Left atrial appendage occlusion is underutilized

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Introduction

Stroke prevention is an essential cornerstone in the treatment of patients with atrial fibrillation (AF) and can be achieved medically through oral anticoagulants (OAC) but also mechanically through left atrial appendage occlusion (LAAO). In the past decade, multiple large randomized controlled trials (RCTs) have confirmed the efficacy and safety of both vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC).\(^1\)\(^-\)\(^4\) As over 90% of thromboembolic strokes in AF patients appear to be caused by thrombi originating from the left atrial appendage, left atrial appendage occlusion (LAAO) is an alternative treatment option to reduce the risk of thromboembolic events that allows patients to discontinue OAC treatment.\(^5\) The PROTECT AF and the PREVAIL trials compared LAAO to VKA. Together they included 1114 patients, and their combined 5-year results showed noninferiority of LAAO to VKA in the prevention of death and thromboembolic complications and superiority of LAAO for the separate endpoints of mortality as well as major bleeding.\(^5\) Since that time a lot of experience with LAAO has been gained, and currently procedural success rates are almost 100%.\(^5\)\(^,\)\(^6\) Furthermore, major complications, of which 50% are major bleeding (of the groin), are nowadays seen in only 2%-4% of patients. Also, improvement of devices has led to a decrease in the occurrence of device-related thrombus.\(^5\)\(^,\)\(^7\) Currently, most experience and published data are gained with the Watchman and Amulet device. The recently published AMULET IDE trial showed noninferiority for safety and effectiveness of the Amulet device compared with the Watchman device.\(^6\) In summary, LAAO appears to offer AF patients a safe and effective option to reduce the risk of AF-related thromboembolisms.

Current indication: Patients contraindicated for the use of OAC

Currently, international guidelines recommend to perform LAAO only in patients who are contraindicated for long-term use of OAC, a minority that represents up to 5% of all AF patients.\(^8\)\(^-\)\(^11\) The only RCT available in this group of patients to date, the PRAGUE-17 trial, compared LAAO to DOAC (n = 402) in AF patients with both a high stroke and bleeding risk and showed noninferiority on the net clinical benefit endpoint of thromboembolic complications and bleeding.\(^12\) In the absence of enough adequately powered RCT data in this patient category, the recommendation for LAAO has remained a class IIB, level of evidence B since it first appeared in the ESC guidelines in 2012. However, on top of the RCT data, a large amount of registry data has been published in thousands of patients in everyday clinical practice, confirming the improved safety of the procedure and the low rate of stroke during follow-up.\(^3\)^\(^,\)\(^7\)\(^,\)\(^13\) Based on the abovementioned data and while awaiting further RCT data, in our opinion LAAO should be offered to all patients with a strong contraindication for the use of OAC, and guideline recommendations should take into consideration to upgrade the indication to a class IIA, level of evidence B recommendation, as many such patients are currently undertreated for AF-related thromboembolism.

A cost-effectiveness analysis of LAAO from the pooled 5-year follow-up data of the PROTECT AF and PREVAIL trials showed that, relative to warfarin and DOACs, LAAO was cost-effective after, respectively, 7 and 5 years and even cost-saving after, respectively, 10 and 5 years.\(^14\) Therefore, it appears to be evident that LAAO would be cost-saving in patients with a high stroke risk and a contraindication for OAC. Cost-effectiveness analyses from observational data support this, but randomized data are desired.\(^15\) At present, LAAO is underutilized for a variety of reasons. Firstly, in many countries LAAO is neither available nor reimbursed, as it has not obtained approval from healthcare authorities. This has led to large geographic differences in the availability of LAAO. In countries without reimbursement, neurologists, gastroenterologists, and pulmonologists are frequently not even aware or are skeptical about LAAO, so that suitable patients are often not identified and referred. As a result, in everyday clinical practice many patients are undertreated with inferior low-dose DOAC, single or dual antiplatelet
Left atrial appendage occlusion (LAAO) is a safe and effective treatment option for stroke prevention in atrial fibrillation (AF) patients and is currently mainly performed in patients with a contraindication for oral anticoagulants (OAC), who represent a minority of up to 5% of all AF patients.

The use of LAAO is underutilized owing to various reasons: despite the overwhelming amount of observational data, the guidelines recommendation still remains class IIIB, level of evidence B. Therefore, there is lack of availability and/or reimbursement in many countries, which leads to nescience or skepticism in referring specialists (eg, neurologists, gastroenterologists).

LAAO has great potential in other patient populations: in patients with stroke under OAC, combined with other structural heart procedures, and ultimately as an alternative treatment option for all AF patients. Several randomized controlled trials are currently pending to provide the required evidence.

Potential patient population that may benefit from LAAO

LAAO may also be performed in other patient populations that are currently not mentioned in the AF guidelines and therefore not widely considered.

Combined procedures

Fear of complications may be one of the arguments to not perform LAAO. However, the access technique of an endovascular LAAO procedure is very similar to procedures such as AF ablation and MitraClip placement. AF ablation is mainly performed for symptom reduction and does not obviate OAC in patients at high risk for stroke. Therefore, if LAAO is performed directly after ablation in the same procedure, it is appealing to offer AF patients a combined procedure, especially if they have strong reasons to stop using OAC. Several observational registry studies as well as a meta-analysis of observational and small randomized studies have demonstrated good safety and efficacy of these procedures. Conclusive evidence from the OPTION RCT (NCT03795298), in which patients scheduled for AF ablation were randomized to LAAO or OAC, is expected in the near future. Also, in other structural heart procedures patients might benefit from the 1-stop-shop principle. Initial experiences of concomitant LAAO with transcatheter aortic valve implantation, MitraClip, or percutaneous coronary intervention have already been reported, and RCTs are pending (Table 1). Furthermore, the randomized LAAO III trial showed lower stroke rates after surgical LAAO compared to standard of care in patients undergoing cardiac surgery. As ischemic strokes still regularly occur in patients while they are being prescribed OAC, a combined approach of (surgical) LAAO and OAC for stroke prevention might be appropriate.

Stroke in anticoagulated patients

A recently published study in pooled individual patient data of 5413 subjects by Seiffge and colleagues demonstrated a higher risk of stroke recurrence in patients with a history of embolic strokes despite adequate OAC, compared to patients with a similar CHA2DS2-VASc score. Switching to another type of OAC after stroke was not associated with a decreased stroke risk. Therefore, these patients might benefit from (adding) LAAO therapy. In the EWOLUTION trial, LAAO was equally effective for stroke reduction in patients after prior stroke as for other indications. Other small observational studies also suggest the effectiveness of LAAO in this population; however, adequately powered controlled trials are needed to further investigate the use of LAAO in patients with previous stroke despite OAC.

LAAO for a broader population

As LAAO is a 1-time procedure that offers patients an alternative to the stringent lifelong use of OAC, the ultimate utilization would be to offer it to potentially all AF patients with...
a need for stroke prevention. Worldwide, the prevalence of AF is increasing and so is the number of patients who require stroke prevention by OAC. At the same time, conditions with an enlarged risk of bleeding, such as cerebral amyloid angiopathy, are also increasing and owing to the rising life expectancy more patients will develop bleeding and comorbidity overall. As the risk factors that govern both are very similar, 79% of patients with a high risk for stroke also have an intermediate bleeding risk and 11% even a high bleeding risk. Although DOACs are now preferred over VKA because of lower risk of ICH, their overall bleeding rate is not negligible. And although ease of use seems attractive, a fundamental disadvantage of DOAC compared to VKA is the inability to monitor patient compliance, while LAAO is a continuous therapy that does not need monitoring. In daily practice, 30% of DOAC patients and 50% of VKA patients discontinue their medication within 2 years, while 30% of patients using OAC are nonadherent and/or noncompliant. The international CHAMPION-AF (NCT04394546) and CATALYST (NCT04226547) RCTs, which both compare LAAO to DOAC in AF patients without a contraindication for OAC and aim to include around 3000 patients each, are currently recruiting. These trials aim to show noninferiority for stroke prevention but superiority for bleeding, which would make LAAO an attractive therapy over lifelong need for OAC.

Table 1 Ongoing trials that investigate various left atrial appendage occlusion indications

| Trial name | Design | Allocation ratio | Intervention | Device | Study population | Estimated sample size | Estimated primary completion date |
|------------|--------|------------------|--------------|--------|------------------|-----------------------|----------------------------------|
| **LAAO for AF patients with a contraindication to OAC** | | | | | | | |
| COMPARE-LAAO (NCT04676880) | PROBE | 2:1 | LAAO vs none | CE mark-approved LAA closure devices | AF & absolute contraindication to OAC | 609 | 05-2026 |
| STROKECLOSE (NCT02830152) | PROBE | 2:1 | LAAO vs medical therapy | Amplatzon Amulet | AF & ICH | 750 | 05-2022 |
| CLOSURE-AF (NCT03463317) | Open label | 1:1 | LAAO vs best medical care | CE mark-approved LAA closure devices | AF & high bleeding risk | 1512 | 09-2023 |
| A3ICH (NCT03243175) | PROBE | 1:1:1 | LAAO vs apixaban vs none | Chosen by local teams | AF & ICH | 300 | 12-2023 |
| **Combined procedures** | | | | | | | |
| OPTION (NCT03795298) | Open label | 1:1 | Ablation+LAAO vs ablation+OAC | Watchman FLX | AF patients scheduled for ablation therapy | 1600 | 11-2024 |
| WATCH-TAVR (NCT03173534) | Open label | 1:1 | TAVR+OAC vs TAVR+LAAO | Watchman | AF patients scheduled for TAVR | 350 | 11-2022 |
| TAVI-LAAO (NCT03088098) | Open label | 1:1 | TAVI+LAAO vs TAVI+standard medical therapy | Amplatzon Amulet | AF patients scheduled for TAVI | 80 | 05-2023 |
| WATCH-TMVR (NCT04494347) | Open label | N/A | TMVR+LAAO | Mitrclip / Watchman FLX | AF patients scheduled for TMVR | 25 | 09-2022 |
| **Broad population** | | | | | | | |
| CHAMPION-AF (NCT04394546) | Single (Outcomes Assessor) | 1:1 | LAAO vs OAC | Watchman FLX | AF + indicated for OAC | 3000 | 12-2025 |
| CATALYST (NCT04226547) | Single (Outcomes Assessor) | 1:1 | LAAO vs OAC | Amplatzon Amulet | AF + indicated for OAC | 2650 | 12-2024 |

AF = atrial fibrillation; APT = antiplatelet therapy; ICH = intracranial hemorrhage; LAA = left atrial appendage; LAAO = left atrial appendage occlusion; N/A = not available; OAC = oral anticoagulants; TAVI = transcatheter aortic valve implantation; TAVR = transcatheter aortic valve replacement; TMVR = transcatheter mitral valve repair.

In conclusion, LAAO should be offered and be available to all AF patients contraindicated for the use of OAC, since these patients have no acceptable alternative. Based on the overwhelming amount of observational data, an upgrade of the guideline recommendation from class IIB to IIA appears to be likely. Furthermore, recommendations for other LAAO indications, such as in patients with “stroke under OAC” and combined interventions for patients scheduled for ablation may deserve a IIB recommendation in the AF guidelines, and RCT data are underway to provide evidence. Offering LAAO to all AF patients would be the ultimate utilization but will require compelling evidence by RCTs comparing LAAO to DOAC.
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