

Left Atrial Appendage Occlusion: Past, Present and Future

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Abstract

There are several situations whereby oral anticoagulation may be unsuitable for stroke prevention in patients with atrial fibrillation (AF). Percutaneous left atrial appendage (LAA) occlusion has received much attention in this area. Various devices have already been developed and tested for this purpose. Data from registries and cohort studies have indicated favourable short- and long-term outcomes with LAA occlusion, and several international guidelines recommend its use in AF patients with contraindications to oral anticoagulation. However, prospective controlled trials in this very population are lacking. Furthermore, while modelling studies on cost analyses have suggested that LAA occlusion may be a cost-effective strategy compared with standard medical therapy, these have not been performed in high-risk patients who may have limited survival in the medium to long term. Thus, while LAA occlusion offers promise, there is a strong need for additional research to investigate its exact role, its long-term outcomes and cost efficacy.

Keywords

- ▶ left atrial appendage
- ▶ occlusion
- ▶ closure
- ▶ percutaneous
- ▶ atrial fibrillation

Introduction

Atrial fibrillation (AF) is associated with significant morbidity and mortality, attributed in part to an increased thromboembolic risk.^{1,2} Observational studies in patients with AF, not necessarily with a history of thromboembolic complications, suggest the left atrial appendage (LAA) as the site for the majority (~90%) of thrombus formation.^{3–5} If left untreated, AF confers a significant stroke risk in all age groups. This risk is often mitigated by anticoagulation therapy using vitamin K antagonists (VKAs), or more recently with non-vitamin K oral anticoagulants (NOACs). However, the use of these medications results in an increased risk of bleeding including serious ones like intracranial haemorrhage. As such, they may not be suitable for all patients. Therefore, alternative strategies such as LAA occlusion which acts to isolate and prevent clot embolisation from this area have been developed.

The feasibility of this intervention was first tested by surgical ligation or excision of the LAA during cardiac surgeries. Over time, it has evolved to two different approaches using either epicardial or endocardial sutures, or excision with staples.⁶ However, as most patients with AF do not require cardiac surgery, this method provides limited clinical impact for the majority. Furthermore, studies evaluating the efficacy of surgical LAA occlusion for prevention of thromboembolic complications did not show a clear benefit.⁷ The observation was largely driven by high rates of incomplete closure which led to a higher risk of embolic events post-surgery.^{8–10} Consequently, percutaneous LAA occlusion was introduced as a potential solution to address some of these issues (▶**Fig. 1**). In this article, we will discuss the various aspects of percutaneous LAA occlusion including the available devices, indications, current recommendations, post-procedural management and cost effectiveness.

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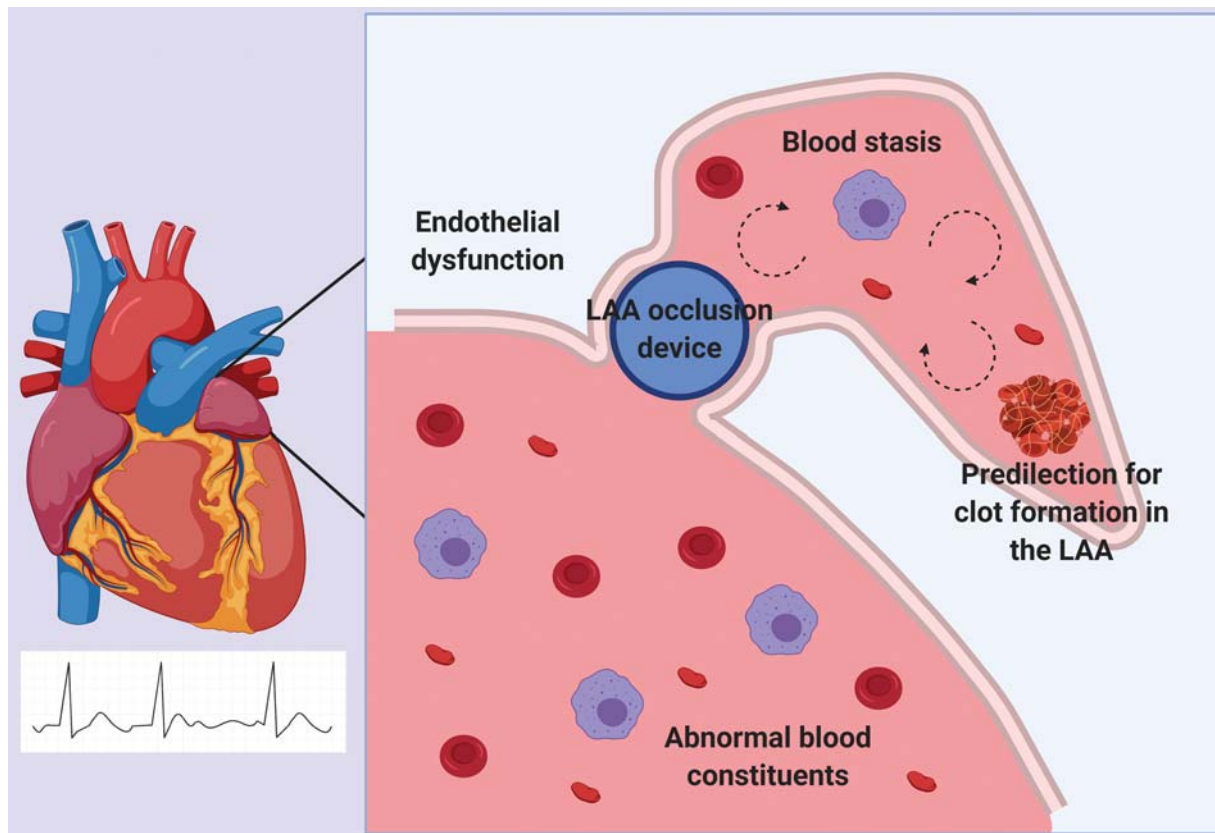


Fig. 1 Principles of left atrial appendage occlusion. LAA, left atrial appendage.

Devices Available

Several devices have been designed to facilitate LAA occlusion. Many of these have received CE mark (Amplatzer Cardiac Plug [ACP], Amplatzer Amulet, Lariat, Watchman, WaveCrest, Atri-clip, Occlutech, LAMBRE and Ultraseal) while others were recalled (Tiger Paw System) or discontinued (PLAATO).¹¹ The first procedure was performed using the PLAATO device (Appriva Medical Inc., Sunnyvale, California, United States), which was a self-expanding nitinol cage covered with a polymeric membrane.¹² Despite initial promising results, the device was subsequently discontinued in 2007.

The Watchman device (Boston Scientific, Marlborough, Massachusetts, United States) was introduced in 2005,¹³ and to date, this remains the only device which has been evaluated in randomised controlled trials which enrolled patients without contraindications to anticoagulation. The PROTECT AF trial found that LAA occlusion was non-inferior compared with warfarin for a composite endpoint of stroke, systemic embolism and cardiovascular death.¹⁴ However, due to both methodological limitations and safety concerns (high rate of procedural adverse events), United States regulators mandated a second trial. At 5-year follow-up, the subsequent PREVAIL trial and a meta-analysis with PROTECT AF found that LAA occlusion missed non-inferiority in its first co-primary efficacy endpoint of stroke, systemic embolism and cardiovascular death. Non-inferiority was met in the rate difference (but not the more stringent rate ratio) in the second co-primary endpoint of stroke, systemic embolism, or cardiovascular

death excluding the 7 days post-procedure.^{15,16} Non-inferiority relative to warfarin was not met in the first co-primary endpoint due to higher rates of ischemic stroke among patients who received LAA occlusion. While safety improved in PREVAIL relative to PROTECT AF, the average rate of serious complications of the four Watchman studies (PROTECT AF, PREVAIL, ASAP [ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology] and CAP2 [Continued Access to PREVAIL]) was 6%.

After multiple unsuccessful reviews, the United States Food and Drug Administration approved the Watchman device in 2015. The device is now widely used. Recently published post-market findings from the National Cardiovascular Data Registry (NCDR) LAA occlusion registry of 38,158 procedures performed between January 2016 to December 2018 were interpreted as favourable.¹⁷ The authors reported that deployment of the device was associated with a success rate of 98.1% to achieve a less than 5 mm leak. Additionally, the incidence of major in-hospital adverse events was low (2.2%), with the two most common complications recorded as pericardial effusion requiring intervention (1.4%) and major bleeding (1.3%). The U.S. NCDR registry uses an adjudication process based on site-reported events and is potentially subject to under-reporting or misclassification bias.

The ACP (Abbott Vascular, Chicago, Illinois, United States) is another self-expanding nitinol device that is used in clinical practice. It was shown to be associated with high procedural success and favourable outcomes for the prevention of AF-related thromboembolism.¹⁸ The Amulet (Abbott Vascular,

Table 1 Comparison of percutaneous left atrial appendage occlusion devices

	Watchman FLX	Amplatzer Amulet	Lariat	WaveCrest
Manufacturer	Boston Scientific Corporation	Abbott Vascular	SentreHeart	Biosense Webster
Design	Single lobe	Double lobe and disc	Magnet-tipped guidewires, and snare	Single lobe
Description	Self-expanding nitinol 18-strut frame with fixation anchors and a permeable polyester fabric cover	Self-expanding nitinol with a distal lobe and proximal disc connected by a flexible waist; secured with stabilising wires	Transvenous and epicardial balloon catheters used to deliver magnet-tipped guidewires and a pre-tied suture made of Teflon-coated, braided polyester	Self-expanding nitinol frame covered by a left atrial-facing expanded polytetrafluoroethylene layer and left atrial appendage-facing foam layer with anchors
Approach	Endocardial	Endocardial	Endoepicardial	Endocardial
Sheath size	14F	12–14F	12F	12F
Device sizes (mm)	20, 24, 27, 31, 35	16, 18, 20, 22, 25, 28, 31, 34	40 mm suture loop	22, 27, 32

Chicago, Illinois, United States) is a second-generation device from Amplatzer that consisted of incremental design enhancements to facilitate implantation and reduce device-related leaks and embolisation. Observational studies of this device were generally positive in terms of successful implantation and clinical outcomes.^{19,20} A comparative analysis between the ACP and Amulet found that both provided similar long-term efficacy, safety and net clinical benefit.²¹ Furthermore, Koskinas et al also demonstrated the feasibility of deploying these devices across the spectrum of LAA anatomies.²²

The Lariat device (SentreHEART Inc., Palo Alto, California, United States) offers an alternative technique to LAA occlusion by utilising both epicardial and trans-septal access. An advantage of this approach is that no foreign material is left within the circulation on completion of the procedure. Implantation of the device involves placement and connection of epicardial and endocardial magnet-tipped guidewires to stabilise the LAA. A snare capture is then used to confirm the final position before deployment of a pre-tied suture for LAA ligation. The Lariat device was associated with high procedural success but with potentially higher rates of complications compared with other devices.^{23–25} A comparison of the commonly used percutaneous LAA occlusion devices is shown in ► **Table 1**.

Indications and Recommendations

There are several situations where an alternative to oral anticoagulants (OACs) in patients with AF may be desirable (► **Fig. 2**). First, the use of OACs is not without risk. As mentioned above, patients are exposed to higher rates of bleeding while taking these medications. Therefore, there are certain situations whereby this may be deemed an inappropriate treatment option by physicians and patients alike (e.g., recent intracranial haemorrhage, cerebral berry aneurysm, end-stage renal failure).²⁶ In addition, some patients may suffer from resistant stroke that occurs despite appropriate guideline-directed anticoagulation therapy.²⁷ The commonly used strategy of switching or implementing

higher doses of OAC in such patients is not supported by trial evidence. There is also an issue of compliance which may be suboptimal with these medications.²⁸ In the landmark studies of NOACs, discontinuation rates were between 21 and 27%.^{29–32} This may be more significant with the use of VKAs,³³ especially in younger patients where lifelong treatment and monitoring may be viewed as imposing significant lifestyle restrictions. Given the lack of options in the aforementioned situations, percutaneous LAA occlusion has been received with much enthusiasm. However, it should be noted that at present there is a stark discrepancy between indications for LAA occlusion in clinical practice and trial-proven indications. It may be worth exercising caution when extrapolating results from clinical trials and those obtained from registry-type data. After all, LAA occlusion is an invasive procedure with potential risks (► **Table 2**). Some of these may necessitate blood transfusion, pericardiocentesis or surgery, and peri-procedural mortality has been described. Furthermore, patients who are deemed unsuitable for VKA may do well with NOACs,³⁴ and the latter have never been directly tested against LAA occlusion.

Thus far, there are no prospective controlled studies that have evaluated LAA occlusion in patients with an absolute contraindication to anticoagulation. Current evidence is derived from registries and cohort studies. The EWOLUTION (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology) study was a prospective observational registry of LAA occlusion involving a total of 1,025 patients, where 72% had a documented contraindication to anticoagulation.³⁵ At 2-year follow-up, the rates of stroke and major non-procedural bleeding were reduced by 83 and 46% compared with predicted rates based on the CHA₂DS₂-VASc and HAS-BLED scores, respectively. Caution is necessary in interpretation of EWOLUTION given that inclusion was at the discretion of investigators. The ASAP study enrolled AF patients who were ineligible for warfarin.³⁶ The authors cited that haemorrhagic tendency was the most common (93%) reason for warfarin ineligibility and found that the rate of ischemic stroke was 1.7% per year with LAA occlusion

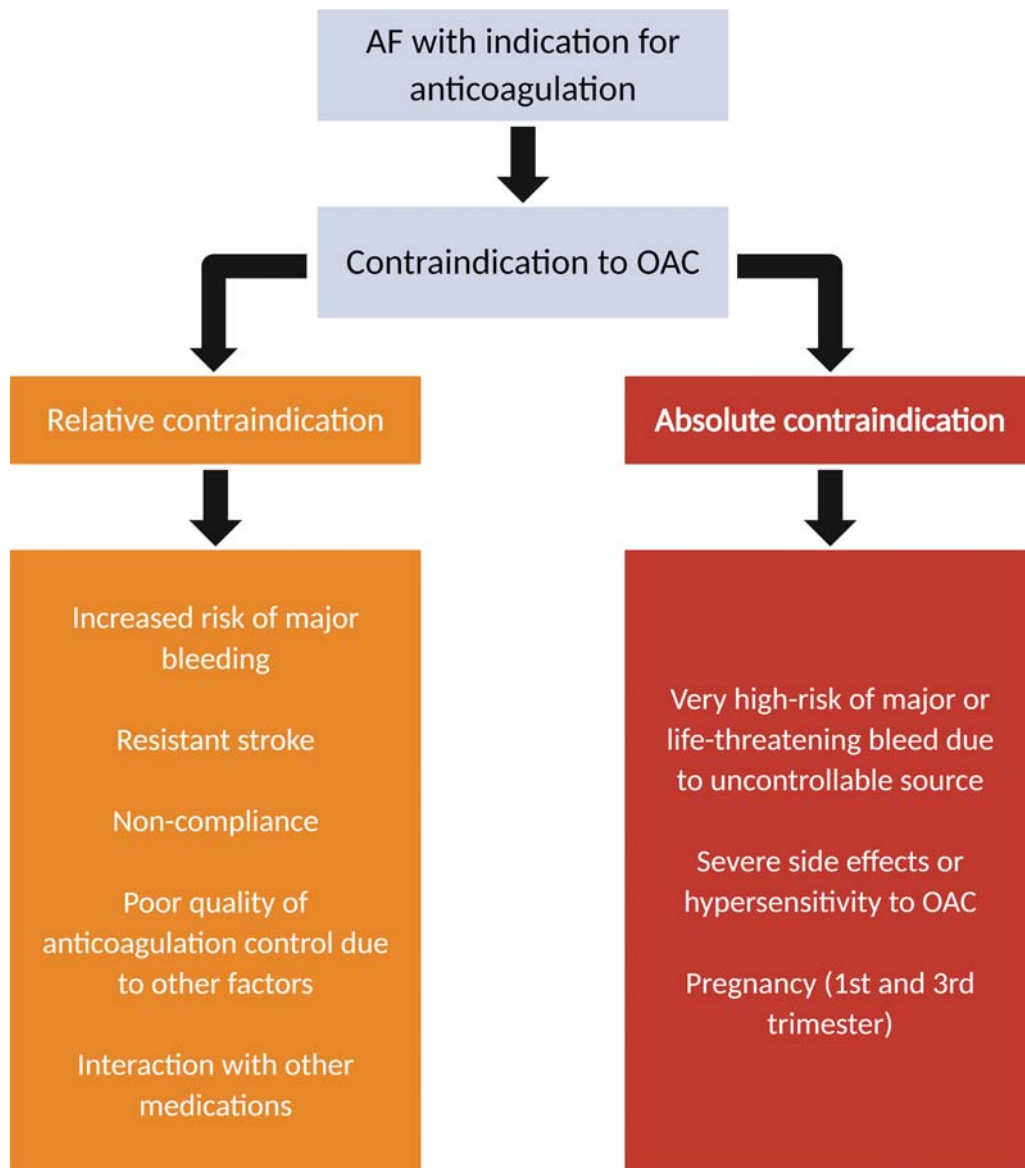


Fig. 2 Potential indications for left atrial appendage occlusion. AF, atrial fibrillation; OAC, oral anticoagulation.

Table 2 Potential complications of left atrial appendage occlusion

Acute complications	Late complications
Femoral vascular complications	Device-related thrombosis
Pericardial effusion	Device embolisation
Cardiac tamponade	Major/minor peri-device leak(s)
Stroke or transient ischemic attack	
Peripheral embolism	
Major bleeding	
Device embolisation requiring urgent open surgery	
Failed implant due to LAA anatomy or large size	
Death	

Abbreviation: LAA, left atrial appendage.

compared with the expected 7.3% per year based on the CHADS₂ score. More recently, a prospective global study of 1,088 patients, where 83% had contraindications to anticoagulation, found that LAA occlusion with the Amulet device was associated with a 67% reduction in ischemic stroke rates compared with predicted risk by the CHA₂DS₂-VASC score.³⁷

Only a single study has specifically investigated the use of LAA occlusion in AF patients with resistant stroke despite OAC therapy. Data from the ACP multicentre registry showed that LAA occlusion was associated with a 65% risk reduction in annual rates of stroke or transient ischemic attack, and a 100% risk reduction in annual rates of major bleeding, compared with predicted rates based on the CHA₂DS₂-VASC and HAS-BLED scores, respectively.²⁷ At present, there are no studies with direct comparison of LAA occlusion to standard medical therapy in patients with resistant stroke. With regards to compliance, an observational study by Zhai et al which included 338 (total n = 658; 51.4%) patients with non-compliance suggested that

LAA occlusion may be feasible for this indication due to low rates of procedural complications.³⁸

Electrical isolation of the LAA has been shown to improve long-term freedom from atrial arrhythmias in some patients undergoing AF ablation. The BELIEF (Effect of Empirical Left Atrial Appendage Isolation on Long-term Procedure Outcome in Patients with Persistent or Long-standing Persistent Atrial Fibrillation Undergoing Catheter Ablation) trial found that patients with long-standing persistent AF who were randomised to empirical electrical LAA isolation along with extensive ablation had significantly lower recurrence of atrial arrhythmias compared with those who received extensive ablation alone.³⁹ The findings were supported in two subsequent independent meta-analyses which demonstrated that the rates of arrhythmia recurrence were reduced by 56 to 62% with the addition of LAA electrical isolation to standard AF ablation.^{40,41} However, small studies have suggested that this technique was associated with increased thromboembolic risk.⁴²⁻⁴⁴ Therefore, LAA occlusion may have a potential role for prevention of thromboembolic complications following electrical LAA isolation to facilitate improvement in long-term success with AF ablation. Nonetheless, the evidence in this area is lacking and warrants further research.

At present, international guidelines pertaining to the use of percutaneous LAA occlusion in patients with AF are broadly similar. Current American College of Cardiology/American Heart Association/Heart Rhythm Society and European Society of Cardiology guidelines recommend that percutaneous LAA occlusion may be considered in patients with AF at increased stroke risk and with contraindications to long-term anticoagulation (class of recommendation: IIb; level of evidence: B).^{45,46} This recommendation was largely based on observational registry data.^{36,47} The National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand guidelines advocate that LAA occlusion may be considered in patients with non-valvular AF with contraindications to OAC (GRADE quality of evidence: low; GRADE strength of recommendation: strong).⁴⁸ The Canadian Cardiovascular Society suggests that non-approved LAA closure devices should not be used except in research protocols or in AF patients with high risk of stroke for whom antithrombotic is contraindicated (conditional recommendation; quality of evidence: low).⁴⁹

Post-procedural Management

Despite increasing evidence to support the use of LAA occlusion for stroke prevention in AF, there is a lack of consensus on the optimal post-procedural management and long-term antithrombotic strategies. Different antithrombotic regimes have been prescribed in various studies. For example, the PROTECT AF and PREVAIL trials used warfarin for 45 days followed by dual antiplatelet therapy (DAPT) with aspirin and clopidogrel up to 6 months, then aspirin alone indefinitely.^{14,16} In the prospective ASAP study, patients received 6 months of DAPT followed by lifelong aspirin.³⁶ Patients from the study by Kleinecke et al were treated with DAPT for 3 months and aspirin for at least 6 months.¹⁹ Data from the real-world EWOLUTION study found that there were different rates of

antithrombotic use following device implantation: DAPT in 60%, VKA in 16%, NOAC in 11%, SAPT in 7% and no antithrombotic in 6%.⁴⁷ Overall, there is a strong need for an assessment of the optimal antithrombotic regime post-LAA occlusion in adequately powered clinical trials.

The European Heart Rhythm Association and European Association of Percutaneous Cardiovascular Interventions updated guidelines recommend that AF patients with low bleeding risk who receive a Watchman device should be given warfarin (or NOAC) for 45 days, followed by clopidogrel for 6 months.⁵⁰ Meanwhile, OAC may be omitted for those with high bleeding risk. In contrast, DAPT including clopidogrel may be prescribed for 1 to 6 months in patients with a Watchman device who were not suitable for anticoagulation, or those who received the ACP or Amulet devices.⁵⁰

Long-term surveillance of patients following successful LAA occlusion remains ill-defined. Many operators perform imaging assessment to assess for leak or device-related thrombus (DRT) at 6 to 12 weeks post-procedure. More recently, the recognition of very late DRT has also prompted repeat imaging during long-term follow-up.⁵¹

Cost Effectiveness

In this current era of constrained health care resources, the potential benefits of LAA occlusion needs to be balanced against procedural-related expenses. Several cost analyses have been performed demonstrating superior cost effectiveness with LAA occlusion compared with warfarin or NOACs.^{15,52,53} It was estimated that the cost benefits of LAA occlusion would be realised within 10 years following successful implantation. Nevertheless, these studies were performed from the perspective of insurance-based health care systems in the United States. In a publicly funded health care system in the United Kingdom, LAA occlusion was forecasted to be cost neutral compared with dabigatran and warfarin within 4.9 and 8.4 years, respectively.⁵⁴ The study by Panikker et al estimated that LAAO may be cost-saving by up to £7,194 at 10 years compared with other therapies. Similar results were obtained in a cost-analysis study conducted from a German health care payer perspective.⁵⁵ Overall, LAA occlusion may indeed be cost effective with higher upfront costs that is subsequently balanced by improved outcomes and quality-of-life scores, and reduced medication. However, without long-term outcome data and a consensus on post-procedural management, it is extremely difficult to estimate cost-efficacy. What's more, a recent observational study has suggested the mortality rate in patients with LAA occlusion may be higher by 1.5- to 2.5-fold compared with those reported in randomised trials.^{14,16,56} This questions the applicability of prior cost-effectiveness modelling to real-world practice.

Unanswered Questions

Despite the increased uptake of LAA occlusion in clinical practice, there remain many unanswered questions such as 'How does LAA occlusion compare with conservative treatment in AF patients with contraindications to anticoagulation?'

Table 3 Current randomised controlled trials on percutaneous LAA occlusion

	ClinicalTrials.gov Identifier	Objective(s)	Target enrolment	Groups	Primary outcome measure(s)	Current status	Estimated Study completion
PRAGUE-17	NCT02426944	Compare LAA occlusion to NOAC treatment	400	LAA occlusion using Amulet or Watchman vs. NOAC	Composite endpoint of stroke, SE, clinically significant bleeding, CV death, or procedure or device-related complications	Follow-up in progress	May 2020
OPTION	NCT03795298	Assess LAA occlusion using Watchman FLX in AF patients	1,600	LAA occlusion using Watchman FLX vs. OAC	Composite endpoint of stroke, all-cause death and SE; non-procedural bleeding	Recruiting	September 2021
SAFE-LAAC	NCT034445949	Evaluate the optimal antiplatelet strategy after LAA occlusion using Amulet	160	30 days of DAPT followed by SAPT vs. 6 months of DAPT	Composite endpoint of stroke, TIA, SE, nonfatal MI, CV death, all-cause death, moderate and severe bleeding (BARC type 2, 3 and 5), LAA thrombus	Recruiting	January 2022
ASAP-TOO	NCT02928497	Evaluate LAA occlusion in AF patients not eligible for OAC	888	LAA occlusion using Watchman vs. SAPT or no therapy	Time to first ischemic stroke or SE; composite rate of death, ischemic stroke, SE and complications requiring intervention	Recruiting	December 2023
Amulet IDE	NCT02879448	Compare the outcomes of LAA occlusion using different devices	1,878	LAA occlusion using Amulet vs. Watchman	Composite endpoint of procedural-related complications, all-cause death and major bleeding; composite of ischemic stroke and SE; successful device closure at 45-days post-procedure	Active, not recruiting	August 2024
ANDES	NCT03568890	Compare short-term NOAC to DAPT post-LAA occlusion	350	8 weeks of NOAC vs. 8 weeks of DAPT	Device-related thrombosis	Recruiting	September 2025
SWISS-APERO	NCT03399851	Compare the outcomes of LAA occlusion using different devices	200	LAA occlusion using Amulet vs. Watchman/FLX	Composite of LAA patency at 45 days using CCTA or crossover due to technical considerations during device implantation	Recruiting	December 2025
WAVECREST2	NCT03302494	Assess LAA occlusion using WaveCrest in AF patients	1,250	LAA occlusion using WaveCrest vs. Watchman	Procedure or device-related complications; all-cause death; major bleeding; ischemic stroke or SE	Recruiting	December 2027
CATALYST	NCT04226547	Evaluate LAA occlusion compared with NOAC therapy in patients with non-valvular AF	2,650	LAA occlusion using Amulet vs. NOAC	Composite endpoint of ischemic stroke, SE and CV death (non-inferiority); major bleeding or clinically relevant non-major bleeding events (non-inferiority); major bleeding or clinically relevant non-major bleeding events (superiority)	Not yet recruiting	April 2029
STROKECLOSE	NCT02830152	Evaluate LAA occlusion in patients with non-valvular AF and prior ICH	750	LAA occlusion using Amulet vs. standard medical therapy	Composite endpoint of stroke, SE, life-threatening or major bleeding and all-cause death	Recruiting	May 2030
Occlusion-AF	NCT03642509	Evaluate LAA occlusion in AF patients with prior ischemic stroke or TIA	750	LAA occlusion using Watchman or Amulet vs. NOAC	Composite endpoint of stroke, SE, major bleeding and all-cause death	Recruiting	October 2030

Abbreviations: AF, atrial fibrillation; BARC, Bleeding Academic Research Consortium; CCTA, cardiac computed tomography angiography; CV, cardiovascular; DAPT, dual antiplatelet therapy; ICH, intracranial haemorrhage; LAA, left atrial appendage; MI, myocardial infarction; NOAC, non-vitamin K oral anticoagulants; OAC, oral anticoagulation; SAPT, single antiplatelet therapy; SE, systemic embolism; TIA, transient ischemic attack.

'What are the outcomes of LAA occlusion compared with standard medical therapy in AF patients with relative contraindications due to high risk of bleeding?', 'How does LAA occlusion compare with NOACs for stroke prevention in AF?', 'Are all the devices comparable in terms of efficacy and safety profile?', and 'What is the optimal antithrombotic regime post-procedure?'. Thankfully, many studies are underway to provide some answers (→ **Table 3**).

Conclusion

LAA occlusion might offer an alternative to OACs in selected patients with AF. Given the risks of this invasive procedure, the requirement for continued anti-thrombotic therapy to prevent DRT and the improved safety profile of NOAC agents, there is a strong need for additional controlled clinical trials to investigate its role and define the long-term outcomes associated with a successful procedure.

Conflict of Interest

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References

- Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;113(05):359–364
- Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22(08):983–988
- Aberg H. Atrial fibrillation. I. A study of atrial thrombosis and systemic embolism in a necropsy material. *Acta Med Scand* 1969;185(05):373–379
- Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996;61(02):755–759
- Mahajan R, Brooks AG, Sullivan T, et al. Importance of the underlying substrate in determining thrombus location in atrial fibrillation: implications for left atrial appendage closure. *Heart* 2012;98(15):1120–1126
- Regazzoli D, Ancona F, Trevisi N, et al. Left atrial appendage: physiology, pathology, and role as a therapeutic target. *BioMed Res Int* 2015;2015:205013
- Dawson AG, Asopa S, Dunning J. Should patients undergoing cardiac surgery with atrial fibrillation have left atrial appendage exclusion? *Interact Cardiovasc Thorac Surg* 2010;10(02):306–311
- García-Fernández MA, Pérez-David E, Quiles J, et al. Role of left atrial appendage obliteration in stroke reduction in patients with mitral valve prosthesis: a transesophageal echocardiographic study. *J Am Coll Cardiol* 2003;42(07):1253–1258
- Healey JS, Crystal E, Lamy A, et al. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. *Am Heart J* 2005;150(02):288–293
- Lee R, Vassallo P, Kruse J, et al. A randomized, prospective pilot comparison of 3 atrial appendage elimination techniques: Internal ligation, stapled excision, and surgical excision. *J Thorac Cardiovasc Surg* 2016;152(04):1075–1080
- Moussa Pacha H, Al-Khadra Y, Soud M, Darmoch F, Moussa Pacha A, Alraies MC. Percutaneous devices for left atrial appendage occlusion: a contemporary review. *World J Cardiol* 2019;11(02):57–70
- Sievert H, Lesh MD, Trepels T, et al. Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. *Circulation* 2002;105(16):1887–1889
- Sick PB, Schuler G, Hauptmann KE, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. *J Am Coll Cardiol* 2007;49(13):1490–1495
- Holmes DR, Reddy VY, Turi ZG, et al; PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;374(9689):534–542
- Holmes DR Jr, Doshi SK, Kar S, 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(24):2614–2623
- Holmes DR Jr, Kar S, Price MJ, 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(01):1–12
- Freeman JV, Varosy P, Price MJ, et al. The NCDR Left Atrial Appendage Occlusion Registry. *J Am Coll Cardiol* 2020;75(13):1503–1518
- Tzikas A, Shakir S, Gafoor S, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. *EuroIntervention* 2016;11(10):1170–1179
- Kleinecke C, Park J-W, Gödde M, Zintl K, Schnupp S, Brachmann J. Twelve-month follow-up of left atrial appendage occlusion with Amplatzer Amulet. *Cardiol J* 2017;24(02):131–138
- Landmesser U, Tondo C, Camm J, et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: one-year follow-up from the prospective global Amulet observational registry. *EuroIntervention* 2018;14(05):e590–e597
- Kleinecke C, Cheikh-Ibrahim M, Schnupp S, et al. Long-term clinical outcomes of Amplatzer cardiac plug versus Amulet occluders for left atrial appendage closure. *Catheter Cardiovasc Interv* 2019. Doi: 10.1002/ccd.28530
- Koskinas KC, Shakir S, Fankhauser M, et al. Predictors of early (1-week) outcomes following left atrial appendage closure with Amplatzer devices. *JACC Cardiovasc Interv* 2016;9(13):1374–1383
- Lakkireddy D, Afzal MR, Lee RJ, et al. Short and long-term outcomes of percutaneous left atrial appendage suture ligation: results from a US multicenter evaluation. *Heart Rhythm* 2016;13(05):1030–1036
- Bartus K, Han FT, Bednarek 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(02):108–118
- Massumi A, Chelu MG, Nazeri A, et al. Initial experience with a novel percutaneous left atrial appendage exclusion device in patients with atrial fibrillation, increased stroke risk, and contraindications to anticoagulation. *Am J Cardiol* 2013;111(06):869–873
- Schulman S, Beyth RJ, Kearon C, et al. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(6 Suppl):257S–298S
- Cruz-González I, González-Ferreiro R, Freixa X, et al. Left atrial appendage occlusion for stroke despite oral anticoagulation (resistant stroke). Results from the Amplatzer Cardiac Plug registry. *Rev Esp Cardiol (Engl Ed)* 2020;73(01):28–34

- 28 Raparelli V, Proietti M, Cangemi R, Lip GY, Lane DA, Basili S. Adherence to oral anticoagulant therapy in patients with atrial fibrillation. Focus on non-vitamin K antagonist oral anticoagulants. *Thromb Haemost* 2017;117(02):209–218
- 29 Granger CB, Alexander JH, McMurray JJV, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365(11):981–992
- 30 Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365(10):883–891
- 31 Connolly SJJ, Ezekowitz MDD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361(12):1139–1151
- 32 Giugliano RP, Ruff CT, Braunwald E, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369(22):2093–2104
- 33 Shen JJ, Montez-Rath ME, Lenihan CR, Turakhia MP, Chang TI, Winkelmayer WC. Outcomes after warfarin initiation in a cohort of hemodialysis patients with newly diagnosed atrial fibrillation. *Am J Kidney Dis* 2015;66(04):677–688
- 34 Li XS, Deitelzweig S, Keshishian A, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in “real-world” clinical practice. A propensity-matched analysis of 76,940 patients. *Thromb Haemost* 2017;117(06):1072–1082
- 35 Boersma LV, Ince H, Kische S, et al; following investigators and institutions participated in the EWOLUTION study. Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the WATCHMAN Left Atrial Appendage Closure technology: final 2-year outcome data of the EWOLUTION trial focusing on history of stroke and hemorrhage. *Circ Arrhythm Electrophysiol* 2019;12(04):e006841
- 36 Reddy VY, Möbius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA plavix feasibility study with Watchman Left Atrial Appendage Closure technology). *J Am Coll Cardiol* 2013;61(25):2551–2556
- 37 Hildick-Smith D, Landmesser U, Camm AJ, et al. Left atrial appendage occlusion with the Amplatzer™ Amulet™ device: full results of the prospective global observational study. *Eur Heart J* 2020:ehaa169
- 38 Zhai Z, Tang M, Su X, et al. Experience of left atrial appendage occlusion with the WATCHMAN device in Chinese patients. *Anatol J Cardiol* 2019;21(06):314–321
- 39 Di Biase L, Burkhardt JD, Mohanty P, et al. Left atrial appendage isolation in patients with longstanding persistent AF undergoing catheter ablation: BELIEF trial. *J Am Coll Cardiol* 2016;68(18):1929–1940
- 40 Romero J, Michaud GF, Avendano R, et al. Benefit of left atrial appendage electrical isolation for persistent and long-standing persistent atrial fibrillation: a systematic review and meta-analysis. *Europace* 2018;20(08):1268–1278
- 41 Friedman DJ, Black-Maier EW, Barnett AS, et al. Left atrial appendage electrical isolation for treatment of recurrent atrial fibrillation: a meta-analysis. *JACC Clin Electrophysiol* 2018;4(01):112–120
- 42 Kim YG, Shim J, Oh S-K, Lee KN, Choi JI, Kim YH. Electrical isolation of the left atrial appendage increases the risk of ischemic stroke and transient ischemic attack regardless of postisolation flow velocity. *Heart Rhythm* 2018;15(12):1746–1753
- 43 Fink T, Schlüter M, Heeger C-H, et al. Combination of left atrial appendage isolation and ligation to treat nonresponders of pulmonary vein isolation. *JACC Clin Electrophysiol* 2018;4(12):1569–1579
- 44 Rillig A, Tilz RR, Lin T, et al. Unexpectedly high incidence of stroke and left atrial appendage thrombus formation after electrical isolation of the left atrial appendage for the treatment of atrial tachyarrhythmias. *Circ Arrhythm Electrophysiol* 2016;9(05):e003461
- 45 January CT, Wann LS, Calkins H, et al. 2019 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(01):104–132
- 46 Kirchhof P, Benussi S, Kotecha D, et al; ESC Scientific Document Group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37(38):2893–2962
- 47 Boersma LV, Ince H, Kische S, et al; EWOLUTION Investigators. 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(09):1302–1308
- 48 Brieger D, Amerena J, Attia JR, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. *Med J Aust* 2018;209(08):356–362
- 49 Verma A, Cairns JAA, Mitchell LBB, et al; CCS Atrial Fibrillation Guidelines Committee. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. *Can J Cardiol* 2014;30(10):1114–1130
- 50 Glikson M, Wolff R, Hindricks G, et al; ESC Scientific Document Group. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update. *Europace* 2019:euz258
- 51 Pracon R, Bangalore S, Dzielinska Z, et al. Device thrombosis after percutaneous left atrial appendage occlusion is related to patient and procedural characteristics but not to duration of postimplantation dual antiplatelet therapy. *Circ Cardiovasc Interv* 2018;11(03):e005997
- 52 Reddy VY, Akehurst RL, Gavaghan MB, Amorosi SL, Holmes DR Jr. Cost-effectiveness of left atrial appendage closure for stroke reduction in atrial fibrillation: analysis of pooled, 5-year, long-term data. *J Am Heart Assoc* 2019;8(13):e011577
- 53 Reddy VY, Akehurst RL, Amorosi SL, Gavaghan MB, Hertz DS, Holmes DR Jr. Cost-effectiveness of left atrial appendage closure with the WATCHMAN device compared with warfarin or non-vitamin K antagonist oral anticoagulants for secondary prevention in nonvalvular atrial fibrillation. *Stroke* 2018;49(06):1464–1470
- 54 Panikker S, Lord J, Jarman JWE, et al. Outcomes and costs of left atrial appendage closure from randomized controlled trial and real-world experience relative to oral anticoagulation. *Eur Heart J* 2016;37(46):3470–3482
- 55 Reddy VY, Akehurst RL, Armstrong SO, et al. Cost effectiveness of left atrial appendage closure with the Watchman device for atrial fibrillation patients with absolute contraindications to warfarin. *Europace* 2016;18(07):979–986
- 56 Fauchier L, Cinaud A, Brigadeau F, et al. Major adverse events with percutaneous left atrial appendage closure in patients with atrial fibrillation. *J Am Coll Cardiol* 2019;73(20):2638–2640