European Heart Journal Supplements (2023) **25** (Supplement B), B126–B130
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad091

ESC
European Society
of Cardiology

Indications, evidence, and controversy in the closure of the left atrial appendage

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KEYWORDS
Closure of the left auricle;
Cardioembolic stroke;
Atrial fibrillation

Closure of the left atrial appendage (LAAO) represents a valid option for the prevention of cardio-embolic stroke in patients with atrial fibrillation (AF) at high bleeding risk. Previous studies had shown that the atrial appendage represents the site of atrial thrombus formation in about 90% of cases in the presence of non-valvular AF. In all patients with AF and higher thromboembolic risk (in particular with CHA2DS2VASc score ≥2 in women and ≥1 in men) there is an indication for thromboembolic prophylaxis with AOC (oral anti-coagulants). The main guidelines and international consensus documents place the indication for the LAAO in patients with the need for thrombo-embolic prophylaxis who have contraindications to oral anticoagulant therapy (class of recommendation IIb).

Introduction

Closure of the left auricle (LAAO) represents a valid option for the prevention of cardioembolic stroke in patients with atrial fibrillation (AF) at high bleeding risk, due to the risk of bleeding, even major, linked to oral anticoagulant therapy (OAT), especially in the long term. It should be emphasized that, while OAT guarantees systemic protection from thrombo-embolism at the level of the entire vascular system, the prerequisite for LAAO to be effective is that the cardioembolism responsible for stroke or systemic embolism in AF would always be localized at the level of the left auricle. Previous studies had shown that the atrial appendage represents the site of atrial thrombus formation in ~90% of cases in the presence of non-valvular AF.[1] There is evidence, however, that in the event of severe atrial dilatation and/or severe stasis, especially in conditions of hypercoagulability, the prevalence of thrombosis in the free cavity of the left atrium can be increased. In fact, the factors that participate in the formation of atrial thrombosis are represented by Virchow's triad, i.e. the slowing of blood flow, the appearance of alterations in the atrial endocardium and the activation of inflammatory processes, with a tendency to hypercoagulability.[2] In all patients with AF and higher thrombo-embolic risk (in particular with CHA2DS2VASc score ≥2 in women and ≥1 in men), there is an indication for thrombo-embolic prophylaxis with OAT.[3] The main guidelines and international consensus documents place the indication for the LAAO in patients with the need for thrombo-embolic prophylaxis who have contraindications to oral anticoagulant therapy (Class of recommendation IIb).[3,4]

Evidence

As far as randomized trials are concerned, to date two studies have been published that evaluated the safety and efficacy of LAAO performed with the Watchman device vs. OAT with warfarin, namely the PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) and the PREVAIL (Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy).[5,6] Both of these trials demonstrated the non-inferiority of the LAAO strategy in the prevention of ischaemic stroke at a follow-up of 12 and 18 months, respectively. A meta-analysis of the two aforementioned randomized trials with a longer follow-up (5 years) then confirmed the non-inferiority of the interventional approach for the composite endpoint of stroke, systemic embolization, and cardiovascular death, with statistically significant superiority for it concerns the most serious bleedings,

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mainly intracranial haemorrhages.[7] The subsequent international real-world multicentre registry EWOLUTION collected data on more than 1000 patients undergoing LAAO with Watchman: 62% of patients had contraindications to warfarin OAC and 45% had had a previous stroke. Procedure-related adverse events occurred in 2.8% of patients, significantly less than PROTECT-AF and PREVAIL. The 1-year follow-up of EWOLUTION showed a mortality of 9.8% and an ischaemic stroke rate of 1.1% with the percutaneous strategy (relative risk reduction of 84% compared with the estimated risk based on the thrombo-embolic score).[8]

As regards the Amplatzer device, an Italian registry of ~600 high-risk patients undergoing LAAO (average CHA2DS2VASc 4.2, average HASBLED 3.2) demonstrated high procedural success and an adequate safety and efficacy profile, with a reduction of ~50% for ischaemic stroke and ~40% for major bleeding compared with the rates of such events expected from thrombo-embolic and bleeding risk scores.[9] The subsequent register on the AMULET device, which represents the evolution of the Amplatzer, conducted on 1088 patients, of which 83% with contraindications to OAT, confirmed these data, highlighting a procedural success of 99%, an ischaemic stroke rate of 2.9%/year, and a low incidence of device-related thrombosis (DRT, 1.7%).[10]

However, both aforementioned randomized trials were conducted on patients without contraindications to OAT, which is currently the main indication for LAAO. Furthermore, most of the observational studies have collected data on patients with 'contraindication to OAT' understood as a contraindication to oral anticoagulants vitamin K antagonists (VKA). However, the presence of a contraindication to VKA does not necessarily preclude the use of direct oral anticoagulants (DOACs), which have superior safety. From this point of view, there is therefore a strong need to have data comparing OAT with DOAC and LAAO, also in the light of the fact that patients with very high bleeding risk had been excluded from the Phase III registration studies of DOACs (for example, those with very low haemoglobin or platelet counts or with severe renal insufficiency). The PRAGUE-17 trial conducted on 402 patients at high thrombo-embolic and haemorrhagic risk (CHA2DS2VASc 4.7 and HASBLED 3) randomized 1:1 to LAAO vs. OAT with DOAC recently demonstrated the non-inferiority of the interventional strategy in the prevention of the net composite endpoint of cardiovascular death, major adverse cardiovascular/cerebrovascular events, or major bleeding events [hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.56–1.18; non-inferiority $P < 0.0006$]. LAAO was also associated with similar protection from thrombo-embolic events and a significantly reduced incidence of non-procedural bleeding (HR 0.55, 95% CI 0.31–0.97; $P < 0.038$).[11] However, the study can be considered underpowered due to low-incidence adverse clinical events.

Indications

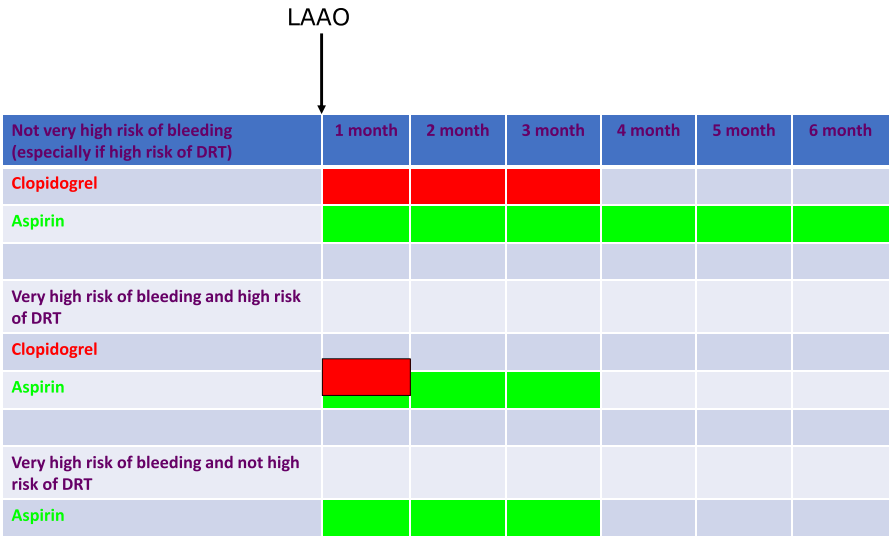
At present, the main international guidelines agree on the use of LAAO in patients with CHA2DS2VASc ≥ 2 in men or ≥ 3 in women and absolute contraindication to OAT due to high risk of bleeding or intolerance to it. In case of high bleeding risk, for example, due to previous intracranial haemorrhage, cerebral vascular malformations, cerebral neoplasms, angiodysplasias, inflammatory bowel disease with evidence of bleeding, recurrent anaemia during OAT, haematological diseases with increased bleeding risk or the presence of chronic renal failure in the pre-dialysis stage or on dialysis, there is in fact a reasonably strong indication for LAAO to be able to implement thrombo-embolic prophylaxis without exposing the patient to the prohibitive risk of major bleeding.[3,4]

A history of thrombo-embolic event (cerebral or systemic) in therapy with OAT at the correct dosage (in the case of DOAC) or with international normalized ratio in the therapeutic range (in the case of VKA) may represent a further indication for LAAO.[3,4] The LAAO procedure could be considered as an alternative to OAT even in patients with poor compliance with medical anticoagulant therapy, especially in the presence of a high CHA2DS2VASc score. Any decision regarding the implementation of the LAAO must in any case be shared with the patient, also hearing her preferences. Ongoing large randomized trials will provide further robust specific data on the safety and efficacy of LAAO compared with current standard DOAC anticoagulant therapy in AF and specifically on the placement of LAAO in the contemporary era (CHAMPION-AF, NCT 04394546; CATALYST, NCT 04226547; STROKE-CLOSE, NCT 02830152, which is enrolling patients with recent intracranial haemorrhage).

Antithrombotic therapy after LAAO

The incidence of DRT is a non-uncommon finding after LAAO, with the rate ranging from 1.7 to 7.2% in recent observational and randomized studies.[5,6,8-11] This complication has been associated with a > 4.5-fold increase in the risk of stroke and systemic embolization.[12] Predisposing factors for DRT are older age, high CHA2DS2VASc score, presence of left ventricular dysfunction, post-implant evidence of residual leak, use of large devices or deep implantation of the Watchman device in the earpiece.[12] Both the use of OAT and antiplatelet therapy have been associated with a reduction in the risk of DRT.[12] It is therefore recommended to start antithrombotic therapy in the post-procedure period, generally at least for the time necessary to have the endothelialization of the device, which according to anatomical-pathological studies can take up to 3 months.[13] The type of optimal antithrombotic therapy after LAAO, as well as its duration, remains a matter of debate.

In both the PROTECT-AF and PREVAIL studies, the patients had in any case taken warfarin combined with aspirin 75 mg for the first 45 days after LAAO with the Watchman device, followed by dual anti-platelet therapy (DAPT) with aspirin and clopidogrel 75 mg for 6 months and finally aspirin 325 mg chronically. Given this use of a VKA, the occurrence of bleeding complications was high, especially in the early post-operative period (annual incidence of bleeding >10%).[7] During the period of DAPT, the rate of bleeding events was instead reduced (0.6%).[7] According to the latest consensus of the European Association for Percutaneous Cardiovascular Interventions (EAPCI), an OAT regimen, with a DOAC instead of warfarin, may be considered for patients undergoing LAAO with Watchman without contraindication to OAT, who do not have a high bleeding risk profile. A DAPT for 3–6 months is instead suggested, regardless of the



- **High risk of bleeding: history of major bleeding, gastrointestinal disease at risk of bleeding, advanced age, severe chronic renal insufficiency, anemia**
- **High risk of DRT: high CHA2DS2VASc, severe chronic renal failure, left ventricular dysfunction, large device, deep Watchman implant, residual leak after implant**

Figure 1 Different antiplatelet strategies after LAAO, individualized according to the patient's device-related thrombosis and bleeding risk.

type of device, in patients with a contraindication to OAT,[4] and this represents the generally prevailing post-intervention strategy in the real world. However, the aforementioned consensus indications are not supported by specific randomized studies.

Since there are no large randomized trials comparing different post-LAAO antithrombotic strategies, the management of therapy for the prevention of DRT after the procedure is mainly based on the physician's personal conceptions and on the results of observational registries, often mono centric, conducted on limited numbers of patients, without rigorous event assignment or outcome definition. In patients with a high bleeding risk profile in the real world, the use of OAT is generally avoided, preferring therapeutic schemes with DAPT or single antiplatelet aggregation (SAPT), of variable duration. The exclusion of periprosthetic leaks or device thrombosis by transoesophageal echocardiography can be of great use in guiding the suspension of an antiplatelet drug during the post-implantation follow-up. Treatment with aspirin should then be definitively suspended 6–12 months after surgery, unless there are other specific indications to do so.[14]

The lower thrombogenicity of the devices of the Amplatzer family, as observed by some studies,[8-10] makes it possible to avoid resorting to post-implantation OAT and limit the antithrombotic therapy to antiplatelet treatment regimens of variable duration, based on the risk profile of patient's bleeding. The aforementioned registry of patients treated with Amplatzer AMULET observed that patients discharged in therapy with DAPT, or with aspirin alone in case of particularly high bleeding risk, did not have a higher incidence of DRT than the group in therapy with DOAC,[10] and in the aspirin-only group there was apparently no increased risk of DRT. On the other hand, there are no randomized studies that have demonstrated that SAPT is as effective as DAPT in terms of prevention of ischaemic events and DRT. However, patients treated with DAPT post-implantation may reasonably present a higher risk of bleeding compared with SAPT.[15] The optimal duration and type of post-LAAO antiplatelet therapy therefore remain controversial and not supported by adequate clinical studies.

The possibility that the use of a DOAC instead of DAPT could attenuate the increase in post-implantation thrombin, ensuring a more complete protection from DRT, has recently been investigated. In particular, in the randomized study ADRIFT (Assessment of Dual Antiplatelet Therapy Versus Rivaroxaban in Atrial Fibrillation Patients Treated With Left Atrial Appendage Closure) treatment for 3 months with rivaroxaban 10 mg vs. rivaroxaban 15 mg vs. DAPT after LAAO was compared: the use of rivaroxaban (both 10 and 15 mg doses) was associated with lower thrombin formation, but the study was underpowered to evaluate whether this reduction could translate into a clinical benefit.[16]

A subsequent study also evaluated the safety and efficacy of an anti-Xa agent (rivaroxaban) compared with the direct thrombin inhibitor dabigatran: the incidence of DRT was 1.9 and 8.2% ($P = 0.038$); there was no significant difference between the two groups in bleeding risk.[17] Finally, in an observational study, the use of low-dose DOACs alone (50% of the standard dose), after 45 days in combination with aspirin, was associated with a reduced rate of DRT and major bleeding at 18 months compared with a more 'conventional' treatment consisting of aspirin + DOAC at a regular dose for the first 45 days, followed by DAPT for another 6 months and subsequently aspirin alone.[18] However, evidence from large randomized trials is still lacking on the use of low-dose DOACs. In patients at particularly high bleeding risk, however, even a low dose of anticoagulant could be contraindicated and DAPT can be associated with a high incidence of bleeding. Post-LAAO antithrombotic strategies are therefore desirable which, on the one hand, guarantee a high level of safety and, on the other hand, provide adequate anti-ischaemic protection. A recent retrospective, multicentre

Italian study on 610 patients (280 treated with SAPT vs. 330 with DAPT) demonstrated a lower risk of major bleeding events with the first approach (BARC 3–5) [2.9 vs. 6.7% in the DAPT group; HR 0.37 (95% CI 0.16–0.88), $P < 0.02$], with no significant difference in the incidence of ischaemic events (DRT or major adverse cardiovascular events): 7.8 vs. 7.4%, HR 1.34 (95% CI 0.70–2.55, $P < 0.38$).[19] With the aim of obtaining more robust data on optimal antithrombotic therapy after LAAO, the multicentre randomised trial ARMYDA AMULET (ClinicalTrials.gov Identifier NCT02879448; https://clinicaltrials.gov/ct2/show/NCT02879448) is currently underway, in which patients are randomized 1:1 to receive DAPT (aspirin + clopidogrel) for 3 months and subsequently aspirin alone for another 3 months vs. SAPT with aspirin for 6 months. The primary non-inferiority endpoint will be the 6-month evaluation of the incidence in the two arms of the net composite endpoint of death from all causes, DRT, ischaemic stroke, systemic embolism, and BARC bleeds ≥ 3. Other randomized trials are currently underway on the topic: in ASPIRIN-LAAO (ClinicalTrials.gov Identifier: NCT03821883) is investigated aspirin therapy vs. no antithrombotic therapy; ESCORT-AF (NCT04135677) includes three treatment arms with rivaroxaban 20 mg vs. rivaroxaban 10 mg vs. DAPT; ANDES (NCT03568890) compares an 8-week treatment with one of the DOACs vs. DAPT; ADALA (EudraCT number 2018-001013-32) compares three treatment groups (apixaban 5 mg vs. apixaban 2.5 mg vs. DAPT) for 3 months. Finally, studies are underway to compare different durations of antithrombotic therapy after device implantation, such as the SAFE-LAAC (NCT03445949), which randomizes patients to DAPT for 6 months vs. DAPT for just 1 month.

Pending the results of the randomized studies in progress, since the majority of patients receiving LAAO have a high bleeding propensity, the management of antiplatelet therapy after device implantation should be individualized, considering both the risk bleeding than the risk of DRT (*Figure 1*).

Comparison between devices

Several LAAO devices are currently on the market, especially in Europe, with different characteristics and theoretically different DRT risk profiles. At the moment, the evidence regarding the direct comparison between different devices is limited. In this regard, the randomized trial AMULET IDE compared the Watchman vs. Amulet device on a large population (>1800 patients).[20] The primary endpoints considered: the safety of the prostheses (composite endpoint of complications related to the procedure death from all causes or major bleeding at 12 months); the effectiveness of the procedure (composite endpoint of ischaemic stroke or systemic embolization at 18 months); and the percentage of complete occlusion of the auricle at 45 days. The Amulet device was non-inferior to the Watchman for both the primary safety endpoint (14.5 vs. 14.7%; non-inferiority $P < 0.001$) and the primary efficacy endpoint (2.8 vs. 2.8%; non-inferiority P inferiority <0.001). For other adverse events, major bleeding and all-cause mortality were similar in the two groups (10.6 vs. 10.0% and 3.9 vs. 5.1%, respectively). Procedure-related complications were higher in the Amulet group (4.5 vs. 2.5% in the Watchman arm; P superiority 0.02), mainly due to a higher incidence of pericardial effusion and device embolization. The occurrence of the primary endpoint of complete occlusion of the appendage, defined as successful implantation of the device in the absence of a periprosthetic leak > 5 mm, was better in the Amulet arm (98.9 vs. 96.8% in the Watchman arm; P of superiority 0.003).

Conclusions

LAAO represents a useful option for patients with AF and indication for thrombo-embolic prophylaxis, in which there is a high risk of major bleeding. Current evidence supports individualization of post-procedural antithrombotic therapy based on the individual patient's risk profile. The results of ongoing studies in the future will demonstrate whether LAAO represents a superior strategy to treatment with DOACs and, in patients undergoing LAAO, will clarify what is the optimal post-implantation antithrombotic treatment of the device.

Funding

None declared.

Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

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