Device-based Approach to Prevention of Stroke in Atrial Fibrillation

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ABSTRACT. Thromboembolism in patients with atrial fibrillation (AF) is a significant cause of stroke. The left atrial appendage (LAA) has been implicated in an overwhelming majority of these cases. LAA remodeling seen in AF, including interstitial fibrosis, increased volume, and endocardial fibroelastosis, and echocardiographic changes visualized with echocardiography, such as low emptying LAA peak flow velocity and mechanical discordance of the left atrium and LAA have been suggested as mechanisms of thromboembolism. The current mainstay of stroke prevention in high-risk patients with AF is oral anticoagulation agents, although the risk of major bleeds and difficulty for patients to remain within the therapeutic range remain major shortcomings. To address this need for alternative stroke prevention interventions, several percutaneous and epicardial devices have been developed and are under clinical investigation. Here, we review current clinical trials of surgical and device-based approaches to stroke prevention and the safety and efficacy data of the forerunners of LAA exclusion devices, including the recently Food and Drug Administration-approved Watchman, and present a discussion of future challenges.

KEYWORDS. appendage closure, atrial fibrillation, left atrial appendage, stroke prevention.

Introduction

Atrial fibrillation (AF) is a major global public health challenge, placing a significant burden on health-care systems.1,2 Thromboembolism in patients with AF frequently leads to a devastating stroke. Risk stratification models and approaches to reduce thrombus formation and to prevent stroke remain an important clinical issue and an exciting field of investigation. The left atrial appendage (LAA) has been implicated in more than 90% of strokes in AF.3 Recently, there has been significant progress in the innovation and approval of methods of exclusion or isolation of the LAA with the hope of reducing strokes. We present a review of these recent developments and insights in the field.

Will appendage-directed therapy mitigate stroke risk in atrial fibrillation?

While stroke risk is unlikely ever to be zero as strokes can result from aortic arch atheromas, carotid arteries, and intracranial arteries (LAA-independent), the majority of strokes in AF are LAA-dependent, as suggested by recent long-term data from the PROTECT AF randomized controlled trial comparing warfarin therapy with...
Device-based Stroke Prevention in AF

LAA closure. In this study, LAA occlusion (LAAO) was found to be non-inferior and superior compared with warfarin, for the prevention of combined outcomes of stroke, systemic embolism, and cardiovascular death, as well as superior for cardiovascular and all-cause mortality.\(^4\)\(^-\)\(^5\) Thus it is intuitive to imagine that a therapy directed at excluding the LAA from circulation could theoretically minimize LAA-dependent stroke risk.

Excision of the LAA at the time of cardiac surgery is a common practice. However, prevailing literature on the effectiveness of surgical excision or occlusion on reducing stroke in patients with AF is limited to observational studies. A retrospective study of 242 patients with previous mitral valve replacement reported the absence of LAA ligation as an independent predictor of embolic events (17 versus 3.4\%, OR 6.7; 95\% CI 1.5–31.0, \(p = 0.02\)).\(^6\) A recent meta-analysis of both comparative randomized and observational studies of LAAO versus no LAAO in patients undergoing cardiac surgery found decreased incidence of stroke (1.4 versus 4.1\%, OR 0.48, \(p = 0.0003\)).\(^7\) Several prospective randomized surgical and device trials are currently investigating the efficacy of LAAO in preventing stroke (Table 1). Most of the surgical trials involve patients already undergoing cardiac surgery for another indication.

### Why is the LAA an important source for thrombus in AF?

The LAA is a tubular remnant of the embryonic left atrium (LA), which develops during the third week of gestation. In postnatal life it becomes an irregular tubular diverticulum and grows until the second decade of life. The LAA is morphologically different from the main LA and may be distinguished by its network of fine endocardial trabeculations and muscle bars that form the pectinate muscle.\(^8\) These muscular trabeculations can occasionally be found to extend inferiorly from the appendage to the vestibule of the mitral valve and are associated with a thin area of atrial wall that may be prone to perforation.\(^9\) A narrow tissue invagination, the left lateral ridge, separates the LAA ostium from the left superior pulmonary vein, and the vein and associated ligament of Marshall may be found on its epicardial aspect.\(^9\) The left lateral ridge, “Coumadin ridge,” may be visualized on echocardiography and is useful in defining the superoposterior border of the LAA ostium.\(^1\)\(^0\)

Understanding of LAA regional anatomy is essential. The LAA is contained within the pericardial sac and extends directly from the left atrial free wall to rest above the left ventricular free wall and directly under the main pulmonary artery (Figure 1).\(^8\) The left phrenic nerve travels with the pericardiophrenic neurovascular bundle outside the pericardium with a variable course that typically crosses over the LAA.\(^1\)\(^1\) Epicardially, vessels in relation to the ostium are as follows: the left aortic sinus and main coronary artery lie posterior and medial, the great cardiac vein and circumflex artery lie inferior, and the left anterior descending artery runs underneath.\(^1\)\(^0\) Functionally, the LAA is an adaptive chamber that responds to increased filling pressure. The compliance of the LAA exceeds that of the LA, a property that becomes significant during high left atrial pressure and volume states. Reservoir function of the LAA has also been observed during surgical clamping of the LAA during cardiac surgery.\(^1\)\(^2\) The LAA also has endocrine functions and is a major source of atrial natriuretic peptide (ANP). The concentration of these natriuretic and vasodilatory hormones further increases during hemodynamic stress and remains decreased postoperatively in patients who have undergone surgical LAA excision.\(^1\)\(^3\)

The LAA shape has also been implicated in predicting stroke risk independent of age, CHADS2 score and AF subtype, as increased morphologic complexity determined by computed tomography, such as degree of trabeculations, was associated with increased cerebrovascular event risk.\(^1\)\(^4\) There has been a considerable study of the correlation between the shape of the LAA and stroke risk prediction. Morphologies described among 932 patients varied in the degree of trabeculations and complexity, and correspondingly increased the risk of cerebrovascular events: chicken wing (48\%, event rate 4.4\% [20/451]); windsock (19\%, event rate 10.6\% [19/179]); cactus (30\%, event rate 12.6\% [35/278]); and cauliflower (3\%, event rate 16.7\% [4/24]).\(^1\)\(^5\)

### Atria and LAA in diseased states

Left atrial changes seen in AF include cardiomyocyte hypertrophy, myocyteolysis with loss of perinuclear sarcomeres, interstitial fibrosis, and oxidative stress changes reflected by increased heme oxygenase-1 and 3-nitrotyrosine levels. Oxidative stress has been implicated in AF pathogenesis and myocardial inflammatory markers such as C-reactive protein.\(^1\)\(^6\),\(^1\)\(^7\) Several studies have characterized LAA structural remodeling, but a definite link between these changes and a pro-thrombotic state have yet to be made. In a study of post-mortem hearts, patients with AF had a significantly greater LAA volume, a finding also consistent in patients with left ventricular hypertrophy, myocardial scar, or thrombus.\(^1\)\(^6\)

In non-valvular AF, the LAA had larger luminal surface areas, reduced pectinate muscle, and endocardial fibroelastosis with smooth luminal surfaces. These morphologic changes were similar to those observed in previous studies of AF with mitral valve disease.\(^1\)\(^9\)

Echocardiography studies suggest that low-emptying LAA peak flow velocity, associated spontaneous echo contrast, and even mechanical discordance of the LA and LAA are mechanisms of thromboembolism in AF.\(^1\)\(^4\),\(^1\)\(^9\)-\(^2\)\(^1\)

The association between the presence of LAA thrombus and mitral E’/e’ (an estimate of increased left ventricular filling pressures) and B-type natriuretic peptide, independent of the CHADS2 score, is further evidence that increased filling pressure transmitted to the atrium is important in LAA thrombogenesis. The Stroke Prevention in Atrial Fibrillation III trial reported a 2.5-fold increase in thrombus and cardioembolic events in clinically high-risk patients with a reduced peak LAA emptying velocity of less than 20 cm/s.\(^1\)\(^4\),\(^1\)\(^7\)

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\(^1\)\(^0\) The Journal of Innovations in Cardiac Rhythm Management, June 2015

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2039
<table>
<thead>
<tr>
<th>Device</th>
<th>Study</th>
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<th>Randomized</th>
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<th>Start date</th>
<th>Estimated completion date</th>
<th>Phase</th>
<th>Clinical Trial ID</th>
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<tbody>
<tr>
<td>Watchman (Boston Scientific, Natick, MA)</td>
<td>Left Atrial Appendage Occlusion vs. Usual Care in Patients With Atrial Fibrillation and Severe Chronic Kidney Disease</td>
<td>U of Magdeburg, Germany</td>
<td>- Non-valvular AF - Indication for OAC by CHA₂DS₂-VASc - Severe to End Stage Chronic Kidney Disease (eGFR &lt; 30)</td>
<td>Y</td>
<td>- Watchman - Aspirin (indefinitely) - Clopidogrel (6 mo)</td>
<td>- OAC</td>
<td>Safety/Efficacy</td>
<td>2014–2017</td>
<td>NCT02039167</td>
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<td></td>
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<tr>
<td>Watchman</td>
<td>Atrial and Brain Natriuretic Peptide Secretion After Percutaneous Closure of the Left Atrial Appendage</td>
<td>U of Leipzig, Germany</td>
<td>- Non-valvular AF - CHADS₂ ≥ 2</td>
<td>N</td>
<td>- Watchman --</td>
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<td>Efficacy</td>
<td>2010–2012</td>
<td>NCT01522911</td>
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<tr>
<td>Watchman</td>
<td>Evaluation of the Next Generation WATCHMAN LAA Closure Technology in Non-Valvular AF Patients (EOLVE)</td>
<td>Boston Scientific; Czech Republic, Germany</td>
<td>- Non-valvular AF - CHADS₂ ≥ 1</td>
<td>N</td>
<td>- Next generation Watchman --</td>
<td>--</td>
<td>Safety/Efficacy</td>
<td>2009–2013</td>
<td>NCT01196897</td>
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<td>LARIAT (SentreHEART, Redwood City, CA)</td>
<td>Left Atrial Appendage Exclusion Study (PLACE II)</td>
<td>SentreHEART, Inc.</td>
<td>- AF - Warfarin - contraindication or poor compliance</td>
<td>--</td>
<td>- LARIAT Suture Delivery Device</td>
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<td>Safety/Efficacy</td>
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<td>NCT01983605</td>
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<td>WaveCrest LAA Occlusion Study</td>
<td>Coherex Medical</td>
<td>- Non-valvular AF - CHADS₂ ≥ 1</td>
<td>N</td>
<td>- WaveCrest LAA occlusion device</td>
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<td>Safety/Efficacy</td>
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<td>Amplatzer (St. Jude Medical, St. Paul, MN)</td>
<td>ELIGIBLE (Efficacy of Left atrial Appendage Closure After Gastrointestinal BLEeding)</td>
<td>Hospital Clinic of Barcelona, Spain</td>
<td>- Non-valvular AF - CHADS₂-VASc ≥ 3 - Prior digestive bleeding without any treatable cause</td>
<td>Y</td>
<td>- Amplatzer - Aspirin - Clopidogrel</td>
<td>- OAC</td>
<td>Safety/Efficacy</td>
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<td>Occlutech (Helsingborg, Sweden)</td>
<td>Prospective, Non-randomized, Safety and Efficacy Study of a New Occluder Design for Minimally Invasive Closure of the Left Atrial Appendage (LAA) in Patients With Atrial Fibrillation (OLAAC)</td>
<td>Occlutech International AB</td>
<td>Non-valvular AF, CHA2DS2-VASc ≥ 2 and/or HAS-BLED score equal or greater than 2</td>
<td>N</td>
<td>Occlutech LAA closure device -- Safety/Efficacy</td>
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<td>Intervventional strategies in treatment of Atrial Fibrillation: Percutaneous Closure of the Left Atrial Appendage versus Catheter Ablation</td>
<td>Deutsches Herzzentrum Muenchen, Germany</td>
<td>AF</td>
<td>Y</td>
<td>LAA percutaneous closure, AF rate control</td>
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<td>NCT00486915</td>
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<td>Other</td>
<td>Impact of Left Atrial Appendage Exclusion on Short-Term Clinical Outcomes and Long-Term Stroke Incidence</td>
<td>London Health Sciences Centre</td>
<td>Patients undergoing mitral valve repair or replacement surgery</td>
<td>Y</td>
<td>LAA ligation -- No ligation</td>
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<td>Exclusion of the left atrial appendage (LAA) with the LAAx Inc. TigerPaw System (Phase II)</td>
<td>LAAx, Inc.</td>
<td>Patients undergoing elective non-endoscopic cardiac surgery, EF &gt; 30%, CHA2DS2 ≥ 2, AF/AFLE, Patients undergoing heart surgery for other reasons</td>
<td>N</td>
<td>LAAx TigerPaw System -- Safety/Efficacy</td>
<td>2009-2010</td>
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<td>NCT01561651</td>
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<td>Exclusion of the LAA in Patients undergoing Concomitant Cardiac Surgery</td>
<td>Population Health Research Institute</td>
<td>AF, CHA2DS2-VASc ≥ 2, Undergoing elective cardiac surgical procedure</td>
<td>Y</td>
<td>LAA occlusion: suture and/or surgical stapler -- Efficacy</td>
<td>2012-2019</td>
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<td>AtriCure Exclusion of the LAA in Patients undergoing Concomitant Cardiac Surgery</td>
<td>AtriCure Inc.</td>
<td>AF, CHA2DS2 ≥ 2, Undergoing elective cardiac surgical procedure</td>
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Abbreviations: AF = atrial fibrillation, OAC = oral anticoagulants, eGFR = estimated glomerular filtration rate, LAA = left atrial appendage.
Thus, diastolic impairment and resultant increased ventricular pressure transmitted to the LAA appear to play an important role in LAA thrombogenesis. In addition, AF may increase thrombogenesis through irregular or reduced time for ventricular filling, resulting in acutely decreased LAA emptying.

**LAA closure for cardioembolic risk reduction**

The understanding of the mechanism for stroke risk in AF patients strongly indicates the need for LAAO in patients who are not candidates for prolonged anticoagulation therapies. Currently, there are multiple approaches and several are still in clinical trial stages. They can be classified into three broad categories: transseptally placed endocardial plug devices (occlusion), epicardial LAA ligation procedures (exclusion), and hybrid ligation approaches, which use both transseptal and epicardial access (exclusion).

**Surgical exclusion**

Surgical exclusion for LAAO is usually reserved for patients undergoing cardiac surgery for valvular heart disease or coronary artery bypass graft surgery. Techniques vary from appendectomy to staple or suture exclusion. There is a considerable disparity in completeness of LAA closure via surgical techniques, reported to be between 0% and 100%. However, current data on the effectiveness of surgical excision or occlusion on reducing stroke in patients with AF is limited to observational studies and retrospective studies. A retrospective study of 242 patients with previous mitral valve replacement reported the absence of LAA ligation as an independent predictor of embolic events (17 versus 3.4%, OR 6.7; 95% CI 1.5–31.0, \( p = 0.02 \)). Because of the wide variability in surgical methods and the heterogeneity of patients with AF, there is some disagreement about when, why, and how adjunctive surgical exclusion of LAA should be applied.

A recent study to determine the effectiveness of surgical ablation of AF in patients undergoing mitral valve repair or replacement showed surprisingly very low stroke rates in both groups, as all patients in both groups underwent LAA exclusion.

While the AtriClip Device System (AtriCure, Inc., West Chester, OH) and the Tiger Paw System (Maquet Cardiovascular LLC, Wayne, NJ) have demonstrated promising occlusion rates both immediately after the procedure and at follow-up imaging, no efficacy and...
safety data from randomized controlled trials are available.20,29 Thoracoscopic stand-alone left atrial appendectomy in 30 patients with contraindications to anticoagulation demonstrated excellent safety, with no reported thromboembolic events at a mean follow-up of 16 months.30 However, the impact on stroke risk by a hybrid, minimally invasive method for AF ablation has not been systematically studied.

The Left Atrial Appendage Occlusion Study (LAAOS) III is an ongoing, large-scale, randomized controlled trial comparing LAAO during cardiac surgery to non-LAAO with a primary endpoint of time to stroke or systemic embolization. This well-powered and well-designed study promises to address conclusive evidence of surgical closure of the LAA. In the meantime, it is not prudent to argue for open surgical procedures specifically to target LAA in patients who are not undergoing cardiac surgery for other reasons. The American College of Cardiology/American Heart Association/Heart Rhythm Society Atrial Fibrillation Guidelines currently have a class IIb recommendation (i.e. may be considered, although overall efficacy is less established) for surgical LAA closure.31

**Intracardiac left atrial appendage occlusion devices**

There are multiple transseptal devices in various stages of safety and efficacy investigation. These include the Amplatzer Cardiac Plug (ACP) and Amulet (St. Jude Medical, St. Paul, MN), the Watchman (Boston Scientific, Natick, MA), the WaveCrest LAA Occluder (Coherex Medical, Salt Lake City, UT), the Transcatheter Patch (Custom Medical Devices, Athens, Greece), Occlutech (Helsingborg, Sweden), the Ultrascept LAA closure device (Cardia Inc., Eagan, MN), and the LAmbre device (Lifetech Scientific Corp., Shenzhen, China) (Figure 2). The Watchman is currently the only percutaneous occlusion device approved in the United States, receiving Food and Drug Administration (FDA) approval in March 2015. The Amplatzer, Watchman, and Wavecrest occlusion devices have the Conformité Européenne (CE) European mark of approval.32

**Percutaneous LAA transcatheter occlusion (PLAATO) system**

The PLAATO system (Appriva Medical, Inc., Sunnyvale CA, now intellectual property of Atritech/Boston Scientific) was the first percutaneous LAA closure device deployed in humans for use in AF patients with high risk of stroke and contraindications to warfarin anticoagulation. The PLAATO device is a self-expanding nitinol cage with an occlusive expanded polytetrafluoroethylene membrane directly laminated to the frame structure. This allows the perimeter to be snugged with the inner wall of the appendage. Small anchors located along the struts and passing through the occlusive membrane assist with device anchoring and encourage healing response. The North American study of the PLAATO device reported an annualized stroke/transient ischemic attack (TIA) rate of 3.8% compared with the anticipated stroke/TIA rate (with the CHADS2 scoring method) of 6.6%/year. There was one implant-related tamponade.33 The European PLAATO study registry of 180 patients with contraindications to anticoagulation demonstrated 162 implant success, with reports of two deaths within 24 hours of the procedure, and six cardiac tamponades (2 cases requiring surgical drainage). In a follow-up time of 129 patient-years, a stroke rate of 2.3% compared favorably with the CHADS2 predicted rate of 6.3%. It was confirmed that the PLAATO apparatus is relatively safe and effective.34 Currently, however, PLAATO has been discontinued by the manufacturer (Appriva Medical, Inc. from Sunnyvale, CA).

**Amplatzer cardiac plug**

The ACP is based on Amplatzer septal occluders, which were originally used for atrial septal defect and patent foramen ovale closure. The ACP (St. Jude Medical, St. Paul, MN) is a self-expandable device made of nitinol mesh with a polyester patch inside. It has a left atrial disk connected to a lobe with hooks, achieving dual-layer occlusion.35 The disc seals the outer shape of the LAA orifice while the lobe is anchored distally in the appendage.

Several multicenter observational studies have reported feasibility and safety of the Amplatzer, though, pending the Amplatzer Cardiac Plug Clinical Trial, no randomized prospective clinical trial data are available. The largest retrospective multicenter study to date included 1,047 patients from 22 centers with indication(s) for LAAO. The most common indication was previous bleeding on oral anticoagulation (47%). Implant success was 97.3% with mean follow-up at 13 months. Efficacy was determined by comparing observed event rates (stroke, TIA, and systemic embolism) with the predicted event rate by CHA2DS2-VASc score. The annual rate of systemic thromboembolism and major bleeding was 2.3% (59% risk reduction) and 2.1% (61% risk reduction), respectively.36 Drawing from experience with Amplatzer septal occluders, dual antiplatelet therapy with aspirin and clopidogrel for 1–3 months followed by aspirin monotherapy for ≥ 5 months is recommended for patients with ACPs.36

The Amplatzer Amulet is a second-generation ACP with modifications, including increased size, aimed at decreasing procedural complications including device embolization (longer distal lobe, more stabilizing wires), peri-device leak (increased diameter of the proximal disc), and thrombus formation (recessed end-screw). Initial observational experiences are promising in patients with a larger LAA and in patients with contraindications to anticoagulation; it has demonstrated high procedural success, low periprocedural complications (one pericardial effusion), and no strokes reported at 90 days.37 The US pivotal ACP randomized controlled trial commenced enrollment in early 2013, randomizing AF patients with CHADS2 ≥ 2 to ACP versus anticoagulation (warfarin or dabigatran) in a 2:1 ratio. However, due to slow enrollment and imminent FDA approval of Watchman, this study was discontinued.
in December 2013 after enrollment of ~80 patients. The study is now being redesigned, and it is anticipated that the new randomized study will involve a non-inferiority comparison to the Watchman device. An ongoing clinical trial in Europe, ELIGIBLE (Efficacy of Left Atrial Appendage Closure After Gastrointestinal Bleeding) (NCT01628068), is designed to compare the Amplatzer device with aspirin and clopidogrel.

**Watchman device**

The Watchman device (Boston Scientific) is a self-expanding nitinol frame with fixation barbs. It has a permeable polyethylene membrane and comes in five sizes, ranging from 21 mm to 33 mm, to accommodate variations in LAA anatomy. It seals the LAA ostium, resulting in a smooth endocardial lining. The device is delivered via a 12-French transseptal catheter and...
deployed under fluoroscopic and transesophageal echocardiography (TEE) guidance to seal the ostium of the LAA.

PROTECT AF is the first randomized, controlled trial comparing device therapy with warfarin, randomizing 707 patients with non-valvular AF and a CHADS2 score of at least 1 to therapy with the Watchman device compared with warfarin (target international normalized ratio of 2–3) at a 2:1 device to control ratio. After successful device implantation, patients were treated with warfarin therapy for 45 days to prevent thrombus formation during endothelialization. A TEE at day 45 was performed, and if there was complete LAA occlusion or residual peri-device flow of <5 mm, warfarin was discontinued and dual antiplatelet therapy with aspirin, 81–325 mg, and clopidogrel, 75 mg daily, was initiated. At 6 months, clopidogrel was stopped and aspirin was continued indefinitely. The primary composite efficacy endpoint was a combination of stroke (ischemic and hemorrhagic), cardiovascular death, and systemic embolism. The first published results at a mean follow-up of 18 months demonstrated statistical non-inferiority of the Watchman device compared with warfarin. However, treatment analysis showed primary efficacy events occurred in only 2.3% of patients per year in the Watchman group compared with 4.1% in the warfarin group, suggesting that successful occlusion of the LAA is an effective alternative to warfarin. Recently published final results after 3.8 years of follow-up among non-valvular AF patients treated with the Watchman device met criteria for both non-inferiority and superiority compared with warfarin for preventing the combined outcome of stroke, systemic embolism, and cardiovascular death, as well as superiority for cardiovascular and all-cause mortality.

There was initial skepticism due to a high rate of periprocedural adverse events in the Watchman group. At 2 years the primary safety event rate (excessive intracranial or gastrointestinal bleeding, procedure-related complications, such as serious pericardial effusion, device embolization, and procedure-related stroke) was 10.2% in the intervention group versus 6.8% in the control group. Significant procedural complications were reported in 12% of patients and included pericardial effusion requiring drainage, embolic stroke, device migration, and device sepsis. The most common adverse event in the device arm was the development of periprocedural pericardial effusions, which, although significantly prolonging hospital stays, did not result in the death of any patients.

Most safety events in the device group were periprocedural, whereas in the warfarin arm, safety events continued to accumulate over time. Periprocedural ischemic strokes occurred in five patients and were attributed to air embolism. Procedure- or device-related safety events within 7 days of the procedure decreased from the first temporal half of PROTECT AF (10.0%) to the second half (5.5%) of the Continued Access (CAP) registry (3.7%). Major criticisms of PROTECT AF include small sample size, low CHADS2 score, and contribution of the initial 45-day warfarin period in the device group to enhanced outcome.

The initial concern about the early safety events led the United States FDA to request a second randomized trial. Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) randomized 407 patients to the Watchman device therapy or to warfarin at a 2:1 ratio. The trial addressed criticisms of the PROTECT AF trial by targeting a higher-risk patient population: all patients were now required to have a CHADS2 score of ≥2, or a score of 1 with high-risk characteristics (female, age ≥75, baseline ejection fraction ≥30% but <35%, age 65–74 with either diabetes or coronary artery disease, or age ≥65 with congestive heart failure). Although the study group (Watchman) did not achieve the pre-specified criteria for non-inferiority at 18 months' follow-up compared with the control group (warfarin) during this trial, the overall periprocedural early events were lower than in the PROTECT AF trial, at 2.2% versus 4.9%, respectively. Overall, adverse events in the PREVAIL trial were significantly lower than in the PROTECT AF trial, at 4.2% versus 8.7% (p = 0.004).

The ASAP Study (ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology) was a feasibility study designed to evaluate the use of the Watchman device in patients who had absolute contraindications to warfarin therapy. In this non-randomized study of 150 patients with an average CHADS2 score of 2.8 and a contraindication to anticoagulation, patients were treated with both aspirin and clopidogrel for 6 months after implantation instead of the standard warfarin. During follow-up, three ischemic strokes were observed, corresponding to 1.7 events per 100 patient-years (a 77% reduction in the expected stroke rate based on the CHADS2 score estimate). In fact, despite not using warfarin, the event rate was lower than that in the PROTECT AF study (2.2 strokes per 100 patient-years). The Watchman device has been recently approved by the FDA in the United States to reduce the risk of thromboembolism from the LAA in patients with non-valvular AF who 1) are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores and are recommended for anticoagulation therapy, 2) are deemed by their physicians to be suitable for warfarin, and 3) have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and efficacy of the device compared to warfarin. Performance of the next-generation Watchman in comparison to novel oral anticoagulation agents will be assessed in the non-randomized EVOLVE study (Evaluation of Next Generation Watchman LAA Closure Technology in Non-Valvular AF Patients), NCT01196897.

WaveCrest

The WaveCrest Left Atrial Appendage Occlusion System (Coherex Medical) is designed for positioning at the LAA ostium, with an impermeable and less thrombogenic material facing the LA and independently deployable
distal anchors. The WaveCrest I trial 130 (multicenter, prospective, non-randomized registry) included 73 patients from Europe, Australia, and New Zealand, with baseline characteristics of mean CHADS2 score of 2.5, previous cerebral embolism in 34%, and a warfarin contraindication in 49%. Initial results presented at the TCT EUROPCR meeting suggested successful deployment with acute closure in 68 of 73 (93%), with 3 mm or less peri-device flow at 6 weeks in 65 of 68 (96%). Acute tamponade occurred in two of 73 (3%), and there was no procedural stroke, device embolization, or device-related thrombosis. After TEE-guided deployment, dual anti-platelet therapy was administered for 90 days, after which aspirin was continued long term. The final results of this trial are pending.

**Transcatheter Patch**

The Transcatheter Patch (Custom Medical Devices, Athens, Greece) is a frameless, balloon-deliverable device used for the occlusion of heart defects. The patches are tailored from polyurethane foam (Foamex, Media, PA). The supporting balloon is made from Latex (NuMED, Hopkinton, NY) and is inflated to diameters of 15–25 mm by diluted contrast. A 2-mm nylon loop is sutured at the bottom of the patch, to which a double nylon thread is connected for retrieval purposes. It is attached by a surgical adhesive and is released in 45 min.43

The safety and efficacy of several more transeptal devices, such as the Occlutech LAA-Occluder, Cardia Ultracept LAA occlusion system, and Lifetech LAmbre device, are currently being investigated with clinical trials, but data on these devices are not yet available.32

**Percutaneous LAA closure: epicardial approach**

Although most of the experience with LAAO devices has been with endocardial devices, isolation of the LAA using an epicardial transcatheter-based approach has more recently emerged as a method of simulating LAA closure with suture ligation during cardiac surgery and has been shown to be feasible for acute closure of the LAA that results in LAA necrosis and atrophy.44 Epicardial suture ligation is an attractive option, as it attempts to circumvent potential causes of incomplete closure by the surgical approach. These include the flaccid condition of the heart during cardiopulmonary bypass, difficult access for suturing, and delayed assessment of successful LAA closure and absence of leaks until after the patient is off cardiopulmonary bypass. In addition, since epicardial approaches involve non-implantable devices, this theoretically obviates the need for short-term anticoagulation. One major disadvantage of the epicardial approach may be the need for dry pericardial access, a skill that has a significant learning curve. In addition, patients who have had prior sternotomy or unsuitable LAA anatomy on pre-procedure imaging likely may not be suitable candidates. Currently there are two device systems that utilize an epicardial approach for LAA exclusion, the AEGIS system and the Lariat, which have both FDA and CE approval for commercial use.

**AEGIS system**

The epicardial AEGIS system (Aegis Medical, Vancouver, Canada, Epitek, Minneapolis, MN) is a novel occlusion approach that avoids the complications of septal puncture and need for both procedural and short-term post-procedural anticoagulation, as no foreign bodies are introduced into the cardiac chamber.45 The AEGIS system comprises an appendage grabber and a hollow suture loop tool (Figure 3). The grabber has embedded electrodes that allow the operators to distinguish between epicardial adipose tissue and underlying LAA myocardia. Contrast is injected adjacent to the LAA for visualization. After the appendage has been grabbed, the suture loop is used to close off the LAA. Closure may be confirmed with lack of P waves and electrical activity in the now atretic LAA.

Preliminary and intermediate term results in canines showed safety and efficacy of the AEGIS system; no adjacent structures were damaged and local LAA electrograms disappeared following ligation. Residual flow in the LAA at a mean follow-up of 54 days was only found in the first two canines. A small series in humans has demonstrated feasibility.46

**LARIAT system**

The LARIAT system (SentreHeart, Redwood City, CA) utilizes a combined transeptal access to the LAA and subxiphoid approach into the pericardial sac. Magnet-tipped guidewires are maneuvered to meet across the LAA wall, and an epicardial suture is advanced to the base of the LAA, where it is tightened, thereby occluding the opening of the LAA. The device is commercially available via FDA 510(k) clearance for soft-tissue approximation.

The initial clinical experience consisted of a single-arm registry of 89 patients who had relative contraindications to warfarin therapy and 1-year follow-up.47 Immediate complete closure, defined as <1-mm jet by color flow Doppler, was achieved in 96% of patients, and complete closure persisted in 98% of patients at 1 year. The most frequent immediate adverse event was chest pain (20 of 85 patients) related to pericardial access, with a 2.4% rate of persistent pericarditis requiring medical treatment. Recently, there were retrospective data reported from eight US sites with 154 patients undergoing attempted LAA ligation with the LARIAT device. The patients had high risk for stroke as documented by a median CHADS2 score of 3 and a median CHA2DS2-VASc score of 4; the median HAS-BLED (Hypertension, Abnormal renal or liver function, Stroke, Bleeding, LaBile INR, Elderly, Drugs or alcohol) was 3.48 Device success, defined as suture deployment and a leak of <5 mm in the post-procedure TEE examination, was achieved in 94%. Major complications, defined as death, myocardial infarction, stroke, Bleeding Academic Research Consortium bleeding ≥ type 3, or cardiac surgery, were
observed in 9.7% of the patients. The most frequent complications were major bleedings (9.1%), in which a significant proportion required blood transfusion, and significant pericardial effusion (10.4%). Notably, laceration or perforation of the LAA was seen in four patients. Follow-up data were available for 134 patients. A composite of death, myocardial infarction, or stroke occurred in 2.9%, and late pericardial effusion in 2.2%. Sixty-three of these patients underwent a follow-up TEE showing complete closure in 50 patients (79% of those imaged), leak of <5 mm in six patients (14%), and leak of ≥5 mm in four patients (6%). Many of the patients with adverse outcomes represented the initial experience at their respective institutions, and not all patients underwent computed tomography guidance for procedural planning, suggesting the importance of hospital and operator experience in reducing complication rates, especially in the initial phase of device implant. Novel approaches to seal leaks in post-LARIAT implants with Amplatzer septal occluders have been described.

Among the pleiotropic effects of LAA ligation with the LARIAT device is its effect on LAA electrical activity. In a study with 100% implant rate, 94% of the patients had a reduction in the LAA voltage after the closure of the snare, with 33% of the patients having complete elimination of LAA voltage on initial tightening of the suture. These preliminary results are intriguing in that LAAO with this particular device may help decrease recurrence of AF in this patient population. There have also been preliminary reports of decreased P-wave duration and P-wave dispersion following LAA ligation, suggesting its role with pulmonary vein isolation procedures to reduce AF burden.

Procedure planning and minimizing risks

LAA appendage obliteration is emerging as a niche procedure, and experiences related to device implant and specific troubleshooting for each device pose a unique set of challenges. Prior to undertaking the procedure, a detailed discussion with the patient, careful choice of device and access, periprocedural imaging, anticoagulation management, and a follow-up plan should be instituted. Consideration of the implant physician’s and hospital’s experience should be made. A “heart team” approach has been suggested before undertaking these procedures to identify suitable candidates and minimize anticipated and unanticipated risks.
As noted in PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) and all other oral anticoagulation-versus-device evaluations, there is a higher initial rate of adverse events in patients undergoing device implantation. However, data from the Watchman studies show the importance of operator experience, such that the rate of serious pericardial effusions was 7% at the start of PROTECT AF and declined to 2% during CAP. Similar results are seen from administrative claims databases that suggest procedure-related mortality, complication rates, length of hospitalization, and cost are significantly associated with annual hospital volume. Operators should have a thorough understanding of the anatomy of the LA, interatrial septum, and LAA, as well as considerable experience with transseptal puncture and troubleshooting difficult access (redundant septum, presence of interatrial septal occluders, thick septum). Meticulous management of the transseptal sheath, continuous flushing, assessment of fluid balance, prevention of thrombus and air embolism, and close monitoring of anticoagulation therapy are paramount. PROTECT AF reported that five of 449 patients with implantation of a Watchman device suffered from a periprocedural stroke. The most common cause was air embolism, which is usually short-lived. Air emboli may enter the LA due to accidental injection of air, trapped air despite appropriate flushing of the catheter, or deep inspiration of the patient resulting in air intrusion driven by a gradient between atmospheric and intracardiac pressure. Depending on the familiarity of the operator with either intracardiac echo or TEE, an imaging modality should be utilized during the case to assess correct deployment and procedural success. The operator should be accustomed to the regional anatomy of the left circumflex coronary arteries with the LAA, as they are prone to injury during both endovascular and epicardial suture closure. Because epicardial devices can risk injury to vessels near the LAA tip, including the left anterior descending artery, systems using hybrid or epicardial-only approaches appear promising, as there is no foreign body implanted in the vascular system and thus no reason for anticoagulation. However, epicardial approaches have specific limitations, such as those found in patients with prior cardiothoracic surgery. Pericardial effusion and pericarditis are the most frequent complications for epicardial access. In addition, inadvertent puncture of the right ventricle is relatively common, as is possible inadvertent puncture of intra-abdominal organs such as the liver and spleen. However, in patients who are not anticoagulated, right ventricle perforations are usually benign. Another complication may arise when positioning the pericardial sheath and introducing the delivery system through the sheath. Air may be inadvertently aspirated into the pericardial space, which may rarely cause cardiac tamponade, but may increase the defibrillation threshold for a transthoracic defibrillator. Similarly, phrenic nerve injury and damage to coronary arteries are possible. Transseptal, epicardial, and hybrid-based approaches each have unique advantages and limitations (Table 2).

**Future directions**

LAA closure may have a larger “net clinical benefit” than oral anticoagulation therapy in patients with a high stroke risk, and the safety and efficacy of LAA closure for the prevention of thromboembolism in AF patients.

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Table 2: Non-surgical left atrial appendage closure for stroke prevention in atrial fibrillation. (From Friedman PA, Holmes DR. J Cardiovasc Electrophysiol 2011;22(10):1190; with permission.)

<table>
<thead>
<tr>
<th>Device/Method</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transseptal device placement</td>
<td>Extensive experience with transseptal technique&lt;br&gt;Available in the setting of previous cardiac surgery&lt;br&gt;Validated as non-inferior to warfarin for stroke prevention (PROTECT-AF)</td>
<td>Need for procedural and short term antithrombotics until endothelialization&lt;br&gt;Foreign body left in central circulation (small risk of embolization, erosion, dislodgement)</td>
</tr>
<tr>
<td>Epicardial</td>
<td>No foreign body left behind&lt;br&gt;No need for procedural anticoagulation because no contact with systemic circulation and no transseptal</td>
<td>Learning curve for epicardial access</td>
</tr>
<tr>
<td>Hybrid</td>
<td>No foreign body left behind</td>
<td>Need for both transeptal and epicardial access with risks of both, and delivery failure if cannot achieve both</td>
</tr>
</tbody>
</table>

**Overview of Percutaneous Approaches for Left Atrial Appendage Closure**

- **Transseptal device placement**
  - Extensive experience with transseptal technique
  - Available in the setting of previous cardiac surgery
  - Validated as non-inferior to warfarin for stroke prevention (PROTECT-AF)
  - Need for procedural and short term antithrombotics until endothelialization
  - Foreign body left in central circulation (small risk of embolization, erosion, dislodgement)

- **Epicardial**
  - No foreign body left behind
  - No need for procedural anticoagulation because no contact with systemic circulation and no transseptal
  - Adjustable size loop to accommodate variable LAA shape/morphology without need for sizing
  - Pericardial control facilitates management of effusion should one develop
  - Learning curve for epicardial access

- **Hybrid**
  - No foreign body left behind
  - Pericardial control facilitates management of effusion should one develop
  - Superiorly directed LAA, multiple lobes and pectus excavatum may preclude use

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are promising. However, there are several unmet challenges:

- There is an urgent need for randomized trial data in patients not treated with anticoagulants following device deployment.
- The different morphologies of the LAA and suitability of specific devices are not known.
- The stroke risk after the most efficacious device deployment or closure in the most experienced hands in an ideal patient is still not zero.
- The role of the non-LAA-dependent stroke also deserves further exploration, especially the role of anticoagulation in these strokes.
- In the current health-care economics, cost effectiveness and quality-of-life data should be further assessed to confirm benefit of LAA closure.
- Additionally, the impact of LAA closure on arrhythmia burden reduction, autonomic modulation, and heart failure treatment requires further study.

Despite these challenges, LAAO is an attractive option to reduce LAA-dependent strokes in patients with AF. We are optimistic about the growth of this niche field of appendage closure and urge caution in the “one size fits all” approach in LAA closure.

References


42. US Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED) for WATCHMAN LAA Closure Technology – device summary cdrh_docs/pdf13/P130013b.pdf


