

Review

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Ralf Martz Sulague , Tarik Whitham , Lester Mico Lopez Danganan , Victory Effiom , Katherine Candelario , Nida Latif , [Irbaz Hameed](#) \*

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Review

# The Left Atrial Appendage and Atrial Fibrillation – A Contemporary Review

Ralf Martz Sulague <sup>1</sup>, Tarik Whitham <sup>2</sup>, Lester Mico Danganan <sup>3</sup>, Victory Effiom <sup>4</sup>, Katherine Candelario <sup>5</sup>, Nida Latif <sup>6</sup> and Irbaz Hameed <sup>6,\*</sup>

<sup>1</sup> Graduate School of Arts and Sciences, Georgetown University, Washington, DC, United States of America; rs2141@georgetown.com

<sup>2</sup> College of Medicine, Northeast Ohio Medical University, Ohio, United States of America; twitham@neomed.cedu

<sup>3</sup> Faculty of Medicine and Surgery, University of Santo Tomas, Sampaloc, Manila, Philippines; dangananlester@gmail.com

<sup>4</sup> College of Medical Sciences, University of Calabar, Calabar, Nigeri; vefiom24@gmail.com

<sup>5</sup> Cardiac Research Outcomes Group, Division of Cardiac Surgery, Department of Surgery, Yale School of Medicine, 330 Cedar Street, New Haven, Connecticut, United States of America; katherinemarinac@gmail.com

<sup>6</sup> Division of Cardiac Surgery, Department of Surgery, Yale School of Medicine, 330 Cedar Street, New Haven, Connecticut, United States of America; nida.latif268@gmail.com; irbaz.hameed@yale.edu

\* Correspondence: irbaz.hameed@yale.edu; +1 203-432-4771

**Abstract:** In patients with atrial fibrillation, the left atrial appendage may serve as the site of thrombus formation due to stasis that occurs within the appendage because of its shape and trabeculations. Although thrombus formation can be reduced with anticoagulants, this may be contraindicated in some patients. The need for a better alternative treatment prompted study of left atrial appendage occlusion for thromboembolism prophylaxis. Due to this, procedures that excise or occlude the left atrial appendage have gained attention because of its ability to prevent thromboembolic events. This article provides a comprehensive review of the left atrial appendage and its associated procedures' clinical utility.

**Keywords:** left atrial appendage; left atrial appendage occlusion; atrial fibrillation

## 1. Introduction

The left atrial appendage (LAA) is an anatomical structure that protrudes from the left wall of the most prominent atrium[1]. Found within the pericardium close to the left ventricle, it is noted to act as a decompression chamber during the left ventricular systole. Such a role is influenced by its high position within the left atrium, increased distensibility, high concentrations of atrial natriuretic factor (ANF), and neuronal configuration [2].

In patients with atrial fibrillation (AF), the LAA may serve as site of thrombus formation due to stasis that occurs within the appendage because of its shape and trabeculations. About 90% of atrial thrombi in non-rheumatic atrial fibrillation and 60% of atrial thrombi patients with rheumatic mitral valve disease originate in the LAA [3]. Due to this, procedures that excise or occlude the LAA have gained attention because of its ability to prevent thromboembolic events. Furthermore, transesophageal echocardiography has offered clearer imaging of LAA allowing assessment of the clinical implications of the LAA based on its size, shape, content and flow patterns [4]. Although thrombus formation can be reduced with anticoagulants, specifically warfarin, this may be contraindicated in some patients. The need for a better alternative treatment prompted study of LAA occlusion for thromboembolism prophylaxis (3). Although thrombus formation can be reduced with anticoagulants, specifically warfarin, this may be contraindicated in some patients. Hence, the need for a better alternative treatment prompted study of LAA occlusion for thromboembolism

prophylaxis.[3] This paper focuses on the anatomy, embryology, functions, imaging, and procedures involving the LAA. The objective of this paper is to provide a comprehensive review regarding the LAA and the clinical utility of its associated procedures.

## 2. Left Atrial Appendage Anatomy

### 2.1. Embryology

The LAA begins to develop during the 3rd week of gestation as a remnant from the embryonic left atrium, while the remaining portion of the left atrium is formed from the branches of the primordial pulmonary veins [5].

Following 4 weeks gestation, the primitive atrium starts moving toward its ultimate location. Subsequent cellular protrusion phase solidifies the basal mesodermal layer and forms the trabeculae or pectinate muscles that lead to the rough endocardium. One characteristic of the LAA, is that it has ultrastructural, and physiological characteristics distinct from the left atrium [6].

The genesis and ultimate location of the left atrial appendage and its surrounding structures originate from a simple connection of paired cardiac mesoderm that fuse to form a two-cell thick tubular heart [7].

Initial development involves a pro-myocardial plate of cells that gradually develops into a three dimensional tubular formation. This folds in an area that develops into a heart residing in what will eventually become the pericardial space. The left atrial appendage begins to emerge as early as in these stages of embryonic growth [8].

During the fourth week of embryonic development, the structurally and physiologically distinct LAA is derived from the primary atrium left the wall. Further development of the left atrium occurs around the six weeks of embryonic life [9].

### 2.2. Anatomy

Unlike the right appendage that is broad and triangular with a wide junction, the LAA is a finger-like, long, tubular, hooked structure, which is usually crenelated and has a narrow junction with the venous component of the atrium. The extent of the pectinate muscles enables appendages to be designated as morphologically right or left [10].

LAA is a blind-ended pouch located within the pericardium emerging from the left atria, which makes its spatial relationship of importance. The structures surrounding the LAA include: 1) superiorly directed pulmonary artery; 2) tip of the appendage, oriented towards the left ventricle free wall pointing inferomedial; 3) The left phrenic nerve running over the appendage; 4) fibers of Bachmann's bundle towards the LAA from arising from the medial aspect of the atrial roof; 5) left superior pulmonary vein superiorly; and 6) mitral valve inferiorly [8].

LAA cellular composition could vary both in composition and density since it contains both endocardial and epicardial layers that are structurally complicated by a disarray of myocyte orientation [2].

Evora et al. noted that the three-dimensional LAA morphology is, by itself, the substrate for thrombus generation, due to its direct connection to the left-sided circulation [9]. The heart is internally covered by the endocardial endothelium. These cells have a large surface area, providing a very high ratio of cavity surface area to atrial volume, a finding that suggests an important sensory role for the endocardial endothelium [9,11].

### 2.3. Comparative Anatomy

The "Lobe classification" into 4 types of LAA was first described by Veinot et al. in which they determined the orifice diameter, width, length, and number of lobes. The dominant type, which occurred in 54% of the hearts is composed of two lobe 23% of the hearts studied has three-lobed LAA. The third type, which occurred in 20% of the hearts is for one-lobed appendage while the fourth type, occurring in 3% of the examined heart is for four lobed appendages. [4]. Kaminski et al. also found LAA orifice diameters to be sex-related. In women, they observed a smaller orifice size in all

types of LAA with the biggest difference in the orifice size seen in LAA type 2, and accounted for 9.0 mm for females and 12.3 mm for males [12].

Having a short overall length, more complex internal characteristics, a variable number of lobes with lack of a dominant lobe, and a more irregular shape of the orifice, the “cauliflower” morphology was noted by Beigel et al. to be most often associated with an embolic event. The “cactus” has a foremost central lobe and secondary lobes arise from it superiorly and inferiorly. The “windsock” has a dominant lobe as its primary structure with the location and number of secondary or even tertiary lobes varying. The most common morphology, “chicken wing”, has a dominant lobe that presents with a sharp bend in its proximal or middle part, folding back on itself, and may present with secondary lobes [13].

### 3. Left Atrial Appendage Physiology

The anatomy of the left atrial appendage facilitates its function as a reservoir during left ventricular systole, a drain for blood from the pulmonary veins to left ventricle in early diastole, a contractile room that assists in late diastolic left ventricular filling, and an early systolic suction source [14]. Early studies have also discovered its endocrine function as it contains the greatest density of atrial natriuretic factor (ANF) granules in the left atrium, which approximates 30% of all the cardiac ANF [15]. Aside from these, the left atrial pressure helps in maintaining the LAA through the presence of stretch-sensitive receptors that can regulate the heart rate. [10] Kappagoda et al found that distension of LAA through fluid infusion led to diuresis, increased Na(+) excretion rate, and increased heart rate [16].

The LAA has a first passive phase of emptying in the protodiastole and another active phase of emptying during left atrial contraction and a monophasic pattern of filling [17]. During sinus rhythm, a washout from the LAA prevents blood from pooling and stagnating. After the mitral valve opening, the normal flow cycle begins with an early diastolic forward flow or LAA emptying, determined by the intracavitary suction via ventricular filling [18]. The cycle begins with a phase of forward flow (out of the appendage) following the beginning of transmitral flow in early diastole, then a short phase of backward flow (into the appendage) commences. The forward flow phase is fixed to the start of early diastole, suggesting a causal relation between left ventricular relaxation and early appendageal emptying [10]. LAA filling occurs immediately following the LAA contraction and is a result of the combined effects of LAA relaxation and elastic recoil. This is followed by systolic reflection waves which are low-velocity, multiple, alternate inflow–outflow and are usually seen in patients with slow heart rate [19].

### 4. Pathological Role in Thrombus Formation

It is when disruptions in this normal flow happen that pathology arises. The flow pattern in patients with atrial fibrillation is characterized by a rapid alternation of emptying and filling, with lower velocities [17]. Furthermore, flow pattern of atrial fibrillation patients can be characterized either as a saw-tooth emptying pattern or one without any active emptying pattern that is linked to highest incidence of spontaneous echo-contrast and thrombus [20].

Zabalgoitia et al. associated LAA peak flow velocities of  $\leq 20$  cm/s (RR 1.7,  $p=0.008$ ), disruptions in LAA peak flow velocities, and fractional area change, with occurrence of thrombus formation secondary to blood stasis. Compared to low risk individuals, atrial fibrillation patients with hypertension (moderate risk) are at risk for atrial appendage thrombi (RR 2.6,  $p < 0.001$ ) and reduced flow velocity (RR 1.8,  $p=0.003$ ) [21]. A study by Takada et al which found low flow velocity as a predisposing factor for stroke among nonvalvular atrial fibrillation patients without other sources of emboli further supports this [22].

Non-treatment and even undertreatment with oral anticoagulation of patients with atrial fibrillation led to high incidence of stroke [23]. CHA2DS2-VASc score was created to assess the risk of stroke or other thromboembolic events among non-anticoagulated patients with non-valvular atrial fibrillation. It uses clinical parameters (i.e. age, sex) and clinical history of diabetes,

hypertension, congestive heart failure, thromboembolism, and vascular disease to risk stratify non-valvular atrial fibrillation patients as low (0), intermediate (1), and high risk (>1) [24].

## 5. Assessment and Imaging

Currently, the modality of choice for evaluating LAA is the transesophageal echocardiography (TEE). Other non-invasive imaging modalities such as cardiac magnetic resonance (CMR), multi-detector computed tomography (MDCT), and intracardiac echocardiography (ICE) can also be used.

### 5.1. Echocardiography

Transesophageal echocardiography is the main type of echocardiography used in assessing LAA. Other types include Intracardiac echocardiography and Doppler echocardiography. TEE has high sensitivity and specificity (close to 100%) to assess presence of atrial thrombi[25]. The use of TEE to exclude LAA thrombi allows safe and early cardioversion, preventing the need for an extended anticoagulation therapy prior to cardioversion[26]. Ultrasound contrast agents are useful to enhance visualization of the LAA[13] and can demonstrate filling defects in the LAA[27,28]. TEE provides higher-resolution images because of a better frame rate but is limited by inadequate imaging planes.

Intracardiac echocardiography (ICE) is a less sensitive alternative in the absence of TEE[29]. Multiple views and detailed imaging of the LAA can be provided to diagnose the presence of thrombi[30,31]. ICE is also helpful in evaluating LAA anatomy and dimension to guide device placement and selection. Moreover, it is helpful in imaging the fossa ovalis to guide transseptal puncture and verifying LAA occlusion device efficacy and stability[32,33]. The main limitations of ICE are the cost and lack of multiplanar capabilities and as a result, only provide suboptimal imaging of LAA.

Doppler echocardiography is often used for functional evaluation of the LAA to better assess the LAA and the risk of thromboembolism[34]. To exclude LAA thrombi, evaluation of LAA Doppler velocities is essential. Color flow Doppler imaging can show areas with absent or decreased color flow within the appendage, which may indicate the presence of thrombi[35]. Furthermore, the Color-Doppler assessment of LAA flow signals is acquired from the LAA long axis view (between 60 and 90 degrees) then it is sampled at the site of maximum flow velocity, which was determined by color flow imaging scale (normally at the proximal third or mouth of the appendage). This maintains an optimal parallel angle with flow and averaging different cardiac cycles.[35]

### 5.2. Multi-Detector Computed Tomography

Multi-detector computed tomography (MDCT) produces 3D volumetric data of the whole heart, which can be reconstructed along different cardiac phases and planes to give accurate evaluation of LAA anatomy. Recent advances in MDCT now allow 3D imaging, high spatial and temporal resolution, and quantitative assessment to allow successful identification of LAA thrombi and non-dense clearing Spontaneous Echocardiographic Contrast (SEC) as shown by TEE[36–39]. An MDCT scan that is positive is not very specific for the presence of a thrombus. Hence, the high rate of false-positive test results and poor interobserver variability are the main limitations for precise detection of thrombi by MDCT[40]. Other limitations of MDCT include; the use of significantly higher radiation doses, the use of iodine-based contrast media, and significantly lower temporal resolution than TEE[41].

### 5.3. Cardiac Magnetic Resonance (CMR)

CMR is a non-invasive imaging modality which is used as an alternative for those cases in which TEE is not possible, such as, in patients with unsuccessful TEE probe insertion. This imaging modality visualizes LAA size and function accurately, and can also detect thrombus in patients with atrial fibrillation[42]. Tissue characterization can be facilitated non-invasively with the ability to differentiate fresh (increased signal intensity) from old (decreased signal intensity) thrombus. Compared to TEE, CMR imaging has been shown to be good at detecting thrombi, although with an



overestimation of thrombi size[43]. The disadvantages of CMR include increased cost, lower spatial resolution, increased time duration of study, dependence on breath holds, risks reported with gadolinium-based contrast agents, presence of certain devices precluded from CMR imaging, and inability to be performed in patients with implanted cardiac devices[44].

6. Current Clinical Approach

The left atrial appendage poses significant risk for thromboembolism in patients with atrial fibrillation[45]. Treatment for atrial fibrillation includes rate and rhythm control, anticoagulation therapy, cardioversion, ablation, and more recently, closure, exclusion, or excision of the left atrial appendage[46]. This section discusses the currently available options for thromboembolism prevention by LAA closure, exclusion, and excision.

6.1. Indications for Left Appendage Occlusion (LAAO)

The EHRA/European Association of Percutaneous Cardiovascular Interventions expert consensus statement on catheter based LAAO, have identified five patient categories in whom LAAO should be considered with regards to its risks and benefits. Clinically, the most widely recognized indication for LAAO is stroke prevention patients at high thromboembolic risk (CHA2DS2-VASc  $\geq 2$ ) and those with contraindications to oral anticoagulants (OAC) due to history of significant bleeding like intracranial bleeding[47].

Another indication is stroke prevention in high thrombo-embolic risk patients (CHA2DS2-VASc  $\geq 2$ ) and increased bleeding risk associated with systemic OACs in three patient groups: 1.) patients with HAS-BLED score  $\geq 3$ , 2.) patients requiring the prolonged period of triple anticoagulant and antiplatelet therapy for severe coronary artery disease treated with stents, and 3.) patients with end-stage renal dysfunction (creatinine clearance 15–30 mL/min) but decision to implant LAAO is still individualized risk-benefit evaluation with novel oral anticoagulants (NOACs) being still the main strategy of choice[47].

LAAO is potentially indicated in using the device as an alternative to OAC in patients who are eligible for OACs in whom there is no increased risk of bleeding which only represents a small minority of current LAAO procedures[48].

The last indication according to EHRA consensus on potential indication for LAAO is in patients at high thrombo-embolic risk (CHA2DS2-VASc  $\geq 2$ ) undergoing pulmonary vein isolation that are planning to discontinue OAC after ablation[49].

6.2. Devices

Currently approved devices for LAAO include WATCHMAN and Amplatzer Amulet. Patients who undergo left atrial appendage occlusion need to be suitable for short-term anticoagulation therapy, as the post-procedural guidelines indicate warfarin and anti-platelet therapy in the short term or indefinitely[50]. Percutaneous left atrial appendage occlusion has shown that it can be effective in the reduction of thromboembolic events in patients with aversion to oral anticoagulation therapy. Devices used for the procedure are discussed below and summarized in Table 1.

Table 1. Left Atrial Appendage Occlusion Devices. PLAATO (51), Watchman (54), Amplatzer Amulet (60), and Lariat (58).

Device**	PLAATO[51]	Watchman [54]	Amplatzer Amulet [60]	Lariat [58]
Success Rate of Implantation	90.0%	95.1%	98.4%	86.0%
Complication Rate	Not assessed*	2.2%	4.5%	10.0%

<b>Stroke</b>	<b>2.3%</b>	<b>2.3%</b>	<b>2.8%</b>	<b>1.0%</b>
<b>Bleeding</b>	<b>3.3%</b>	<b>0.8%</b>	<b>10.6%</b>	<b>9.0%</b>
<b>Mortality</b>	<b>Not assessed*</b>	<b>2.6%</b>	<b>3.9%</b>	<b>0.14%</b>

\*Study discontinued at 5-year follow up due to financial constraint. \*\*Please note comparison is not direct, each study reports findings differently, based on different definitions. Please see the cited studies for greater detail regarding endpoints, follow-up period, definitions of events, etc.

#### 6.2.1. Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) System

PLAATO was the first percutaneous device used to close the left atrial appendage[51]. The device consists of a self-expanding nitinol cage that is placed proximally in the orifice of the LAA. This functionally removes the LAA, preventing blood from entering or escaping. Multiple studies indicated a high success rate (90%) of occlusion and reduced risk of stroke(2.3% vs expected 6.6%)[52]. In the PLAATO study, two patients died in the first 24 hours after the procedure(1.1%) and seven patients had serious adverse events(3.9%) (cardiac tamponade or device embolization) [52]. In 2007, the device was discontinued and replaced with the Watchman device[51].

#### 6.2.2. Watchman

The Watchman device was approved for LAAO by the FDA in 2007. Much like the PLAATO device, it is a self-expanding nitinol cage. Barbs are used for device fixation. A permeable polyester mesh covers one end of the implant[51]. Based on the National Cardiovascular Data Registry Left Atrial Appendage Occlusion Registry, the most common procedural indications for WATCHMAN implantation were increased thromboembolic risk, history of major bleed, and high fall risk with the majority of patients having multiple procedural indications[54].

Multiple randomized control studies have indicated that the watchman device is non-inferior to warfarin therapy for patients with increased risk of clotting[48,55,56]. Furthermore, a recent meta-analysis of three randomized control trials indicated that Watchman has reduced risk of hemorrhagic stroke (RR: 0.22; 95% CI: 0.08 to 0.58; p=0.002), cardiovascular mortality(RR: 0.65; 95% CI: 0.44 to 0.95;p=0.03), all-cause mortality (RR: 0.78; 95% CI: 0.62to 0.99; p=0.04), and non-procedure-related major bleeding (RR: 0.53; 95% CI: 0.38 to 0.74;p=0.0002) when compared to OACs[57].

#### 6.2.3. Amplatzer Amulet

The Amplatzer Amulet was approved for LAAO in 2021. It consists of a braided nitinol mesh disk and lobe connected by a waist[58]. Clinical trials have demonstrated non-inferiority to traditional warfarin therapy for patients with atrial fibrillation who are at increased risk of stroke or systemic embolism[58]. Furthermore, when compared to the Watchman device, LAA closure with Amplatzer Amulet was non-inferior with a high success rate at 45 day follow-up[58]. The Amplatzer Amulet demonstrated more procedure related complications (4.5% versus 2.5%) however, major bleeding and all-cause mortality were similar between the two devices (10.6% vs. 10.0% and 3.9% vs. 5.1%, respectively). The Amplatzer Amulet also demonstrated a higher rate of successful occlusion of the LAA compared to Watchman (98.9% versus 96.8%; difference=2.03 [95% CI, 0.41-3.66]; P<0.001 for noninferiority; P=0.003 for superiority)[59].

#### 6.2.4. Lariat

The Lariat system is a combination of percutaneous and epicardial LAA closure using a soft tissue snare. Through a percutaneous access, a magnet tipped catheter is placed in the LAA as a guide for the snare that is delivered via the pericardium. Currently this device has 510K clearance from the FDA[60]. Despite not having full FDA approval, the Lariat device is a popular option (off-label) for atrial fibrillation patients with contraindication to oral anticoagulation. Many studies have indicated a relatively high success rate of LAA closure (86%) [61]. In one study, Lariat showed reduced

incidence of LAA leak at one year follow-up compared to Watchman (14% vs 21%;  $P = .019$ ) [62]. Multiple studies have shown high post-procedural complication rates, however it appears to be comparable to Watchman (2.7% vs 2.7%) [61].

### 6.3. Surgical LAAO

It is common for patients with atrial fibrillation undergoing cardiac surgery to receive concomitant LAA obliteration. Techniques for obliteration include excision, stapler removal, running sutures, and use of specialized devices such as AtriClip®. Individual techniques have been well described elsewhere, here we will discuss surgical obliteration as a whole.

A recent meta-analysis by Tsai et al. concluded that when compared to patients who underwent cardiac surgery (either valve surgery or CABG), those who received LAAO concomitantly had significantly reduced risk of stroke, and all-cause-mortality; without increased risk of bleeding[63]. Another meta-analysis by Homamed et al. concluded that LAAO provides a significant reduction in thromboembolic events, but no significant change in all-cause mortality, major bleeding, or myocardial infarction[64]. A large study by Melduni et al. ( $n=10,633$ ) suggested that those who underwent surgical LAAO were more likely to have early post-operative atrial fibrillation than those who did not undergo LAAO, without significant change in risk of stroke or mortality[65]. A study by Yao et al. reports that those who undergo LAAO have more health care appointments related to atrial fibrillation and more hospitalizations compared to those who do not undergo LAAO[27]. A randomized control trial comparing LAAO with anticoagulation to anticoagulation alone found that LAAO recipients had reduced risk of stroke, but no change in perioperative bleeding, heart failure or death[66]. There have been no studies comparing Surgical LAAO to percutaneous LAAO.

### 6.4. Risks and Disadvantages of Left Atrial Appendage Closure

Whether done percutaneously or surgically, left atrial appendage closure is not without risk. Major risks for percutaneous procedure include cardiac effusion/tamponade, stroke, and device-associated thrombus[67]. Based on the most recent WATCHMAN clinical trials and registries, cardiac tamponade incidence is limited to 1.3 percent[68,69]. Freeman et al. reported hemorrhagic stroke in 0.01 percent and ischemic stroke in 0.12 percent based on the National Cardiovascular Data LAAO registry[70]. Aside from these, further catastrophic complications that may occur intraoperatively or post-operatively include device embolization into the aorta, left atrial cavity, and left ventricle[71]. Real world data from the National Cardiovascular Data LAAO registry reported a 0.07 percent incidence[70].

A study by Simard et al. identified the following as risk factors for device-associated thrombus: hypercoagulability disorders, pericardial effusion, renal impairment, implantation depth  $>10$  mm from the pulmonary vein limbus, and nonparoxysmal AF[72]. Moreover, one study found that risk factors associated with incomplete closure include female sex, hyperlipidemia, and hypertension[73]. Darden et al. found females to have higher risk of in-hospital adverse events relative to males such as major bleeding (1.7 versus 0.8 percent) and pericardial effusion (1.2 versus 0.5 percent)[74].

Incomplete closure of the LAA is not uncommon with a surgical approach. This results in a patent communication, which only exacerbates the risk of stroke. In addition to this, the left circumflex artery is often proximal to the site of obliteration necessitating mastery of surgical anatomy and skills.

### 6.5. LAA Occlusion Outcomes

Clinical results of LAA occlusion in comparison to oral anticoagulation were explored in multiple studies. Table 2 shows the outcomes of LAA occlusion in comparison to oral anticoagulation in previous studies from 2001 to the present.



**Table 2.** Clinical Studies on Left Atrial Appendage Occlusion Outcomes.

Author	Year	Study Period	Multicenter	Study Type	Findings
Ding, W.Y.	2022	Dec. 2010- Jan. 2019	Yes	Cohort study	For stroke prevention in patients with atrial fibrillation, LAA occlusion was found to be the suitable alternative to NAOC therapy
Godino, C.	2019	July 2009 - Dec. 2016	No	Observational prospective study	NOACs and LAAO performed similarly in terms of major bleeding and thromboembolic events up to two-year follow-up in non-valvular atrial fibrillation patients at HBR
Korsholm, K.	2022	2015-2016	No	Cohort study	In comparison with DOAC, LAAO therapy showed lower risk of the composite outcome of stroke, major bleeding and all-cause mortality in patients with atrial fibrillation and prior stroke.
Nielsen-Kudsk, J.E.	2021	June 2015- Sept. 2016	Yes	Cohort study	LAAO may have similar stroke prevention efficacy but lower risk of major bleeding and mortality as compared to DOACs among high-risk atrial fibrillation patients.
Nielsen-Kudsk, J.E.	2017	2009- March 2015	Yes	observational propensity score-matched study	In atrial fibrillation patients having sustained an ICH, LAAO was suggested to be of major clinical benefit
Noseworthy, P.	2022	March 2015- Dec.2018	Yes	Cohort study	When compared with non-vitamin k antagonist oral anticoagulants, LAAO was linked with lower risk of mortality and no significant difference in the risk of the composite outcome and this showed that LAAO might be a better option in select patients with atrial fibrillation. It was observed that there was higher bleeding risk which was associated with LAAO and because of this, there was need to optimize systemic efforts and postprocedural antithrombotic regimens to assess and address bleeding predispositions,
Paiva, L.	2022	2015-2018	No	Cohort Study	It was found that six months after device implantation, one-fifth of LAAO patients had to stop antiplatelet treatment as a result of recurrent minor bleeding, no major bleeding or adverse cardiovascular event occurred
Holmes, D.	2014		Yes	Randomized Controlled Trial	In this study, it was shown that LAA occlusion was noninferior to warfarin for SE> 7 days post-procedure or ischemic stroke prevention. Furthermore, this study provided more data that LAA occlusion is a better alternative to warfarin therapy for stroke prevention in patients with non-valvular atrial fibrillation who are without absolute contraindication to short-term warfarin therapy.
Belgaid, D.	2016		Yes	Randomized	This study showed that LAA occlusion is a good alternative to chronic warfarin therapy in stroke prevention for patients with atrial fibrillation

				Controlled Trial	
Healey, J.	2005	June 2001- october 2002	No	Randomize d Controlled Trial	At the time of CABG, LAA occlusion is safe. With increased experience and the use of a stapling device, the rate of complete occlusion improves to acceptable levels..
Whitlock, R.P.	2021		Yes	Randomize d Controlled Trial	In this study, the risk of systemic embolism or ischemic stroke was lower with accompanying left atrial appendage occlusion performed during the surgery than without it.
Whitlock, R.P.	2013	7 months	Yes	Cross- sectional study	LAA occlusion can be safely performed at the time of cardiac surgery. A large trial to evaluate the clinical efficacy of LAA occlusion in patients undergoing cardiac surgery is possible in motivated centers with some modifications to the design of LAAOS II. This study showed that LAA occlusion could be safely performed at the time of cardiac surgery. Furthermore, in motivated centers with some modifications to the design of LAAOS II, it was possible to evaluate the clinical efficacy of LAA occlusion using a large trial in patients undergoing cardiac surgery
Zhou, X.	2016			Systematic Review	In stroke reduction, left atrial occlusion with Watchman device had the same effectivity as compared with Warfarin. Also, as compared to Warfarin, Surgical LAAO also had positive outcomes but due to the small sample size the evidence was less powerful

In LAAOS III study, which first explored prevention of ischemic stroke or systemic embolism in patients who had LAAO coupled with usual post-operative care, including oral anticoagulant, ischemic stroke or systemic embolism occurred in 114 participants (4.8%) in the LAAO group and 116 participants (7.0%) in the non-occlusion group. This showed a significant reduction in risk of ischemic stroke or systemic embolism (HR 0.67, 95% CI 0.53-0.85, p=0.001)[66].

It is noteworthy to highlight multiple randomized controlled trials, including PREVAIL, PROTECT AF and PRAGUE 17, which have shown the efficacy and safety of LAAO in comparison to medical management [48]. The PROTECT AF trial demonstrated non-inferiority of LAAO versus warfarin in both primary efficacy rate and primary safety events. The primary efficacy rate (composite endpoint of stroke, cardiovascular death, and systemic embolism) of the LAAO group was 3.0 per 100 patient-years (95% credible interval [CrI] 1.9–4.5) compared to 4.9 per 100 patient-years (2.8–7.1) in the warfarin group (rate ratio [RR] 0.62, 95% CrI 0.35–1.25). Similarly, the primary safety events were more frequent in the LAAO group than the warfarin group (7.4 per 100 patient-years, 95% CrI 5.5–9.7, versus 4.4 per 100 patient-years, 95% CrI 2.5–6.7; RR 1.69, 1.01–3.19)[48].

In PREVAIL trial, stroke or death at 18 months was found to occur in 0.064 in the LAAO group compared to 0.063 in the warfarin group, which did not reach the pre-established non-inferiority criteria for the trial [56]. The rate for stroke or systemic embolism >7 days’ post-randomization was 0.0253 in the LAAO group compared to 0.0200 in the warfarin group (risk difference 0.0053 [95% CrI: -0.0190-0.0273]), which achieve noninferiority [56].

The PRAGUE17 trial showed that LAAO was noninferior to NOAC. The Amulet or WATCHMAN device was used for the LAAO, while the control group was given antiplatelet therapy for 3 months. Primary clinical findings showed that the net outcome of CV death, stroke, TIA,

systemic embolism, etc., was similar in both treatment groups (hazard ratio [HR] 0.84, p value for noninferiority = 0.004) [77].

After 3.8 years of follow-up, the combined outcome of preventing stroke, systemic embolism, and cardiovascular death among LAAO patients were shown to be non-inferior and superior than those of warfarin patients in the PROTECT AF trial, 8.4% vs. 13.9%, respectively (rate ratio [RR] 0.60, 95% credible interval, 0.41-1.05). There was reduced cardiovascular mortality (3.7% vs 9.0%; hazard ratio [HR], 0.40; 95% CI, 0.21-0.75; P = .005) and all-cause mortality (12.3% vs 18.0%; HR, 0.66; 95% CI, 0.45-0.98; P = .04) [78].

## 7. Conclusion

The LAA is clinically important because it is a major site of thrombus formation in atrial fibrillation and mitral valve disease. Due to the LAA's properties and relations, it may be utilized as a decompression chamber in cases where left atrial pressure is increased. The exact pathogenesis of the thrombus formation is not known, but it is hypothesized that stasis of blood flow within the LAA is a key factor.

Obliteration of the LAA is an alternative to warfarin for stroke prophylaxis. It will not prevent every episode of thromboembolism, especially in patients with mitral valve disease. This is important because patients with left ventricular failure and valvular disease may be more affected.

Alternative treatments are needed to be explored to further understand how to create more effective outcomes for thromboprophylaxis in patients with atrial fibrillation. This will help determine which course of treatment should be selected, as well as how to manage significant adverse effects from the specific treatments.

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