

# Some good reasons to proceed with the occlusion of the auricle

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## KEYWORDS

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Atrial fibrillation (AF) is the most common arrhythmia. The most fearful complication of AF is represented by cardio-embolic stroke and 30% of ischaemic strokes are attributable to AF. The prevention of cardio-embolic risk is therefore based on oral anti-coagulant therapy (OAT). Some categories of patients do not benefit from OAT. These are patients at increased bleeding risk and with varying degrees of contraindication to long-term anticoagulant therapy. On the opposite are those patients who develop an embolic event related to AF despite a well-conducted OAT. These types of patients benefit from an interventional approach, percutaneous closure of the left auricle (LAAO), aimed at eliminating what is the primary source of AF-related thrombo-embolism, precisely the left auricle. Percutaneous closure of the left auricle has proven to be an effective and safe procedure, significantly reducing the bleeding risks of patients who, after the procedure, will no longer have to take OAT. Furthermore, it has been shown to be effective in reducing cardio-embolic risk. Uncertainty still remains as to what is the optimal antithrombotic therapy after LAAO. In any case, LAAO represents a valid alternative to OAT for those patients in whom it is contraindicated or ineffective.

## Introduction

Non-valvular atrial fibrillation (AF) is the most common cardiac arrhythmia and its prevalence is continuously increasing as a consequence of the ageing of the population.<sup>1</sup>

About 30% of ischaemic strokes are attributable to AF and the main treatment is consequently oral anticoagulant therapy (OTA).<sup>2</sup> In recent years, direct oral anti-coagulant drugs (DOACs) have been associated with traditional oral anticoagulant therapy with vitamin K antagonists (VKAs).

Vitamin K antagonists, over the years, have shown the ability to reduce the relative risk of ischaemic stroke by about 60%, with a bleeding complication rate ranging

from 1.2 to 3.4% per year. The DOACs showed equal efficacy with a lower risk of cerebral haemorrhagic complications and an easier handling.<sup>2</sup> The decision regarding each antithrombotic treatment must, therefore, weigh both the risk of ischaemic stroke, the main complication of untreated AF, and the haemorrhagic risk, primarily the cerebral haemorrhagic risk, certainly the most fearful of haemorrhagic complications.

European guidelines recommend OAT in male patients with CHA2DS2-VASc  $\geq 2$  and female patients with CHA2DS2-VASc  $\geq 3$ . The same guidelines recommend considering anticoagulation in male patients with CHA2DS2-VASc  $\geq 1$  and female patients with a CHA2DS2-VASc  $\geq 2$ .<sup>2</sup>

The final decision on the effective prescription of OAT will have to derive from a careful balance between the risk of ischaemic stroke and the risk of bleeding.

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There are various bleeding risk scores. Among these, the most used is HAS-BLED. A HAS-BLED score  $\geq 3$  identifies the patient at increased risk of bleeding, although this condition is not an absolute contraindication to OAT.<sup>2</sup>

In fact, many other conditions can cause an increase in bleeding risk without affecting, if at all, the bleeding risk scores. In these borderline situations, which are actually very frequent in clinical practice, OAT determines a high or unacceptable level of bleeding risk. A further possible scenario is represented by those patients who developed a cardio-embolic stroke related to AF despite a well-conducted OAT. For these two opposite types of patients, there is room for percutaneous occlusion of the left auricle (LAAO).<sup>3</sup>

### **Percutaneous occlusion of the left auricle: rationale and evidence**

The rationale for this intervention is based on the evidence that 90% of thrombi in non-valvular AF originate at the level of the left auricle. 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).<sup>2</sup>

Despite the lukewarm recommendation, a series of 'fragile' patients are increasingly being referred to LAAO, as a consequence of the growing supporting evidence.<sup>4,5</sup>

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.<sup>6</sup>

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

### **Severe chronic renal failure (severe CKD) or end-stage (ESRD)**

The prevalence of AF is particularly high in patients with severe CKD and the presence of severe nephropathy is associated with a particularly high thrombo-embolic risk. On the other hand, the presence of severe CKD represented an exclusion criterion from randomized trials on DOACs, which are contraindicated in the case of GFR less than 15 mL/min. The therapeutic alternative represented by VKAs also has little evidence to support it, as there is no evidence that, in this population, the use of dicumarolics is effective in reducing the thrombo-embolic risk.<sup>7</sup> Based on pharmacokinetic studies and limited scientific evidence, the use of apixaban for patients with ESRD has been proposed (and approved by the FDA) in the USA. The Renal-AF trial, which compared apixaban and VKA in patients with ESRD, showed that apixaban was safer than warfarin, without any efficacy data. In fact, the study was terminated prematurely with a number of patients enrolled approximately equal to 20% of the expected total. Furthermore, the comparison with warfarin is in fact of little use, having shown that VKA therapy is ineffective in reducing the cardio-embolic risk in ESRD patients.

In this particular clinical scenario, LAAO has been shown to significantly reduce both mortality and the risk of major bleeding.<sup>8,9</sup>

### **Increased risk of intracranial bleeding**

The risk of cerebral haemorrhage represents one of the most significant contraindications to OAT. In fact, the consequences of cerebral haemorrhage can be disastrous, with a lethality of 50% and a high risk of permanent disability.

Briefly, an increased risk of cerebral haemorrhage is characteristic of patients with previous spontaneous cerebral haemorrhage or of patients with local or systemic predisposing conditions.

Among the local predisposing conditions, cerebral amyloid angiopathy,<sup>10</sup> the finding of cerebral arteriovenous malformation, cerebral neoplasms at risk of bleeding should be mentioned. Systemic conditions include disorders of the coagulation system (for example, haemophilia), the presence of persistent thrombocytopenia, rare forms of arterial hypertension that cannot be controlled by therapy.

Often the only risk factor detected is represented by the oral anticoagulant therapy itself. Generally, the evaluation of cerebral haemorrhagic risk is undertaken when there is a clinical-instrumental antecedent of intracranial bleeding or when, even accidentally, radiological stigmata of increased haemorrhagic risk are occasionally found. In the future, with the spread of diagnostic imaging methods and with the ageing of the population, this finding will become more and more frequent.

Once a condition of increased cerebral haemorrhagic risk has been identified or in the case of a previous cerebral haemorrhagic event, it becomes essential to consider alternative methods. In this clinical setting, LAAO has shown the ability to reduce both thrombo-embolic and haemorrhagic risk,<sup>11</sup> thus representing a priority option in these patients.<sup>12</sup>

### **Increased risk of gastrointestinal bleeding**

Although the management of gastrointestinal bleeding is easier than other types of bleeding complications, these can significantly affect the quality of life, requiring frequent and prolonged hospitalizations, and being burdened by a high rate of relapse. It is therefore not surprising that this is one of the most frequent indications for oral anticoagulant therapy. The registry data showed that LAAO is able to reduce the relative risk of bleeding by about 20%.<sup>13</sup>

### **Other categories with high bleeding risk**

The list of clinical conditions capable of conferring an increased risk of bleeding is very extensive. Among the various conditions, the congenital or acquired coagulopathies (such as haemophilia, dysfibrinogenemia, etc.), blood dyscrasias (plateletopenias, platelet diseases, leukaemia), bleeding neoplasms or increased risk of bleeding (in particular, referable to the gastrointestinal or urinary tract, deserve to be mentioned), patients with

Rendu-Osler syndrome. Finally, a particular category of patients deserves to be mentioned. These are patients undergoing complex endovascular procedures (both coronary angioplasty and implantation of various types of vascular endoprotheses), in which the thrombotic risk is judged to be particularly high. In these cases, as an alternative to prolonged triple antithrombotic therapy, it might be reasonable to hypothesize a hybrid solution (LAO and dual antithrombotic therapy).

### Patients with ischaemic events during well-conducted OAT

A not rare occurrence in clinical practice is represented by a cerebral ischaemic event or a systemic embolism despite anticoagulant therapy.<sup>14</sup> This group of patients appears heterogeneous, and within it various phenotypes must be distinguished:

*patients with suboptimal anticoagulation (patients on non-range VKA therapy; patients on under-dosed DOACs);*

*patients with alternative mechanisms of cerebral ischaemia (atherosclerotic disease of the extracranial vessels; pathology of the small vessels; coagulopathies; arteritis; endocarditis; antiphospholipid antibody syndrome; etc.);*

*patients with ischaemic events despite well-conducted anticoagulation therapy and in which further causes have been excluded.*

It seems obvious that only patients in the latter group can benefit from a percutaneous closure procedure of the left auricle. Therefore, careful screening should be conducted before recommending patients for an LAO procedure.

### General risks of the procedure

The incidence of procedural complications is constantly decreasing both in controlled clinical trials and in registries. This improvement in safety is essentially linked to the evolution of the techniques and skills of the operators. In fact, in the Evolution study the incidence of adverse events related to the procedure reached 2.8%, compared to 8.7% described in Protect AF.<sup>6</sup>

The registry data show that the main complications are represented by major bleeding (0.6%), pericardial effusion (0.4%), complications in the vascular access site (0.4%), and periprocedural ischaemic stroke (<0.5%).<sup>14</sup>

In fact, the systematic use of ultrasound guidance (transesophageal or intracardiac) has practically eliminated the risks of complications resulting from the puncture of the interatrial septum. Complications related to manipulations in the left auricle, essentially pericardial effusion and cardiac tamponade, have been significantly reduced following the evolution of techniques and better management of complications.<sup>15</sup>

### Post-procedural therapy

After implantation of a device in the left auricle, antithrombotic therapy is recommended for the purpose of preventing device thrombosis (DRT). Despite this statement, there is a wide heterogeneity of behaviour both

in controlled clinical trials and in clinical practice and registry data. In fact, in the aforementioned Evolution trial,<sup>6</sup> 60% of patients received dual antiplatelet therapy, 16% VKAs, 11% DOACs, 7% a single antiplatelet therapy, and 6% no antithrombotic therapy. This attitude essentially reflects the reduced evidence and the considerable heterogeneity of the patients treated, ranging from patients with high embolic risk to patients with high bleeding risk. In fact, in patients with ischaemic recurrence despite a well-conducted OAT it is usual to continue anticoagulation therapy after implantation. Conversely, in patients with high or prohibitive bleeding risk (for example, patients with ongoing bleeding), it is not unusual to prescribe a single antiplatelet agent or even no antithrombotic therapy.

### Conclusions

Over the past decade, a growing body of evidence has shown that left auricle closure is a valid alternative to oral anticoagulant therapy in patients with a contraindication to OAT or in those patients who, despite a well-conducted OAT, develop a secondary ischaemic event to the AF. With the evolution of techniques and the growing experience of operators, procedural risks have been significantly reduced and the procedure has become increasingly safe. Future studies will need to assess which treatment regimen is optimal after LAO, as there is currently no clear evidence for this.

**Conflict of interest:** None declared.

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