Published in final edited form as:

Cardiol Clin. 2014 November ; 32(4): 601–625. doi:10.1016/j.ccl.2014.07.006.

Left Atrial Appendage Exclusion for Atrial Fibrillation

Faisal F. Syed, B.Sc. (Hons.), M.B.Ch.B., M.R.C.P.¹, Christopher V. DeSimone, M.D., Ph.D.¹, Paul A. Friedman, M.D., F.A.C.C., F.H.R.S.¹, and Samuel J. Asirvatham, F.A.C.C, F.H.R.S.^{1,2}

¹Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota

²Department of Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota

SYNOPSIS

Percutaneous left atrial appendage (LAA) closure is increasingly being used as a treatment strategy to prevent stroke in patients with atrial fibrillation (AF) who have contraindications to anticoagulants. A number of approaches and devices have been developed in the last few years, each with their own unique set of advantages and disadvantages. We review the published studies on surgical and percutaneous approaches to LAA closure; focusing on stroke mechanisms in AF, LAA structure and function relevant to stroke prevention, practical differences in procedural approach, and clinical considerations surrounding management.

Keywords

Left atrial appendage; Percutaneous appendage closure; Stroke Prevention; Atrial fibrillation

Introduction

Patients with atrial fibrillation (AF) may have LAA dependent (LAA thromboembolism)^{1, 2} and LAA independent (aortic arch, carotid and intracerebral artery disease) stroke mechanisms (Figure 1).^{3, 4} The majority of strokes in AF are associated with left atrial thrombi, found in approximately 15% of patients with non-valvular AF, with 90% located in the left atrial appendage (LAA).^{2, 5} Given that warfarin does not significantly affect atheroembolic or arterial occlusive disease, and yet it dramatically reduces stroke in AF, it is reasonable to expect that an LAA occlusion strategy will prevent most warfarin-sensitive strokes in AF.^{6, 7} Evidence of the non-inferiority of LAA exclusion compared with warfarin therapy in the PROTECT randomized controlled trial,⁸ provides proof for this concept. Further evidence comes from a randomized trial reporting similar event rates after electrical

Corresponding Author: Samuel J. Asirvatham, MD, Professor of Medicine and Pediatrics, Division of Cardiovascular Diseases, 200 First Street SW, Rochester, MN 55905, asirvatham.samuel@mayo.edu, Phone number: 507-293-3376, Fax number: 507-255-2550.

Co-Authors Contact Details:

- Desimone.Christopher@mayo.edu
- Friedman.Paul@mayo.edu
- Syed.Faisal@mayo.edu

Disclosures: None

cardioversion when TEE was used to exclude LAA thrombus as compared to conventional anticoagulation.⁹

A number of techniques at obliterating the LAA have emerged^{10, 11} as a strategy to simultaneously reduce both stroke risk, the need for anticoagulation and hemorrhagic complications.^{12, 13} We review the published studies on surgical and percutaneous approaches to LAA closure; focusing on stroke mechanisms in AF, LAA structure and function relevant to stroke prevention, practical differences in procedural approach, and clinical considerations surrounding management.

Left Atrial Appendage Structure and Function

Morphology

The LAA is the remnant of the embryonic left atrium which forms during the third week of gestation and derives a blood supply from the left circumflex and right coronary arteries at the atrioventricular groove.^{14,15} In post-natal life it is an irregular, tubular diverticulum which continues to grow until the end of the second decade of life, with an ostium which is wider in taller individuals. It is differentiated from the pulmonary vein-derived smooth-walled cavity of the remaining left atrium by rich endocardial trabeculations formed by parallel-running muscle bars, termed pectinate muscles.¹⁵ The LAA ostium is separated from the left superior pulmonary vein by a narrow tissue invagination (the left lateral ridge)¹⁶ in which lies the ligament of Marshall, a developmental remnant of the left-sided vena cava of importance in AF arrhythmogenesis.^{17, 18} The left lateral ridge clearly defines the superoposterior border of the LAA ostium endocardially, seen as a “q-tip” on echocardiography, with the other borders being less well defined.¹⁹ The ostial rim is smooth and the atrial tissue immediately surrounding the outside of the ostium may be pitted and focally quite thin.¹⁹ In approximately 30% of individuals, muscular trabeculations can be found extending inferiorly from the appendage to the vestibule of the mitral valve.¹⁶ The muscular architecture of the LAA is complex, with overlapping cardiomyocytes of different orientations, and is invested by extensions of Bachmann’s bundle which bifurcate around the LAA neck, with contributions from the septopulmonary and septoatrial bundles.^{16, 20} In dogs, the epicardial LAA tip is the last to activate²¹ although similar human data is lacking.^{22–25}

Regional Anatomy

The LAA arises from the free wall of the left atrium and extends superiorly to drape forward and down onto the left ventricular free wall, with the main pulmonary artery positioned immediately superior.^{15, 16, 19} It rests freely within the confines of the pericardial sac with the left phrenic nerve having a variable superimposed course as part of the pericardiophrenic neurovascular bundle.^{26, 27} The ostium shares important relationships with the left superior pulmonary vein endocardially and the coronary vessels epicardially, with the left aortic sinus and main coronary artery lying posterior and medial, and the great cardiac vein and circumflex artery lying inferior.¹⁹ The circumflex artery is usually less than 2mm from the LAA ostium.²⁸ The left anterior descending artery runs underneath the body, emerging at a point immediately below the LAA tip, although the tip’s position can vary.¹⁶ In a minority

of patients, the sinus node artery arising from the circumflex artery runs nearby¹⁹ and can assume an S-shape as it courses between the LAA and left superior pulmonary vein.¹⁶

Morphological Variation

The LAA has marked variation in size and shape between individuals,^{19, 29–32} including the degree of curvilinearity, size and number of pectinate muscles, and the amount of “branches and twigs” formed by outpouchings and lobes.^{19, 29,30} The number of lobes also varies, with 20 – 70% of individuals having a single lobe, 16 – 54% having two, and the remainder having up to 4 lobes.^{30, 33, 34} The ostium is oval shaped in the majority (70%), but can be ovaloid (18%), triangular (8%) or round (6%).³³ In AF, it has been reported to have a more elliptical shape compared to age-matched controls.³⁵ It lies horizontal to the left superior pulmonary vein in most, but can assume a position superior or inferior to it.²⁸ The left lateral ridge usually extends from the upper border of the left superior to the lower border of the left inferior pulmonary vein, whilst in a minority terminates at the junction between the two left pulmonary veins.²⁸ Congenital anomalies include LAA aneurysm^{36, 37}, absence,³⁸ juxtaposition,³⁹ inversion,⁴⁰ and obstructive membrane at the LAA ostium.⁴⁰ Rarely, the appendage can be closely adherent to the underlying left ventricular wall.

Function

The LAA is ideally positioned to act as an adaptive chamber in conditions of volume overload.¹⁵ In dogs, its compliance far exceeds the remaining left atrium^{41, 42} and its contractility obeys a Frank-Starling mechanism^{43, 44} with ejection velocity increasing from tip to ostium.⁴⁵ It is the main source of atrial natriuretic peptide at supranormal levels of wall stress,^{46–49} thus mediating major adaptive responses which reduce circulating blood volume. The LAA is a rich source of cardiac progenitor cells.⁵⁰ In humans, LAA relaxation declines with age,⁵¹ as does the thickness of pectinate muscles.³⁰

Dog studies of LAA exclusion demonstrate acute reduction in reservoir atrial function and increased restrictive physiology in keeping with loss of the atrial compliance chamber,^{52, 53} findings which are also reflected in patients undergoing surgical LAA closure,^{54, 55} and with a reduction in atrial booster function by up to a third when the appendage is removed.^{56, 57} Patients with AF undergoing LARIAT percutaneous LAA ligation (detailed below) have a marked reduction in circulating renin, aldosterone, and noradrenaline levels (unpublished).⁵⁸

Stroke Mechanisms in Atrial Fibrillation

Systemic factors, clinical risk prediction and ventricular-vascular interactions

In patients with AF, the best validated methods of identifying patients at increased risk of stroke, are the CHADS₂^{59, 60} and CHA₂DS₂-VASC score,^{61, 62} the constitutive components of which are mainly risk factors for vascular disease. Indeed, in AF, a complex interaction exists between these scores, the presence of atherosclerotic arterial (especially aortic) disease, increasing AF burden, progressive left atrial dysfunction and LAA thrombus formation^{63, 64, 65, 66–71, 72–76, 77} One possible unifying mechanism is reduced aortic compliance resulting in ventricular diastolic dysfunction from abnormal ventricular-vascular interactions.⁷⁸

Left atrial appendage dysfunction and myopathy

Studies of LAA function have provided increasing insight into the importance of blood stasis within the LAA. The Stroke Prevention in Atrial Fibrillation III trial demonstrated a 2.5-fold increase in stroke risk if appendage thrombi were visualized on TEE,⁷⁹ with an association between reduced peak LAA emptying velocity of < 20 cm/s, the presence of dense spontaneous echocardiographic contrast, thought to reflect blood stasis and red cell clumping, and appendage thrombi.⁸⁰ The close association between the presence of LAA thrombus and mitral E/e' (an estimate of elevated left ventricular filling pressures)^{71, 81} and B-type natriuretic peptide,⁷⁰ independently of the CHADS₂ score, is further evidence that increased diastolic ventricular pressure transmitted to the atrium is important in LAA thrombogenesis. There may be a lack of correlation between AF and LAA thrombus,⁸² as LAA mechanical function may be relatively preserved during fibrillatory activity whilst significantly reduced in others that are in sinus rhythm with left ventricular diastolic dysfunction.⁸³ AF may additionally increase thrombogenesis through irregular and/or reduced time for ventricular filling, resulting in acutely lowered LAA emptying,⁸⁴ whilst left ventricular diastolic dysfunction sensitizes LAA emptying velocity to changes in atrio-ventricular synchrony.⁸⁵

Atrial tissue changes which accompany AF include cardiomyocyte hypertrophy, interstitial fibrosis, and molecular changes of oxidative stress.⁸⁶ The degree of atrial fibrosis as assessed by late gadolinium enhancement on MRI has been associated with the presence of LAA thrombi and spontaneous contrast,⁸⁷ as has left atrial dysfunction identified by strain imaging which identifies abnormalities in myocardial deformation.^{88, 89} Bipolar voltage mapping of the left atrium in AF has correlated the extent of myopathic low voltage electrograms (< 0.5 mV) with reduced LAA emptying velocity.⁹⁰ These tissue changes have been proposed to contribute to increased local thrombogenicity at the blood-endocardium interface.⁹¹ However, a recent small study comparing markers of endothelial damage and inflammatory-hemostatic cascade activation between right atrial (which has a lower incidence of thrombi in AF) and left atrial blood found no differences.⁹² In contrast, the acute, transient decline in LAA function that accompanies electrical cardioversion from AF is accompanied by an increase in spontaneous contrast.⁹³

Left atrial appendage morphology and microstructure complexity

Increased complexity of appendage morphology and microstructure is associated with risk of stroke independently to clinical risk scores. In a study of 932 patients with non-valvular AF in the USA and Europe, LAA morphology as characterized by CT or MRI was significantly associated with cerebrovascular event risk, independent of CHADS₂ score, age, and AF subtype.⁹⁴ The morphologies described varied in degree of trabeculations and complexity, and a corresponding increased 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]). The least complex “chicken wing” morphology was found to confer significantly less event risk than the others (OR 0.21, p=0.036), with odds ratio for stroke rising from 4.1 to 8.0 with increasing morphological complexity.⁹⁴ A substudy of 348 patients with MRI-detected silent cerebral ischemia noted an 85% cerebral event rate with a repeat of the above risk

profile findings.⁹⁵ In a Japanese study of 30 stroke patients with AF matched to 50 controls with AF and no stroke, although the distribution in these morphologies was different (chicken wing 17.5%, windsock 37.5%, cactus 5%, cauliflower 40%), the “cauliflower” morphology was associated with increased stroke risk independent to CHADS₂Vasc score (OR 3.4, p=0.017).⁹⁶ In a study of 678 patients from the USA, with a similar distribution of morphologies (45% chicken wing, 26% windsock, 18% cactus and 10% cauliflower), the presence of extensive trabeculations (i.e. if seen throughout the LAA wall), reflecting pectinate muscles, was independently associated with risk of stroke (OR 3.1; p = .012).⁹⁷ No independent effect of morphology classification on stroke risk was demonstrated, although the cauliflower morphology was associated with increased trabeculations and present in 11/65 (17%) of patients with stroke compared to 57/613 (9%) without. In a Japanese study of 564 patients with 3D-TEE, left atrial volume and number of LAA lobes were independently associated with LAA thrombus, with 94% (32/34) of those with thrombus having 3 or more lobes.⁹⁸ In contrast, LAA ostial size has been associated with both an increased³² and decreased⁹⁷ risk with larger ostial size. Dimensional changes need to be interpreted with caution, as AF itself is associated with larger atrial and LAA dimensions.^{30, 99}

Left Atrial Appendage Closure for Cardioembolic Risk Reduction

LAA closure as a strategy for stroke prevention can be performed surgically or percutaneously. Percutaneous approaches can be divided into three broad categories: transseptally placed endocardial plug devices, epicardial LAA ligation procedures, and hybrid ligation approaches that use transseptal and epicardial access.¹⁰

Surgical Approaches

Techniques for surgical LAA closure are suture closure from an endocardial or epicardial aspect, stapling with or without excision, or surgical amputation and oversewing.¹⁰⁰ A significant factor determining success is incomplete closure, affecting 35 – 50% of patients,^{101, 102} as both residual leak from incomplete ligation and residual stump with stapled excisions have been associated with subsequent atrial thrombus,^{101–106} with recurrent thrombus formation in up to 50% and thromboembolic clinical events in 15 – 20% of patients with incomplete closure.^{101, 102, 104} Surgical amputation with oversewing appears to be the most successful approach.^{100, 101, 104} A recent, large retrospective propensity matched case-control study reports significant stroke risk reduction with surgical LAA closure in patients with AF undergoing cardiac surgery.¹⁰⁷ Prospective randomized data currently is in the form of two small, inconclusive trials (LAAOS [the Left Atrial Appendage Occlusion Study, n=77]¹⁰³ and LAAOS II, n=51¹⁰⁸) which have set the scene for the LAAOS III randomized trial of a planned 4,700 AF patients with CHA₂DS₂-VASc score ≥ 2 .¹⁰⁹ Until the results of this trial become available, the effects on stroke reduction from the current literature is hard to determine as most studies are retrospective, successful closure rates vary, and overall benefit is variable.¹¹⁰ In addition, it is difficult to justify the risks of an open surgical procedure specifically to target the LAA in patients who are not undergoing cardiac surgery for other reasons. Surgical closure currently has a Class IIb recommendation (i.e may be considered, though overall efficacy is less well established) by

the 2014 ACC/AHA/HRS Atrial Fibrillation Guidelines,¹¹¹ the 2014 ACC/AHA Valvular Heart Disease Guidelines (which specify its use for mitral stenosis surgery patients with recurrent embolic events despite therapeutic anticoagulation)¹¹² and the 2012 ESC focused update of AF guidelines.¹¹³

Minimally invasive and hybrid surgical approaches

Clinical experience has been reported with video-assisted thoracoscopy using either Endoloop or staple exclusion^{1, 114, 115} or excision¹¹⁶ with good outcome and low rates of subsequent thromboembolism. Minimally invasive approaches have also been utilized in conjunction with treatment for AF, with bilateral video-assisted thoracoscopic pulmonary vein isolation, atrial ganglia ablation, ligament of Marshall division and LAA staple excision, with a reported success rate of 50 – 90% in maintaining sinus rhythm for paroxysmal AF, 30 – 85% for persistent AF and 30 – 75% for long-standing persistent AF,^{117–119} and up to 90% if followed by a “touch-up” catheter ablation procedure.¹²⁰ The effects on stroke risk reduction of these hybrid approaches is currently unknown.

Percutaneous LAA Closure

Percutaneous LAA closure offers a less invasive strategy than surgical closure, which may be better tolerated in an often frail and elderly population,¹²¹ and typically employs concomitant confirmation of closure at the time of procedure. However, as with surgical strategies, the evidence demonstrating stroke prevention remains limited, and significant complications may occur. The 2012 ESC guidelines have given a Class IIb recommendation (i.e. may be considered, though overall efficacy is less well established) for percutaneous LAA closure for patients with a high stroke risk and contraindications for long term oral anticoagulation.¹¹³ The United Kingdom 2006 NICE guidelines recommend percutaneous LAA occlusion as an efficacious strategy for reducing the risk of thromboembolic complications associated with non-valvular AF.¹²² Although a number of devices have been developed, currently only the LARIAT®^{123, 124} (SentreHEART, Inc., Redwood City, CA, USA) suture delivery device LAA occlusion system has FDA approval and commercial availability in the USA. It also has CE-Mark approval for commercial use in Europe. The AMPLATZER®^{125, 126} (St. Jude Medical, Saint Paul, MN, USA) cardiac plug (ACP) received CE-Mark approval in December 2008 with a trial planned towards attaining FDA approval.¹¹ A second generation ACP, the Amplatzer Amulet Left Atrial Appendage Occluder, received European CE mark approval in 2013. The WATCHMAN®^{8, 127–129} (Boston Scientific, Natick, MA, USA) LAA occluder has received CE-Mark, whilst use in the USA is restricted to clinical trials, with the PREVAIL trial (clinicaltrials.gov: NCT01182441) and ensuing Continued Access to PREVAIL (CAP2) registry (clinicaltrials.gov: NCT01760291) having recently stopped recruiting. The newer WAVECREST®¹³⁰ Left Atrial Appendage Occlusion System (Coherex Medical Inc., Salt Lake City, UT, USA) has received CE-Mark in 2013.

Transeptal Approach

PLAATO

The Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) system (eV3 Inc., Sunnyvale, CA, USA) was the first device designed specifically for LAA occlusion. It consisted of a self-expanding nitinol cage covered with a blood impermeable material which sealed the LAA. It is no longer available as the manufacturer discontinued production for financial reasons despite initially promising clinical results.^{131–134} The intellectual property rights for PLAATO were acquired by Atritech in 2007 during their development of the WATCHMAN® program.¹³⁵

AMPLATZER® Cardiac Plug

The ACP (St. Jude Medical, Saint Paul, MN, USA) is a nitinol device composed of a lobe designed to prevent migration and a proximal disc that occludes the LAA orifice, with an interconnecting articulating waist to facilitate adequate positioning in variable ostial configurations.¹³⁶ It is available in sizes 16 – 30 mm and oversizing by least 2 mm to the diameter of the LAA ‘landing zone’ is necessary for secure placement. Following AMPLATZER® implantation, dual antiplatelet therapy with aspirin and clopidogrel for 1 month and aspirin monotherapy thereafter is recommended^{122, 137}.

There has been increasing clinical experience published to date of using this device in patients with contraindications to oral anticoagulant therapies. In a European registry, successful deployment was reported in 132 of 137 patients.¹²⁶ Complications were seen in 7 % and included 3 ischemic stroke, 3 device embolization, and 5 clinically significant pericardial effusions. One center in Germany, which also contributed to the above initial report, recently published its 10 year experience with endovascular LAA occlusion.¹³⁸ A total of 152 patients had attempted LAA closure, and the investigators used non-dedicated devices in 32 (PFO, ASD, and VSD occluders) and the AMPLATZER® cardiac plug in the remaining 120. Procedure-related complications (pericardial effusion, device embolization, and procedure-related stroke) and major bleeds were seen in 8 (6.7%) with cardiac plug and 7 (22%) with non-dedicated devices ($p=0.0061$), the major difference being due to difference in device embolization rates (2 [1.6%] vs 5 [12%], $p=0.0048$). Thus, in successfully treated patients, the annual incidence of stroke and major bleeding was 0.8% after a mean follow-up period of 2.6 years.

In the Belgian registry of 90 consecutive patients across 7 centers at high stroke risk (mean CHA₂DS₂-VASc 4.4) and bleeding risk (mean HAS-BLED score 3.3), acute procedural success was 95%, with 3 patients developing tamponade, of whom 1 died.¹³⁹ Minor complications were reported to be 3 insignificant pericardial effusions, 2 transient myocardial ischaemia due to air embolism, and 1 femoral pseudoaneurysm. At 1 year, the observed stroke rate was lower than the expected annual stroke rate estimated by the CHA₂DS₂-VASc score (2.1% vs 5.1%). There were 4 deaths, 2 minor strokes, 1 tamponade, and 1 myocardial infarction.

Cumulated experience has also been reported from seven centers in Canada reported on 52 patients with 98.1% acute procedural success, with serious adverse effects of device

embolization (1.9%) and pericardial effusion (1.9%).¹⁴⁰ At a mean follow-up of 20 months, the rates of death, stroke, systemic embolism, pericardial effusion, and major bleeding were 5.8%, 1.9%, 0%, 1.9%, and 1.9%, respectively. The presence of mild peri-device leak was observed in 16.2% of patients at the 6-month follow-up as evaluated by transesophageal echocardiography. There were no cases of device thrombosis.

Data from other published series globally reported similar success rates of between 92% – 100% acute success rate and complications of tamponade, coronary air embolism, catheter-related thrombosis, acute pulmonary edema, and pulmonary artery tear, with complications on follow-up being mainly thrombus formation on device or thromboembolism.¹⁴¹¹⁴²¹⁴³¹⁴⁴¹⁴⁵¹⁴⁶

Unlike WATCHMAN®, there is currently no randomized trial data on AMPLATZER®. A small, prospective 1:1 comparison with WATCHMAN® reported no significant differences in procedural times or outcome. In the US, a randomized open-label non-inferiority trial comparing ACP to optimal medical therapy with either warfarin or dabigatran is currently on hold given limited enrollment ([clinicaltrials.gov/ NCT01118299](https://clinicaltrials.gov/ct2/show/study/NCT01118299)). In Europe, the ELIGIBLE randomized trial is randomizing patients with history of gastrointestinal bleeding and high embolic risk to LAA closure or usual oral anticoagulant therapy ([clinicaltrials.gov/ NCT01628068](https://clinicaltrials.gov/ct2/show/study/NCT01628068)).

The second generation AMPLATZER® Amulet has a similarly designed lobe-disc structure but the lobe is deeper with more wires for stability, the left atrial disc is larger to better cover the ostium and prevent, and an end screw sits flush with the disc to ensure a smoother surface facing the left atrium.¹⁴⁷ Having larger available sizes (31 and 34mm), it is better suited for closure of larger LAA.¹⁴⁸

WATCHMAN®

The WATCHMAN® (Boston Scientific, Natick, MA, USA) device is made of a self-expanding nitinol frame with fixation barbs and a permeable polyester fabric cover and is available in sizes between 21 and 33 mm in diameter. Proper positioning and stability of the device are verified by TEE and angiography before device release¹¹. The WATCHMAN® is currently the only percutaneous LAA closure device with randomized prospective trial-based data guiding its use. In the PROTECT-AF trial, 707 patients with nonvalvular AF and a CHADS₂ score of 1 or more were randomized 2:1 to percutaneous LAA occlusion or warfarin.¹⁴⁹ Warfarin was continued after WATCHMAN® placement for 45 days minimum (longer if TEE showed residual leak 5mm or wider) and thereafter switched to long-term aspirin. With the WATCHMAN® device, 86% of patients were able to stop warfarin therapy at 45 days and 93% were off warfarin at 12 months. Early results demonstrated non-inferiority of closure to warfarin although placement of a device in the LAA shifted the stroke mechanisms. Thrombus was identified on the device in 3.7 % of patients, including one in whom it was detected 6 days after an ischemic stroke. During the trial, ischemic stroke was more common in the device group (3.0 % vs 2.0 % for control), and tended to occur early. Approximately 5% of patients developed a peri-procedural pericardial effusion and although this did not affect the clinical endpoints, did increase hospital stay.¹⁵⁰ However, the hemorrhagic risk was significantly lower in the device group (relative risk

0.009, 0.00–0.45). With extended follow-up, the benefits of reduced hemorrhagic risk accrued with time such that after a mean 3.8 year follow-up there was superiority of closure over warfarin with a reduction in the trial's primary end-point of stroke, cardiovascular death, and systemic embolism (2.3 vs. 3.8 events per 100 patient-years, HR 0.61, CI 0.38–0.97, $p=0.03$), and a 34% relative reduction in all-cause mortality ($p=0.04$).¹⁵⁰ A net clinical benefit analysis supported closure over warfarin both in the trial (1.73%/year) and the subsequent Continued Access Protocol (CAP) registry (4.97%/year), having greater benefit in those with higher CHADS₂ scores.¹⁵¹

Significant procedural complications were reported in 12% of patients and included pericardial effusion requiring drainage, embolic stroke, device migration and device sepsis. Incomplete endothelialization at 10 months in a patient requiring device explantation due to thromboembolism is also described.¹⁵² With increased procedural experience and device redesign, the complication rate has significantly fallen by over 50 %, with periprocedural stroke falling from 0.9 % to 0 % in a subsequent report of 542 patients in the PROTECT-AF and 460 patients in the Continued Access Protocol (CAP) registry ($p=0.04$).¹²⁸

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.¹⁵⁰ Whether a similar success can be achieved in a higher risk population (CHADS₂ score of 2 or greater) is being tested by the PREVAIL study, the formal results of which are awaited ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00129545) identifier NCT00129545). Although the trial protocol still mandates the use of warfarin in the USA, the ASA-Plavix (ASAP) feasibility study performed in Europe prospectively evaluated 150 patients undergoing WATCHMAN® implantation with 6 months of clopidogrel or ticlopidine, and lifelong aspirin, with only a 1.7%/year ischemic stroke risk, approximately 70–80 % lower than expected given the CHADS₂ score.¹⁵³

The interplay with the novel oral anticoagulants is uncertain, as they confer lower bleeding risk to warfarin.^{154–156}¹⁵⁷ As compared to the favorable comparisons of closure vs. warfarin, predicted 10 year performance of closure was only marginally better than against dabigatran 150mg as bleeding especially hemorrhagic stroke was less than with warfarin (all-cause mortality 29% vs 30%; ischemic stroke 12% vs 8%, hemorrhagic stroke 3% vs 1%, major bleeding 12% vs 27%).¹⁵⁸ There are currently no head-to-head comparisons of device closure against the novel anticoagulants. How the next generation WATCHMAN®, which is under development, influences this is uncertain and an initial European non-randomized evaluation is planned (EVOLVE, [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01196897):NCT01196897).

WAVECREST®

The WAVECREST® Left Atrial Appendage Occlusion System (Coherex Medical Inc., Salt Lake City, UT, USA) is designed to be positioned at the LAA ostium with an impermeable, less thrombogenic material facing the left atrium to minimize thrombosis and leaks, and independently deployable distal anchors which allows the device to be use in a range of appendages depths.¹⁵⁹ It is available in 3 sizes (22mm, 27mm, 32 mm). The WAVECREST I trial (multicenter, prospective, non-randomized registry) recruited 73 patients from Europe, Australia, and New Zealand, with mean CHADS₂ score of 2.5, prior cerebral embolism in

34%, and a warfarin contraindication in 49%.¹³⁰ After TEE-guided deployment, dual antiplatelet therapy was administered for 90 days and then aspirin continued long-term. Successful deployment with acute closure was seen in 68/73 (93%), with 3 mm peri-device flow at 6 weeks in 65/68 (96%). Acute tamponade occurred in 2/73 (3%) and there was no procedural stroke, device embolization or device-related thrombosis. The pivotal US WaveCrest II trial is anticipated in 2014.¹⁵⁹

Other Transeptal Devices

The Transcatheter Patch (Custom Medical Devices, Athens, Greece)¹⁶⁰ is a frameless bioabsorbable device deployed by balloon inflation, with adherence of the patch to cardiac tissues over 48 hours via fibrin formation. The Cardia Ultrasept LAA Occluder (Cardia Inc, Eagan, MN) consists of distal cylindrical bulb anchoring into the LAA and a separately articulated sail unfolding over the ostium.¹⁶¹ The Lifetech LAMBRE™ (Lifetech Scientific Corp., Shenzhen, China) (clinicaltrials.gov/NCT01920412) also incorporates an articulation at the waist between the LAA plug and ostial lip, allowing self-orientation, and is fully repositionable after deployment. The Occlutech LAA Occluder (Occlutech International AB, Helsingborg, Sweden) has a conical shape designed for improved expansile force and wire loops at the side to anchor to the LAA trabeculae.¹⁵⁹

Epicardial Approach

Epicardial approaches offer advantages of avoiding the need for transeptal puncture, risk of acute procedure-related thromboembolism, device embolism, erosion, infection and necessary anticoagulation therapy.¹⁰ Such an approach was first reported with video assisted thoracoscopy and subsequent left lung collapse with surgical pericardiotomy to access the LAA.¹

The Aegis system (Aegis Medical, Vancouver, Canada, Epitek, Minneapolis, MN, USA)^{21, 162} introduces an appendage grabber, via percutaneous sub-xiphoid pericardial access, with embedded electrodes within the jaws permitting electrical navigation onto the appendage via bipolar electrograms that identify the electrical activity of the tissue captured by the jaws. A hollow suture preloaded with a support wire to permit remote suture loop manipulation and fluoroscopic visualization is advanced to the appendage base and looped around the appendage. The loop can be variably sized to accommodate multiple LAA lobes and shapes. Following loop closure, the wire is removed leaving only suture behind, which is remotely locked with a clip to maintain closure. A loop may be opened and repositioned if the initial closure is unsatisfactory, or additional loops may be placed for multilobed LAAs that are not fully closed with the first loop, using the suture tails from the first loop as a rail. A firm closure is confirmed by the elimination of LAA electrical activity, which occurs within seconds and is accompanied by shortening of the surface ECG P wave in dogs.²¹ Chronically, the LAA involutes and becomes atretic.¹⁶² Whether LAA elimination by this means will impact rhythm control (by eliminating a mass of fibrillating atrial tissue) is not known. A small series has demonstrated feasibility in humans.¹⁶³ Major limitations for the use of this approach are prior cardiac surgery or adhesions from prior pericarditis.

The EPITEK is a fiberoptic endoscope system that utilizes a grabber deployed under direct vision, but in early human testing there were technical difficulties with pericardial access and device positioning.¹⁶⁴

Hybrid Approach

The LARIAT system (SentreHEART, Inc, Palo Alto, CA).^{7, 123} uses percutaneous epicardial LAA ligation guided by an endocardial magnet tipped wire placed in the LAA via the transeptal approach, with a second magnet-tipped wire placed epicardially in union to form a rail over which an epicardial suture loop is advanced and then closed. An endocardial balloon at the LAA ostium defines where the epicardial suture needs to be placed. Specific advantages include ability to reposition the snare and ease of deployment over a stable loop. Limitations include the combined risks of both transeptal and epicardial approaches, limited utility in appendages superiorly directed, greater than 40mm diameter (limit of snare on first generation devices) or with multiple lobes; and difficult use in patients with pectus excavatum.^{7, 10} It is estimated that 90% of LAAs have morphologies amenable to closure via this system. After initial human reports,¹²³ experience in a series of 89 patients has been reported, with successful closure in 85 (96%).¹¹⁸ Three patients had a < 2mm residual leak, and one had a < 3mm leak. There were two complications related to percutaneous epicardial access and one related to transeptal puncture. Adverse events include severe pericarditis post operatively (n=2), late pericardial effusion (n=1), late strokes (n=2) and unexplained death (n=2). A subsequent report of 27 patients with AF and high stroke risk unable to take anticoagulants, acute success was seen in 25 with TEE-confirmed persistent closure at 4 months in 22.¹⁶⁵ Complications included LAA perforation (n=1), pericarditis (n=3), transeptal sheath thrombus causing stroke (n=1), and late CVA (n=1).¹⁶⁵ Although promising, there is no controlled data, and even though the acute closure rate is high, the clinical relevance of this as a surrogate for stroke prevention is unproven.¹⁵⁰

Prevention and Management of Complications

Data from the WATCHMAN® studies demonstrates the importance of procedural experience in preventing complications, such that rate of serious pericardial effusions was 7% starting PROTECT-AF and declined to 2% during CAP.^{8, 128} Appropriate selection of procedural approach (Table 1), preprocedural anatomical definition towards procedure planning (Table 2), and procedural technique (Table 3) are all important in optimizing chances of successful closure and avoiding complications. Imaging with CT or TEE prior to implantation has complementary roles, with CT better able to image LAA morphological features, LAA tip orientation, and the coronary vasculature, and TEE better suited to identify thrombus and differentiate it from pectinate muscles.¹¹ Therefore, for a planned LARIAT procedure, a preprocedural CT scan will identify patients with unsuitable appendage morphology, size or orientation, whilst TEE will confirm absence of mobile left atrial thrombus. Another example is confirming a minimum LAA depth of 10mm for the AMPLATZER®, checking in multiple planes. With certain shapes, such as the oval LAA ostium, 2D TEE tends to underestimate area and 3D TEE or CT may be better.¹⁶⁶ It is important to have familiarity with the anatomy of the inter-atrial septum¹⁶ and techniques of transeptal¹⁶⁷ and epicardial puncture.¹⁶⁸ Intraprocedural imaging, either with TEE or

ICE,¹⁶⁹ can assist with these, as well as monitoring for complications after LAA occlusion including checking that patency of the left superior pulmonary vein and left circumflex coronary artery is maintained. The left circumflex coronary arteries is vulnerable to injury during both endovascular and epicardial suture closure, whilst epicardial devices can additionally risk injury to vessels near the LAA tip, including the left anterior descending artery, venous grafts to obtuse marginal or diagonal arteries, or the S-shaped sinus node artery.

The most common long-term complication following device closure is thromboembolism and *de novo* thrombus formation at the site of closure. A study of 34 patients with AMPLATZER® screened systematically for up to a year with TEE identified CHADS₂ CHA₂DS₂VASC, lower left ventricular ejection fraction and higher platelet count as risk factors for thrombus development, seen in 3 of 34 (9%) patients.¹⁷⁰ Whether recurrence of AF or endothelial damage from the procedure,^{171,172} Anecdotally, flush coverage of the ostium may be important to obliterate remnant cul-de-sacs which act as a nidus for thrombus formation.¹³⁶ Unlike in surgical closure, persistent leaks following endovascular occlusion, which are commonly seen (30-60%) because of mismatch between the oval shaped LAA ostium and circular device profiles, do not appear to increase risk of thromboembolism.^{146,127,127,132,134,146} Whether this is also the case for epicardial ligation is unknown. The velocity of the leak, the degree of residual exposed LAA anatomic complexity, and the ability of the leak to accommodate a thrombus may be quite different between patients with a surgical leak, epicardial ligation leak and peri-device leak. In addition, an important unknown is how to determine when the appendage is adequately closed, and whether the definition should be anatomical, electrical or functional^{7, 10} and whether transesophageal or intracardiac echocardiography, CT or MRI is the optimal imaging study.^{140, 141, 166, 173–176} All closure devices and techniques will leave a small “beak” where tissues are approximated or adjacent to a device; whether these impact stroke prevention is not known. Additionally, accessory lobes, pectinate muscles or other structures may exist proximal to a device or closure; their impact is uncertain.

Unanswered Questions

There is, however, a need for randomized trial data in patients not treated with anticoagulants.¹⁵⁰ There is also limited data against the novel oral anticoagulants which may demand increased safety profile from device closure to demonstrate net clinical benefit. However, not all devices are created equal and it remains to be seen whether epicardial suture ligation provides similar clinical benefit to endovascular occlusion strategies, noting that there is no strong evidence that complete LAA closure is a surrogate for clinical efficacy,¹⁵⁰ and if they are as sensitive to incomplete closure¹⁷⁷ as surgical ligation strategies appear to be. The role of LAA morphology in clinical risk stratification remains undefined at present, whilst the same microstructural elements that act as potential nidus for stroke are also thought to increase arrhythmia. Given the emerging role for LAA occlusion as a treatment strategy for refractory appendage arrhythmia,¹⁷⁸ the strategy of combined LAA closure with AF ablation requires further study to define the predicted reduction in stroke risk and recurrent AF. In addition to any arrhythmic effects, the clinical

hemodynamic and humeral effects of LAA closure remain poorly defined and are the area of ongoing study.

Summary

Percutaneous epicardial closure is increasingly used as a treatment strategy to prevent thromboembolism in high risk patients with AF treated with warfarin. With the advent of emerging devices, increasing procedural and clinical experience and clinical trial data, LAA closure has the potential for becoming an attractive option for stroke prevention in those at greatest risk of both stroke and bleeding. For patients with previous cardiac surgery, recurrent pericarditis, or thoracic radiation, endovascular strategies will be attractive as pericardial access and manipulation may be quite limited. For patients with a strict contraindication to anticoagulation or with a high infection risk, epicardial/non-device strategies are appealing, as entry to the central circulation is avoided. Ultimately, the availability of multiple approaches will allow the physician to select the optimal approach for a given patient based on physiologic, anatomical, and clinical considerations.

References

1. Blackshear JL, Johnson WD, Odell JA, et al. Thoracoscopic extracardiac obliteration of the left atrial appendage for stroke risk reduction in atrial fibrillation. *Journal of the American College of Cardiology*. 2003; 42(7):1249–1252. [PubMed: 14522490]
2. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *The Annals of thoracic surgery*. 1996; 61(2):755–759. [PubMed: 8572814]
3. Hart RG, Pearce LA, Miller VT, et al. Cardioembolic vs. noncardioembolic strokes in atrial fibrillation: frequency and effect of antithrombotic agents in the stroke prevention in atrial fibrillation studies. *Cerebrovascular diseases (Basel, Switzerland)*. 2000; 10(1):39–43.
4. Naya T, Yukiiri K, Hosomi N, et al. Brain natriuretic peptide as a surrogate marker for cardioembolic stroke with paroxysmal atrial fibrillation. *Cerebrovascular diseases (Basel, Switzerland)*. 2008; 26(4):434–440.
5. Mahajan R, Brooks AG, Sullivan T, et al. Importance of the underlying substrate in determining thrombus location in atrial fibrillation: implications for left atrial appendage closure. *Heart (British Cardiac Society)*. 2012; 98(15):1120–1126. [PubMed: 22572045]
6. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *The New England journal of medicine*. 2005; 352(13):1305–1316. [PubMed: 15800226]
7. Syed FF, Asirvatham SJ. Left atrial appendage as a target for reducing strokes: justifiable rationale? Safe and effective approaches? *Heart Rhythm*. 2011; 8(2):194–198. [PubMed: 21078413]
8. Holmes DR Jr, Fountain R. Stroke prevention in atrial fibrillation: WATCHMAN versus warfarin. *Expert review of cardiovascular therapy*. 2009; 7(7):727–729. [PubMed: 19589108]
9. Klein AL, Grimm RA, Murray RD, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *The New England journal of medicine*. 2001; 344(19):1411–1420. [PubMed: 11346805]
10. Friedman PA, Holmes DR. Non-surgical left atrial appendage closure for stroke prevention in atrial fibrillation. *Journal of cardiovascular electrophysiology*. 2011; 22(10):1184–1191. [PubMed: 21914028]
11. Yu CM, Khattab AA, Bertog SC, et al. Mechanical antithrombotic intervention by LAA occlusion in atrial fibrillation. *Nature reviews*. 2013; 10(12):707–722.
12. Brass LM, Krumholz HM, Scinto JM, et al. Warfarin use among patients with atrial fibrillation. *Stroke; a journal of cerebral circulation*. 1997; 28(12):2382–2389.

13. Onalan O, Lashevsky I, Hamad A, et al. Nonpharmacologic stroke prevention in atrial fibrillation. Expert review of cardiovascular therapy. 2005; 3(4):619–633. [PubMed: 16076273]
14. James TN. Small arteries of the heart. Circulation. 1977; 56(1):2–14. [PubMed: 16706]
15. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. Heart (British Cardiac Society). 1999; 82(5):547–554. [PubMed: 10525506]
16. Cabrera JA, Saremi F, Sanchez-Quintana D. Left atrial appendage: anatomy and imaging landmarks pertinent to percutaneous transcatheter occlusion. Heart (British Cardiac Society). 2014
17. De Simone CV, Noheria A, Lachman N, et al. Myocardium of the superior vena cava, coronary sinus, vein of Marshall, and the pulmonary vein ostia: gross anatomic studies in 620 hearts. Journal of cardiovascular electrophysiology. 2012; 23(12):1304–1309. [PubMed: 22830489]
18. Macedo PG, Kapa S, Mears JA, et al. Correlative anatomy for the electrophysiologist: ablation for atrial fibrillation. Part I: pulmonary vein ostia, superior vena cava, vein of Marshall. Journal of cardiovascular electrophysiology. 2010; 21(6):721–730. [PubMed: 20158562]
19. Su P, McCarthy KP, Ho SY. Occluding the left atrial appendage: anatomical considerations. Heart (British Cardiac Society). 2008; 94(9):1166–1170. [PubMed: 17488765]
20. Lemery R, Guiraudon G, Veinot JP. Anatomic description of Bachmann's bundle and its relation to the atrial septum. The American journal of cardiology. 2003; 91(12):1482–1485. A1488. [PubMed: 12804741]
21. Friedman PA, Asirvatham SJ, Dalegrave C, et al. Percutaneous epicardial left atrial appendage closure: preliminary results of an electrogram guided approach. Journal of cardiovascular electrophysiology. 2009; 20(8):908–915. [PubMed: 19368585]
22. De Ponti P, Ho SY, Salerno-Uriarte JA, et al. Electroanatomic analysis of sinus impulse propagation in normal human atria. Journal of cardiovascular electrophysiology. 2002; 13(1):1–10. [PubMed: 11843475]
23. Markides V, Schilling RJ, Ho SY, et al. Characterization of left atrial activation in the intact human heart. Circulation. 2003; 107(5):733–739. [PubMed: 12578877]
24. Cosio FG, Martin-Penato A, Pastor A, et al. Atrial activation mapping in sinus rhythm in the clinical electrophysiology laboratory: observations during Bachmann's bundle block. Journal of cardiovascular electrophysiology. 2004; 15(5):524–531. [PubMed: 15149420]
25. Lemery R, Birnie D, Tang AS, et al. Normal atrial activation and voltage during sinus rhythm in the human heart: an endocardial and epicardial mapping study in patients with a history of atrial fibrillation. Journal of cardiovascular electrophysiology. 2007; 18(4):402–408. [PubMed: 17394455]
26. Matsumoto Y, Krishnan S, Fowler SJ, et al. Detection of phrenic nerves and their relation to cardiac anatomy using 64-slice multidetector computed tomography. The American journal of cardiology. 2007; 100(1):133–137. [PubMed: 17599455]
27. Lachman N, Syed FF, Habib A, et al. Correlative anatomy for the electrophysiologist, part II: cardiac ganglia, phrenic nerve, coronary venous system. Journal of cardiovascular electrophysiology. 2011; 22(1):104–110. [PubMed: 20807274]
28. Wongcharoen W, Tsao HM, Wu MH, et al. Morphologic characteristics of the left atrial appendage, roof, and septum: implications for the ablation of atrial fibrillation. Journal of cardiovascular electrophysiology. 2006; 17(9):951–956. [PubMed: 16948738]
29. Ernst G, Stollberger C, Abzieher F, et al. Morphology of the left atrial appendage. The Anatomical record. 1995; 242(4):553–561. [PubMed: 7486025]
30. Veinot JP, Harrity PJ, Gentile F, et al. Anatomy of the normal left atrial appendage: a quantitative study of age-related changes in 500 autopsy hearts: implications for echocardiographic examination. Circulation. 1997; 96(9):3112–3115. [PubMed: 9386182]
31. Ramaswamy P, Lytrivi ID, Srivastava S, et al. Left atrial appendage: variations in morphology and position causing pitfalls in pediatric echocardiographic diagnosis. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2007; 20(8):1011–1016. [PubMed: 17588716]
32. Beinart R, Heist EK, Newell JB, et al. Left atrial appendage dimensions predict the risk of stroke/TIA in patients with atrial fibrillation. Journal of cardiovascular electrophysiology. 2011; 22(1):10–15. [PubMed: 20662984]

33. Wang Y, Di Biase L, Horton RP, et al. Left atrial appendage studied by computed tomography to help planning for appendage closure device placement. *Journal of cardiovascular electrophysiology*. 2010; 21(9):973–982. [PubMed: 20550614]
34. Heist EK, Refaat M, Danik SB, et al. Analysis of the left atrial appendage by magnetic resonance angiography in patients with atrial fibrillation. *Heart Rhythm*. 2006; 3(11):1313–1318. [PubMed: 17074637]
35. O'Brien J, Al-Hassan D, Ng J, et al. Three-dimensional assessment of left atrial appendage orifice geometry and potential implications for device closure. *The international journal of cardiovascular imaging*. 2014; 30(4):819–823. [PubMed: 24599646]
36. Chowdhury UK, Seth S, Govindappa R, et al. Congenital left atrial appendage aneurysm: a case report and brief review of literature. *Heart, lung & circulation*. 2009; 18(6):412–416.
37. Bramlet DA, Edwards JE. Congenital aneurysm of left atrial appendage. *British heart journal*. 1981; 45(1):97–100. [PubMed: 7459169]
38. Collier P, Cavalcante JL, Phelan D, et al. Congenital absence of the left atrial appendage. *Circulation Cardiovascular imaging*. 2012; 5(4):549–550. [PubMed: 22811419]
39. Frescura C, Thiene G. Juxtaposition of the atrial appendages. *Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology*. 2012; 21(3):169–179. [PubMed: 21489823]
40. Zhang H, Sun JP, Zhao Y, et al. Inverted left atrial appendage. *International journal of cardiology*. 2014; 170(3):e57–e58. [PubMed: 24290072]
41. Davis CA 3rd, Rembert JC, Greenfield JC Jr. Compliance of left atrium with and without left atrium appendage. *Am J Physiol*. 1990; 259(4 Pt 2):H1006–H1008. [PubMed: 2221109]
42. Hoit BD, Walsh RA. Regional atrial distensibility. *Am J Physiol*. 1992; 262(5 Pt 2):H1356–H1360. [PubMed: 1590438]
43. Hondo T, Okamoto M, Yamane T, et al. The role of the left atrial appendage. A volume loading study in open-chest dogs. *Japanese heart journal*. 1995; 36(2):225–234. [PubMed: 7596042]
44. Killeen RP, Ryan R, MacErlane A, et al. Accessory left atrial diverticulae: contractile properties depicted with 64-slice cine-cardiac CT. *The international journal of cardiovascular imaging*. 2010; 26(2):241–248. [PubMed: 19768571]
45. Goldberg YH, Gordon SC, Spevack DM, et al. Disparities in emptying velocity within the left atrial appendage. *European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology*. 2010; 11(3):290–295.
46. Moe GW, Grima EA, Angus C, et al. Response of atrial natriuretic factor to acute and chronic increases of atrial pressures in experimental heart failure in dogs. Role of changes in heart rate, atrial dimension, and cardiac tissue concentration. *Circulation*. 1991; 83(5):1780–1787. [PubMed: 1827057]
47. Stewart JM, Dean R, Brown M, et al. Bilateral atrial appendectomy abolishes increased plasma atrial natriuretic peptide release and blunts sodium and water excretion during volume loading in conscious dogs. *Circulation research*. 1992; 70(4):724–732. [PubMed: 1532351]
48. Stewart JM, O'Dea DJ, Shapiro GC, et al. Atrial compliance determines the nature of passive atrial stretch and plasma atrial natriuretic factor in the conscious dog. *Cardiovascular research*. 1991; 25(9):784–792. [PubMed: 1839242]
49. Tabata T, Oki T, Yamada H, et al. Relationship between left atrial appendage function and plasma concentration of atrial natriuretic peptide. *Eur J Echocardiogr*. 2000; 1(2):130–137. [PubMed: 12086211]
50. Winter EM, van Oorschot AA, Hogers B, et al. A new direction for cardiac regeneration therapy: application of synergistically acting epicardium-derived cells and cardiomyocyte progenitor cells. *Circ Heart Fail*. 2009; 2(6):643–653. [PubMed: 19919990]
51. Yoshida N, Okamoto M, Nanba K, et al. Transthoracic tissue Doppler assessment of left atrial appendage contraction and relaxation: their changes with aging. *Echocardiography (Mount Kisco, NY)*. 2010; 27(7):839–846.
52. Hoit BD, Shao Y, Tsai LM, et al. Altered left atrial compliance after atrial appendectomy. Influence on left atrial and ventricular filling. *Circ Res*. 1993; 72(1):167–175. [PubMed: 8417839]

53. Kamohara K, Popovic ZB, Daimon M, et al. Impact of left atrial appendage exclusion on left atrial function. *The Journal of thoracic and cardiovascular surgery*. 2007; 133(1):174–181. [PubMed: 17198808]
54. Tabata T, Oki T, Yamada H, et al. Role of left atrial appendage in left atrial reservoir function as evaluated by left atrial appendage clamping during cardiac surgery. *The American journal of cardiology*. 1998; 81(3):327–332. [PubMed: 9468076]
55. Melduni R, Wiggins M, Suri R, et al. Physiological significance of left atrial appendage closure: implication for postoperative atrial fibrillation. *Journal of the American College of Cardiology*. 2013; 61(10_S)
56. Lee CH, Kim JB, Jung SH, et al. Left atrial appendage resection versus preservation during the surgical ablation of atrial fibrillation. *The Annals of thoracic surgery*. 2014; 97(1):124–132. [PubMed: 24075500]
57. Bois JP, Sheldon S, Stulak J, et al. Surgical therapy for atrial fibrillation: impact of left atrial appendage exclusion or amputation on atrial mechanical function. *Journal of the American College of Cardiology*. 2014; 63(12_S)
58. Lakkireddy, D. Left atrial appendage exclusion as adjunct strategy for AF ablation. Paper presented at: Heart Rhythm Society Annual Sessions; 05/09/2014; San Francisco. 2014.
59. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *Jama*. 2001; 285(22): 2864–2870. [PubMed: 11401607]
60. Rietbrock S, Heeley E, Plumb J, et al. Chronic atrial fibrillation: Incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack (CHADS2) risk stratification scheme. *American heart journal*. 2008; 156(1):57–64. [PubMed: 18585497]
61. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010; 137(2):263–272. [PubMed: 19762550]
62. Lip GY, Frison L, Halperin JL, et al. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke; a journal of cerebral circulation*. 2010; 41(12): 2731–2738.
63. Blackshear JL, Pearce LA, Hart RG, et al. Aortic plaque in atrial fibrillation: prevalence, predictors, and thromboembolic implications. *Stroke; a journal of cerebral circulation*. 1999; 30(4):834–840.
64. Asinger RW, Koehler J, Pearce LA, et al. Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: II. Dense spontaneous echocardiographic contrast (The Stroke Prevention in Atrial Fibrillation [SPAF-III] study). *J Am Soc Echocardiogr*. 1999; 12(12):1088–1096. [PubMed: 10588785]
65. Welles CC, Whooley MA, Na B, et al. The CHADS2 score predicts ischemic stroke in the absence of atrial fibrillation among subjects with coronary heart disease: data from the Heart and Soul Study. *American heart journal*. 2011; 162(3):555–561. [PubMed: 21884876]
66. Wang YC, Lin JL, Hwang JJ, et al. Left atrial dysfunction in patients with atrial fibrillation after successful rhythm control for > 3 months. *Chest*. 2005; 128(4):2551–2556. [PubMed: 16236922]
67. Azarbal F, Welles CC, Wong JM, et al. Association of CHADS2, CHA2DS2-VASc, and R2CHADS2 scores with left atrial dysfunction in patients with coronary heart disease (from the Heart and Soul study). *The American journal of cardiology*. 2014; 113(7):1166–1172. [PubMed: 24507169]
68. Puwanant S, Varr BC, Shrestha K, et al. Role of the CHADS2 score in the evaluation of thromboembolic risk in patients with atrial fibrillation undergoing transesophageal echocardiography before pulmonary vein isolation. *Journal of the American College of Cardiology*. 2009; 54(22):2032–2039. [PubMed: 19926009]
69. Fukuda S, Watanabe H, Shimada K, et al. Left atrial thrombus and prognosis after anticoagulation therapy in patients with atrial fibrillation. *Journal of cardiology*. 2011; 58(3):266–277. [PubMed: 21824749]

70. Doukky R, Gage H, Nagarajan V, et al. B-type natriuretic peptide predicts left atrial appendage thrombus in patients with nonvalvular atrial fibrillation. *Echocardiography* (Mount Kisco, NY. 2013; 30(8):889–895.
71. Doukky R, Garcia-Sayan E, Gage H, et al. The value of diastolic function parameters in the prediction of left atrial appendage thrombus in patients with nonvalvular atrial fibrillation. *Cardiovasc Ultrasound*. 2014; 12(1):10. [PubMed: 24568305]
72. Di Angelantonio E, Ederhy S, Benyounes N, et al. Comparison of transesophageal echocardiographic identification of embolic risk markers in patients with lone versus non-lone atrial fibrillation. *The American journal of cardiology*. 2005; 95(5):592–596. [PubMed: 15721097]
73. Glotzer TV, Daoud EG, Wyse DG, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circulation*. 2009; 2(5):474–480. [PubMed: 19843914]
74. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. *The New England journal of medicine*. 2012; 366(2):120–129. [PubMed: 22236222]
75. Boriani G, Glotzer TV, Santini M, et al. Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices). *European heart journal*. 2014; 35(8):508–516. [PubMed: 24334432]
76. Boriani G, Botto GL, Padeletti L, et al. Improving stroke risk stratification using the CHADS2 and CHA2DS2-VASc risk scores in patients with paroxysmal atrial fibrillation by continuous arrhythmia burden monitoring. *Stroke; a journal of cerebral circulation*. 2011; 42(6):1768–1770.
77. Daoud EG, Glotzer TV, Wyse DG, et al. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. *Heart Rhythm*. 2011; 8(9):1416–1423. [PubMed: 21699833]
78. Coutinho T, Borlaug BA, Pellikka PA, et al. Sex differences in arterial stiffness and ventricular-arterial interactions. *Journal of the American College of Cardiology*. 2013; 61(1):96–103. [PubMed: 23122799]
79. Zabalgaitia M, Halperin JL, Pearce LA, et al. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. *Stroke Prevention in Atrial Fibrillation III Investigators*. *Journal of the American College of Cardiology*. 1998; 31(7):1622–1626. [PubMed: 9626843]
80. Goldman ME, Pearce LA, Hart RG, et al. Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: I. Reduced flow velocity in the left atrial appendage (The Stroke Prevention in Atrial Fibrillation [SPAF-III] study). *J Am Soc Echocardiogr*. 1999; 12(12):1080–1087. [PubMed: 10588784]
81. Iwakura K, Okamura A, Koyama Y, et al. Effect of elevated left ventricular diastolic filling pressure on the frequency of left atrial appendage thrombus in patients with nonvalvular atrial fibrillation. *The American journal of cardiology*. 2011; 107(3):417–422. [PubMed: 21257008]
82. Pollick C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. Implications for the development of thrombus. *Circulation*. 1991; 84(1):223–231. [PubMed: 2060098]
83. Fatkin D, Feneley MP. Patterns of Doppler-measured blood flow velocity in the normal and fibrillating human left atrial appendage. *American heart journal*. 1996; 132(5):995–1003. [PubMed: 8892774]
84. Obel OA, Luddington L, Maarouf N, et al. Effects of ventricular rate and regularity on the velocity and magnitude of left atrial appendage flow in atrial fibrillation. *Heart (British Cardiac Society)*. 2005; 91(6):764–768. [PubMed: 15894771]
85. Kanadasi M, Cayli M, Sahin DY, et al. The effect of different atrioventricular delays on left atrium and left atrial appendage function in patients with DDD pacemaker. *Echocardiography* (Mount Kisco, NY. 2011; 28(6):626–632.
86. Corradi D, Callegari S, Manotti L, et al. Persistent lone atrial fibrillation: Clinicopathologic study of 19 cases. *Heart Rhythm*. 2014
87. Akoum N, Fernandez G, Wilson B, et al. Association of Atrial Fibrosis Quantified Using LGE-MRI with Atrial Appendage Thrombus and Spontaneous Contrast on Transesophageal

Echocardiography in Patients with Atrial Fibrillation. *Journal of cardiovascular electrophysiology*. 2013

88. Karabay CY, Zehir R, Guler A, et al. Left atrial deformation parameters predict left atrial appendage function and thrombus in patients in sinus rhythm with suspected cardioembolic stroke: a speckle tracking and transesophageal echocardiography study. *Echocardiography (Mount Kisco, NY)*. 2013; 30(5):572–581.
89. Leong DP, Penhall A, Perry R, et al. Speckle-tracking strain of the left atrium: a transoesophageal echocardiographic validation study. *Eur Heart J Cardiovasc Imaging*. 2013; 14(9):898–905. [PubMed: 23313918]
90. Sung SH, Chang SL, Hsu TL, et al. Do the left atrial substrate properties correlate with the left atrial mechanical function? A novel insight from the electromechanical study in patients with atrial fibrillation. *Journal of cardiovascular electrophysiology*. 2008; 19(2):165–171. [PubMed: 17916141]
91. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet*. 2009; 373(9658):155–166. [PubMed: 19135613]
92. Jesel L, Arentz T, Herrera-Siklody C, et al. Do atrial differences in endothelial damage, leukocyte and platelet activation, or tissue factor activity contribute to chamber-specific thrombogenic status in patients with atrial fibrillation? *Journal of cardiovascular electrophysiology*. 2014; 25(3):266–270. [PubMed: 24172190]
93. Grimm RA, Stewart WJ, Maloney JD, et al. Impact of electrical cardioversion for atrial fibrillation on left atrial appendage function and spontaneous echo contrast: characterization by simultaneous transesophageal echocardiography. *Journal of the American College of Cardiology*. 1993; 22(5): 1359–1366. [PubMed: 8227792]
94. Di Biase L, Santangeli P, Anselmino M, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation?: results from a multicenter study. *Journal of the American College of Cardiology*. 2012; 60(6):531–538. [PubMed: 22858289]
95. Anselmino M, Scaglione M, Di Biase L, et al. Left atrial appendage morphology and silent cerebral ischemia in patients with atrial fibrillation. *Heart Rhythm*. 2014; 11(1):2–7. [PubMed: 24120872]
96. Kimura T, Takatsuki S, Fukuda K. The left atrial appendage: can anatomical characteristics be used to predict strokes in nonvalvular atrial fibrillation patients? *Future cardiology*. 2013; 9(4): 451–453. [PubMed: 23834682]
97. Khurram IM, Dewire J, Mager M, et al. Relationship between left atrial appendage morphology and stroke in patients with atrial fibrillation. *Heart Rhythm*. 2013; 10(12):1843–1849. [PubMed: 24076444]
98. Yamamoto M, Seo Y, Kawamatsu N, et al. Complex left atrial appendage morphology and left atrial appendage thrombus formation in patients with atrial fibrillation. *Circ Cardiovasc Imaging*. 2014; 7(2):337–343. [PubMed: 24523417]
99. Shirani J, Alaeddini J. Structural remodeling of the left atrial appendage in patients with chronic non-valvular atrial fibrillation: Implications for thrombus formation, systemic embolism, and assessment by transesophageal echocardiography. *Cardiovasc Pathol*. 2000; 9(2):95–101. [PubMed: 10867359]
100. Chatterjee S, Alexander JC, Pearson PJ, et al. Left atrial appendage occlusion: lessons learned from surgical and transcatheter experiences. *The Annals of thoracic surgery*. 2011; 92(6):2283–2292. [PubMed: 22029943]
101. Kanderian AS, Gillinov AM, Pettersson GB, et al. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. *Journal of the American College of Cardiology*. 2008; 52(11):924–929. [PubMed: 18772063]
102. Katz ES, Tsiamtsiouris T, Applebaum RM, et al. Surgical left atrial appendage ligation is frequently incomplete: a transesophageal echocardiographic study. *Journal of the American College of Cardiology*. 2000; 36(2):468–471. [PubMed: 10933359]
103. Healey JS, Crystal E, Lamy A, et al. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass

- surgery in patients at risk for stroke. *American heart journal*. 2005; 150(2):288–293. [PubMed: 16086933]
104. Cullen MW, Stulak J, Li Z, et al. Value of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation after cardiac surgery. *Journal of the American College of Cardiology*. 2013; 61(10_S)
 105. Klemm HU, Steven D, Johnsen C, et al. Catheter motion during atrial ablation due to the beating heart and respiration: impact on accuracy and spatial referencing in three-dimensional mapping. *Heart Rhythm*. 2007; 4(5):587–592. [PubMed: 17467625]
 106. Stergiopoulos K, Seifert F, Brown DL. Thrombus formation after successful stapler exclusion of the left atrial appendage. *Journal of the American College of Cardiology*. 2010; 55(4):379. [PubMed: 20117445]
 107. Kim R, Baumgartner N, Clements J. Routine left atrial appendage ligation during cardiac surgery may prevent postoperative atrial fibrillation-related cerebrovascular accident. *The Journal of thoracic and cardiovascular surgery*. 2013; 145(2):582–589. discussion 589. [PubMed: 23137520]
 108. Whitlock RP, Vincent J, Blackall MH, et al. Left Atrial Appendage Occlusion Study II (LAAOS II). *The Canadian journal of cardiology*. 2013; 29(11):1443–1447. [PubMed: 24054920]
 109. Whitlock R, Healey J, Vincent J, et al. Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. *Annals of cardiothoracic surgery*. 2014; 3(1):45–54. [PubMed: 24516797]
 110. Dawson AG, Asopa S, Dunning J. Should patients undergoing cardiac surgery with atrial fibrillation have left atrial appendage exclusion? *Interactive cardiovascular and thoracic surgery*. 2010; 10(2):306–311. [PubMed: 19942634]
 111. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014
 112. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014
 113. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *European heart journal*. 2012; 33(21):2719–2747. [PubMed: 22922413]
 114. Yilmaz A, Van Putte BP, Van Boven WJ. Completely thoracoscopic bilateral pulmonary vein isolation and left atrial appendage exclusion for atrial fibrillation. *The Journal of thoracic and cardiovascular surgery*. 2008; 136(2):521–522. [PubMed: 18692667]
 115. Muhammad MI. Role of video-assisted thoracoscopy in the management of stroke. *Asian cardiovascular & thoracic annals*. 2014; 22(2):155–159. [PubMed: 24585785]
 116. Ohtsuka T, Ninomiya M, Nonaka T, et al. Thoracoscopic stand-alone left atrial appendectomy for thromboembolism prevention in nonvalvular atrial fibrillation. *Journal of the American College of Cardiology*. 2013; 62(2):103–107. [PubMed: 23433566]
 117. Santini M, Loiaconi V, Tocco MP, et al. Feasibility and efficacy of minimally invasive stand-alone surgical ablation of atrial fibrillation. A single-center experience. *J Interv Card Electrophysiol*. 2012; 34(1):79–87. [PubMed: 22231157]
 118. Wolf RK. Treatment of lone atrial fibrillation: minimally invasive pulmonary vein isolation, partial cardiac denervation and excision of the left atrial appendage. *Ann Cardiothorac Surg*. 2014; 3(1):98–104. [PubMed: 24516806]
 119. Zheng S, Li Y, Han J, et al. Long-term results of a minimally invasive surgical pulmonary vein isolation and ganglionic plexi ablation for atrial fibrillation. *PLoS One*. 2013; 8(11):e79755. [PubMed: 24244556]
 120. Kurfurst V, Mokracek A, Bulava A, et al. Two-staged hybrid treatment of persistent atrial fibrillation: short-term single-centre results. *Interactive cardiovascular and thoracic surgery*. 2014; 18(4):451–456. [PubMed: 24421207]

121. Gafoor S, Franke J, Bertog S, et al. Left atrial appendage occlusion in octogenarians: short-term and 1-year follow-up. *Catheter Cardiovasc Interv.* 2014; 83(5):805–810. [PubMed: 24259397]
122. National Institute for Health and Clinical Excellence: Percutaneous occlusion of the left atrial appendage for atrial fibrillation. 2006 <http://www.nice.org.uk/nicemedia/pdf/IPG181guidance.pdf>.
123. Bartus K, Bednarek J, Myc J, et al. Feasibility of closed-chest ligation of the left atrial appendage in humans. *Heart Rhythm.* 2011; 8(2):188–193. [PubMed: 21050893]
124. Bartus K, Han FT, Bednarek J, et al. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. *Journal of the American College of Cardiology.* 2013; 62(2):108–118. [PubMed: 23062528]
125. Meier B, Palacios I, Windecker S, et al. Transcatheter left atrial appendage occlusion with Amplatzer devices to obviate anticoagulation in patients with atrial fibrillation. *Catheter Cardiovasc Interv.* 2003; 60(3):417–422. [PubMed: 14571497]
126. Park JW, Bethencourt A, Sievert H, et al. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. *Catheter Cardiovasc Interv.* 2011; 77(5):700–706. [PubMed: 20824765]
127. Bai R, Horton RP, et al. L DIB. Intraprocedural and long-term incomplete occlusion of the left atrial appendage following placement of the WATCHMAN device: a single center experience. *Journal of cardiovascular electrophysiology.* 2012; 23(5):455–461. [PubMed: 22082312]
128. Reddy VY, Holmes D, Doshi SK, et al. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation.* 2011; 123(4):417–424. [PubMed: 21242484]
129. Viles-Gonzalez JF, Kar S, Douglas P, et al. The clinical impact of incomplete left atrial appendage closure with the Watchman Device in patients with atrial fibrillation: a PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) substudy. *Journal of the American College of Cardiology.* 2012; 59(10):923–929. [PubMed: 22381428]
130. Reddy, VY.; Franzen, O.; Worthley, S., et al. Clinical experience with the Wavecrest LA Appendage Occlusion Device for stroke prevention in AF: acute results of the WAVECREST I trial. the Heart Rhythm Society's 35th Annual Scientific Sessions; San Francisco. 2014. p. PO01-PO112.
131. Sousa JE, Costa MA, Tuzcu EM, et al. New frontiers in interventional cardiology. *Circulation.* 2005; 111(5):671–681. [PubMed: 15699286]
132. Ostermayer SH, Reisman M, Kramer PH, et al. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. *Journal of the American College of Cardiology.* 2005; 46(1):9–14. [PubMed: 15992628]
133. Block PC, Burstein S, Casale PN, et al. Percutaneous left atrial appendage occlusion for patients in atrial fibrillation suboptimal for warfarin therapy: 5-year results of the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) Study. *Jacc.* 2009; 2(7):594–600. [PubMed: 19628179]
134. Bayard YL, Omran H, Neuzil P, et al. PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) for prevention of cardioembolic stroke in non-anticoagulation eligible atrial fibrillation patients: results from the European PLAATO study. *EuroIntervention.* 2010; 6(2):220–226. [PubMed: 20562072]
135. Supreme Court Proceedings of the State of Delaware. 2013; 2013 Filing ID 54541646. Case Number 515.
136. Berti S, Santoro G, Palmieri C, et al. Tools and Techniques Clinical: transcatheter closure of left atrial appendage using the Amplatzer Cardiac Plug. *EuroIntervention.* 2013; 9(4):524–526. [PubMed: 23965358]
137. Jain AK, Gallagher S. Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism: NICE guidance. *Heart (British Cardiac Society).* 2011; 97(9):762–765. [PubMed: 21378010]

138. Cruz-Gonzalez I, Martin Moreiras J, Garcia E. Thrombus formation after left atrial appendage exclusion using an Amplatzer cardiac plug device. *Catheter Cardiovasc Interv.* 2011; 78(6):970–973. [PubMed: 21523900]
139. Kefer J, Vermeersch P, Budts W, et al. Transcatheter left atrial appendage closure for stroke prevention in atrial fibrillation with Amplatzer cardiac plug: the Belgian Registry. *Acta cardiologica.* 2013; 68(6):551–558. [PubMed: 24579432]
140. Mohrs OK, Wunderlich N, Petersen SE, et al. Contrast-enhanced CMR in patients after percutaneous closure of the left atrial appendage: a pilot study. *J Cardiovasc Magn Reson.* 2011; 13:33. [PubMed: 21726450]
141. Lockwood SM, Alison JF, Obeyesekere MN, et al. Imaging the left atrial appendage prior to, during, and after occlusion. *Jacc.* 2011; 4(3):303–306. [PubMed: 21414580]
142. Guerios EE, Schmid M, Gloekler S, et al. Left atrial appendage closure with the Amplatzer Cardiac Plug in patients with atrial fibrillation. *Arquivos brasileiros de cardiologia.* 2012; 98(6): 528–536. [PubMed: 22584492]
143. Lopez-Minguez JR, Eldoayen-Gragera J, Gonzalez-Fernandez R, et al. Immediate and One-year Results in 35 Consecutive Patients After Closure of Left Atrial Appendage With the Amplatzer Cardiac Plug. *Revista espanola de cardiologia.* 2012
144. Lam YY, Yip GW, Yu CM, et al. Left atrial appendage closure with AMPLATZER cardiac plug for stroke prevention in atrial fibrillation: initial Asia-Pacific experience. *Catheter Cardiovasc Interv.* 2012; 79(5):794–800. [PubMed: 21542102]
145. Versaci F, Sacca S, Mugnolo A, et al. Simultaneous patent foramen ovale and left atrial appendage closure. *Journal of cardiovascular medicine (Hagerstown, Md.* 2012; 13(10):663–664.
146. Viles-Gonzalez JF, Reddy VY, Petru J, et al. Incomplete occlusion of the left atrial appendage with the percutaneous left atrial appendage transcatheter occlusion device is not associated with increased risk of stroke. *J Interv Card Electrophysiol.* 2012; 33(1):69–75. [PubMed: 21947786]
147. Freixa X, Chan JL, Tzikas A, et al. The Amplatzer Cardiac Plug 2 for left atrial appendage occlusion: novel features and first-in-man experience. *EuroIntervention.* 2013; 8(9):1094–1098. [PubMed: 23339815]
148. Freixa X, Kwai Chan JL, Tzikas A, et al. Percutaneous closure of a very large left atrial appendage using the Amplatzer amulet. *The Canadian journal of cardiology.* 2013; 29(10):1329 e1329–1329 e1311. [PubMed: 23541662]
149. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet.* 2009; 374(9689):534–542. [PubMed: 19683639]
150. Holmes DR Jr, Lakkireddy DR, Whitlock RP, et al. Left atrial appendage occlusion: opportunities and challenges. *Journal of the American College of Cardiology.* 2014; 63(4):291–298. [PubMed: 24076495]
151. Gangireddy SR, Halperin JL, Fuster V, et al. Percutaneous left atrial appendage closure for stroke prevention in patients with atrial fibrillation: an assessment of net clinical benefit. *European heart journal.* 2012; 33(21):2700–2708. [PubMed: 23008509]
152. Massarenti L, Yilmaz A. Incomplete Endothelialization of Left Atrial Appendage Occlusion Device 10 Months After Implantation. *Journal of cardiovascular electrophysiology.* 2012
153. Reddy VY, Mobius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *Journal of the American College of Cardiology.* 2013; 61(25):2551–2556. [PubMed: 23583249]
154. Albers GW, Diener HC, Frison L, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *Jama.* 2005; 293(6):690–698. [PubMed: 15701910]
155. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *The New England journal of medicine.* 2009; 361(12):1139–1151. [PubMed: 19717844]

156. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *The New England journal of medicine*. 2011; 365(10):883–891. [PubMed: 21830957]
157. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *The New England journal of medicine*. 2011; 365(11):981–992. [PubMed: 21870978]
158. Amorosi SL, Armstrong S, Da Deppo L, et al. The budget impact of left atrial appendage closure compared with adjusted-dose warfarin and dabigatran etexilate for stroke prevention in atrial fibrillation. *Europace*. 2014
159. Whisenant B, Weiss B. Left atrial appendage closure with transcatheter-delivered devices. *Interventional Cardiology Clinics*. 2014; 3(2):209–218.
160. Toumanides S, Sideris EB, Agricola T, et al. Transcatheter patch occlusion of the left atrial appendage using surgical adhesives in high-risk patients with atrial fibrillation. *Journal of the American College of Cardiology*. 2011; 58(21):2236–2240. [PubMed: 22078431]
161. Cheng Y, Conditt G, Yi G, et al. TCT-765 First In-Vivo Evaluation of the Ultrasept Left Atrial Appendage Closure Device. *Journal of the American College of Cardiology*. 2012; 60(17_S)
162. Bruce CJ, Stanton CM, Asirvatham SJ, et al. Percutaneous epicardial left atrial appendage closure: intermediate-term results. *Journal of cardiovascular electrophysiology*. 2011; 22(1):64–70. [PubMed: 20662983]
163. Bruce CJ, Asirvatham SJ, McCaw T, et al. Novel percutaneous left atrial appendage closure. *Cardiovasc Revasc Med*. 2013; 14(3):164–167. [PubMed: 23773498]
164. Santoro F, Di Biase L, Santangeli P, et al. Catheter-based epicardial closure of the left atrial appendage. *Interventional Cardiology Clinics*. 2014; 3(2):219–227.
165. Stone D, Byrne T, Pershad A. Early Results With the LARIAT Device for Left Atrial Appendage Exclusion in Patients With Atrial Fibrillation at High Risk for Stroke and Anticoagulation. *Catheter Cardiovasc Interv*. 2013
166. Nucifora G, Faletta FF, Regoli F, et al. Evaluation of the left atrial appendage with real-time 3-dimensional transesophageal echocardiography: implications for catheter-based left atrial appendage closure. *Circ Cardiovasc Imaging*. 2011; 4(5):514–523. [PubMed: 21737601]
167. Earley MJ. How to perform a transseptal puncture. *Heart (British Cardiac Society)*. 2009; 95(1): 85–92. [PubMed: 19047447]
168. Syed F, Lachman N, Christensen K, et al. The pericardial space: obtaining access and an approach to fluoroscopic anatomy. *Cardiac Electrophysiology Clinics*. 2010; 2(1):9–23.
169. Baran J, Stec S, Pilichowska-Paszkiel E, et al. Intracardiac echocardiography for detection of thrombus in the left atrial appendage: comparison with transesophageal echocardiography in patients undergoing ablation for atrial fibrillation: the Action-Ice I Study. *Circulation*. 2013; 6(6): 1074–1081. [PubMed: 24243787]
170. Plicht B, Konorza TF, Kahlert P, et al. Risk factors for thrombus formation on the Amplatzer Cardiac Plug after left atrial appendage occlusion. *Jacc*. 2013; 6(6):606–613. [PubMed: 23787233]
171. Baker MS, Paul Mounsey J, Gehi AK, et al. Left atrial thrombus after appendage ligation with LARIAT. *Heart Rhythm*. 2013
172. Giedrimas E, Lin AC, Knight BP. Left atrial thrombus after appendage closure using LARIAT. *Circulation*. 2013; 6(4):e52–e53. [PubMed: 23962862]
173. Krishnaswamy A, Patel NS, Ozkan A, et al. Planning left atrial appendage occlusion using cardiac multidetector computed tomography. *International journal of cardiology*. 2012; 158(2): 313–317. [PubMed: 22622059]
174. Chue CD, de Giovanni J, Steeds RP. The role of echocardiography in percutaneous left atrial appendage occlusion. *Eur J Echocardiogr*. 2011; 12(10):i3–i10. [PubMed: 21998466]
175. MacDonald ST, Newton JD, Ormerod OJ. Intracardiac echocardiography off piste? Closure of the left atrial appendage using ICE and local anesthesia. *Catheter Cardiovasc Interv*. 2011; 77(1): 124–127. [PubMed: 20517996]
176. Budge LP, Shaffer KM, Moorman JR, et al. Analysis of in vivo left atrial appendage morphology in patients with atrial fibrillation: a direct comparison of transesophageal echocardiography,

planar cardiac CT, and segmented three-dimensional cardiac CT. J Interv Card Electrophysiol. 2008; 23(2):87–93. [PubMed: 18686024]

177. Briceno DF, Fernando RR, Laing ST. Left atrial appendage thrombus post LARIAT closure device. Heart Rhythm. 2013
178. Guo XG, Zhang JL, Ma J, et al. Management of focal atrial tachycardias originating from the atrial appendage with the combination of radiofrequency catheter ablation and minimally invasive atrial appendectomy. Heart Rhythm. 2014; 11(1):17–25. [PubMed: 24103224]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

KEY POINTS

- Given that the left atrial appendage is the predominant site of thrombus formation in patients with non-valvular atrial fibrillation, resecting or closing it is an attractive alternative strategy to prevent strokes in patients who cannot tolerate anticoagulation therapy.
- Current approaches to left atrial appendage closure are surgical or percutaneous. Percutaneous approaches can be classified as endocardial occlusion, epicardial ligation, or hybrid epi-endocardial ligation, with an increasing number of devices becoming available for clinical use.
- Percutaneous endovascular occlusion of the left atrial appendage has been shown to be equivalent to warfarin in preventing stroke in atrial fibrillation, and is associated with a lower bleeding risk.

Table 1

Appropriate Selection of Percutaneous Approaches for Left Atrial Appendage Closure

Device/Method	Advantages	Limitations
Transseptal device placement	Transseptal technique widely available Available in the setting of previous cardiac surgery Validated as noninferior to warfarin for stroke prevention (Watchman)	Need for procedural and short term anticoagulation and/or antithrombotic regimen until endothelialization occurs Foreign body left in central circulation (small risk of embolization, erosion, dislodgement) Device must be sized to match LAA Previous atrial septal defect closure may preclude transseptal delivery
Epicardial	No foreign body left behind No need for procedural anticoagulation because no contact with central circulation and no transseptal puncture (which exposes blood to tissue factor) Adjustable size loop to accommodate variable LAA shape/morphology without need for sizing Pericardial control facilitates management of effusion should one develop	Human experience not yet reported Previous cardiac surgery limits pericardial access and maneuverability Epicardial access techniques less widely available than transseptal puncture
Hybrid	No foreign body left behind Pericardial control facilitates management of effusion should one develop	Need for both transseptal and epicardial access with risks of both, and delivery failure if cannot achieve both Superiorly directed LAA, multiple lobes and pectus excavatum may preclude use

From Friedman, J Cardiovasc Electrophysiol 2011; 22 (10): 1184 – 91, with permission.

Table 2**Anatomic and Imaging Determinant for LAA occlusion**

Left atrium
Dimensions of the LA: for all devices
Myocardial thickness: anterior wall and venoatrial junctions may be very thin
Distance from the OF to the LAA ostium: for all devices
Accessory LAA: mainly anterior wall and mitral isthmus
Webs and septa
Interatrial septum: should be a low posterior transseptal puncture. OF dimensions, rim thickness, proximity to the aortic root, PFO, patches, occluder devices, and septal aneurysm
Left atrial appendage
Morphological variants: LAA apex directed behind the pulmonary trunk (exclusion criteria for LARIAT)
Ostial diameters/circumference: 17–31 mm (Watchman) and 12.6–28.5 mm (ACP)
LAA length: LAA width >40 mm (LARIAT), should exceed the maximal ostial diameter (Watchman)
LAA angulation: for all devices, less able to be angled a special concern for the Watchman
Maximal length of dominant lobe: for all devices
Multilobular LAA: multilobed LAA oriented in different planes >40 mm (exclusion criteria for LARIAT)
Distance from the ostium to the first bend of the LAA: landing zone that exceeds the maximal ostial diameter for the Watchman, landing zone 10 mm for the ACP
Trabeculations (pectinate muscle): should not be mistaken for thrombus
Myocardial thickness: thinner posterior wall and risk of cardiac perforation for all devices
Extra-appendicular trabeculations: risk of cardiac perforation and periprosthetic leaks
Ostial diameters of LSPV
Relation LSPV and LAA orifices: usually at the same level
Lateral ridge orientation and width: poor definition of the orifice limits in ellipsoid LAA
Thrombus: contraindication for ablation
Neighbouring structures
Left circumflex artery: risk for artery compression between the anchoring lobe and the disc for the ACP
Left sinus node artery
Great cardiac vein and obtuse marginal vein
Persistent left superior vena cava
Post-CABG venous grafts
Pericardial adhesions: of special concern for the LARIAT
Left phrenic nerve: of special concern for the LARIAT

ACP, Amplatzer Cardiac Plug; CABG, coronary artery bypass graft; LA, left atrium; LAA, left atrial appendage; LSPV, left superior pulmonary vein; OF, oval fossa; PFO, patent foramen ovale.

From Cabrera, Heart Published Online First: March 6, 2014 doi:10.1136/heartjnl-2013-304464

Table 3

Major procedural complications of percutaneous left atrial appendage closure devices

Complication	Cause	Preventative Strategy
Pericardial effusion	Initial transseptal puncture	TEE guidance (eg, X-plane)
		Avoid severe tenting of IAS (increases the risk of free-wall puncture) - alternative strategies eg application of radiofrequency energy
		Puncturing at the fossa ovalis
	Guidewire or catheter into LAA after initial transseptal puncture	Advance dilator into LAA under fluoroscopy over 0.32-in wire with distal curve or coronary wire
	Manipulation of delivery sheath/system into and within LAA	Advance delivery sheath into LAA over pigtail catheter rather than guidewire
		Posterior-inferior puncture to optimize coaxial approach to LAA; avoid using PFO which guides entry superiorly and suboptimally to work within LAA
Procedural stroke	LARIAT endocardial wire pulls epicardial wire into the LAA	Recognize tension on LARIAT endocardial wire when connected to epicardial wire including when balloon being placed at ostium
	Device deployment and retrieval	Maintain delivery sheath position; minimize retrievals and reimplantations if possible
Device embolization	Preexisting thrombus in LAA	Careful baseline TEE
	Insufficient anticoagulation	Monitor anticoagulation, if possible; consider anticoagulation before transseptal puncture
	Air embolus from delivery sheath/system	Flush sheath only after entering LAA, and after device exchange, if performed
	Inappropriate size	Tug-test; confirm device compression (Watchman should be 8–20% compressed) or appropriate fluoroscopic appearance
	Inappropriate position	Confirm device position and seal by TEE and fluoroscopy
Vascular (hematoma, arteriovenous fistula, pseudoaneurysm, bleeding)	Venous access	Careful technique; consider ultrasound guidance as needed
Pericardial pain	Common after LARIAT closure - ? pericardial inflammation / LAA necrosis	Anecdotal: prophylactic NSAIDs, oral colchicine course, intrapericardial therapy eg local anesthetic flushes

Modified from Price, Intervent Cardiol Clin 3 (2014) 301–311