

Left atrial appendage closure devices for cardiovascular risk reduction in atrial fibrillation patients

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Abstract: Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice. AF is associated with a 4–5-fold increased risk of stroke and systemic embolism. Oral anti-coagulant is the first-line therapy for this purpose, but it has various limitations and is often contraindicated or underutilized. Autopsy and surgical data have suggested that 90% of atrial thrombi in nonvalvular AF patients originate from the left atrial appendage, leading to the development of percutaneous closure for thromboembolic prevention. This paper examines the current evidence on left atrial appendage closure devices for cardiovascular risk reduction in AF patients.

Keywords: atrial fibrillation, left atrial appendage, stroke, oral anticoagulant, percutaneous closure, thromboembolic prevention

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, and it is associated with substantial morbidity and mortality.^{1,2} The prevalence of AF in the United States is expected to rise up to 5.6–12 million in 2050.³ Patients with AF have a 5-fold increased risk of stroke, and it is estimated that 15%–20% of all strokes are attributable to AF.⁴ Moreover, strokes related to AF have been observed to be associated with a higher mortality and morbidity when compared with non-AF strokes, emphasizing the need for more effective stroke prevention in these patients.⁵ The risks of thromboembolic complications and stroke remain the same regardless of whether a person has paroxysmal, persistent, or long-standing persistent AF.^{6–8} In clinical practice, the CHADS₂ and CHA₂DS₂-VASc scoring systems provide risk stratification data on the likelihood of stroke or systemic embolism and are used to guide therapy (anticoagulation or aspirin).⁹

Oral anticoagulants (OACs) reduce the risk of thromboembolism, yet they are underused.^{10–12} The warfarin efficacy to prevent thromboembolism in patients with AF and risk factors for stroke has been well established.^{13,14} However, the biggest risk of long-term warfarin therapy is major bleeding, which has an incidence of 2%–4% per year, and it can be even higher if predisposing factors are present.^{15–17} Also, warfarin is limited by a narrow therapeutic window, inconvenience of frequent monitoring, and multiple medication and food interactions.¹⁸ Previous studies have suggested that warfarin discontinuation rates are estimated to be as high as 38% per year.¹⁴

Novel OACs are noninferior or superior to warfarin for the prevention of stroke and systemic embolism and they do not require ongoing monitoring.^{15–17,19} However, the risk of bleeding, long-term compliance, cost, and the lack of an available antidote

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represent substantial challenges for the management of stroke prevention in patients with AF.²⁰

In patients with AF, blood flow velocity in the left atrial appendage (LAA) frequently decreases, resulting in stasis and increasing the probability of thrombus formation.^{21,22} Autopsy and surgical data have suggested that 90% of atrial thrombi in nonvalvular AF (NVAF) patients originate from the LAA.²³ Also, thrombi have been detected by transesophageal echocardiography (TEE) in approximately 15% of patients with AF.^{24,25} Accordingly, several transcatheter LAA closure devices to reduce the risk of stroke and to obviate the need for long-term systemic anticoagulation therapy in patients with AF have been developed.

In this review, we summarize the current status of LAA closure devices for cardiovascular risk reduction in AF patients.

Transcatheter devices for left atrial appendage closure

Percutaneous LAA closure has been shown as an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with NVAF.²⁶ Consequently, several transcatheter devices for LAA closure has been developed and tested. The most studied include the PLAATO system (ev3 Endovascular, Plymouth, MN, USA), the WATCHMAN device (Boston Scientific, Plymouth, MN, USA), the Amulet/Cardiac Plug (St Jude, Golden Valley, MN, USA), the LARIAT® device (SentreHEART, Palo Alto, CA, USA), and the LAmBRE device (Lifetech Scientific Corp, People's Republic of China) (Table 1).

Cardiac imaging is of primary importance for LAA anatomical characterization, device size choice, ruling out LAA thrombus before the procedure, and minimizing complications.^{27,28} Currently, the best preprocedural imaging modalities are cardiac computed tomography (CCT),²⁹ cardiac magnetic resonance,³⁰ and three-dimensional TEE.³¹ Two- and three-dimensional TEE are commonly used during LAA closure procedure.³²

PLAATO

The PLAATO system was the first approved device for LAA closure (Figure 1A).³³ It was made up of a self-expanding nitinol cage covered with polytetrafluoroethylene (PTFE). The device production was discontinued in 2007 for commercial reasons.

Two prospective multicenter trials evaluated the efficacy of the PLAATO device. In the international multicenter feasibility trial,³⁴ the PLAATO system was used in 111 patients

Table 1 Summary of different devices for LAA occlusion

Deployment	Devices			
	PLAATO	WATCHMAN	ACP I	Amulet
	Endovascular	Endovascular	Endovascular	Endovascular
Sizes, mm	15–32	21, 24, 27, 30, and 33	16–30	16–34
Device selection	20%–40% larger than the LAA neck diameter	10%–20% larger than the LAA neck diameter	10%–20% larger than the LAA neck diameter	3–6 mm larger than LAA neck diameter
Implant success, %	97.3, ³⁴ 90 ³⁶	90.9, ²⁶ 95.1 ³⁹	97.3 ⁵¹	96, ⁶⁹ 100 ⁷⁰
Complications in pivotal trials	Hemopericardium (2.7%), ³⁴ need for CV surgery (0.9%), ³⁴ death (1.1%), ³⁶ tamponade (3.3%), ³⁶ device embolization (0.6%) ³⁶	Device embolization (0.4%), ²⁶ (0.7%), ³⁹ stroke (1.1%), ²⁶ (0.7%), ³⁹ PE requiring surgery (1.6%), ²⁶ (0.4%), ³⁹ PE with pericardiocentesis (2.4%), ²⁶ (1.5%) ³⁹	Deaths (0.8%), ⁵¹ stroke (0.9%), ⁵¹ MI (0.1%), ⁵¹ cardiac tamponade (1.2%), ⁵¹ device embolization (0.1%), ⁵¹ major bleeding (1.2%) ⁵¹	Device thrombosis (4.1%), ⁶⁹ PE with pericardiocentesis (6%) ⁷⁰
				Maximum target size: W 40× H 20× L 70 Minimum access size: 4.3 (12.9F) NA 96 ⁵² Chest pain (23.5%), ⁵² pericarditis (2.3%), ⁵² late PE (1.2%) ⁵²

Abbreviations: ACP, AMPLATZER™ Cardiac Plug; NA, not applicable; LAA, left atrial appendage; CV, cardiovascular; PE, pericardial effusion; MI, myocardial infarction.

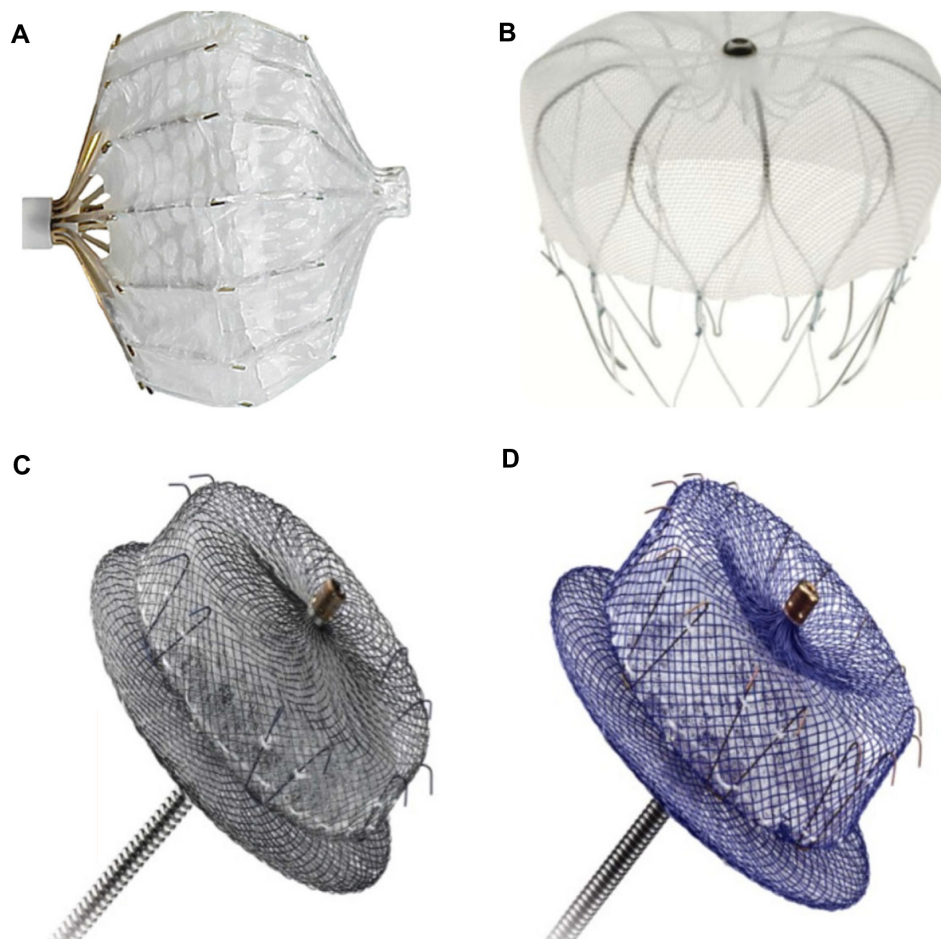


Figure 1 LAA occlusion devices.

Notes: (A) PLAATO device, (B) WATCHMAN device, (C) AMPLATZER™ Cardiac Plug I device, (D) Amulet device.

Abbreviation: LAA, left atrial appendage.

with NVAf with contraindications to warfarin therapy. The primary end point was the incidence of major adverse events. Implantation was successful in 108 of 111 patients (97.3%). One patient experienced two major adverse events within the first 30 days: need for cardiovascular surgery and in-hospital neurological death. Three other patients underwent in-hospital pericardiocentesis due to a hemopericardium, and two patients experienced stroke. After up to 5 years of follow-up, the annualized stroke/transient ischemic attack (TIA) rate was 3.8%.³⁵ The anticipated stroke/TIA rate (with the CHADS₂ scoring method) was 6.6% per year.³⁵

The European PLAATO study³⁶ enrolled 180 patients with NVAf and contraindications to warfarin. The primary end points were LAA closure (as determined by TEE) at 2 months after the procedure and a stroke rate per 150 patient-years. Complete occlusion was achieved in 90% of the patients. There were two deaths within 24 hours of the procedure and six cardiac tamponades. Successful occlusion of the LAA was achieved in 90% of the patients (determined by TEE) at

the 2-month follow-up. Over a follow-up period of 129 documented patient-years, three strokes occurred (2.3% per year). The expected incidence of stroke according to the CHADS₂ score was 6.6% per year.

WATCHMAN

The WATCHMAN device was specifically designed for percutaneous LAA closure. It consists of a self-expanding nitinol frame and a perforated polyethylene terephthalate (PET) membrane cap that is delivered from the right femoral vein via a transseptal delivery sheath (Figure 1B). The device is fully retrievable prior to the release from the delivery cable. It is available in five sizes, ranging from 21 to 33 mm in diameter, and is normally selected 10%–20% larger than the LAA neck diameter to ensure stable device positioning.³⁷

The feasibility and early experience using the WATCHMAN LAA system were reported in 2007.³⁷ In this study, 66 patients underwent device implantation. At 45 days, 93% (54 of 58) devices showed successful sealing of LAA.

Two patients experienced device embolization and two patients experienced TIA. There were two cardiac tamponades and two deaths, neither device-related. No strokes were reported during a mean follow-up of 740 ± 341 days. Subsequently, two prospective, controlled, randomized trials have evaluated the efficacy of the WATCHMAN device.

The WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) trial²⁶ was a prospective multicenter randomized noninferiority trial comparing percutaneous LAA occlusion with the WATCHMAN device vs chronic adjusted-dose warfarin therapy in patients with NVAf. The study population consisted of 707 patients in 59 centers in Europe and the United States, with a CHADS₂ score of ≥ 1 and without contraindication to warfarin. They were randomly assigned in a 2:1 ratio to device implantation or warfarin therapy. Efficacy was assessed by a primary composite end point of stroke, cardiovascular death, and systemic embolism. The primary safety end point consisted of events related to excessive bleeding or procedure-related complications.

Implantation of the device was successful in 88% (408/463) of patients assigned to this intervention and in 91% of those in whom it was attempted (408/449). At 1,065 patient-years of follow-up, the primary efficacy event rate was 3.0 per 100 patient-years (95% credible interval [CrI], 1.9–4.5) in the WATCHMAN group and 4.9 per 100 patient-years in the Warfarin group (rate ratio [RR], 0.62; 95% CrI, 0.35–1.25), which met the noninferiority end point. In this study, the noninferiority margin for the event RR for the primary effectiveness end point was set at 2.0. This margin is larger than margins typically used in anticoagulation drug trials and meant that the WATCHMAN device could be found noninferior to warfarin, with an event rate up to two times that in the control group. Primary safety events were more frequent in the WATCHMAN group than in the Warfarin group (7.4 per 100 patient-years; 95% CrI, 5.5–9.7 vs 4.4 per 100 patient-years; 95% CrI, 2.5–6.7; RR, 1.69, 1.01–3.19). It was mainly a result of periprocedural complications and occurred early in the trial.

In view of these findings, a continued access protocol (CAP) registry³⁸ was designed to gain further safety and efficacy data seen in the PROTECT AF trial. This registry included the 542 patients who underwent attempted LAA device closure in the intervention group of the PROTECT AF trial and a further 460 patients from centers that participated in the trial with the same inclusion criteria, follow-up, and medication. The efficacy composite end point was similar to that of PROTECT AF. Results revealed a significant

decline in the rate of procedure- or device-related safety events within 7 days of the procedure across the two studies and between the first and second halves of PROTECT AF and CAP.

The PREVAIL study³⁹ was designed to further explore the safety and efficacy of the device and confirm an improved procedural safety profile. In this trial, 407 patients with AF who had a CHADS₂ score of ≥ 2 or 1 and another risk factor were randomly assigned to undergo LAA occlusion and subsequent discontinuation of warfarin or receive chronic warfarin therapy.

Implantation of the device was successful in 95% of the patients in whom it was attempted (252/256). At 18 months, the rate of the first coprimary efficacy end point (composite of stroke, systemic embolism, and cardiovascular/unexplained death) was 0.064 in the WATCHMAN group vs 0.063 in the Warfarin group (RR, 1.07; 95% CrI, 0.57–1.89) and did not achieve the prespecified criterion noninferiority. The rate of the second coprimary efficacy end point (stroke or systemic embolism >7 days postrandomization) was 0.0253 vs 0.0200 (risk difference, 0.0053; 95% CrI, –0.0190 to 0.0273), achieving noninferiority. Early safety events occurred in 2.2% of the WATCHMAN arm, significantly lower than in PROTECT AF, satisfying the prespecified safety performance goal.

Long-term results of PROTECT AF trial have been recently published.⁴⁰ After 3.8 years of follow-up, percutaneous LAA closure met criteria for both noninferiority and superiority, compared with warfarin, for preventing the combined outcome of stroke, systemic embolism, and cardiovascular death, as well as superiority for cardiovascular and all-cause mortality. Efficacy outcomes and complications in the randomized, clinical trials of the WATCHMAN compared with warfarin are shown in Table 2.

AMPLATZER™ Cardiac Plug

The AMPLATZER™ Cardiac Plug (ACP) is a self-expanding nitinol device consisting of a distal lobe and a proximal disk, each with a sewn polyester patch connected by a short central waist (Figure 1C and D).^{41,42} The lobe has diameters of 16–30 mm.⁴³ The ACP has a CE mark, but it has not been approved yet for use in the United States.

The device is delivered from the femoral vein through a transseptal sheath using a combination of fluoroscopic and TEE guidance. It is usually selected to be 10%–20% larger than the narrowest diameter of the LAA neck.⁴⁴ The proximal disc covers the ostium of the LAA from within the left atrium; therefore, the mechanism of LAA occlusion differs

Table 2 Efficacy outcomes and complications in the randomized, clinical trials of the WATCHMAN compared with Warfarin

	PROTECT-AF²⁶ (n=707)	PREVAIL³⁹ (n=407)
Population studied	Warfarin eligible CHADS ₂ score \geq 1	Warfarin eligible CHADS ₂ score \geq 2 or 1 plus an additional risk factor
Control	Warfarin	Warfarin
Primary end point	CVD, any stroke, or SE	CVD, any stroke, or SE Any stroke or SE >7 days after the procedure
Duration of follow-up	1,065 patient-years	11.8 \pm 5.8 m
RR NI criterion (upper bound of 95% CrI)	RR <2.0	RR, <1.75 Rate difference, <0.0275
Treatment effect (95% CrI)	RR, 0.62 (0.35–1.25)	RR, 1.07 (0.57–1.89) Difference, 0.0053 (–0.0190 to 0.0273)
NI achieved?	Yes	No Yes
All 7-day procedural complications (%)	8.7	4.5
Procedure-related stroke (%)	1.1	0.7
PE requiring surgery (%)	1.6	0.4
PE requiring pericardiocentesis (%)	2.4	1.5
Device embolization (%)	0.4	0.7

Abbreviations: AF, atrial fibrillation; CrI, credible interval; CVD, cardiovascular death; NI, noninferiority; PE, pericardial effusion; RR, rate ratio; SE, systemic embolism; CHADS, Congestive heart failure, Hypertension, Age, Diabetes, Stroke.

from that of the WATCHMAN, which occludes the LAA from within the appendage itself.

A second-generation of the ACP (ACP2 or Amulet) was designed with strategic modifications to facilitate the implantation process and minimize the occurrence of complications. The Amulet has a lightly longer distal lobe, a longer central waist, and a larger-diameter proximal disk. Also, it has stiffer hooks, and the number of stabilizing wires has been increased from 6 pairs in the ACP1 to up to 10 pairs.⁴¹ It is fully retrievable and repositionable⁴¹ and is recommended that the device be selected such that it is approximately 3–6 mm larger than the LAA neck.⁴¹

Data regarding the safety and efficacy of the ACP are limited to observational studies.^{42–49} Park et al⁴² reported that LAA occlusion using the ACP device was successfully performed in 132 of 137 patients (96%). There were serious complications in 10 (7.0%) patients (three patients had ischemic stroke, two patients experienced device embolization, and five patients had clinically significant pericardial effusions). In a retrospective study, Nietlispach et al⁴⁸ evaluated 152 patients who received ACP device implantation. The short-term safety end points (procedural complications, bleeds) occurred in 15/152 (9.8%) and the efficacy end points (death, stroke, systemic embolization) in 0 patients. Device embolization occurred in 4.6% (7/152) of patients. Mean intermediate-term follow-up of the study population was 32 months (range, 1–120). Late deaths occurred in 15 patients, neurologic events occurred

in 2, peripheral embolism in 1, and major bleeding in 4 patients.

In the AMPLATZER™ Cardiac Plug European Multi-center Observational Study,⁵⁰ a total of 197 patients underwent ACP implantation in Europe in 2009–2011. The majority of patients (57.9%) had a history of permanent AF, and the mean age was 74.20 \pm 9.0 and the mean CHADS₂ score was 2.6 \pm 1.3. The ACP device was successfully implanted in 96.6% of patients, with a closure rate of 99.5% at implant and 98.9% at 6 months. Device/procedure-related safety events included 0 (0.0%) periprocedural strokes, 3 (1.5%) serious pericardial effusions, 5 (2.4%) device-related thrombus, and 3 (1.5%) device embolizations. The stroke rate was 1.98% at 101 patient-years compared with a CHADS₂ prediction of 5.6%.

Recently, Tzikas et al⁵¹ presented the data from 1,047 consecutive patients treated in 22 centers. Procedural success was 97.3%, and there were 45 (4.3%) periprocedural major adverse events: 8 deaths (0.8%), 9 strokes (0.9%), 1 myocardial infarction (0.1%), 13 cardiac tamponades (1.2%), 13 major bleeding episodes (1.2%), and 1 device embolization needing surgery (0.1%). Follow-up was complete in 98.2% of successfully implanted patients (average, 13 months – a total of 1,349 patient-years). One-year all-cause mortality was 4.2%, and no death at follow-up was reported as device related. There were 9 strokes (0.9%) and 9 TIAs, and the annual rate of systemic thromboembolism (periprocedural and follow-up) was 2.3%, which is a 59% risk reduction.

LARIAT®

The LARIAT® system device requires both epicardial and endocardial approaches to occlude the LAA (Figure 2A). The device has three components: 1) a 20 mm compliant occlusion balloon, 2) 0.025-inch and 0.035-inch magnet-tipped guidewires, and 3) a 12F suture delivery device. Four steps are required: 1) accessing the pericardial and transseptal spaces, 2) placing the endocardial magnet-tipped guidewire in the apex of the LAA with balloon identification of the LAA, 3) connection of the epicardial and endocardial magnet-tipped guidewires for stabilization of the LAA, and 4) snare capture of the LAA with closure confirmation and release of the pre-tied suture for LAA ligation.⁵² Preprocedural CCT imaging is mandatory to assess anatomic eligibility. Contraindications to this approach include an LAA width greater than 40 mm, a superiorly oriented LAA, and historical conditions that would result in pericardial adhesions.

The initial LARIAT® study was performed from February 2010 to February 2011 in 21 patients with AF.⁵³ The LAA was occluded in 100% of patients. There were no strokes reported during the follow-up period (mean, 352 ± 143 days). In another study,⁵⁴ 27 patients with AF and OAC therapy contraindications or intolerance were selected. Preserved LAA closure was confirmed with a 45-day follow-up TEE in 22 of 25 patients completing the procedure. In a major study conducted by Bartus et al,⁵² LAA ligation was successful in 85 of 89 patients (96%). Eighty-one of 85 patients had complete closure (determined by TEE imaging) immediately after the procedure. Of the patients undergoing 1-year TEE (65), there was 98% complete LAA closure.

Complications of using LARIAT® include pericarditis,⁵³ thrombogenicity at the endocardial site in the left atrium,^{55,56} partial reopening of the LAA,⁵⁷ and laceration and cardiac tamponade.⁵⁸

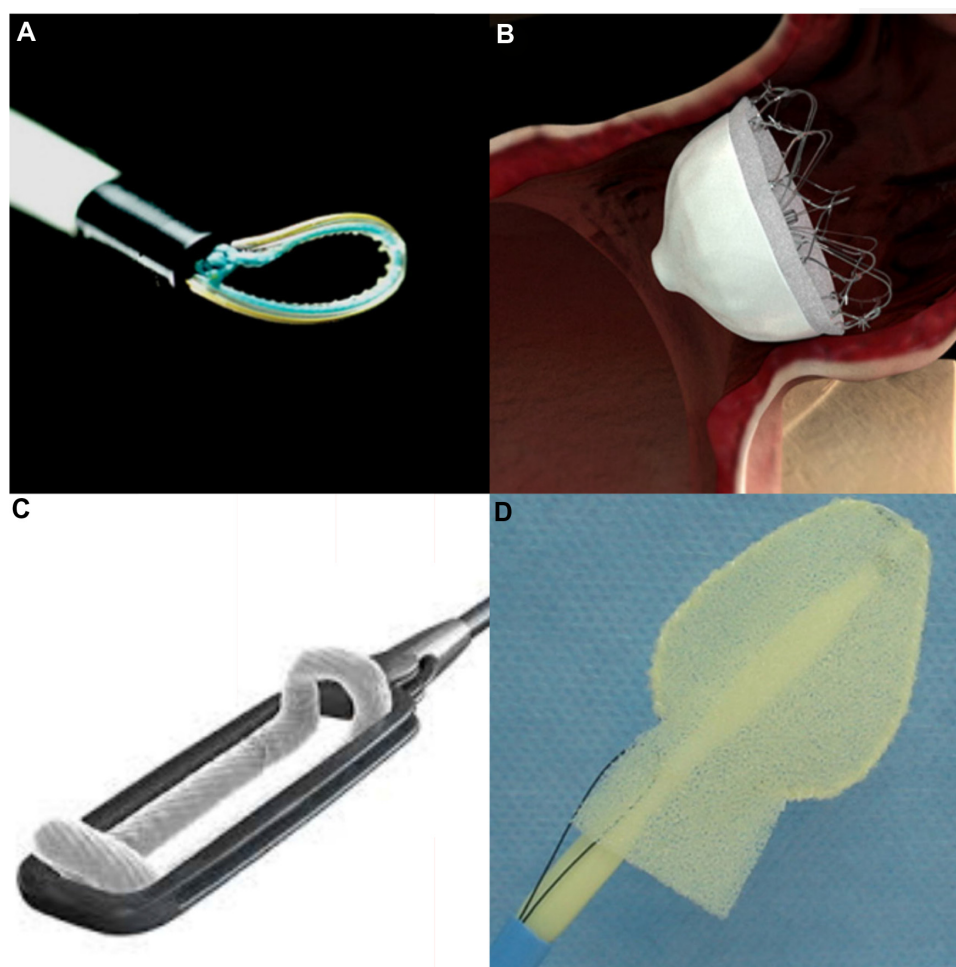


Figure 2 LAA occlusion devices.

Notes: (A) LARIAT® device, (B) WaveCrest® device, (C) AtriClip device, (D) Transcatheter Patch device.

Abbreviation: LAA, left atrial appendage.

LAmbre

LAmbre is a self-expanding LAA occluder constructed from a nitinol mesh and polyester membranes and consists of an umbrella and a cover connected by a short central waist. The device comes in various sizes, ranging from 16 to 36 mm. It is delivered by an 8F–10F sheath and has fully recapturable and repositioning capabilities.⁵⁹ The Feasibility and Safety Study of LAMBRE Left Atrial Appendage Occluder trial is currently recruiting participants (ClinicalTrials.gov; identifier: NCT01920412).

Other devices

The WaveCrest® device (Coherex Medical, Salt Lake City, UT, USA) consists of a nitinol structure without exposed metal hub and with a foam layer facing the LAA and a PTFE layer facing the left atrium (Figure 2B).⁶⁰ The WaveCrest® I trial⁶¹ recruited 73 patients from Europe, Australia, and New Zealand, with a mean CHADS₂ score of 2.5, previous cerebral embolism in 34%, and a warfarin contraindication in 49%. Successful deployment with acute closure was seen in 68 of 73 (93%). Acute tamponade occurred in 2 of 73 (3%), and there was no procedural stroke, device embolization, or device-related thrombosis. The WaveCrest® device received a CE mark in 2013.

The AtriClip (Atricure Inc, West Chester, OH, USA) device is a clip made of two parallel rigid titanium tubes with elastic nitinol springs covered with a knit-braided polyester

sheath (Figure 2C). It is placed epicardially around the LAA and compresses the appendage at its base. The EXCLUDE clinical trial (Exclusion of Left Atrial Appendage with AtriClip Exclusion Device in Patients Undergoing Concomitant Cardiac Surgery) was a nonrandomized, multicenter trial designed to assess the safety and efficacy of this device.⁶² A total of 71 patients undergoing open cardiac surgery were enrolled in the study. Intraprocedural success occurred in 67 of 70 patients (95.7%), with significant adverse events occurring in 48.6%, which were not device related. At 3-month follow-up of 65 of 70 patients, 1 case of mortality was reported. Sixty-one patients underwent computed tomographic angiography or TEE, and 60 (98.4%) had successful LAA occlusion. The AtriClip device was approved by the US Food and Drug Administration for LAA occlusion under direct visualization, in conjunction with other open-heart cardiac procedures. The Transcatheter Patch (Custom Medical Devices, Athens, Greece) is a frameless, bioabsorbable, balloon-deliverable device that can be adjusted for the shape and size of the appendage without the risk of perforation (Figure 2D). It was studied in 20 patients, showing successful placement in 17 cases.⁶³

The Aegis system is an epicardial electrocardiography-guided LAA capture and ligation system. It permits LAA closure in the closed pericardial space with a single sheath puncture.^{64,65}

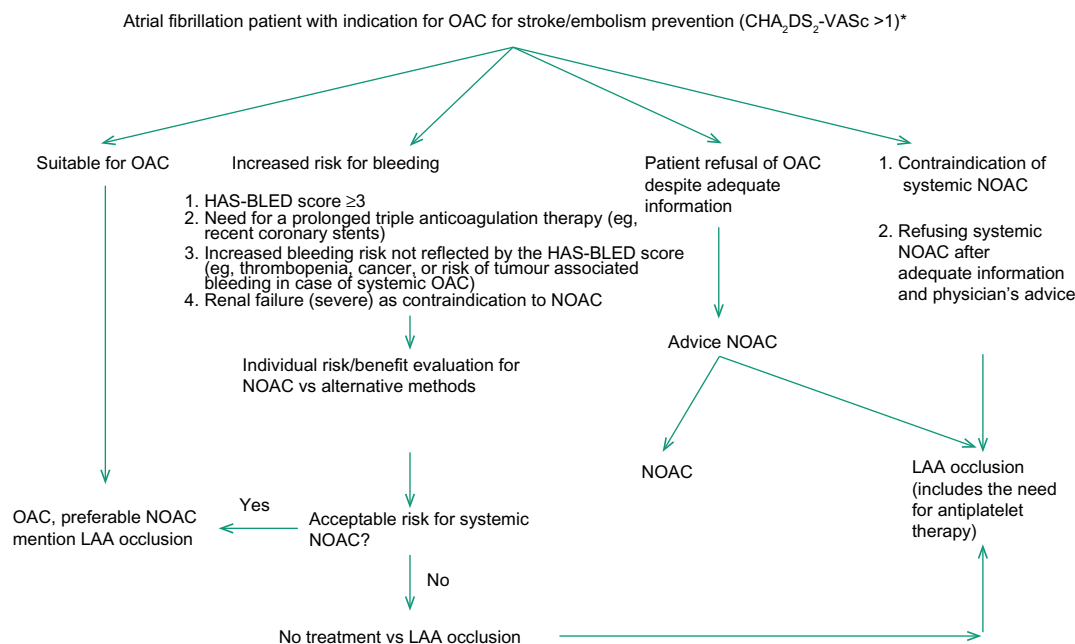


Figure 3 Algorithm for stroke prevention in patients with atrial fibrillation.

Note: In all: adequate and intensified rhythm control (ablation or amiodarone) in combination with continuous rhythm control by implanted devices with remote monitoring. Reprinted from EuroIntervention 16(10), Meier B, Blaauw Y, Khattab AA, et al, EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion, 1397–1416. Copyright © 2014, with permission from Europa Digital & Publishing.⁶⁸

Abbreviations: LAA, left atrial appendage; NOAC, novel (nonvitamin K antagonist) oral anticoagulant; OAC, oral anticoagulant.

Indications for left atrial appendage occlusion

A recent systematic review suggested comparable efficacy of LAA occlusion devices compared with anticoagulation strategies for prevention of stroke in patients with NVAF.⁶⁶ Also, percutaneous LAA occlusion is cost-effective compared with warfarin.⁶⁷

The percutaneous LAA closure as an alternative to OAC when OACs are not contraindicated is the only potential indication that is currently based on randomized controlled data.^{26,39} However, the main indication for LAA occlusion is a relative or absolute contraindication to OACs (eg, a history of a significant bleeding or life-threatening bleeding) in patients with AF and a CHADS₂ score of ≥ 1 or a CHA₂-DS₂-VASc score of ≥ 2 . This recommendation is based on observational studies and registries only.

An EHRA/EAPCI expert consensus statement on catheter-based LAA occlusion has been recently published, and it summarizes the recommended current indications (Figure 3).⁶⁸

Conclusion and future directions

Stroke is the most serious complication of AF. The main treatment for stroke prevention in AF patients is OAC, which has proven efficacy. However, multiple adverse effects limit its use. Percutaneous LAA closure devices have been developed as a nonpharmacologic alternative to warfarin for stroke prevention in patients with AF. Reported results confirm the technical feasibility of percutaneous LAA closure and its effectiveness in preventing ischemic stroke. To get good results, a team with experience and a substantial learning curve for the operator are critical.

In future studies, it will be important to identify patients who may benefit most from percutaneous LAA closure as a valid strategy for the prevention of stroke, try to minimize periprocedural complications, and contribute to improving the design of the LAA closure devices. Also, prospective head-to-head comparisons among devices and using the novel OACs are needed.

Disclosure

Dr Cruz-Gonzalez is proctor and consultant for St Jude Medical and Boston Scientific. The authors report no other conflicts of interest in this work.

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