

## Left Atrial Appendage Ligation And Exclusion Technology In The Incubator

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### Abstract

Stroke is the most feared complication of atrial fibrillation (AF). Targeting the left atrial appendage (LAA) mechanically is attractive as a means to simultaneously reduce stroke risk, the need for anticoagulation, and hemorrhagic complications in patients with non-valvular AF. The results of the PROTECT-AF and PREVAIL randomized clinical trials support this approach as a viable therapeutic alternative to warfarin in selected patients and add to accumulating evidence regarding the importance of the LAA in thromboembolism in AF. A number of devices for percutaneous LAA closure are under investigation or development. In this article, key design features of these ligation and exclusion technologies will be discussed, with a focus on aspects of LAA morphology, relational anatomy, thrombosis, and thromboembolism relevant for successful device development and deployment.

### Introduction

Left atrial appendage (LAA) closure, by altering the balance of Virchow's triad within the appendicular cavity,<sup>1</sup> is an attractive strategy for stroke prevention in nonvalvular atrial fibrillation (AF).<sup>2-5</sup> An appreciation of the pathophysiological influence of the LAA on stroke risk traditionally hinged on the observation that 15% of patients with nonvalvular AF have intracardiac thrombi, of which 90% are located within the LAA.<sup>6-9</sup> Recent advances in cardiac imaging have allowed investigators to demonstrate that morphological complexity of the LAA significantly influences thromboembolic risk, supporting a structural approach to thromboprophylaxis.<sup>10-16</sup> This principle was tested by the PROTECT-AF and PREVAIL randomized clinical trials, which demonstrated that LAA exclusion using the WATCHMAN percutaneous occlusion device (Boston Scientific, Natick, MA) was not clinically inferior to warfarin in preventing strokes, whilst reducing bleeding risk.<sup>3, 17</sup> Till now, the only percutaneous LAA closure device available in the USA for ameliorating AF-related stroke risk has been the LARIAT appendage

ligation system (Sentre-HEART, Redwood City, CA),<sup>18-22</sup> which provides an attractive alternative approach for stroke prevention in patients with a high bleeding risk on systemic anticoagulation. A number of other technologies have received CE (Conformité Européenne) mark approval for commercial use in Europe, of which the AMPLATZER cardiac plug (ACP, St Jude Medical, Saint Paul, MN)<sup>23-27</sup> and the now discontinued PLAATO system (eV3, Sunnyvale, CA)<sup>28-30</sup> have been the most widely implemented. Others are currently in the incubator, although reporting preclinical or early clinical results (Table 1).

In this article, aspects of LAA morphology, relational anatomy, thrombosis, and thromboembolism relevant for successful percutaneous LAA closure will be discussed initially, drawing from published observations on devices currently in clinical use. Subsequent focus will be on key design features of devices under clinical investigation or development.

### Endpoints For Effective LAA Closure: Epicardial Ligation Versus Endocardial Exclusion

As a broad overview, devices have utilized either an endovascular exclusion-based approach, in which a foreign occlusive body is introduced via atrial transeptal puncture and deployed within the LAA, thereby excluding it from the main atrial chamber (WATCHMAN, ACP, and PLAATO), or an epicardial ligation-based approach where epicardial puncture permits navigating to and tying down a noose over the LAA neck (LARIAT).<sup>4, 31-36</sup> Aside from specific variations in device design and application, which translate into important procedural and patient selection considerations, the resulting structural changes that follow are observably dissimilar

### Key Words:

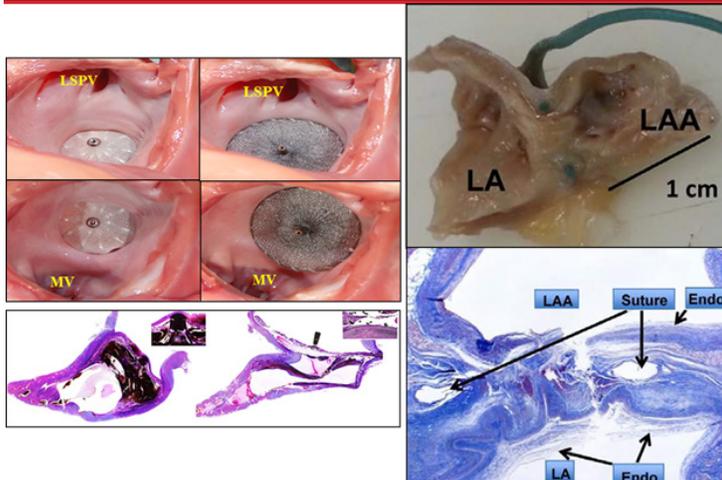
Left Atrial Appendage, Ligation, Exclusion, Technology, Anatomy, Thromboembolism, Device.

### Disclosures:

None.

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**Figure 1:** Left and middle columns: canine specimens demonstrating comparative positioning of the WATCHMAN (left) and ACP (right), with histological sections (bottom) demonstrating cross sectional relationship to ostium and neo-endothelialization (inset). Note the intra-appendicular positioning of the WATCHMAN compared to the external disc of the ACP, and the incomplete endothelial coverage of the ACP mesh wires near the inferior edge of the disk and end-screw hub.<sup>38</sup> Right column: Changes following LARIAT occlusion with suture (green) in the explanted heart of a patient who underwent cardiac transplantation 1 year 11 months after the procedure, with corresponding Mason trichrome staining (bottom) demonstrating extensive scarring (dark blue) within the appendage and suture site that extends into the left atrium.<sup>37</sup> LSPV – left superior pulmonary vein. MV – mitral valve. LAA – left atrial appendage. LA – left atrium. Endo – endocardial surface.

between these approaches (Figure 1).<sup>37,38</sup> The endpoints for adequate closure are therefore also likely to differ, and whether adequate closure is best defined using anatomical, electrical, or functional criteria<sup>4,31</sup> will ultimately depend on recognizing the respective association with clinical effectiveness. Data from surgical ligation suggests that both residual leak from incomplete ligation and residual stump from too distal a ligation point predispose to subsequent atrial thrombus.<sup>39-43</sup> Late LAA leakage has been reported in 20% to 25% of patients at 3 months with LARIAT,<sup>21,22,44,45</sup> and a predisposition to subsequent atrial thrombus formation is speculated<sup>46</sup> though not proven. Late thrombus formation at the site of closure has been reported in 5% of patients between 17 to 104 days after LARIAT ligation<sup>22</sup> and both in the presence<sup>46</sup> and absence of a residual leak.<sup>47</sup> Peri-device leaks following endovascular occlusion are also common, being noted in 41%, 34% and 32% at 45 days, 6 months and 12 months respectively in patients from PROTECT-AF after WATCHMAN closure,<sup>48</sup> although the currently published data suggest no associated increase in rates of thromboembolism.<sup>48-51</sup> 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 ligation-related leak versus those with a peri-device leak. Thrombosis mechanisms in device exclusions are often related to the device itself (3.7% of patients in PROTECT-AF receiving WATCHMAN)<sup>32</sup> and more likely to be influenced by seating of the device within the LAA and subsequent device endothelialization,<sup>52</sup> with less complete endothelialization of the ACP compared to WATCHMAN on account of the ACP's larger surfaced extra-appendicular disc and more prominent end-screw hub in a comparative dog study with WATCHMAN (Figure 1).<sup>38</sup> Ligation results in acute appendage ischemia leading to appendage

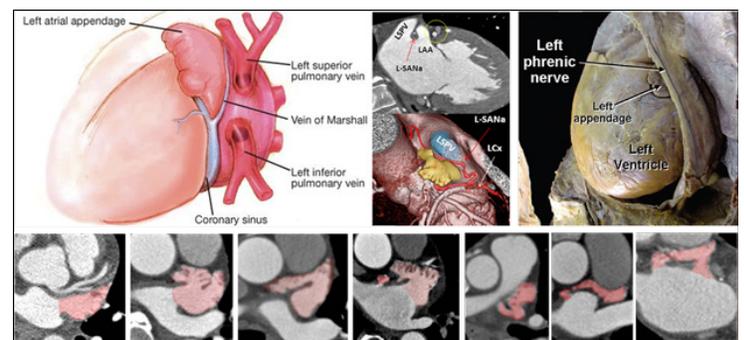
atrophy and cavity obliteration<sup>5, 37, 53, 54</sup> although the contribution of this remodeling to preventing thrombus formation is currently unknown. This is also the case with residual "beaks" where tissues are approximated, residual diverticula or extra-appendicular pectinate ridges.<sup>4,31</sup>

## Key Considerations For Device Design

### Epicardial Ligation

The LAA is a tubular projection arising from the free wall of the left atrium, typically extending superiorly to project a variably curvilinear course, bending noticeably in 75% individuals at  $98 \pm 20$  degrees after the initial  $14 \pm 4$  mm, running adjacent and parallel to the left superior pulmonary vein (LSPV), underneath the main pulmonary artery, and draping down over the right ventricular outflow tract, left main coronary artery bifurcation, left atrioventricular groove which houses the left circumflex artery and great cardiac vein, and a portion of the mitral annulus (Figure 2).<sup>55-61</sup> The sinoatrial node artery can be related when it arises directly from the left circumflex artery (30% of individuals) or coursing from the left lateral atrial artery (8% of individuals) rightward between the appendage and LSPV towards the sinoatrial node (Figure 2).<sup>58</sup> The left phrenic nerve runs along the overlying pericardium<sup>62</sup> traversing the appendage variably from over its tip to over the roof of the ostium.<sup>63</sup>

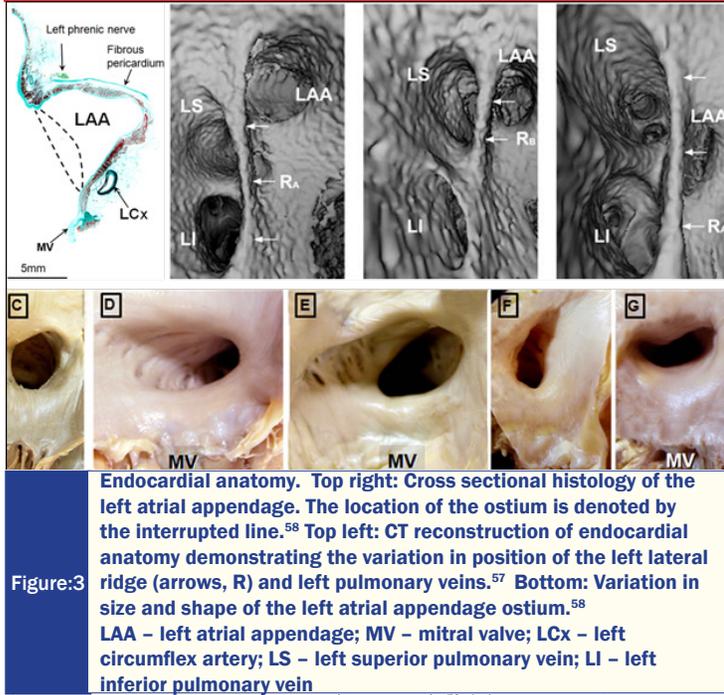
A transcutaneous epicardial approach to the LAA must therefore first negotiate the anterior pericardial space, with free passage superiorly to engage the appendage whilst avoiding the above mentioned neurovascular structures. Such an approach to the LAA may be restricted in individuals with pericardial adhesions from prior open heart surgery, pericarditis, epicardial VT ablation, or uremia, anatomical distortion such as with pectus excavatum, kyphoscoliosis or severe obesity<sup>58, 64</sup> or congenital abnormalities such as pericardial



**Figure 2:** External anatomy of the LAA. Bottom: CT images with the appendage highlighted in pink, demonstrating variation in morphology and orientation.<sup>55, 63, 58</sup> LAA – left atrial appendage; LSPV – left superior pulmonary vein; L-SANa – left sinoatrial node artery; LCx – left circumflex artery.

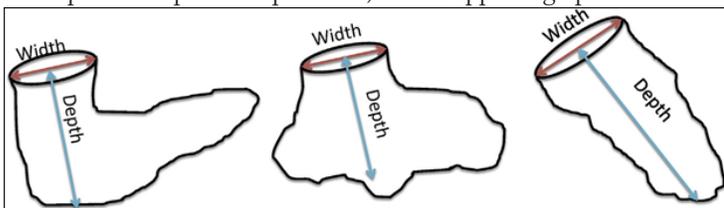
absence which may additionally be associated with appendage herniation.<sup>65</sup>

Detailed morphological LAA definition on an individual basis is integral to success of epicardial ligation approaches as there is marked inter-individual variation in appendage size, number of lobes, crenulations, and pectinate musculature,<sup>56,66,67</sup> with 20 to 70 percent of individuals having a single lobe, 16 to 54 percent having two, and the remainder having up to 4 lobes.<sup>68, 69</sup> Occasionally a second posterior lobe is sandwiched between the right and left ventricular outflow tracts.<sup>55</sup> Although the appendage tip points inferiorly in the majority, usually pointing down in line with the course of the left anterior descending artery, it can sometimes be directed posteriorly or into



the transverse pericardial sinus (Figure 2).<sup>58</sup> These considerations are important as a noose-based ligature has to first engage and be slipped past the appendage tip. Without an effective method to manipulate or re-orientate the appendage tip, the LARIAT is unsuitable for patients with a superiorly oriented LAA or a posteriorly rotated heart.<sup>58</sup> Ensuring the noose is large enough to capture the appendage and any additional lobes is also key; the LARIAT's noose has a maximal diameter of 40 mm.<sup>18</sup> Identifying the relationship of the left main coronary artery and its bifurcation to the neck, and the course of the phrenic nerve, are also important. Appendages may in addition be closely adherent to the underlying left ventricular wall, congenitally aneurysmal,<sup>70</sup> inverted,<sup>71</sup> juxtaposed,<sup>72</sup> or absent altogether.<sup>73</sup>

The above anatomical and pathophysiological constructs present distinct, sequential challenges in executing a successful strategy for percutaneous epicardial LAA ligation.<sup>4</sup> First, in contrast to the ease with which the appendage can be instrumented through transeptal access, negotiating it accurately from within the pericardial space is difficult even when guided by preprocedural CT and intraprocedural TEE. Secondly, once identified, the freely mobile appendage requires stabilization to allow for controlled ligation. LARIAT addresses both these steps simultaneously by using an adjunctive transeptal endocardial approach to first advance one magnet-tipped wire to the appendage tip, and approximate another from the epicardium onto it, thereby grasping the appendage whilst establishing a supporting monorail over which to advance a looped suture.<sup>18</sup> This unique approach does, however, introduce risks from both transeptal and epicardial puncture, risk of appendage puncture from

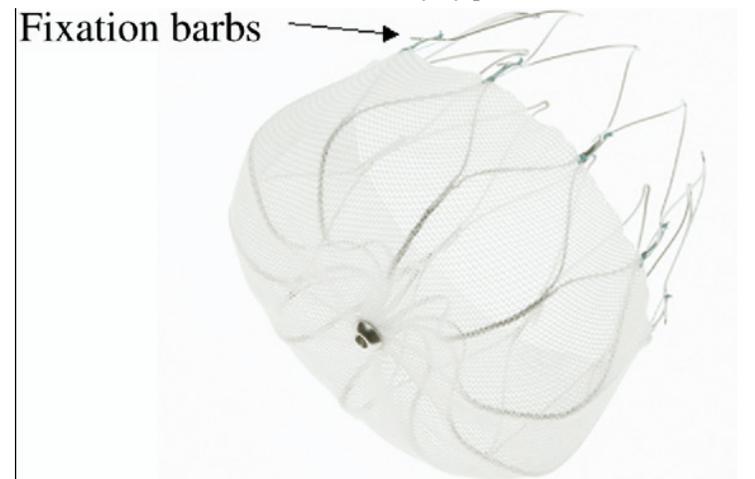


**Figure 4** Appendage width and depth takes precedence to morphology for endocardial device closure.<sup>80</sup>

deep intubation of the appendage by the transeptal sheath, risk of appendage laceration, and the procedural complexity of maintaining correct orientation of two curved sheath-based platforms relative to each other and the appendage wall.<sup>64, 74-76</sup> Thirdly, although the optimal ligation site along the LAA is not known, closure is targeted at the ostium based on surgical data implicating persistent leaks and residual stumps for recurrent thrombosis, yet the boundary between the LAA and main atrial chamber is indistinct both anatomically and electrically. To overcome this, both endocardial and epicardial strategies attempt to close the appendage as proximally and snugly as possible,<sup>33</sup> which for LARIAT involves placing an endocardial balloon-tipped catheter at the ostium, overriding it when tying down the epicardial suture, and ensuring a tight seal using contrast fluoroscopy and Doppler TEE.<sup>18, 64</sup> However, the final tightening is reserved for once the endocardial citing balloon is deflated and withdrawn. Despite ensuring an adequate seal, which can be by radiocontrast injection as well as Doppler color flow imaging, recent clinical experience with the LARIAT has reported that leaks reoccur and can be seen in 20% to 25% of patients within a few months,<sup>21, 77</sup> cause or consequence is unknown at present.

### Endocardial Exclusion

The LAA can be identified internally by pectinate muscles, which



**Figure 5** WATCHMAN device, demonstrating active fixation barbs.<sup>105</sup>

impart the characteristic combed appearance of its endocardial surface, although in a significant proportion of individuals these can extend inferiorly to the vestibule of the mitral valve.<sup>56, 58, 63</sup> The smooth-walled LAA ostium, whilst demarcated by the LLR superiorly and posteriorly, has indistinct borders anteriorly and inferiorly which therefore have to be approximated (Figure 3).<sup>56</sup> Approaches for endocardial exclusion have relied upon TEE-visualization of the left main coronary artery, circumflex artery or mitral annulus to define the plane of the ostium in relation to the LLR.<sup>33, 78-80</sup> The shape of the LAA ostium is usually oval, rather than round, though varies significantly between individuals,<sup>56, 66, 69</sup> and the orientation of the ostium relative to the plan of the mitral annulus is oblique rather than vertical.<sup>56</sup> The ostium can be at the same level as the LSPV (60% to 65% of individuals), superior to it (25% to 30%) or inferior (10% to 15%) (Figure 3).<sup>57, 69</sup> The intervening LLR is formed by an infolding of the lateral atrial wall, is narrow superiorly where it is predominantly muscular, becomes up to 5 mm wide inferiorly and houses the ligament of Marshall (remnant of the left sided superior vena cava), autonomic nerves and a small atrial artery which

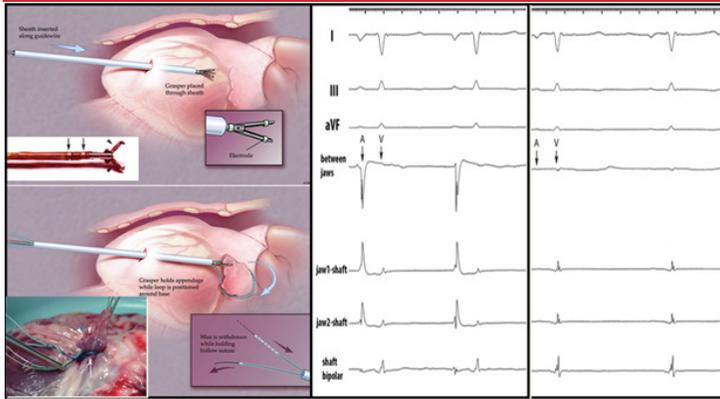


Figure:6

**Aegis electrogram guided intrapericardial ligation approach. Left: Demonstration of intrapericardial navigation to the appendage tip using grabber and shaft electrodes, and preformed looped suture application. Right: From top to bottom on the tracing are shown surface ECG leads I, III, aVF, jaw-to-jaw bipolar electrogram (EGM), jaw1-to-shaft EGM, jaw2-to-shaft EGM, and a shaft bipolar recording. Tracings on the left are pre LAA ligation, and on the right are post LAA ligation. Note the disappearance of the atrial signal from the appendage following ligation, and the predominant ventricular signal on the shaft bipolar electrogram.<sup>5</sup>**

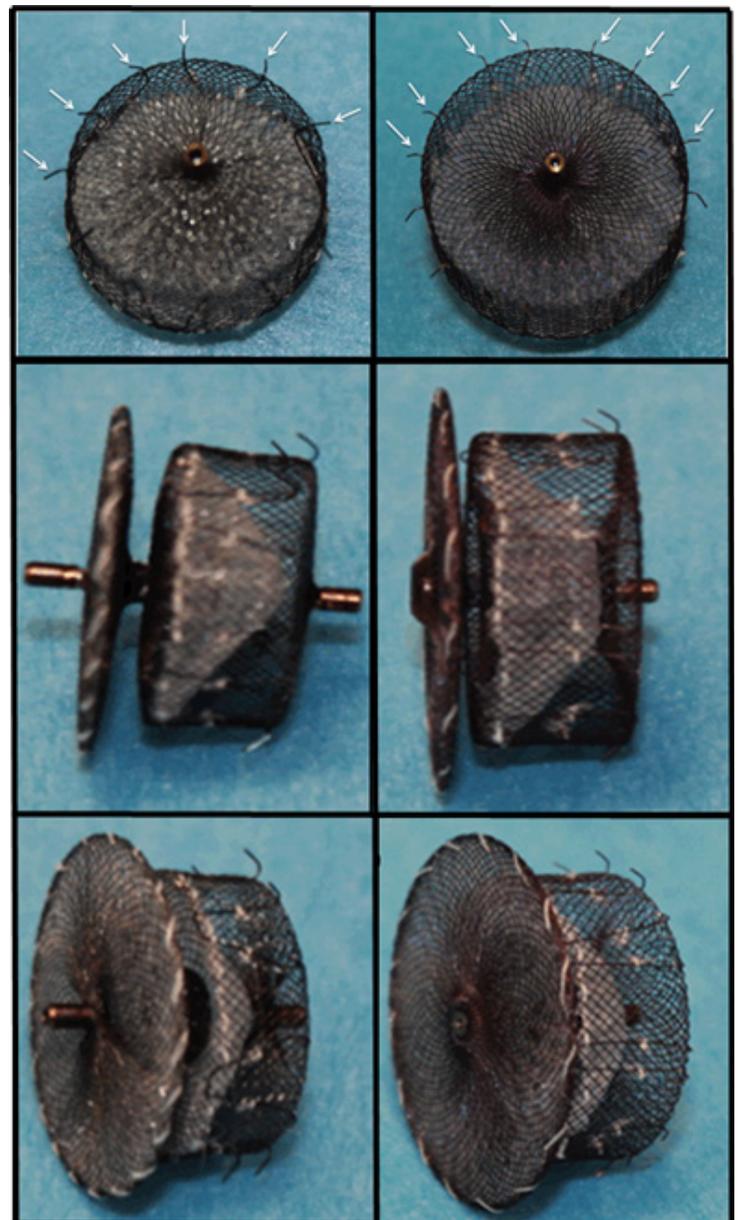
sometimes is the sinoatrial nodal artery.<sup>56, 58, 62, 63</sup> Distance from the LAA ostium to the LSPV is 5-10 mm in 45% of individuals, and 10-15 mm in 40%, can be up to 24 mm in the remainder, with distance from LAA ostium to mitral annulus being similar.<sup>56</sup>

By engaging the ostium directly from within, the success of an endocardial exclusion strategy is dependent on the interaction of ostial size and shape with accurate device positioning and adequate exclusion, the internal anatomy of the LAA relied upon by the device for a safe and secure landing, and how well transeptal access orientates engagement with the appendage ostium.<sup>33, 58</sup> Devices design is required to incorporate ways to minimize and compartmentalize thrombosis such as by using resistant materials or minimizing device profile and exposed structures, a delivery platform that facilitates accurate and safe device positioning, a deployment mechanism which can be adjusted for size and position to achieve an adequate seal, a seating mechanism which prevents device embolization, and a profile which does not interact significantly with related structures including the left lateral ridge (LLR), mitral valve, pulmonary vessels and coronary arteries.

The WATCHMAN is designed to be deployed 10 mm below the LAA ostium such that its self-expanding nitinol cage fills the appendicular cavity and its 160  $\mu$ m thick covering made from microporous polyethylene terephthalate entraps thrombi and promotes endothelialization.<sup>31</sup> The device is unfurled by gradual pullback of the access sheath and delivery catheter while maintaining device position using fluoroscopic and TEE guidance, with Doppler flow to identify adequacy of the seal and the sheath to facilitate partial recapture and adjustment.<sup>33</sup> The ACP has a braided nitinol frame with overlying polyester patch and is designed to cover the ostium with a disc articulated to a distal lobe which anchors within the LAA.<sup>31</sup> The ACP lobe is deployed first by partial unsheathing, followed by the proximal disc by further unsheathing, whilst effectiveness of occlusion is confirmed using distal radiocontrast injection through the delivery system and/or Doppler flow<sup>78</sup> and with partial or full retraction into the sheath for repositioning.<sup>33</sup> Currently available devices are for ostial sizes of 17-31.9 mm for WATCHMAN and 12.6-28.5 mm for ACP.<sup>33</sup>

In contrast to the epicardial approach, accurate and standardized measurement of width of the ostium and depth of the landing zone take precedence to other morphological considerations in ensuring that the device is compatible with the appendage and correctly sized (Figure 4).<sup>33, 80</sup> The WATCHMAN requires the LAA length to be in excess of the maximal ostial diameter and is therefore better suited for long and narrow appendage profiles, whilst the ACP is better suited for short and broad profiles as the anchoring lobe requires the landing zone to be at least 10 mm wide.<sup>33, 80</sup> Challenging morphologies include appendages which taper significantly from ostium to tip, where usual sizing of the ACP landing site may result in an undersized disc at the ostium<sup>33</sup> and "chicken wing" morphologies which can have an excessively early and severe bend.<sup>81</sup> Rarely, there may be an ostial membrane manifesting with elevated gradient across the ostium.<sup>82</sup>

Accurate appendage sizing is also important in ensuring a snug fit and reducing risk of device embolization, and accordingly



**Figure:7 The Amplatzer first generation ACP (left) compared to second generation Amulet (right).<sup>84</sup>**

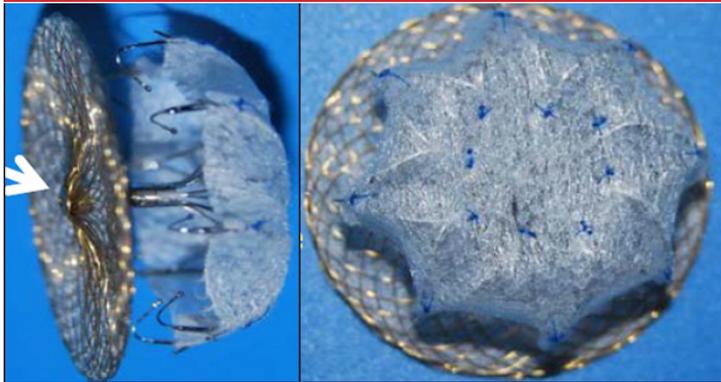


Figure 8 The Lifetech LAMBRE device.<sup>97</sup>

WATCHMAN devices are sized 10% to 20% larger and ACP 1.5-3.4 mm larger than the maximal ostial diameter.<sup>33</sup> However, relying on radial expansion forces alone has been shown to be insufficient in ensuring device stability: the very early AMPLATZER septal occluders which relied on this strategy when deployed within the LAA had high rates of device embolization.<sup>31, 78</sup> AF is associated with an increase in appendage size and reduction in the internal trabecular structure due to pectinate muscle atrophy and endocardial fibroelastosis<sup>83</sup> whilst the ostium progressively increases in size and adopts a more rounded shape with increasing AF burden.<sup>79</sup> In addition, with appendages which taper distally, radial forces may paradoxically result in device expulsion as the pressures generated deeper in the appendage will be greater than those at the ostium.<sup>33</sup> Current devices use active fixation mechanisms which are engaged using gentle application of negative traction upon deployment and take advantage of the appendage's trabeculated endocardium (Figure 5).<sup>33, 78</sup> A strategy of oversizing devices serves also to reduce the incidence of peri-device leaks,<sup>84</sup> the significant incidence of which is likely related to the variably oval shape of the ostium<sup>56, 66, 69</sup> in contrast to the uniform and rounded design of devices in current clinical use.<sup>23, 48-51, 84, 85</sup> However, care must be taken not to distend aggressively, as the appendage is paper-thin in areas between the pectinates and may perforate, and the ostium is critically located immediately anterolateral to the left main coronary artery, superior to the great cardiac vein and circumflex artery, and anterior to the LSPV,<sup>56, 58, 63</sup> any of which may become compressed. Reported complications following endovascular exclusion procedures have also included erosion into the overlying main pulmonary artery.<sup>86-88</sup>

All current endocardial exclusion strategies utilize a sheath based delivery platform with access across the interatrial septum.<sup>33, 80</sup> Given the ostium's oblique orientation,<sup>56</sup> a posteroinferior septal puncture allows approaching the ostium at an optimal angle without excessive sheath manipulation and torque, which increases risk of atrial perforation.<sup>33, 58</sup> Slight adjustment of the approach is required for each case to accommodate for the inter-individual variation in the angle adopted by the septum in its left anterior to right posterior course.<sup>58</sup> Puncture should be at the true anatomical septum which is defined by the thin floor of the fossa ovalis, measuring 1-3 mm in thickness, whilst the muscular rim is formed by invagination of the atrial wall, though location and size vary between individuals and in those with kyphoscoliosis and marked left ventricular hypertrophy.<sup>63</sup> Echocardiography-guided puncture is to be recommended given the high prevalence of a septal ridge,<sup>57</sup> pouch at the fossa,<sup>63</sup> or other structural abnormalities including atrial septal aneurysm, patent

foramen ovale, atrial septal defect, septal flap, thickened interatrial septum, or thrombus.<sup>89</sup>

### Device Technology In The Incubator

The ideal AF stroke prevention technique should completely remove any thromboembolic risk and substrate, confer minimal clinical risk, be cost effective and applicable to all.<sup>4</sup> Towards this goal, the experience with WATCHMAN and ACP, and more recently LARIAT, add further insight into determinants of success and current shortcomings of device design and approach, even though no study has to date directly compared one device to the other.<sup>90</sup> With development ongoing, opportunities arise for improving efficacy, universal applicability, safety and simplicity.

### Aegis

The Aegis system (Aegis Medical, Vancouver, Canada)<sup>5, 53, 91</sup> is a totally intrapericardial ligation approach which harnesses the appendage as the most inferior site of atrial electrical activity obtained from an anterior subxiphoid epicardial approach.<sup>4</sup> A steerable epicardial sheath, placed via standard subxiphoid puncture, supports the introduction of an appendage grabber with embedded electrodes within the jaws and further electrodes on the shaft proximally. The grabber is electrically navigated onto the atrial appendage, which it then captures and stabilizes, whilst ventricular signals on the proximal shaft electrodes confirms an orientation towards the appendage tip (Figure 6). 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, with a range of appendage sizes, shapes and lobes enabled by the variable loop size. After loop closure, the wire is removed, leaving only suture behind, which is remotely locked with a clip to maintain closure. If initial closure is unsatisfactory, the loop can be undone and repositioned, or additional loops placed



Figure 9 The Occlutech LAA Occluder.<sup>98</sup>



Figure:10 The Transcatheter Patch.<sup>99</sup>

over the first. Successful closure is confirmed within seconds by the elimination of LAA electrical activity, accompanied by shortening of the surface electrocardiographic P wave in dogs<sup>5</sup> and followed by the LAA becoming atretic.<sup>53</sup> As compared to LARIAT, the major advantage offered by Aegis is that transeptal access is not required and, therefore, neither is anticoagulation. Similar to LARIAT, previous cardiac surgery or adhesions from previous pericarditis are the major limitations. Feasibility in humans has been demonstrated,<sup>91</sup> with approximately 50 patients having had the procedure to date.<sup>92</sup>

#### Amulet

A second generation ACP, the Amplatzer Amulet Left Atrial Appendage Occluder (St. Jude Medical, Saint Paul, MN, USA)<sup>93-95</sup> received European CE Mark approval in 2013 although it is currently voluntarily withdrawn from the USA market by St. Jude. The design is similar to ACP, with a lobe-disc structure made from nitinol mesh covered by polyester patches (Figure 7). In comparison to the ACP, the Amulet is designed for superior seating whilst requiring less oversizing, with a 2-3 mm longer lobe housing stiffer, more evenly distributed and more numerous stabilizing barbs (from six pairs in ACP to 10 pairs), and longer articulating waist between the distal lobe and the proximal disc. Having larger available sizes (31 and 34mm), it is better suited for closure of larger LAA. Aimed at reducing device thrombosis, the screw facing the atrial chamber is now flush to the device, and the larger disc designed to be seated flush to the LLR and less prone to prolapsing into the ostium, which is thought to predispose to thrombus formation with the current ACP by creating a cul-de-sac with the LLR. To facilitate deployment, it now comes pre-mounted on a modified pusher cable inside the delivery system. Recently published non-randomized clinical experience in 25 patients in Europe reported successful implantation in 24, with complications of 1 device thrombosis; there were no leaks >3 mm or other complications.<sup>96</sup>

Table 1:

FDA-approved and CE mark	LARIAT
CE mark only	Amplatzer Cardiac Plug Amplatzer Amulet Transcatheter Patch Watchman (FDA-approval applied for, awaiting decision) Wavecrest
Published preclinical or human studies	Aegis Epitek (withdrawn) LifeTech LAmBRE (Phase 0 trial ongoing) Ultrasept
Others	Occlutech (Phase 1 trial registered, not yet recruiting)

#### Epitek

The Epitek (Medford, NJ, USA) multilumen system utilizes a fiberoptic endoscope, jaws to grasp the LAA visualized endoscopically, a pre-tied suture, and shape-set nitinol wire. Testing in porcine and canine models was performed from December 2006 to February 2008, leading on to early human testing where difficulties were encountered with access (achieved in 78%) and good device positioning (achieved in 41%) with subsequent development halted.<sup>92</sup>

#### LAmBRE

The Lifetech LAmBRE device (Lifetech Scientific Corp., Shenzhen, China)<sup>97</sup> has some similarities to ACP, though in place of the lobe there is a nitinol-based, fabric covered, self-expanding umbrella which is introduced into the LAA (Figure 8). The umbrella is secured within the LAA via 8 distal ball-tipped frames with side facing hooks, and articulates via a waist to a disc which orientates onto and seals the ostium. The device is deployed through a sheath, and is retrievable and repositionable. After testing in a dog model,<sup>97</sup> a feasibility and safety human study is underway (clinicaltrials.gov/

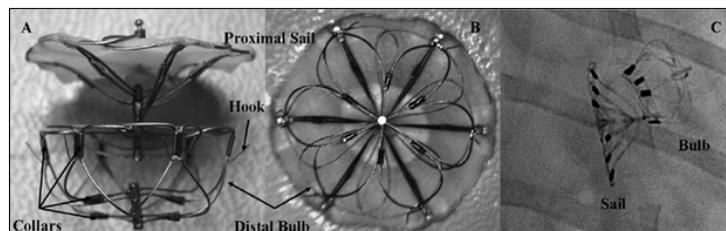


Figure:11 The Cardia Ultrasept LAA Occluder.<sup>100</sup>

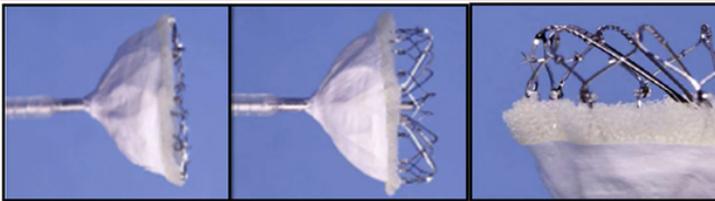
NCT01920412) and CE Mark is expected in the near future once adequate patient experience is obtained.

#### Occlutech

The Occlutech LAA Occluder (Occlutech International AB, Helsingborg, Sweden) is based on a braided nitinol frame which is introduced into the LAA (Figure 9).<sup>98</sup> The contour tapers distally to better distribute radial expansion forces and it is anchored distally with closed loops designed to engage the trabeculated LAA whilst avoiding perforation. A polymer covering seals against blood flow and promotes endothelialization. Delivery is via an endocardial sheath, and a ball-shaped connection hub allows the occluder to pivot during delivery. Sizes of 17-39 mm are available. Phase 1 feasibility and safety study has not started enrolling as yet (clinicaltrials.gov/NCT02105584). No published data using this device is available currently.

#### Transcatheter Patch

The Transcatheter Patch (Custom Medical Devices, Athens, Greece)<sup>99</sup> is also deployed endocardially within the LAA to occlude it (Figure 10). The unique features are that it is frameless, being made from bioabsorbable polyurethane foam and kept inflated by radiocontrast to diameters of 15-25 mm. It is secured within the LAA initially by polyethylene glycol glue, activated by an alkaline solution followed by a prolonged (45 minute) inflation, and over the subsequent 48 hours via fibrin formation. A 2-mm nylon loop is sutured at the bottom of the patch, and a double nylon thread is connected for retrieval purposes. The Transcatheter Patch has CE-Mark approval for the use of occlusion of heart defects in general. Feasibility in LAA occlusion was reported in 17 patients, although in 3 the patch did not attach and in 1 it was placed beyond the LAA ostium, whilst sheath thrombosis was seen in 1 patient.<sup>99</sup> There were



**Figure 12** The WAVECREST Left Atrial Appendage Occlusion System. Courtesy of Coherex Medical, Salt Lake City, UT

no strokes at 1 year follow-up.

### Ultrasept

The Cardia Ultrasept LAA Occluder (Cardia Inc, Eagan, MN) is made from a nitinol frame with a distal cylindrical anchor which is deployed endocardially within the appendage, secured therein using 12 hooks strengthened onto platinum/iridium collars, thereby providing support via a flexible articulation to a round sail made from polyvinyl alcohol foam which orientates onto and covers the ostium (Figure 11).<sup>100</sup> The stranded design of its frame reportedly increases fatigue resistance and allows fine tuning of the tension applied to the sail and anchor, the long and flexible waist allows increases positional versatility, whilst the sail is reported to be designed to minimize blood flow disturbance within the LAA.<sup>100</sup> Successful deployment in 5 dogs has been reported with complete neointimal coverage on histology at 30 days.<sup>100</sup> The device comes in five sizes for human use, based on the diameter of the distal bulb:<sup>16, 20, 24, 28</sup> and 32mm. No human data is currently published.

### Wavecrest

The WAVECREST<sup>®101</sup> Left Atrial Appendage Occlusion System (Coherex Medical Inc., Salt Lake City, UT, USA) is nitinol framed, Gore-Tex covered device (Figure 12) similar in principle to WATCHMAN but with a number of design features to overcome current WATCHMAN limitations.<sup>80, 98</sup> It has an umbrella-shaped frame designed for shallow deployment making it suitable for a wide range of appendage sizes. This is coupled with less stringent sizing criteria allowing for 3 sizes (22 mm, 27 mm, 32 mm), coverage for ostial sizes of 18-30 mm, a completely retrievable and repositionable sheath-based system, and a distal radiocontrast delivery system to guide adequate positioning. Expanded polytetrafluoroethylene (ePTFE), which has low thrombogenicity, covers the occluding cap. Safety features include 20 anchoring nitinol microtines that are extended in a controlled fashion once the device is landed, thereby limiting potential damage from abrupt release, and polyurethane foam surrounding which forms a foamed leading edge when the constrained device is unsheathed.

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%.<sup>101</sup> 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  $\leq 3$ 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 device has received CE-Mark in 2013. The pivotal US WaveCrest II trial is anticipated in 2014.<sup>98</sup>

### The Future

With the evidence supporting LAA occlusion for stroke

prophylaxis in AF, the increasingly diverse technologies becoming available for LAA ligation and exclusion, and the parallel development of medical technologies such as novel anticoagulant agents, there is an armamentarium of therapeutic options. Coupled with this, several questions have arisen and remain unanswered, including the role of LAA ligation when used in conjunction with or in place of novel anticoagulant agents, if post procedural antiplatelet agents or anticoagulants are required, the mechanism of recurrent thrombosis and late appearing leaks, the risk attributable to residual or recurrent leaks, structural remnants such as beaks, pits, and side lobes, and what the differences are with ligation versus exclusion.

For now, the current range of products allows for individually tailored therapy. For example, patients with absolute contraindications for any anticoagulation, even temporary, an epicardial technique which does not require adjunctive endocardial access may be better suited, whilst others with pericardial adhesions would be best served with an endocardial approach, and some patients may require combined approaches including with direct surgical visualization.<sup>4</sup> There is evidence that ligation, by silencing the electrical activity of the appendage,<sup>102-104</sup> may provide additional antiarrhythmic benefit in atrial fibrillation. With increased understanding of the interactions between device design, appendage anatomy, clinical risk of thrombosis, and medium to long term success of occlusion, we may recognize how specific strengths can be harnessed and geared towards the patient at hand. Ultimately, through better understanding these determinants, improved device design and deployment technique, and controlled clinical comparisons of strategies, an ideal closure approach may be realized.

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