Stroke

TOPICAL REVIEW

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Left Atrial Appendage Occlusion and Its Role in Stroke Prevention

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ABSTRACT: Atrial fibrillation is a frequent cardiac arrhythmia and is associated with an increased risk of cardioembolic stroke. The left atrial appendage is a finger-like extension originating from the main body of the left atrium and the main location of thrombus formation in patients with atrial fibrillation. Surgical or percutaneous left atrial appendage occlusion (LAAO) aims at preventing clot formation in the left atrial appendage. Here, we describe available surgical and percutaneous approaches to achieve LAAO and discuss the available evidence for LAAO in patients with atrial fibrillation. We discuss the role of LAAO and its role in stroke prevention in frequent scenarios in cerebrovascular medicine: LAAO as a potential alternative to oral anticoagulation in patients with a history of intracranial hemorrhage, and LAAO as a promising add-on therapy to direct oral anticoagulant therapy in patients with breakthrough stroke despite anticoagulation. Finally, we provide an outlook on currently ongoing trials that will provide further evidence in the next years.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: anticoagulants ■ atrial appendage ■ atrial fibrillation ■ embolic stroke ■ intracerebral hemorrhage

Atrial fibrillation (AF) is one of the most common cardiac rhythm disorders and is associated with increased risks of morbidity and mortality.[1] Although AF is relatively uncommon in middle-aged adults, it affects nearly 10% of individuals over the age of 80 years.[2] Moreover, AF is an important independent risk factor for stroke.[3] Several risk stratification schemes, such as $CHADS_2$ and CHA_2DS_2-VASc, and most recently, CHA_2DS_2-VA,[4] have been developed to evaluate and quantify the individual risk of stroke for patients with AF.

Up to 25% of all ischemic strokes are associated with AF.[5] Stroke survivors with a concomitant diagnosis of AF are more likely to experience a recurrent stroke than those without AF.[6] AF-associated ischemic strokes tend to be more severe and are more likely to be disabling or fatal than strokes unrelated to AF. This is presumably mediated by a high rate of cardioembolic large vessel occlusions,[7] resulting in larger-sized cerebral infarcts, a higher likelihood of hemorrhagic transformation, and more severe initial neurological impairment.[8,9]

The left atrial appendage (LAA) plays a crucial role in cardiac thrombus formation. LAA occlusion (LAAO) is a promising approach to reduce the risk of cardioembolic stroke. In this review, we summarize the available evidence for LAAO for stroke prevention in patients with AF.

PRINCIPLES OF STROKE PREVENTION IN PATIENTS WITH AF

Stroke prevention is a cornerstone of AF management,[10] and an integral part of the AF-CARE pathway suggested in the recently published 2024 European Society of Cardiology Guidelines for the management of AF[4] and the 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation.[11]

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Oral anticoagulation is the mainstay to prevent ischemic stroke and thromboembolism in patients with AF and risk factors.[12,13] Antiplatelet therapy (eg, aspirin) alone provides a ≈20% risk reduction[12] but is not recommended for stroke prevention in patients with AF, because oral anticoagulation is much more effective.[13]

The evidence for oral anticoagulation in patients with AF is based on 6 pivotal randomized trials enrolling 2900 patients that established the efficacy and safety of dose-adjusted warfarin for stroke prevention >3 decades ago.[13] Here, warfarin reduced stroke by almost 64%. Between 2009 and 2013, another 4 randomized controlled trials enrolling a total of 71 683 patients with AF demonstrated the noninferiority of the oral thrombin inhibitor, dabigatran, and the oral factor Xa inhibitors, apixaban, rivaroxaban, and edoxaban, compared with warfarin for stroke prevention.[14] This led to strong recommendations for the use of oral anticoagulation in patients with AF and high risk for stroke, with a preference for the direct oral anticoagulants due to their favorable safety profile and ease of use.[15–17]

Although oral anticoagulation is the gold standard for stroke prevention in patients with AF, there are certain scenarios where alternative or additional measures for stroke protection could be considered. These include (1) patients with a (recent) history of bleeding, particularly intracerebral hemorrhage (ICH) or who are at high risk of bleeding (ie, cerebral amyloid angiopathy [CAA][18,19]), (2) patients unwilling to take oral anticoagulation, and (3) patients who may benefit from additional protection on top of oral anticoagulation.[20]

LAA AND ITS ROLE IN INTRACARDIAC THROMBUS FORMATION

The LAA is a finger-like extension originating from the main body of the left atrium. There are considerable variations in LAA size and shape and the anatomic relationship with adjacent cardiac and extracardiac structures.[21] The LAA morphology has been classified into 4 major types: chicken wing, cactus, windsock, and cauliflower, with the former 2 predominating.[22]

Several studies have reported that the majority of thrombi forming in the left atrium originate from the LAA: for example, 75% of all left atrial thrombi in a sample of patients with AF undergoing heart surgery,[23] 82% in a sample of patients with AF who had a recent stroke,[24] and up to 91% in patients with nonvalvular AF free of stroke.[25] Both transesophageal echocardiography (Figure 1) and cardiac computed tomography (Figure 2) are sensitive and specific for LAA thrombus detection.[26] In patients with acute stroke and AF, a thrombus can be found in the LAA in a significant proportion of patients, ranging between 8%[24] and 15%.[27] A recently presented study (Sposato et al., World Stroke Congress 2024) found that in patients presenting with acute ischemic stroke, single-phase, nongated computed tomography angiography extended to the heart identified cardioaortic thrombi in 8.8% of all patients, most frequently LAA thrombi in patients with AF.

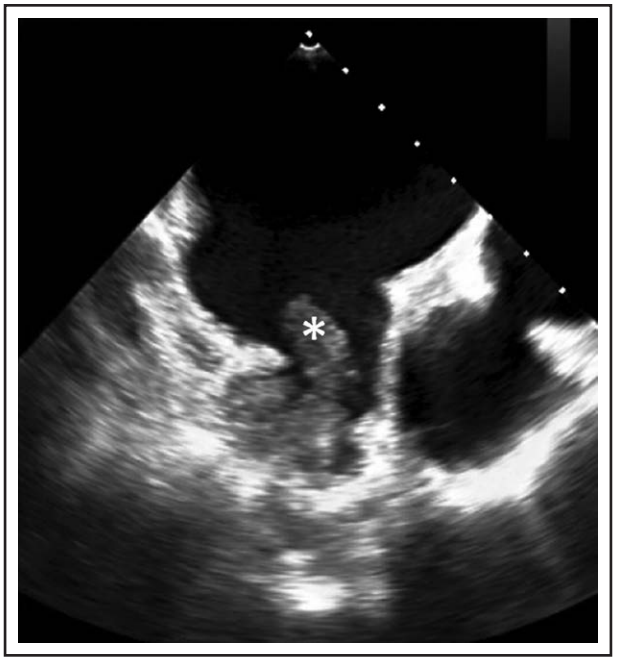

Figure 1. Example of a thrombus (*) in the left atrial appendage on transesophageal echocardiography.

Therefore, the LAA represents a biologically plausible target for stroke prevention. Several approaches with the aim of reducing the risk of stroke by means of excluding or occluding the LAA have been developed.[28–30] These include surgical excision, endocardial, or epicardial suture during concomitant cardiac surgery, epicardial exclusion by stapling or clips, or endovascular occlusion by percutaneous intervention (Figure 3).

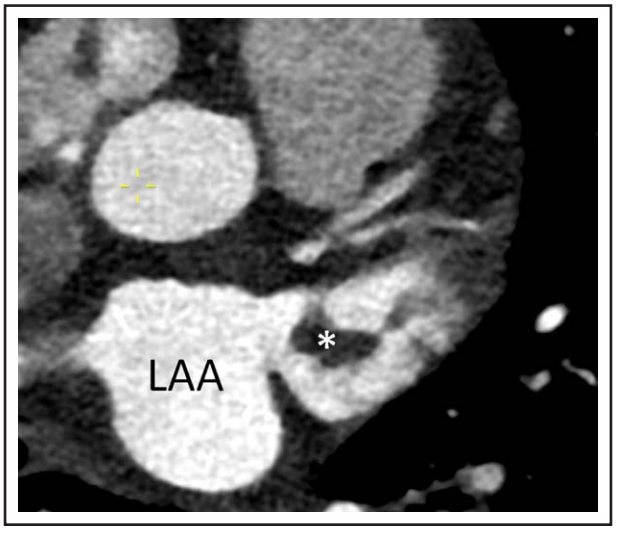

Figure 2. Example of a thrombus (*) in the left atrial appendage (LAA) on cardiac computed tomography.

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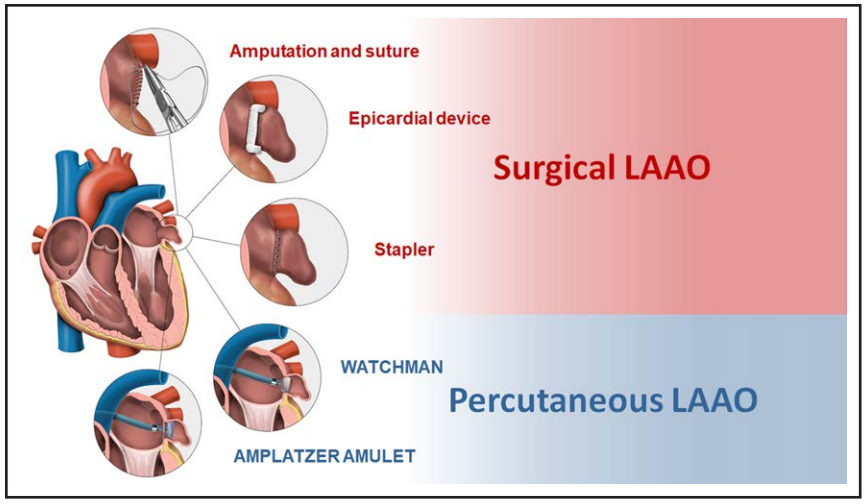

Figure 3. Commonly used surgical and percutaneous approaches to left atrial appendage occlusion (LAAO; clockwise): (1) surgical amputation and suture closure (cut and sew), (2) surgical stapler occlusion, (3) epicardial closure device (eg, AtriClip), (4) percutaneous closure device (Amplatzer Amulet), and (5) percutaneous closure device (WATCHMAN FLX).

EVIDENCE FOR SURGICAL LAAO

Until recently, the evidence for surgical occlusion of the LAA was largely limited to data from observational studies.[31] In 2021, the LAAOS (Left Atrial Appendage Occlusion Study) III provided solid evidence for stroke risk reduction with concomitant surgical LAAO.[32] This trial enrolled patients with AF undergoing cardiac surgery for another indication. LAAOS III included 4770 patients (9% with prior stroke) who were randomized 1:1 to occlusion or no occlusion of the LAA during cardiac surgery (66.7% valve procedure, 21.0% isolated coronary artery bypass graft). The technique for surgical LAAO was left at the discretion of the treating surgeon (55.7% cut and sew, 11.2% stapler, and 15.1% closure device; Figure 3). During a mean follow-up of 3.8 years, there was a 33% relative risk reduction in the primary end point of ischemic stroke or systemic embolism in patients assigned to receive LAAO (hazard ratio, 0.67 [95% CI, 0.53–0.85]). This benefit was observed in addition to usual care, with >75% of patients in both groups receiving oral anticoagulation with a vitamin K antagonist or a direct oral anticoagulant at any point during the trial. A prespecified secondary analysis found that stroke risk reduction with LAAO was independent of anticoagulation therapy in LAAOS III.[33] Patients who continued anticoagulation therapy throughout the study had the lowest risk of stroke (2.2% in patients who continued anticoagulation after LAAO versus 7.5% in patients who stopped anticoagulation after LAAO).[33] This finding highlights the potential of a combined mechanical/pharmacological approach to stroke prevention in patients with AF.

The results of LAAOS III have led to class I recommendations for surgical LAAO in addition to oral anticoagulation in patients with AF undergoing cardiac surgery to prevent stroke and thromboembolism in the most recent 2023 ACC/AHA/ACCP/HRS and 2024 ESC Guidelines for the management of AF.[4,34] The results of LAAOS III do not support surgical LAA occlusion as a standalone replacement for oral anticoagulation and do not support cardiac surgery for LAAO without any other indication for cardiac surgery.

EVIDENCE FOR PERCUTANEOUS LAAO

Percutaneous LAAO may represent an alternative to surgical LAAO. There are currently 2 devices for percutaneous LAAO that were approved by the US Food and Drug Administration based on 3 randomized trials that enrolled a total of 2992 patients.[35–37] Approval mechanisms for medical devices differ from those for novel drugs, and device studies typically enroll only a fraction of participants enrolled in drug trials.

The Food and Drug Administration approval of the first-generation WATCHMAN LAAO device (Boston Scientific, Marlborough, MA) is based on results from the PROTECT AF and PREVAIL randomized noninferiority trials, testing the device against warfarin.[35,36] PROTECT AF, published in 2009, enrolled 707 patients with AF and a $CHADS_2$ score ≥1 who were randomized in a 2:1 fashion to percutaneous LAAO (N=463) or warfarin (target international normal ratio, 2.0–3.0; N=244).[36] Patients randomized to the device arm were treated with warfarin and aspirin for 45 days after implantation, then received dual antiplatelet therapy with aspirin and clopidogrel until the 6-month visit, and then aspirin alone indefinitely thereafter. The primary end point was a composite of all-cause stroke, systemic embolism, or cardiovascular or unexplained death. During a mean follow-up of 18 months, 21 patients (4.5%) in the device group and 18 patients (7.4%) in the warfarin group had a primary end point event (rate ratio, 0.62 [95% credible interval, 0.35–1.25]; *P* value for noninferiority <0.001), driven by a reduction in hemorrhagic stroke and cardiovascular or unexplained death. The rate of ischemic stroke was numerically higher in the device group (2.2 versus 1.6 per 100 patient-years, rate ratio, 1.34 [95% credible interval, 0.60–4.29]).[36]

PREVAIL, published in 2014, enrolled 407 patients with AF and a $CHADS_2$ score ≥2, or a $CHADS_2$ score of 1 with a least 1 additional risk factor.[35] Study participants were randomized 2:1 to percutaneous LAAO (N=269) or warfarin (N=138). The coprimary efficacy end points were (1) a composite of all-cause stroke, systemic embolism, cardiovascular, or unexplained death and (2) all-cause stroke or systemic embolism >7 days after randomization. The postimplant antithrombotic regimen was identical to that used in PROTECT AF. At 18 months, the rates for the first coprimary efficacy end point were 6.4% in the device arm and 6.3% in the warfarin group (rate ratio, 1.07 [95% credible interval, 0.57–1.89], not meeting the prespecified noninferiority criteria). Rates of the second coprimary efficacy end point were 2.5% versus 2.0%, meeting noninferiority. The overall rate of ischemic stroke was higher in the device group (1.9% versus 0.7%).[35] Subsequent longer-term follow-up results from both PROTECT AF and PREVAIL have been published.[38] In a meta-analysis of patient-level data, the rate of the composite of stroke, systemic embolism, or cardiovascular death was 2.8% and 3.4% per year in patients randomized to percutaneous LAAO and warfarin, respectively. Corresponding rates of ischemic stroke or systemic embolism were 1.6% versus 1.0%, and of major bleeding were 3.1% and 3.5%, respectively.

The company's second-generation device, WATCHMAN FLX, was evaluated in a prospective, nonrandomized, single-arm study that enrolled 400 patients with AF and "a rationale for a nonpharmacological approach to stroke prevention."[39] The postimplant antithrombotic regimen was direct oral anticoagulation (with a recommendation for apixaban or rivaroxaban) and aspirin for 45 days, then dual antiplatelet therapy with aspirin and clopidogrel until the 6-month visit, and then aspirin alone indefinitely thereafter. The study met both its primary safety (death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring cardiac surgery) and efficacy performance goals (peri-device flow ≤5 mm on transesophageal echocardiography, assessed at 12 months). At 2 years, the annualized rate of ischemic stroke in patients undergoing implantation of a WATCHMAN FLX device was 1.7%.[39]

The Food and Drug Administration approval of the Amplatzer Amulet LAA Occluder (Abbott, Green Oaks, IL) is based on a randomized noninferiority trial testing the device against the first-generation WATCHMAN system.[37] The Amulet IDE trial enrolled 1878 patients with AF and an "appropriate rationale to seek a nonpharmacological alternative." Patients were randomized 1:1 to 1 of the 2 devices. The 3 coprimary end points were (1) a safety composite of procedure-related complications, major bleeding, or all-cause death at 12 months; (2) an effectiveness composite of ischemic stroke or systemic embolism at 18 months; and (3) the rate of successful LAA occlusion on transesophageal echocardiography at 45 days. The Amulet device was noninferior to the WATCHMAN device for safety (14.5% versus 14.7% at 12 months) and efficacy (2.8% in both groups at 18 months), both *P* values for noninferiority <0.001. The rate of successful LAA occlusion at 45 days was high in both groups (98.9% versus 96.8%, *P*=0.003 for superiority).[37] The rate of major bleeding at 12 months was similar in both groups (10.6% with Amulet and 10.0% with WATCHMAN), with the majority being nonprocedure related (7.9% and 8.0%, respectively). However, the rate of procedure-related complications was higher with Amulet compared with WATCHMAN (4.5% versus 2.5%, *P*=0.02), primarily driven by an increase in pericardial effusion/tamponade.[37]

Unresolved issues in percutaneous LAAO include the potential of peri-device leak, device-related thrombus formation, and uncertainty regarding the optimal postimplant antithrombotic regimen.[40]

High-quality evidence in support of percutaneous LAAO beyond the regulatory trials is sparse. The 402-patient PRAGUE-17 trial claimed noninferiority of percutaneous LAAO with any approved device with direct oral anticoagulation for a primary end point that consisted of both efficacy and safety events.[41] Several observational studies aimed at comparing percutaneous LAAO versus oral anticoagulation have been published, but carry an immense risk of bias.[42–44] The recent OPTION trial enrolling 1600 patients with AF undergoing catheter ablation found that, compared with direct oral anticoagulation therapy, percutaneous LAAO was superior for a safety end point of nonprocedure-related major or clinically relevant nonmajor bleeding and noninferior for an efficacy end point of all-cause mortality, ischemic stroke or systemic embolism.[45] However, the observed rate of ischemic stroke or systemic embolism was low (≈0.5% per year in both groups), and the trial was not powered to demonstrate noninferiority of LAAO for the prevention of thrombotic events. In addition, only a fraction of participants (10.8%) had a history of ischemic stroke or transient ischemic attack, limiting the applicability of these findings to patients with (a recent) stroke.

LAAO IN PATIENTS WITH CEREBROVASCULAR DISEASE AT HIGH RISK OF INTRACRANIAL BLEEDING

One appealing scenario for the use of LAAO for stroke prevention is as an alternative to standard of care oral anticoagulation in people with AF at increased risk of bleeding. There are several cerebrovascular comorbidities that potentially increase the risk of intracranial bleeding, for example, a history of ICH, a diagnosis of CAA, or cerebral microbleeds.

ICH is a devastating disease and is associated with high rates of permanent disability and death.[46–49] Patients with AF are at increased risk for ICH secondary to oral anticoagulation use,[13,50] likely mediated by the

concomitant presence of bleeding-prone cerebral small vessel disease.[51] AF and ICH share common risk factors, resulting in up to 25% of all patients with ICH having AF.[52]

In general, the risk of recurrent ICH depends on the underlying cause of the ICH ranging between 1.3% and 7.4% annually,[47] with the highest risk of recurrence among those with CAA of up to 7.4% per year.[53] In patients with CAA free of ICH, the risk of ICH is also elevated as it is in patients with cerebral microbleeds but without a formal diagnosis of CAA.[54] Whether and how oral anticoagulation increases these incremental risks is currently unknown.[55,56]

Several small randomized controlled trials compared restarting versus avoiding anticoagulation in patients with ICH but results were mainly exploratory.[57,58] A recent individual patient data meta-analysis demonstrated that anticoagulation significantly reduces the risk of ischemic stroke, systemic embolism, and cardiovascular death (similar to the risk reduction observed in patients with AF without ICH), but the effect on recurrent ICH was uncertain with numerically higher numbers of recurrent ICH in patients who restarted anticoagulation.[18] From a patient and physician's perspective, reinitiating oral anticoagulation after an ICH event is frequently associated with fear.[56] However, when comparing the estimated risks of an ICH associated with oral anticoagulation and of a cardioembolic stroke in the absence of oral anticoagulation, the anticipated benefit of reinitiating treatment is generally felt to outweigh the risk, with both the American Stroke Association, and the American College of Chest Physicians guidelines suggest the decision be tailored to the individual patient.[59]

The pivotal trials comparing LAAO with warfarin[35,36] or direct oral anticoagulants[41] excluded patients unsuitable for anticoagulation therapy (ie, with a history of ICH), and it is uncertain whether the results from these trials apply also to patients with a history of ICH, CAA, or cerebral microbleeds. Therefore, evidence on this topic is currently limited to observational data only.

LAAO Among Patients With Prior ICH

Several retrospective[60–64] and prospective[19,65,66] observational studies assessed the risk of recurrent ICH and ischemic thromboembolic complications. Table 1 summarizes key findings of these studies. Most studies included a mixed population of intracranial bleedings including subdural hematoma, subarachnoid hemorrhage, and intraparenchymal/ICH with diverging follow-up periods and heterogenous postinterventional antithrombotic treatments. Overall, 8 individual studies included 268 patients with a history of ICH. Overall, procedural success of LAAO was good, and the observed rates of both ischemic stroke/systemic embolism and recurrent ICH after LAAO were low. Post-LAAO antithrombotic therapy was heterogenous, including short periods of oral anticoagulation or dual antiplatelet therapy and mostly lifelong single antiplatelet therapy (aspirin). Only 2 studies included a comparator group which was patients with AF who received LAAO without a history of ICH and none included any comparator arm for patients with AF and a history of ICH (ie, no treatment, antiplatelet, or anticoagulation therapy without LAAO). Overall, the risk of bias

Table 1. Observational Studies of LAAO in Patients With a History of Intracranial Hemorrhage

	Horstmann et al[19]	Gilhofer et al[60]	Pouru et al[61]	Ajmal et al[62]	Hucker et al[63]	Hutt et al[64]	Renou et al[65]	Tzikas et al[66]
Study design	Observational, prospective	Observational, retrospective	Observational, retrospective	Observational, retrospective	Observational, retrospective	Observational, retrospective	Observational, prospective	Observational, prospective
Study population	20 patients with AF and a history of IcraH	138 patients with and history of IcraH	104 patients with and history of IcraH	16 patients with AF and a history of IcraH	63 patients with AF and a history of IcraH	38 patients with AF and a history of IcraH	46 patients with AF and a history of IcraH	198 patients with AF and a history of IcraH
Type of intracranial bleeding	5 SDH/SAH; 15 ICH	73 SDH/SAH; 64 ICH	32 SDH/SAH; 69 ICH	9 SDH/SAH; 7 ICH	23 SDH/SAH; 44 ICH	15 SDH/SAH; 23 ICH	46 ICH	Not reported
CHA_2DS_2-VASc	4.5	4.4	4.7	4.5	4.9	5.0	5.2	4.5
HAS-BLED	4.7	3.7	3.3	4	3.5	4.2	4.0	3.5
Comparator	None	None	None	None	95 patients without a history of IcraH	None	None	849 patients without a history of IcraH
Intervention	LAAO	LAAO	LAAO	LAAO	LAAO	LAAO	LAAO	LAAO
Antithrombotic treatment after LAAO	3 mo DAPT+lifelong APT	1–6 mo DAPT+6 mo ATP	<6 mo of ATP post-LAAO	DOAC+APT for 45 d, DAPT for 6 mo, lifelong ATP	Mixed (51% DOAC, 19% DAPT, 43% OAC+ATP)	DOAC for 45 d, DAPT for 6 mo, lifelong ATP	6 mo ATP, 56% lifelong ATP	ATP lifelong
Follow-up	Mean 14 mo	Median 15 mo	Median 3.6 y	Mean 13 mo	6 mo	Median 13 mo	Mean 13 mo	Mean 18 mo
Rate of ischemic stroke/thromboembolsm	0	1.8%/y	3.4%/y	0	0	0	4.3%/y	Not reported
Rate of ICH	0	1.5%/y	1.9%/y	0	0	0	2%/y	Not reported

AF indicates atrial fibrillation; ATP, single antiplatelet therapy; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; ICH, intracerebral hemorrhage; IcraH, intracranial hemorrhage; LAAO, left atrial appendage occlusion; OAC, oral anticoagulation; SAH, subarachnoid hemorrhage; and SDH, subdural hematoma.

Table 2. Summary of Ongoing Randomized Controlled Trials in Patients With AF Assessing Safety and Efficacy of LAAO in Different Patient Populations

	Patients with high risk of ischemic stroke		Patients with high risk of bleeding		
Trial name	ELAPSE	LAAOS-4	ASAP-TOO	STROKE-CLOSE	CLEARANCE
Trial number	https://www.clinicaltrials.gov; Unique identifier: NCT05976685	https://www.clinicaltrials.gov; Unique identifier: NCT05963698	https://www.clinicaltrials.gov; Unique identifier: NCT02928497	https://www.clinicaltrials.gov; Unique identifier: NCT02830152	https://www.clinicaltrials.gov; Unique identifier: NCT05976685
Patient population	AF and breakthrough stroke	AF and CHA_2DS_2-VASc score ≥4	Patients with AF not deemed suitable for OAC	Patients with AF with a history of IcraH (<6 mo)	Patients with AF with a history of IcraH (>6 wk)
Interventional group	LAAO (any device)+DOAC	LAAO (WATCHMAN)+OAC	LAAO (WATCHMAN)	LAAO (Amulet)	LAAO (WATCHMAN)
Comparator group	DOAC alone	OAC alone	ATP or no AT	OAC or ATP or no AT	DOAC
Primary outcome	Recurrent ischemic stroke, SE, or CVD (superiority)	Ischemic stroke or SE (superiority)	Ischemic stroke or SE (superiority)	Stroke (ischemic or hemorrhagic), SE, life-threatening or major bleeding, or all-cause mortality (superiority)	CVD, stroke (ischemic or hemorrhagic), SE, or bleeding (BARC type 2–5)
Sample size	482–1000	4000	481	750	550
Estimated completion	2029	2029	2025	2030	2025

AF indicates atrial fibrillation; AT, antithrombotic treatment; ATP, antiplatelet agent; BMT, best medial therapy; CVD, cardiovascular death; DOAC, direct oral anticoagulants; IcraH, intracranial hemorrhage; LAAO, left atrial appendage occlusion; OAC, oral anticoagulation; SE, systemic embolism; and TIA, transient ischemic attack.

for published studies is significant due to selection and reporting bias, and study quality was low.

LAAO in Patients With Cerebral Microbleeds or a Diagnosis of CAA

Cerebral microbleeds are magnetic resonance imaging–defined lesions indicating recent or old microhemorrhages.[54] They are increasingly found in the context of cerebrovascular disease or dementia.[54] Some of them may be due to CAA but the underlying spectrum of causes is heterogeneous.[67] They are usually indicators of advanced cerebrovascular disease and associated with a high risk of both ICH and ischemic stroke.[54,68] CAA is characterized by amyloid-beta deposits in small leptomeningeal vessels leading to vessel fragility and bleeding.[69] The diagnosis of CAA may include cerebral microbleeds using the Boston 2.0 criteria.[70]

Percutaneous LAAO might have a role in this particularly vulnerable subset of patients with AF and a diagnosis of CAA. Recently, a large randomized trial assessing the role of oral anticoagulation with edoxaban in patients with AF and prior intracranial hemorrhage has stopped the recruitment of patients entering the trial with lobar intracranial hemorrhage and convexity subarachnoid hemorrhage, subtypes of intracranial hemorrhage that are often associated with CAA. After a safety review of the first 699 study participants, the Data and Safety Monitoring Board made a recommendation to stop oral anticoagulation and to not enroll any additional patients with these intracranial hemorrhage subtypes, due to an observed unacceptably high risk of hemorrhage stroke in this group.[71] In the absence of high-quality evidence, percutaneous LAAO might be an alternative for these patients, but the optimal postimplantation antithrombotic regimen remains unclear. A multicenter, observational study based out of Vanderbilt[72] included patients with AF and probable CAA, with at least 1 lobar hemorrhage without severe hypertension, who had undergone percutaneous LAAO using any commercially available device. Patients with a history of symptomatic ICH or who were otherwise high risk were placed on single or dual antiplatelet therapy for 6 weeks after the closure procedure while patients who had previously tolerated anticoagulation were continued for 6 weeks after the procedure. In this small study of 26 patients, 1 patient had an ischemic stroke, and another patient had a recurrent ICH.[72]

LAAO IN PATIENTS WITH BREAKTHROUGH STROKES

Approximately, 40% of all AF-related ischemic strokes occur in patients who are already on therapy with oral anticoagulants (breakthrough strokes).[7] The risk of recurrent stroke is particularly high in those patients, with annualized rates of recurrent stroke ranging between 5% and 9%.[10,20,73–76] Although approximately one-quarter of breakthrough strokes are related to non-AF–related stroke causes,[77,78] the majority are cardioembolic in origin but only in part related to medication errors (ie, off-label dosing,

			Patients without contraindications for OAC		
COMPARE LAAO	**CLOSURE-AF**	**LAA-KIDNEY**	**CHAMPION-AF**	**CATALYST**	**Occlusion-AF**
https://www.clinicaltrials.gov; Unique identifier: NCT04676880	https://www.clinicaltrials.gov; Unique identifier: NCT03463317	https://www.clinicaltrials.gov; Unique identifier: NCT05204212	https://www.clinicaltrials.gov; Unique identifier: NCT04394546	https://www.clinicaltrials.gov; Unique identifier: NCT04226547	https://www.clinicaltrials.gov; Unique identifier: NCT03642509
Patients with AF not deemed suitable for OAC	AF with CHA_2DS_2-VASc ≥2, HAS-BLED ≥3 or prior IcraH	AF with end-stage renal disease, with or without hemodialysis	Patients with AF recommended for OAC therapy	Patients with AF recommended for OAC therapy	Patients with AF with prior ischemic stroke or TIA
LAAO (any device)	LAAO (any device)	LAAO (Amplatzer or Amulet)	LAAO (WATCHMAN)	LAAO (Amulet)	LAAO (any device)
ATP or no AT	OAC	OAC or BMT	DOAC alone	DOAC alone	DOAC alone
Stroke (ischemic, hemorrhagic, or undetermined; superiority)	Stroke (ischemic or hemorrhagic), SE, major bleeding (BARC type 3–5), or CVD (superiority)	Net clinical benefit, defined as, time to first stroke (including ischemic or hemorrhagic strokes), SE, CVD, or major bleeding (BARC 3–5)	Stroke, SE, or CVD (noninferiority)	Ischemic stroke, SE, or CVD (noninferiority)	Stroke (ischemic or hemorrhagic), SE, major bleeding, or all-cause mortality
609	1512	430	3000	2650	750
2026	2025	2028	2027	2029	2030

noncompliance).[77] Current treatment strategies include switching anticoagulants between different agents and adding antiplatelet agents, without any high-quality evidence that any of these strategies reduce the risk of recurrent ischemic stroke.[20,77,79,80] Therefore, additional treatment options are warranted. A recent matched cohort study compared 433 patients with AF who underwent LAAO after a breakthrough stroke (or systemic embolism/LAA thrombus) despite anticoagulation therapy with 433 patients with AF who continued oral anticoagulation alone after a breakthrough stroke.[81] The risk of recurrent stroke was lower in patients who received LAAO compared with anticoagulation alone (hazard ratio, 0.33 [95% CI, 0.19–0.58]; $P<0.001$). In this study, only 33% of patients continued anticoagulation therapy after LAAO. Among patients who received LAAO, the rate of recurrent stroke was numerically lower in those who continued anticoagulation therapy compared with those who stopped anticoagulation. Given the findings from LAAOS III where patients who continued anticoagulation after LAAO had the lowest risk of ischemic stroke,[33] these results suggest that combining LAAO with oral anticoagulation therapy may provide the highest risk reduction for recurrent ischemic stroke, but confirmation of this hypothesis in a randomized trial is warranted.

ONGOING TRIALS

The available evidence for percutaneous LAAO for stroke prevention is largely based on a few, relatively small randomized controlled trials with several limitations. Emerging evidence from observational studies suggests that LAAO could be a useful tool in several specific patient populations, as outlined above. Several randomized controlled trials are ongoing to evaluate the efficacy and safety of LAAO in patients with an increased risk of bleeding, as an alternative for long-term direct oral anticoagulation therapy in patients without a contraindication and as combined therapy in top of direct oral anticoagulants in patients with a high risk of ischemic stroke (Table 2).

CONCLUSIONS

Surgical LAAO is proven to reduce the risk of stroke or systemic embolism in patients with AF undergoing cardiac surgery for another indication. Percutaneous LAAO is promising, but evidence from randomized controlled trials supporting its use is limited. However, LAAO may have great potential for several selected patient groups. Currently, ongoing trials will determine whether LAAO is safe and effective as alternative to long-term anticoagulation therapy in patients with an increased risk of bleed or a history of ICH, as add-on therapy to direct oral anticoagulation therapy in patients with breakthrough strokes despite anticoagulation therapy and as alternative to long-term anticoagulation therapy in patients without contraindications. All efforts should be made to maximize enrollment in ongoing trials to strengthen the evidence base for percutaneous LAAO.

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