

# Current views on the prevention of thromboembolic complications in atrial fibrillation

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## Abstract

Atrial fibrillation (AF) is the most common arrhythmia and a direct cause of thromboembolic complications. The most common site of thrombus formation is the left auricle also referred to as the left atrial appendage (LAA). Pharmacotherapy with vitamin K antagonists (VKA) and non-vitamin K antagonist oral anticoagulants (NOACs), as well as, percutaneous and surgical interventions have all been used to prevent these complications. Interventional management is the treatment of choice in patients with contraindications to oral anticoagulants; the efficacy of such management is comparable to that of pharmacotherapy while the risk of adverse events, i.e., severe haemorrhage or haemorrhagic stroke, is lower. Hence, some extensions to the existing indications for interventional treatment might be worth considering under specific clinical circumstances. A hybrid therapy combining left atrial appendage occlusion (LAAO) with AF ablation seems to hold particularly notable potential due to high therapeutic efficacy unassociated with a significant increase in complication rates.

**Key words:** atrial fibrillation (AF), thromboembolic complications, oral anticoagulants, left atrial appendage occlusion (LAAO), AF ablation

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## Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide [1–3]. The prevalence ranges between 1% and 2% in the general population and increases with age to 7% in people over 65 years and 15–20% in those aged ≥ 80 years [4–6]. It has been estimated that, by 2050, 25% of all people over the age of 45 will have suffered at least one episode of AF [7]. AF is associated with a 5-fold higher risk of ischemic stroke

[3, 8] yielding a 5% risk of ischemic stroke per year [3–5, 8]. Cardioembolic strokes are considered more lethal than other sources of strokes [9]. A vast majority of cardiac thrombi are formed in the left atrial appendage (LAA) [2, 3, 10–12] and approximately 90% of all strokes originate from this structure [7]. LAA is a tubular body with a blind-ending sac. Its shape, wall trabeculations and AF-related compromise in left atrial contractile function lead to blood stasis and thrombus formation [5, 13, 14].

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The primary goal of systemic thromboembolism prevention is to protect the patient against the development of the most severe AF complication, i.e., ischemic stroke. The currently available methods for ischemic stroke prevention are anticoagulant pharmacotherapy, surgical LAA closure, percutaneous LAA occlusion, and ablation for atrial fibrillation. The latter cannot directly prevent thrombus formation but markedly restricts the pathomechanism thereof via reducing the incidence of atrial fibrillation.

The aim of this paper is to present and compare the above-mentioned stroke prevention strategies and discuss possible combinations targeted at achieving the best therapy outcomes.

### Pharmacotherapy of thromboembolic complications of atrial fibrillation

The CHA<sub>2</sub>DS<sub>2</sub>-VASc score has been recommended in the ESC guidelines for the assessment of stroke risk in patients with AF; a 0 score means *low risk* while patients with a score of 1 or more are anticoagulation candidates [4, 15]. Each point increase is associated with a higher risk of complication development. Low-risk patients do not need antithrombotic therapy but those with moderate or high risk should be administered anticoagulants [14]. A classic oral anticoagulant warfarin, a vitamin K antagonist (VKA), significantly reduces the risk of ischemic stroke. However, it increases the risk of major bleeding [5, 7, 15] unless INR is between 2 and 3 [3, 14]. INR monitoring and the resultant need for VKA therapy modification are quite bothersome [15], and INR level can be affected by a number of factors including a change in diet or medications, genetic factors, drugs and alcohol. Non-vitamin K antagonist oral anticoagulants (NOACs) provide an alternative to warfarin; their antithrombotic effect does not require routine monitoring [7, 15]. However, patients with mechanical heart valve prosthesis or moderate/severe mitral stenosis require anticoagulation with a vitamin K antagonist and not NOACs [15].

Contrary to VKAs, NOACs (rivaroxaban, apixaban and edoxaban) selectively inhibit factor Xa in the coagulation cascade being more effective than warfarin [5, 14, 16, 17]. Compared to warfarin, rivaroxaban-treated patients were at a lower risk of hemorrhagic stroke and lethal hemorrhage although mortality rates did not differ significantly between the groups. Hemorrhagic stroke, major bleeding and mortality rate were lower in patients receiving apixaban as compared to those receiving warfarin [3, 14, 16].

Another effective antithrombotic is dabigatran (direct thrombin inhibitor), the first NOAC approved for stroke prevention [15, 17]. Contrary to VKAs, dabigatran does not inhibit the synthesis of natural

anticoagulant proteins, i.e., protein C and protein S. At low doses, its effectiveness is comparable to that of warfarin while the risk of hemorrhagic complications decreases by 20%. High doses make it 35% more efficient than warfarin, the risks of hemorrhagic complications being comparable [3, 15].

Therapeutic effects of aspirin and the combination of aspirin with clopidogrel were also studied but have been questioned in patients with AF [14, 15, 17]. However, they can be used as perioperative "bridging" in patients with contraindications to even short-term anticoagulant therapy but still scheduled for percutaneous left atrial appendage occlusion [18, 19].

There are no studies comparing direct-acting medications of the NOAC group. Hence, the selection of a particular NOAC can be quite challenging. Patients at high-risk for gastrointestinal hemorrhage should receive a NOAC associated with the lowest risk of such bleedings reported in large clinical trials. The patient's condition should also be considered as well as adverse effects such as dabigatran-related dyspepsia. Other contraindications might include a risk of kidney failure in rivaroxaban-treated patients [17]. Obtaining an optimal therapeutic effect associated with the least amount and severity of adverse effects might require a patient tailored protocol with several drug and dosage modifications.

VKAs and NOACs are the predominant pharmacological agents for the prevention of thromboembolic events. Novel oral factor Xa inhibitors are being developed. The results of phase 2, randomized, dose-ranging study (*Explore-Xa*) showed that betrixaban in a dose of 40 and 60 mg daily had a lower rate of bleeding compared with warfarin [20, 21]. Similar results were obtained in atrial fibrillation study 2 (OPAL-2), where a darexaban dose of 120 mg was found to decrease plasma D-dimer levels [22].

Some proportion of AF sufferers cannot be administered oral anticoagulants, and especially long-term anticoagulant therapy, due to a history of life-threatening bleeding episodes [15, 23, 24]. Hence, a particular need for a therapy that would reduce the occurrence of thromboembolic events and, at the same time, lower the risk of bleeding. These patients might benefit from the percutaneous or surgical closure of the left atrial appendage, a protocol highly recommended by the current ESC guidelines.

### Atrial fibrillation ablation

AF ablation has been used for protection against recurrent AF episodes when oral antiarrhythmics or cardioversion prove ineffective [25–27].

At least 2% of anticoagulated patients with AF will experience a serious bleeding event per year, which

usually results in pharmacotherapy discontinuation. An argument for AF ablation is the ESC conclusion that, in patients with persistent and long-standing AF, ablation performed by an adequately trained and experienced operator is more effective than antiarrhythmic drug therapy [27]. However, this recommendation disregards the age-related risk – it has been shown that the number of LAA occlusion complications increases considerably in patients over the age of 75 years [28].

The aim of AF ablation is to eliminate triggers for sinus rhythm disturbances resulting in atrial fibrillation. In 90% of AF cases, the site of additional signal generation is the left atrial-pulmonary vein junction. Hence, pulmonary vein isolation has become central for ablation approaches. Except for the site, ablation technique is also of importance, the most common being radiofrequency ablation, cryoablation, and ultrasound ablation. These techniques have comparable efficacy and high success rates, ie., 85% of patients undergoing ablation are free from atrial fibrillation within one year [29]. Nevertheless, other investigations have shown that pulmonary vein isolation alone might not be sufficient [14, 30].

Di Biase *et al.* [30] assessed the effectiveness of electrical left atrial appendage isolation combined with extensive ablation (Group 1) and extensive ablation alone (Group 2). A 12-month follow-up revealed a significant difference between the groups, ie., 56% and 28% of Group 1 and 2 patients, respectively were recurrence-free. Hence, the majority of Group 2 patients required a repeat procedure. Cumulative success at 24-month follow-up was reported in 76% of Group 1 and 56% of Group 2 participants [30].

### **Percutaneous left atrial appendage occlusion — an alternative method of preventing thromboembolic complications in patients with atrial fibrillation**

Although oral anticoagulants have markedly diminished the rate of thromboembolism in patients with AF, a high risk of anticoagulation-related bleeding complications as well as difficulty in maintaining target INR levels resulted in a search for alternative treatment options [31]. Percutaneous left atrial appendage occlusion is among the possible solutions.

#### **PLAATO**

Percutaneous left atrial appendage transcatheter occlusion (PLAATO) was the first catheter-based device to be implanted in 2002 [31]. The annual stroke risk (3.8%) was lower than that expected based on CHADS<sub>2</sub> score (6.6%). However, despite the promising results, the device was withdrawn from the market due to the lack of funding [11, 12].

#### **WATCHMAN**

Another FDA-approved device for left atrial appendage occlusion was the Watchman [32]. An initial study of 66 patients showed a 93% rate of successful LAA sealing [31]. The Watchman clinical program comprising several studies with more than 2,400 patients and 5,931 patient-years of clinical evidence confirmed 90-95% efficacy of the device in LAA closure and its advantage over warfarin regarding the following clinical aspects: prevention of haemorrhagic stroke, cardiovascular death of unknown cause and major bleeding unrelated to the procedure [12]. A meta-analysis carried out by Reddy *et al.* [19] revealed that the overall mortality of Watchman-implanted patients was significantly lower compared to the warfarin cohort. The ASAP study also confirmed the advantage of Watchman use in patients with contraindications for even short-term anticoagulation therapy and those intolerant of long-term oral anticoagulants. All this was incorporated in the FDA's recommendations regarding the indications for the Watchman device [12, 19].

#### **Amplatzer**

The Amplatzer Cardiac Plug (ACP) is a device that was originally designed for closure of atrial septal defect and not for LAA sealing [13]. Although no randomized studies have been carried out so far, the clinical data from the ACP multicenter registry including 1,047 patients revealed that procedural success was achieved in 97 to 98%. The risk of stroke and bleeding unrelated to the procedure was lower than that estimated based on CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED [11, 25, 33].

#### **Coherex**

Unlike the Watchman and Amplatzer Cardiac Plug, the Coherex WaveCrest device is deployed at the LAA orifice and can, therefore, be used in small-sized LAAs where the placement of other occluders might pose problems [7]. The device implantation was successful in 96% of 63 patients with a complication rate of 2.7% [25].

#### **Lariat**

The Lariat device has been approved by the FDA for soft tissue approximation. Its efficacy for LAA closure was first studied in a series of 89 patients ineligible for oral anticoagulant therapy; 98% of the patients had complete LAA closure [2]. Subsequent multi-center register revealed successful deployment in 96 to 100% of patients. However, long-term observation of in over 100 patients revealed both efficacy of the device and rare but severe complications such as hemopericardium and complete LAA detachment from the heart [11, 18, 25, 32].

## LAmbre

The LAmBre system is a novel LAA occluder. Over 180 human implants were performed in two clinical trials with 99.4% to 100% implant success. LAmBre implantation takes approximately 60 minutes [34]. During a 12-month follow-up, ischemic stroke occurred in 2 patients (1.3%) and major procedure-related complications in 5 patients (3.3%) [34, 35]. LAmBre left atrial appendage closure system received CE Mark certification in June 2016 indicating approval for use in the European Union.

Except for Lariat, all devices are inserted using femoral venous access with transseptal puncture under transesophageal echocardiographic guidance [32, 36] while Lariat device requires both transseptal puncture and epicardial access [18].

At present, the Amplatzer Cardiac Plug and Watchman are considered the most efficient among percutaneous LAA closure devices [5].

The Watchman and Lariat are the only two devices approved by the FDA for use in the United States. Lariat received FDA's approval for soft tissue ligation. PLAATO was initially approved by the but then withdrawn from the market for commercial reasons [18].

All the above-mentioned devices received CE Marking and can be used in EU member states.

## Hybrid therapy — a successful combination of catheter ablation and percutaneous left atrial appendage closure

Patients at high risk for stroke might benefit from catheter ablation combined with percutaneous left atrial appendage closure (LAAC). Several studies have shown that Watchman occluder implantation performed in combination with catheter ablation did not significantly increase the peri-procedural risk [25, 37]. Left atrial appendage occlusion combined with radiofrequency ablation or cryoablation effectively eliminated AF in 72% of patients [18].

Phillips *et al.* [37] observed that patients after ablation combined with successful implantation of the Watchman device had a 0.5% risk of ischemic stroke, which is a startling improvement compared to 4.5% calculated according to the CHADS<sub>2</sub> scoring system. It can, therefore, be concluded that AF patients qualified for ablation are likely to benefit more from a combination of ablation and LAA occluder implantation [25]. Occluder-implanted patients may, in turn, experience additional improvement after ablation [38]. This conclusion is lent support by the results of a large multicentre registry including 349 patients, which revealed a decrease in the risk for stroke from an expected rate of 3.2% (CHA<sub>2</sub>DS<sub>2</sub>-VASc) to 0.9%. However, the predominant advantage of the hybrid therapy is

a significant reduction in the incidence of procedure-unrelated bleedings characteristic of patients with chronic OAC use [39, 40]. This is of particular importance as, in the study of Calvo *et al.* [40], the median HAS-BLED score in these patients was 3 points; hence clinically relevant bleeding might be expected in a large proportion of oral anticoagulant users [40].

## Surgical left atrial appendage occlusion (during cardiac surgery)

There are three groups of non-pharmacological interventions for the prevention of venous thromboembolism in patients with AF, i.e., the above-mentioned endocardial and epicardial closure of the left atrial appendage and surgical LAA exclusion. According to a meta-analysis performed by Tsai *et al.* [41], surgical LAA occlusion performed during cardiac surgery reduces the risk of thromboembolic complications and mortality should atrial fibrillation develop following surgery. LAA occlusion might also help decrease the risk for thromboembolic events in patients undergoing cardiac surgery. An example might be mitral valve replacement in AF patients with or without LAA clot as well as in patients with sinus rhythm and LAA clot [42].

At 30-day follow-up, post-LAAO patients had a significant reduction in stroke incidence (0.95%) compared to the non-LAAO group (1.9%). At the latest follow-up, the respective values were 1.4% and 4.1% [2, 41]. Nevertheless, numerous studies revealed that LAA occlusion might prove incomplete in 10–36% of patients resulting in life-threatening complications including stroke (newly formed thrombus might slip out through the existing gap and enter the circulation) [10, 43].

At present, surgical techniques for LAA exclusion comprise suture-closure of the LAA orifice, LAA excision with suture placement and amputating or non-amputating stapler exclusion [44]. Stapler exclusion yielded a higher proportion of complete LAA occlusion (72%) compared to suture closure (45%) [43]. There is much hope regarding the AtriClip LAA Exclusion System and TigerPaw II devices, but studies on the efficacy thereof are scarce [10].

A multicenter trial demonstrated the AtriClip System was a safe and effective device for LAA closure (no severe complications within a mean 36-month observation period); the risk of thromboembolic complications decreased to 0.5/100 patient-years from the expected stroke rate of 4.0/100 patient years based on individual CHA<sub>2</sub>DS<sub>2</sub>-VASc scores. Left atrial appendage AtriClip occlusion can therefore be used in cardiosurgical patients at high risk for thromboembolic complications [44, 45].

Suwalski *et al.* [46] compared the efficacy of the AtriClip and TigerPaw II systems in patients undergoing coronary artery bypass grafting (CABG) and

concomitant left atrial epicardial ablation. Although TigerPaw II application was quicker and easier, it turned out unsuccessful in 25% of the patients. Ventosa-Fernandez *et al.* [47] also reported a high proportion of TigerPaw II System's malfunction.

### Pharmacoeconomic analysis of presently available modalities for prevention of thromboembolic complications in atrial fibrillation

Data obtained in the United States [48, 49] indicate that — from the pharmacoeconomic perspective - despite being the cheapest, warfarin proved the least cost-effective treatment strategy. Considering the relatively early onset of several cardiovascular diseases, a long-term analysis should be employed. However, although a large patient cohort was analyzed using the Markov model, the mean observation period was below 3 years. Nevertheless, high stability of warfarin market and costs of single LAAO implementation causes that these short-observation periods do not affect the reliability of long-term therapy cost estimation. It has been estimated that, relative to warfarin, LAAC is cost-effective at 7 years. By year 10, LAAC was dominant over warfarin as, at this time point, the costs of warfarin treatment exceeded those of LAAC. Also, the number of quality-adjusted life-years (QALYs) gained with warfarin was lower compared to LAAC [48].

A cost-effectiveness analysis of NOACs is much more difficult as the expectation is that prices for the oldest types of NOACs (eg. dabigatran) will drop following patent expiry. Hence, estimations based on the present day prices are hardly reliable. LAAC has been shown to be superior over NOACs since it becomes cost-effective at 5 years. This time frame may extend once lower-priced generics enter the market; data update for the model will then be needed. LAAC will remain dominant over NOACs for a long time yet. In the model used, NOACs become cost-effective relative to warfarin but only at approximately 15 years and this will most probably hold for the recently developed NOACs. Of the available NOACs, apixaban has been shown to be the most cost-effective, but, as already mentioned, the expected drop in prices for the oldest types of NOACs might lead to their dominance over apixaban and other recent NOACs [48, 49].

Summing-up, irrespective of predicted changes in NOAC prices, LAAC is the most cost-effective therapy for prevention of thromboembolic complications in AF, and especially when the estimated survival time exceeds 10 years. During that period LAAC becomes cost-effective relative to both warfarin and NOACs [48].

The choice of therapy should be determined by the patient's condition and not financial considerations.

However, the comparable efficiency of pharmacotherapy and LAAC is a strong argument to always consider the latter — also for financial reasons.

Owing to unavailability of relevant data, the above cost-effectiveness analysis does not include surgical LAA exclusion.

## Summary

The main objective of modern antithrombotic pharmacotherapy is to minimize adverse effects of oral anticoagulants, and especially haemorrhagic complications. The main challenge is the lack of antidotes or reversal agents for newly developed direct oral anticoagulants.

Clinical experience has shown that numerous AF sufferers cannot undergo long- or even short-term anticoagulant therapy, which fact has created a niche for percutaneous left atrial appendage occlusion. The efficiency of occluder implantation is not lower than that of warfarin while the risk of bleeding is reduced and survival time increases. Hence, some extensions to the existing indications for LAAO might be worth considering. New devices with improved efficacy and safety continue being developed and introduced onto the market.

A hybrid procedure, ie., a combination of catheter ablation and left atrial appendage closure, seems particularly promising. However, despite high primary efficacy, AF ablation alone is associated with a considerable risk of recurrent atrial fibrillation. Occluder-implanted patients are protected against thromboembolic events, should AF recur. According to CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score, hybrid therapy of atrial fibrillation shows notably high efficacy. Nevertheless, there is a need for randomized clinical trials to compare this treatment option with other methods used to prevent AF complications.

In patients undergoing cardiac surgery for reasons other than AF, indications for surgical LAA occlusion include atrial fibrillation or LAA thrombus. A number of researchers suggest LAAO should be performed in all elderly patients undergoing cardiac surgery considering their high risk of developing AF. The AtriClip System outperforms other surgical modalities and can be applied during cardiac surgery as well as during thoracoscopy and mini-thoracotomy.

The risk associated with combined catheter ablation and left atrial appendage closure and surgical LAA occlusion increases slightly but is disproportionate in relation to LAA closure benefits. Furthermore, a pharmacoeconomic analysis indicates the superiority of LAAC over antithrombotic pharmacotherapy.

## Conflict of interest

None.

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