAC by their physician based

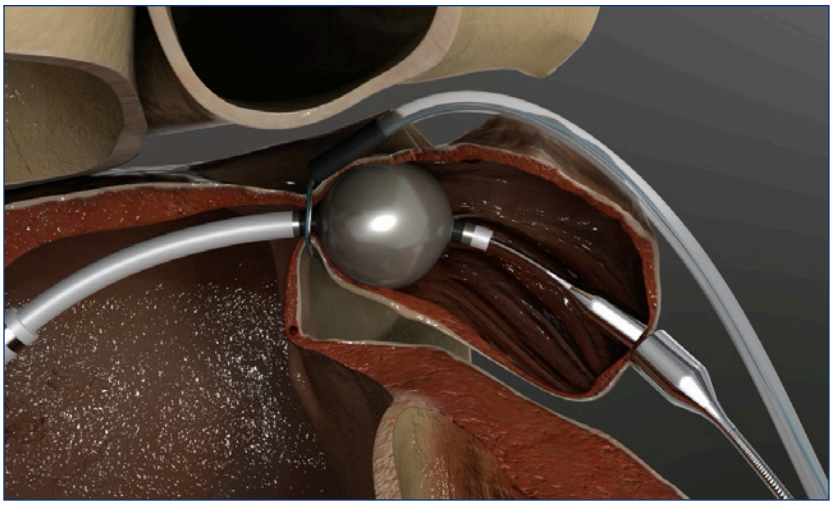
on factors such as inability to adhere to OAC use, bleeding history, or high risk for bleeding as dictated by their elevated HAS-BLED score. The EWOLUTION (15) registry demonstrated high procedural success rate (98.5%) with a low 7-day serious adverse event rate (2.8%). An interesting feature of this trial was the inclusion of patients who would have been OAC candidates, in contrast to the PROTECT-AF and PREVAIL trials in the U.S., which restricted enrollment to patients deemed unsuitable for OAC administration. The flexibility regarding enrolling individuals who are OAC candidates was made possible by current European Society of Cardiology (ESC) guidelines for AF. Under current ESC guidelines, LAAO is given a Class IIb, Level of Evidence B recommendation (8).

PERCUTANEOUS LAA LIGATION AND LAA ABLATION

Percutaneous LAA ligation devices such as the LARIAT offer a method of LAA exclusion by ligation, utilizing a novel pericardial and transseptal process. **See Figure 3**. While less well-studied than the LAAO devices, the benefit of the LARIAT lies in the establishment of tissue-to-tissue exclusion of the LAA from the circulation and the lack of an implantable device with a risk of embolization. The downside of the LARIAT stems from its procedural complexity and the exclusion of individuals with a history of pericarditis, cardiothoracic surgery, recent myocardial infraction, or a prior embolic event within 30 days of the procedure. The first single-center trial of the LARIAT device was done in Poland. It included 89 patients, mean age 62 years and a mean CHA2DS2-VASc score of 2.8. Technical success was achieved in 96%, with 2 epicardial complications and 1 transseptal complication. Major post-operative adverse events included severe pericarditis in 2 patients, 1 late pericardial effusion, 2 unexplained sudden deaths, and 2 late strokes (9). While complete closure was verified by TEE one year later, only 65 of the 89 patients underwent follow-up TEE. In 2013, the results from the U.S. Transcatheter LAA Ligation Consortium, a multi-center retrospective analysis of 154 LARIAT procedures (16) were published. Their findings included a procedural time of 76.6 minutes, a technical success rate of 94%, and procedural success rate of 86%. Major adverse events included significant pericardial effusion requiring intervention in 10.64%, bleeding requiring transfusion 4.5%, and emergent cardiac surgery 2.0%. Their median follow-up was 112 days with TEE performed in 63 patients demonstrating residual leak in 20%, and presence of thrombus in 4.8%. The U.S. experience showed that technical success is possible, but not without concerning pericardial bleeding and effusion.

The application of radiofrequency energy to achieve electrical isolation of the LAA represents a departure from implantable device or surgical exclusion therapies. In the BELIEF Trial, a randomized trial of patients with long-standing persistent AF (LSPAF), patients underwent two different ablative strategies; an extended pulmonary vein (PV) antrum ablation plus non-PV trigger ablation (Group 1) versus standard ablation plus non-PV trigger ablation plus empiric LAA isolation (Group 2) (10). The primary endpoint of the study was freedom from atrial arrhythmia, defined as atrial fibrillation, atrial flutter, and atrial tachycardia lasting >30 seconds. The secondary endpoints assessed at a <12-month interval included stroke, death, and rehospitalization. Patients were followed at 12- and 24-month intervals with no patients lost to follow-up. If the patients had breakthrough arrhythmia at their 12-month evaluation, they were rescheduled for another ablation. Individuals in the BELIEF trial underwent an average of 1.3 procedures and all were followed out to 24 months. At 24 months, the cumulative success rates were 76% and 56% in Group 1 and Group 2 respectively. Four patients (4.5%) in Group I suffered a stroke but there were no strokes or TIAs among Group 2 patients at the 24 month follow-up. While the success rates for complete electrical isolation are relatively low, the lack of stroke or TIA in the electrically isolated LAA remains an interesting finding. Larger studies will need to be done to see if electrical isolation of the LAA remains a viable alternative to device-based or suture-mediated LAA exclusion.

Figure 3. LARIAT (SentreHEART Inc.) Left Atrial Appendage Ligation Device showing transeptal and epicardial delivery catheters and ligature being deployed at the neck of the left atrial appendage.



CONCLUSION

Exclusion of the LAA as a nidus for thromboembolic stroke in patients with AF stands as a viable alternative therapy, especially in light of the risks posed by OAC. Leading the charge in excluding the LAA, the Watchman device is well studied, touting efficacy data from PROTECT-AF and further bolstered by

long-term registries such as PREVAIL(17) and CAP. Currently, the Watchman device is FDA-approved for patients with non-valvular AF at increased risk for stroke, recommended for OACs, and have an appropriate reason for seeking an alternative to OACs. Emerging devices and technologies, such as the LARIAT and LAA isolation via ablative strategies clearly warrant further investigation and are currently only available through clinical trials and registries but are not currently approved alternatives to either OAC or the Watchman device.

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