REVIEW

Percutaneous Left Atrial Appendage Occlusion Therapy: Past, Present, and Future

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Abstract

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is increasing in incidence and prevalence worldwide. AF significantly increases the risk of intracardiac thrombus formation and, if left untreated, ischemic stroke. In patients with nonvalvular AF (NVAF), the left atrial appendage (LAA) has been determined to be the source of thrombus development in 91% to 99% of cases. In this regard, oral anticoagulants (OACs) have become the standard treatment for stroke prevention in most patients with AF; however, OACs are associated with a risk of bleeding complications, and their efficacy depends on optimal patient compliance. Among alternative approaches to embolic stroke prevention, surgical LAA excision for stroke prevention for valvular AF was attempted as early as the late 1940s. LAA excision remains recommended in surgical guidelines for patients with NVAF requiring open-heart coronary bypass or valvular replacement/repair surgeries. However, owing to the traumatic/invasive nature and suboptimal outcomes of conventional surgical LAA intervention, clinical application of this approach is limited in current cardiology practice. Percutaneous LAA occlusion (LAAO) is increasingly being performed as an alternative to OAC for stroke prevention, particularly in patients with elevated bleeding risk.

Substantial progress has been made in percutaneous LAAO therapy since its inception approximately 20 years ago. This article systematically reviews the literature leading to the development of LAAO and the evidence-based clinical experience supporting the application of this treatment strategy for NVAF, with a focus on recently published critical evaluations of US FDA and CE mark approved LAAO devices. Future perspectives regarding knowledge and technology gaps are also discussed, recognizing the many ongoing clinical trials that are likely to be transformative and the critical unanswered questions regarding LAAO therapy.

Keywords: Atrial Fibrillation; Left Atrial Appendage Occlusion; Stroke Prevention

Abbreviations: AF, Atrial Fibrillation; LAA, Left Atrial Appendage; LAAO, Left Atrial Appendage Occlusion; NVAF, Nonvalvular Atrial Fibrillation; ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; ISTH, International Society on Thrombosis and Hemostasis; US FDA, United States Food and Drug Administration; CE Mark, Conformité

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Européenne (Commercial Sale of Licensed Product in the EU); CMS, Centers for Medicare and Medicaid Services; IDE, Investigational Device Exemption; ICE, Intracardiac Echocardiography; TEE, Transesophageal Echocardiography; NOACs, Novel Oral Anticoagulants; DOACs, Direct Oral Anticoagulants.

Introduction to LAAO Therapy

Background

Thromboembolic complications, particularly stroke, are among the most important complications associated with atrial fibrillation (AF) [1–3]. The left atrial appendage (LAA), with its muscular trabeculations and often complex multilobular structure, has long been considered the principal site of atrial clot formation [4, 5]. Consequently, beyond pharmacologic prevention of clot formation and embolization, which are critical in long-term AF treatment [6, 7], a substantial body of clinical experience supports the use of other methods to decrease LAA-induced embolic risk, including device therapy [8]. In this context, a degree of thrombotic risk reduction has been achieved with techniques that modify the LAA anatomy to decrease thrombus formation ability. These techniques began with surgical methods to amputate the LAA or suture the LAA os closed [9, 10], and thereby eliminate clots and the release of thrombi from the LAA into the central systemic circulation. These surgical approaches, although imperfect, have achieved some success, as discussed below. Later, catheter based LAA occlusion (LAAO) systems were introduced and have gradually increased in importance.

The goals of this review are to examine the role of the LAA in intra-atrial thrombus development in AF and to summarize the recent evolution of the LAAO approach for thromboembolic prophylaxis. Particular emphasis is placed on trans-catheter LAAO, given its potential value for stroke prevention in many patients with AF who cannot tolerate, or have contraindications for, long-term conventional oral anticoagulation.

AF Terminology

The term nonvalvular AF (NVAF), sometimes also called nonrheumatic AF, has been used since the 1970s to differentiate AF in association with rheumatic heart disease from AF in the absence of rheumatic heart disease. A consistent definition of NVAF was lacking until 2012, when the European Society of Cardiology (ESC) defined it as AF in the absence of "rheumatic native or prosthetic heart valves." Shortly thereafter, the AHA/ACC/HRS 2014 guidelines refined the definition to AF occurring in the absence of "rheumatic mitral stenosis, mitral valve repair, mechanical, or bioprosthetic heart valve." The current definition of valvular AF is limited to AF in the presence of any mechanical heart valve or moderate to severe mitral stenosis, either rheumatic or nonrheumatic in origin. The current definition is accepted by the AHA/ACC/HRS and ESC, but the ESC further recommends that the term of NVAF be abandoned. Thus, AF associated with severe mitral regurgitation or aortic stenosis is not included in the current definition of "valvular" AF, unless a mechanical valve has been placed in the patient for any etiology. Herein, the historic descriptions of both "valvular" and "rheumatic" are used to differentiate the subtype of AF from "nonvalvular" AF.

The Left Atrial Appendage

The LAA is generally considered a vestigial remnant of the primordial LA, which forms during the fourth week of embryonic development. Detailed discussions of LAA anatomy, physiology, and pathophysiology can be found in several excellent reviews [11–13]. In general, the hook-like diverticulum of the LAA consists of one or more lobes with a trabeculated wall, owing to parallel-running pectinate muscles [14, 15]. The LAA is a highly contractile structure (which contracts from its apex toward the base); in sinus rhythm, the blood flow within the lumen is sufficient to minimize thrombus formation. However, during AF, the contractility of the LAA is markedly diminished, and the blood flow in the lumen may become sufficiently slow to create a hemodynamic "dead-space" that favors thrombus formation [16, 17]. The highly trabeculated wall of the LAA, and the often-concomitant presence of fibrous tissue in the muscular wall of the LAA and atria in patients with AF, are also likely to play an important part in thrombogenicity. As such, the fibrillating trabeculated LAA with blood stasis and facilitation of coagulation activation increases the risk of

thromboembolism, thus resulting in an overall risk of stroke of approximately 5% every year [1, 18].

In the 1950s, when rheumatic valve disease was the main cause of AF, 50% of thromboses were recognized to be in the LAA; consequently, a 50% embolic risk reduction was observed after LAA obliteration at the time of the commissurotomy [19]. By the mid-1990s, with the extensive clinical application of transesophageal echocardiography (TEE), LA thrombi were suggested to be present in the LA cavity or in the LAA, and to extend into the cavity in 57% of patients with rheumatic AF. However, in nonrheumatic AF, approximately 91% of left atrial thrombi are largely isolated to the LAA [4]. Regarding NVAF, by the late 1970s, increased risk of ischemic stroke had been clearly associated with AF in the absence of significant valvular heart diseases [20–22]. According to the most recent data, approximately 99% of thrombi in NVAF form in the LAA [5].

The first amputations of the LAA in humans [23] were reported shortly after the procedure was performed in animal experiments [24, 25]. After these successful pioneering attempts, these procedures were subsequently performed at the time of mitral commissurotomy, to alleviate the well-known high thrombogenicity associated with mitral stenosis [19, 26]. Systematic exclusion of the LAA has recently been recommended in addition to surgical ablation procedures in surgical guidelines [27]. The exclusion procedure is commonly performed by resection, epicardial stapling, clip application, or endoatrial double-layer longitudinal suture closure [28–30]. Stapling has particularly poor outcomes, leaving most patients with a residual LAA stump and/or surgical line leakage, which can be thrombogenic. LAA obliteration may decrease early and late stroke rates by more than 50%, and provide modest survival benefits [10]. Regardless of the LAA exclusion method used, the potential thrombogenicity of the remaining appendage pouch is a matter of major concern [31–33]. In a nonrandomized retrospective study comparing the efficacy of several surgical methods for LAA closure, TEE revealed successful closure in only 40% of patients [34]. LAA thrombus was present in 41% of patients with unsuccessful LAA exclusion. Importantly, 13% of these patients had experienced strokes between the operation and the time when TEE was performed, regardless of

whether the closure was successful or unsuccessful [34]. Despite these shortcomings and suboptimal outcomes, the recent LAAO III trial further supports the efficacy of surgical LAA obliteration in ischemic stroke prevention in patients with NVAF [35].

LAAO Devices

The impetus for investigating the possibility of percutaneous left atrial appendage obliteration or occlusion was fourfold: (1) As noted earlier, thrombi associated with nonrheumatic AF occur predominantly within the LAA in 91–99% of patients [4, 5]. (2) In many patients, anticoagulant drugs (warfarin or NOACs/DOACs) are not a suitable therapy to decrease embolic stroke, because of relative or absolute contraindications, particularly bleeding disorders. In addition, real-world experience has indicated that adherence to anticoagulation is far from optimal, thereby leaving many patients unprotected [36, 37]. (3) Even in patients with chronic anticoagulation using either warfarin or NOACs/DOACs, a substantial risk of thrombus formation in the LAA remains despite medication compliance [35, 38–41]. Finally, (4) surgical approaches are invasive, thus making their widespread application inappropriate for most patients with AF; patients are additionally exposed to residual risks associated with remnants of the LAA or residual leakage regardless of the surgical exclusion method. Below, the major LAAO devices are described in chronological order. A timeline of device preclinical, IDE trials, and FDA and CE mark commercial approval is shown in Table 1.

Percutaneous LAAO with the PLAATO Device (Early Stage)

After a pilot feasibility study in animals [42], the first percutaneous left atrial appendage transcatheter occlusion (PLAATO, Figure 1) device in humans was described two decades ago [44]. The detailed technique for implantation was nicely summarized a decade ago [43]. The device is made of a self-expanding nitinol cage covered with a polymeric membrane (ePTFE). The implant is available with diameters of 15–32 mm and is delivered through a 12 F transseptal sheath under TEE guidance and

Table 1 Timeline of Major LAAO Devices.

Devices	Preclinical	IDE	FDA	CE Mark	Withdrawn
PLAATO	2001				2007
Amplatzer: Occluder	2002				
ACP1	2008			2008	
Amulet	2013	2016–2020	2020	2013	
Watchman 2.5	2005	2005–2014	2015	2005	2021
FLX		2018–2020	2020	2015	
LAmbre	2013			2016	
WaveCrest	2010–2011			2013	
LARIAT	2010		2006	2015	
			2009		
			2014		
Ultraseal I/II	2015–2016			2016	
CLAAS	2021				

fluoroscopy. The LAA was found to be successfully occluded under TEE guidance and fluoroscopy in 15 of 15 patients with "chronic" AF with an average age 69 ± 5 years and contraindications for warfarin. At the 1-month follow-up, chest fluoroscopy and TEE revealed continued stability of the implant position with a smooth atrial-facing surface and no evidence of thrombi. At the 6-month follow up, PLAATO continued to achieve an adequate seal of the neck of the LAA without apparent effects on the structure or function of the LA and left upper pulmonary vein.

A prospective, non-randomized, multi-center trial of PLAATO enrolling 111 patients from August 2001 to November 2003 was published in 2005 [45]. With an average follow-up of 9.8 months, the study demonstrated overall success of the procedure in 108 of 111 patients (97.3%), with no migration or mobile thrombi on TEE at 1 and 6 months after device implantation. The three patients who did not receive a PLAATO device included one with left atrial thrombus at the time of the procedure, one with vessel perforation of the right femoral artery while the right femoral vein was being accessed, and one who developed cardiac tamponade after trans-septal puncture. At that time, the study led to the conclusion that percutaneous LAA occlusion with the PLAATO system could be performed with acceptable risk, and this approach provided an alternative therapeutic strategy for patients with AF with elevated risk of ischemic stroke and contraindications for long-term warfarin treatment. Additional studies in small and moderate numbers of patients with AF with high stroke risk reinforced the concept that LAAO with PLAATO is relatively safe and effective, although severe complications can occur [46–49]. Despite its apparent effectiveness, the PLAATO device has not been available since 2007, because of commercial rather than medical reasons.

Amplatzer Cardiac Plug (ACP I) and Amulet (ACP II)

The first study of LAA occlusion with Amplatzer atrial septal occluder devices (Figure 2A) was published in 2003 [51]. A total of 16 patients with NVAF 58–83 years of age were treated at four centers, 14 of whom were under local anesthesia. One acute device embolization occurred, and the device was surgically removed. At the 4-month follow-up, no further complications were observed; the devices remained in stable position, and the LAA was completely occluded in all cases. Notably, the device was initially developed for atrial septal defect closure but was not specifically designed for LAA occlusion purposes. No further clinical data for use of the septal occluder were available until a new system, the Amplatzer Cardiac Plug (ACP I), was designed specifically for occlusion of the LAA [50, 52, 53]. The device (Figure 2B-D, left) is constructed from a nitinol mesh and Dacron, and it consists of a lobe and a disk connected by a central waist. Twelve stabilizing wires are equally spaced
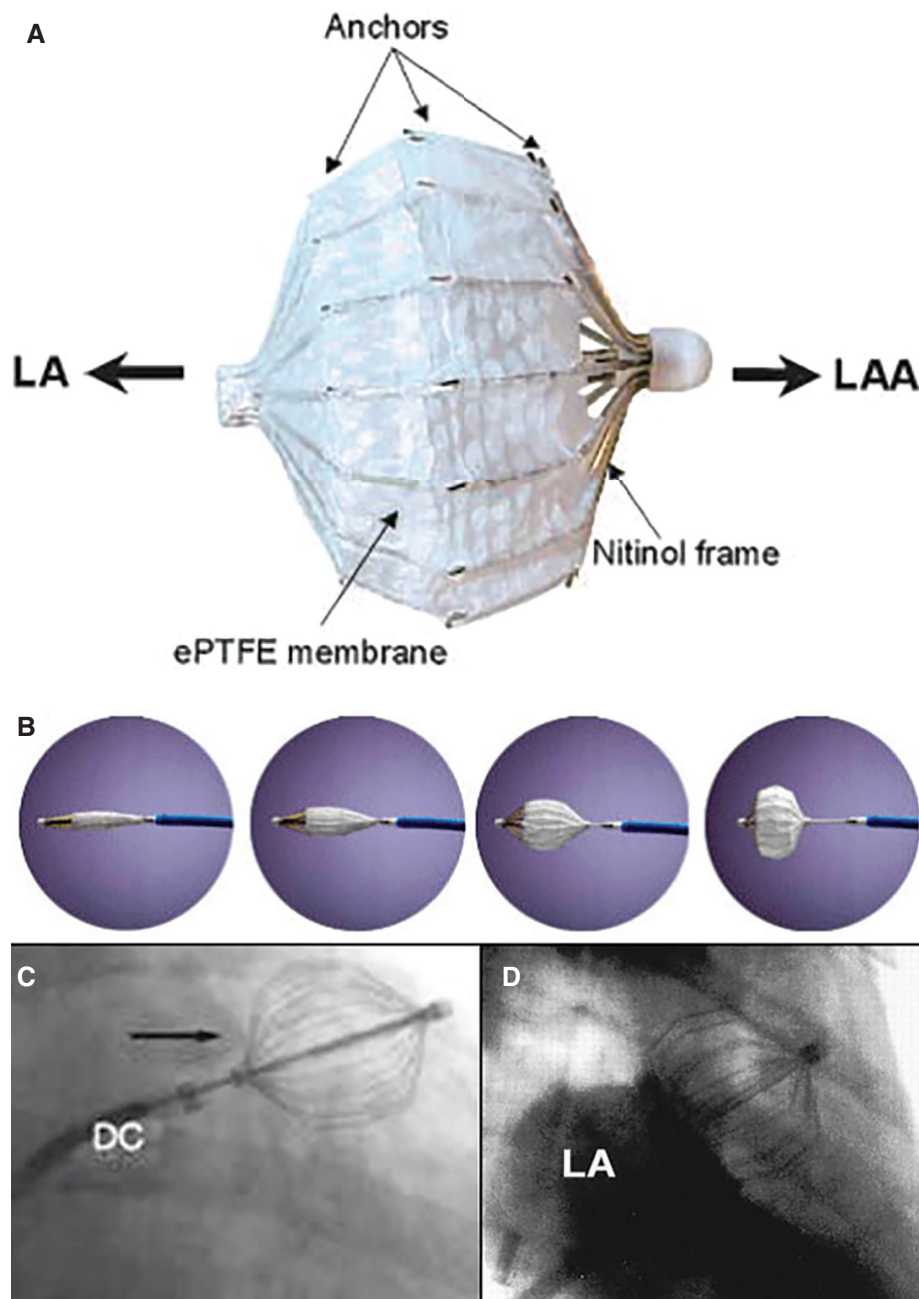
Figure 1   PLAATO Device.
A: Original shape. B: Partially (left) and fully (right) opened device during delivery through the delivery catheter and sheath.
C: Fully opened device under fluoroscopy. D: Contrast injection demonstrating occlusion of the LAA. LA, left atrial side,
LAA = left atrial appendage side, DC = delivery catheter (modified with permission from refs. [42, 43]).

around the main disc. The sizes of the lobes range between 16 and 30 mm. This device is retrievable and can be repositioned, and successful deployment has been confirmed by TEE [53].

Most clinical data for ACP I have come from the ACP multicenter registry [54], which contains data from 1047 consecutive patients treated at 22 centers between December 2008 and November 2013. A total of 1001 patients who underwent LAAO with the ACP I and had complete follow-up were included and further analyzed for stroke and bleeding reduction, their outcomes were compared with the predicted risks with the CHA2DS2-Vasc and HAS-BLED scores. The mean follow-up time was 13 months, thus resulting in a total of 1349 patient years. Procedural success was achieved in 1019/1047 patients (97.3%),
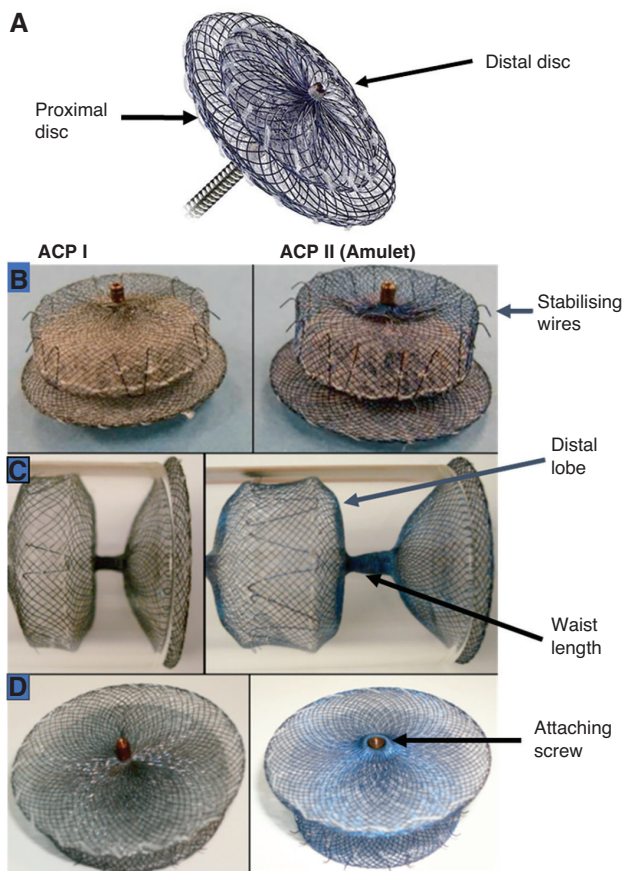
Figure 2 Amplatzer Septal Occluder (A), ACP I, and ACP II (Amulet) Devices. Distal (B), horizontal (C) and proximal (D) views of APC I (left) and ACP II (right). APC: Amplatzer Cardiac Plug.
A key feature is the double-disc design. Major differences between ACP I and ACP II include that in the latter 1) the stabilising hooks are stiffer and increased from six pairs to as many as ten pairs; 2) the length of the distal lobe and the diameter of the proximal disc are increased; 3) the waist between the distal lobe and the proximal disc is lengthened; and 4) the attaching screw on the proximal disc is inverted (modified from St Jude medical and ref. [50]).

and a total of 52 peri-procedural major adverse events (4.97%) were observed, including eight procedure-related deaths, nine strokes, nine transient ischemic attacks (TIAs), and 13 cardiac tamponades. Major study limitations included 1) the non-randomized study design (without a control group), 2) the lack of availability of TEE follow-up data for all patients, and 3) the self-reported study results (without independent adjudication).

The major complications observed with the first generation ACP I [54–56], including peri-procedural stroke (0–2.3%), device embolization (0–2.3%), device thrombosis (0–2.4%), and pericardial

effusion (1.1–3.5%), indicated the need for further technological improvements. Consequently, a new generation of the Amplatzer™ Cardiac Plug, the Amulet™ (ACP II) was designed (Figure 2B-D, right), without altering the main design of the ACP I. The modifications to the design of the ACP I were made to facilitate implantation and improve sealing performance after implantation. The first in-human percutaneous LAA closure using the ACP II/Amulet was performed in 2012, and a case report was published in 2013 [50]. A multicenter prospective real-world registry study including 1088 patients (75 ± 8.5 years, 64.5% men, CHA2DS2-VASc: 4.2 ± 1.6, HAS-BLED: 3.3 ± 1.1) with NVAF was published in 2017 [57]. In this population, 82.8% of patients were considered to have absolute or relative contraindications for long-term anticoagulation, and 72.4% had prior major bleeding. Successful device implantation was achieved in 99.0% of patients. During the procedure and index hospitalization, major adverse events including death, major bleeding, tamponade requiring pericardial drainage or surgery, major vascular complications, stroke, and device embolization occurred in 3.2% of patients. Available TEE follow-up in 673 patients after implantation indicated adequate (<3 mm jet) occlusion of the appendage in 98.2% of patients and device thrombus in 1.5%. As with all registry studies, selection bias, or at least perceived selection bias, is a major limitation, particularly given that only approximately 62% of the study population had follow-up TEE data available. Nonetheless, in this study population, a total of 1078 patients successfully received an Amulet device. Compared with a propensity score–matched control cohort of patients with AF (n = 1184) identified from Danish national patient registries, who were treated with direct oral anticoagulants (NOACs/DOACs), patients receiving LAAO with the Amulet have been found to show similar stroke prevention efficacy, but a lower risk of major bleeding and mortality, at the 2-year follow-up, on the basis of analysis of the composite primary outcome of ischemic stroke, major bleeding, or all-cause mortality [58]. After the IDE trial [59] confirmed the noninferior safety and effectiveness of stroke prevention in patients with NVAF with respect to the first US FDA approved Watchman Legacy (March 2015), the Amulet became the second US FDA approved LAAO device (August

2020) in the United States. Higher than expected rates of procedure-associated complications were observed with the Amulet occluder but decreased with operator experience.

Watchman 2.5/Legacy

The first description of the Watchman™ device (Watchman 2.5 or Legacy) was published in 2006 [60, 61]. Enrollment in the PROTECT AF trial started in February of 2005 and ended in the summer of 2008. The pilot data were published in 2007 [62],

and the complete study was published in 2009 [63]. The Watchman™ Left Atrial Appendage System includes an implant/device, a delivery sheath (14 F), and a catheter (12 F). The Watchman™ implant comprises a self-expanding nitinol frame structure with fixation barbs and a permeable polyester fabric that covers the left atrial facing surface of the device (Figure 3A). Before delivery, the device is constrained in a 12 F delivery catheter and is available in five sizes (21 mm, 24 mm, 27 mm, 30 mm, and 33 mm) to accommodate various LAA morphologies. The Watchman™ system and the
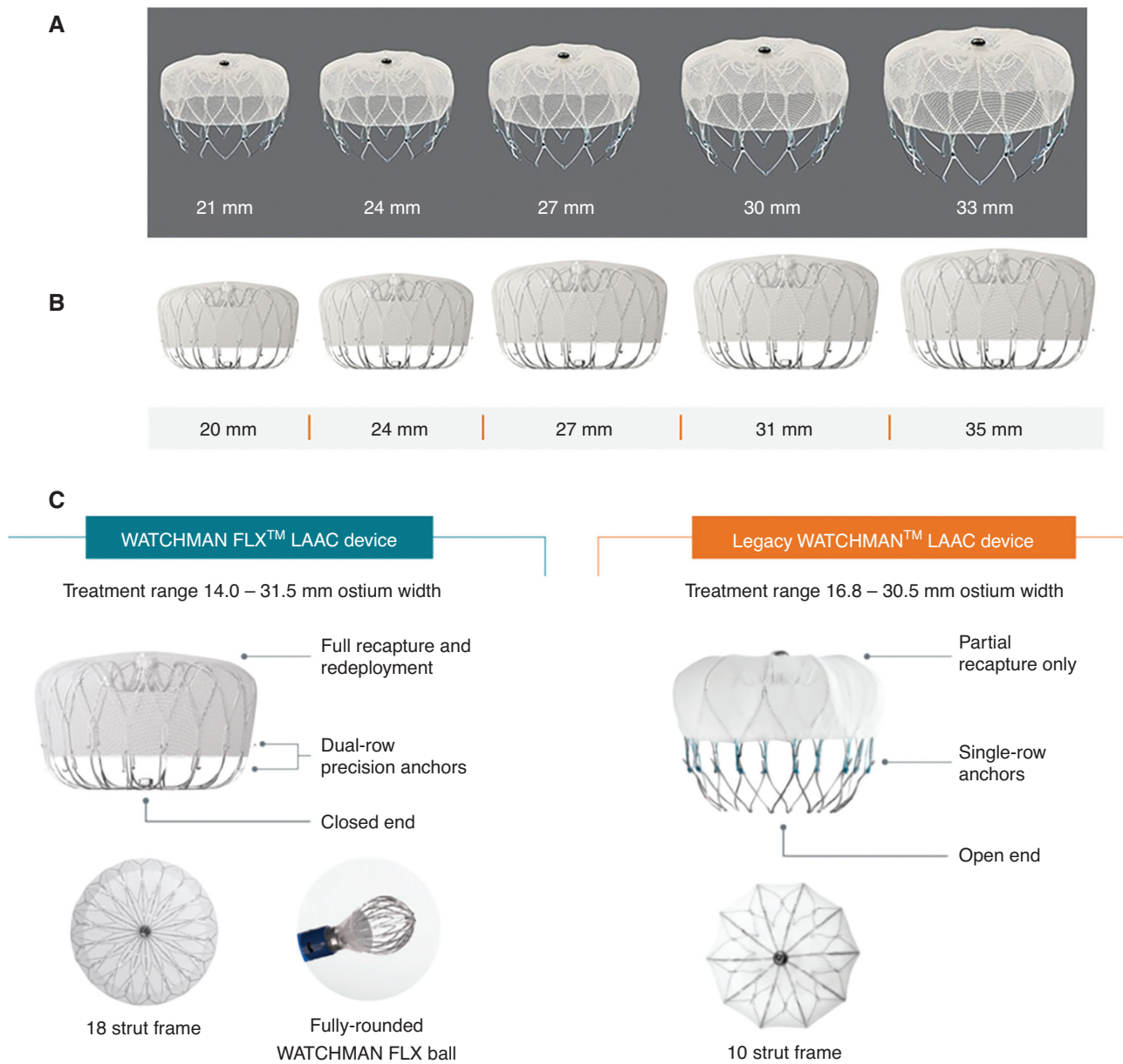

Figure 3 First and Second Generation Watchman Devices.
A: Watchman 2.5 (Legacy); B: Watchman FLX; C: Comparison of detailled parameters. Watchman 2.5 has been off the US market since the first quarter of 2021 (modified from Boston Scientific).

PLAATO system are similar in material, design concept (occlusive), and delivery. In the pilot study, 75 patients were recruited, but only 66 patients successfully received the implants. Nine patients did not receive the device because of anatomical difficulties or device wire malfunctions. Because of complications (in 5 of the first 16 cases) the device and delivery system were modified to the current format. Pericardial effusion occurred in two of the 75 cases (2.6%). At the 45 day TEE follow-up, 93% of devices showed successful sealing of the LAA, according to the protocol. These preliminary data suggested safe and feasible LAA occlusion with the first-generation Watchman™ system [62].

PROTECT AF, a randomized non-inferiority trial comparing the Watchman™ to warfarin, was published in 2009 [63]. A total of 707 eligible patients were randomly assigned in a 2:1 ratio to Watchman™ 2.5 implantation or warfarin, with a target INR of 2–3. A primary composite endpoint of stroke, cardiovascular death, and systemic embolism was analyzed on the basis of intention to treat. At 1065 patient-years of follow-up, the primary efficacy event rate was 3.0 per 100 patient-years in the intervention group and 4.9 per 100 patient-years in the control group, and the probability of non-inferiority of the intervention exceeded 99.9%. This trial provided strong evidence favoring the efficacy of percutaneous closure of the LAA with the Watchman™ 2.5 and provided the first alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with NVAF. However, two major concerns were raised regarding PROTECT AF: 1) inclusion of NVAF with a relatively low CHADS2 score (2.6 for each group) and 2) periprocedural complications, which were driven primarily by pericardial effusion requiring intervention. Despite the substantial improvement in procedural safety and clinical benefits observed in combined analysis of the PROTECT AF trial and Continued Access Protocol Registry [64, 65] with the Watchman™ 2.5 device, these concerns remained. Consequently, the prospective randomized PREVAIL trial was designed and conducted, and the data were published in 2014 [66]. A total of 407 patients with NVAF were enrolled 2:1 to receive the Watchman™ 2.5 (mean CHA2DS2-Vasc 3.8) or warfarin (mean CHA2DS2-Vasc 3.9), with a mean follow-up of 18 months. Two efficacy endpoints and one safety co-primary endpoint were assessed. LAAO with the Watchman™ 2.5 was found to be noninferior to warfarin for ischemic stroke prevention or systemic embolism >7 days post-procedure. The adverse event rates were low and were numerically comparable between arms. This trial confirmed that the periprocedural complications significantly improved with increasing operator experience [64, 65] and provided additional data indicating that LAAO with the Watchman™ 2.5 is a reasonable alternative to warfarin therapy for stroke prevention in patients with NVAF who do not have absolute contraindications for short-term warfarin therapy. In Europe, the EWOLUTION study [67] was designed to prospectively collect data on Watchman™ 2.5 performance in a real-world clinical setting in a high-risk patient cohort. Enrollment began in October 2013 and ended in May 2015. A total of 1025 participants with a mean age of 73.4 years were scheduled to receive the implant in 47 centers in 13 countries. With a mean CHA2DS2-Vasc of 4.5 and HAS-BLED score of 2.3 (73.3% contraindicated for oral anticoagulation) this population was deemed high risk. A high success rate of device implantation (98.4%) and efficacy in patients with ischemic stroke were observed; the major bleeding rate was 2.6% and was predominantly (2.3%) unrelated to the procedure or device.

The Watchman™ 2.5 became the first LAAO device approved in the US (March 2015), although it was removed from the US market shortly after the second-generation device, the Watchman™ FLX, was released in August 2020. The 5-year outcomes of the PREVAIL trial combined with the 5-year outcomes of the PROTECT AF trial clearly demonstrated that LAAO with the Watchman™ 2.5 device achieved stroke prevention in NVAF comparable to that of warfarin, and provided additional decreases in major bleeding, hemorrhagic stroke, and mortality [68, 69]. Even before US FDA approval of the Watchman™ 2.5 device, the National Cardiovascular Data Registry (NCDR) considered developing a LAAO Registry in mid-2014. Comprehensive post-approval data collection and analysis are essential for any potentially transformative new therapeutic modality, such as LAAO. NCDR, the Society of Cardiovascular Angiography and Interventions, US FDA, CMS,

and Boston Scientific were all participants, and collected data on 38,158 Watchman procedures performed by 1318 physicians in 495 hospitals in the United States between January 2016 and December 2018. The report of this "real world" experience [70] revealed a rate of major in-hospital adverse events of 2.16%, including pericardial effusion requiring intervention (1.39%) and major bleeding (1.25%), whereas stroke (0.17%) and death (0.19%) were rare. These real-world patients were older (mean 76.1 years), and had a higher mean CHA2DS2-Vasc score (4.6) and HAS-BLED score (3.0), than previous trial and registry patients. The median number of LAAO procedures performed annually was 28 for hospitals and 12 for physicians. Another network meta-analysis included 19 randomized controlled trials in a total of 87,831 patients with NVAF receiving anticoagulants, anti-platelet therapy, placebo, or LAAO [71]. Indirect comparison with warfarin indicated an efficacy benefit favoring LAAO over placebo and anti-platelet therapy; similar performance to NOACs/DOACs in preventing mortality and stroke or systolic embolism; and similar bleeding risk in patients with NVAF. Although these studies are limited by the heterogeneity of the design and patients, as well as the use of indirect comparisons, they do provide reassuring evidence in the absence of stronger data.

Watchman™ FLX: The Next Generation Device

Although the first-generation device was associated with a relatively low risk of procedure-related complications in practice, several important limitations persisted regarding the matrix size, ability to fully recapture the device, risk of perforation, device-related thrombus formation, and peri-device leak. To address these concerns, the second-generation device, the Watchman FLX (Figure 3B), was designed and has been available since November 2015 in Europe. The device includes three major modifications in the 1) size, 2) shape, and 3) fixation anchor (Figure 3C). The five available sizes (20, 24, 27, 31, and 35 mm) allow for wider coverage of both smaller and larger LAA ostia than provided by the Watchman™ 2.5. A shortened length enables implantation in shallower LAAs. The closed distal end also has a fluoroscopic

marker, which enhances procedural visibility. The left atrial face is flat and has a reduced, minimal metal screw area, thus facilitating endothelialization and decreasing post-implant thrombus formation. The nitinol 18-strut frame, as compared with the 10-strut frame in the Watchman 2.5, provides more contact points at the LAA ostium and radially expands to maintain a proper position in the LAA. Twelve J-shaped fixation anchors in two rows create a proximal and a distal line to aid in device stabilization for different anatomies of the LAA (in contrast to ten in one row in the Watchman™ 2.5). The new features of the Watchman™ FLX also allow for a wide range of compression (10–30% vs 8–20% recommended for the Watchman™ 2.5), and repeated full recapture and redeployment before the final release.

The clinical trial leading to the US approval of the Watchman™ FLX, PINNACLE FLX, started in May and ended in November of 2018; 400 patients were enrolled, with a mean age of 73.8 years, a mean CHA2DS2-Vasc score of 4.2, and a HAS-BLED score of 2.0. The new device was associated with very low incidence of pericardial effusion (0.5%) requiring intervention (4/400), which occurred between 7 and 340 days post implantation. According to the 12-month TEE, the rate of procedural success was 100% at implant, and 0% peri-device leak was observed [72]. The clinical value of the Watchman™ FLX was further ascertained by comparing the in-hospital outcomes for the Watchman™ FLX and Watchman™ 2.5 devices. On the basis of data from NCDR, the primary endpoint of in-hospital major adverse events, defined as a composite of death, cardiac arrest, stroke, TIA, intracranial hemorrhage, systemic arterial embolism, major bleeding, major vascular complication, myocardial infarction, pericardial effusion requiring intervention (percutaneous or surgical), and device embolization, was compared between the Watchman™ FLX (implanted between August 2020 and June 2021) and Watchman™ 2.5; each arm included 27,013 patients [73]. Significantly lower major adverse events were observed in the Watchman™ FLX group (1.35% vs 2.40%); in addition, in-hospital mortality (0.12% vs 0.24%), major bleeding (1.08% vs 2.05%), cardiac arrest (0.13% vs 0.24%), and device embolization (0.02% vs 0.06%) were significantly lower. Myocardial

infarction, stroke, and major vascular complications did not differ between groups. To date, no trial has directly compared the Amulet™ (2nd generation ACP) and Watchman™ FLX (2nd generation Watchman), although Amulet IDE and multiple other studies have demonstrated comparable outcomes between the Watchman 2.5 and Amulet. The Watchman™ FLX currently dominates the US market, whereas both the Amulet™ and Watchman™ FLX occupy a substantial share of the European market. High device and implantation costs have played an important role in slowing the adoption of LAAO treatment in the US (Global Market Insights 2022).

LAmbre™

In Europe, Lifetech received CE mark approval for the LAmbre™ closure system in June 2016. The device is self-expanding, and is constructed from a nitinol mesh and polyester membranes. (Figure 4). It consists of a hook-embedded umbrella (lobe) and a cover (disc) connected by a short central waist, which functions as an articulating, compliant connection between the cover and the umbrella, thus allowing the cover to self-orient to the cardiac wall. The distal lobe is composed of a nitinol frame with two rows of eight perimetral anchors to ensure stability. The waist allows the disc and lobe to lie at
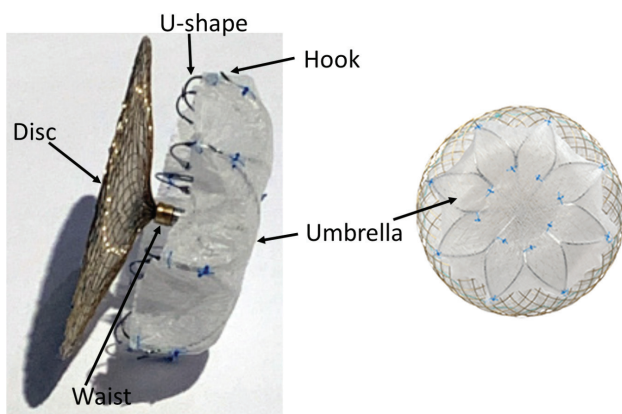

Figure 4 LAmbre Device.
The LAmbre is a self-expanding nitinol-based device consisting of a sewn-in polyethylene terephthalate fabric-enriched cover disc and an umbrella connected with a short central waist. The distal umbrella comprises eight claws with individual stabilizing hooks, with a polyethylene terephthalate membrane on the distal face (modified from Lifetech Scientific (Shenzhen) Co., Ltd.).

different angles without affecting the device stability. The device is packaged in a pre-loaded delivery sheath and is delivered in the LAA through an 8–10 F access sheath with full recapture and repositioning capabilities. Two different types of manufactured LAmbre™ device have been designed to accommodate single- and double-lobe LAA anatomies; the single-lobe sizing is between 16 and 36 mm, and the double-lobe sizing is between 16 and 26 mm.

Preclinical data in animal experiments demonstrating the feasibility and high success rate of the "an umbrella in the left atrial appendage" were published in 2013 [74, 75]. A preliminary study of 15 patients [76] and reports of the initial European experience in 60 patients [77] demonstrated an excellent implant success rate, favorable implant properties, very low incidence of complications, and good mid-term performance regarding stroke prevention. A prospective, multicenter study [78] conducted in 153 patients with NVAF with a CHADS2 score ≥1 has demonstrated high success (152/153) and a relatively low complication rate (5/153). A systematic review including 403 patients with NVAF [79] receiving the LAmbre™ device has demonstrated an excellent implantation success rate, promising follow-up clinical data, and favorable properties for challenging LAA anatomies. The first-in-human implantation of the LAmbre device in the United States was described in 2021 [80], and the clinical trial remains ongoing. US FDA approval will be necessary before wide clinical application can be achieved. Nonetheless, limited clinical comparison studies appear to suggest that the LAmbre™, Amulet™, and Watchman™ 2.5 all have high implant success rates, low risk of periprocedural adverse events, and good clinical outcomes [76, 81–83].

WaveCrest

The WaveCrest™ (Biosense Webster, Diamond Bar, CA, USA) LAAO device is a single lobe device consisting of a self-expanding nitinol frame covered by a polytetrafluoroethylene (ePTFE; also known as Gore-Tex) knit fabric (Figure 5A). In addition, a rim of polyurethane is located at the end of the membrane where the device contacts the myocardium, to promote endothelialization. Initial preclinical testing and first-in-human studies were
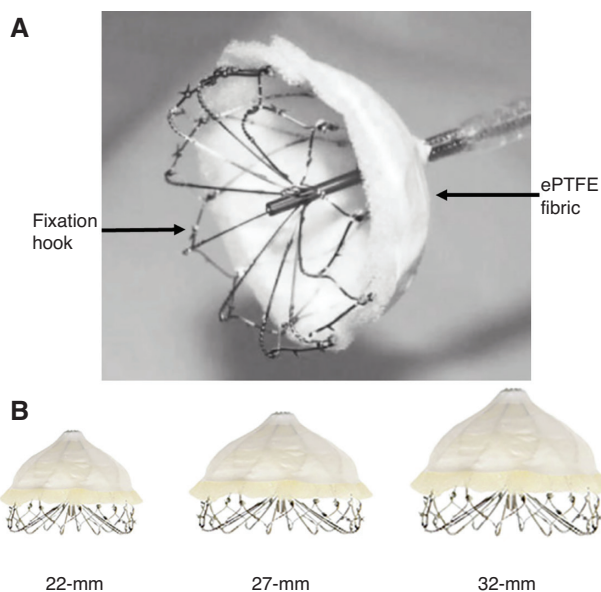
Figure 5 WaveCrest Device.
Initially named the Coherex Wavecrest LAAO System by Coherex Medical, this device was purchased by Biosense Webster in 2015 and is now named Wavecrest 1.3 (modified from Biosense Webster).

performed in New Zealand in 2010. Enrolment in the WaveCrest™ 1 phase II clinical study began in 2011, and the acute results for 63 patients were presented at EuroPCR 2013 [84]. The current generation device (WaveCrest™ 1.3) is available in three sizes (22, 27, and 32 mm; Figure 5B) to cover LAA ostia between 18 and 30 mm. The WaveCrest 1.3 device is an upgrade from the previous WaveCrest™ 1.2 device, which received CE mark approval in Europe in 2013. At the distal end, the frame perimeter is equipped with 20 fixation hooks to anchor the device to the LAA and ensure its stability. The hooks are retractable, thus separating the positioning of the device from its anchoring. The device is packaged in a pre-loaded delivery sheath and delivered into the LAA with a 12 F access sheath. The WaveCrest has no radial force to aid in stability. The major differences between the WaveCrest 1.2 and 1.3 devices are that the 1.3 device has more anchors and an extended ePTFE cover.

The WaveCrest™ device implantation is a two-step process: first the proximal expanded polytetrafluoroethylene cap/occluder is positioned, and then the distal anchors are deployed. Incorporation of foam into the edges of the occluder could potentially enhance LAA sealing. Although this device

was granted a CE mark in 2013 and has been marketed in Europe, it has not yet been approved in the US.

A critical trial in the United States, WAVECREST II, was designed to be a prospective, multicenter, randomized, active controlled clinical trial to evaluate the safety and effectiveness of this LAAO System. Participants (n = 1550) were to be randomized in a 1:1 ratio to the treatment arm (WaveCrest™ II) or the control arm (Watchman™ 2.5), to test the hypothesis that the safety and effectiveness of the WaveCrest™ II device are non-inferior to those of the comparator Watchman™ 2.5. The trial enrolled the first patient in January 2018 [85] and remains "active" but not recruiting. As previously described, the Watchman™ 2.5 device was removed from the US market in March 2021.

A class I recall by US FDA for the WaveCrest™ LAAO 32-mm device was announced in August 2018 and terminated in November 2020. The reason for the recall was that the tip of the delivery sheath may fold or buckle during attempts to recapture the 32-mm device, thus resulting in increased retraction force, and difficulty or failure to recapture the device. Therefore, any future comparisons will need to be performed with the Watchman FLX or Amulet as the control arm, before the US FDA can grant approval.

LARIAT

The LARIAT is not strictly a "device" but is a loop suture delivery system. It does not "occlude" the LAA but instead "ligates" the appendage at the base/ostia. The LARIAT system was described in detail in preclinical studies [86, 87] as well as in humans as an accompanying procedure during mitral valve surgery or AF ablation more than a decade ago [88]. The delivery techniques have been well described [87–90]. The LARIAT uses a snare (Figure 6A) that is placed around the base of the LAA, and delivers a suture loop that can ligate the LAA from the epicardial surface and thereby exclude it from the left atrium.

The LARIAT technique requires two points of access: endocardial transseptal puncture for placement of the balloon catheter and magnet wire (Figure 6B&C), and epicardial loop suture and magnet wire delivery. At the beginning of the
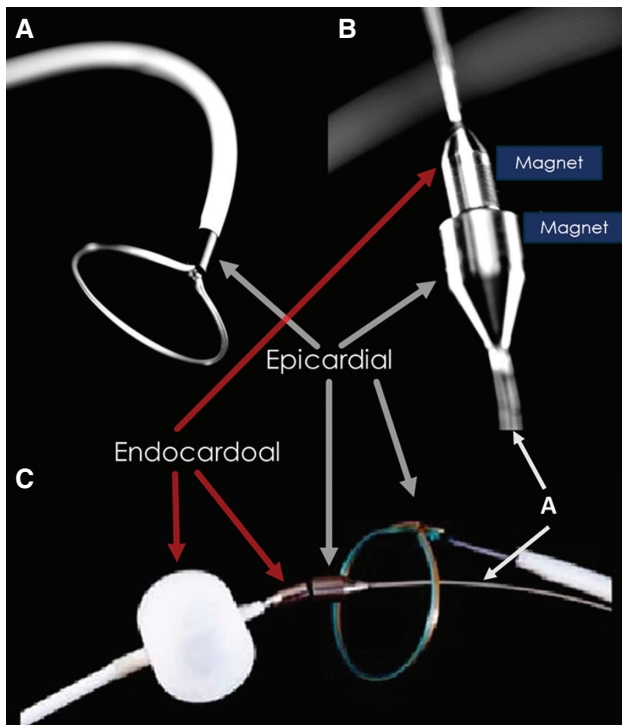
Figure 6 The LARIAT System.
A: Epicardial LARIAT suture loop delivery system with magnet tip guidewire. B: Endocardial and epicardial guidewires with magnet tip of opposite polarity. C: Endocardial balloon catheter with magnet tip (modified from SentreHEART, Inc.).

procedure, a 12 F catheter is placed in the pericardial space to deliver an adjustable, pre-tied suture loop (size 0 Teflon-coated, braided polyester suture; maximum diameter 40 mm) around the LAA. The new system, LARIAT+, has a larger snare accommodating LAA diameters as large as 45 mm. Subsequently, an 8 F catheter with a radiopaque inflatable (up to 20 mm) balloon tip (Figure 6B) is placed in the LAA via a standard transseptal sheath (8.5 F) to aid in precise location of the epicardial suture loop. The first endocardial magnet-tipped guidewire is placed near the apex of the LAA. The second endocardial magnet-tipped guidewire is placed at the tip of the LAA to establish a stable connection between the wires of opposite polarity. Initial clinical experience demonstrated effective LAA closure with the LARIAT device in 85 of 89 patients; 95% of patients at 3 months and 98% of patients at 12 months showed complete ligation, on the basis of TEE, and the access complications and periprocedural adverse events were acceptably low [89]. In the early days

(before 2015), the periprocedural complications were relatively high. Patients required hospital stays at least overnight or potentially longer, and pericardial drains were left in place for overnight or longer [91–93].

Pericardial access remains challenging for most electrophysiologists and interventional cardiologists. A multicenter registry of 712 consecutive patients undergoing LAA ligation with the LARIAT at 18 US hospitals [94] has demonstrated successful deployment in 682 patients (95.5%) and complete closure in 669 patients (98%), and has indicated improved complications because of better patient selection, and improvements in pericardial access techniques and periprocedural care. Nonetheless, notable findings included an acute perforation rate of 3.5%, delayed pericardial and pleural effusion rates of 4.78% after discharge, and follow-up TEE indicating leaks in 6.5% and thrombi in 2.5% of patients. Despite a favorable report of collective European experience in 141 patients demonstrating the feasibility of LAA exclusion with the LARIAT+, which indicated 97.1% complete closure by TEE at 6 months [95], an American study in 306 patients [96] has reported a much higher rate of postprocedural leak of 26.5% at the 1 month follow-up and 19.6% at the 6 month follow-up, according to TEE. At the median follow-up period of 15.9 months, nine patients developed thromboembolic events (2.9%). Thus, until randomized, controlled, prospective trials compare results with those of newer anticoagulants or the Watchman™ FLX/Amulet™ and report long term efficacy and safety data, the clinical applications of the LARIAT system will remain relatively limited.
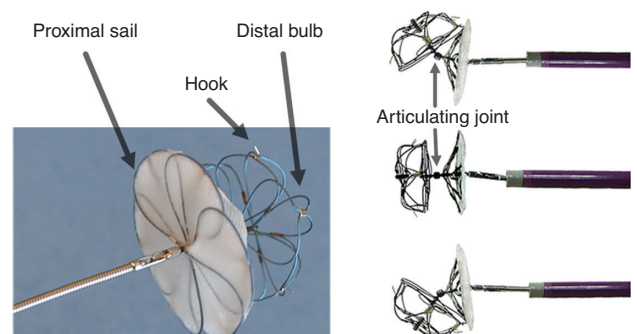

Figure 7 Ultraseal II Device (modified from Cardia).

Ultraseal Device

The Ultraseal device (Cardia, Eagan, Minnesota) is a self-expandable bulb-and-sail occluder (Figure 7) that received CE mark approval in March 2016. The nitinol device is composed of two parts: a soft distal bulb that anchors the device to the LAA through 12 stabilizing hooks and a three-leaflet multilayered sail, with a proximal polyvinyl alcohol foam layer and a distal polyester layer for LAA occlusion. The delivery system is 10 F to 12 F. The fully retrievable device allows for positioning and re-positioning as many times as necessary to ensure accurate placement.

Modifications between the first- and second-generation device [97, 98] have been made over the past 3 years. The initial experience with the Ultraseal I device preliminarily indicated its safety and feasibility in 12 patients with NVAF: no episodes of bleeding, stroke, pericardial effusion, or device embolization were observed at 45-day follow-up in this small study group [99]. No cases of residual leaks >5 mm were observed through TEE. One patient presented device related thrombus without clinical consequences. Another study in 23 consecutive patients with NVAF has also demonstrated a high success rate of implantation (21/23) and extremely low complication rate at a mean follow-up of 166 ± 80 days [100]. In a multicenter experience of 126 patients from 15 Canadian and European centers [101], this device was successfully implanted in 97% of patients, and major periprocedural adverse events (pericardial effusion, stroke, or device embolization) occurred in only three (2.4%) patients. At a median follow-up of 6 months, the rates of stroke and TIA were 0.8% and 0.8%, respectively, and no systemic emboli were observed. Despite low rates of periprocedural complications reported by previous studies, 2 of 18 patients experienced device fracture in another case series [102].

Recently, a multicenter international registry including 52 patients with NVAF with 6-month follow up [98] has reaffirmed the high success implantation rates, low incidence of peri-procedural complications, and favorable device safety profile of the modified Ultraseal II. Clearly, larger studies with longer clinical follow-up periods, involving comparison of this device with the two currently US FDA approved devices (Watchman FLX and Amulet) are warranted to further evaluate safety and efficacy before this device can be recommended for wide clinical application.
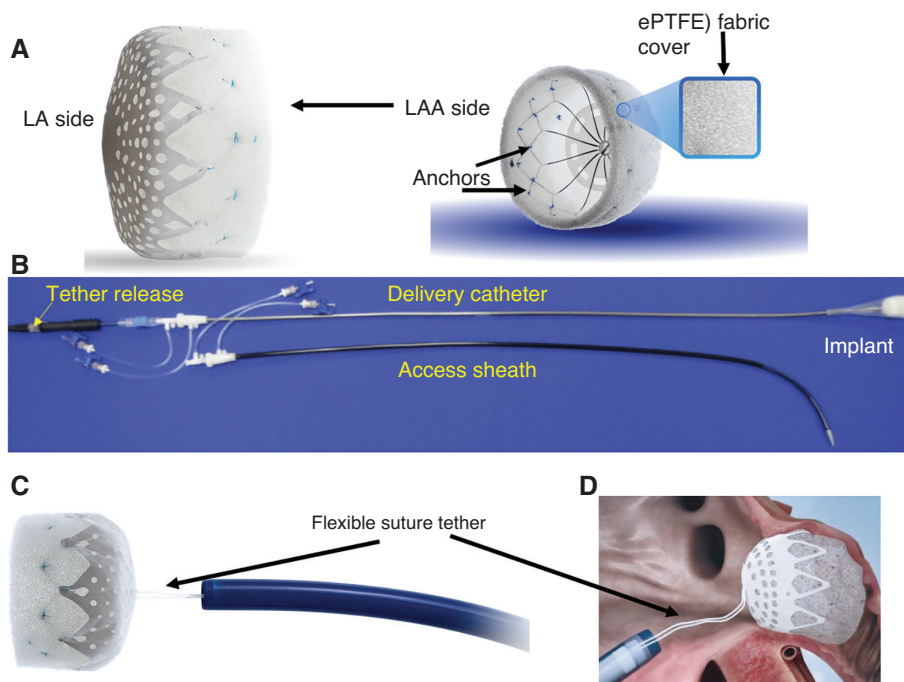

Figure 8 Conformal Left Atrial Appendage Seal (CLAAS) Device.
A: The form-based device, viewed from the LA and LAA sides. B: The delivery catheter and access sheath. C: Device attached to a flexible suture tether and the delivery sheath. D: Model showing the CLAAS device in the LAA before release (modified from Conformal Medical, Inc. and Sommer, et al., 2021).

Conformal Device

The conformal left atrial appendage seal (CLAAS) device (Conformal Medical, Inc., Nashua, NH) includes an implant (Figure 8A) and a delivery system (sheath and delivering catheter, Figure 8B). The implant (27 mm and 35 mm) is a self-expanding occluder consisting of a cylindrical nitinol endoskeleton with low-profile anchor barbs around the midpoint, which is covered with a porous foam cup made of polyurethane-carbonate matrix foam (form-based device). The distal portion of the form cup (LAA side) extends beyond the endoskeleton and serves as an atraumatic leading edge during device implantation. Two rows of anchors are present: ten in each row for the 27 mm device and 12 in each row for the 35 mm device. The foam is highly conformable and has a porous surface promoting tissue ingrowth from the LAA. The 27 mm device fits an 18 F short venous access sheath, and the large system fits a 20 F sheath. The implant is attached to the delivery catheter with a flexible suture tether, which is used for recapture and redeployment before final release (Figure 8C, 8D). Preclinical assessment performed in seven dogs has demonstrated the conformability of the CLAAS implant and its ability to seal the LAA [103]. Histologic examination has indicated complete neointima covering with minimal inflammation at 60 days. In the first clinical experience report, the device was implanted in 18 of 22 patients with NVAF with a CHA2DS2-Vasc score ≥4 and HAS-BLED score ≥3 [104]. TEE at 45 days indicated one leak >5 mm due to an unappreciated large posterior LAA lobe at the time of implantation and one case of device-associated thrombosis, which resolved with prolonged anticoagulation. Four patients did not receive the device because of the unavailability of the large 35 mm device at the time of implantation (the 27 mm device was tested but was recaptured and retrieved because of an inadequate seal). No periprocedural strokes, major pericardial effusions, or systemic or device embolization occurred. This first-in-human study, as part of the ongoing device feasibility trial (NCT03616028), appears to indicate the clinical feasibility of the CLAAS device for LAAO. Another study in 15 patients with NVAF with a CHA2DS2-Vasc score of 4.1 and a lower HAS-BLED score (1.4) has demonstrated 100% success in device implantation, with no procedure/device-associated complications requiring intervention [105]. An adequate LAA seal in all patients was confirmed in follow-up TEE up to 12 months, and device-associated thrombosis was detected in one patient at 6 months. This study was performed by using intracardiac echocardiography guidance. In brief, although little experience has been described to date, LAAO with the CLAAS device guided by ICE imaging appears to be feasible and has shown encouraging 1-year clinical outcomes. Despite the highly promising features of this new device, it has yet to receive CE mark approval. A much larger randomized, controlled trial enrolling 1600 patients and comparing CLAAS with the Watchman/Amulet is currently ongoing (NCT05147792).

LAAO: Current Clinical Status

Both the Watchman™ FLX and Amulet™ are currently US FDA approved and are used in the US, and the former is predominantly used. Both devices share a major part of European market with other CE mark approved devices also in use or in clinical trials. The detailed market shares of various LAAO devices in China and other Asian countries are unclear. Three clinical situations are commonly encountered in current LAAO therapy: advanced age, impaired kidney function, and LAAO at the time of NVAF ablation; thus, further discussion is warranted. Patient age does not appear to be a factor in recommending LAAO therapy, according to available data. A recent analysis of 36,065 LAAO recipients of the Watchman™ device, 34.6% (n = 12,475) of whom were patients with AF 80 years or older, has provided further support in this regard [106]: after adjustment for potential confounding variables, advanced age was not associated with LAAO procedural–related adverse outcomes including major complications, prolonged length of hospital stay, or increased hospitalization costs. In contrast, comparing to younger patients inpatient mortality increased, thus probably reflecting a frail population with a high burden of co-morbidities, such as congestive heart failure, renal failure, and peripheral vascular disease. Analysis of the EWOLUTION Registry has demonstrated similarly high procedural success (98.8% vs 98.5%) and no

differences in 7-day device- or procedure-associated adverse event rates in patients 85 years old or younger [107]. Another multicenter registry study of 1053 participants receiving the ACP I has reported that LAAO was associated with similar procedural success (97.3%) in patients <75 or ≥75 years, and the stroke and major bleeding rates were similar at a mean follow up of 16.8 months [108]. Patients' renal function status also does not appear to affect LAAO therapy. Patients with chronic kidney disease, particularly end-stage renal disease, are well known to be prone to complications due to bleeding on oral anticoagulation. NOACs/DOACs may be preferrable to warfarin [109] in patients with NVAF with impaired renal function. Available evidence indicates that, in those patients, LAAO therapy is safe and effective and can be considered an alternative to NOACs/DOACs for stroke prevention [109–111].

AF catheter ablation and LAAO could reasonably be considered simultaneously, because the two percutaneous interventions share several procedural issues and technical requirements. Clinically, a combined procedure would provide an alternative to antiarrhythmic drug (catheter ablation) for AF symptomatic improvement and anticoagulation for stroke prevention (LAAO). The earliest report in 30 patients, published a decade ago, has demonstrated the safety and feasibility of this treatment [112], and has been further supported by pooled data analysis [113]. A propensity score matching analysis from the US National Readmission Database has indicated an annual growth rate of 63% between 2016 and 2019, and no significant difference in MACE and all-cause 30-day readmission rates among patients receiving the combined procedure, matched LAAO only, or catheter ablation only [114]. A retrospective analysis of 1114 patients who underwent the combined procedure in China has supported the safety and long-term efficacy of this modality [115]. Model analysis has suggested that in symptomatic patients with NVAF with high stroke and bleeding risk who plan to undergo catheter ablation, the combined procedure may be a cost-effective therapeutic option particularly beneficial for patients with a CHA2DS2-VASc risk score ≥3 [116]. Data from the OPTION randomized controlled trial are awaited, as discussed below.

Post LAAO anticoagulation/antiplatelet regimens may vary according to the device and patient clinical status. For the Watchman FLX, patients may continue their anticoagulation (warfarin or NOAC/DOAC) plus ASA 81 mg for 45 days, and thereafter have their anticoagulation switched to double antiplatelet treatment (clopidogrel or other P2Y12 inhibitor, plus ASA 81 mg daily) for another 4.5 months. Six months after device implantation, patients should take only ASA indefinitely. Alternatively, patients may start a P2Y12 inhibitor plus ASA after device implantation for 6 months, then take ASA 81 mg daily indefinitely thereafter. For the Amplatzer Amulet device, patients should take double antiplatelets (P2Y12 inhibitor plus ASA) for 6 months and ASA 81 mg daily indefinitely thereafter. Until new clinical trial data become available, the post LAAO anticoagulation/antiplatelet therapy must be individualized on the basis of patients' risk/benefit profiles.

The current guidelines [6, 7] for LAAO therapy were written when the Watchman™ FLX and Amulet had not yet been approved. The IIb recommendations in both the ACC/AHA/HRS and the ESC guidelines state that percutaneous LAA occlusion may be considered in patients with AF at elevated risk of stroke and contraindications to long-term anticoagulation. With increased clinical experience, improved device technology, decreased periprocedural complication rates, and favorable long-term efficacy and safety outcomes in large numbers of patients, the next guidelines are anticipated to elevate the recommendations, at least in certain populations of patients with NVAF.

Currently, for patients with NVAF at high risk of stroke who would be exposed to excessive bleeding risk with pharmacologic anticoagulation or who have a history of poor drug compliance, any CE mark approved LAAO device could arguably be selected. Although the learning curves for all available devices continue to evolve, the results of ongoing clinical trials are awaited to answer many questions in the LAAO area.

Ongoing Clinical Trials

OPTION (NCT03795298; Comparison of anticoagulation with left atrial appendage closure after atrial fibrillation ablation): The purpose of the OPTION study is to investigate whether LAA

closure with the Watchman™ FLX device is a reasonable alternative to oral anticoagulation after percutaneous catheter ablation for NVAF. This prospective randomized clinical trial aims to enroll 1600 patients from 130 global institutes. Patients with a CHA2DS2-VASc score ≥2 in men or ≥3 in women undergoing AF catheter ablation between 90 and 180 days before randomization (sequential), or planning to undergo catheter ablation within 10 days of randomization (concomitant), will be randomized 1:1 to the Watchman™ FLX and control. Control patients will start or continue market-approved oral anticoagulation for the duration of the trial. Follow-up in both the Watchman™ FLX device and control groups will occur at 3, 12, 24, and 36 months. The primary effectiveness noninferiority endpoint is stroke (ischemic or hemorrhagic), all-cause death, or systemic embolism at 36 months. The primary safety superiority endpoint is nonprocedural bleeding through 36 months. The secondary noninferiority endpoint is International Society on Thrombosis and Hemostasis (ISTH) major bleeding through 36 months (including procedural bleeding). This trial is active and has reached full enrollment. Trial outcomes are expected to be published in 2024.

CHAMPION-AF (NCT04394546; WATCH-MAN™ FLX Versus NOAC for Embolic ProtectION in the Management of Patients with Non-Valvular Atrial Fibrillation): This study is a prospective, randomized, multi-center global investigation enrolling 3000 patients with NVAF with a CHA2DS2-Vasc score ≥2 in men or ≥3 in women, with 5-year follow up. Primary endpoints include 1) non-inferiority of a composite of ischemic stroke/TIA, systemic embolism, and cardiovascular death, and 2) superiority of non-procedural major bleeding (as defined by ISTH major bleeding and clinically relevant non-major bleeding). Participants will be randomized 1:1 to either the Watchman device ("device group") or a commercially available non-vitamin K oral anticoagulant or novel oral anticoagulant/direct oral anticoagulant (NOAC/DOAC). The trial started in October 2020 and was originally expected to be completed by December 2025 but has been postponed to December 2027. **OPTION and CHAMPION-AF** patients have average bleeding risk and could choose either the occlusion device or NOAC/DOAC.

CATALYST (NCT04226547; Clinical Trial of Atrial Fibrillation Patients Comparing Left Atrial Appendage Occlusion Therapy to Non-vitamin K Antagonist Oral Anticoagulants): This clinical investigation is a prospective, randomized, multi-center active control worldwide trial. A total of 2650 patients with NVAF with elevated bleeding risk and a CHA2DS2-Vasc score ≥3 will be randomized 1:1 to the Amulet™ LAAO device ("device group") and a commercially available NOAC/DOAC medication ("control group"). The choice of NOAC/DOAC in the control group will be left to the discretion of the study physician. The objective of this trial is to evaluate the safety and effectiveness of the Amulet device compared with NOAC/DOAC therapy in patients with NVAF at elevated risk of ischemic stroke, who have been recommended to receive long-term NOAC/DOAC therapy. Primary endpoints include 1) non-inferiority of a composite of ischemic stroke/TIA, systemic embolism, and cardiovascular death, and 2) superiority of major bleeding or clinically relevant non-major bleeding (ISTH) excluding procedural bleeding. The trial started in July 2020 and is expected to complete enrollment by December 2024; the expected study completion date is in April 2029.

CLOSURE-AF (NCT03463317; Left Atrial Appendage CLOSURE in Patients With Atrial Fibrillation Compared with Medical Therapy): The study is sponsored by Charite University of Germany and will enroll 1512 patients with NVAF with a CHA2DS2-Vasc score ≥2 who are at risk of bleeding or for whom anticoagulation is contraindicated. Any CE mark approved occlusion device will be included and compared with NOAC/DOAC or VKA with 1:1 randomization. The trial began in February 2018, the primary completion date is in September 2023, and the study completion date is in March 2025. The primary endpoint includes a composite of ischemic or hemorrhagic stroke, systemic embolism, major bleeding, and cardiovascular and unexplained death after a mean follow up of 2 years.

OCCLUSION-AF (NCT03642509; Left Atrial Appendage Occlusion Versus Novel Oral Anticoagulation for Stroke Prevention in Atrial Fibrillation): The Occlusion-AF trial is designed to compare LAAO to NOAC/DOAC therapy for secondary stroke prevention in patients with

NVAF with a high risk of recurrent thromboembolic events, i.e., with previous ischemic stroke or TIA, who are otherwise eligible for anticoagulation. This study is sponsored by the University of Aarhus and involves eight European hospitals. Tested devices include both the Watchman FLX and Amulet. This is a multicenter, randomized, open-label non-inferiority trial with blinded outcome evaluation comparing LAAO to NOAC/DOAC therapy through a 1:1 stratified randomization design in 750 patients with NVAF and ischemic stroke or TIA within 6 months before enrollment. The trial started in January 2019, enrollment is expected to be completed by January 2024, and the study is expected to be completed by October 2030. The primary endpoint is the combined rate of stroke, systemic embolism, major bleeding, and all-cause mortality.

STROKECLOSE (NCT02830152; Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Hemorrhage: A Multicenter Randomized Clinical Trial): This is another European trial, sponsored by Karolinska University Hospital. The aim of STROKECLOSE is to assess the effects of LAAO with the Amulet in decreasing the composite outcome of stroke (ischemic and hemorrhagic), systolic embolism, life-threatening or major bleeding, and cardiovascular mortality in patients with NVAF and prior intracerebral hemorrhage. This is a multicenter prospective randomized open-label clinical trial with blinded outcome evaluation and blinded safety outcome assessment. The active comparison will be LAAO against medical therapy with 2:1 stratified randomization, involving 750 patients with NVAF with a history of ICH within 6 months before enrollment and a CHA2DS2-Vasc score >2. The control group will receive medical therapy according to national standards and guidelines at the treating physicians' discretion, including vitamin-K antagonists, NOAC/DOAC, antiplatelet therapy, or no antithrombotic therapy at all. The trial started in May 2017, the primary completion date was estimated to be in May 2022 (but the study is still recruiting), and the study is expected to be completed by May 2030.

ASAP-TOO (NCT02928497; Assessment of the WATCHMAN™ Device in Patients Unsuitable for Oral Anticoagulation): This is a prospective, randomized, multi-center, global investigation aimed at establishing the safety and effectiveness of the Watchman 2.5 in decreasing the risk of stroke in participants (n = 481) with NVAF who are not candidates for anti-coagulation therapy. Participants will be randomized 2:1 to receive the Watchman 2.5 device or a control treatment of either single antiplatelet medication or no medication, at the discretion of the study physician. The trial began in February 2017, and the anticipated primary and study completion dates are in December 2025. The trial status is active but not recruiting. Watchman™ 2.5 has been off the US market since the first quarter of 2021, shortly after the US FDA approval of the Watchman™ FLX in August 2020.

Conclusion

The earliest interventions designed to modify the LAA for stroke prevention were for patients with "valvular" or "rheumatic" AF, and were initiated by cardiac surgeons. Similarly to current catheter AF ablation therapy, which was adapted from surgical MAZE procedures [117], percutaneous LAAO has followed surgical LAA intervention in terms of its development, progression, and evolution. Nonetheless, although substantial progress, with demonstrated efficacy and safety, has been made in LAAO therapy, many clinically relevant questions remain to be addressed: 1) Compared with DOACs/NOACs, is LAAO more efficacious and safer in patients with NVAF who do not have high bleeding risk but still need stroke prevention? 2) For patients with NVAF who have absolute contraindications for anticoagulation, would LAAO or antiplatelet agents be the preferred treatment option? 3) What is the optimal post-LAAO regimen? Current therapies range from short-term anticoagulation using warfarin or DOACs/NOACs, to single or double antiplatelet agents, to no therapy at all. 4) Which of the two US FDA approved devices, Watchman™ FLX and Amulet™, has better procedural safety and long-term efficacy? 5) For devices that are CE mark approved but not yet US FDA approved, should more clinical trials involving comparison with Watchman™ FLX or Amulet™ be performed before broad guideline recommendations are issued? Currently, high quality long-term follow

up data are lacking for those devices. 6) What are the best/most appropriate preprocedural, intraprocedural, and follow-up imaging modalities, among TEE, Micro-TEE, CCTA, and ICE? 7) What are the safety, efficacy, and cost-effectiveness of LAAO in patients with NVAF who require catheter AF ablation or TAVR? 8) What are the treatment options for patients with recurrent stroke/TIA who have had successful LAAO? 9) Would LAAO be a replacement or just complementary therapy for patients with recurrent stroke/TIA who are already receiving appropriate anticoagulation?

For the medical technology industry, future device design and modification should focus on 1) minimizing the risks of device-related thrombosis and periprocedural pericardial effusion/tamponade, 2) improving ease of use and device stability, 3) developing a smaller delivery sheath to minimize groin access complications, and 4) developing a flexible/steerable sheath mechanism to facilitate device release for various LAA anatomies.

The academic community must also answer several important questions: 1) Which types of LAA anatomy have the highest risk of thrombus formation/stroke/TIA and therefore would benefit most from LAAO? 2) What are the hemodynamic changes, and mechanical and electrical remodeling/reverse remodeling after LAAO [118, 119]? 3) Do important biochemical and/or endocrinologic changes occur after LAAO, and will they affect clinical outcomes [120]? 4) Is LAAO pro-arrhythmic, anti-arrhythmic, or arrhythmia-neutral? 4) Is device intervention cost-effective, and does device intervention remain cost-effective in older people, in whom the operative risk may be greater, and the duration of anticoagulant therapy may be relatively short?

For clinicians, industry, and academic communities, what is the role of LAAO for patients with valvular AFs, who have been excluded from the current LAAO trials? The global burden of valvular AF is substantial. Among patients with AF, 30% have some form of valvular heart disease detectable by echocardiography [121]. Moreover, in developing countries, where the prevalence of rheumatic heart disease remains high, most cases of AF are attributable to rheumatic heart disease and would be considered valvular AF [122]. Answers to these questions will undoubtedly affect the future of LAAO therapy and will ideally improve patient outcomes.

Potential Conflicts of Interest

REFERENCES

1. Wolf PA, Abbott RD, Kannel KB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983–8.
2. Ferro José M. Cardioembolic stroke: an update. Lancet Neurol 2003;2:177–88.
3. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart Disease and Stroke Statistics—2021 Update: A Report From the American Heart Association. Circulation 2021;143(8):e254–e743.
4. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755–9.
5. Cresti A, García-Fernández MA, Sievert H, Mazzone P, Baratta P, Solari M, et al. Prevalence of extra-appendage thrombosis in non-valvular atrial fibrillation and atrial flutter in patients undergoing cardioversion: a large transoesophageal echo study. EuroIntervention 2019;15(3):e225–e30.
6. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019;74:104–32.
7. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and

management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373–498.

8. Domanski MJ, Zipes DP, Benditt DG, Camm AJ, Exner DV, Ezekowitz MD, et al. North American Society of Pacing and Electrophysiology. Central clinical research issues in electrophysiology: report of the NASPE Committee. Pacing Clin Electrophysiol 2001;24:526–34.

9. Apostolakis E, Papakonstantinou NA, Baikoussis NG, Koniari I, Papadopoulos G. Surgical strategies and devices for surgical exclusion of the left atrial appendage: a word of caution. J Card Surg 2013;28:199–206.

10. Tsai YC, Phan K, Munkholm-Larsen S, Tian DH, La Meir M, Yan TD. Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: a meta-analysis. Eur J Cardiothorac Surg 2015;47:847–54.

11. Veinot JP, Harrity PJ, Gentile F, Khandheria BK, Bailey KR, Eickholt JT, et al. Anatomy of the normal left atrial appendage: a quantitative study of age-related changes in 500 autopsy hearts: implications for echocardiographic examination. Circulation 1997;96:3112–5.

12. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. Heart 1999;82:547–54.

13. Glikson M, Wolff R, Hindricks G, Mandrola J, Camm AJ, Lip GYH, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update. EuroIntervention 2020;15:1133–80.

14. Kerut EK. Anatomy of the left atrial appendage. Echocardiography 2008;25:669–73.

15. Barbero U, Ho SY. Anatomy of the atria: a road map to the left atrial appendage. Herzschrittmacherther Elektrophysiol 2017;28:347–54.

16. Beigel R, Wunderlich NC, Ho SY, Arsanjani R, Siegel RJ. The left atrial appendage: anatomy, function, and noninvasive evaluation. JACC Cardiovasc Imaging 2014;7:1251–65.

17. Pollick C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. Implications for the development of thrombus. Circulation 1991;84:223–31.

18. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: A Report from the American Heart Association. Circulation 2017;135:e146–603.

19. Belcher JR, Somerville W. Systemic embolism and left auricular thrombosis in relation to mitral valvotomy. Br Med J 1955;2(4946):1000–3.

20. Hinton RC, Kistler JP, Fallon JT, Friedlich AL, Fisher CM. Influence of etiology of atrial fibrillation on incidence of systemic embolism. Am J Cardiol 1977;40:509–13.

21. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology 1978;28:973–7.

22. Fisher CM. Reducing risks of cerebral embolism. Geriatrics 1979;34:59–61, 65–6.

23. Madden JL. Resection of the left auricular appendix—a prophylaxis for recurrent arterial emboli. JAMA 1949;140:769–72.

24. Hellerstein HK, Sinaiko E, Dolgin M. Amputation of the canine atrial appendages. Proc Soc Exp Biol Med 1947;66:337.

25. Hellerstein HK, Sinaiko E, Dolgin M. Amputation of the canine atrial appendages. Surgery 1948;24:719–23.

26. Bailey CP, Olsen AK, Keown KK, Nichols HT, Jamison WE. Commissurotomy for mitral stenosis: technique for prevention of cerebral complications. JAMA 1952;149:1085–91.

27. Badhwar V, Rankin JS, Damiano RJ Jr, Gillinov AM, Bakaeen FG, Edgerton JR, et al. The Society of Thoracic Surgeons 2017 Clinical Practice Guidelines for the Surgical Treatment of Atrial Fibrillation. Ann Thorac Surg 2017;103:329–41.

28. Caliskan E, Sahin A, Yilmaz M, Seifert B, Hinzpeter R, Alkadhi H, et al. Epicardial left atrial appendage AtriClip occlusion reduces the incidence of stroke in patients with atrial fibrillation undergoing cardiac surgery. Europace 2018;20:e105–e14.

29. Greenberg JW, Lee R, Hui DS. Patient selection and methods of surgical left atrial appendage exclusion. J Thromb Thrombolysis 2019;48:209–14.

30. Rosati F, de Maat GE, Valente MAE, Mariani MA, Benussi S. Surgical clip closure of the left atrial appendage. J Cardiovasc Electrophysiol 2021;32:2865–72.

31. Chatterjee S, Alexander JC, Pearson PJ, Feldman T. Left atrial appendage occlusion: lessons learned from surgical and transcatheter experiences. Ann Thorac Surg 2011;92:2283–92.

32. Aryana A, Singh SK, Singh SM, O'Neill PG, Bowers MR, Allen SL. Association between incomplete surgical ligation of left atrial appendage and stroke and systemic embolization. Heart Rhythm 2015;12:1431–7.

33. Ventosa-Fernandez G, Quintana E, Castellá M, Pereda D. Exclusion of the left atrial appendage with the TigerPaw II system: a word of caution. Interact Cardiovasc Thorac Surg 2015;21:803–4.

34. Kanderian AS, Gillinov AM, Pettersson GB, Blackstone E, Klein AL. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. J Am Coll Cardiol 2008;52:924–9.

35. Whitlock RP, Belley-Cote EP, Paparella D, Healey JS, Brady K, Sharma M, et al. Left atrial appendage occlusion during cardiac surgery to prevent stroke. N Engl J Med 2021;384:2081–91.

36. Martinez C, Katholing A, Wallenhorst C, Freedman SB. Therapy persistence in newly

diagnosed non-valvular atrial fibrillation treated with warfarin or NOAC. A cohort study. Thromb Haemost 2016;115:31–9.

37. Brown JD, Shewale AR, Talbert JC. Adherence to rivaroxaban, dabigatran, and apixaban for stroke prevention in incident, treatment-naïve nonvalvular atrial fibrillation. J Manag Care Spec Pharm 2016;22:1319–29.

38. Durmaz E, Karpuz MH, Bilgehan K, Ikitimur B, Ozmen E, Ebren C, et al. Left atrial thrombus in patients with atrial fibrillation and under oral anticoagulant therapy; 3-D transesophageal echocardiographic study. Int J Cardiovasc Imaging 2020;36:1097–03.

39. Ding WY. Residual stroke risk in atrial fibrillation. Arrhythm Electrophysiol Rev 2021;10:147–53.

40. Ding WY, Rivera-Caravaca JM, Marin F, Torp-Pedersen C, Roldán V, Lip GYH. Prediction of residual stroke risk in anticoagulated patients with atrial fibrillation: mCARS. J Clin Med 2021;10:3357.

41. Kapłon-Cieślicka A, Gawałko M, Budnik M, Uziębło-Życzkowska B, Krzesiński P, Starzyk K, et al. Left atrial thrombus in atrial fibrillation/flutter patients in relation to anticoagulation strategy: LATTEE registry. J Clin Med 2022;11:2705.

42. Nakai T, Lesh MD, Gerstenfeld EP, Virmani R, Jones R, Lee RJ. Percutaneous left atrial appendage occlusion (PLAATO) for preventing cardioembolism: first experience in canine model. Circulation 2002;105:2217–22.

43. Aryana A, Saad EB, d'Avila A. Left atrial appendage occlusion and ligation devices: what is available, how to implement them, and how to manage and avoid complications. Curr Treat Options Cardiovasc Med 2012;14:503–19.

44. Sievert H, Lesh MD, Trepels T, Omran H, Bartorelli A, Della Bella P, et al. Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. Circulation 2002;105:1887–9.

45. Ostermayer SH, Reisman M, Kramer PH, Matthews RV, Gray WA, Block PC, et al. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. J Am Coll Cardiol 2005;46:9–14.

46. Ussia GP, Mulè M, Cammalleri V, Scarabelli M, Barbanti M, Immè S, et al. Percutaneous closure of left atrial appendage to prevent embolic events in high-risk patients with chronic atrial fibrillation. Catheter Cardiovasc Interv 2009;74:217–22.

47. Park JW, Leithäuser B, Gerk U, Vrsansky M, Jung F. Percutaneous left atrial appendage transcatheter occlusion (PLAATO) for stroke prevention in atrial fibrillation: 2-year outcomes. J Invasive Cardiol 2009;21:446–50.

48. Block PC, Burstein S, Casale PN, Kramer PH, Teirstein P, William DO, et al. Percutaneous left atrial appendage occlusion for patients in atrial fibrillation suboptimal for warfarin therapy: 5-year results of the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) Study. JACC Cardiovasc Interv 2009;2:594–600.

49. Bayard Y-L, Omran H, Neuzil P, Thuesen L, Pichler M, Rowland E, et al. PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) for prevention of cardioembolic stroke in non-anticoagulation eligible atrial fibrillation patients: results from the European PLAATO study. EuroIntervention 2010;6:220–6.

50. Freixa X, Chan JL, Tzikas A, Garceau P, Basmadjian A, Ibrahim R. The Amplatzer™ Cardiac Plug 2 for left atrial appendage occlusion: novel features and first-in-man experience. EuroIntervention 2013;8:1094–8.

51. Meier B, Palacios I, Windecker S, Rotter M, Cao QL, Keane D, et al. Transcatheter left atrial appendage occlusion with Amplatzer devices to obviate anticoagulation in patients with atrial fibrillation. Catheter Cardiovasc Interv 2003;60:417–22.

52. Park J-W. Implantation of the AMPLATZERTM Cardiac Plug: tips and tricks. Herzschr Elektrophys 2013;24:33–8.

53. Nietlispach F, Gloekler S, Krause R, Shakir S, Schmid M, Khattab AA, et al. Amplatzer left atrial appendage occlusion: single center 10-year experience. Catheter Cardiovasc Interv 2013;82:283–9.

54. Tzikas A, Shakir S, Gafoor S, Omran H, Berti S, Santoro G, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicenter experience with the AMPLATZER Cardiac Plug. EuroIntervention 2016;11:1170–9.

55. Park JW, Bethencourt A, Sievert H, Santoro G, Meier B, Walsh K, et al. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. Catheter Cardiovasc Interv 2011;77:700–6.

56. Lam YY, Yip GW, Yu CM, Chan WW, Cheng BC, Yan BP, et al. Left atrial appendage closure with AMPLATZER cardiac plug for stroke prevention in atrial fibrillation: initial Asia-Pacific experience. Catheter Cardiovasc Interv 2012;79:794–800.

57. Landmesser U, Schmidt B, Nielsen-Kudsk JE, Lam SCC, Park JW, Tarantini G, et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: periprocedural and early clinical/echocardiographic data from a global prospective observational study. EuroIntervention 2017;13:867–76.

58. Nielsen-Kudsk JE, Korsholm K, Damgaard D, Valentin JB, Diener HC, Camm AJ, et al. Clinical outcomes associated with left atrial appendage occlusion versus direct oral anticoagulation in atrial fibrillation. JACC Cardiovasc Interv 2021;14:69–8.

59. Lakkireddy D, Thaler D, Ellis CR, Swarup V, Sondergaard L, Carroll J, et al. Amplatzer amulet left atrial appendage occluder versus Watchman device for stroke

prophylaxis (Amulet IDE): a randomized, controlled trial. Circulation 2021;144:1543–52.

60. Fountain RB, Holmes DR, Chandrasekaran K, Packer D, Asirvatham S, Van Tassel R, et al. The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation) trial. Am Heart J 2006;151:956–61.

61. Fountain R, Holmes DR Jr, Hodgson PK, Chandrasekaran K, Van Tassel R, Sick P. Potential applicability and utilization of left atrial appendage occlusion devices in patients with atrial fibrillation. Am Heart J 2006;152:720–3.

62. Sick PB, Schuler G, Hauptmann KE, Grube E, Yakubov S, Turi ZG, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. J Am Coll Cardiol 2007;49:1490–5.

63. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomized non-inferiority trial. Lancet 2009;374:534–42.

64. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. Circulation 2011;123:417–24.

65. Gangireddy SR, Halperin JL, Fuster V, Reddy VY. Percutaneous left atrial appendage closure for stroke prevention in patients with atrial fibrillation: an assessment of net clinical benefit. Eur Heart J 2012;33:2700–8.

66. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol 2014;64:1–12.

67. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial. Heart Rhythm 2017;14:1302–8.

68. Holmes DR Jr, Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, et al. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: a patient-level meta-analysis. J Am Coll Cardiol 2015;65:2614–23.

69. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, et al. 5-year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials. J Am Coll Cardiol 2017;70:2964–75.

70. Freeman JV, Varosy P, Price MJ, Slotwiner D, Kusumoto FM, Rammohan C, et al. The NCDR left atrial appendage occlusion registry. J Am Coll Cardiol 2020;75:1503–18.

71. Sahay S, Nombela-Franco L, Rodes-Cabau J, Jimenez-Quevedo P, Salinas P, Biagioni C, et al. Efficacy and safety of left atrial appendage closure versus medical treatment in atrial fibrillation: a network meta-analysis from randomized trials. Heart 2017;103:139–47.

72. Kar S, Doshi SK, Sadhu A, Horton R, Osorio J, Ellis C, et al. Primary outcome evaluation of a next-generation left atrial appendage closure device: results from the PINNACLE FLX trial. Circulation 2021;143:1754–62.

73. Price MJ, Friedman DJ, Du C, Wang Y, Lin Z, Curtis JP, et al. Comparative safety of transcatheter LAAO with the first-generation Watchman and next-generation Watchman FLX devices. JACC Cardiovasc Interv 2022;15:2115–23.

74. Lam YY. A new left atrial appendage occluder (Lifetech LAmbre device) for stroke prevention in atrial fibrillation. Cardiovasc Revasc Med 2013;14:134–6.

75. Lam YY, Yan BP, Doshi SK, Li A, Zhang D, MG, et al. Preclinical evaluation of a new left atrial appendage occluder (Lifetech LAmbre™ device) in a canine model. Int J Cardiol 2013;168:3996–4001.

76. Chen S, Schmidt B, Bordignon S, Bologna F, Nagase T, Tsianakas N, et al. Feasibility of percutaneous left atrial appendage closure using a novel LAmbre occluder in patients with atrial fibrillation: initial results from a prospective cohort registry study. J Cardiovasc Electrophysiol 2018;29(2):291–7.

77. Park J-W, Sievert H, Kleinecke C, Vaskelyte L, Schnupp S, Sievert K, et al. Left atrial appendage occlusion with LAmbre in atrial fibrillation: initial European experience. Int J Cardiol 2018;265:97–102.

78. Huang H, Liu Y, Xu Y, Wang Z, Li Y, Cao K, et al. Percutaneous left atrial appendage closure with the LAmbre device for stroke prevention in atrial fibrillation: a prospective, multicenter clinical study. JACC Cardiovasc Interv 2017;10:2188–94.

79. Ali M, Rigopoulos AG, Mammadov M, Torky A, Auer A, Matiakis M, et al. Systematic review on left atrial appendage closure with the LAmbre device in patients with non-valvular atrial fibrillation. BMC Cardiovasc Disord 2020;20:78.

80. Qintar M, Wang DD, Lee J, Eng MH, Frisoli T, Villablanca P, et al. Left atrial appendage occlusion with the LAmbre device: first-in-human in the United States. J Invasive Cardiol 2021;33:E670–E1.

81. Cheung GS, So KC, Chan CK, Chan AK, Lee AP, Lam YY, et al. Comparison of three left atrial appendage occlusion devices for stroke prevention in patients with non-valvular atrial fibrillation: a single-centre seven-year experience with WATCHMAN, AMPLATZER Cardiac Plug/Amulet, LAmbre: comparison of three LAAO devices for stroke prevention. AsiaIntervention 2019;5:57–63.

82. Schnupp S, Liu XX, Buffle E, Gloekler S, Mohrez Y, Cheikh-Ibrahim M, et al. Late clinical outcomes of lambre

versus amplatzer occluders for left atrial appendage closure. J Cardiovasc Electrophysiol 2020;31:934–42.

83. Ke JY, Jin LS, Lin YN, Xu J, Liu WK, Fu JY, et al. Combined atrial fibrillation ablation and left atrial appendage closure: Watchman vs. LAmbre devices. Front Cardiovasc Med 2022;9:1011037.

84. Bergmann MW, Landmesser U. Left atrial appendage closure for stroke prevention in non-valvular atrial fibrillation: rationale, devices in clinical development and insights into implantation techniques. EuroIntervention 2014;10:497–504.

85. Vainrib AF, Bamira D, Benenstein RJ, Aizer A, Chinitz LA, Saric M. Echocardiographic Guidance of the novel wavecrest left atrial appendage occlusion device. CASE (Phila) 2018;2:297–300.

86. Lee RJ, Bartus K, Yakubov SJ. Catheter-based left atrial appendage (LAA) ligation for the prevention of embolic events arising from the LAA: initial experience in a canine model. Circ Cardiovasc Interv 2010;3:224–9.

87. Singh SM, Dukkipati SR, d'Avila A, Doshi SK, Reddy VY. Percutaneous left atrial appendage closure with an epicardial suture ligation approach: a prospective randomized preclinical feasibility study. Heart Rhythm 2010;7:370–6.

88. Bartus K, Bednarek J, Myc J, Kapelak B, Sadowski J, Lelakowski J, et al. Feasibility of closed-chest ligation of the left atrial appendage in humans. Heart Rhythm 2011;8:188–93.

89. Bartus K, Han FT, Bednarek J, Myc J, Kapelak B, Sadowski J, et al. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108–18.

90. Koneru JN, Badhwar N, Ellenbogen KA, Lee RJ. LAA ligation using the LARIAT suture delivery device: tips and tricks for a successful procedure. Heart Rhythm 2014;11:911–21.

91. Miller MA, Gangireddy SR, Doshi SK, Aryana A, Koruth JS, Sennhauser S, et al. Multicenter study on acute and long-term safety and efficacy of percutaneous left atrial appendage closure using an epicardial suture snaring device. Heart Rhythm 2014;11:1853–9.

92. Price MJ, Gibson DN, Yakubov SJ, Schultz JC, Di Biase L, Natale A, et al. Early safety and efficacy of percutaneous left atrial appendage suture ligation: results from the U.S. transcatheter LAA ligation consortium. J Am Coll Cardiol 2014;64:565–72.

93. Srivastava MC, See VY, Dawood MY, Price MJ. A review of the LARIAT device: insights from the cumulative clinical experience. Springerplus 2015;4:522.

94. Lakkireddy D, Afzal MR, Lee RJ, Nagaraj H, Tschopp D, Gidney B, et al. Short and long-term outcomes of percutaneous left atrial appendage suture ligation: results from a US multicenter evaluation. Heart Rhythm 2016;13:1030–6.

95. Tilz RR, Fink T, Bartus K, Wong T, Vogler J, Nentwich K, et al. A collective European experience with left atrial appendage suture ligation using the LARIAT+ device. Europace 2020;22:924–31.

96. Mohanty S, Gianni C, Trivedi C, Gadiyaram V, Della Rocca DG, MacDonald B, et al. Risk of thromboembolic events after percutaneous left atrial appendage ligation in patients with atrial fibrillation: long-term results of a multicenter study. Heart Rhythm 2020;17:175–81.

97. Cruz-González I, González Ferreiro R, Barreiro Pérez M, Sánchez Fernández PL. First-in-man percutaneous closure of left atrial appendage using the Ultraseal II device. EuroIntervention 2019;15:e816–e7.

98. Pivato CA, Liccardo G, Sanz-SanchezJ, Pelloni E, Pujdak K, Xuareb RG, et al. Left atrial appendage closure with the II generation Ultraseal device: an international registry. The LIGATE study. Catheter Cardiovasc Interv 2022;100:620–7.

99. Regueiro A, Bernier M, O'Hara G, O'Connor K, Paradis J-M, Beaudoin J, et al. Left atrial appendage closure: initial experience with the ultraseal device. Catheter Cardiovasc Interv 2017;90:817–23.

100. Pagnotta PA, Chiarito M, Pllaha E, Zavalloni Parenti D, Rossi ML, Mantovani R. Left atrial appendage closure with the Ultraseal device: initial experience and midterm follow-up. J Interv Cardiol 2018;31:932–8.

101. Asmarats L, Masson JB, Pagnotta PA, Cook S, Foresti M, Ibrahim R, et al. Percutaneous left atrial appendage closure with the ultraseal device: insights from the initial multicenter experience. JACC Cardiovasc Interv 2018;11:1932–41.

102. Ahlgrimm B, Pottgiesser T, Stachon P, Zehender M, Bugger H, Helbing T, et al. The cardia ultraseal left atrial appendage occluder: a case series with significant device-related complications. JACC Cardiovasc Interv 2019;12:1987–9.

103. Sommer RJ, Lamport R, Melanson D, Devellian C, Levine A, Cain CM, et al. Preclinical assessment of a novel conformable foam-based left atrial appendage closure device. Biomed Res Int 2021;2021:4556400.

104. Sommer RJ, Kim JH, Szerlip M, Chandhok S, Sugeng L, Cain C, et al. Conformal left atrial appendage seal device for left atrial appendage closure: first clinical use. JACC Cardiovasc Interv 2021;14:2368–74.

105. Turagam MK, Neuzil P, Hala P, Mraz T, Dukkipati SR, Reddy VY. Intracardiac echocardiography-guided left atrial appendage closure with a novel foam-based conformable device: safety and 1-year outcomes. JACC Clin Electrophysiol 2022;8:197–207.

106. Munir MB, Khan MZ, Darden D, Asad ZUA, Choubdar PA, Din MTU, et al. Association of advanced age with procedural complications and in-hospital outcomes from left atrial appendage occlusion device implantation in patients with atrial fibrillation: insights from the National Inpatient Sample of

36,065 procedures. JICE 2022;65: 219–26.

107. Cruz-González I, Ince H, Kische S, Schmitz T, Schmidt B, Gori T, et al. Left atrial appendage occlusion in patients older than 85 years. Safety and efficacy in the EWOLUTION registry. Rev Esp Cardiol (Engl Ed) 2020;73:21–7.

108. Freixa X, Gafoor S, Regueiro A, Cruz-Gonzalez I, Shakir S, Omran H, et al. Comparison of efficacy and safety of left atrial appendage occlusion in patients aged <75 to ≥ 75 years. Am J Cardiol 2016;117:84–90.

109. Di Lullo L, Mariani MV, Ronco C, Bellasi A, Lavalle C, Chimenti C, et al. Atrial fibrillation and anticoagulant treatment in end-stage renal disease patients: where do we stand? Cardiorenal Med 2022;12:131–40.

110. Genovesi S, Porcu L, Slaviero G, Casu G, Bertoli S, Sagone A, et al. Outcomes on safety and efficacy of left atrial appendage occlusion in end stage renal disease patients undergoing dialysis. J Nephrol 2021;34:63–73.

111. Michlicka-Kłyś W, Kalarus Z, Podolecki T, Mitręga K, Streb W. Long-term results of percutaneous left atrial appendage occlusion in patients with atrial fibrillation and chronic kidney disease. Adv Interv Cardiol 2022;18:43–9.

112. Swaans MJ, Post MC, Rensing BJ, Boersma LV. Ablation for atrial fibrillation in combination with left atrial appendage closure: first results of a feasibility study. J Am Heart Assoc 2012;1(5):e002212.

113. Pasupula DK, Siddappa Malleshappa SK, Munir MB, Bhat AG, Anandaraj A, et al. Combined atrial fibrillation ablation and left atrial appendage occlusion procedure in the United States: a propensity score matched analysis from 2016-2019 national readmission database. Europace 2023;25:390–9.

114. Phillips KP, Pokushalov E, Romanov A, Artemenko S, Folkeringa RJ, Szili-Torok T, et al. Combining Watchman left atrial appendage closure and catheter ablation for atrial fibrillation: multicentre registry results of feasibility and safety during implant and 30 days follow-up. Europace 2018;20:949–55.

115. Chen M, Sun J, Wang QS, Zhang PP, Li W, Zhang R, et al. Long-term outcome of combined catheter ablation and left atrial appendage closure in atrial fibrillation patients. Int J Cardiol 2022;368:41–8.

116. Kawakami H, Nolan MT, Phillips K, Scuffham PA, Marwick TH. Cost-effectiveness of combined catheter ablation and left atrial appendage closure for symptomatic atrial fibrillation in patients with high stroke and bleeding risk. Am Heart J 2021;231:110–20.

117. Han X, Li J. Catheter ablation of atrial fibrillation: where we are? Cardiovasc Innov Appl 2017;2:203–27.

118. Sharma E, Apostolidou E, Sheikh W, Parulkar A, Bilal Ahmed M, Lima FV, et al. Hemodynamic effects of left atrial appendage occlusion. JICE 2022;64:349–57.

119. Liu B, Luo J, Gong M, Li Z, Shi B, Zhang X, et al. Five-year outcomes and cardiac remodeling following left atrial appendage occlusion. Clin Interv Aging 2021;16:655–63.

120. Pommier T, Leclercq T, Guenancia C, Richard C, Porot G, Laurent G, et al. Left atrial remodeling and brain natriuretic peptide levels variation after left atrial appendage occlusion. J Clin Med 2021;10:3443.

121. Kirchhof, Benussi, Kotecha. Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962.

122. Amit V. Management of atrial fibrillation in rheumatic valvular heart disease. Curr Opin Cardiol 2006;21:47–50.