Atrial fibrillation (AF) is the most common arrhythmia in the elderly population. The prevalence of AF in the United States ranged from 2.7 to 6.1 million in 2010, and the projected number of subjects with AF is expected to rise to between 5.6 and 12 million in 2050.1,2 The Framingham study proved that AF is associated with a four- to five-fold increased risk of thromboembolic events and that the percentage of strokes secondary to AF increases dramatically from 1.5% at 50 years of age to 23.5% at 80 years of age.3 Furthermore, the adjusted stroke rate based on the CHADS2 index score ranges from 1.9% to 18.2%.4 It was not until the mid-1950s that the left atrial appendage (LAA), previously considered an insignificant and non-functional anatomic cardiac structure, was identified as the location of thrombus formation.5 Moreover, it is estimated that approximately 47% of thrombi in valvular AF and 91% of those in non-valvular AF are localized in the LAA.6 Shortly after, the LAA became the region of interest of many investigators who have looked deeper into this structure in numerous different perspectives, including understanding its anatomy and physiology, as well as proposing and testing different imaging modalities and techniques to assess its shape, size, blood flow patterns, presence of thrombus and, more importantly, they have developed different devices in order to permanently occlude it. This review will mainly focus on the results of preclinical and clinical studies of the main LAA closure devices.

Embryologically, the LAA is a remnant of the primordial embryonic left atrium, hence its trabecular appearance (i.e., pectinate muscles) (Figure 1). Later, the smooth left atrium develops from an outgrowth of the pulmonary veins. The LAA is a highly mobile and dynamic structure with distinct patterns of contraction and relaxation either in sinus rhythm or in AF.7 It is also a long-angled structure that markedly varies in shape and size (volumes, length, width, and orifice size) on transesophageal echocardiography (TEE), computed tomography (CT), and magnetic resonance imaging (MRI).8,9 The LAA is composed of two lobes in half of the population and three lobes in a third of individuals.10 Several LAA morphologies have been described, yet the four most common and clinically used are chicken wing (48%), cactus (30%), windsock (19%), and cauliflower (3%) (Figure 2). We have recently demonstrated that LAA morphology correlates with the risk of stroke in patients with AF. In this study patients with chicken wing morphology were less likely to have a CVA than other three morphologies (i.e., 4% versus 10–18%).11 Numerous studies have shown the role of the LAA in volume homeostasis based on the fact that atrial natriuretic factor and inclusive brain natriuretic peptide are produced and secreted here in significant amounts.
This has clinical implications, particularly in patients with dilated cardiomyopathy shortly after a LAA closure device is implanted. 

Oral anticoagulation

It is well established that warfarin sodium (Coumadin®) prescriptions have significantly increased to prevent cardioembolic strokes in patients suffering AF over the years. Yet numerous publications have demonstrated marked underutilization of warfarin therapy due to risk of bleeding (e.g., intracranial hemorrhage, gastrointestinal and retroperitoneal bleeding, hematuria), increased fall risk, difficulty with INR monitoring, non-compliance, drug and dietary interaction, renal impairment, and advanced age. It is estimated that up to 30% of patients who would benefit from anticoagulation (AC) based on the CHADS2 score are not on this medication. Chronic AC-related bleeding is a common problem, with average annual frequencies of fatal, major, and minor bleeding of 0.6%, 3.0%, and 9.6%, respectively; these frequencies are five-fold the expected without warfarin therapy. Even though we currently have access to new oral anticoagulants such as the direct thrombin inhibitors (i.e., dabigatran) and direct factor Xa inhibitors (e.g., rivaroxaban and apixaban), which are more selective in the coagulation cascade, most of the aforementioned contraindications for chronic AC still remain. Consequently, surgical LAA exclusion has been used as an alternative therapeutic strategy to prevent embolic strokes in patients with AF.

Surgical therapy

In 1949 Madden performed the first LAA excision in two patients with AF and rheumatic mitral disease. The LAA occlusion study (LAAOS) was the first randomized trial that evaluated safety and efficacy of the LAA occlusion at the time of elective bypass graft surgery. LAAOS included 77 patients with high risk of stroke in whom LAA occlusion was attempted using sutures and staples. Occlusion was achieved in only 66% of the patients and the use of staples had the highest efficacy. The efficacy was assessed with TEE at 8 weeks, where staples had 72% efficacy and sutures only 45%. Likewise, a meta-analysis of clinical trials demonstrated the limitation of the surgical approach given the fact that most studies only reported a 55–66% successful occlusion rate when attempting closure in a variety of methods including stapling, ligation and amputation. In 2008 a prospective study using TEE corroborated that the main limitation of the surgical approach is “incomplete exclusion,” which is approximately 40% (successful LAA closure occurred more frequently with excision (73%) than suture exclusion (23%) and stapler exclusion (0%)).

Percutaneous LAA closure devices

A decade ago, the first study in humans implanting closure devices percutaneously via thoracoscopy was undertaken with a loop snare with encouraging results. Thereafter, several devices have been proposed and tested for efficacy and safety. Numerous small observational studies and a few randomized controlled trials.
LAA Isolation Using Percutaneous Endo/Epi Devices

Figure 2: Left atrial appendage (LAA) morphologies. The four most common LAA morphologies are depicted on the left by CCT and on the right by CMRI. (a) Cactus LAA morphology is composed of a dominant central lobe with secondary lobes extending from the central lobe in both superior and inferior directions. (b) Windsock LAA morphology has one dominant lobe of sufficient length as the primary structure. Variations of this LAA type arise with the location and number of secondary or even tertiary lobes arising from the dominant lobe. (c) Cauliflower LAA morphology presents with a limited overall length with more complex internal characteristics. Variations of this LAA type have a more irregular shape of the LAA ostium (oval versus round) and a number of number of lobes with lack of a dominant lobe. (d) Chicken wing LAA morphology presents with an obvious bend in the proximal or middle part of the dominant lobe, or folding back of the LAA anatomy on itself at some distance from the perceived LAA ostium. This type of LAA may have secondary lobes or twigs. (Courtesy of Dr Luigi Di Biase).

have shown the feasibility of this approach. Among these devices, the most studied include the (PLAATO) system (ev3 Endovascular, Plymouth, MN), the Amplatzer Cardiac Plug (St. Jude, Golden Valley, MN), the WATCHMAN device (Boston Scientific, Plymouth, MN), and The LARIAT device (SentreHEART, Palo Alto, CA).

PLAATO system

The percutaneous left atrial appendage occlusion (PLAATO) device (ev3 endovascular) was the first endovascular device reported for LAA closure in 2002.22 The device consists of a self-expanding nitinol cage covered with polytetrafluoroethylene and three rows of anchors secure the cage within the LAA ostium. The PLAATO device diameter ranges from 15 to 32 mm and is selected 20–40% larger than the LAA ostium diameter (Figure 3). The ePTFE membrane is echoreflective because of microscopic trapped air and allows for device visualization with TEE or ICE during deployment. Once the device is expanded into the LAA, contrast is injected both distally through a special lumen in the device and proximally in the left atrium to assess for leaks and positioning. If sealing is not adequate, the device is collapsed, repositioned, and re-expanded, or completely retrieved if rendered to be undersized to use one with a larger diameter.

The first experience with the PLAATO device for preventing cardioembolism was in a canine model of 25 dogs that were eventually euthanized in order to grossly and histologically examine their LAA for device healing, migration, perforation, and any thrombosis. The LAA was occluded in all cases with neither thrombi associated with the implantation nor distal infarcts in brain or kidneys.23 These preliminary results encouraged other investigators to test this device in humans as well as developing other similar devices. Later in 2002, the first clinical experience in which feasibility and safety of implating the PLAATO system was evaluated in 15 patients with chronic AF at high risk for stroke who were poor candidates for long-term AC. The LAA was successfully occluded in all patients. However, the implant had to be removed and exchanged for a larger size in four patients. No strokes, device embolization, or LAA perforation were noted. In one patient, the first procedure was complicated by a hemopericardium. At 1-month follow-up, chest fluoroscopy and TEE revealed continued stable implant position with smooth atrial facing surface and no evidence of thrombus.22

Subsequently, a study using the same patients enrolled in the initial PLAATO study was published demonstrating that the PLAATO device implantation has no effect on the anatomic and hemodynamic properties of the mitral valve and left upper pulmonary vein and that all devices remained stable with minimal residual flow around them.24

The feasibility trials (two prospective, multicenter trials) assessed the efficacy of the PLAATO system in a much larger sample of patients (n=111) with a mean age of 71 and chronic non-valvular AF with a contraindication for AC and at least one risk factor for stroke. Almost all the patients had a complete LAA occlusion after device deployment (97%). Two patients experienced stroke and one patient needed cardiovascular surgery and experienced in-hospital neurological death in the first 30 days after procedure. Three other patients required pericardiocentesis due to a hemopericardium. Two patients (1.8%) experienced an ischemic stroke during a mean follow-up of 9.8 months. TEE performed at the 1 and 6-month follow-up on these two patients demonstrated that the device was in a stable position with no thrombus on the surfaces. This trial demonstrated a relative risk reduction of stroke rate of 65% on the basis of the CHADS2 score (2.5) of the studied population (PLAATO 2.2% versus expected by CHADS 6.3%). These promising results suggested that occlusion devices might really become an alternative therapy for patients with AF and a contraindication for long-term AC.25 Long-term follow-up results were published 5 years after the last patient was enrolled in 2009. There was a total of seven deaths, five major strokes, and three minor strokes. After 5 years of follow-up, the annualized stroke/transient ischemic attack (TIA) rate was 3.8%.26

Finally, the results from the European PLAATO trial, which enrolled even a larger sample of patients (n=180) with persistent AF and contraindication for AC, revealed a successful LAA occlusion in 162 patients (90%). Two patients died within 24 h of the procedure (1%) and six cardiac tamponades were observed (3.3%), with two cases requiring pericardiocentesis. In one patient, the chosen device was too small and embolized into the aorta after its release (0.6%). It was snared and replaced without further complications. In a follow-up time of 129 documented patient-years, three strokes occurred (2.3% per year). The expected incidence of stroke according to the CHADS2 score was 6.6% per year. Unfortunately, the trial was stopped prematurely due to financial problems.27

Amplatzer Cardiac Patch device

A year after the PLAATO system was introduced into clinical practice, the Amplatzer Cardiac Patch (ACP) (St
Jude, Golden Valley, MN), which was originally used for patent foramen ovale or atrial septal defect closure, was proposed to occlude the LAA. Investigators initially stated that this device would not require general anesthesia or echocardiography guidance and it could be readily deployed. The first generation of ACP is a self-expanding device made of nitinol wire mesh and a polyester patch and consists of a lobe and a disk connected by a central waist. The lobe has diameters from 16 to 30 mm (Figure 4). The device is selected usually 10–20% larger than the narrowest diameter of the LAA body and it is delivered over a 10F or 13F sheath into the left atrium after transseptal puncture under fluoroscopy. It is anchored in the LAA approximately 1 cm behind the ostium, then the disk unfolds to cover the entrance of the LAA.

This first clinical study enrolled 16 patients with paroxysmal and persistent AF. Eighty-five percent of the procedures were performed with local anesthesia. During a 4-month follow-up, there were no strokes or other complications. Complete LAA occlusion was achieved in all cases, but there was one device embolization that required cardiac surgery. It was not until 2011 that the results from the initial European experience were released. This was a retrospective analysis of 136 patients with paroxysmal/permanent AF not able to take AC, which assessed the efficacy and safety of this device in the first 24 h after procedure. A total of 10 major complications were reported (7%). These included three acute ischemic strokes (2.2%) and two device embolizations, both of which were successfully percutaneously recaptured. Moreover, five patients developed hemopericardium. The first prospective study using the ACP was performed in Switzerland in 2012. Eighty-six consecutive patients were included with AF and contraindication to AC. All the implants were guided with fluoroscopy and LAA was completely occluded in 97% of the cases. There were four major complications: one patient developed cardiac tamponade requiring pericardiocentesis; two TIAs; and one device embolization with percutaneous retrieval. There was one in-hospital death after 6 days, unrelated to the procedure. All other patients were discharged without AC. After 25.9 patient-years of follow-up (mean 4 months)

Figure 3: PLAATO system. The device is constructed of a nitinol frame and an implant occlusion membrane consisting of laminated ePTFE. Note the small anchors along the frame and passing through the occlusive membrane, which assist with device anchoring and stability.
there were neither strokes nor late device embolizations. Six patients showed evidence of thrombus formation on the device, which resolved after 3 months of AC. Concomitantly, the initial Asia-Pacific experience on safety and feasibility reported encouraging results for the ACP 1. Twenty patients were enrolled and followed up for 1 year. The LAA was successfully occluded in 19/20 patients (95%). One procedure was abandoned because of catheter-related thrombus formation. Follow-up TEE showed all the LAA orifices were sealed without device-related thrombus formation. No stroke or deaths occurred at a mean follow-up of 12.7 months. A year later, Lopez-Minguez et al. published another study with 35 consecutive patients in whom the device was implanted under general anesthesia. The results of the implantation and the follow-up were analyzed over a 1-year period. There were no cardiac complications during the implantation or hospital stay. There was one vascular complication (arteriovenous fistula). TEE monitoring was performed at 24 h, 1, 3, 6, and 12 months and they found five thrombi, which were resolved with heparin. In the follow-up period of 21 months, one had TIA without further consequences. Long-term results from prospective studies, one from Canada and one from Switzerland, have also been published last year. The Canada experience included 52 patients with non-valvular AF and contraindication for AC (CHADS2 score of 3). Most patients received short-term dual-antiplatelet therapy after the procedure and single antiplatelet therapy thereafter. The procedure was successful in 98.1% of the patients and the main complications were device embolizations (1.9%) and pericardial effusions (1.9%), with no cases of periprocedural stroke. At a mean follow-up of 20 months, the stroke rate was 1.9%. The presence of mild peri-device leak was observed in 16.2% of patients at the 6-month follow-up by TEE. Similarly, this was observed in the 10-year experience in Switzerland with 152 patients in which all procedures were performed under local anesthesia without TEE guidance. Patients were discharged on acetylsalicylic acid and clopidogrel for a couple of months. Short-term safety endpoints (procedural complications) occurred in 15 (9.8%): neurologic events (n=3) and

Figure 4: Amplatzer Cardiac Patch (ACP). ACP 1 (left) and the new generation ACP 2 (right). The device is composed of a lobe and a disk connected by a central waist, which occludes the left atrial appendage ostium like a pacifier. Note that the lobe is anchored 1–2 cm distal of the LAA orifice, whereas the disc totally covers the ostium of the LAA.
device embolization (n=7) were the most common ones. Device embolization occurred more frequently in the non-dedicated Amplatzer devices than the ACP group (5 patients versus 2 patients). Mean intermediate-term follow-up of the study population was 32 months. Neurologic events occurred in two (1.3%), peripheral embolism in one, and major bleeding in four patients.33 Although the ACP 1 does not require immediate post-procedure AC, there have been some cases in every single study of thrombus formation around the device. Plicht et al.34 performed serial TEE before discharge and after 3, 6, and 12 months, and found an incidence of 17% of thrombus formation on the Amplatzer device despite dual anti-platelet therapy. A CHADS2 score greater than 4.3, CHA2DS2-VASc score greater than 6.8 and pre-interventional platelet count higher than 282.5 nL, and ejection fraction less than 40% were all independent risk factors for thrombus formation on the ACP 1. These results emphasize the need for close and serial TEE follow-up, and suggest the use of post-procedural AC.34 The ACP 2 Amulet (St. Jude Medical, Saint Paul, MN) is a second-generation Amplatzer device, which allows closure of larger LAAs and improved stability and decreased risk of embolization. The Amulet is a self-expanding device that has a longer distal lobe, and larger diameter of the proximal disc and waist than the ACP 1. This device is implanted in a similar fashion to its predecessor but it is repositionable. Compared to ACP 1 the Amulet has more hooks (10 pairs versus 6 pairs), which are stiffer, and it has diameters from 16 to 34 mm. It is recommended to select a device about 3–6 mm larger than the LAA orifice (Figure 4).35

**WATCHMAN device**

The WATCHMAN device (Atritech, Inc., Boston Scientific, Plymouth, MA) is a self-expanding nitinol frame with fixation anchors and a permeable polyester cover, which comes in five sizes (21, 24, 27, 30, and 33 mm) (Figure 5). Appropriate sizing requires that the device be approximately 10–20% bigger than the LAA. After access is obtained under TEE and fluoroscopy guidance a pigtail catheter is advanced into the LAA and the sheath is then advanced over the pigtail into the LAA. The pigtail catheter decreases the chance of LAA perforation. This device requires AC for at least 45 days post-implantation. The first worldwide experience of the WATCHMAN device was a prospective study that included 66 patients with permanent or paroxysmal non-valvular AF who were eligible for warfarin therapy with a mean follow-up of 740. At 45 days, 93% of devices showed successful sealing of LAA. Two patients experienced device embolization, both successfully retrieved percutaneously. Fixation barbs were modified with the second-generation device to prevent further device embolization. There were two cardiac tamponades, two TIA s, one air embolism, and one delivery wire fracture (first-generation device), which required surgical intervention. Four

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**Figure 5:** WATCHMAN device. Nitinol cage with a polytetrafluoroethylene membrane. Parachute-shaped device that incorporates a row of fixation barbs.
patients developed a flat thrombus layer on the device at 6 months, which resolved with additional AC. No strokes occurred during follow-up despite >90% of patients discontinuing AC. The PROTECT AF (WATCHMAN® Left Atrial Appendage Closure device) study was the first multicenter randomized controlled trial comparing LAA closure device (WATCHMAN) versus Coumadin in order to evaluate efficacy and safety in 707 patients with non-valvular AF eligible for AC. This study was designed in a non-inferiority fashion, and patients were randomized in a 2:1 ratio to percutaneous closure of the LAA (n=463) or to AC treatment (n=244) and followed up for 18 months. A WATCHMAN device was successfully deployed in 91% of patients in whom implantation was attempted. At the 45-day follow-up, warfarin was discontinued in 86% of patients who received the device, and 92% of patients met the criteria by 6 months, mainly because of a reduction in peri-device leaks. The primary endpoint for safety was a composite of stroke, cardiovascular death, and systemic embolism, and the primary endpoint for safety included major bleeding, pericardial effusion, and device embolization. The primary efficacy event rate was 3.0 per 100 patient-years in the intervention group and 4.9 per 100 patient-years in the control group (RR 0.62, 95% CI 0.35–1.25). At 1,065 patient-years of follow-up, the probability of non-inferiority of the intervention was more than 99.9%. Primary safety events were more frequent in the control group (7.4 per 100 patient-years versus 4.4 per 100 patient-years; RR 1.69, 1.01–3.19). There were five (1.1%) procedure-related ischemic strokes, three (0.6%) device embolizations, and 22 pericardial effusions (3.5%). Nonetheless, despite these results the device did not get approved by the Food and Drug Administration (FDA) due primarily to high initial rate of pericardial effusions and procedure-related strokes. Consequently, the Continued Access Registry (CAP) and the PREVAIL trial were designed to confirm the efficacy of the WATCHMAN device and to provide more data about safety.

The CAP Registry was designed to allow continued access to the WATCHMAN device for a subset of the PROTECT AF study, and to gain further safety and efficacy data about the device for a non-randomized registry of patients undergoing WATCHMAN implantation. The safety endpoint included bleeding and procedure-related events (pericardial effusion, stroke, device embolization). There was a significant decline in the rate of procedure- or device-related safety events within 7 days of the procedures in comparison to the initial PROTECT AF study (7.7% versus 3.3%) (p=0.007). Likewise, the rate of complications was significantly lower between the first and second halves of PROTECT AF, and even lower in patients who participated in CAP (10.0%, 5.5%, and 3.7%, respectively). The rate of serious pericardial effusion within 7 days of implantation was 2.2%, which was 50% of the safety events in PROTECT AF, and was lower in the CAP Registry (5.0% versus 2.2%, respectively; p=0.019). No procedure-related strokes occurred. They postulated that as with any interventional procedure, there will be improvement in safety as operator experience increases, yet this hypothesis was not proved by the PREVAIL study, in which there was no difference between new and experienced operators.

A few years later, the results of the 2.3-year follow-up of the PROTECT AF trial were published. After 1,588 patient-years of follow-up (mean 2.3±1.1 years), the primary efficacy event rates were 3.0% in the WATCHMAN group and 4.3% in the warfarin group (percent per 100 patient-years) (RR, 0.71; 95% CI, 0.44–1.03% per year), which met the criteria for non-inferiority (probability of non-inferiority >0.999). Although not statistically significant, there were more primary safety events in the WATCHMAN group (5.5% per year) than in the control group (3.6% per year) (RR, 1.53; 95% CI, 0.95–2.70).

Additionally, the results from the PROTECT AF trial were presented at the Heart Rhythm Society meeting 2013 but have not been published yet. The mean follow-up was 45 months, and non-inferiority (>0.999) for the primary efficacy endpoint (composite of stroke, cardiovascular death and systemic embolism) was repeatedly demonstrated (WATCHMAN 2.3% (1.7–3.2) warfarin 3.8% (2.5–4.9)). Interestingly, for the first time the primary safety endpoint was similar to the warfarin group (3.6% versus 3.1% HR 1.17 (0.78–1.95)). As expected, the WATCHMAN group revealed a significantly lower rate of hemorrhagic strokes (0.2 versus 1.1 RR: 0.15 (0.09–0.49)). Furthermore, total mortality was also significantly lower in the device group, with a 34 relative risk reduction HR 0.66 (95% CI 0.45–0.98).

Surprisingly, a sub-study from the PROTECT AF trial using TEE revealed that 32% of implanted patients had at least some degree of peri-device at 12 months. These data indicate that residual peri-device flow into the LAA after percutaneous closure with the WATCHMAN LAA closure device was very common. However, there were not associated with an increased risk of thromboembolism even including moderate (1–3 mm) or severe (>3 mm). The authors are aware that given the low event rate in this sub-study, this conclusion must be interpreted with caution.
The second co-primary endpoint was a composite of stroke, systemic embolism, and cardiovascular or unexplained death at 18 months of follow-up. Unfortunately, this trial did not meet this endpoint. The observed adverse event rate for both the WATCHMAN group and the warfarin group was 0.064, resulting in a RR of 1.07 with an observed upper bound of 1.88, slightly greater than the pre-specified criterion of 1.75 (95% CI) to demonstrate non inferiority. This might in part be explained given the fact that the stroke rate in the PREVAIL control group was lower than in any other published studies using AC (1.6–2.2%). Moreover, only a small percentage of patients were actually followed up at 18 months in both study arms. A significant increase in implant success rate (95.1%) compared with PROTECT AF (90.9%) was noted, with no difference in the success rate between new and experienced implanters (p=0.282). This study was supposed to be officially presented at the ACC scientific meeting in 2013, but it was cancelled since the embargo had been broken. The PREVAIL study has not yet been published.

The fact that the WATCHMAN device requires short- to intermediate-term AC is of primary importance given the fact that the main indication for LAA closure devices is for patients who cannot take chronic oral AC. Nevertheless, the ASAP study (the ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology) for patients at high risk for stroke but with contraindications to oral AC was conducted. This was a multicenter, prospective, non-randomized study with 150 patients with non-valvular AF (mean CHADS2 score was 2.8 and CHA2DS2-VASc 4.4) who received dual anti-platelet therapy (i.e., continuous ASA and Plavix for 6 months) instead of oral AC for 45 days. The primary efficacy endpoint was a composite of ischemic stroke, hemorrhagic stroke, systemic embolism, and cardiovascular or unexplained death, and the mean follow-up was 14 months. Serious procedure- or device-related safety events occurred in 13 out of 150 patients (8.7%). All-cause stroke or systemic embolism occurred in four patients (2.3% per year): ischemic stroke in three patients (1.7% per year) and hemorrhagic stroke in one patient (0.6% per year). This ischemic stroke rate was less than that expected (7.3% per year) based on the CHADS2 and CHA2DS2-VASc scores of the studied patients. These data support that the WATCHMAN device can be safely performed without post-procedural AC.

On December 11, 2013, the FDA advisory panel voted 13 to 1 that the benefits associated with Boston Scientific’s WATCHMAN device outweighed the risks in AF patients, and a new verdict will be made soon by this organization.

**LARIAT system**

The LARIAT (SentreHEART, Palo Alto, CA) device consists of three components: 1) a balloon catheter (EndoCATH 15 mm), 2) magnet-tipped guidewires (FindrWIRZ 0.025–0.035 inch), and 3) an epicardially delivered 12F suture delivery device (LARIAT) (Figure 6). The LARIAT system device requires both endocardial and epicardial approaches to exclude the LAA. Four steps are required: 1) pericardial and transseptal access, 2) placement of the endocardial magnet-tipped guidewire in the apex of the LAA with balloon identification of the LAA os, 3) connection of the epicardial and endocardial magnet-tipped guidewires for stabilization of the LAA, and 4) snare capture of the LAA with closure confirmation and release of the pre-tied suture for LAA ligation (Figure 7). The endoluminal balloon inflated in the LAA markedly when the suture is being delivered significantly decreases the possibility of an incomplete isolation of this structure from the LA. Since the LAA is closed from outside with a single ligature, there is no permanent intracardiac foreign body left behind and no risk of device embolization or risk of infection. Contrast cardiac CT scan is routinely obtained in AF patients being considered for LARIAT to ensure that the size and orientation of the appendage is amenable to ligation. In brief, contraindications to this approach include LAA width greater than 40 mm, a superiorly oriented LAA behind the left pulmonary artery, and a history of conditions that would result in pericardial adhesions (e.g., history of pericarditis, open-heart surgery, thoracic radiation, prior epicardial ablation, etc.).

The first pre-clinical experience with this device was carried out in a canine model, in which the investigators evaluated the safety and effectiveness of the LARIAT device. All the LAAs in the 26 dogs included in this study were completely isolated, and follow-up echocardiography demonstrated no flow between the LA and LAA. This study demonstrated that LARIAT was safe, effective, and without the risk of device migration or embolization, thrombus formation, and cardiac tamponade. Subsequently, Bartus et al. published the first and largest clinical experience using the LARIAT device in Poland in 2013. This study screened a total of 119 patients (CHADS2: 1.9), but 16 (13.4%) patients were excluded based on LAA size <40 mm (n=8) and a superior-posterior orientation of the LAA apex, generally behind the pulmonary artery (n=8). Moreover, three cases were cancelled when attempting to place the device due to pericardial adhesions that precluded pericardial access. A total of 81 of 85 (95%) patients had complete closure right after the suture was tightened. Three patients had a ≥2-mm residual LAA leak and one had a ≥3-mm jet by TEE color Doppler evaluation. There were no complications secondary to device deployment. However, as expected, there were two pericardial access-related complications and one due to transseptal puncture. One patient had a right ventricular (RV) puncture, which was dilated over the guidewire with hemopericardium requiring drainage. The second one was a laceration of a superficial epigastric vessel. A third complication occurred during the transseptal catheterization, resulting in perforation and hemopericardium. Two patients developed severe acute pericarditis and one patient was found to have late pericardial effusion.
There were also two unexplained sudden deaths and two late strokes thought to be non-embolic. At 1 month all the patients who had complete occlusion immediately after the procedure revealed no communication between the left atrium and the LAA. A year later, 65 patients underwent TEE examination with a 98% complete LAA closure. This prospective observational study demonstrated that this new device using an endo-epicardial approach offers an alternative to OAC with an excellent success rate and an acceptable low risk of complications.48

One more small retrospective study was also published thereafter. The first US experience included 21 patients with AF, CHADS2 score ≥2 and contraindications to AC. Patients in whom the LARIAT device was delivered had a 95% success rate for complete LAA exclusion that was preserved at 3 months. No patient had a stroke during a 1-year follow-up. Two patients developed hemopericardium due to RV perforation: one patient required open heart surgery, and the second several paracentesis. Three patients developed pericarditis <1 month after the procedure with one requiring drainage.49 In general, the prior studies reported that the LARIAT device can be readily deployed with low rates of adverse events, most of which are complications attributable to obtaining epicardial access (i.e., left hepatic lobe puncture, epigastric vessels laceration, RV perforation). Similarly, LAA tear and post-procedure pericarditis are well-known complications. Colchicine seems to be the most effective treatment for patients who develop pericarditis in our experience, and this is partially supported by the results from the randomized, double-blind CROP-2 trial.50 Although the major benefit or the LARIAT device when compared with the other endovascular devices, particularly the WATCHMAN device, is that there is no need of AC after successful complete isolation of the LAA, we and others have showed early (1 month) and late (2–4 months) partial reopenings with bidirectional flow between the LAA and the LA. This obviously has relevant clinical implications, and we consider that AC should be continued for at least 1–3 months after device placement in order to corroborate complete occlusion and avoid strokes if no absolute contraindications are present.51,52 The GoreVR HelexVR Septal Occluder (W. L. Gore and Associates, Newark, Delaware) might be used to address and close these gaps given that spontaneous resolution is unlikely.53 Surprisingly, even with complete LAA occlusion, thrombus formation at the stump of the ligated LAA has been seen. Thrombus at the site of closure may represent thrombus extension from an appendage that has slightly opened after the procedure. Another interesting theory is that by pulling the balloon-tipped catheter and endocardial magnet-tipped wire through a very narrow LAA neck the endothelium is traumatized, creating a pro-thrombotic environment.54 However, between 3% and 5% of thrombi after successful closure have been observed by centers that discontinue AC immediately after the procedure. On the contrary, this finding has not been reported by centers that confirm successful complete

Figure 6: LARIAT device. See the endocardial and epicardial magnet-tipped guidewires in the left atrial appendage, which create a monorail that allows the suture loop to be positioned at the base of the appendage.
The arrhythmogenic role of the LAA is well established in the literature. At least 30% of patients with persistent AF have triggers in this structure, which have been implicated in maintaining persistence of this arrhythmia. LAA catheter ablation for LAA isolation improved AF ablation success rates, but may cause electromechanical dissociation with the potential for LAA thrombus formation.

Preclinical models and surgical studies postulated that the LAA could potentially be electrically isolated by surgical epicardial clipping occlusion. One group demonstrated complete electrical isolation of the LAA in 10 AF patients who underwent off-pump coronary artery bypass surgery with bilateral pulmonary vein isolation and an LAA clip occlusion. Before and after the clip was placed, pacing maneuvers were performed to assess electrical exit and entry blocks from the LAA. Han and colleagues enrolled 68 patients who underwent LLA ligation with the LARIAT device. They demonstrated a significant decrease in LAA unipolar and bipolar voltages before and after the snare was tightened. Ninety-four percent of these patients had a reduction in LAA voltage, with a third of these having complete elimination of LAA voltage. Pacing from the LAA after the closure of the snare demonstrated complete isolation of the appendage with no capture of LA in 90% of those individuals. These changes might be consistent with LAA ischemic necrosis. Whether or not LAA ligation might indeed play an important role in decreasing the AF burden remains to be elucidated. This device is 510 (k) FDA approved in the United States for soft-tissue approximation and/or ligation with a pre-tied polyester suture.

**LAMBRE**

This is a self-expanding nitinol-based device comprising a hook-embedded umbrella with a cover connected to a short central waist. The cover is larger than the umbrella, approximately 4–6 mm, and filled with sewn in polyethylene terephthalate fabric. The devices come in various sizes ranging from 16 to 36 mm. The size of the LAA is measured by angiogram and the size of the devices chosen would be 4–8 mm larger. The delivery system is placed on the proximal part of the LAA and the umbrella device is deployed by pushing out the device from the delivery sheath to the desired landing zone, opening the umbrella, and the hooks grasping the LAA walls. The sheath is removed to expose the disc and permit it to expand in the atrium and cover the LAA ostium. This new device has two main
Figure 9: (a) WaveCrest left atrial appendage (LAA) closure device. (b) Reproduction of the device placed into LAA.
advantages: a small delivery system and the ability to reposition during implantation.  

New LAA closure devices

The AEGIS permits LAA closure by an epicardial approach and it has two parts: 1) appendage grabber and 2) ligator. The first component (Grabber) has an articulating jaw with mounted electrodes, allowing identification and positioning of the LAA by means of electrical signals. When positioning near the LAA, injection of contrast is achieved to outline the LAA and prove proper capture by ICE or TEE. The ligator is a preloaded hollow suture that can be opened and closed repeatedly until proper closure has been achieved. This system has been tested in animals.

The Transcatheter Patch (Custom Medical Devices, Athens, Greece) is a soft, frameless, bioabsorbable balloon-deliverable device delivered similarly to other LAA occluders, but the difference is that it is fixed within the LAA with surgical adhesive, which reduces the risk of LAA perforation. The supporting balloon is made of latex and the patch from polyurethane foam. It was studied in 20 patients, showing successful placement in 17 cases.

The Coherex WaveCrest (Salt Lake City, UT) LAA occlusion system is a one of the latest developments in closure devices. This device has an umbrella shape, and it is deployed similarly to other endovascular devices. It has more anchors than any other device to avoid embolization, and the material that faces the LA minimizes thrombus formation and allows rapid endothelialization (Figure 9A,B). It was initially tested in animals with satisfactory results, and the results from the WaveCrest I trial were presented last year. Acute procedural success and acute closure were obtained in 93% of patients (68/73), and complete LAA closure at 45 days in 92% of cases (67/73) enrolled patients (92%). Two pericardial effusions and no procedural stroke, device embolization or device associated thrombus.

Guidelines

The 2012 focused update of the ESC Guideline for the Management of AF state that a percutaneous LAA closure device may be considered in patients with high stroke risk and contraindications for long-term AC (class IIb and level of evidence B).  

Conversely, the recently published 2014 AHA/ACC/HRS guideline for the Management of Patients With Atrial Fibrillation make no recommendations about these devices.

Future perspective

Percutaneous LAA occlusion devices without a doubt represent a very provocative therapeutic option to reduce the stroke burden in patients with non-valvular AF. The main indication for these devices has been absolute contraindications for oral AC, yet some authors have suggested to use them as an alternative for long-term oral AC in order to avoid the risk of major and fatal hemorrhagic events, which makes them even more appealing. Furthermore, percutaneous LAA occlusion devices have proved to be cost-effective compared with warfarin. Nevertheless, the European and American guidelines for the management of these patients are still non-committal and evasive, respectively. This is in part because most of the studies have had small samples and short-term follow-up, some of them with conflicting data.

Additionally, it has been well established that LAA devices do not fully prevent the risk of cardioembolic stroke, probably because thrombi can form in locations other than the LAA even in non-valvular AF patients (5%). CT studies have demonstrated a significant number of subclinical small strokes in AF patients, which are not treated with AC, and which have a marked impact in learning capacity and memory loss when compared with non-AF patients. More importantly, all the studies using devices have not had “control” groups, and a few have used warfarin as a comparison. An indirect analysis presented at ACC 2010 from the PROTECT AF trial and RELY showed that the WATCHMAN would not have reached the non-inferiority endpoint if Pradaxa had been the control group. It would be interesting to analyze and compare the data from the Aristotle study given the fact that Apixaban is the only oral anticoagulant that not only demonstrated to be non-inferior but superior to warfarin in reducing the risk of stroke and systemic embolism in patients with AF. Moreover, apixaban showed a significant reduction in bleeding risk and total mortality. Finally, prospective head-to-head comparisons among devices and using the new oral agents for AC are needed to discover which device is best and if indeed they are as good as AC in this patient population.

References


