

## Advances in Left Atrial Appendage Occlusion Strategies

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### Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide and associated with an elevated risk of thromboembolic stroke and systemic embolization. The evidence suggests that ~90% of thrombi in patients with non-valvular AF are localized to the left atrial appendage (LAA). Therefore, it seems reasonable to consider LAA exclusion in selected patients with AF for stroke prevention. LAA exclusion can be achieved through a variety of surgical and percutaneous techniques. Surgical methods include LAA amputation, ligation, clipping and stapling. Whereas percutaneous strategies consist of endocardial closure using an LAA occlusion device and epicardial LAA ligation using a snare device. Even though several trials and registries of LAA exclusion have yielded promising outcomes, at this time evidence for long term safety and efficacy seems insufficient to recommend this approach to all patients with non-valvular AF. Future prospective randomized trials are needed to assess the precise role for these therapeutic options. Furthermore, there is a paucity of data on the comparison of these strategies to the novel oral anticoagulants which also deserves further attention. This review will carefully examine the current LAA exclusion techniques and the available data.

### Introduction

Atrial fibrillation (AF) is the most commonly encountered cardiac arrhythmia worldwide. Its prevalence is estimated at ~3 million in the US but projected to increase to >10 million by 2050.<sup>1</sup> This poses a significant public health problem as AF-related stroke accounts for ~1 in every 6 symptomatic ischemic strokes. Although complete elimination of AF itself would obviously be the preferred treatment strategy, this is often not possible or difficult to achieve with catheter ablation or antiarrhythmic therapy.<sup>2</sup> Furthermore, there is no clear evidence that treatment strategies such as catheter ablation can effectively reduce the risk of systemic embolization in patients with AF. As such, oral anticoagulation (OAC) aimed at reducing the thromboembolic risk remains the mainstay in prevention of stroke in AF patients. Until recently, OAC with warfarin, a vitamin K

antagonist, was the primary therapy employed for prevention of stroke in patients with AF, yielding a relative stroke risk reduction of ~70% compared to placebo.<sup>3</sup> However, its narrow therapeutic range, need for frequent monitoring, interaction with other drugs, dietary restrictions, and risk of bleeding have led to vast underutilization of warfarin in patients at an elevated risk for stroke.<sup>4</sup>

Direct thrombin (i.e., dabigatran) and factor Xa (i.e., apixaban and rivaroxaban) inhibitors have been recently introduced with the hope of providing stroke prevention while eliminating the need for frequent monitoring, minimizing drug and dietary interactions, and bleeding risk. Pivotal prospective randomized controlled trials have confirmed that these agents are at least comparable and in some cases superior to warfarin in reducing stroke/systemic embolization risk in patients with non-valvular AF.<sup>5-7</sup> In addition, they are associated with significantly reduced risk of intracranial hemorrhage as compared to warfarin. Although promising, novel OACs are not yet entirely benign. In clinical trials, general intolerance resulting in medication discontinuation was reported in at least 20% of patients.<sup>5,6</sup> Additionally, while certain bleeding complications occur less frequently with these agents as compared with warfarin, the risk of bleeding is not completely eliminated with these agents and can be further heightened in patients receiving concomitant antiplatelet therapy.<sup>8</sup> Moreover, novel OACs are contraindicated in patients with advanced renal dysfunction – a subgroup of patients who often have elevated risk of stroke and systemic embolization in the setting of AF. Finally, clinically-proven 'antidotes' are currently not available. Thus,

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Atrial fibrillation, Device Implant, Left Atrial Appendage, Ligation, Oral Anticoagulation, Stroke

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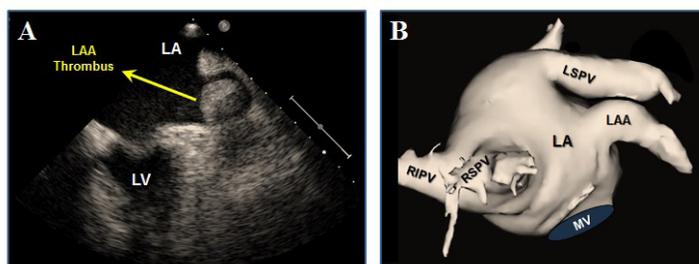


Figure 1:

Panel A, illustrates a pre-cardioversion TEE image in a patient with non-valvular AF and a large LAA thrombus. Panel B, shows a CT image of a patient with a 'chicken wing' LAA morphology. In a study of 932 patients<sup>14</sup>, prevalence of stroke was significantly lower in AF patients with this type of morphology (0.7% with 'chicken wing' versus 4.6% with 'non-chicken wing'). In addition, this was also the most prevalent LAA morphology encountered (in nearly ~50% of the cohort). Abbreviations: LA, indicates left atrium; LSPV, left superior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; and LV, left ventricle.

while novel OACs represent a paradigm shift in the treatment of patients with non-valvular AF, the described shortcomings support the ongoing need for non-pharmacologic therapies for stroke prevention in this patient population.

### The LAA and Rationale for Exclusion

It is widely believed that failure of the fibrillating atrium to contract in patients with AF can lead to atrial stretch and dilatation, in turn promoting stasis and thrombus formation (Figure 1-A) inside the LAA.<sup>9</sup> The LAA arises from the pulmonary veins and is an embryological remnant of the left atrium.<sup>10</sup> It consists of a trabeculated 2–4 cm long structure in direct continuity with the left atrium.<sup>11</sup> Its unique shape and anatomy may predispose to in-situ thrombus formation.<sup>12</sup> A review on the location of atrial thrombi in AF patients reported that 89% were localized to the LAA in patients with non-valvular as compared to 44% with valvular AF<sup>13</sup>, thus rendering this structure an attractive target for therapeutic interventions in those with predominantly non-valvular AF.<sup>9</sup> Investigation into the risk of stroke associated with a variety of LAA morphologies is also underway. While it has been suggested that the 'chicken wing' appearance (Figure 1-B) may be associated with a lower risk of stroke, none of the morphologies are believed to be associated with absence of stroke risk.<sup>14</sup> As a result, suitable techniques directed at LAA exclusion must be applicable to all LAA morphologies. Moreover, LAA exclusion techniques must be sensitive to particular anatomical challenges and the structures adjacent to the LAA. In particular, the LAA is a thin-walled compartment that can be easily disrupted resulting in cardiac perforation and tamponade. Additionally, injury to important neighboring structures such as the circumflex artery, coronary veins, and mitral apparatus could similarly lead to catastrophic consequences.<sup>15</sup>

Given the absence of current guideline recommendations, several indications for LAA exclusion may be taken into consideration. Such indications may include stroke reduction: 1) in those with absolute contraindications to OAC, 2) in patients with relative contraindications to OAC, or 3) as alternative to OAC therapy. Although LAA exclusion procedures may be well-suited for those with contraindications to OAC with limited nonrandomized data supporting this practice, it still remains unclear whether these

procedures would be appropriate as alternative therapy to OAC. To date, 3 general approaches have been devised for LAA exclusion: 1) a surgical approach aimed at amputation, ligation, or clipping of the LAA, 2) a subxiphoid percutaneous technique directed at epicardial LAA ligation, and 3) a percutaneous strategy to deploy an endovascular device inside the LAA to physically occlude this structure. Selection of a given approach will highly depend on several factors including local expertise, device availability, need for concomitant cardiac surgery, ability to access the pericardial space, and patient ability to tolerate OAC and/or antiplatelet therapy.

### Surgical LAA Exclusion

First reported in 1949, surgical LAA ligation or amputation is frequently performed in patients undergoing mitral valve (MV) surgery or as an adjunct to a surgical MAZE procedure for treatment of AF.<sup>16,17</sup> From the initial report of patients undergoing the Cox MAZE procedure, it was suggestive that surgical LAA exclusion may be effective in stroke prevention. Specifically, only 1/178 patients in this series developed a stroke during 8.5 years of follow-up even though majority of the cohort were not receiving OAC post-operatively.<sup>18</sup> Although highly suggestive, it remained unclear if this benefit was a direct result of LAA amputation, concomitant surgical ablation which restored sinus rhythm in majority of the patients, or the inherent patient stroke risk as most of the patients in this series simply had lone AF. In fact, subsequent randomized studies have failed to demonstrate a clear benefit associated with surgical LAA exclusion. To date, there have been only 2 randomized prospective trials evaluating the benefit of LAA surgical exclusion at the time of cardiac surgery. The Left Atrial Appendage Occlusion Study (LAAOS)<sup>19</sup> was a pilot study assessing stroke rates among those randomized to LAA exclusion by suture ligation (n=11) or stapling (n=33), versus no LAA exclusion at all (n= 33). Complete LAA closure was achieved in only 34% of patients, and 2.6% suffered thromboembolic events during 13 months of follow-up. Similarly, the Prague 12 Study,<sup>20</sup> a prospective randomized controlled trial involving 224 patients with AF undergoing cardiac surgery, evaluated the efficacy of surgical AF ablation with concomitant LAA excision. Although in this study there was a trend favoring AF ablation and LAA excision, still a significant reduction in stroke rate was not reached during 1 year of follow-up (2.7% versus 4.3%; p=0.319).

It may be argued that the lack of observed efficacy in these trials is due to relatively small sample sizes, short follow-up durations, and suboptimal LAA exclusion techniques. In fact, as shown in Figures 2-A and B, a fundamental limitation of surgical exclusion is that it frequently yields incomplete surgical ligation of the LAA (ISLL). Several transesophageal echocardiography (TEE) studies have reported ISLL rates ranging between 10 and 80%.<sup>17</sup> For instance, in LAAOS<sup>19</sup> successful LAA closure was only achieved in 45% of patients receiving suture ligation. Although the clinical significance of ISLL warrants further investigation, it too has been implicated in harboring intracardiac thrombi and predisposing to a higher stroke risk. For example, one study suggested that absence of complete LAA exclusion served as an independent predictor for embolic events following MV surgery.<sup>21</sup> The inability to reliably exclude the LAA surgically is related to certain factors that can inadvertently increase the complication rate of this procedure. These primarily include LAA friability and proximity to key structures such as the circumflex artery and coronary veins limiting the surgeon's ability

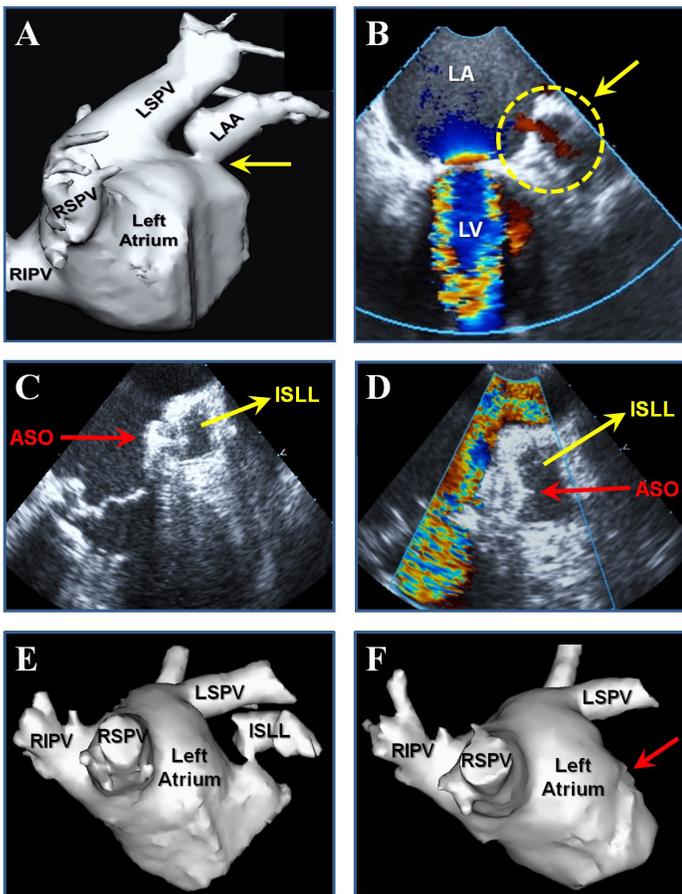


Figure 2:

Shown, are CT (A) and TEE (B) images of the left atrium and its associated structures, illustrating ISLL (yellow arrows) in a patient with a history of non-valvular AF, CHADS2 score of 3, prior MV repair and concomitant suture ligation of the LAA. As shown in panel B, there is turbulent blood flow into the ISLL (neck diameter: 7.9 mm) by color Doppler imaging (dashed circle). Panels C and D, illustrate follow-up TEE images obtained after endocardial ISLL occlusion using a 9-mm ASO device with and without color Doppler. As shown in panel D, there is absence of blood flow around the ASO device into the ISLL consistent with complete occlusion of this structure. The last 2 panels show CT images of the left atrium in another patient with ISLL (neck diameter: 3.5 mm) at baseline (E) and at 6 weeks following endocardial ISLL occlusion using a 5-mm ASO device (F). As depicted in panel F, the ISLL is completely excluded by the ASO device without residual blood flow into this structure (red arrow).

in properly placing sutures. Some have suggested that ‘over-sewing’ the LAA from within the left atrium may be the most durable approach to LAA exclusion. However, this approach requires the use of cardiopulmonary bypass and a left atrial incision which is not always performed routinely at the time of surgery. On the other hand, staple excision has been reported to be efficacious and may entirely avoid the need for a separate left atrial incision. In LAAOS<sup>19</sup> it was noted that 72% of staple LAA exclusions were complete as compared with only 45% of suture ligations. More recently, the feasibility of a minimally-invasive thoracoscopic approach has also been described.<sup>22</sup> Nonetheless, regardless of the approach, as with percutaneous methods a learning curve seems to exist with all these techniques. Evaluation of local expertise and post-operative follow-up imaging to assess the durability of LAA exclusion is mandatory. Should a residual LAA leak be identified, a decision on reinstating OAC versus an attempt at percutaneous closure will be necessary.

We recently demonstrated the safety and the feasibility of percutaneous endocardial ISLL occlusion using an Amplatzer septal occluder (ASO) device in non-valvular AF patients intolerant to long-term OAC therapy, guided by TEE and fluoroscopy (Figures 2-C and D).<sup>23</sup> It should be emphasized that in most ISLL patients the residual LAA ostial dimension measures only a few millimeters (mean in our series: 4.6 mm x 3.0 mm), thus precluding the use of conventional LAA occlusion devices. Briefly, a 0.035 inch guide wire is advanced into the ISLL via a transseptal approach. Next, a 4.0 x 20 or an 8.0 x 20 mm percutaneous transluminal angioplasty balloon catheter (EverCross, ev3 Endovascular, Inc., Plymouth, MN) is advanced inside the residual LAA over the guide wire to carefully size the ISLL neck diameter. Subsequently, the balloon and guide wire are exchanged for an ASO device (generally measuring 1–2 mm larger than the ISLL neck diameter). The device is then ‘unsheathed’ such that the distal ASO disc is deployed inside the ISLL, the waist within the neck, and the proximal disc overlying the left atrial surface. To date, serial TEE and CT angiography (Figures 2-E and F) have shown complete ISLL occlusion in all the subjects, in the absence of embolic events, without device-related thrombus during 1 year of follow-up.

#### Percutaneous Epicardial LAA Ligation

The LARIAT snare device (SentreHEART Inc., Palo Alto, CA) is a suture delivery system allowing percutaneous closed-chest epicardial LAA ligation. The LARIAT II suture delivery system currently has an FDA approval for only soft tissue ligation – but not specific for the LAA. The tools utilized for this strategy are somewhat different from other percutaneous LAA occlusion delivery systems and consist of: (i) a 14-Fr epicardial guide cannula, (ii) a 20-mm compliant balloon catheter, (iii) a 0.025” endocardial and a 0.035” epicardial magnet-tipped guide wire, (iv) a 12-Fr suture delivery system, (v) a suture tightener, and (vi) a suture cutter. Briefly, a 14-Fr epicardial guide cannula is placed inside the pericardial space after obtaining subxiphoid epicardial access via an anterior approach, based on the technique previously described by Sosa et al (Figure 3-A).<sup>24</sup> Next, the balloon catheter is positioned inside the LAA over the 0.025” magnet-tipped endocardial guide wire via a transseptal access using an 8-Fr SL1 sheath. The 0.035” magnet-tipped epicardial guide wire is subsequently advanced through the epicardial cannula such that the endocardial and epicardial guide wires are approximated. Using the epicardial wire as a monorail, the LARIAT snare is advanced and positioned over the LAA (Figure 3-B). Every effort is made to ensure capturing all LAA lobes within the snare and that the snare is placed as close to the LAA base as possible. Upon verifying proper snare position by TEE and angiography, the preloaded suture is released from the snare and tightened to completely exclude the LAA (Figure 3-D).

This strategy could offer several inherent advantages. First, the duration of systemic anticoagulation for this method of LAA exclusion may be brief. Second, the absence of a foreign device permanently implanted inside the LAA may obviate the need for post-procedural OAC. On the other hand, the principal limitation of this approach is the requirement for epicardial access – a technique that is not familiar to many operators and one that is often not possible in patients with a prior history of cardiac surgery or those with extensive pericardial adhesions. In addition, anatomical considerations are critical when determining the suitability of LAA ligation using a percutaneous

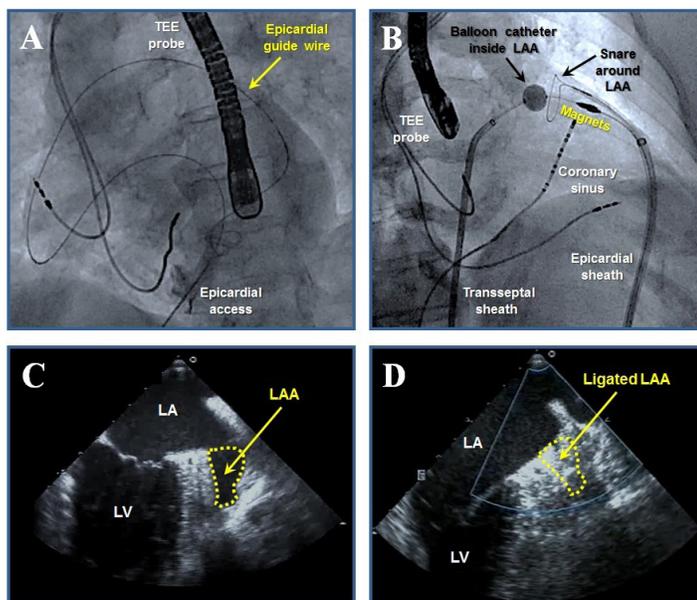


Figure 3:

Panel A, illustrates a Cine (left anterior oblique projection) during epicardial access through an anterior subxiphoid approach, during LAA ligation by the LARIAT snare device. Using this strategy a long guide wire is inserted inside the pericardial space, later replaced by a 0.035" epicardial magnet-tipped wire. Panel B, shows approximation of the magnet-tipped epicardial and endocardial guide wires. Briefly, the endocardial magnetic wire is positioned inside the LAA via a transseptal approach, over which a 20-mm balloon catheter is advanced for stabilization. Then, the LARIAT snare is advanced over the LAA using the epicardial guide wire as a monorail, and proper positioning is confirmed by TEE and angiography before final closure. Panels C and D, reveal TEE images before (C) and after (D) LAA ligation using the LARIAT snare exhibiting complete exclusion of this structure.

approach. For instance, difficulties in advancing the snare over the LAA may be encountered when attempting to ligate a posteriorly- or superiorly-directed LAA. Additionally, as the LARIAT snare loop is able to expand to a maximum diameter of 40 mm, complete closure may not be feasible in patients with larger or multi-lobed LAAs. Given the importance of anatomical considerations in device selection, our bias is to perform pre-procedural imaging with TEE and/or CT angiography to better appreciate the LAA anatomy.

In the initial experience with the LARIAT snare device, 10/11 patients with AF successfully underwent acute LAA ligation using this approach<sup>25</sup>. In a subsequent registry, after screening 119 patients with non-valvular AF 89 underwent this procedure (CHADS<sub>2</sub> score:  $1.9 \pm 0.9$ ).<sup>26</sup> Screening failure occurred due to presence of unsuitable LAA anatomy, LAA thrombus, or pericardial adhesions precluding successful epicardial access. LAA ligation was observed acutely in 96% of 85 patients and in 98% of 65 patients with available TEE data at 1 year. Despite this outcome, 55% of patients were still maintained on warfarin at 1 year. Altogether, 3 access-related complications occurred, as well as 2 cases of severe post-operative pericarditis, 2 unexplained deaths, and 2 late strokes presumed to be non-embolic. The predictors and significance of incomplete LAA ligation with a persistent leak are currently unknown. Initial work has not suggested an increase risk in adverse events with a leak jet of <3 mm. However, our own personal experience in patients with ISLL and residual leaks of 2–3 mm following surgical ligation suggests otherwise. Furthermore, the role of short-term post-procedural OAC to allow

endothelialization of residual leaks, management of ongoing leaks, and the potential lack of sustained and durable suture ligation all remain unclear given the limited follow-up and number of patients undergoing this procedure.

### Endocardial LAA Occlusion

Unlike surgical and percutaneous ligation techniques, endocardial LAA occlusion involves deployment of a device inside the LAA in an attempt to completely occlude it while leaving it intact. Prior to the availability of specific LAA occlusion devices the ASO device was employed in an "off-label" manner with some success.<sup>27</sup> However, the PLAATO was the first device particularly designed for endocardial LAA occlusion (Figure 4-A). Despite preliminary clinical experience supporting its potential efficacy,<sup>28</sup> this device was withdrawn from the market due to commercial reasons. Presently, 3 devices specifically designed for endocardial LAA closure are clinically available or under investigation, including: (i) the Amplatzer Cardiac Plug (ACP) device which will soon be replaced by the next generation Amplatzer Amulet LAA occluder device (St. Jude Medical, Inc., Plymouth, MN), (ii) the Watchman LAA closure device (Boston Scientific Corp., Natick, MA), and (iii) the WaveCrest LAA occluder device (Coherex Medical, Inc., Salt Lake City, UT). None of these devices have yet been approved by the FDA. However, the ACP, the Amulet, and the Watchman devices have all received the CE mark and are being utilized clinically in Europe. Each system has unique features but the implant methods are quite similar. These devices are delivered via a transseptal approach under TEE or intracardiac echocardiography. A specific delivery system has been devised for each device type allowing for its collapse, repositioning, or removal in the event of suboptimal results.

#### The ACP Device

The ACP device is constructed from a nitinol mesh and Dacron, consisting of a lobe and a disk connected by a waist (Figure 4-B). The sizes of the lobes range between 16–30 mm and there are 12

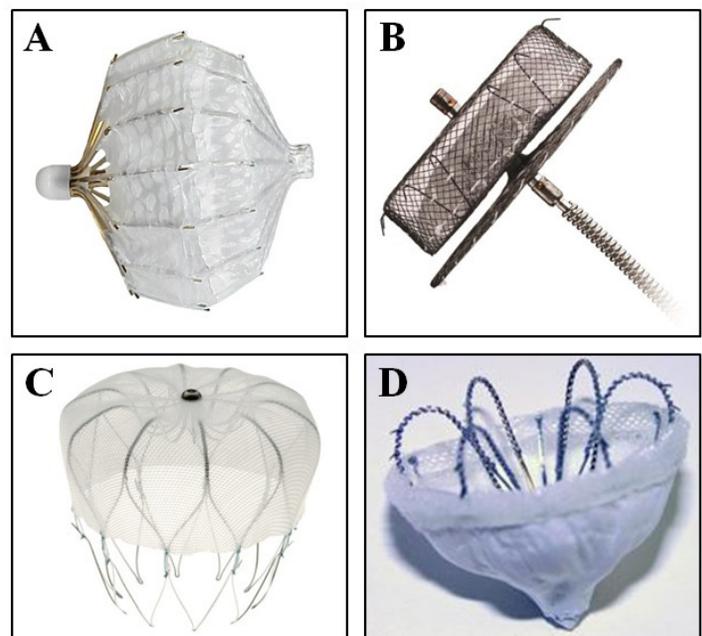


Figure 4: Shown, are the PLAATO (A), the ACP (B), the Watchman (C), and the WaveCrest (D) LAA occluder devices.

stabilizing wires equally spaced about the main disc. The lobe is designed to conform to the inner LAA wall with a depth of 10 mm or more to secure placement of the device. The Amulet device was redesigned with a longer waist and lobe and a larger disc size. The size of the device should be at least 2 mm greater than the diameter of the LAA landing zone. The device may be retrieved and redeployed. Successful device deployment is generally confirmed by TEE. To date, several small registries have reported on the safety and efficacy of the ACP device.<sup>29–32</sup> In the initial experience with the ACP, LAA occlusion was attempted in 137 AF patients with a technical success rate of 96%.<sup>33</sup> Dual antiplatelet therapy (aspirin and clopidogrel) was recommended for 1–3 months followed by aspirin alone for 5 months. Serious complications occurred in 7%, including 3 ischemic strokes, 2 device embolizations, and 5 serious pericardial effusions; while minor complications occurred in 5%. A subsequent European post-market registry including 204 non-valvular AF patients (CHADS<sub>2</sub> score:  $2.6 \pm 1.3$ ),<sup>34</sup> reported a 97% implant success rate and a 99% LAA closure rate at 6 months. Serious complications included pericardial effusion (1.5%), device embolization (1.5%), and device-related thrombus (2.4%). The observed stroke rate during follow-up was 1.98%, suggesting possibly a 65% relative stroke risk reduction estimated based on this cohort's predicted stroke risk. A pivotal, prospective randomized multicenter controlled trial is presently under way to compare this device head-to-head to long-term OAC with warfarin or dabigatran in a 2:1 randomization scheme.

#### The Watchman LAA Closure Device.

The Watchman LAA closure device is a self-expanding nitinol frame structure with fixation barbs and a 160  $\mu$ m thick polyethylene membrane that covers the left atrial surface of the device (Figure 4-C). The device is available in 5 different sizes ranging from 21–33 mm, and normally selected to be 10–20% larger than the LAA diameter to ensure stable positioning. The safety and feasibility of the Watchman was initially evaluated in a pilot study involving 75 patients with AF, demonstrating an implant success rate of 88%.<sup>35</sup> Complications occurred in ~1/3 of the patients treated with the first-generation device including device embolization, delivery system failure, incorrect positioning requiring surgical explantation, and air embolism. The device and delivery system were consequently redesigned and as a result no further device embolization was observed in the successive 53 patients.<sup>35</sup>

The PROTECT AF trial was a multicenter randomized controlled trial that prospectively compared the Watchman to warfarin.<sup>36</sup> To date, this is the only published randomized prospective study evaluating percutaneous LAA exclusion against OAC therapy. In this study, 707 non-valvular AF patients (CHADS<sub>2</sub> score:  $2.2 \pm 1.2$ ) from US and Europe were randomized to the WATCHMAN or warfarin in a 2:1 fashion. Patients who received the Watchman device were treated with warfarin for 45 days post-implant to allow device endothelialization, thereby facilitating resolution of residual peri-device leaks. Warfarin was subsequently replaced with 6 months of clopidogrel and lifelong aspirin in 86% of patients. At 12 months, 93% of Watchman recipients were permanently off OAC. The trial showed that LAA occlusion using the Watchman was non-inferior to warfarin with regards to the primary composite endpoints of ischemic/hemorrhagic stroke, cardiovascular/unexplained death or systemic embolization during 18 months of follow-up. However, the trial was underpowered with respect to the endpoint of ischemic

stroke itself. On the other hand, implantation of the Watchman did carry a substantial procedural risk.<sup>36</sup> Among 449 attempted Watchman implants, 12.3% had serious procedural complications including pericardial effusion requiring drainage/surgery in 5% and acute ischemic stroke due to air/thromboembolism in 1%. Four patients required device removal due to device embolization or post-implant sepsis.

An analysis of the nonrandomized Continued Access Protocol (CAP) registry including 460 non-valvular AF patients demonstrated significant improvements in the safety of the Watchman with operator experience.<sup>37</sup> These findings are also consistent with the PLAATO experience which showed that increasing operator experience was associated with reduced procedural complications.<sup>28</sup> More recently, the 4-year results of the PROTECT AF trial were reported,<sup>38</sup> demonstrating a 40% reduction in the primary composite endpoints favoring the Watchman (Figure 5-A). This benefit was

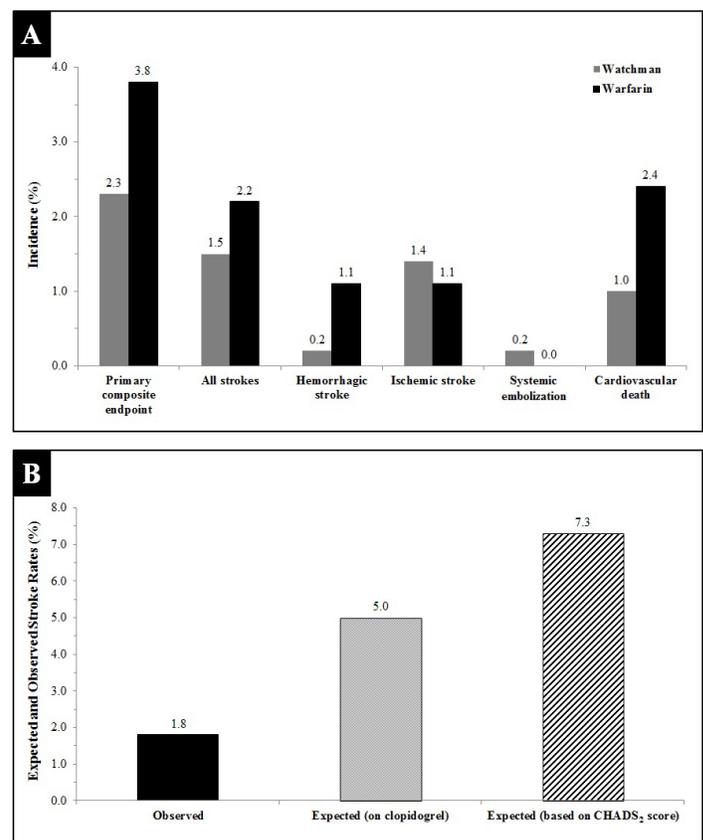


Figure 5:

Panel A, depicts a graphical illustration of the 4-year follow-up data from the PROTECT AF trial. As shown, Watchman implantation was associated with a reduction in the primary composite endpoints of ischemic/hemorrhagic stroke, cardiovascular/unexplained death or systemic embolization (2.3% versus 3.8%), as compared to warfarin. This benefit was primarily driven by a decrease in the hemorrhagic stroke risk (0.2% versus 1.1%) and cardiovascular death (1.0% versus 2.4%) in the Watchman arm. The rates of ischemic stroke (1.4% versus 1.1%) and systemic embolization (0.2% versus 0%) were on the other hand similar between the 2 groups. Panel B, illustrates the results from the ASAP registry. As shown, the overall stroke rate in this registry was 1.8% (observed). But assuming expected stroke rates of 5.0% (based on therapy with clopidogrel) and 7.3% (based on the cohort's mean CHADS<sub>2</sub> score of 2.8), this could suggest an ischemic stroke risk reduction by 64 and 75%, respectively.

driven primarily by an 85% decrease in the long-term hemorrhagic stroke risk and 60% reduction in cardiovascular death (34% all-cause mortality). However, rates of ischemic stroke and systemic embolization were similar between the 2 groups.

The PREVAIL trial was the second prospective randomized trial using the Watchman device including 269 non-valvular AF patients (CHADS<sub>2</sub> score: 2.6 ± 1.0).<sup>39</sup> The full details of this study are not yet published in a peer-reviewed journal. However, preliminary analysis suggests that the study met its first and third co-primary endpoints of acute safety and late ischemic stroke and systemic embolization at 18 months. But interestingly, the observed stroke rate in PREVAIL was strikingly low for both the device and the warfarin arms (0.7%), highlighting the necessity of adequately-powered randomized controlled trials to allow meaningful comparisons (Table 1). Meanwhile, the necessity of short-term OAC with warfarin following device implantation as practiced in the PROTECT and PREVAIL trials was examined in the ASA Plavix (ASAP) registry,<sup>40</sup> which reported on 150 AF patients (CHADS<sub>2</sub> score: 2.8 ± 1.2) with contraindications to OAC receiving the Watchman. All patients were treated with 6 months of clopidogrel and lifelong aspirin. The observed reduction in ischemic stroke rate during 14 months of follow-up was 77% fewer than predicted by the CHADS<sub>2</sub> risk stratification scheme (Figure 5-B).<sup>40</sup> Lastly, a follow-up study demonstrated that residual flow into the LAA following percutaneous closure with the Watchman can be encountered in as many as 32% of patients at 1 year.<sup>41</sup> But despite this, presence of residual peri-device leak was not associated with an increased risk of embolic events in this cohort.

#### The WaveCrest LAA Occluder Device

The Coherex WaveCrest LAA occluder device is the latest addition to the list of endocardial LAA occlusion devices. It is composed of a nitinol frame covered by a non-thrombogenic expanded polytetrafluoroethylene membrane (Figure 4-D). The device is available in 3 sizes: 22, 27 or 32 mm. The current experience with this device consists of a single nonrandomized registry involving 63 patients with non-valvular AF (mean CHADS<sub>2</sub> score: 2.5).<sup>42</sup> All patients were treated with dual antiplatelet therapy for 90 days post-implant, followed by lifelong aspirin. LAA occlusion was successfully achieved in 58/60 patients at 45 days, based on the criteria of ≤3 mm of residual peri-device flow and no residual leak >5 mm. A CE mark is presently anticipated for this device.

#### Complications

Major complications related to implantation of LAA occlusion devices are primarily related to the procedure itself, and associated with inexperience. For instance, the rate of major pericardial effusion and tamponade was 50% higher at less-experienced centers, as noted in the PROTECT AF study.<sup>37</sup> Aside from vascular complications, acute ischemic stroke due to air or thromboembolism, device embolization, or sepsis may also occur. Finally, as with any foreign body implant, device-related infection also remains a concern.

#### Limitations of the Available Data on the Use of Endocardial LAA Occlusion

It is clear that endocardial LAA occlusion devices will likely play an important role in prevention of stroke in the future. However, several limitations prevent us from broadly extrapolating the clinical results of the existing 'non-inferiority' clinical trials to justify their

**Table 1:** A comparison of various LAA exclusion trials and registries.

Clinical trial or registry	n	Implant success (%)	CHADS <sub>2</sub> score	Procedural complication (%)	Stroke/systemic embolization (per 100 patient years)
<b>Watchman LAA closure device</b>					
*PROTECT AF <sup>36</sup>	463	91	2.2	10.4	3.0
CAP registry <sup>37</sup>	566	94	2.5	5.5	3.0
*PREVAIL <sup>39</sup>	269	95	2.6	4.4	0.7
ASAP registry <sup>40</sup>	150	94	2.8	8.7	2.3
<b>ACP device</b>					
Initial European registry <sup>33</sup>	137	96	2.6	12.4	2.1
Post-market registry <sup>34</sup>	204	97	2.6	5.4	2.0
LARIAT snare device <sup>28</sup>	89	96	1.9	7.9	2.2

\*Denotes multicenter prospective randomized controlled trial; all others represent registries

widespread use as a substitute for OAC therapy.

#### What is the Significance of Residual Peri-Device Leak?

As mentioned previously, presence of incomplete LAA closure following prior surgical ligation has been associated with increased embolic risk. A study of 205 patients who underwent MV replacement with and without LAA ligation, suggested that absence of LAA exclusion served as an independent predictor for embolic events following MV surgery with an odds ratio of 6.721. Other reports have even suggested that presence of ISLL may actually be worse than no occlusion at all; given that reduced blood flow velocities in and out of the ISLL may in fact promote a higher risk of thrombus formation.<sup>23,43,44</sup> Consistent with this, several patients in our own ISLL series suffered embolic strokes shortly after incomplete LAA surgical ligation (within 3 weeks).<sup>43</sup> Surprisingly, all these patients had history of long-standing non-valvular AF without prior embolic events, at a low predicted thromboembolic risk (CHADS<sub>2</sub> score ≤1), and on antiplatelet therapy at the time of their stroke. Of note, all 3 patients had developed acute stenosis of the LAA ostia following surgical ligation with markedly tapered ISLL necks measuring only 2–3 mm. In fact, these were among the most constricted ISLL neck diameters observed in our series. These observations are obviously in sharp contrast to the reported findings from the PROTECT AF trial using the Watchman which suggested that presence of peri-device leak was not associated with an increased embolic risk during long-term follow-up.<sup>41</sup> As such, at this time it remains unclear whether peri-device leaks require ongoing OAC for stroke prevention.

#### Is there need for a 'Superiority trial' to Compare LAA Exclusion Techniques to OAC?

The development of novel OACs has led to a new era in stroke management. As already discussed, several large randomized controlled trials have demonstrated the superiority of novel OACs to warfarin with respect to prevention of stroke and systemic embolization (Table 2). In addition, all novel OACs are associated with a significantly lower risk of hemorrhagic stroke and intracranial hemorrhage. Since the principal value of LAA exclusion also lies in its sustained, long-term reduction of hemorrhagic stroke risk, this benefit could be considerably attenuated if compared against novel OACs. Thus, all future LAA exclusion studies must include not only head-to-head comparisons against warfarin but also these approved novel therapies. In addition, given the decreasing stroke rate with

**Table 2: A comparison of prospective randomized controlled trials evaluating novel OACs.**

Clinical trial	n	CHADS <sub>2</sub> score	Stroke or systemic embolization per year (%)	Hemorrhagic stroke per year (%)	Mortality per year (%)	Median follow-up (years)
<b>RE-LY<sup>6</sup></b>						
Dabigatran	12,091	2.1	1.1*	0.1*	3.6	2.0
Warfarin	6,022	2.1	1.7	0.4	4.1	2.0
<b>ROCKET AF<sup>6</sup></b>						
Rivaroxaban	7,131	3.5	2.1**	0.5*	4.5	1.9
Warfarin	7,133	3.5	2.4	0.7	4.9	1.9
<b>ARISTOTLE<sup>7</sup></b>						
Apixaban	9,120	2.1	1.3*	0.2*	3.5*	1.8
Warfarin	9,081	2.1	1.6	0.5	3.9	1.8

\*p < 0.05 for superiority when compared to OAC with warfarin

\*\*p < 0.05 for non-inferiority when compared to OAC with warfarin

time, such studies should be adequately powered to assess for non-inferiority and/or superiority.

### Is LAA Exclusion Cost-Effective?

The economic impact of LAA exclusion also warrants further investigation in various healthcare systems. Recently, an economic evaluation of LAA occlusion with the Watchman was compared with warfarin and dabigatran, using a microsimulation model based on 10,000 non-valvular AF patient iterations in the setting of universal public healthcare in Ontario, Canada<sup>45</sup>. In this study, therapy with warfarin was associated with the lowest discounted quality adjusted life expectancy (4.55 years) followed by dabigatran (4.64), while LAA occlusion had the greatest survival (4.68). The average discounted lifetime costs were \$21,429 CDN for warfarin, \$25,760 CDN for dabigatran, and \$27,003 CDN for LAA occlusion. As a result, compared with warfarin, the incremental cost-effectiveness ratio was \$46,560 for dabigatran and \$41,565 for LAA occlusion. Sensitivity analysis demonstrated LAA occlusion was cost-effective compared to warfarin in 43% of the simulations with a willingness to pay a threshold of \$50,000 CDN, and 47% of the simulations with a willingness to pay a threshold of \$100,000 CDN. The uncertainty in the model reflected parameter uncertain – the risk reduction of stroke with LAA occlusion being most important. The uncertainty in the absolute risk of ischemic stroke with LAA occlusion is also reflected in the variability in stroke rates observed in the PROTECT AF, ASAP, and PREVAIL trials (3.0, 2.3, and 0.7 per 100 patient years, respectively). Larger studies with longer follow-up may allow for more accurate examination of stroke risk reduction by LAA occlusion. In addition, further analyses in other health systems are equally essential to better define these variables and to allow firm conclusions regarding the cost-effectiveness of these interventions in various healthcare models.

### Is the LAA the Only Culprit for Stroke in Non-Valvular AF Patients?

It should be emphasized that non-LAA causes of stroke have also been reported in up to 50% of non-valvular AF patients<sup>46</sup>, indicating that non-LAA embolic sources can play a significant role in these patients. For instance, in the SPAFI, II, and III trials,<sup>47–49</sup> 32% of the 217 strokes in patients with non-valvular AF were classified as non-cardioembolic. In SPAFI III<sup>18</sup>, 57% of patients were found to have

additional significant risk factors for stroke such as atherosclerotic plaque in the aorta; whereas in the absence of such risk factors the stroke risk was as low as 1.2% per year.<sup>50</sup> Thus, it remains unclear whether OAC could also provide additional benefits in reducing non-LAA-related stroke risk otherwise not provided by mechanical LAA exclusion.

### Future Directions

A search of clinicaltrials.gov with the term “left atrial appendage” reveals at least 6 clinical studies actively recruiting patients to evaluate the role and efficacy of surgical or percutaneous LAA exclusion. Publication of the outcomes from the recently completed and currently ongoing trials will better define the role for LAA exclusion techniques in stroke prevention in patients with non-valvular AF. Necessitated extensions of this work must also include comparisons of various LAA exclusion strategies to novel OACs as well as catheter ablation of AF. As novel OACs have demonstrated superiority with respect to intracranial bleeding,<sup>5–7</sup> stroke,<sup>5,7</sup> and even death<sup>7</sup> compared to warfarin, it is quite possible that these agents may attenuate differences observed in the bleeding/complication risk between LAA exclusion and warfarin therapy. Thus, some may argue that this coupled with the suggestion of a mortality benefit could in fact favor the use of novel OACs over LAA exclusion. Given the hazards of indirect comparisons, we would strongly support a prospective randomized clinical trial of LAA exclusion to novel OACs to address these uncertainties.

Finally, recent work has also suggested that successful catheter ablation of AF may dramatically reduce stroke risk in some patient with non-valvular AF.<sup>51–54</sup> Should this be validated, catheter ablation could then provide both symptomatic improvement and stroke reduction in certain patients with non-valvular AF. The merit of this strategy compared to LAA exclusion will be prospectively evaluated in the Interventional Strategies in Treatment of Atrial Fibrillation: Percutaneous Closure of the Left Atrial Appendage Versus Catheter Ablation (ISAR-AF) clinical trial (ClinicalTrials.gov identifier: NCT01363895). Given the increasingly low rates of ischemic stroke reported in the recent trial of novel OACs, sample sizes must be sufficiently large to allow detection of superiority of one strategy over another.

### Conclusions:

Over the past two decades, various catheter-based cardiac electrophysiology procedures have been pioneered and perfected, in some cases successfully replacing the need for pharmacologic therapy in patients with cardiac rhythm disorder. It would be remarkable to achieve similar outcomes with respect to stroke risk reduction through LAA exclusion technologies in patients with non-valvular AF. While the preliminary work seems encouraging, it is by far not definitive. Despite more than 6 decades of experience with surgical LAA exclusion, there have only been 2 randomized prospective trials evaluating the surgical techniques – both of which have demonstrated lack of efficacy with regards to stroke risk reduction. On the other hand, the combined total number of patients randomized in the 2 prospective clinical trials of endocardial LAA occlusion (~1,000 patients in PROTECT AF and PREVAIL) is >1 order of magnitude less than the number of subjects enrolled in each of the pivotal, prospective randomized controlled trials of novel OACs (RE-LY ~18,000 patients, ARISTOTLE ~18,000 patients, and ROCKET AF ~14,000 patients). While no direct comparisons

of LAA exclusion and novel OACs exist thus far, this may indeed be a more appropriate comparison when assessing the merits of stroke prevention in patients without contraindications to OAC. Lastly, the significance of incomplete LAA closure by either ligation or device occlusion deserves further examination.

For now, additional forthcoming data and well-designed clinical trials are mandatory to better position LAA exclusion technologies in our armamentarium of tools for stroke prevention in patients with non-valvular AF. Given the importance of appropriateness of healthcare interventions and lessons learnt from other cardiac interventions such as drug-eluting stents and defibrillator leads, cardiac electrophysiologists must critically evaluate the precise role of LAA exclusion technologies in the treatment of patients with non-valvular AF.

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