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SECONDARY PREVENTION AND INTERVENTION (D. STEINBERG, SECTION EDITOR)

Review on Future Targets and Current Trends in Transcatheter Left Atrial Appendage Closure

Nicholas S. Amoroso [1]

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Abstract

Purpose of Review Atrial fibrillation is cause for a growing burden of thromboembolic stroke. Transcatheter left atrial appendage closure is an alternative to lifelong oral anticoagulation for many patients with nonvalvular atrial fibrillation. Reviewed here are three commonly used devices (Watchman, Amplatzer Cardiac Plug/Amulet, and Lariat) and their key clinical trials, special candidate patient populations, and recent investigations of the impact of post-procedure antithrombotic strategies.

Recent Findings Transcatheter left atrial appendage closure devices provide noninferior thromboembolic stroke risk reduction and superior bleeding risk reduction compared with oral anticoagulation in nonvalvular atrial fibrillation. Very recent studies of post-procedure antithrombotic regimens describe a variety of anticoagulant and antiplatelet pharmacotherapies without clear impact on device-associated thrombus or post-procedure embolic stroke though more study is needed.

Summary Transcatheter left atrial appendage closure is a viable alternative to lifelong oral anticoagulation to decrease thromboembolism and bleeding in patients with nonvalvular atrial fibrillation who are at increased risk of adverse event with anticoagulants. Patient populations at risk of bleeding on anticoagulants have been demonstrated to benefit from this technology, but there are several additional benefits of left atrial appendage closure unrelated to bleeding risks for specific patient populations. Data on the optimal short-term (weeks to months) post-procedure antithrombotic regimens is emerging and will play a significant role in how to best treat patients and which patients will benefit most from left atrial appendage closure.

Keywords Left atrial appendage closure · Left atrial appendage occlusion · Left atrial appendage ligation · Atrial fibrillation · Watchman · Amplatzer cardiac plug · Amulet · Lariat · Transcatheter

Introduction

The burden of atrial fibrillation has continued to drastically mount as the population of the developed world ages. The estimated prevalence of atrial fibrillation (afib) is currently at 3% of adults 20 years of age or older, predicted to reach 12.1 million people in the USA alone by 2030 [1, 2]. Arguably, the most significant burden of afib is the associated thromboembolic strokes which total more than 20–30% of the millions of stroke sufferers per year [3, 4]. Reducing the incidence of atrial fibrillation-related thromboembolic cerebrovascular accidents is a chief concern for both physician and patient.

The most recent 2019 ACC/HRS guidelines provide a 1A recommendation for oral anticoagulation (OAC) for patients with CHA2DS2Vasc score ≥ 3 in women or ≥ 2 in men but acknowledge that many patients are at increased risk of bleeding or have poor medication adherence making them poor candidates for anticoagulation [5]. For these patients, many will go without anticoagulation while others have previously been treated with less effective antiplatelet medication regimens [6].

Prior studies have suggested that 90–95% of afib-related thromboemboli originate in the left atrial appendage making it an attractive target for nonpharmacologic therapies [7, 8]. Initial attempts to offer nonpharmacologic thromboembolism reduction were only available through surgical intervention to exclude or remove the left atrial appendage. This was observed to have mixed success, depending greatly on the surgical technique or device employed, with problems of surgical

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✉ Nicholas S. Amoroso
amoroson@musc.edu

[1] Division of Cardiology, Department of Medicine, Medical University of South Carolina, 30 Courtenay Drive, MSC 592, BM 205, Charleston, SC 29425, USA

complications, incomplete appendage exclusion, and discouraging invasiveness of the techniques [9]. The experience with transcatheter left atrial appendage closure (LAAC) has proven more palatable for patients and first offered a head-to-head comparison with oral anticoagulation on the scale of a large randomized trial in the PROTECT-AF trial in 2009 showing that exclusion of the appendage reduced the risk of thromboembolic stroke [10].

This review will discuss the most common of transcatheter LAAC devices, the literature base supporting LAAC in various patient populations of interest, and the shifting trends of periprocedural pharmacotherapy used after LAAC. While there are ongoing trials testing the utility of surgical left atrial appendage exclusion with different devices, the clinical experience is smaller, the technique varies between devices, and the patient population it is used in differs (chiefly undergoing cardiac surgery for other primary indications) from many patients undergoing transcatheter LAAC. Accordingly, this review will forgo a detailed discussion of surgical left atrial appendage exclusion and focus on transcatheter therapies, but acknowledge it is a technique to consider in patients undergoing cardiac surgery worthy of separate review.

Common Currently Available Left Atrial Appendage Closure Devices

To date, the Watchman™ (Boston Scientific, Marlborough MA, USA), Amulet™(Abbott, Lake Bluff Il, USA), and Lariat®(SentreHEART, Redwood City CA, USA) devices are currently available commercially for use in patients and include two different methods of LAAC: endocardial plugging of the appendage (Watchman/Amulet) and epicardial ligation of the appendage (Lariat). All three devices utilize transvenous access and a catheter across the interatrial septum; Lariat deployment additionally uses percutaneous epicardial access. The indications for commercial use for each are similar, offering nonpharmacologic thromboembolism risk reduction in patients at increased risk of bleeding or otherwise poor candidates for lifelong oral anticoagulation. The observed long-term rates of stroke, rates of bleeding, and periprocedural complications rates seen in major trials with each device are marginally different, as discussed briefly below.

Watchman™

The Watchman device currently produced by Boston Scientific is a truncated, conical, nitinol self-expanding device with fixation anchors around its distal end. A screw hub is centered on its abluminal PTFE-fabric covered surface which allows it to be connected to a cable. The device is loaded in a catheter through which it is delivered to the left atrial appendage. The cable and catheter are removed, leaving the device lodged in the appendage. Over the following weeks, endothelium grows to cover the abluminal surface and seal off the appendage os.

Watchman is the only LAAC device which has undergone head-to-head comparison with OAC in large randomized trials. The PREVAIL and PROTECT-AF trials are the landmark randomized trials which earned Watchman approval for clinical use in the USA and worldwide. The PROTECT-AF trial recruited nonvalvular afib patients between 2005 and 2008 with CHADS2 score of 1 or greater, randomized them to warfarin or Watchman device and followed them for 4 years. Aggregately, 98% had successful implant, the rate of stroke or thromboembolism was 1.75/100 patient-years (significantly fewer hemorrhagic strokes and similar ischemic strokes compared with warfarin), nonprocedural bleeding occurred in 6.0%, and major adverse periprocedural events 4–5% [11••, 12••]. The authors concluded that LAAC with Watchman met noninferiority and superiority to warfarin in preventing a combined endpoint of cardiovascular death, stroke, or systemic embolism as well as cardiovascular and all-cause mortality [13••].

Amplatzer Cardiac Plug/Amulet®

The Amplatzer Cardiac Plug (and its second generation device called Amulet) is another nitinol, self-expanding, polyester fabric covered, plug-like device attached via a recessed central screw to a cable delivered through a sheath to the LAA. The occluding portions of the device include a cylindrical portion (which sits deeper inside the LAA) and a flat circular portion (which covers the more proximal LAA os) connected together at the middle, much like a drain stop or an infant's pacifier. The changes in design with the second generation, Amulet, are discussed elsewhere and notably include larger dimensions and inverted end screw [14]. Similar to the Watchman, endothelialization of the device occurs weeks after implant.

The first-generation device received CE mark in 2008 followed by Amulet CE mark approval in 2013. One of the largest sources of clinical data on the Amplatzer device comes from the multicenter registry where Tzikas et al. described procedural events and clinical outcomes at an average follow-up of 13 months (interquartile range of 6–25 months) in 1047 patients undergoing LAAC for nonvalvular Afib [15•]. With 97.3% successful implant rate in a "real world" experience, major adverse periprocedural events occurred in 4.97% including 1.24% tamponade and 0.76% death. In clinical follow-up, there was a 2.30% annual stroke rate and 2.08% annual bleed rate, both of which were roughly 60% relative risk reductions to predicted rates. The next contemporary large trial to evaluate the Amulet device will be the randomized clinical trial STROKECLOSE (ClinicalTrials.gov Identifier: NCT02830152) with a focus on patients with prior intracranial hemorrhage.

Lariat

The Lariat device is a lasso-like suture system that is delivered percutaneously into the epicardial space, guided to encircle the LAA with endocardial magnet and balloon catheter transvenous transseptal system which sits inside the LAA, allowing the epicardial suture lasso to tighten ligating the LAA closed. Feasibility testing was reported in 2011 [16] and its first clinical trial reported successful implant in 85/89 patients in 2013 lending 95% and 98% complete closure on TEE at 3 months and 1 year respectively [17]. Since initial study, the Lariat device has been used in more than 4500 patients in the USA alone though initial results from early clinical series raised concerns for periprocedural complications requiring emergent cardiac surgery, often related to pericardial access complications [18]. The rates of procedural complications improved with improvements in access techniques. Lakkireddy et al. reported in the largest study to date in 2016 a cohort of 712 patients, demonstrated 2.2% major procedural complications with updated micropuncture access technique, 1.44% requiring surgery, rather than 9% with early technique. Improvements in post-procedural pericarditis were also made with the use of colchicine and nonsteroidal anti-inflammatory drugs [19•]. Observed rates of thromboembolism after 4 years in a small series of 139 patients after LAAC with Lariat were reduced 81% compared with predicted (0.6% observed events, mean CHA2DS2-Vasc 2.9), major bleeding was seen with 78% relative risk reduction(0.8% bleeding with mean HASBLED 3.1), 1.6% mortality though this data is very limited given the small sample size [20]. A series of 259 patients observed 1.1% incidence of thromboembolism/stroke after implant [21].

Of mention, current ongoing trials with the Lariat device investigate improvements in atrial rhythm control, in addition to thromboembolic protection (e.g., aMAZE trial, ClinicalTrials.gov Identifier: NCT02513797).

Patient Populations

There are numerous patient populations who could benefit from LAAC as an alternative to lifelong OAC and can be grossly divided into those avoiding the bleeding risks of OAC and those avoiding nonbleeding risks, admittedly with common overlap. Much of the systematic literature has focused on the bleeding risks of OAC and has not delineated a difference between patients undergoing LAAC based on their contraindication for OAC (relative or absolute).

Avoid Anticoagulation to Avoid Bleeding

When considering nonpharmacologic therapies over anticoagulation, the most obvious difference has been reduction in bleeding risk. According to current recommendations noted in the 2019 ACC/HRS guidelines, patients with increased risk of bleeding can be considered for the transcatheter LAAC (IIb recommendation) [5]. This determination of risk is supported by previously validated clinical calculators including the HASBLED or ORBIT scores [22, 23]. These calculators include risk factors such as other medical comorbidities history of prior bleeding, hepatic or renal disease, ethanol abuse, age, uncontrolled hypertension, stroke, anemia, and other antiplatelet medication requirements to predict a patient annual risk major bleed. A cutoff of 2–4% is considered to be an elevated risk of bleeding in which a patient would be a reasonable candidate for nonpharmacologic therapy for stroke reduction. Unfortunately, when weighing the risks and benefits of anticoagulation it is true that patients with more risk factors for thromboembolic stroke also incur higher risk of annual bleeding, making this a high-risk population for medical morbidity with or without anticoagulation. Thusly, patients with a history of bleeding are frequently referred for transcatheter left atrial appendage closure.

Avoid Anticoagulation to Avoid Nonbleeding Risks

Though the evidence best illustrates the bleeding risk reduction, the current practice trends also include patients with other reasons to avoid anticoagulation and have expanded the use of this technology across the globe.

Of the other rationales for seeking nonpharmacologic thromboembolism prevention, end stage renal disease deserves special mention. These patients have not been studied for OAC in randomized trials and observational data on efficacy of OAC for stroke prevention is sparse and mixed in this population [24, 25]. Many end stage renal disease patients require hemodialysis which has long been considered a relative contraindication for warfarin use given its association with systemic calcinosis [26]. Calcinosis in its severe forms can go on to cause worsening of coronary artery disease, peripheral artery disease, valvular heart disease, and cutaneous pathology [26]. The compliance in dialysis patients is also reduced often for practical reasons such as hemodialysis access site oozing in addition to more commonplace bleeding issues as discussed above. This is certainly not the only population with issues with medication regimen adherence.

Patients noncompliant with prescribed anticoagulation are a population who expectedly benefit. Even compliant patients who are treated with warfarin struggle with labile INRs as demonstrated by a time-spent-in-therapeutic-range of ~ 60% seen in large high-quality afib trials with tightly supervised patient cohorts [27]. With the advent of direct oral anticoagulants such as apixaban, rivaroxaban, dabigatran, and edoxaban, that do not require INR checks or frequent dose adjustments, improved medication adherence and time-spent-in-therapeutic-range was expected to improve though

superiority of these medications over warfarin for stroke prevention was not dramatic and many patients struggle with prescription regimen adherence with a 30% nonadherence with OAC (warfarin or DOAC) after 2 years from diagnosis of atrial fibrillation [28]. While many patients are nonadherent with medications unintentionally, there is also a group of patients who refuse anticoagulation, or are not prescribed it, for perceived bleeding risks associated with injury-prone occupations or adventure sporting. Regardless of the reason for nonadherence, it is a major risk for stroke which is solved with successful LAAC. Medication compliance has been and always will be a considerable downfall of medical therapies and is an important practical indication for LAAC to prevent embolic stroke.

Inappropriate Populations

First and foremost, it is important to remember LAAC only prevents thrombus from embolizing from the left atrial appendage. If a person has any separate indication for anticoagulation, LAAC will not obviate the person from need for anticoagulation and therefore has no known benefit from undergoing LAAC. Transcatheter LAAC has never been studied as an adjunct to anticoagulation, only as a replacement for anticoagulation. As LAAC is still an invasive procedure with acceptable but inevitable major risks, it should not be performed in patients who will be taking anticoagulants regardless of left atrial appendage patency until clinical evidence to support such strategy is collected, if ever. Arguably, an optimal cost-benefit ratio will be achieved if use is limited to patients with reasonably long life expectancy (e.g., not performing LAAC in those with less than 1-year life expectancy); however, the long-term costs and savings between LAAC and OAC require continued long-term follow-up before definitive calculation is made.

The labeling and indication for transcatheter LAAC has consistently excluded "valvular atrial fibrillation," in other words afib due to mitral stenosis. This is important and appropriate. A large majority of valvular afib in the world is due to rheumatic heart disease and therefore the mechanisms and potential location for thrombus generation is different. With rheumatic heart disease, thrombi are not as isolated to the stasis-prone left atrial appendage and have been demonstrated to collect all around the atrial endomyocardium [7, 8].

There is not yet data to support that LAAC is categorically superior to OAC in such a way that it would become a first line therapy choice for the Afib population as a whole. Noninvasive OAC should continue to be first line therapy given the longstanding and large body of evidence behind it, but LAAC is a vital alternative for a growing swath of afib patients.

Trends and Considerations for Periprocedural Anticoagulation and Antiplatelet Therapy

An inconvenient irony of transcatheter LAAC is patients are supposed to take anticoagulation preceding and following the procedure for a set period. For Watchman, warfarin is recommended preceding implant and for at least 45-days post-implant [11••]. For Amulet, a wide range of antithrombotic strategies has been commonly used after implant though more often single antiplatelet [15•]. Interestingly, though the Lariat device does not leave any prosthesis in the intracardiac space, the clinical trials used 6 weeks of anticoagulation in those patients not felt to be "prohibitive" bleeding risk [19•].

The purpose of anticoagulation on either end of the timeline differs, but the inherent risks of anticoagulation mentioned above remain. Prior to the procedure, anticoagulation is used to lower the probability of left atrial appendage clot presence when the patient presents for LAAC. The manipulation of the appendage during LAAC is opportunity for thrombus dislodgement and embolization; therefore, one of the chief reasons for using transesophageal echocardiogram (TEE) during the procedure, other than device guidance, is to rule out the presence of atrial thrombus. After the procedure, anticoagulation and antiplatelet therapies are prescribed to prevent device thrombus formation while endothelium grows over the device surface (for Watchman or Amulet) or thrombus from residual leaks with any device. Prescribing anticoagulation for many patients presenting with relative contraindications can be a source of bleeding and significant worry for patient and prescriber alike. This is illustrated, to be discussed below, in recent documented prescribing patterns globally with many patients receiving alternative antiplatelet regimens post-procedure instead of the suggested regimens used in the above landmark clinical trials.

In the largest prospective real-world registry of Watchman patients, the EWOLUTION trial, 1005 patients scheduled to undergo Watchman implant were enrolled and received "routine" periprocedural care at the discretion of the care team. Notably, 99.8% of implanted patients were without significant device leak. The data reported after 1 year showed an interesting pattern very different from the periprocedural anticoagulation regimens used in the PROTECT-AF or PREVAIL trials: immediately post-implant, post-discharge medication regimens included 16% warfarin, 11% direct oral anticoagulants, 60% dual antiplatelet therapy, 7% single antiplatelet therapy, and neither anticoagulant or antiplatelet in 6% of successfully implanted patients [29]. This is likely representative of the relative post-procedure prescribing patterns in many medical centers but worldwide practice patterns are not well defined.

The EWOLUTION trial went on to describe 1-year rates of mortality, stroke, embolism, and bleeding. Ischemic stroke occurred in 1.1% and no hemorrhagic strokes were recorded;

none of these were procedural. Of those suffering ischemic strokes, half were on the same pharmacotherapy as the time of discharge and half had been changed to a less intensive anticoagulation regimen, including 55% single antiplatelet therapy, 27% dual antiplatelet therapy, 9% vitamin K antagonist, and 9% none. This rate of ischemic strokes is similar to those seen in PREVAIL and PROTECT-AF. The rate of nonprocedural bleeding was 2.3%. Both the observed rates of stroke and bleeding were significantly less than predicted rates for this population by individual CHA_2DS_2-Vasc and HAS-BLED calculations, respectively. The investigators also reported another intriguing outcome of unclear significance, device thrombus which can be defined as echocardiographic signs of thrombus collection on the abluminal surface of the implanted device in contact with active intracardiac blood flow. This type of thrombus would commonly be found attached to the edge or a screw hub but does not include any collections behind the occluded appendage space. Per routine, patients (87%) had follow-up exams with transesophageal echocardiogram and device thrombus was found in 3.7% (28 patients) of these cases. Importantly, device thrombus was not correlated to drug regimen and none of these patients went on to have subsequent adverse event during this follow-up period. One patient with stroke had device thrombus observed by CT [30•].

The question of post-procedure pharmacotherapy has been questioned in other trials. The ASAP trial was a nonrandomized study of 150 patients not eligible for warfarin who underwent LAAC with Watchman and received dual antiplatelet therapy alone for 6 months. The ischemic stroke and systemic embolism annualized rate were 1.8% (versus 7.3% expected with aspirin alone) and major bleeding event rates were 1.8% after a mean of 55.4 months of follow-up and $CHADS_2$ 2.8 [31].

Weise and colleagues examined outcomes after the use of 100 mg aspirin and 75 mg clopidogrel daily for 6 weeks after implant of any LAAC device (Watchman FLX, Watchman, Amplatzer Cardiac Plug, Amulet, or WaveCrest®(Biosense Webster, Irvine CA USA)) followed by single antiplatelet therapy in the absence of peridevice leak or device thrombus on 6-week TEE. Nonprocedure-related major bleeding occurred in 4.4% of patients taking DAPT and 4.0% after cessation of DAPT and the only risk factors for bleeding on univariate and multivariate analysis were age > 75 years old or renal impairment. Device thrombus on 6-week TEE was seen in 2% of patients on DAPT with only one patient having significant per-device flow. Due to various clinical indications, one-third of the patients went on to have TEE at $341 +- 271$ days while on single antiplatelet therapy and again 2.0% of patients had device thrombus detected. Thromboembolism was observed at an annual rate of 1.7% during 644.7 patient-years. The group went on to describe the scenario in which each patient had suffered an ischemic stroke which was very intriguing: six of the stroke patients were on single antiplatelet therapy, three on no antithrombotic, and two on DAPT. The strokes occurred at a wide range of timepoints after device implant between 28 and 934 days and eight of the 11 were later than 6 months after implant, a period when the standard of care would be single antiplatelet therapy. The investigators concluded that 6 weeks of DAPT was a sensible alternative for patients after LAAC and provided observations supporting that many ischemic strokes after LAAC may have little to do with antithrombotic pharmacotherapy [32]. Pracon et al. similarly found device thrombus to be unrelated to DAPT use, but more dependent on history of thromboembolism, lower left ventricular ejection fraction, device implant depth, and larger required device size [33•].

Others have gone on to study the use of aspirin alone post-LAAC including Korsholm et al. who studied 110 patients undergoing Amplatzer Cardiac Plug/Amulet implant with imaging at 6 weeks and 12 months. Device thrombus was detected in 1.9% of cases, stroke occurred in 2.3% though neither group overlapped [34].

Collectively, these above studies show that OAC may not provide much benefit over antiplatelet therapy in the weeks following LAAC though, randomized trial data of clinical outcomes is needed before making a conclusion. Thankfully, trials such as the ASAP-TOO trial (ClincalTrials.gov Identifier: NCT02928497) are in progress to gather such data. There should be an important distinction made between study cohorts of patients who are absolutely contraindicated to OAC and cohorts of patients at elevated risk with OAC; they should not be lumped together as one cohort. There is likely a difference in these patients' clinical demographics and potentially, therefore, a difference in their risk profiles for bleeding, thromboembolism, and procedural outcomes. Accordingly, the potential benefits and risks with LAAC are different. Data, like those presented above, about periprocedural antithrombotic regimens could guide which patients are considered benefiting candidates for LAAC; if short-term OAC is deemed unimportant to overall clinical benefit, patients with absolute contraindications to OAC may be considered better LAAC candidates or vice versa.

Conclusions

Transcatheter left atrial appendage closure has proven to be a reasonable alternative to lifelong systemic oral anticoagulation for the prevention of thromboembolism including embolic stroke for patients with nonvalvular atrial fibrillation. The price of LAAC includes periprocedural complications which have improved with operator experience and technique improvements though vary some between technologies. The relative risk reduction for embolic stroke is similar to that provided with oral anticoagulation and LAAC provides

superior reduction of long-term bleeding events in populations at increased risk of bleeding.

Though the body of evidence has focused on patients with higher bleeding risks, there are other patient populations for whom this nonpharmacologic therapy is expected to benefit significantly. Afib patients with end stage renal disease who are at high-risk for nonbleeding adverse medication effects and the general patient population at large who have demonstrated poor long-term medication regimen adherence despite adoption of DOACs are two large target groups who deserve more systematic study given potential benefits.

With growing experience with LAAC, there is accumulating data on the types of antithrombotic medications used in the first weeks to months post-procedure and the impact (or lack-thereof) it has on periprocedural thromboembolism or device thrombus. This information has important implications for how LAAC patients' bleeding and thromboembolism risks are best managed, if a patient's short-term tolerance for anticoagulants or antiplatelets should play a role in their candidacy for LAAC, and understanding the pathogenesis of thromboembolism in this cohort. Upcoming systematic studies of different patient populations in the context of latest DOAC therapies, of future iterations of LAAC devices, and studies to better define clinical outcomes with different antithrombotic regimens post-procedure will be critical to providing the best therapy for patients in the future.

Compliance with Ethical Standards

Conflict of Interest Nicholas S. Amoroso declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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PROTECT-AF trial which was the first large randomized controlled clinical trial examining left atrial appendage closure versus warfarin anticoagulation in nonvalvular atrial fibrillation patients. Patients in the device arm received the Watchman device which was found to be noninferior (like the earlier 18-month and 2.3-year follow-up findings) and superior to warfarin for the composite primary outcome of stroke, systemic embolism, cardiovascular, or unexplained death.

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