REVIEW

Endocardial Left Atrial Appendage Occlusion and its Place in Contemporary Management of Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia, affecting 1-2% of the general population in Western countries and it is a well-known risk factor for cardioembolic ischemic stroke, which increases the risk 4 to 5 times. Stroke is responsible for 14% of all annual deaths and every year 8 million people suffer a stroke in European countries. The standard stroke preventive strategy in patients with AF is the administration of anticoagulants. However, contraindications to these agents are not rare, the use of anticoagulants, especially the vitamin-K antagonists, is quantitatively sub-optimal, and many patients with high thromboembolic risk also have increased bleeding risk. Considering that the most frequent location of intracardiac thrombi associated with AF is the left atrial appendage (LAA), the endocardial occlusion of this structure has emerged as a potential alternative treatment. ***Rhythmos 2022;17(1): 100-104.***

Key words: atrial fibrillation; left atrial appendage; percutaneous occlusion; anticoagulation

Abbreviations: AF = atrial fibrillation; LAA = left atrial appendage; NOAC = non-vitamin K oral anticoagulant; OAC = oral anticoagulant; VKA = vitamin K antagonist

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, affecting 1-2% of the general population in western countries. Its prevalence increases with advancing age, from 0.5% at 50 to 59 years to 10% at ≥80 years. [1] On the other hand, stroke is the second leading cause of death worldwide and the third cause of death in most Western countries. [2] Stroke is responsible for 14% of all annual deaths and every year 8 million people suffer a stroke in European countries, posing a financial burden of about €62 billion. [2] Of the stroke cases, ischemic stroke accounts for about 67% to 81%. [3] Atrial fibrillation is a well-known risk factor for cardioembolic ischemic stroke, which increases the risk 4 to 5 times, and is present in 25% to 30% of patients with an acute ischemic stroke. [4] Atrial fibrillation is more frequently associated with anterior circulation infarcts, and is accompanied by a poor outcome in terms of 30-day and 1-year mortality and rate of stroke recurrences within the first year of follow-up. [5] Moreover, it accounts for 15% of all strokes regardless of age and 30% in individuals older than 80 years. [6] The risk of AF-related stroke increases from 1.5% per year in the age group of 50-59 years old individuals to 24% per year in individuals over 80 years old, in relation to other well described clinical risk factors. [7] The most frequent location of intracardiac thrombi associated with AF is the left atrial appendage (LAA). A meta-analysis of previous studies revealed that in patients with non-valvular AF only 11% of atrial thrombi were found outside the LAA; left ventricular dysfunction, history of stroke and poor anticoagulation status were associated with these rare locations. [8]

Stroke Prevention: Anticoagulants

In order to prevent systemic thromboembolism, a vitamin-K antagonist (VKA) or one of the new non-vitamin-K oral anticoagulants (NOACs) is used in patients with AF and clinical characteristics indicating increased susceptibility for stroke, based on the CHA2DS2-VASc score. [9] According to data from a meta-analysis, the odds ratio of stroke for warfarin versus placebo is 0.3 (95% CI 0.19-0.48). [10] Novel oral anticoagulants have been proven non-inferior in comparison to warfarin, [11–13] and recent guidelines recommend these agents over the VKAs. [9] However, the real use of anticoagulants is not as widespread as it should be, which undermines their effectiveness. One-year discontinuation rates for warfarin-naive patients initiating VKAs are reported consistently high (26-35%), while 40-50% of non-valvular AF patients do not even start VKA therapy, often due to the fear of fatal complications. [14–16] In a more recent prospective study, adherence to oral anticoagulation (OAC) therapy declined during 6 months, to 88.3% for VKA and 95.5% for NOAC, not differing between different NOACs. [17] Time within therapeutic INR values is also reported suboptimal, being around 60%, while it is recommended to be over 70%.[11–13]

Furthermore, hemorrhagic complications constitute the Achilles' heel of anticoagulant medications. Both VKAs and NOACs pose a risk for major or clinically significant bleeding which approximates 3% per year. [11–13] This probability is not negligible considering that these drugs are intended for long-term use, expanding over many years. Moreover, frequently the patients in need of anticoagulation have concomitant heart problems necessitating the administration of antiplatelet agents as well, significantly increasing the bleeding risk.

Stroke Prevention: Alternative Approaches

An appealing solution to the problems associated with anticoagulants is the mechanical prevention of left atrial thrombosis. The left atrial appendage (LAA) is not only the most frequent site of thrombus formation in non-valvular AF, but also the structure most eligible to minimally invasive (percutaneous) intervention. So far,

several devices have been manufactured, but only the Watchman and the Amplatzer ACP and Amulet devices have been currently approved for the endocardial closure of the LAA.

The Watchman Device

The Watchman device (Boston Scientific Corporation) consists of a parachute-shaped self-expanding nitinol device with 10 active fixation barbs and a 160-mm permeable polyester fabric membrane covering its proximal face. It is delivered through a 14-F sheath and is available in anterior, double, and single curve shapes, with the double curve used most often. The implantation is typically performed under general anesthesia or conscious sedation, through transfemoral venous access and transseptal puncture under fluoroscopy. [18] The device has been evaluated in terms of efficacy (compared to warfarin) and safety in two randomized clinical trials. [19,20] The PROTECT AF trial randomized 707 patients with non-valvular AF and an indication for anticoagulation (CHADS2 score≥1) in a 2:1 ratio to percutaneous closure of the LAA (n=463) or to warfarin treatment (n=244). The primary efficacy endpoint was a composite of stroke, cardiovascular death, and systemic embolism. Analysis was by intention to treat. Over a follow up period of approximately 3 years and 1065 patient-years, the primary efficacy event rate was 3/100 patient-years in the intervention group and 4.9/100 patient-years in the control group (rate ratio - RR 0.62, 95% CI 0.35–1.25). Adverse events (major bleeding, pericardial effusion, and device embolization) were more frequent in the intervention group (7.4/100 patient-years vs 4.4/100 patient-years, RR 1.69, 1.01–3.19). Overall, the device was proven non-inferior to the standard anticoagulant treatment at the time. Interestingly, in the "successfully treated" patients, the device was significantly more efficient and safer than warfarin, which suggests that the intervention can work under ideal circumstances, although in real world practice things may be different. [20] A more prolonged follow up of the same population (mean observation duration 3.8 years or 2621 patient-years) fulfilled the prespecified criteria both for non-inferiority and superiority of the interventional approach. Patients receiving Watchman device showed lower rates of both cardiovascular mortality (3.7% vs 9.0%, HR= 0.40, 95% CI, 0.21-0.75 p =0.005) and all-cause mortality (12.3% vs 18.0%, HR=0.66, 95% CI 0.45-0.98=0.04), in comparison to warfarin. [21] The rate of adverse effects did not differ between the device and pharmacological arms (HR=1.2, p=0.41), but major bleeding and hemorrhagic stroke were less frequent in the device group. [21] Notably, the timing of the complications' occurrence differed between arms, since pericardial effusion, procedure-related stroke, and device embolization were more frequent in the periprocedural period. This probably explains the higher occurrence of ischemic stroke in the device group during the first months of follow up, which progressively equalizes with the rate of the warfarin patients. [21]

The PREVAIL trial, which was similarly designed, randomized 407 patients to Watchman device implantation or warfarin in a 2:1 ratio. At 18 months the composite of stroke, systemic embolism, and cardiovascular/ unexplained death was numerically similar in the two groups (rate ratio 1.07, 95% credible interval=0.57-1.89) but it did not achieve the prespecified noninferiority criterion which required the upper boundary of the 95% credible interval to be less than 1.75. Stroke or systemic embolism risk more than 7 days post-randomization was 0.0253 versus 0.0200 (risk difference 0.0053, 95% credible interval: –0.0190 to 0.0273), achieving noninferiority. As far as the safety assessment is concerned, the endpoint was a composite of all-cause death, ischemic stroke, systemic embolism, or device-/procedure-related events requiring open cardiovascular surgery or major endovascular intervention between randomization and within 7 days of the procedure or during the index hospitalization. This endpoint was evaluated only in the device group, it was compared to a value derived from a Bayesian model that used previous studies and registries and the trial was proven successful. [19]

The optimal performance of any closure system depends on proper technique and procedural success. In a trial involving 1025 patients, WATCHMAN implantation was successful in 1005 (98.5%), without leaks >0.5 mm in 1002 (99.7%). One-year, mortality was 9.8%, but one has to take into account the age distribution of the population studied (mean age 73.4±9 years) and its comorbidities (previous transient ischemic attack or ischemic stroke 30.5%, previous hemorrhagic stroke 15.1%, history of major bleeding 31.3%). Device-related thrombosis was noted in 3.7%, ischemic stroke in 1.1% and major bleeding in 2.6% of the patients. [22] In the short term, technical success is defined with regard to the integrity of the sealing, as assessed by transesophageal echocardiography. Indeed, an incomplete occlusion could pose a thrombotic risk because of the potential embolization of a newly formed thrombus. An analysis of the PROTECT AF population demonstrated that the degree of leakage, minor, moderate, or major, based on peri-device flow jet width <1 mm, 1-3 mm, >3 mm, respectively (maximum width 6.8 mm) did not significantly affect the composite endpoint of stroke, systemic embolism, and cardiovascular death. [23] In recent guidelines a peri-device flow jet width ≤5 mm is considered complete occlusion. This evaluation also determines the nature and duration of the concomitant anti-thrombotic therapy. [9]

The Amplatzer Cardiac Plug and the Amplatzer Amulet device

The Amplatzer cardiac plug (ACP) is a self-expandable Nitinol platform with a distal lobe and a proximal disk. Two initial trials reported high procedural success (97-98%) and a low rate of stroke (no strokes after 25.9 patient-years and 1.9% at 20 months of follow up respectively). [6, 24, 25] The ACP registry, including 1047 patients from 22 centers, showed a procedural success of 97.3%. At 13 months of mean follow up, nine strokes (0.9%) and nine transient ischemic attacks (0.9%) occurred. The annual rate of systemic thromboembolism and major bleeding was 2.3% and 2.1% respectively. [26] In a sub-study in 344 patients followed up with transesophageal echocardiography disclosed device-associated thrombus in 3.2% and significant peri-device leak in 1.2%. [27] The ACP has now been largely replaced by the newer generation device, called the Amplatzer Amulet. In a single center retrospective cohort study enrolling 212 patients (102 on ACP and 112 on Amulet), after 1244.2 days of mean follow up or 674 patient-years, the risk rate was 2.2 thromboembolic events per year, representing a 61% reduction compared with the theoretical risk according to the CHA2DS2–VASc score. The two devices performed similarly, with Amulet recording slightly fewer strokes, without reaching statistical significance. [28] A retrospective analysis of 563 patients (344 ACP vs. 219 Amulet) with a mean follow-up of 2.9 ± 1.6 and 1.9 ± 0.9 years respectively, confirmed the equivalence of the two devices in terms of efficacy and safety. [29]

The Amulet IDE trial compared the Watchman and the Amulet device in 1878 patients with non-valvular AF. Randomization was performed in a 1:1 manner. The primary safety end point was a composite of procedure-related complications, all-cause death, or major bleeding at 12 months and the effectiveness endpoint was a composite of ischemic stroke or systemic embolism at 18 months. The Amulet device was non inferior with regard to the safety and efficacy, and it was superior (secondary end point) for LAA occlusion. [30]

The Role of Non-Vitamin K Oral Anticoagulants (NOACs)

The most robust data so far concern the comparison between LAA occlusion and warfarin. In the last decade however, the NOACs have appeared and they have claimed a major part of the non-valvular AF population from vitamin-K antagonists, because of their equal efficacy and more favorable safety profile. [11–13] These facts are confirmed in a relatively recent meta-analysis which includes information from the trials using the Watchman device. According to the authors, NOACs were significantly better than warfarin for stroke and/or systemic embolism (OR 0.84, 95% CI 0.72-0.97, p=0.01) and all-cause mortality (OR 0.89, 95% CI 0.84-0.94, p<0.001), while Watchman device and warfarin performed similarly. This pattern did not change in the subgroup of elderly patients (≥75 years-old). The safety end-point was a composite of major bleeding or device-/procedure-related complications. The results favored NOACs once more over warfarin (OR 0.79, 95% CI 0.65-0.97, p=0.026). LAA occlusion was associated with more complications when compared to warfarin (OR 1.85, 95% CI 1.14-3.01, p=0.012). [31] Thus, NOACs are preferred over warfarin and the latter and Watchman device are of similar efficacy.

However, since the transitive property is not always valid in biological systems, we cannot conclude on the comparison between NOACs and LAA occlusion through indirect evidence. The PRAGUE-17 trial attempted to clarify the situation. [32] It enrolled 402 patients with non-valvular AF and an indication for anticoagulation but with a history of bleeding requiring intervention or hospitalization, a history of a cardioembolic event while taking an OAC, and/or a CHA2DS2-VASc of ≥3 and HAS-BLED of >2. They were randomized to receive LAA occlusion (with the Amulet or Watchman device) or NOAC (the vast majority was administered apixaban), and were compared over a primary composite outcome of stroke, transient ischemic attack, systemic embolism, cardiovascular death, major or non-major clinically relevant bleeding, or procedure-/device-related complications. At a median follow-up of 19.9 months, the two groups showed no significant difference both for the composite end-point (HR=0.84, 95% CI 0.53-1.31, p=0.44, p=0.004 for noninferiority) and its components. Successful occlusion was achieved in 90% of patients receiving the device, while major procedure or device-related complications occurred in 4.5%. After 3.5 years of mean follow up, the picture remained the same, except for the non-procedural clinically-relevant bleeding which favored the device group (HR=0.55, 95% CI 0.31-0.97, p=0.039). [33]

Another study has recently addressed the same question using data from pre-existing registries. Patients with AF included in the Amulet Observational Registry who had successful LAA occlusion with the Amplatzer Amulet device (n=1078) were compared with a propensity score–matched control cohort of AF patients (n=1184) treated by NOACs retrieved from Danish national patient registries.[34] Propensity matching was based on the components of the CHA2DS2-VASc HASBLED scores, so that the two final groups would have almost identical stroke and bleeding risks. The primary outcome was a composite of ischemic stroke, major bleeding, or all-cause mortality. After 2 years of follow-up, patients in the LAA

occlusion arm had significantly lower risk of the primary composite outcome (HR=0.57, 95% CI 0.49-0.67). Ischemic stroke risk was comparable between groups (HR=1.11, 95% CI 0.71-1.75), while risk of major bleeding (HR=0.62, 95% CI: 0.49-0.79) and all-cause mortality (HR=0.53, 95% CI 0.43-0.64) were significantly lower in patients undergoing LAA occlusion. [34]

Conclusions

It is not a rare situation to encounter patients with AF and contraindications to anticoagulation therapy or a very high bleeding risk, and they form a difficult to manage population. The procedures aiming at the occlusion of the left atrial appendage constitute an attractive alternative to anticoagulants, and according to the existing data they are non-inferior to oral anticoagulants in terms of stroke prevention, and they cause less bleeding complications in the long term. Due to the still limited evidence, they are assigned a IIb recommendation by the European guidelines. [9] The major advantage of the LAA occlusion would be to eliminate the need of antithrombotic medication. However, this is not the case. The Watchman device requires anticoagulation with warfarin for 1.5 months or until adequate LAA sealing is confirmed by transesophageal echocardiography, followed by dual antiplatelet therapy (aspirin and clopidogrel) up to 6 months and then aspirin indefinitely. The Amplatzer ACP or Amulet need only dual antiplatelet coverage for the endothelialization period and aspirin monotherapy thereafter. [9] The new oral anticoagulants have been tested at lower doses in initial trials in this clinical setting with promising results, but they are not yet officially indicated. [35, 36] In any case, the antithrombotic medication can still be a problem in patients at high risk of hemorrhage, but it is less intense when endorsing LAA occlusion compared to the conventional anticoagulant treatment employed in atrial fibrillation; thus, this method could provide a viable alternative for this category of patients. In cases of absolute contraindication to any antithrombotic therapy, the epicardial catheter approach or thoracoscopic clipping of the LAA could be considered as an option.

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