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Chapter

Left Atrial Appendage Occlusion: Current and Future

Dian Andina Munawar, Anggia Chairuddin Lubis and Muhammad Munawar

Abstract

Patients with non-valvular atrial fibrillation (NVAF) are at an increased risk of ischemic stroke due to the risks of thrombus formation. The left atrial appendage (LAA) is shown to be “the culprit” of thromboembolic events in NVAF and is currently a therapeutic target to prevent stroke. The absolute benefit of oral anticoagulation in the management of NVAF to improve cardiovascular outcomes has been well established. However, some patients are not good long-term candidates for oral anticoagulation for many reasons, including risks of bleeding, noncompliant to oral anticoagulation (OAC). Left atrial appendage occlusion (LAAO) provides an attractive alternative to reduce the risk of stroke for those who are contraindicated to OAC therapy.

Keywords: atrial fibrillation, left atrial appendage closure, left atrial appendage device, ischemic stroke, oral anticoagulation

1. Introduction

In patients with non-valvular atrial fibrillation (NVAF), oral anticoagulation (OAC) is part of mainstream therapy to prevent ischemic stroke [1], and the left atrial appendage (LAA) remains a focus of thrombus formation [2]. However, there are several situations that oral anticoagulation may be unsuitable, due to any individual history of major bleeding, personal risks of bleeding (e.g., fall risk in elderly or cerebral anomalies), noncompliant patients to OAC, or patients with high-risk occupation. Left atrial appendage occlusion (LAAO) has emerged as an alternative management to prevent stroke in NVAF patients who are not eligible for continuous OAC [3].

2. Left atrial appendage anatomy

The embryonic origin of LAA is different to atria. It is originated from the embryonic remnant of left atrium (LA) during first trimester, with a multilobed structure positioned anteriorly in the atrioventricular sulcus close to the left circumflex artery, the left phrenic nerve, and the left pulmonary veins [4]. The appendage contains numerous trabeculae, with a complex and highly variable anatomy. The LAA typically consists of three major components:
a. Ostium or “os,” which defines its junction with body of the LA;

b. Lobar region, which is known to be the most variable anatomically. The difference of lobar region of LAA as seen by computed tomography angiography (CTA) is categorized into: (1) chicken wing; (2) cactus; (3) windsocks; and (4) cauliflower. It has been shown that the difference in the LAA morphology was independently associated with thromboembolic events [5, 6]. The first type of chicken-wing LAA can be a challenge for device implantation; [7] however, it has been associated with a lower stroke risk compared with the other three main morphologies described [8]. Multiple lobes with LAA greater than 40 mm will limit the use of certain devices. Deployment of LAAO device will be difficult for LAA with multiple lobes with branching close to ostium.

c. “Neck” is a narrow junction between the ostium, lobar region, and the landing zone for LAAO device. The size of the neck determines the applicability to use of certain occlude devices. The Watchman requires an equivalent implant depth and the device diameter. The Amplatzer device requires 10 mm space for deployment from the ostium [7].

3. Rationale for LAAO

Thromboembolic events in AF are correlated to loss of atrial contraction, stasis of blood flow, and thrombus formation, particularly in the LAA. The LAA is notoriously labeled as “human most lethal attachment,” as it has been demonstrated that thrombus in the LAA is the primary source for thromboemboli [2]. A review of studies in patients with nonrheumatic heart disease demonstrated that 90% of LA thrombi examined by transesophageal echocardiography (TEE), cardiac surgery, or autopsy, were located in the LAA [9]. Another study also showed that LA thrombus was evident in 15% of patients without OAC after 48 hours of AF, in which almost all thrombi were found in LAA. The LAA is particularly prone to thrombus formation in AF due to its inherent anatomy with extensive trabeculations, increased blood stasis and hypercoagulability, and endothelial damage [10].

The role of the LAA as a source for thromboemboli in AF patients provides the rationale for ligation, amputation, or occlusion of the LAA structure, especially if patients are indicated for stroke prevention strategy; on the other hand, they are either contraindicated or noncompliant to long-term OAC. In addition, some LAAO techniques may have an additional role in sinus rhythm maintenance through non-pulmonary vein triggers elimination, atrial mass decrease, and atrial electrical remodeling reversion [11, 12].

4. Techniques for LAAO

Currently, there are two major different strategies in LAA exclusion from systemic circulation:

4.1 Surgical approach

The first reported resection of LAA in a human was by John Madden in 1949 [13]. In his report, he performed surgical excision of LAA structure during open
heart surgery specifically aimed for stroke prevention in AF patients. This approach was not routinely done after this report was published. Nevertheless, LAA surgical closure is now class IIa indication in the 2020 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for management of patients with valvular heart disease undergoing heart surgery [14] and has currently become widely performed. Similarly, in patients with AF undergoing cardiac surgery, surgical LAA closure is also a class IIb indication based on 2019 ACC/AHA/Heart Rhythm Society (HRS) guidelines [15].

The method of LAA exclusion is usually dictated by the concomitant cardiosurgical procedure.

**4.2 Percutaneous LAAO device**

To date, several LAAO devices have been approved to be used worldwide (Figure 1).

### 4.2.1 Endocardial system

a. the Watchman (Boston Scientific, Natick, MA)

This device has been approved by the Federal Drug Administration (FDA) in the year of 2015 as an alternative to warfarin OAC based upon data from the PREVAIL and PROTECT-AF trials. The device system comprises of a 14 Fr (outer diameter), frame with fixation barbs, and fabric cover [16].

b. the Amplatzer Cardiac Plug/ACP (St. Jude Medical, St. Paul, MN)

The Amulet is a second-generation self-expanding LAAO. The device system includes 14.4–16.5 Fr delivery sheath, lobe and stabilization hook, and fixed-size cover disk [16].

<table>
<thead>
<tr>
<th>Endocardial</th>
<th>Epicardial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplatzer</td>
<td></td>
</tr>
<tr>
<td>Watchman</td>
<td></td>
</tr>
<tr>
<td>Lambre</td>
<td></td>
</tr>
<tr>
<td>Lariat</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.**

LAAO devices (modified from [10, 16–18]).
c. LAmbre™ LAA Closure System (Lifetech Scientific Corporation)

LAmbre occluder is a Conformité Européenne (CE) recognized LAA closure device. It is a self-expanded device consisting of a 10.4–12.3 Fr sheath (delivery system), hook-embedded umbrella, and size adaptive cover [19]. In 2020, LAmbre™ LAA Closure System has obtained the approval by FDA for the commencement of an investigator-initiated clinical trial in the United States.

4.2.2 Epicardial system

a. the LARIAT suture delivery system (SentreHeart, Redwood City, CA)

The LARIAT device is a percutaneous epicardial ligation of the LAA. The device comprises of a snare with a pre-tied suture for LAA ligation, a 15-mm compliant occlusion balloon catheter, magnet-tipped guidewires, and a 12-F suture delivery device.

5. Indications and current recommendation

Indication for LAAO occlusion procedure is similar to standard indication of OAC in patients with AF. The need of OAC is justified by stroke risk factors that are summarized in the clinical risk-factor-based on established CHA₂DS₂-VASc score [Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke, Vascular disease, and Sex category (female)]. However, when initiation of OAC strategy, individual potential risk of bleeding also needs to be assessed (Table 1).

<table>
<thead>
<tr>
<th>Non-modifiable</th>
<th>Potentially modifiable</th>
<th>Modifiable</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age &gt; 65 years</td>
<td>• Extreme frailty ± excessive risk of falls</td>
<td>• Hypertension/elevated SBP</td>
<td>• GDF-15</td>
</tr>
<tr>
<td>• Previous major bleeding</td>
<td>• Anemia</td>
<td>• Concomitant antiplatelet/NSAID</td>
<td>• Cystatin C/CKD-EPI</td>
</tr>
<tr>
<td>• Severe renal impairment (on dialysis or renal transplant)</td>
<td>• Reduced platelet count or function</td>
<td>• Excessive alcohol intake</td>
<td>• cTnT-hs</td>
</tr>
<tr>
<td>• Severe hepatic dysfunction (cirrhosis)</td>
<td>• Renal impairment with CrCl &lt; 60 mL/min</td>
<td>• Non-adherence to OAC</td>
<td>• von Willebrand factor</td>
</tr>
<tr>
<td>• Malignancy</td>
<td>• VKA management strategy</td>
<td>• Hazardous hobbies/occupations</td>
<td>• other coagulation markers</td>
</tr>
<tr>
<td>• Genetic factors (e.g. CYP 2C9 polymorphisms)</td>
<td>•</td>
<td>• Bridging therapy with heparin</td>
<td></td>
</tr>
<tr>
<td>• Previous stroke, small-vessel disease, etc.</td>
<td>•</td>
<td>• INR control (target 2.0–3.0), target TTR &gt; 70%</td>
<td></td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
<td>•</td>
<td>• Appropriate choice of OAC and correct dosing</td>
<td></td>
</tr>
<tr>
<td>• Cognitive impairment/ dementia</td>
<td>•</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CrCl = creatinine clearance; cTnT-hs = high-sensitivity troponin T; CYP = cytochrome P; GDF-15 = growth differentiation factor-15; INR = international normalized ratio; NSAID = non-steroidal anti-inflammatory drug; OAC = oral anticoagulant; SBP = systolic blood pressure; TTR = time in therapeutic range; VKA = vitamin K antagonist.*

Table 1.
Risk factors for bleeding with OAC and antiplatelet therapy (ESC guidelines 2020) [1].
There are few absolute contraindications that potentially prevent some patients to have OAC as stroke prevention therapies. These include active major bleeding with unidentified and untreated source, comorbidities [e.g., severe anemia (Hb<80 g/L) or thrombocytopenia (<50 platelets/microliter)], or a high-risk bleeding episode such as intracranial hemorrhage. In such cases, non-drug options such as LAAO should be considered. Based on current existing guidelines, the recommendations of LAAO as stroke prevention option are:

5.1 Percutaneous approaches

Currently available recommendation for percutaneous LAAO is described in Table 2. According to 2020 ESC guidelines for Atrial Fibrillation, recommendations for antithrombotic therapy after LAAO are mentioned in Table 3 [1].

5.2 Surgical approaches

Table 4 shows current available recommendation for surgical LAA excision/occlusion approach.

<table>
<thead>
<tr>
<th>Device/patient</th>
<th>Aspirin</th>
<th>OAC</th>
<th>Clopidogrel</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchman/low bleeding risk</td>
<td>75–325 mg/day indefinitely by TOE</td>
<td>Start warfarin after procedure (target INR 2–3) until 45 days or continue until adequate LAA sealing is confirmed. NOAC is a possible alternative</td>
<td>Start 75 mg/day when OAC stopped, continue until 6 months after the procedure</td>
<td>Some centers do not withhold OAC at the time of procedure (no data to support/deny this approach)</td>
</tr>
<tr>
<td>Watchman/high bleeding risk</td>
<td>75–325 mg/day indefinitely</td>
<td>None</td>
<td>75 mg/day for 1–6 months while ensuring adequate LAA sealing</td>
<td>Clopidogrel often given for shorter time in very high-risk situations</td>
</tr>
<tr>
<td>ACP/Amulet</td>
<td>75–325 mg/day indefinitely</td>
<td>None</td>
<td>75 mg/day for 1–6 months while ensuring adequate LAA sealing</td>
<td>Clopidogrel may replace long-term aspirin if better tolerated</td>
</tr>
</tbody>
</table>

Table 2. Current recommendation for percutaneous LAAO.

Table 3. Anti-thrombotic recommendation after LAAO.
6. Post-procedural management and complications of percutaneous LAAO

6.1 Acute procedural-related complications

i. Access-related complications

The most common complication for percutaneous LAA closure is the risk of having vascular complications, including bleeding or hematoma in the groin, arteriovenous fistula, pseudoaneurysm, or retroperitoneal bleed. Some of these complications may require further intervention or blood transfusion. These risks are slightly higher than other interventional procedure, especially due to large delivery sheath used, and the procedure is commonly performed under oral anticoagulation [21]. Furthermore, frailty or tortuosity in the vascular anatomy is also very common in elderly patients [22].

ii. Transeptal access-related complications

There are few complications that can be related to transeptal access. Large delivery sheath for this procedure increases the risk of air embolism and subsequently increases the risk of stroke or myocardial infarction. In addition, transeptal puncture is also correlated with increased risk of pericardial effusion or tamponade that may require pericardiocentesis, with incidence of 1.39% [22, 23]. The risk of incidental aortic puncture from transeptal was also reported, which was closed by percutaneous approach with Amplatzer Septal Occluder [24].

iii. Device embolization

Due to anatomical variability of LAA, the risk of embolization of LAAO is higher. The incidence of LAA device embolization ranges between 0% and 2%. Recent reports suggest that The Amplatzer family of devices carries a higher risk of
embolization as compared with the Watchman device, with incidence of 0.78% (3,585 patients) vs. 0.26% (7,236 patients); p < 0.001) [25]. Device embolization can be located either in the LA, left ventricle (LV), or aorta (Ao). Although the majority cases can be managed in semi-elective manner, some can be life-threatening and need emergency procedure. Limited data of secondary adverse events related to LAA device embolization such as mitral or aortic valve damage, LV outflow tract obstruction, cardiogenic shock, or death have been described [26]. Percutaneous retrieval is preferable as compared with surgical approach. Identification of the location of the embolized device is crucial to determine the retrieval strategy. Successful retrieval using percutaneous snare has been reported [27]. However, several complications such as iatrogenic aortic rupture requiring endovascular repair may occur [28].

iv. Other complication

Complications related to traumatic damage to surrounding structures (i.e., the circumflex coronary artery, pulmonary arteries, or pulmonary veins) have been previously described [29]. The NCDR registry showed that major complications, including in-hospital adverse events (2.16%), major bleeding (1.25%), were quite prevalent, whereas stroke (0.17%) and death (0.19%) were rare [23].

6.2 Long-term issues related to percutaneous LAAO

i. Iatrogenic atrial septal defects

Following transseptal LA access, iatrogenic atrial septal defects can be notable from either transthoracic or transesophageal echocardiogram. This complication can either disappear within 6 months after the procedure or persist in a small proportion of patients. Nevertheless, no hemodynamic consequences have been reported from this [30].

ii. Peri-device leakage

The target of LAAO procedure is to get a complete closure of the LAA in order to lower the risk of thromboembolism in AF patients. In the early experience of LAAO, peri-device leakage was quite prevalent. The PROTECT-AF study showed that approximately 32% of patients still have residual leak at 1 year after procedure. However, this did not seem to increase the risk of thromboembolism [31]. Furthermore, the incidence of this outcome has markedly reduced in the more recent registries, which ranging from 0.2 to1% [23, 32].

iii. Device-related thrombosis (DRT)

The main reasons of DRT remain unknown. It is postulated that the incidence of DRT is combination of either procedural factors (i.e., technique of implant or type of devices used), patient factors (i.e. patient frailty, LV dysfunction, or AF duration), or post-implant management factors (i.e., duration and type of antithrombotic therapies used) [33]. Few large studies of DRT for Watchman device such as the PROTECT AF, PREVAIL trials, CAP, and CAP2 evaluated procedural outcomes with TOE at 45 days and 12 months and at 6 months in the RCTs. Over 4 years of mean follow-up, it was demonstrated that the rate of DRT was 3.74%. The main characteristics of patients
with DRT observed in this study are higher CHA2DS2VASc scores, permanent AF, and larger LAAs. The presence of DRT was also shown to be associated with a 3.55-fold increase rate of thromboembolic events [34].

7. Current evidence of short- and long-term outcomes after LAAC

The difficulties in managing patients with AF and high bleeding risk pursued a new approach of stroke prevention in AF patients. The first randomized study of LAAC with Watchman device, PROTECT AF [21], which was published in 2009, showed non-inferiority results as compared with standard warfarin therapy. This study randomized AF patients with a CHADS2 score ≥ 1, to either Watchman implantation or OAC with warfarin. At 1.5 years of follow-up, it is shown that LAAC was equivalent for stroke prevention or all-cause mortality. The efficacy of LAAC occlusion was also demonstrated in a longer-term follow-up of PROTECT AF trial. At a mean follow-up of 2.3 years, the primary efficacy endpoint is shown to be non-inferior for device [35].

Similar results were shown by the second randomized trial, PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy) [36]. The PREVAIL trial has given additional information to PROTECT AF trial by a Bayesian non-inferiority design approach. The study showed that LAAC with the Watchman device was not non-inferior to warfarin for the primary efficacy composite endpoint, including all-cause stroke, cardiovascular or unexplained death, and serious events (SE). In addition, LAAC was non-inferior to warfarin for the occurrence of late ischemic events after the first 7 days following randomization. Furthermore, the safety endpoint and successful rate of LAAC are high, even in the center with high numbers of limited experience operators of LAAC implantation within a higher-risk patient population.

In a long-term 5-year outcomes report from the PREVAIL trial and PROTECT AF trial [37], it was demonstrated that LAAC with the Watchman device provides a similar degree of stroke prevention in non-valvular AF patients to OAC with warfarin. Furthermore, with its ability to minimize major bleeding, particularly hemorrhagic stroke. LAAC results in less death than Warfarin [37].

The more recent randomized prospective, multicenter, randomized noninferiority study, PRAGUE-17, compared two treatment strategies in moderate to high-risk AF patients (i.e., patients with history of significant bleeding or history of cardiovascular event(s) or a with CHA2DS2VASc ≥ 3 and HAS-BLED score ≥ 2) [38]. This study randomized 402 patients with AF into percutaneous LAAC versus NOAC. After median follow-up of 3.5 year, LAAC was shown to be non-inferior to DOACs for the primary endpoint and the components of the composite endpoint, such as cardiovascular death, all-stroke/transient ischemic attack, clinically relevant bleeding, and for nonprocedural clinically relevant bleeding [39].

8. Conclusion

LAA is an important anatomic area that is involved in thrombus formation in the left atrium, which is also a determinant in the risk of thromboembolic events in patients with AF. LAAC procedure provides an important alternative to pharmacological strategy in AF patients, especially for patients with stroke prevention indication.
and contraindicated or noncompliant to oral anticoagulation. It is evident that LAAO is safe and effective with high implant success rate and improving complication rate. Long-term data regarding the stroke outcomes as compared with standard strategy are necessary.

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