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REVIEW

An update and current expert opinions on percutaneous left atrial appendage occlusion for stroke prevention in atrial fibrillation

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Oral anticoagulation (OAC) remains the mainstream therapy for ischaemic stroke prevention in patients with atrial fibrillation (AF). However, for patients contraindicated to OAC and those who experienced a stroke while on therapeutic OAC, no reasonable pharmacotherapy is available. Although surgical left atrial appendage (LAA) excision offers a non-pharmacological alternative, effective stroke prevention by this treatment is not demonstrated by randomized clinical studies.

Percutaneous occlusion of the LAA may be an alternative therapy for selected AF patients. Recently reported results confirm the technical feasibility of this technique and its effectiveness in preventing ischaemic stroke. With increasing operator experience, successful and event-free device implantation is achieved in typically 97% of the cases. Moreover, in non-randomized cohorts implanted with LAA occlusion devices, stroke rates are markedly reduced compared with rates predicted by risk stratification schemes such as $CHADS_2$ and CHA_2DS_2-VASc. This paper summarizes recently published results from clinical studies on percutaneous LAA occlusion and current expert opinions with respect to patients who may be suitable for this therapy. In addition, several aspects regarding the safety of device implantation for LAA occlusion and follow-up of patients are discussed.

Keywords Atrial fibrillation • Stroke prophylaxis • Left atrial appendage • Percutaneous occlusion

Recent clinical results

Recently, results have been reported from studies to establish the effectiveness of percutaneous left atrial appendage (LAA) occlusion and to further explore patient selection and safety-related aspects. The PROTECT-AF study,[1] a major trial in this area using the Watchman device, demonstrated that percutaneous LAA occlusion is non-inferior to warfarin in the prevention of all-cause stroke, all-cause mortality, and systemic embolism.

Studies with recently reported results are summarized in *Table 1*.

Overall, successful implantation is achieved in 94.0–98.8% of the cases.[3–5] Typical peri-procedural complications include pericardial effusion, tamponade, device embolization, and myocardial infarction.

Increased operator experience is associated with higher implant success rates as well as safer procedures, as shown in *Table 2*, comparing early and more recent results reported by the same operators. With increasing operator experience the incidence of peri-procedural complications, such as stroke and pericardial effusion, is markedly reduced, procedures are shorter and implantations more often successful and free of serious events.

Consistent with earlier results, recently reported results continue to show a reduced stroke rate, compared with the stroke risk based on established stroke risk stratification schemes, as indicated by the data summarized in *Table 3*.

The most recent update of the ESC guidelines for the management of atrial fibrillation (AF)[8] recommend that percutaneous LAA occlusion may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation (OAC). This recommendation is based on expert consensus, and the guidelines emphasize the need for randomized studies to compare percutaneous LAA occlusion with OAC, including novel anticoagulants.

Overall, recent clinical results indicate that device-based LAA closure can be safely achieved, especially after overcoming the initial learning curve effect. Stroke rates in implanted cohorts are markedly lower than predicted by established risk stratification schemes.

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Table 1 Recently reported results from studies on percutaneous LAA occlusion

Study	Device	Description	Reported follow-up
Continued Access Protocol (CAP) Registry [2]	Watchman[a]	Allowing PROTECT-AF investigators to continue LAA occlusion, awaiting device approval	460 patients Median follow-up: 0.4 years
Aspirin and Plavix (ASAP) Registry[3]	Watchman[a]	Evaluation of safety and effectiveness of LAA occlusion in patients contraindicated or intolerant to warfarin	150 patients Mean follow-up: 14.2 months
European post-market observational study[4]	Amplatzer cardiac plug[b]	Follow-up from earlier study, representing results from more experienced operators	204 patients 101 patient years of follow-up
Belgian Registry[5]	Amplatzer cardiac plug[b]	Cumulative experience from seven Belgian centres	82 patients 34 patients followed >12 months
Initial single-centre experience[6]	Amplatzer cardiac plug[b]	Initial experience from a single centre with first longer term follow-up reported	100 patients 30 patients followed >12 months

[a]Boston Scientific, Natick, MA, USA.
[b]St Jude Medical, Plymouth, MN, USA.

Table 2 Learning curve effects associated with device implantation for LAA occlusion

Initial study	Recent study	Device	Initial vs. recent results
PROTECT-AF[1]	CAP Registry[2]	Watchman	• Significantly reduced procedure time (62 vs. 50 min) • Increased implant success rate (89.5 vs. 95.0%) • Reduced rate of procedure/device related safety events (7.7 vs. 3.7%)
Initial European experience[7]	European post-market observational study[4]	Amplatzer cardiac plug	• Higher rate of event-free procedures (97.1 vs. 93.0%) • Reduction in peri-procedural stroke rate (0 vs. 2.1%) • Reduced rate of serious pericardial effusion (1.5 vs. 3.5%)

Table 3 Stroke rates from recently reported studies on percutaneous LAA occlusion

Study	Implants and follow-up	Mean stroke risk score	Expected stroke rate based on mean stroke risk score	Observed stroke rate (reduction compared with expected rate)
ASAP Registry[3]	141 implants Mean follow-up: 14.2 months	$CHADS_2 = 2.8$	7.1%	1.8% (77% reduction)
European post-market observational study[4]	197 implants 101 patient-years	$CHADS_2 = 2.6$	5.6%	2.0% (65% reduction)
Belgian Registry[5]	81 implants 34 patients with 12 months follow-up	CHA_2DS_2-VASc = 5	NR	No strokes
Initial single-centre experience[6]	100 implants 30 patients with 12 months follow-up 50 patient-years	$CHADS_2 = 3.9$	NR	No strokes, 1 Transient Ischaemic Attack

NR: not reported.

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Patients for left atrial appendage occlusion

Percutaneous LAA occlusion offers an alternative to physicians who are facing a complicated risk–benefit analysis in AF patients who should receive OAC based on their stroke risk but who are also at high risk of bleeding. Increasing this awareness across relevant medical disciplines may offer an alternative stroke prevention strategy for patients who are currently inappropriately protected.

Gastro-intestinal (GI) bleeding is the most common type of extracranial bleeding in AF patients receiving either warfarin or novel OAC drugs.[9,10] In the setting of intestinal angiodysplasia, overanticoagulation is an independent risk factor for recurrent bleeding (odds ratio: 4.1).[11] As a result, initiation of OAC in patients with an increased risk for GI bleeding or continuation after OAC-associated GI bleeding with well-controlled anticoagulation is questionable.

Data from neurological patients, obtained in real-life clinical practice, show the actual underuse of OAC as well as the complicated management of patients on OAC.

In a Canadian registry, only 10% of patients hospitalized for stroke had a warfarin-managed International Normalized Ratio (INR) value within the therapeutic range.[12] A Danish stroke registry found that among patients without contraindications, ~30% of males ≤65 years of age to 70% of females >80 years of age, were not treated with OAC at 6 months after diagnosis.[13]

Haemorrhagic complications of OAC therapy remain a significant clinical problem, especially in the elderly.[14,15] Given the high mortality of warfarin-associated Intracerebral Hemorrhage (ICH) (~50 vs. 10% for ischaemic stroke) this increase strongly impacts the life expectancy of AF patients taking OAC. Usually, OAC is reversed immediately after ICH, but the decision to resume OAC after an ICH is complicated and may depend on the location of the haemorrhage and additional risk factors.[16] Besides considering novel OAC drugs, percutaneous LAA occlusion may be an alternative option after an ICH while on OAC. Approximately one-third of the patients suffering ischaemic stroke develop haemorrhagic transformation after infarction[17] and specifically the risk for parenchymal haematomas seems to be increased due to OAC.[18]

In summary, percutaneous LAA occlusion should be considered for AF patients at high risk for stroke ($CHADS_2$ or CHA_2DS_2-VASc score of 2 or higher) and who bleed or are at a high risk of bleeding (indicated by a HAS-BLED bleeding risk score ≥3). In addition, patients who suffered an ischaemic stroke despite OAC may be potential candidates. Conditions in which percutaneous LAA occlusion may be considered are summarized in *Table 4*. For each situation in which LAA occlusion is considered the associated risks and benefits of the procedure should be carefully weighed and explained to the patient.

Table 4 Conditions in which percutaneous LAA occlusion may be considered

Condition	Details
Recurrent ischaemic stroke despite well-controlled therapeutic OAC	Percutaneous LAA occlusion may be considered after exclusion of other sources of embolism
Previous ICH	Percutaneous LAA occlusion may be considered as an alternative to the use of novel anticoagulants, acknowledging individual patient factors, and bleeding aetiology
Recurrent GI bleeding	Bleeding from unknown origin or intestinal angiodysplasia despite endoscopic therapy. Lesions that are not accessible for endoscopic therapy
Co-morbidities	Uncontrolled hypertension, cerebral microbleeds, cerebral amyloid angiopathy
Coagulopathies	Low platelet counts, myelodysplastic syndrome
Intolerance to new OAC drugs	GI intolerance, severe liver and kidney dysfunction. Vitamin K antagonists are the first option to consider, percutaneous LAA occlusion may be considered as a secondary alternative

Device implantation and procedural safety

Peri-procedural complication rates are similar for both commercially available devices (i.e. the Watchman and Amplatzer Cardiac Plug devices) and are typically between 2 and 4%,[2,7] while decreasing with operator experience.[2,4,7]

Irrespective of the applied device, several aspects have a substantial impact on the safety of device implantation.

First of all, an extensive pre-procedural transoesophageal echocardiography (TEE) examination should be performed to exclude a thrombus in the left atrium or LAA and to fully explore the anatomy of the LAA. Important aspects to assess by multiple two-dimensional (2D) TEE views or 3D TEE are the shape and size of the LAA ostium, the 'landing zone' (the area within the LAA where the device will be positioned), the length of the LAA, and the number, shape, and location of lobes. In case of a complicated anatomy, additional pre-procedural imaging techniques, such as computed tomography (CT) scan or cine-magnetic resonance imaging (MRI) should be considered.

The appropriate device type should be selected based on pre-procedural imaging and while accounting for specific design characteristics of the available devices. The Amplatzer device is implanted in a relatively proximal position in the LAA, whereas the Watchman device requires a more distal location. This allows implantation of the Amplatzer device in a relatively shallow LAA. Furthermore, the Amplatzer device seals the ostium of the LAA, and thereby avoids the anatomical challenges posed upon the Watchman device that achieves more distal occlusion within the LAA,[19] such as a complex anatomy of the distal LAA or a proximal LAA lobe.

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Percutaneous LAA occlusion is usually performed under general anaesthesia and with TEE and fluoroscopic guidance. Multiple angiographic views or rotational angiography are helpful. Standard cardiac catheterization routines should be followed, including measures to avoid air embolism and thrombus formation. Critical steps with respect to air embolism include guidewire and dilator removal, device loading, and device introduction. Anticoagulation should be used at least after performing the transseptal puncture (target Activated Clotting Time (ACT) is >250 s if heparin is used). Arterial punctures have to be avoided and echocardiographic guidance should be considered for obtaining vascular access.

As one of the most critical procedural steps, transseptal puncturing needs to be performed under transoesophageal or intracardiac echocardiographic guidance and using multiple fluoroscopic views.

Operators will have to anticipate immediate resolution of cardiac perforation or device embolization. Potential causes for cardiac perforation include the use of stiff guidewires and guiding catheters, multiple device repositioning and implanting the device deep inside the LAA. Immediate treatment of a cardiac perforation includes percutaneous drainage and possible transfusion. For this purpose, units of red blood cells and surgical back-up should always be available. Retrieval tools (snares, forceps, etc.) should be available to resolve device embolizations.

Post-procedural follow-up preferably includes a trans-thoracic echocardiography before discharge to detect pericardial effusion with or without tamponade. At 45 days to 3 months post-implant a TEE should also be performed to exclude thrombus formation on the device. TEE can also be used to detect residual leaks, although the relevance of this finding is not clear from current clinical data.[20] Computed tomography scan and cardiac MRI are potential alternatives to TEE to detect thrombus and/or residual leak after LAA occlusion.

Antithrombotic medication after left atrial appendage occlusion

Until now, the only antithrombotic protocol that was consistently applied in a clinical study included the use of warfarin for 45 days after implantation in the PROTECT-AF study.[1] If TEE showed complete LAA closure or a residual flow jet <5 mm in width, warfarin was discontinued and replaced by a combination of aspirin and clopidogrel. At 6 months clopidogrel was discontinued and aspirin only was administered indefinitely. Further clinical testing of post-procedural antithrombotic therapy in patients with high bleeding risk may not be feasible. As a result there are currently no formal guidelines for antithrombotic therapy after the implantation procedure.

Besides other factors, the decision regarding post-procedural antithrombotic therapy depends on the occurrence of device-related thrombus and residual flow from the LAA. Although both factors may play a role in post-procedural stroke, there is insufficient clinical data to substantiate their influence. In the PROTECT-AF study, 20 (4.2%) out of 478 patients had thrombus on the device, and 3 of them suffered an ischaemic stroke.[2] In a European observational study[4] late device-related thrombus (>7 days post-procedure) was found in 2.4% of 197 successfully implanted devices.

The need for OAC in response to the presence of residual peri-device flow during follow-up is still being debated. Twelve months TEE in the PROTECT-AF trial revealed at least some degree of peri-device flow in 32% of the implanted patients.[20] While these results do not indicate a relationship with an increased risk of thromboembolism, the low event rate warrants careful interpretation. In recently reported registries,[3,4] aspirin and clopidogrel and no OAC are prescribed after percutaneous LAA occlusion. Results suggest that the level of residual flow observed with the current devices would not constitute a general indication for OAC. However, limited clinical data and detailed assessments do not yet justify definitive conclusions.

Given the fact that the majority of patients referred for LAA occlusion have an OAC-associated bleeding risk, careful consideration is warranted with respect to post-procedural antithrombotic therapy. Consensus seems to emerge about the application of a combination therapy of aspirin and clopidogrel during the first 3–6 months after device implantation, and to switch to aspirin alone subsequently. This approach has been applied in recent registries with satisfactory results.[3,4,19] An individual approach is required, based on controlled TEE examination to reveal device-related thrombus and residual LAA flow. If device-related thrombus is observed, antithrombotic therapy to resolve the thrombus should be considered. While the therapeutic options include OAC, aspirin, or a combination of aspirin and clopidogrel, it should be acknowledged that the contribution of clopidogrel has not been clinically tested and that the evidence for long-term aspirin is changing.[8]

Summary and conclusions

- Recent clinical data confirms the proof of concept of percutaneous LAA occlusion to reduce the risk of stroke.
- Implantation is successful and event-free in ~97% of the cases, especially after overcoming the initial learning curve.
- Additional evidence from randomized trials is required to assess the safety and efficacy of percutaneous LAA occlusion, compared with warfarin and novel anticoagulants. Evidence is required with respect to stroke prevention in patients contraindicated to warfarin and/or novel anticoagulants and with regard to health economics and cost-effectiveness.
- Various imaging modalities, including TEE, CT scan, and MRI, should be considered throughout the application of percutaneous LAA occlusion (before/during the implantation procedure and at follow-up) to assess stable device position, pericardial effusion, residual leak, and device-related thrombus.
- Increased awareness of percutaneous LAA occlusion across various medical disciplines may offer an alternative to patients at high stroke risk who are currently inappropriately protected due to their risk of bleeding.

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