SCIENTIFIC EDITORIAL

Left atrial appendage occlusion for prevention of thromboembolic events in patients with non-valvular atrial fibrillation: Closing the door to hell

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Atrial fibrillation (AF) is one of the most challenging arrhythmias — perhaps even one of the most challenging diseases — because of its high prevalence (close to 2% of the population [1]) and associated risks of thromboembolism and stroke. Stroke is a devastating complication with a reported annual incidence of 4.4%. At least 25% of the 130,000 strokes that occur each year in France are complications of AF. For patients with AF-related cardioembolic stroke, up to 70% will result in death or significant disability.

Prevention of thromboembolic complications in AF is an old story leading to clear guidelines and robust therapies. The CHADS2 score [2] and more recently the CHA2DS2-VASc score [3] were developed to assess stroke risk in individuals with non-valvular AF, and their use is recommended to identify patients at moderate to high-risk of stroke but also to identify those considered truly low-risk [4].

Anticoagulation therapy with vitamin K antagonists (VKAs) such as warfarin has remained the standard of care for stroke prevention in AF. Despite clear evidence of efficacy, the limitations of VKAs, including potential bleeding complications and narrow therapeutic window, have resulted in poor compliance to treatment, low rates of time-in-therapeutic range, and important underutilization in patients with AF, even in those at high-risk. Antiplatelet therapy with aspirin has low efficacy compared with VKAs, and dual antiplatelet therapy with aspirin and clopidogrel, despite demonstrating an additional effect, has not matched the efficacy of VKAs.

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The first revolution in anticoagulation for stroke prevention

A number of large randomized studies have proved the efficacy of several new oral anticoagulants for prevention of thromboembolic events in AF. The direct thrombin inhibitor dabigatran [5,6] and the factor Xa inhibitors rivaroxaban [7] and apixaban [6] are non-inferior and even superior to warfarin for prevention of thromboembolic events in non-valvular AF. We have waited a long time for the advent of these new drugs; but despite their indisputable contribution to stroke prevention in AF not all of the problems of anticoagulation have been solved, leaving both clinicians and patients still facing difficult choices:

- a large proportion of patients at risk of stroke or systemic embolism remains untreated [8];
- compliance to treatment remains problematic, with almost one-quarter of patients stopping medication within 2 years;
- anticoagulation is a life-long treatment, with necessary periods of interruption (e.g. for a surgical intervention), after which risk of thromboembolism is increased [9];
- contraindications to warfarin are frequent, affecting around 17% of the AF population;
- treatment-associated bleeding still exists;
- the combination of antiplatelet and oral anticoagulant therapy dramatically increases risk of bleeding.

An alternative to anticoagulation: occlusion of the left atrial appendage

In non-valvular AF blood stasis in the left atrium is the major mechanism of thrombus formation, with clot migration in the cerebral circulation inducing stroke. The left atrial appendage (LAA) is the most important cardiac source of thromboemboli in non-valvular AF [10], and its exclusion should therefore prevent most cases of thrombus formation, without the need for life-long anticoagulation. Based on this hypothesis, surgeons widely perform LAA appendage exclusion as a concomitant procedure during open-heart surgery and several systems for percutaneous occlusion of the LLA have been developed. The randomized Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (PROTECT-AF [11]) trial demonstrated the validity of the concept and the therapeutic non-inferiority of LAA closure as an alternative to long-term warfarin treatment in preventing stroke in non-valvular AF patients with a CHADS2 score ≥ 1. The primary composite efficacy endpoint was stroke, systemic embolism and cardiovascular death. Patients randomized to the LAA closure strategy had a lower event rate than those randomized to warfarin (3.0 vs. 4.9 per 100 patient-years, respectively), with a relative rate ratio of 0.62 (95% confidence interval 0.35–1.25), which translated to non-inferiority of the LAA closure strategy to warfarin treatment.

Even if the findings are extremely debatable, a systematic review of eight prospective non-comparative observational studies with the different systems of percutaneous LLA occlusion has estimated the annual stroke risk based on historical controls and CHADS2 score. This comparison indicated an overall stroke reduction from 1.9–8.6% to 0–3.8% in respective studies [12].

Device and procedure description

In 2006 the manufacturer of Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) — the first device to be developed for percutaneous LAA occlusion (PLAADO) — discontinued product development despite two prospective multicentre observational studies suggesting the feasibility of this technique with an acceptable risk [13]. Two devices — Watchman™ (Boston Scientific, Natick, MA, USA) and Amplatzer Vascular Plug™ (Saint-Jude Medical, Saint-Paul, MN, USA) — are currently available in clinical practice and a third is in development.

The LAA occlusion implantation must be performed in centres with cardiac surgical facilities. The implantor must be experienced or have received specific training. The procedure is performed under transesophageal echocardiogram (TOE) control, requiring a general anaesthesia. A sheath is introduced into the right femoral vein. Access to the left atrium takes place via a transseptal puncture. After approximating the size and shape of the LAA under TOE or fluoroscopic guidance, the device is sized using a standardized chart and is then advanced into the LAA orifice. Imaging is used to confirm optimal positioning before the device is released and the delivery system withdrawn into the right atrium. To avoid thrombus formation and stroke during the procedure strong anticoagulation with low-molecular weight heparin is performed to reach an activated clotting time of 250–350 seconds.

In PROTECT-AF, warfarin was administrated for at least 45 days after device implantation to avoid excessive thrombus formation on the device, until device endothelialization supervened. In the ASA and Plavix (ASAP) study, involving 150 patients contraindicated to warfarin, post-procedural anticoagulation was replaced by an antiplatelet regimen with clopidogrel up to 6 months and aspirin indefinitely. An antiplatelet regimen is also used after Amplatzer device implantation. Follow-up TOE imaging was performed to assess for device stability, peridevice leaks and device-related thrombus.

Safety concern

Periprocedural complications must be taken into account and balanced against the risks of long-term anticoagulation. Transseptal puncture occasionally occurs in patients with very large atria; manipulation of ‘complex’ material, sometimes with various sheaths, within the atria and particularly within the thin LAA can be a challenging and risky procedure. In a recent review of the major studies and registries, periprocedural death occurred in five patients, with an overall rate of 1.1%. Percardial effusion/cardiac tamponade was the most frequent procedure-related adverse event: 6.5% in PROTECT-AF [11] and 4.1% among all studies reported. Percardial effusion was the primary reason for urgent cardiac surgery. Periprocedural device embolization occurred in 0.7% of the implanted patients. Some occurred during the procedure but several were discovered at the first
echocardiographic control. Per-procedural stroke occurred in 0.6% of cases and in several was due to air embolism. In PROTECT-AF three of five strokes were air embolots. Clot formations on the implanted device, without embolization but requiring modification of anticoagulation management, have also been reported.

The complication rate is strongly influenced by operator experience. In PROTECT-AF the rate decreased between the early and late phases, and continued to decrease, as shown by data from the Continued Access Protocol (CAP) registry [14]. The implant success rate in CAP improved from 91% to 95% (P = 0.033), while the rate of pericardial effusion decreased from 4.1% to 2.2%, with no strokes. The overall procedure- or device-related safety adverse events within 7 days decreased from 6.5% in PROTECT-AF to 3.7% in the CAP registry (P = 0.061). Fewer data are available for the Amplatzer plug, but a recent registry [15] reported 10/137 (7%) severe complications of which three (2%) were ischaemic strokes, two (1.4%) were device embolizations and five (3.6%) were significant pericardial effusions. The effect of operator experience is also clear, with most of the complications occurring in the first patients implanted in the centres, highlighting the need to perform these implantations in centres with cardiac surgical facilities, sufficient volume of implantations and comprehensive operator training.

Which patients should undergo percutaneous left atrial appendage occlusion?

Strong trial evidence is available to support anticoagulation as the first-line therapy for prevention of thromboembolism in AF. The latest European Society of Cardiology (ESC) recommendations are clear: Although the concept of LAA closure seems reasonable, the evidence of efficacy and safety is currently insufficient to recommend these approaches for any patients other than those in whom long-term OAC is contraindicated. Additional, adequately powered, randomized studies in patients with high stroke risk and long-term follow-up, comparing interventional/percutaneous/surgical LAA closure with [oral anticoagulant] therapy including novel oral anticoagulant drugs, are needed for adequate assessment of such techniques’ PLAAO may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation (Class IIb, Level B) [4]. But what is a contraindication for long-term oral anticoagulation? Several proposals are listed in AVERROES [16] and ACTIVE A, many of which are debatable or practitioner-dependent.

The indication for LAA occlusion retained in the ESC guidelines is not the indication of the single randomized study with PLAAO, but is the first indication in clinical practice. In the European registry with the Amplatzer plug [15], 78.9% of indications for PLAAO were due to high bleeding risk, 8.9% to haemorrhagic history and 11.3% to stroke under anticoagulation. Even if these populations are probably the most logical, caution must be exercised. Haemorrhagic risk increases with age, comorbidity and CHADS2 score. The CHADS2 score was 2.4 in the Amplatzer plug European registry and 2.8 in the ASAP study, versus 2.2 in PROTECT-AF. Patients with a contraindication to anticoagulation are sicker than those without, with several possible consequences in favour of anticoagulation rather than PLAAO:

- the risk of complications during the procedure may be higher in this population;
- in addition to the risk of stroke due to stasis within the left atria, other mechanisms and origins of stroke could be higher in this population, increasing with the presence of a comorbidity;
- a recent publication has shown that absence of anticoagulation, left ventricular dysfunction or prior stroke is associated with a higher proportion of extra LLA thrombi [17].

Based on the above indications for PLAAO, most such cases will be difficult, with several possible solutions. The indication for LLA closure must therefore be based on a multidisciplinary decision involving, for example, the neurologist, neurosurgeon or gastroenterologist. At the same time the therapeutic management of AF should be discussed, such as ablation following device implantation.

Conclusion

Stroke must be prevented in high-risk patients with AF. Anticoagulation remains the first-line therapy, but when this approach is contraindicated or associated with a high-risk of bleeding, other solutions must be considered to avoid the potentially devastating consequences of an embolic event. PLAAO has a strong rationale and encouraging data exist to show the feasibility of such an approach, with an acceptable risk if undertaken in experienced centres. While further research into this therapeutic option is clearly necessary, PLAAO may, for some patients, offer a way of closing the door to hell.

Disclosure of interest

The author has not supplied his declaration of conflict of interest.

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