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Left atrial appendage occlusion: behind the bleeding risk

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Atrial fibrillation (AF) is the most common arrhythmia in adults and is associated with an increased risk of embolic stroke. The main prevention strategy for cerebral embolic events is based on the use of oral anticoagulant therapy (OAT). Left atrial appendage occlusion (LAAO) has demonstrated non-inferiority to OAT in clinical trials for prevention of stroke in non-valvular atrial fibrillation (NVAF). Patients with NVAF may still suffer ischemic strokes despite receiving adequate OAT.The physiopathological substrate remains unclear and only few theories can be proposed to explain the phenomenon and the approach to secondary prevention in these 'resistant strokes' remains largely empirical.Several therapeutic strategies have been proposed. Among these, LAAO should be taken into consideration. The procedure requires special planning in well selected patients, but can be performed successfully in most cases.

Introduction

NVAF is the cause of 30% of ischemic strokes. It's the most common cardiac arrhythmia and its prevalence is continuously increasing as a consequence of the ageing of the population. Guidelines recommended OAT as first line therapy.[1]

Historically, vitamin K antagonists (VKAs) were used to reduce the relative risk of ischemic stroke by about 60%, with a bleeding complication rate ranging from 1.2% to 3.4% per year.[2]

Direct oral anticoagulants (DOACs) showed equal efficacy with a lower risk of cerebral hemorrhagic complications and an easier handling compared to with VKAs. For this reason, DOACs have been associated with traditional oral anticoagulant therapy. The decision regarding each antithrombotic treatment must, therefore, weigh both the risk of ischemic stroke, the main complication of untreated AF, and the hemorrhagic risk, primarily the cerebral hemorrhagic risk, certainly the most fearful of hemorrhagic complications.[3]

European guidelines recommend OAT in male patients with CHA2DS2-VASc ≥2 and female patients with CHA2DS2-VASc ≥3. The same guidelines recommend considering anticoagulation in male patients with CHA2DS2-VASc ≥1 and female patients with a CHA2DS2-VASc ≥2.

The AF guidelines of the European Society of Cardiology (ESC) have recently eliminated gender from the risk score, considering OAT indicated in case of CHA2DS2-VA ≥2 and to be evaluated if CHA2DS2-VA = 1.[4,5]

The final decision on the effective prescription of OAT will have to derive from a careful balance between the risk of ischemic stroke and the risk of bleeding[6]

There are various bleeding risk scores. Among these, the most used is hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs, elderly, drugs or alcohol (HAS-BLED). A HAS-BLED score ≥3 identifies the patient at increased risk of bleeding.

In particular, it is necessary to identify patients with absolute or relative contraindications to OAT.

OAT strategy must be considered particularly dangerous in case of particular fragility of patients with:

- history of previous significant bleeding or bleeding in noble organs (such as the spinal cord or intraocular);

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- potentially non-correctable sources of significant bleeding in gastrointestinal, pulmonary or urogenital tracts;
- coagulation disorders;
- chronic renal failure with a glomerular filtration rate (GFR) < 15 mL/min;
- end-stage liver failure;
- presence of neoplastic disease;
- risk of frequent falls.

OAT must be avoided patients with severe thrombocytopenia (< 50 platelets/mcl); severe anemia conditions during diagnostic evaluation; recent high-risk bleeding (for example, intracranial hemorrhage).

In these actually very frequent in clinical scenarios, OAT determines a high or unacceptable level of bleeding risk and LAAO must be taken into consideration.[7]

The rationale for this intervention is based on the evidence that 90% of thrombi in NVAF originate at the level of the left appendage. The European guidelines recommend considering LAAO in patients with an indication for anticoagulant therapy and a contraindication to long-term OAT (recommendation class IIb, level b).

This procedure must be considered to treat patients who developed cardio-embolic stroke related to AF despite a well-conducted OAT.

Despite the lukewarm recommendation, a series of 'fragile' patients are increasingly being referred to LAAO, as a consequence of the growing supporting evidence.

In fact, the registry data showed that in patients with contraindication to oral anticoagulant therapy, LAAO represents a method capable of effectively reducing the embolic risk, with an acceptable procedural risk.

Among the various categories of patients in whom long-term OAT is contraindicated, it is worth mentioning a few categories

LAAO after ischemic stroke oN oat ('recurrent stroke')

Despite a correct regimen of oral anticoagulant therapy (DOACs or VKAs), a significant residual risk of ischemic stroke is present both in case of primary prevention therapy (0.7% per year) and secondary prevention therapy (2.3% per year).

Despite progress and declining trends, recurrent stroke is still frequent. Studies demonstrate varying recurrence rates, ranging from 7%-20% at 1 year to 16%-35% at 5 years.[8]

The most alarming finding is that patients who experience an ischemic stroke during OAT have a higher risk of future recurrences than patients who were not previously taking OAT.[9]

Numerous risk factors have been identified as a potential cause of recurrence of cerebral ischemic events during OAT. Some of these are part of common risk scores (age, sex, history of ischemic heart disease), others are represented by ethnicity, smoking, renal insufficiency, dyslipidemia, size of the left atrium and characteristics of the arrhythmia (permanent or paroxysmal) (*Figure 1*).

Unfortunately, the cause of this poor coverage by OAT is unclear. Poor adherence to therapy is an insufficient explanation. Several pathophysiological theories have been proposed in addition:

- thromboembolic mechanisms other than cardioembolism;
- insufficient anticoagulant activity of drugs or inappropriate prescription of low doses of DOACs;
- AF-related cardioembolism despite sufficient anticoagulation, defined as stroke without evidence for either.[10]

The treatment of this category of patients remains controversial in the absence of defined clinical evidence. Switching from one molecule to another, even with a different mechanism of action, or the addition or

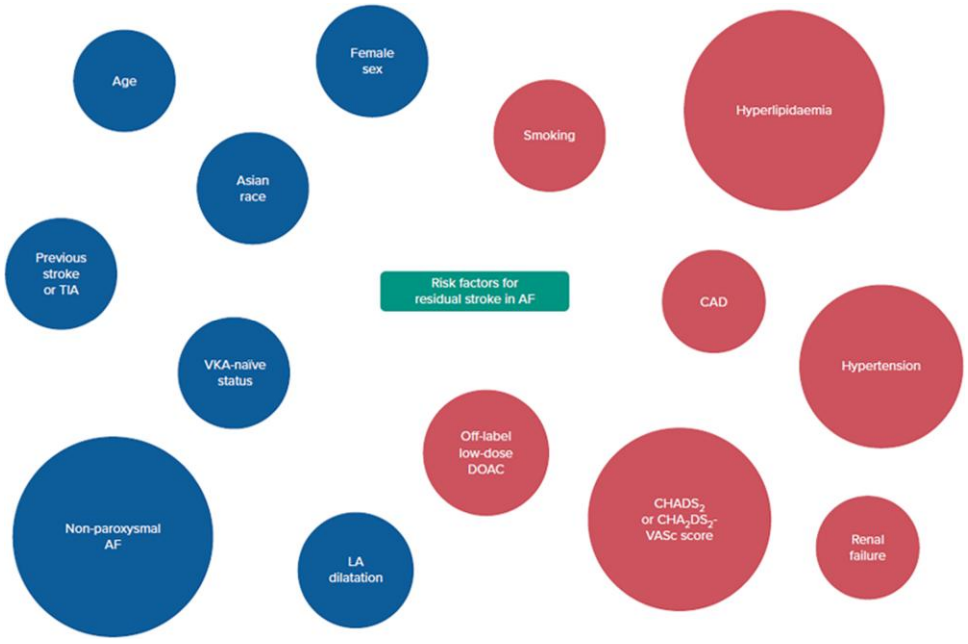

Figure 1 Risk factors for residual stroke in AF.

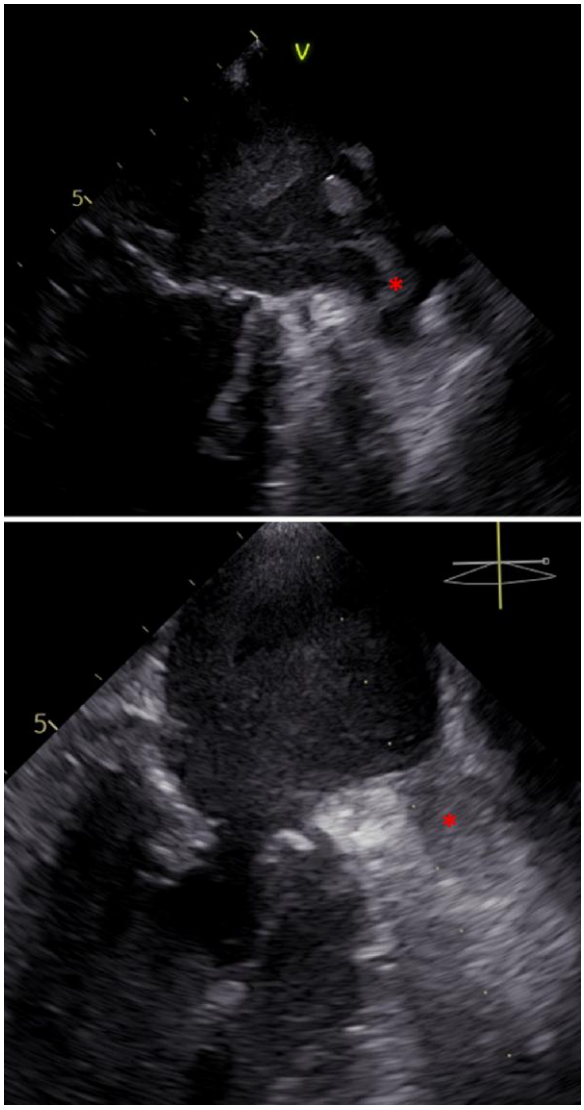

Figure 2 Left atrial appendage thrombi (red asterisks) visualized with transesophageal echocardiography.

replacement with an antiplatelet drug, or change the strategy of taking the drug throughout the day, do not seem to be an effective solution.[11]

In this scenario and in well-selected patients, LAAO must be considered, as also indicated by the consensus documents of scientific societies.[12]

A particularly important limitation of the procedure is the presence of thrombotic formation within the left atrial appendage in patients who are correctly taking oral anticoagulant therapy and who have an ischemic stroke.

LAAO in the presence of thrombus runs the risk of dislodgement and embolization (*Figure 2*). However, it has been demonstrated that LAAO can be performed even in the presence of a thrombus by modifying the routine implantation technique. In particular, the procedure should be carefully planned outside the catheterization laboratory and both the left atrium end the appendage should be studied with imaging techniques to adequately establish the morphology and location of the thrombus and therefore select the most suitable device and its size. Among the technical aspects, it is suggested not to use contrast or to administer the smallest possible quantity, not to advance the delivery sheet too deeply into the left appendage, and to avoid recapture of the device for further repositioning attempts ('one shot technique').[13]

A single center experience

We performed a retrospective cohort study of patients undergoing LAAO for paroxysmal or permanent NVAF who experienced ischemic stroke despite appropriately conducted OAT between March 2020 and January 2024. Each LAAO was preceded by a transesophageal echocardiogram (TEE) to evaluate the anatomy and morphology of the appendage and left atrium, the landing zone, thrombotic formations, and the degree of echo-contrast. The implants were performed in general anesthesia with transesophageal echocardiographic (TEE) guidance or intracardiac echocardiographic (ICE) guidance. The average price of the devices we routinely use in the percutaneous closure of the left atrial appendage is €5500 and the cost of the procedure is approximately €1300.

Other potential causes of ischemic stroke were excluded through transthoracic echocardiography, TEE and color Doppler ultrasound of the supra-aortic vessels. All patients were followed up clinically and by phone until 4th March 2024, or in case of death.

From an instrumental perspective, all patients underwent post-procedural TEE to assess the presence and extent of any leaks and device-related thrombosis. Device-related complications that were evaluated included pericardial effusion with or without cardiac tamponade, device displacement or embolization, while procedure-related complications included air embolism, and transient ischemic attack (TIA) or ischemic stroke diagnosed within the first 30 days post-procedure.

The number of patients with NVAF and resistant stroke despite anticoagulant therapy is 36. Thrombotic and hemorrhagic risks were evaluated using the CHA2DS2-VASc and HAS-BLED scores. The CHA2DS2-VASc score was 5.86 ± 1.15, while the HAS-BLED score was $3.06 \pm 0{,}92$.

Bleeding during oral anticoagulant therapy was present in 8.33% of patients, with 67% experiencing hemorrhagic infarcts post-stroke and 33% rectal bleeding. 97% of the patients enrolled experienced ischemic stroke, 3% TIA, and 14% both conditions (*Figure 3*). Diagnosis was made with cranial computerized tomography (CT) scan in all patients, and 35% also underwent magnetic resonance imaging (MRI). 36% of patients had hemodynamically significant carotid artery stenosis, which should be considered an independent risk factor for cerebral ischemia along with potential amyloid angiopathy and hypertensive encephalopathy, as well as parenchymal brain diseases frequently found in patients with similar age and comorbidities to those in the study cohort. After initial treatment failure, therapies were modified in some cases following hospitalization for LAAO to optimize anticoagulation outcomes and tailor the treatment to the clinical characteristics of individual patients. 35 continued the prescribed oral anticoagulant at follow-up after discharge from the LAAO procedure. In our cohort of patients, no cases of device-related complications were detected.

The follow-up period for the patients was a combined 52.45 person-years of observation. The recurrence of ischemic

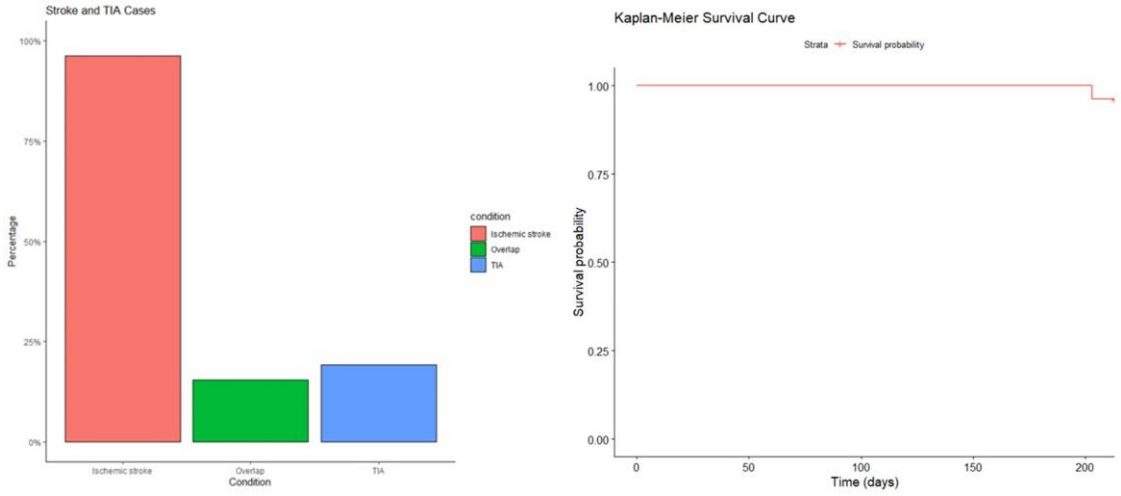

Figure 3 Clinical conditions of the enrolled patient (ischemic stroke, TIA, overlap) and survival curve (Kaplan-Meier).

stroke or TIA after LAAO was 0% during the observed period (*Figure 3*). The mortality outcome involved only one 83-year-old patient with multiple comorbidities, who died after 203 days of follow-up from non-cardiovascular, non-cerebrovascular causes unrelated to the LAAO (urinary tract infection complicated with septic shock). 100% of the procedures were successfully performed without periprocedural complications. No patients experienced death, TIA, stroke, acute myocardial infarction, significant bleeding with anemia, or required transfusions within the 7 days following the procedure. The average hospital stay post-LAAO was 4 ± 2 days, with a mode of 2 and 3 days.

The main limitation of this retrospective cohort study is the small sample size, the absence of a control group and the impossibility of determining the level of anticoagulation of patients undergoing DOAC therapy. As the data are observational, retrospective, and non-randomized, they present an intrinsic limitation related to the study design. Additionally, the statistical calculation is indirect and is based on incidence rates calculated from cohorts described in the literature.

Conclusion

LAAO is a procedure well identified by the guidelines for the treatment of patients with NVAF and contraindication to OAT. However, the procedure can also be performed in particular patients with cerebral ischemic episodes despite OAT.

The experience of our Cath Lab confirms the possibility of performing the procedure safely in a selected cohort of patients with excellent peri- and post-procedural results.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

REFERENCES

1. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT *et al*. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the framingham heart study. *BMJ* 2018;**361**:k1453-k1453.
2. Michaud GF, Stevenson WG. Atrial fibrillation. *N Engl J Med* 2021;**384**: 353-361.
3. Xian Y, O'Brien EC, Liang L, Xu H, Schwamm LH, Fonarow GC *et al*. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. *JAMA* 2017;**317**:1057-1067.
4. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M *et al*. 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**:534-542.
5. Seiffge DJ, De Marchis GM, Koga M, Paciaroni M, Wilson D, Cappellari M *et al*. Ischemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. *Ann Neurol* 2020;**87**:677-687.
6. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns HJGM *et al*. 2024 ESC guidelines for the management of atrial fibrillation developed in collaboration with the European association for cardio-thoracic surgery (EACTS). *Eur Heart J* 2024;**45**:3314-3414.
7. Merella P, Lorenzoni G, Delitala AP, Sechi F, Decandia F, Viola G *et al*. Left atrial appendage occlusion in high bleeding risk patients. *J Interv Cardiol* 2019;**2019**:6704031.
8. Khanevski AN, Bjerkreim AT, Novotny V, Naess H, Thomassen L, Logallo N *et al*. Recurrent ischemic stroke: incidence, predictors, and impact on mortality. *Acta Neurol Scand* 2019;**140**:3-8.
9. Lin SY, Liao YT, Tang SC, Lin CC, Wang CC. Changing or retaining direct oral anticoagulant after ischemic stroke despite direct oral anticoagulant treatment. *J Am Heart Assoc* 2024;**13**:e032454.
10. Casu G, D'Angelo G, Ugo F, Ronco F, Simonetto F, Barbierato M *et al*. Left atrial appendage occlusion in atrial fibrillation patients with previous intracranial bleeding: a national multicenter study. *Int J Cardiol* 2021;**328**:75-80.
11. Polymeris AA, Meinel TR, Oehler H, Hölscher K, Zietz A, Scheitz JF *et al*. Aetiology, secondary prevention strategies and outcomes of ischaemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. *J Neurol Neurosurg Psychiatry* 2022;**93**:588-598.
12. Sharma SP, Cheng J, Turagam MK, Gopinathannair R, Horton R, Lam YY *et al*. Feasibility of left atrial appendage occlusion in left atrial appendage thrombus: a systematic review. *JACC Clin Electrophysiol* 2020;**6**:414-424.
13. Merella P, Talanas G, Lorenzoni G, Denurra C, Atzori E, Casu G. Percutaneous left atrial appendage occlusion: what the practising physician should know. *Eur Cardiol* 2023;**18**:e57.