Transcatheter devices for left atrial appendage occlusion

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Summary

Atrial fibrillation (AF) patients are at inherent risk for thromboembolic stroke. Since the left atrial appendage (LAA) is known to be the primary site for thrombus formation in nonvalvular AF, its exclusion may offer an attractive alternative to long-term oral anticoagulation therapy in such patients. Accordingly, simultaneous LAA closure became common practice during cardiac surgery and was recently adopted by surgical guidelines. Alternatively, while thoracoscopic epicardial occlusion under general anaesthesia has been successfully performed, the actual breakthrough came with the introduction of transcatheter LAA exclusion in 2001. Although this device technology was beset with initial difficulties which even led to withdrawal of the original device line, several events in the recent past have revived interest in this catheter-based technology as a valid and safe option for stroke prevention in AF patients. This review discusses the relation of the LAA to the development of AF-related stroke and provides detailed insight into different transcatheter devices for LAA occlusion.

Rationale behind LAA exclusion

The rationale behind LAA exclusion was derived from transoesophageal echocardiographic, surgical and autopsy findings identifying the LAA as the primary site of thrombus formation (some 90% of stroke-related thrombi) in patients with nonvalvular AF [1]. This crucial observation aroused interest in obliteration of the LAA in order to replace or supplement oral anticoagulation as a means of preventing stroke in patients with AF. Against this background, and even before the availability of randomised data demonstrating safety or efficacy, surgical closure or excision of the LAA has become a frequent practice at the time of mitral valve surgery or surgical MAZE procedures in patients with AF, and is even recommended by surgical guidelines [2]. A randomised clinical trial examined the potential of surgical LAA ligation (suture or stapling), without removing the right atrial appendage, to reduce the stroke risk in patients with or at high risk for development of AF undergoing coronary artery bypass grafting (CABG) [3]; 52 patients were randomised to LAA occlusion and 25 served as controls. Two patients (2.6%) randomised to the ligation group and with documented complete occlusion of the LAA developed perioperative thromboembolic events. There were no deaths and no haemorrhagic strokes in either group. The study was too small to determine whether surgical LAA occlusion reduces stroke. The authors concluded at that time that surgical ligation of the LAA can be successfully performed at the time of routine CABG without significantly increasing operative time, bleeding or heart failure. Heart failure may be a concern when removing (instead of occluding) the LAA [4] or when removing the right atrial appendage in addition, since up to 30% of atrial natriuretic factor (ANF) regulating volume status is produced in the atrial appendages [5].

Embolic stroke is still a major cause of serious disability and death in AF patients, despite the fact that oral anticoagulants can dramatically reduce its incidence [6, 7]. This discrepancy is multifactorial and related to significant underuse of vitamin K antagonists due to the need for regular measurements of the international normalised ratio (INR), which is both costly and associated with patient discomfort, a narrow therapeutic window, variability in pharmacokinetics, food dependence of efficacy, contraindications and fear of bleeding complications [8–10]. In practice the estimated number of AF patients adequately receiving this medication is less than 50% [11]. Accordingly, the annualised stroke rate may reach up to 18% among AF patients with the maximum $CHADS_2$ score of 6 not receiving therapy. The $CHADS_2$ score represents risk points attributed as follows: 1 point each for congestive heart failure (C), hypertension (H), age over 75 years (A) and diabetes (D), and 2 points for prior stroke (S_2). A further compounding factor is that even under treatment with oral anticoagulants stroke prevention is incomplete. Hence it is becoming apparent that there is a true need for additional

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or more effective alternative approaches to stroke prophylaxis in patients with AF. Newer oral anticoagulants, including factor Xa antagonists and direct thrombin inhibitors, are promising avenues. Likewise, transcatheter LAA exclusion is progressively gaining ground. Rhythm control strategies, both medical by means of membrane active antiarrhythmic drugs and interventional by transcatheter pulmonary vein isolation to abort and prevent AF, are also of help but not sufficient alone to reduce the risk of stroke.

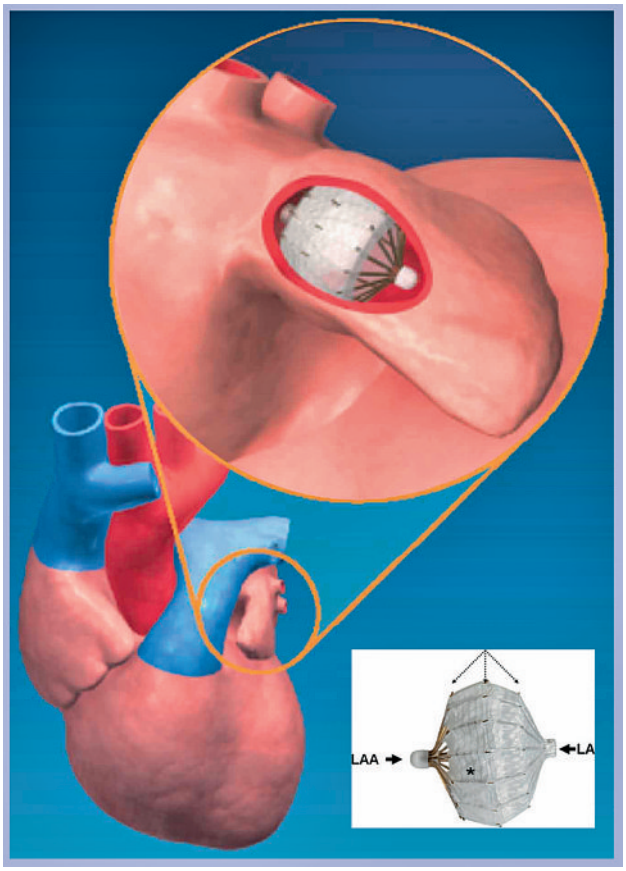
Transcatheter LAA exclusion

The basic principle of transcatheter LAA exclusion is to plug the LAA cavity, close to its orifice, to induce stasis, controlled thrombosis, and ultimately organisation and fibrosis of the LAA and coverage of the atrial surface of the device by endocardium, resulting in complete exclusion of the LAA (and the device for that matter) from the circulation. Several devices exist, and the basic implantation procedure is similar for all. The LAA is reached from the right atrium via a transseptal puncture or a patent foramen ovale (PFO) or atrial septal defect (ASD) if present, accessing from the right femoral vein. Localisation of the LAA is either by fluoroscopic contrast injection alone or under additional guidance using transoesophageal echocardiography (TEE) or intracardiac ultrasound. The device is delivered through a transseptal sheath placed within the LAA. The following sections focus on the specific features of the different devices and point out the advantages and disadvantages of each system.

Percutaneous left atrial appendage occluder (PLAATO) system

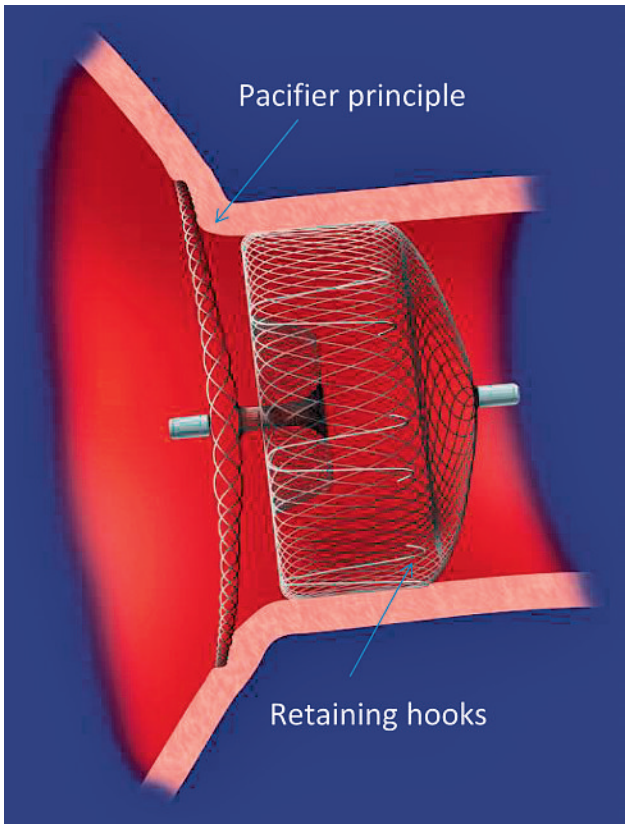
Encouraging results using the PLAATO system (EV3 Endovascular, Inc., North Plymouth, MN, USA) in animals in the late 1990s demonstrated complete LAA occlusion, no evidence of thrombi on the implant surface, and complete healing 3 months after device implantation. They led to the world's first percutaneous LAA occlusion in man on 30 August 2001 by Horst Sievert, MD, and the inventor, Michael Lesh, MD, in Frankfurt, Germany [12]. The PLAATO system consists of a self-expandable nitinol cage covered with an occlusive expanded polytetrafluoroethylene membrane (fig. 1). The membrane occludes the orifice of the LAA but allows tissue incorporation into the device, and has small anchors along the struts for device anchoring. The delivery catheter, which is 11 French or larger, houses the restrained implant whose sizes range between 15 and 32 mm in diameter. The implant position is checked by a series of criteria including effective occlusion of the LAA by the device, residual compression (>10%) of the device and a wiggling manoeuvre. If the result is suboptimal, the device can be collapsed into the delivery sheath and replaced with another size to fit the LAA anatomy better. The clinical performance of the device has been investigated in a series of clinical reports [13, 14] as well as in a multicentre prospective observational study encompassing 111 patients (age 71 ± 9 years) [15]. All the patients had a contraindication for anticoagulation therapy and at least one additional risk factor for stroke. The primary endpoint was incidence of major adverse events (MAEs), a composite of stroke, cardiac or neurological death, myocardial infarction, and requirement of procedure-related cardiovascular surgery within the first month. Implantation was successful in 108 of 111 patients (97%) who underwent 113 procedures. One patient experienced two MAEs within the first 30 days: need for cardiovascular surgery and in-hospital neurological death. Three other patients underwent in-hospital pericardiocentesis due to haemopericardium. Average follow-up was 10 months. Two patients had a stroke. No migration or mobile thrombus was noted on TEE at one and six months after device implantation. In another series of 71 patients treated by the PLAATO device and followed for 24 months, no fatal or nonfatal strokes occurred, while ten overall deaths were reported. Statistically, 7 strokes would have been expected in this patient cohort without treatment within 24 months. In 52 patients who received a TEE at follow-up, stable anchoring of the PLAATO device without migration or dislocation was documented and no thrombotic deposi-

Figure 1
PLAATO device (no longer available) for percutaneous LAA occlusion.



tion was found on the LA luminal surface of the device [16]. A few hundred devices had been implanted worldwide until its withdrawal by the company in 2006 due to over-large financial investment projected to obtain clinical approval.

Figure 2
Amplatzer Cardiac Plug for percutaneous LAA occlusion.



Amplatzer devices

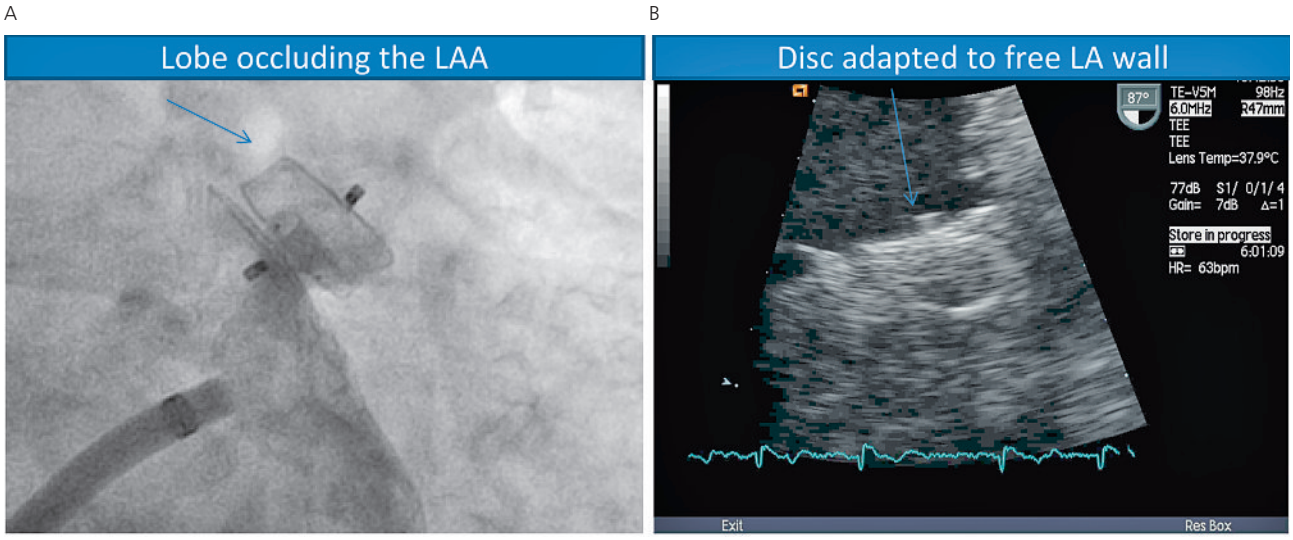
Amplatzer devices (AGA Medical Corp., North Plymouth, MN, USA) have been in successful clinical use for transcatheter treatment of structural heart defects, particularly closure of the patent foramen ovale and atrial septal defects (ASD), for over 15 years. Their user-friendliness and safety led to investigation of the Amplatzer technique for percutaneous obliteration of the LAA by means of a variety of devices designed for other purposes. On 10 April 2002 the world's first percutaneous LAA occlusion in a conscious patient (without general anaesthesia or echocardiographic guidance) was performed in Bern, Switzerland, using an Amplatzer ASD occluder [17]. An initial series including 16 patients treated at 4 centres using the Amplatzer ASD, or PFO or ventricular septal defect occluders was reported [17]. All but two procedures were done under local anaesthesia of the groin with only one technical failure (device embolisation requiring surgery). All other patients left the hospital a day after the procedure without complications. No further complications were recorded during an overall follow-up of 5 patient-years, and all the LAAs were completely occluded without evidence of thrombosis on the atrial side of the device at the latest echocardiographic follow-up.

On the basis of these promising results and further clinical evaluation, the Amplatzer Cardiac Plug (ACP, fig. 2, table 1) was developed as a dedicated LAA occlusion device taking advantage of its ease of use and low thrombogenicity of the Amplatzer devices in general. Its primary feature distinguishing it from other Amplatzer occluders is a crown of retaining hooks at the distal end. Two additional specific features facilitate manipulation during implantation and device fixation after release. (1). A double-bend tip of the delivery sheath and the softness of the tip make it steerable in a 3-dimensional plane

Table 1
Comparison between the two commercially available dedicated percutaneous LAA occlusion devices.

Amplatzer Cardiac Plug	Device specification	Watchman
AGA Medical, Corp., North Plymouth, MN, USA	**Manufacturer**	Atritech, Inc., North Plymouth, MN, USA
No	**FDA Approval**	Yes
Yes	**CE-Mark**	Yes
Nitinol mesh and polyester patch and retaining hooks	**Material and design**	Nitinol frame and polyester fabric with fixation barbs
8 sizes from 16 to 30 mm	**Available sizes**	5 sizes from 21 to 33 mm
Double bend	**Delivery sheath tip**	Simple bend
9–13 French	**Delivery sheath size**	12 French
Recommended by manufacturer	**Ultrasound guidance**	Recommended by manufacturer
Possible before release	**Device retrieval**	Possible before release
Usually not given	**Oral anticoagulants**	At least 45 days afterwards
Yes	**Initial dual antiplatelet therapy**	Yes (after withdrawal of oral anticoagulant)
No	**Long-term antiplatelet therapy**	Recommended

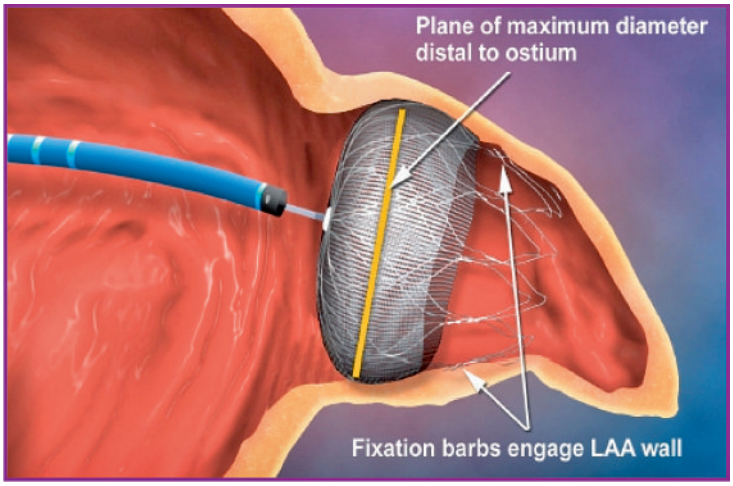
Figure 3
Fluoroscopic (A) and echocardiographic (B) documentation of an Amplatzer Cardiac Plug correctly positioned in the LAA.



facilitating parallel engagement of the LAA and decreasing the risk of free wall perforation during manipulation. (2.) A flexible distal end of the pusher cable allows near uninfluenced observation of the device situation before detachment from the delivery gear (point of no return in terms of reversibility of the procedure).

Made of flexible braided nitinol mesh with a polyester fabric, the ACP consists of a distal lobe connected by a central waist to a proximal disc, and is designed to provide occlusion with full cross-sectional coverage. The ACP self-expands to hug the LAA wall, covering the orifice of the LAA with its proximal disk (pacifier principle). Positional adaptivity is achieved through a waist that acts as an articulating, compliant connection between proximal disc and distal lobe, allowing the disc to self-orient to the left atrial wall, reminiscent of a pacifier in a toddler's mouth, the disc completely covering the orifice of the LAA (outside plate of the pacifier) and providing apposition against the left atrial wall under gentle tension (fig. 3).

Figure 4
Watchman device for percutaneous LAA occlusion.



Like other devices, the ACP has the capability to be retrieved, repositioned or replaced, if necessary until release from the delivery cable. The ACP is available in 8 sizes ranging from 16 to 30 mm, requiring delivery sheaths from 9 to 13 French. Device oversizing of at least 2–4 mm above the LAA neck diameter where the distal lobe is placed is recommended to enhance fixation.

Currently over 200 ACPs have been implanted worldwide. There were no implantation failures but 2 device embolisations and 2 pericardial effusions requiring drainage. The Cardiac Plug European Registry is an ongoing, prospective, post-market, open-label registry of 100 patients with paroxysmal, persistent or permanent AF in 8 centres. The recommended antiplatelet therapy is low-dose acetylsalicylic acid for 6 months and clopidogrel 75 mg for 1 month. A follow-up TEE at 1 and 6 months is also recommended and results are expected in late 2010. The ACP received CE-Mark certification in December 2008.

Watchman system

The Watchman device (Atritech, Inc., North Plymouth, MN, USA, fig. 4, table 1), the third device line introduced, was first implanted on 12 August 2002 in Siegburg, Germany [18]. It comprises a self-expanding nitinol frame structure with fixation barbs and a permeable polyester fabric that covers the atrial face of the occluder. The device is constrained in a 12 French delivery catheter and is available in 5 sizes from 21 mm to 33 mm expanded diameter. Device embolisation was frequent in initial studies, resulting in redesign of the barbs to achieve better fixation. The PROTECT-AF study was a prospective randomised trial comparing closure of the LAA with long-term warfarin therapy [19]. Almost 800 patients from 59 enrolling centres in the US and Europe were randomised in a device-to-control ratio of 2:1. Patients were followed up by TEE at 45 days, six months and one year, were

seen for clinical follow-up biannually for up to five years, and had regular INR monitoring while on warfarin. Patients included were those with documented nonvalvular AF who could take long-term warfarin but had no indication that would require warfarin. The $CHADS_2$ score had to be ≥1. In fact, 65% of patients in the trial were ultimately $CHADS_2$ 1 or 2, i.e., relatively low-risk. After randomisation patients either began treatment with warfarin or underwent device implantation. Device patients were also treated with warfarin until day 45. Thereafter warfarin was replaced by acetylsalicylic acid.

The study was designed to assess the non-inferiority of device therapy against chronic warfarin therapy. Efficacy was assessed by a primary composite endpoint of stroke, cardiovascular death, and systemic embolism. The primary safety endpoint included device embolisation requiring retrieval, pericardial effusion requiring intervention, and cranial, gastrointestinal or any other significant bleeds. At 1065 patient-years of follow-up the primary efficacy event rate was 3.0 per 100 patient-years (95% credible interval 1.9–4.5) in the device group and 4.9 per 100 patient-years (2.8–7.1) in the control group (rate ratio 0.62, 95% CI 0.35–1.25). The probability of non-inferiority of the intervention was >99.9%. Primary safety events were more frequent in the device group than in the control group (7.4 per 100 patient-years, 95% CI 5.5–9.7, vs 4.4 per 100 patient-years, 95% CI 2.5–6.7; RR 1.69, 1.01–3.19). Adverse safety events in the intervention group were mainly a result of periprocedural complications. Implantation of the Watchman device carries substantial up-front procedural risk, which may, however, decrease with increasing experience [20]. Among 449 attempted implantations the device was successfully placed in 408 patients (91%); 12% of patients had serious procedural complications: pericardial effusion requiring drainage (5%), acute ischaemic stroke due to air or thromboembolism (1%), device embolisation and removal (3 patients), postimplantation sepsis and removal (1 patient).

The Watchman device received FDA approval on 23 April 2009. The vote to recommend approval was conditional, i.e., that implantation be performed in centres with surgical backup and the creation of a physician certification programme. The panel also recommended the creation of a registry and extended follow-up of current clinical trials.

Transcatheter LAA exclusion as an alternative to antithrombotic therapy

Today we have come nearer than ever before to the target of transcatheter LAA exclusion as an alternative to antithrombotic therapy for AF patients. The promising results of the PROTECT-AF trial in spite of the limitations of the Watchman device are a landmark on the way to establishment of this treatment concept. The availability of the ACP with the excellent record of low thrombogenicity of the roughly 300 000 Amplatzer devices implanted over the past 15 years, and its user-friendliness, will facilitate the adoption of the technique by more operators and centres and render it even safer. However, further evidence is still needed before this becomes a widespread treatment modality, especially bearing in mind the imminence of warfarin-alternative drugs.

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