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## Cardiovascular Therapies Targeting Left Atrial Appendage

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### Abstract

Left atrial appendage (LAA) closure has evolved as an effective strategy for stroke prevention in patients with atrial fibrillation who are considered suitable for oral anticoagulation. There is strong evidence based on randomized clinical trials with 1 percutaneous device, as well as a large registry experience with several devices, regarding the safety and efficacy of this strategy. In addition, there is encouraging data regarding the effect of epicardial LAA closure on decreasing arrhythmia burden and improvements in systemic homeostasis by neurohormonal modulation. However, there

are several unresolved issues regarding optimal patient selection, device selection, management of periprocedural complications including device-related thrombus, residual leaks, and pericarditis. In this review, we summarize the rationale, evidence, optimal patient selection, and common challenges encountered with mechanical LAA exclusion.

### Keywords

anticoagulants; atrial fibrillation; cardiac surgical procedures; stroke; thromboembolism

Atrial fibrillation (AF) is the most common cardiac dysrhythmia, affecting 32 million individuals worldwide and 5 million in the United States, with an estimated U.S. annual health care cost of \$26 billion (1). AF is associated with a significant risk of stroke, congestive heart failure, and overall mortality (2,3). The left atrial appendage (LAA) is the most common source of thrombus in patients with AF who have experienced a stroke (4,5). Specific LAA shape, concomitant trabeculations, pectinate muscle morphology, AF-related inflammation, atrial remodeling, and a hypercoagulable state contribute to thrombogenicity (6). Currently, oral anticoagulation (OAC) with warfarin or direct oral anticoagulants (DOACs) is the treatment of choice for the prevention of stroke and systemic thromboembolism in patients with AF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score (congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category [female]) ≥ 2; OAC has consistently been shown to improve survival (7,8). Despite its well-established efficacy, a large percentage of patients who are at risk of stroke are considered to have absolute or relative contraindications for OAC due to high bleeding risk, patient noncompliance, drug interactions, and costs (9,10). Furthermore, there are substantial data showing that 45% of patients discontinue OAC (including DOACs) within 2 years (11,12). Recently, various LAA occlusion strategies have emerged as safe and effective alternatives for prevention of stroke and systemic thromboembolism in patients with AF who are considered suitable for OAC (13–15). In addition to stroke prevention, there are encouraging data suggesting that epicardial LAA occlusion may decrease arrhythmia burden and has a significant effect on atrial remodeling; systemic homeostasis, including blood pressure; and fluid and electrolyte balance (Central Illustration) (15–18). However, there are several unresolved issues regarding optimal patient selection, device selection, and management of periprocedural complications, including device-related thrombus and residual leaks, as well as pericarditis. In this paper, we discuss the rationale, benefits, and practical considerations of various LAA exclusion strategies in the management of AF.

### WHY DO WE HAVE AN LAA?

The LAA is a vestigial structure in the human body similar to the appendix. It is the remnant of the primordial left atrium, which develops during the third to sixth week of fetal cardiac development, whereas the smooth left atrial cavity develops later from the pulmonary venous bud (19). Our knowledge regarding the function and activity of the LAA is limited but can be broadly divided into 3 categories: neurohormonal, reservoir, and electrical functions (15,20).

The human atria are a rich source of atrial natriuretic peptide (ANP) and contribute to natriuresis and diuresis, accounting for the salt and fluid balance in the cardiovascular system. Both the left atrium and the LAA have specialized endothelial cells that are involved in the production and release of natriuretic peptides, both ANP and B-type natriuretic peptide (BNP) (20). The LAA appears to be the primary production site of ANP in the human heart and stores about 30% of cardiac ANP in the granulocytes, which are secreted in response to atrial stretch receptors (21,22). The concentration of ANP in the left atrial wall is about 40× higher than in the rest of the atrium and ventricles (22). Higher levels of ANP can promote early natriuresis and diuresis, which can lead to variable hemodynamic and physiological effects in patients with and without heart failure. In patients with a history of congestive heart failure, volume overload leads to activation of stretch receptors in the left atrium and LAA, leading to higher ANP levels; this can result in diuresis and natriuresis of salt and water, which leads, in turn, to normalization of sodium ion levels. In patients with no history of heart failure, increased ANP levels lead to hypotension and hypotonic hyponatremia from excessive diuresis and natriuresis.

In addition, the LAA also has a reservoir function and is the most distensible structure within the left atrium, acting as a decompression chamber in patients with increased LA pressure and volume (23). In patients with sinus rhythm, LAA amputation diminishes the reservoir and conduit function of the left atrium (24). Furthermore, the ratio of reservoir to conduit function diminishes and there is slower left ventricular filling (24). In patients with AF, LAA remodeling occurs, which results in the LAA functioning as a static pouch with decreased Doppler flow velocities and reduced distensibility, increasing the predisposition to thrombus formation. Similar changes occur in patients with dilated cardiomyopathy and elevated filling pressures with reduced contractile function of the LAA, even in the absence of AF (25).

## WHY DOES THE LAA TURN ROGUE IN AF?

Prior studies have demonstrated that LAA is the most common source of thrombus formation in AF. AF can lead to impairment in the conduit function of the LAA with a decrease in LAA flow velocity, which is a major predictor for thrombus in the LAA (26). Furthermore, AF can cause a prothrombotic state manifested by endothelial dysfunction, activation of coagulation factors including platelet aggregation, prothrombin fragments, interleukin-6, thrombin–antithrombin complexes, and D-dimer (27–29). Longstanding AF also leads to atrial remodeling, fibrosis, and inflammation of the endothelium of the left atrium, especially the LAA, leading to focal triggers and re-entry arrhythmias, contributing to a vicious cycle (30). This evidence provided the rationale regarding the benefit of LAA closure for stroke prevention and decreasing arrhythmia burden in AF.

## LAA ANATOMY AND STROKE RISK

Previous studies have reported that the LAA is the source of thrombus in about 90% of nonvalvular AF and 57% of valvular AF (4,5). This high thrombus burden is attributed to the shape, ostium of the neck, and extent of trabeculations (31). Di Biase et al. (32) described a strong correlation between LAA shape and morphology and risk of stroke

by computed tomography (CT) imaging. Four different types of LAA shapes have been described: 1) chicken wing; 2) windsock; 3) cactus; and 4) cauliflower. Patients whose LAA has a chicken-wing morphology were found to be 79% less likely to have a stroke/transient ischemic attack (TIA) history (odds ratio [OR]: 0.21; 95% confidence interval [CI]: 0.05 to 0.91;  $p = 0.036$ ). Furthermore, compared with chicken wing, patients with other LAA morphologies were more likely to have a stroke/TIA: cactus morphology had an OR of 4.08 (95% CI: 1.04 to 17.27;  $p = 0.046$ ), windsock morphology had an OR of 4.8 (95% CI: 1.89 to 22.50;  $p = 0.038$ ), and cauliflower LAA morphology had an OR of 8.02 (95% CI: 0.92 to 27.86;  $p = 0.056$ ) (32).

Another study reported that the extent of LAA trabeculations and a smaller orifice are associated with prevalent history of stroke and systemic thromboembolism (33) by determining low LAA flow velocity (34). Currently, the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system is the standard approach for stroke risk assessment in AF, but this does not include LAA shape or morphology (35,36).

## LAA EXCLUSION FOR STROKE PREVENTION

The earliest documented work in humans, by John Madden in 1948, showed that the LAA was a source of thrombus in patients with AF and that its removal could prevent systemic thromboembolism (37). Over the next few decades after Madden's work, surgeons routinely excluded the LAA during mitral valve operations. Further evidence of efficacy came from Dr. Cox's early Maze series, which included LAA amputation; follow-up revealed virtual elimination of stroke (38). Efficacy of LAA elimination in stroke prophylaxis is, however, clouded by 2 factors. Most series include patients who remained on OAC. Further, it has been shown that patients with electrical sinus rhythm who have poor contractile function have a persistent stroke risk, despite the absence of the LAA (39). Figure 1 demonstrates the various types of surgical and percutaneous LAA exclusion techniques.

## LAA EXCLUSION TECHNIQUES

### SURGICAL LAA EXCLUSION.

The current 2016 European Society of Cardiology and the 2014 American Heart Association/American College of Cardiology guidelines both appropriately have a Class IIb recommendation regarding routine surgical LAA excision in patients undergoing cardiac surgery due to lack of randomized controlled trials (RCTs) (35,36). However, the 2017 Society of Thoracic Surgeons guideline statement gives a Class IIa recommendation for LAA closure (40). Despite these recommendations, several patients undergoing mitral valve surgery or patients with AF and a high risk of stroke routinely undergo LAA amputation, either during surgery or thoroscopically under general anesthesia by stapling or a loop snare. Several studies were performed examining surgical LAA exclusion techniques with inconclusive results, as these were all observational, nonrandomized studies with limited follow-up (41–43). A meta-analysis reported a LAA exclusion rate of 55% to 68% with various surgical methods (44). Data from multiple studies, however, have raised concerns about the efficacy of surgical LAA closure techniques, especially suture exclusion with incomplete closure on follow-up transesophageal echocardiographic (TEE) imaging, risk of

thrombus formation, and higher risk of subsequent stroke (43,45–47). Kanderian et al. (42) reported an overall success rate of 40% for LAA closure, with surgical excision achieving higher success rates (73%) than suture exclusion (23%) after a mean follow-up of  $8.1 \pm 12$  months. However, it needs to be noted that this study represented only 5% of patients who underwent evaluation for cause. Thus, it is not representative of the surgical sample. In general, techniques that do not amputate the appendage have high failure rates, either due to incomplete closure or due to a residual neck  $>1$  cm. In the modern era, the LAA can be excluded under direct visualization during open sternotomy or a minimally-invasive thorascopic/minithoracotomy approach with and without a device. It appears that LAA amputation followed by epicardial suture closure was the most effective strategy, as a high rate of reconnections were seen with both epicardial and endocardial suture ligation (41).

Surgical enabling technology has centered around the introduction of several epicardially applied clipping devices (Figure 2) (48–53). Only the AtriClip LAA exclusion system (Atricure, Westchester, Ohio) is currently available. The LAA exclusion system has gone through 3 generations with  $>100,000$  devices used worldwide, mostly during concomitant procedures and some standalone LAA exclusions. A long-term follow-up of implanted clips showed that at 36 months, all clips were stable with no displacement, intracardiac thrombi, perfused LAA, residual neck  $>1$  cm, strokes, TIAs, or neurological events. The advantages of this approach are: minimal risk of bleeding; immediate electrical isolation of the LAA; no need for anticoagulation during or after the procedure; and no foreign body in the blood stream. A multicenter evaluation of the AtriCure clip reported a  $>98\%$  closure rate at 3-month follow-up with TEE/computed tomography angiography (54). The LAA exclusion system is currently CE marked and has received U.S. Food and Drug Administration (FDA) 510K approval for LAA ligation.

Based on the available data, prophylactic LAA closure during concomitant cardiac surgery is currently not recommended. The question remains as to whether there is a high-risk group of patients who would benefit from prophylactic closure of the LAA concomitant to another cardiac procedure. ATLAS (AtriClip Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures) (NCT02701062) is a prospective randomized trial currently underway to evaluate the efficacy of LAA occlusion in surgical patients without pre-operative AF, but with a high CHA<sub>2</sub>DS<sub>2</sub>-VASc score in combination with a high HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol) score. The prospective randomized LAAOS III (Left Atrial Appendage Occlusion Study III) (NCT01561651) evaluating prophylactic LAA occlusion in surgical patients with known pre-operative AF is also currently underway.

## **PERCUTANEOUS LAA EXCLUSION/ENDOCARDIAL LAA EXCLUSION**

### **PLAATO DEVICE.**

The first device in the percutaneous LAA occlusion space was the PLAATO device (Appriva Medical, Sunnyvale, California) (55). The device consisted of a self-expanding nitinol cage covered by a polytetrafluoroethylene membrane that was held in position by small anchors.

Although the early experience was favorable, it quickly fell out of use due to significant complications and was withdrawn from the market in 2006 for business reasons (56–58).

### **NITINOL CAGE PERCUTANEOUS LAA CLOSURE DEVICE.**

The Watchman nitinol cage percutaneous LAA closure device (Boston Scientific, Marlborough, Massachusetts) remains the most extensively studied LAA occlusion device to date; the bulk of the data is from experience in patients eligible for OAC, but not in those with an absolute contraindication for OAC. The device has been used in clinical practice in Europe since 2005 and was FDA-approved in the United States in 2015 for the prevention of stroke and systemic thromboembolism in AF. This approval was based on the data obtained from 2 RCTs and several post-market registries, demonstrating safety and efficacy compared with warfarin. The current second-generation device consists of a self-expanding nitinol frame covered with a permeable polyethylene terephthalate (PET) membrane and includes 10 active fixation anchors (Figure 3). To accommodate this device, the maximum LAA ostium size should be 17 and 31 mm.

PROTECT AF (Watchman Left Atrial Appendage Closure Device for Embolic Protection in Patients with Atrial Fibrillation) was a worldwide prospective RCT, including 707 patients with nonvalvular AF with a CHADS<sub>2</sub> score 1, comparing the nitinol cage percutaneous LAA closure device and warfarin with 2:1 randomization (59). The post-procedural antithrombotic strategy included 45 days of warfarin, which was discontinued if a TEE showed a 5 mm peridevice leak, followed by aspirin and clopidogrel for 6 months and then aspirin indefinitely. Successful device implantation was documented in 88% of subjects, whereas TEE criteria for warfarin discontinuation were met in 86% and 92% at 45 days and 6 months, respectively. The results demonstrated that the nitinol cage percutaneous LAA closure device was noninferior to warfarin (3% vs. 4.3%; relative risk [RR]: 0.62; 95% CI: 0.35 to 1.25) for the combined primary efficacy endpoint of cardiovascular mortality, all-cause mortality, and systemic thromboembolism with 1,065 patient-years follow-up. The nitinol cage percutaneous LAA closure device group had more adverse events (7.4% vs. 4.4%; RR: 1.69; 95% CI: 1.01 to 3.19), mostly related to the implant procedure, which included major bleeding, pericardial effusion, and stroke in 3.5%, 4.8%, and 1.1%, respectively. The PREVAIL (Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial was conducted to answer some of the safety concerns raised by the FDA from the PROTECT AF study. The PREVAIL RCT (59) included 407 patients with a similar 2:1 randomization between the nitinol cage percutaneous LAA closure device and warfarin. The study required at least 25% of patients to be treated by new operators with no previous experience with the nitinol cage percutaneous LAA closure device. The post-procedural antithrombotic strategy was similar to that in the PROTECT AF trial. The results demonstrated that, when compared with warfarin, the nitinol cage percutaneous LAA closure device did not achieve the first pre-specified criterion for non-inferiority for the composite rate of stroke, systemic thromboembolism, or cardiovascular/unexplained death (0.064 vs. 0.063; RR: 1.07; 95% CI: 0.57 to 1.89) with a pre-specified noninferiority margin of 1.75. However, the nitinol cage percutaneous LAA closure device met both the second noninferiority criterion and safety endpoint of rate of stroke or systemic thromboembolism

>7 days post-implantation. The trial faced some criticism from various experts regarding the failure to reach the first pre-specified efficacy endpoint. Although the nitinol cage percutaneous LAA closure device fared as expected, with a 65% relative risk reduction of stroke compared with the risk of stroke in patients with similar CHA<sub>2</sub>DS<sub>2</sub>-VASc scores, the ischemic stroke rate in the warfarin arm was only 0.3%, which was very low compared with any prior RCT where stroke rates in the warfarin arm were >1% (8,59). Despite not meeting the first coprimary efficacy endpoint, the FDA Circulatory System Advisory Panel reviewed the data from both of these trials (PROTECT AF and PREVAIL) in totality, deemed the device to be safe, and approved the nitinol cage percutaneous LAA closure device for routine clinical practice in 2015.

Further post-marketing data from the PROTECT AF trial, the CAP (Continued Access to PROTECT AF) Registry, and the EWOLUTION registry demonstrated that implantation safety improved with the operator's experience (60,61). A patient-level meta-analysis including 2,406 patients from PROTECT AF, PREVAIL, and the CAP registry demonstrated that, compared with warfarin, the nitinol cage percutaneous LAA closure device had lower rates of hemorrhagic stroke (hazard ratio [HR]: 0.22; p = 0.004), cardiovascular/unexplained death (HR: 0.48; p = 0.006), and nonprocedural-related bleeding (HR: 0.51; p = 0.006). However, implantation of the nitinol cage percutaneous LAA closure device was associated with higher rates of ischemic stroke compared with dose-adjusted warfarin (1.6 events vs. 0.9 events/100 patient-years; HR: 1.95; p = 0.05) (59). Recently, 5-year clinical outcomes from the PREVAIL and PROTECT AF trials demonstrated that the nitinol cage percutaneous LAA closure device, when compared with OAC, had similar efficacy for prevention of both ischemic strokes (HR: 1.71; p = 0.080) and all strokes (HR: 0.961; p = 0.87). However, there was significant benefit with the nitinol cage percutaneous LAA closure device over OAC in reduction of hemorrhagic strokes (HR: 0.20; p = 0.0022), cardiovascular death (HR: 0.59; p = 0.027), and all-cause death (HR: 0.73; p = 0.035) (62). Based on the favorable results even at 5-year follow-up, continued evaluation of the long-term impact of LAA closure on stroke risk through national registries will be important.

The 1 major drawback of both the PROTECT AF and PREVAIL trials was the use of post-procedural short-term warfarin, as the LAA closure device was supposed to be the answer to patients with major bleeding risk on OAC. Two real-world registries demonstrated safety and feasibility with post-procedural dual antiplatelet therapy (DAPT), without using OAC (61,63). The ASAP (ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology) observed an ischemic stroke rate of 1.7%/year with a 77% relative risk reduction of stroke, adjusted for a predicted stroke risk of 7.3% for the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (Figure 4A). The study effectively demonstrated that post-nitinol cage percutaneous LAA closure device management with aspirin and 6 months of clopidogrel was safe and feasible. These findings on DAPT were further supported by data from the ongoing EWOLUTION registry. About 59.6% of patients were treated with DAPT, 11.1% with a DOAC, and 15.6% with warfarin. There was no significant difference in stroke, device-related thrombus, or bleeding adverse events among the 3 groups (61). Data comparing the nitinol cage percutaneous LAA closure device to DOAC use, however, remain limited.

## TRANSCATHETER SELF-EXPANDING NITINOL PLUG.

There were 2 prior versions of Amplatzer devices, including the atrial and ventricular septal occluder. The atrial septal occluder was previously used off-label for LAA closure, but was associated with high rates of device embolization, as it lacked active fixation struts (64). The Amplatzer Cardiac Plug (Abbott Vascular, Santa Clara, California) was a first-generation device specifically developed for LAA closure. It consists of a self-expanding nitinol platform with a distal lobe, proximal disc, and 6 pairs of distal wires for stabilization (Figure 3). To accommodate the self-expanding nitinol plug, the maximum LAA ostium size should be 12.6 or 28.5 mm.

To date, there are mostly prospective observational studies but no RCTs comparing the transcatheter self-expanding nitinol plug with OAC (65–67). Tzikas et al. (66) reported the largest multicenter experience with the transcatheter self-expanding nitinol plug including 1,047 patients. Stroke and systemic thromboembolism were reported in 2.3% patients/year, with a 59% relative risk reduction of stroke, adjusted for a predicted stroke risk of 5.6%/year for the CHA<sub>2</sub>DS<sub>2</sub>-VASc score at a median follow-up of 13 months (Figure 4B). Similarly, the major bleeding risk was 2%/year, with a 61% relative risk reduction adjusted for a predicted bleeding risk of 5.34%/year. Procedural success occurred in 97.3%, whereas adverse events were reported in 4.97%. On follow-up, aspirin monotherapy increased from 31% to 63.7%, whereas warfarin decreased from 16% to 1.6%, demonstrating that this could be a useful strategy in patients who are not eligible for OAC and who can be safely managed with DAPT.

The second-generation transcatheter self-expanding nitinol plug, Amulet (Abbott Vascular), has been developed to promote ease of deployment, safety, and efficacy. To accommodate the second-generation transcatheter self-expanding nitinol plug, the optimal LAA ostium size should be 17 and 32 mm. To date, there are no RCTs comparing the second-generation transcatheter self-expanding nitinol plug with OAC. Both generations of the transcatheter self-expanding nitinol plug are currently not FDA-approved in the United States but are available in Europe. In the United States, the second-generation transcatheter self-expanding nitinol plug is currently being randomized to the nitinol cage percutaneous LAA closure device in the ongoing Amulet-IDE (AMPLATZER Amulet LAA Occluder Trial) clinical trial ([NCT02879448](https://clinicaltrials.gov/ct2/show/study/NCT02879448)) to evaluate its safety and efficacy for stroke prevention in AF.

## PERCUTANEOUS ENDO-EPICARDIAL SUTURE DELIVERY SYSTEM.

The hybrid Lariat system (Sentre Heart, Palo Alto, California) is a percutaneous endo-epicardial suture delivery system. An epicardial delivery snare with a preformed suture is delivered over a magnet-tipped wire placed epicardially at the LAA that aligns with another magnet-tipped wire delivered endocardially via a transseptal approach and positioned at the LAA apex (Figure 3). There are no RCTs evaluating the role of the percutaneous endo-epicardial suture delivery system for stroke prevention in AF. The initial feasibility trials on the system were fraught with significant procedural complications, despite a high rate of adequate LAA closure (13,68). A prospective multicenter trial including 139 patients with nonvalvular AF CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $3.6 \pm 1.8$  contraindicated to OAC

demonstrated a stroke risk of 1% over a mean follow-up of  $2.9 \pm 1.1$  years, with an 84% relative risk reduction compared with an expected stroke risk of 6.2% for the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (Figure 4C) (69). All patients received post-procedural aspirin, clopidogrel, aspirin plus clopidogrel, or no antithrombotic agents. Total adverse events were reported in 11.5% with a death rate of 1.8%, of which 1 death was periprocedural. The largest multicenter study to date, including 712 patients, demonstrated complete closure of the LAA in 98%, with no periprocedural strokes and 98% LAA closure on TEE at 1 year of follow-up. In addition, the low complication rates included bleeding requiring transfusion in 1.3%, emergent cardiac surgery in 1.4%, and death in 0.14%, respectively (70). The study demonstrated the importance of using a micropuncture needle with post-procedural colchicine to mitigate the pericarditis from ischemic necrosis of tissue from suture ligation. Currently, the percutaneous endo-epicardial suture delivery system has received a CE mark and 510K FDA approval for soft tissue apposition, but not for stroke prevention in AF.

#### **OTHER INVESTIGATIONAL DEVICES.**

Currently, there are several LAA exclusion devices in various phases of clinical investigation and not approved for routine clinical practice in the United States (Figure 5).

The Coherex WaveCrest (Biosense Webster, Irvine, California) (Figure 5) system received CE mark approval in August 2013, following the initial safety and feasibility trial (71). WAVECREST 2 (WaveCrest Vs. Watchman Transseptal LAA Closure to Reduce AF-Mediated Stroke 2) (NCT03302494), an RCT comparing the WaveCrest device and LAA occlusion using the nitinol cage percutaneous LAA closure device, is currently being planned in the United States.

The LAMBRE LAA occluder system (Lifetech Scientific Corp., Shenzhen, China) (Figure 5) received CE mark approval in 2016, following encouraging results from the initial feasibility trial (72). A first-in-human, prospective, nonrandomized study evaluating its feasibility and safety (Feasibility and Safety Study of LAMBRE Left Atrial Appendage Occluder; NCT01920412) is currently ongoing.

Several other devices are in the clinical investigation pipeline, such as the: 1) Occlutech device (Occlutech International, Helsingborg, Sweden) (73); 2) Ultraseal LAA closure device (Cardia, Eagan, Minnesota) (74); 3) Transcatheter Patch (Custom Medical Devices, Athens, Greece) (75); and 4) Sierra Ligation System (Aegis Medical Innovations, Vancouver, Canada). The Sierra Ligation System has the advantage of being completely extravascular in the epicardial space compared with the other devices.

#### **ARRHYTHMIA MANAGEMENT**

The LAA, due to its complex pectinate muscle architecture and associated fibrosis, facilitates slow conduction and re-entry, and has recently been reported to be an important structure in the initiation of non-pulmonary vein triggers in the initiation and maintenance of AF, especially persistent AF (16,76). Di Biase et al. (16), in 987 patients undergoing redo catheter ablation for AF, identified the LAA as a source of triggers in 27%, more so in longstanding persistent AF. Furthermore, the BELIEF (Effect of Empirical Left

Atrial Appendage Isolation on Long-term Procedure Outcome in Patients With Persistent or Longstanding Persistent Atrial Fibrillation Undergoing Catheter Ablation) trial showed that electrical isolation of the LAA, in addition to extensive ablation, reduced AF recurrence by 50% in persistent AF (77). However, LAA isolation with catheter ablation is limited by the difficulty in complete isolation, risk of thromboembolism due to loss of contractile function of the LAA, cardiac tamponade, and electromechanical dissociation and the need for possible surgery.

Whereas the percutaneous endo-epicardial suture delivery system, LAA exclusion system, and surgical excision do electrically isolate the LAA, LAA exclusion performed endocardially using the nitinol cage percutaneous LAA closure device or either generation of the transcatheter self-expanding nitinol plug can provide mechanical LAA exclusion suitable for stroke prevention, but there are no data to support a role in decreasing arrhythmia burden. Application of the LAA exclusion system results in immediate total electrical isolation (78). Epicardial LAA exclusion with percutaneous endo-epicardial suture delivery system was associated with a significant drop in LAA voltage post-ligation and elimination of voltage with initial tightening using the percutaneous endo-epicardial suture delivery system suture (76). When compared with baseline, LAA ligation with the percutaneous endo-epicardial suture delivery system also significantly decreased AF burden at 3 months ( $76 \pm 33\%$ ;  $p < 0.0001$ ) and 12 months ( $59 \pm 26\%$ ;  $p < 0.001$ ), respectively (79). It has been proposed that LAA ligation with the suture causes transmural necrosis of the epicardial structures, including the autonomic ganglia that lay between the LAA and left superior pulmonary veins (PVs) and the vein of Marshall, which might be the reason it may improve clinical outcomes (79–81).

The feasibility and safety of performing adjunctive LAA exclusion with the percutaneous endo-epicardial suture delivery system following PV isolation was demonstrated in a prospective observational study including 69 patients who underwent percutaneous endo-epicardial suture delivery followed by staged AF ablation after 1 month. The results showed significantly higher freedom from AF off antiarrhythmic drugs in the group with adjunctive percutaneous endo-epicardial suture delivery (45 [65%] vs. 27 [39%];  $p = 0.002$ ) (82). aMAZE (LAA Ligation Adjunctive to PVI for Persistent or Longstanding Persistent Atrial Fibrillation), a multicenter RCT for the treatment of persistent or longstanding persistent AF (NCT02513797), will determine the safety and efficacy of using adjunctive percutaneous endo-epicardial suture delivery in persistent AF.

## IMPACT ON SYSTEMIC HOMEOSTASIS AND NEUROHORMONAL MODULATION

A few studies have recently investigated the impact of endocardial and epicardial exclusion on natriuretic peptides and found significant differences between both groups (15,83–85). However, these studies had limited sample sizes with wide variation in blood sample measurements. Recently, Lakkireddy et al. (84) compared serum aldosterone, adrenaline, noradrenaline, ANP, and BNP at baseline, immediately after the procedure, and at 3 months between patients who received endocardial and epicardial LAA exclusion. The results

demonstrated that with epicardial LAA exclusion, there was significant down-regulation of adrenaline, noradrenaline, and aldosterone immediately post-percutaneous endo-epicardial suture delivery and at 3 months. ANP and BNP levels significantly increased at 24 h and returned back to baseline at 3 months. Furthermore, there was a significant decrease in systemic blood pressure at 24 h and 3 months in the epicardial exclusion. No such effects were demonstrated with any LAA endocardial exclusion.

In addition to a decrease in blood pressure, there are several other metabolic implications of LAA exclusion, including for lipolysis, adipokinins, free fatty acids, and glucose metabolism. The exact mechanism of these implications is poorly understood and appears to be regulated by the LAA-secreted natriuretic peptides and autonomic nervous system innervations, both ultimately resulting in down-regulation of the renin-angiotensin-aldosterone system (84,86–88) (Figure 6). These findings are interesting and need further validation from large-scale clinical trials.

## **WHICH PATIENTS SHOULD BE CONSIDERED FOR LAA CLOSURE?**

### **PATIENTS AT HIGH RISK OF STROKE WITH CONTRAINDICATIONS TO ANTICOAGULATION.**

Oral anticoagulation with warfarin or DOAC remains the first-line therapy for stroke prevention in AF with CHA<sub>2</sub>DS<sub>2</sub>-VASc score 1 (35). Unlike RCTs, there is a discrepancy in real-world practice, where a significant number of eligible patients are deemed ineligible for OAC due to various factors (89,90). There are also substantial data suggesting that patients deemed ineligible for OAC have a higher risk of stroke, systemic embolism, and all-cause mortality (91,92). Studies demonstrating the role of DOACs in patients deemed ineligible for warfarin remain limited and have shown a higher risk of recurrent major bleeding, especially gastrointestinal bleeding, in these patients (35,84). In theory, this group of patients would potentially be a suitable group for LAA closure. However, the RCTs on the nitinol cage percutaneous LAA closure device were conducted in patients who were eligible for warfarin (14,59).

The ASAP trial (63) and EWOLUTION (61) registry support the benefit of the percutaneous LAA closure device in patients who are deemed ineligible for OAC, as a significant proportion of patients were treated with DAPT in both registries, with substantial reductions in stroke and major bleeding. Similar data have been published using the transcatheter self-expanding nitinol plug device (66). It currently remains unclear if endocardial LAA closure is noninferior to DOAC therapy; this subject needs further investigation. The ongoing randomized trial, ASAP-TOO (Assessment of the WATCHMAN Device in Patients Unsuitable for Oral Anticoagulation) (NCT02928497) will further elucidate the benefit of the nitinol cage percutaneous LAA closure device in patients who are ineligible for OAC.

### **PATIENTS ON DIALYSIS.**

There are substantial data on the lack of net benefit and excessive bleeding with OAC in patients with AF on dialysis (93). There are limited data regarding the benefit of DOACs in this group of patients (35). In theory, LAA closure may be a logical strategy in these

high-risk patients. Currently, most LAA studies have excluded patients on dialysis. A recent observational study in patients with chronic kidney disease (including dialysis) receiving the transcatheter self-expanding nitinol plug device reported excellent procedural success with an acceptable rate of complications (94). Further studies are needed to support the safety and efficacy of LAA closure devices in patients with end-stage renal disease.

#### **PATIENTS WITH HIGH HAS-BLED OR HIGH CHA<sub>2</sub>DS<sub>2</sub>-VASC SCORES.**

In theory, patients with high HAS-BLED scores can benefit from LAA closure, as studies have consistently shown a significant reduction in risk of major bleeding that can translate into a survival benefit. Similarly, patients with a very high risk of stroke with high CHA<sub>2</sub>DS<sub>2</sub>-VASC scores can continue to have events despite OAC, as demonstrated in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation), where a subset of patients with CHA<sub>2</sub>DS<sub>2</sub>-VASC score  $\geq 5$  had 5 events/100 patient-years over a 2-year period (95). These patients did not have any bleeding contraindications to OACs, but could potentially benefit from combination therapy with LAA closure and OAC. Currently, there are no data to support such a strategy in these high-risk patients.

#### **PATIENTS WITH PERSISTENT AF.**

As yet, there are no data showing that endocardial LAA exclusion devices reduce the arrhythmia burden in patients with AF. There are several observational studies demonstrating a reduction in AF burden after epicardial LAA ligation with the percutaneous endo-epicardial suture delivery system or LAA exclusion system. The ongoing aMAZE RCT will give further data regarding the benefit of such a strategy in persistent AF.

#### **WHICH TYPE OF LAA CLOSURE SHOULD BE SELECTED FOR WHICH PATIENT?**

There are several factors that should be considered when choosing an appropriate LAA closure strategy (Figure 7). These include device availability in a given country; operator experience; and patient characteristics, including prior surgical history, LAA anatomy, and ability to tolerate OAC. Currently, there are no data comparing one LAA closure device with another.

Pre-procedural imaging, such as cardiac CT or TEE, is of paramount importance in defining the LAA anatomy and aids in procedural planning, including appropriate device selection. Patients with prior history of cardiothoracic surgery and pectus excavatum may not be suitable candidates for percutaneous endo-epicardial suture delivery or for stand-alone totally thoracoscopic application of the LAA exclusion system. Furthermore, additional anatomic features that make the percutaneous endo-epicardial suture delivery system unsuitable include: a superiorly-oriented LAA; LAA width  $>40$  mm; LAA apex directed behind the pulmonary artery; posteriorly rotated heart; and multilobed LAA in which lobes are oriented in different planes, exceeding 40 mm (96). The application of the LAA exclusion system is not limited by these anatomic variations. The totally thoracoscopic LAA exclusion system and the percutaneous endo-epicardial suture delivery system may be

favorable options in patients with symptomatic persistent AF to decrease arrhythmia burden (79,82). If pre-procedural imaging demonstrates a shallow LAA (LAA ostium >31 mm or length <17 mm), the nitinol cage percutaneous LAA closure device is not indicated. Due to its shape, the nitinol cage percutaneous LAA closure device requires as much depth as its width for complete LAA closure. In contrast, either generation of the self-expanding nitinol plug can be a suitable strategy in those patients and can accommodate a maximum LAA landing zone of 12.6 to 28.5 mm, whereas the Amulet can accommodate a slightly larger maximum landing zone of between 12.6 and 32 mm. Other anatomic considerations on pre-procedural imaging that can cause difficulty during implantation of endocardial devices include the shape of the LAA (sharp angles with chicken-wing morphology, short neck <10 mm with cauliflower morphology) and the presence of pectinate muscles, trabeculations, lobes, and pouches, which can cause difficulty in endocardial device implantation.

Concomitant endocardial LAA closure in patients undergoing AF ablation has been previously studied and was reported to be feasible and safe (97,98). Combining these procedures avoids the risk of another transseptal puncture and repeat left atrial intervention. This approach makes theoretical sense, especially in patients with persistent AF with triggers from the LAA, where electrical isolation of the ostium can cause decreased flow and increased risk of thrombogenesis. Furthermore, it avoids re-exposing the patients to short-term OAC twice by combining the 2 procedures. Similarly, combining LAA clipping appears to be feasible in patients undergoing minimally-invasive mitral valve surgery, especially in patients with complex LAA anatomy who are at risk of stroke, but not amenable to percutaneous endo-epicardial suture delivery or percutaneous endocardial exclusion (99). However, the issue of procedure reimbursement will limit the widespread adaptation of combining multiple procedures in 1 clinical setting.

## CHALLENGES WITH LAA CLOSURE

There are several challenges associated with LAA closure. These can be divided into challenges with post-procedural antithrombotic therapy, device-related thrombus, peridevice leaks, and device embolization.

### POST-PROCEDURAL ANTITHROMBOTIC THERAPY.

The biggest challenge associated with percutaneous, but not thoracoscopic, LAA closure is managing post-procedural antithrombotic therapy and the associated bleeding risk. Recent studies have demonstrated that the incidence of device-related thrombus with endocardial devices ranges from 3% to 7.2% (61,63,66,100–102).

Epicardial LAA exclusion (LAA exclusion system or percutaneous endo-epicardial suture delivery system) has the advantages of not having a foreign body in the endovascular system and, theoretically, lower risk of thrombus formation. But real-world data for the percutaneous endo-epicardial suture delivery system suggest similar risk compared with the nitinol cage percutaneous LAA closure device (61,70). If a thrombus is noted on follow-up TEE, continued OAC with follow-up TEE in 3 to 6 months is recommended. As our understanding of clotting and bleeding mechanisms at a cellular and molecular level continues to evolve, targeted therapies may change the clinical practice dramatically.

## POST-PROCEDURAL LEAKS.

Post-procedural leaks are common after percutaneous LAA closure and have been reported with both endocardial and percutaneous endo-epicardial closure, but not LAA exclusion system closure. The incidence of reported leaks has ranged from 0% to 63%, depending on the type of LAA device and the frequency and modality of monitoring (103,104). The consequences of such peridevice leaks remain unclear at this point, with studies reporting conflicting results regarding risk of stroke (105–107).

The contradictions in reported data expose the limitations in imaging modalities and the importance of adequate device sizing. As the field of stroke prevention in AF continues to expand, we will continue to gain further insight into how best to manage post-procedural leaks. Until then, continued surveillance with TEE and temporary initiation of anticoagulation are recommended.

## DEVICE EMBOLIZATION.

Device embolization is a rare, but a potential challenge associated with endocardial LAA devices, such as the nitinol cage percutaneous LAA closure device and the transcatheter self-expanding nitinol plugs, with a reported incidence of <4% (44). It appears that most of the device embolizations reported were acute and occurred during the hospital stay (65%) after the procedure, whereas about 30% were late embolizations picked up on routine TEE follow-up (108). Although most device embolizations in published reports were retrieved percutaneously (108), a surgical approach may be required in some complex cases. It is recommended that inexperienced operators obtain adequate imaging of the LAA anatomy by both TEE and CT scan to facilitate adequate device sizing to minimize this complication. Furthermore, follow-up TEEs are recommended at 45 days, 6 months, and 12 months.

## CATHETER ABLATION WITH LAA CLOSURE.

Patients who undergo LAA closure are usually elderly, high-risk patients with AF who may need additional radiofrequency catheter ablation procedures targeting both PV and other, non-PV sites for symptomatic AF. Performing ablation, especially around the LAA, in the presence of an endocardial device can be challenging, due to remodeling of the ostium of the LAA, potentially increasing the risk of new peridevice leaks (109). As currently there is only limited data, this is conjectural.

## FUTURE DIRECTIONS

Stroke prevention remains a major goal in patients in AF. Although anticoagulation remains the first choice, the low compliance rate is alarming. LAA closure devices will continue to evolve as an alternative strategy with development of new technology, identification of the appropriate patient population, and improvements in operator skills and periprocedural techniques. Currently, LAA closure is being performed in patients who are eligible for long-term anticoagulation. The most important questions that remain is if LAA closure can be safely performed in patients who are ineligible for OAC and what is the preferred medical therapy post-LAA closure. The risks of late device thrombosis and peridevice leaks continue to remain the Achilles heel in wide adoption of this technology. Several

real-world registries have answered these questions (61,63) to some degree, but the results of ASAP-TOO are eagerly awaited. Currently, there are no randomized data comparing LAA closure with DOACs. This remains an important question for future investigation. PRAGUE-17 (Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation) (NCT02426944) is an ongoing RCT comparing LAA closure with DOAC in patients in AF who are at high risk of a cardioembolic event and have a history of major bleeding that required hospitalization or intervention. Furthermore, there may also be a rationale for LAA closure in patients with very high CHA<sub>2</sub>DS<sub>2</sub>-VASc scores who are at risk of stroke despite OAC. The role of combination therapy with LAA closure and OAC will need to be investigated.

The other important question is: what type of LAA closure is preferred? It is encouraging to see the advent of multiple LAA closure strategies in various stages of research and development, with a variety of shapes, sizes, indications, and implantation techniques to suit different patient profiles, LAA anatomy, and comorbid conditions. With similar procedural times and risk profiles, a heart team approach may be important in deciding between percutaneous approaches and totally thoracoscopic approaches.

The effect of LAA closure on hemodynamic and neurohormonal modulation, especially in the management of refractory hypertension in patients with AF, is another area of interest. The feasibility of combining LAA closure with AF ablation and transcatheter aortic valve replacement was reported recently but needs prospective examination in large-scale RCTs. Finally, development of expert consensus documents from professional societies, in conjunction with prospective registries, will help promote best practices to achieve effective results in the prevention of stroke in patients with AF.

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## ABBREVIATIONS AND ACRONYMS

<b>AF</b>	atrial fibrillation
<b>DOAC</b>	direct oral anticoagulant
<b>FDA</b>	U.S. Food and Drug Administration
<b>LAA</b>	left atrial appendage
<b>OAC</b>	oral anticoagulant
<b>RCT</b>	randomized controlled trial

**TEE** transesophageal echocardiography

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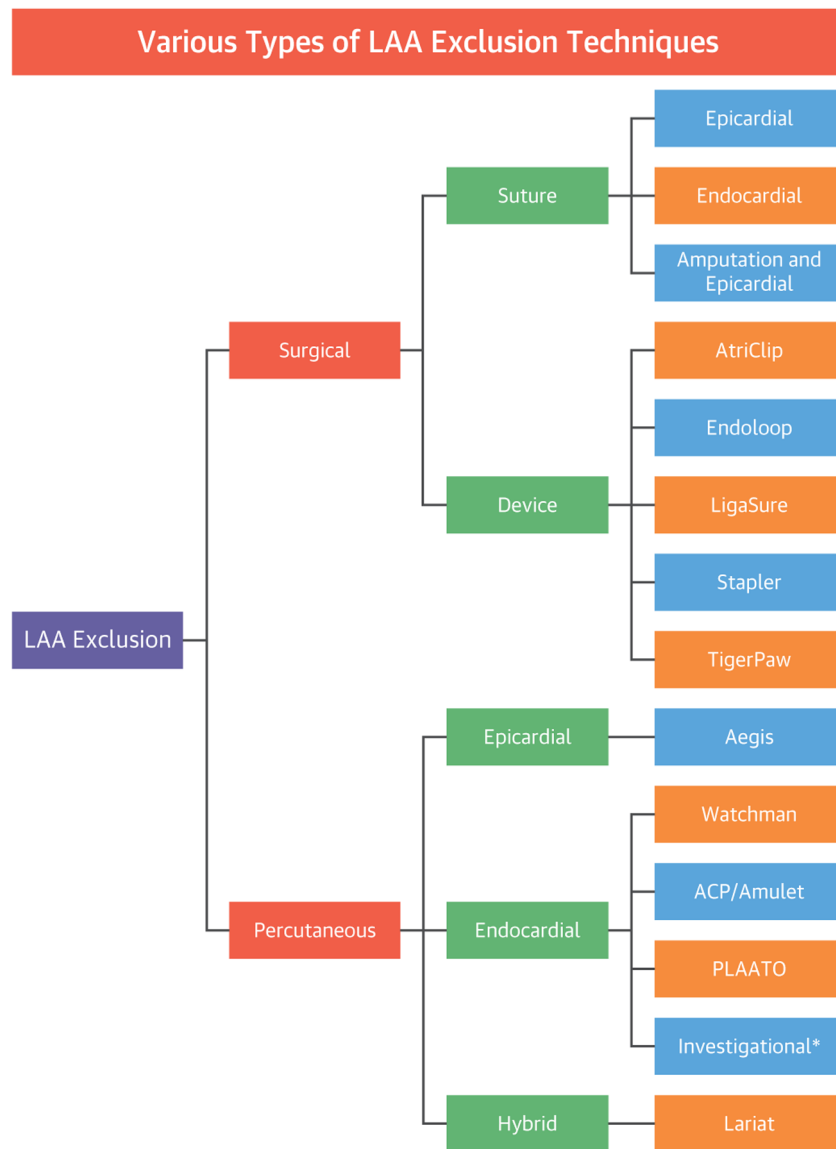
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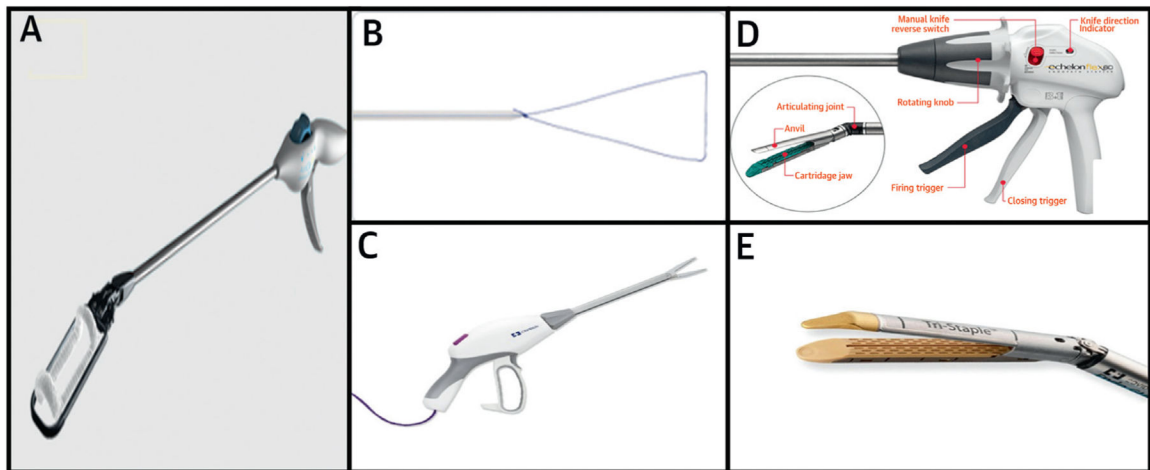
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**FIGURE 1.**

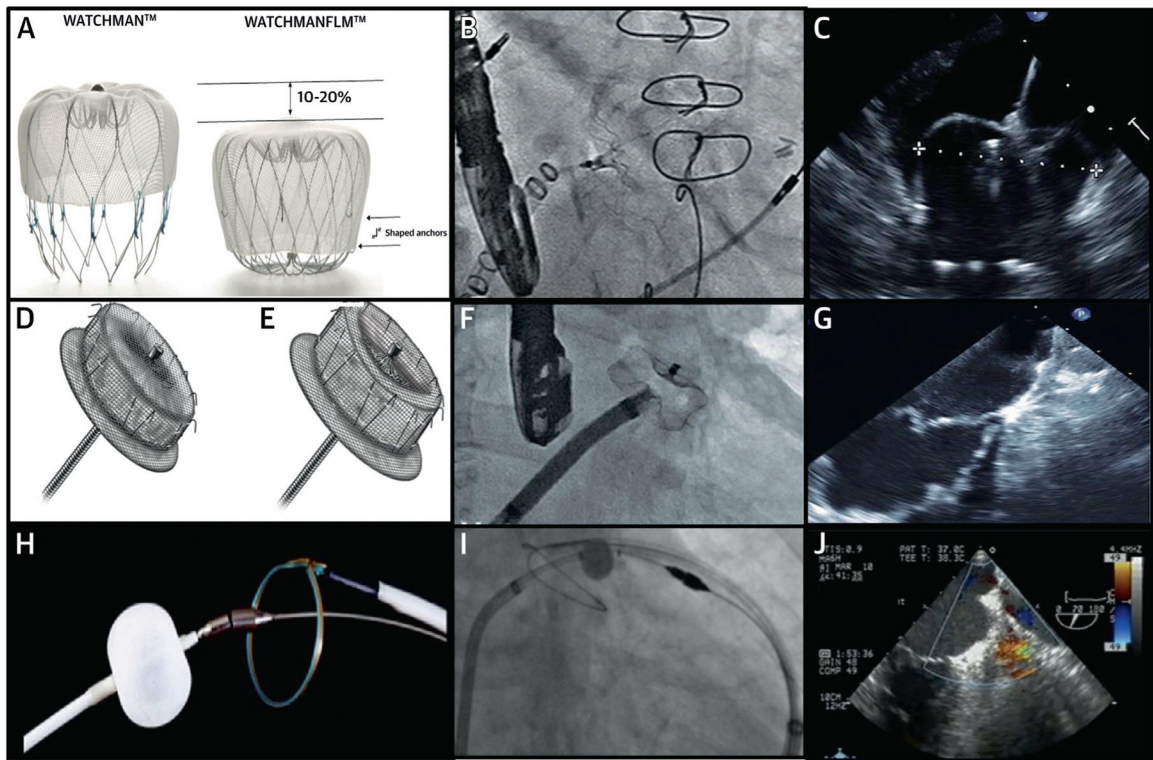
Various Types of LAA Exclusion Devices

\*WaveCrest (Biosense Webster, Irvine, California), LAmbré (Lifetech Scientific Corp., Shenzhen, China), Transcatheter patch (Custom Medical Devices, Greece), Ultrasept (Cardia, Eagan, Minnesota), pfm LAA Occluder (pfm Medical, Cologne, Germany), and Occlutech (Occlutech International, Helsingborg, Sweden). ACP = Amplatzer cardiac plug; LAA = left atrial appendage; PLAATO = percutaneous left atrial appendage transcatheter occlusion.

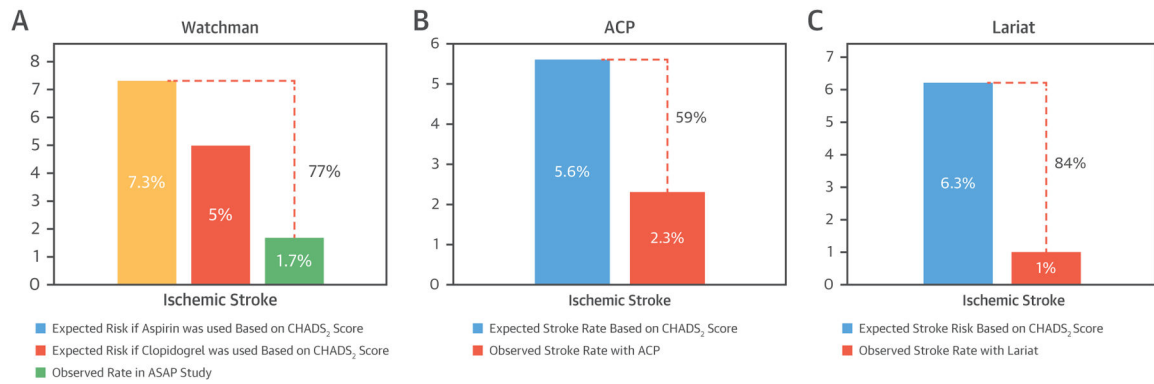
**FIGURE 2.**

## Surgical LAA Exclusion Devices

(A) AtriClip LAA exclusion system. Image courtesy of AtriCure. (B) ENDOLOOP Ligature. Image courtesy of Ethicon. (C) LigaSure Vessel Sealing System. Image courtesy of Medtronic. (D) ECHELON FLEX ENDOPATH Staplers. Image courtesy of Ethicon. (E) Endo Gia. Image courtesy of Medtronic. LAA = left atrial appendage.

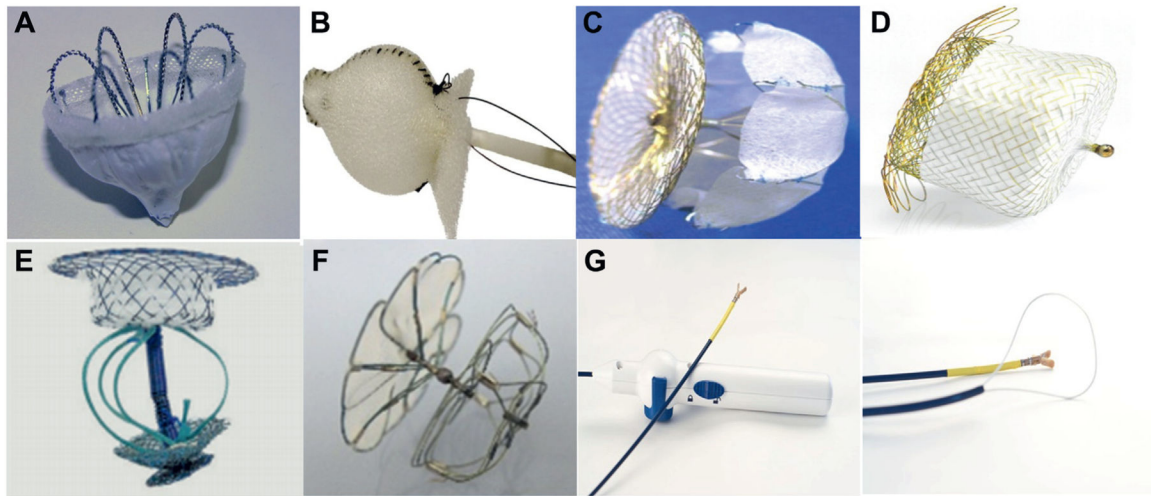
**FIGURE 3.****Percutaneous LAA Exclusion Devices**

(A) Watchman device and Watchman FLX. Image courtesy of Boston Scientific. (B) Fluoroscopy image showing positioning of Watchman in the LAA. (C) TEE image demonstrating Watchman positioned in the LAA. (D) Amplatzer cardiac plug (ACP) device. (E) Amulet. (F) Fluoroscopy image showing positioning of the ACP in the LAA (G). TEE image demonstrating device positioned in the LAA. (H) Lariat suture delivery device. (I) Fluoroscopy image showing positioning of Lariat system at the LAA. (J) TEE image demonstrating device after LAA exclusion. Reprinted from Saw J, Lempereur M. Percutaneous left atrial appendage closure: procedural techniques and outcomes. *J Am Coll Cardiol Interv* 2014;7:1205–20. LAA = left atrial appendage; TEE = transesophageal echocardiography.

**FIGURE 4.**

Expected and Annual Rate of Stroke in Watchman, ACP, and Lariat

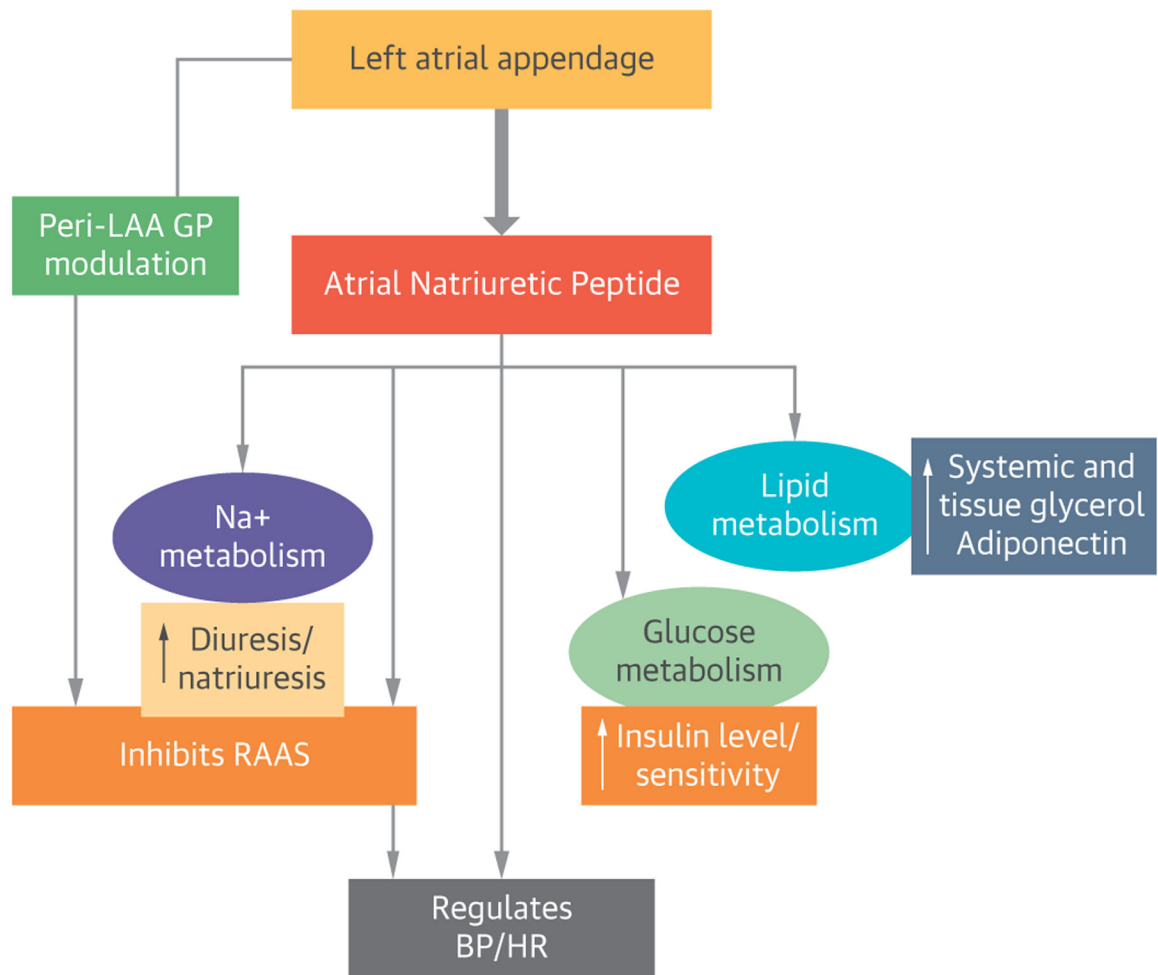
**(A)** Results from the ASAP registry. The observed rate of ischemic stroke was 1.7%, compared with an expected rate of ischemic stroke of 7.3% with similar CHADS<sub>2</sub> score with aspirin and 5% with clopidogrel. Adapted with permission from Reddy et al. (63). **(B)** Results from Tzikas et al. (66). The observed rate of ischemic stroke was 2.3%, compared with an expected rate of ischemic stroke of 5.6% with similar CHADS<sub>2</sub> score with aspirin. Adapted with permission from Tzikas et al. (66). **(C)** Results from Sievert et al. (69). The observed rate of ischemic stroke was 1%, compared with an expected rate of ischemic stroke of 6.2% with similar CHADS<sub>2</sub> score with aspirin. Adapted with permission from Sievert et al. (69). ACP = Amplatzer cardiac plug; ASAP = ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology; CHADS<sub>2</sub> = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack.



**FIGURE 5.**

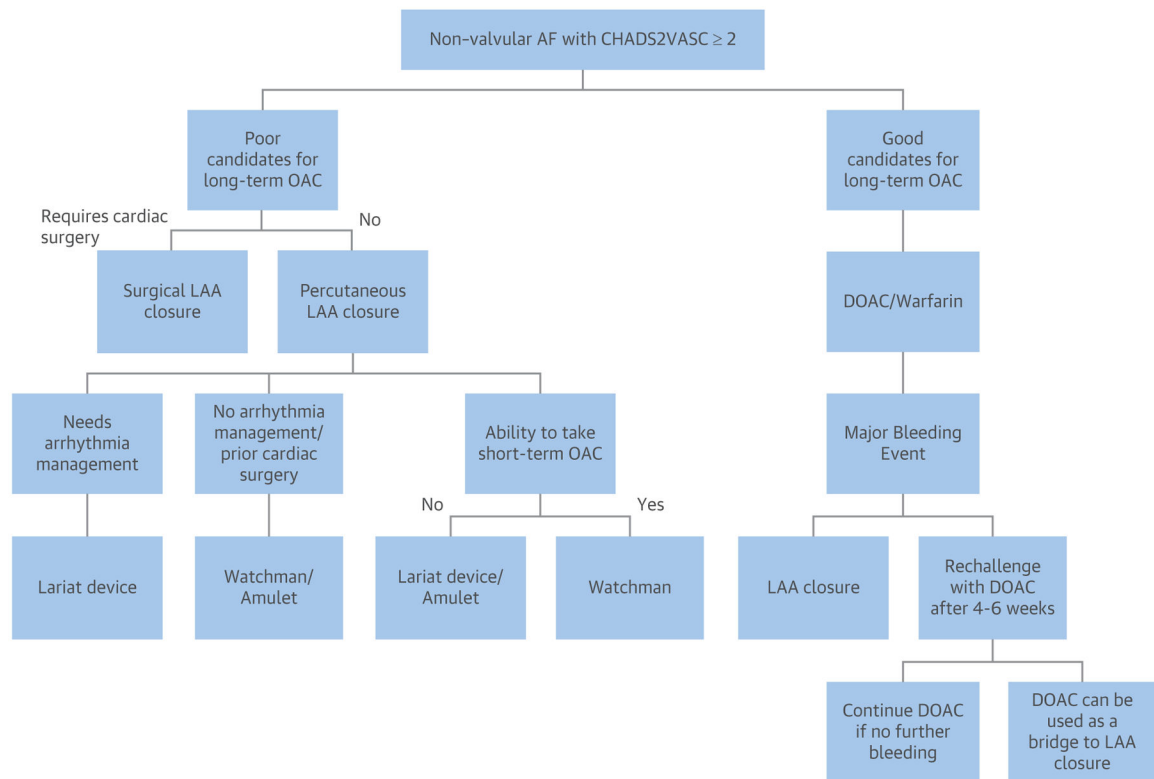
Investigational LAA Exclusion Devices

(A) Coherex Wavecrest device. Wavecrest implant image reprinted from De Backer O, Arnous S, Ihlemann N, et al. Percutaneous left atrial appendage occlusion for stroke prevention in atrial fibrillation: an update. *Open Heart* 2014;1:e000020. (B) Transcatheter patch (Custom Medical Devices). Reprinted with permission from Toumanides et al. (75). (C) LAMBRE device (Lifetech Scientific). Reprinted with permission from Huang et al. (72). (D) Occlutech device. Image courtesy of Occlutech International AB. (E) pfm LAA Occluder. Image courtesy of pfm Medical. (F) Ultraseal device (Cardia). Image courtesy of Cardia. (G) Sierra ligation system. Image courtesy of Aegis Innovations. LAA = left atrial appendage.

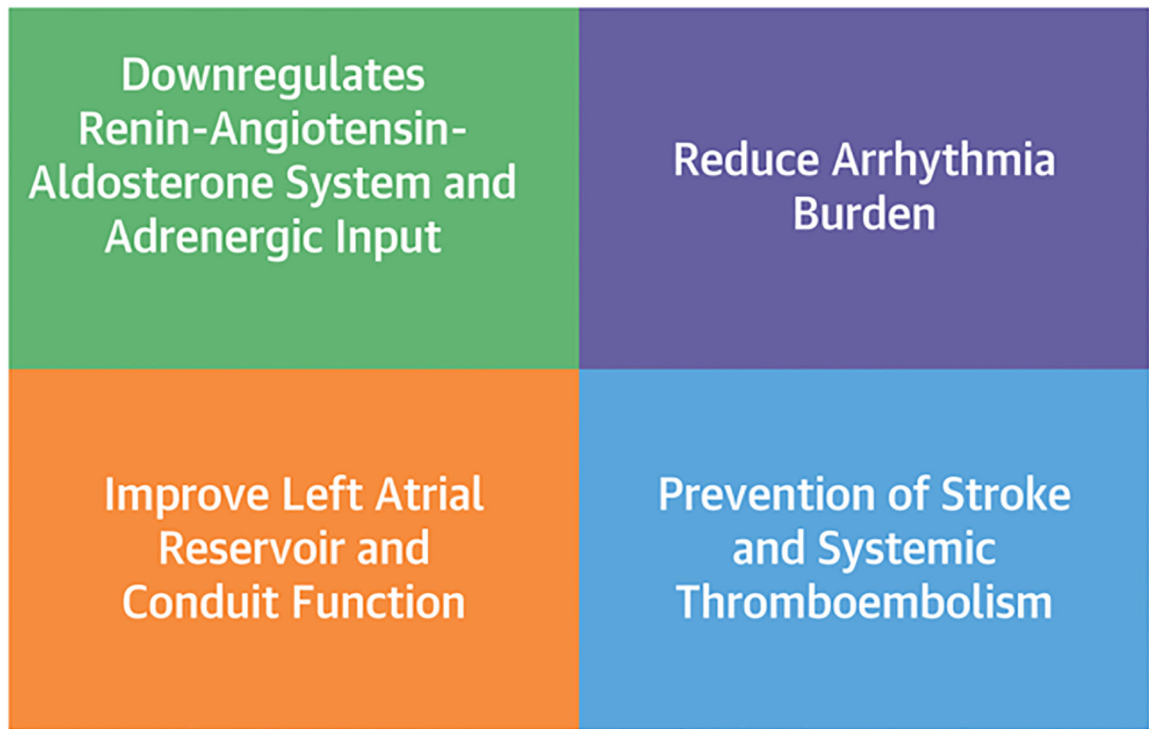
**FIGURE 6.**

## Neurohormonal Modulation With LAA Exclusion

BP = blood pressure; GP = ganglionated plexus; HR = heart rate; LAA = left atrial appendage; Na<sup>+</sup> = sodium ion; RAAS = renin-angiotensin-aldosterone system.

**FIGURE 7.****Guide to Consider LAA Closure in Nonvalvular AF**

AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = congestive heart failure, hypertension, age 75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (female); DOAC = direct oral anticoagulant; OAC = oral anticoagulant; other abbreviations as in Figure 6.



**CENTRAL ILLUSTRATION.**  
Impact of Left Atrial Appendage Exclusion

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