European Heart Journal Supplements (2010) **12** (Supplement E), E35–E40
doi:10.1093/eurheartj/suq008

Transcatheter left atrial appendage exclusion, gold or fool's gold?

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KEYWORDS
atrial fibrillation;
embolic stroke;
left atrial appendage;
left atrial appendage closure

Non-valvular atrial fibrillation (AF) related stroke primarily originates as embolic event from a left atrial appendage (LAA) thrombus. Oral anticoagulants effectively reduce stroke risk among AF patients. Cardiac operations are frequently coupled with surgical closure of the LAA as a measure to prevent stroke in such patients. Transcatheter LAA exclusion was first introduced in 2001, yet faced difficulties which led to the withdrawal of the initial device line. Recently, several events have revived the interest in this catheter-based technology as a safe and effective alternative to oral anticoagulants among AF patients. This review discusses the role of the LAA in health and disease and gives detailed insight into different transcatheter devices for LAA exclusion with the available clinical evidence.

Introduction

Most strokes in patients with non-valvular atrial fibrillation (AF) are known to arise from thrombus formation in the left atrial appendage (LAA);[1] therefore, occlusion of the orifice of the LAA provides an at least theoretically attractive alternative to oral anticoagulation for stroke prevention in such patients. Simultaneous surgical closure during cardiac surgery has been common practice since many years and is recommended in current guidelines.[2] Thoracoscopic epicardial occlusion under general anaesthesia is an option[3] and non-surgical transcatheter LAA exclusion, introduced in 2001,[4] is gaining ground. In the recent past, we recognize two milestones prompting this review: (i) results of the PROTECT-AF (WATCHMAN® Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) randomized study of a percutaneous LAA obliteration device,[5] and (ii) CE-Mark approval of the dedicated Amplatzer device for transcatheter LAA closure, the AMPLATZER Cardiac Plug®.

Role of left atrial appendage in health and disease

The LAA is a remnant of the embryonic left atrium, whereas the left atrial cavity is formed by the outgrowth of the pulmonary veins. The LAA is lined by endothelium and contains pectinate muscles which run largely parallel to each other and perpendicular to the long axis of the LAA. They give rise to its trabeculated inner surface.[6] The LAA lies antero-laterally in the left atrio-ventricular sulcus and is in close contact with the pulmonary artery superiorly and the left ventricular free-wall inferiorly. The anatomy of the LAA is rather complex and highly variable with a windsock-like configuration consisting of one or multiple lobes and usually a narrow junction which is connected to the left atrium.[7,8] The size of the LAA varies considerably with an orifice measuring 5–27 mm in diameter and a LAA length measuring 16–51 mm. Quantification of atrial natriuretic factor (ANF) from excised atrial appendages revealed a content of approximately 30% of all cardiac ANF.[6] The LAA has a distinct pattern of contraction, which is quadriphasic according to Doppler flow measurements. The LAA has been considered a decompression chamber at times of increased atrial pressure due to its high distensibility,

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the anatomical location high in the left atrium, and the ability to secrete ANF. Not withstanding, a clinically relevant problem because of a lacking LAA has yet to be described, with the exception of a potential deleterious influence on heart failure after bilateral atrial appendage removal.[9]

Atrial fibrillation, the most common cardiac arrhythmia, is a strong and independent risk factor for stroke and mortality. The incidence of AF increases with age. It affects approximately 5% of people at the age of 70 years and 10% at the age of >80 years.[10] Atrial fibrillation is deemed responsible for 16% of all ischaemic strokes with about two-thirds (10% of all ischaemic strokes) demonstrating left atrial thrombi.[11] Atrial fibrillation not only affects remodelling of the proper left atrium but also of the LAA. Thus, LAA casts of patients with AF have been found more voluminous with larger orifices and fewer branches compared with patients in normal sinus rhythm. In addition, markedly reduced LAA Doppler flow velocities and ejection fractions have been observed in patients with AF. These pathological changes result in stasis and predispose to thrombus formation within the LAA cavity, particularly in the crypts between the pectinate muscles. Of note, transoesophageal echocardiographic studies and direct inspections revealed that >90% of all thrombi related to AF originate from the LAA.[1] Strokes related to LAA thrombus embolism are larger and more disabling compared with strokes of other aetiology presumably related to the relatively large thrombus size nested within the LAA cavity.

Rationale behind left atrial appendage exclusion

The pivotal transoesophageal echocardiography (TOE) observations or direct surgical or autoptic inspections show that the vast majority (about 90%) of thrombi related to stroke in patients with non-valvular AF originate from the LAA[1] this stirred the therapeutic interest to obliterate the LAA as a means of stroke prophylaxis in patients with AF. Surgical closure or excision of the LAA has been performed for years, without, however, collecting randomized data documenting safety or efficacy. Indeed, it has become common practice to remove the LAA at the time of mitral valve surgery, and it is also a routine part of the surgical MAZE procedure in patients with AF. The concern for LAA occlusion to cause heart failure (up to 30% of ANF regulating volume status are produced in the atrial appendage)[6] prompted a randomized clinical trial to examine the potential of surgical LAA ligation (suture or stapling), leaving the right atrial appendage in place rather than removing it, to reduce stroke risk in patients with or at high risk for the development of AF undergoing coronary artery bypass grafting (CABG).[12] The authors concluded 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. Of the 77 patients randomized (52 to LAA occlusion and 25 to control), two patients (2.6%) had perioperative thromboembolic events: both patients were randomized to the ligation group and had a completely occluded LAA. There were no deaths and no haemorrhagic strokes. However, the study was too small to determine whether surgical LAA occlusion reduces stroke.

Although the use of oral anticoagulants in patients with AF has lead to a significant reduction in stroke, stroke remains a major cause of serious disability and death in AF. Moreover, there is marked underuse of vitamin K antagonist therapy in patients with AF related to the need for regular international normalized ratio (INR) assessments in the blood, the narrow therapeutic window, variability in pharmacokinetics, food dependency of efficacy, contraindications, and fear of bleeding complications (0.5% annual risk of cerebral haemorrhage). Numerous surveys show that usually <50% of patients with AF receive this therapy.[13] This is particularly concerning in patients with a high $CHADS_2$ score.[6] Furthermore, the demonstrated efficacy of chronic anticoagulation is only a 67% relative risk reduction, indicating a considerable residual burden of stroke related to AF, even on best medical therapy. Accordingly, supplementary or alternative methods for stroke prevention in patients with AF are called for. Among them are newer oral anticoagulants with better safety, efficacy, and compliance (e.g. factor Xa antagonists, direct thrombin inhibitors), medical heart rhythm control using membrane active antiarrythmic drugs, transcatheter pulmonary vein isolation to abort and prevent AF, and transcatheter LAA exclusion. Rhythm control strategies (medical and interventional) are not sufficient alone to reduce the risk of stroke.

Transcatheter left atrial appendage exclusion

Several devices have been used and the implantation procedure is basically the same for all. Most centres guide the intervention with TOE or intracardiac ultrasound. It is commenced by a femoral venous puncture followed by transseptal access to the left atrium using standard technique. The LAA is delineated by a left atrial contrast medium injection in several projections in addition to TOE performed either before or during the intervention. The transseptal sheath is exchanged for the special delivery catheter placed within the LAA. The implant is positioned by withdrawal of the catheter from the LAA. Each system, however, has unique properties which influence the ease of implantation, stability of final implant, and risk for complications, hence overall procedural success and late outcome.

PLAATO® system

The world's first percutaneous LAA occlusion procedure was performed on 30 August 2001 by Sievert,[4] MD, in Frankfurt, Germany. The Percutaneous Left Atrial Appendage Occluder (PLAATO®, EV3 Endovascular, Inc., North Plymouth, MN, USA) system consists of an implant made

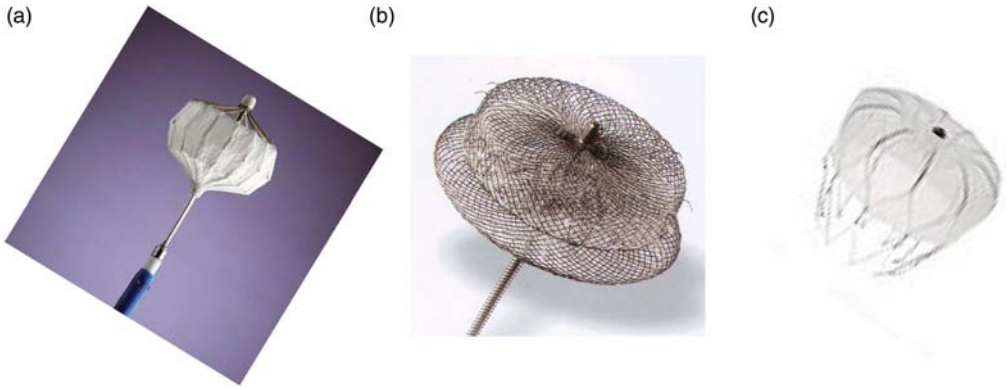

Figure 1 Clinically used left atrial appendage occluders. (*a*) PLAATO® device (no longer available); (*b*) Amplatzer Cardiac Plug®; (*c*) WATCHMAN® device.

of a nitinol metal cage (*Figure 1*) with multiple outwardly bent anchors covered by a polytetrafluoroethylene membrane. The delivery catheter houses the restrained implant and is 11 French or larger. The implant position is checked by a series of criteria including effective occlusion of the LAA by the device, a residual compression (>10%) of the device, and a wiggling manoeuvre. In case of unsatisfactory results, the device is fully retrievable and can be collapsed into the delivery sheath for replacement with another size. Animal studies revealed complete LAA occlusion, no evidence for thrombi on the implant surface, and complete healing 3 months after device implantation. The clinical performance of the device has been investigated in a series of clinical reports as well as in a multicentre prospective observational study encompassing 111 patients (age 71 $\pm$ 9 years).[14] All 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 for 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 experienced a stroke. No migration or mobile thrombus was noted on TOE at 1 and 6 months after device implantation. In another series of 64 patients treated by the PLAATO® device, a 5-year follow-up revealed seven deaths, five major strokes, three minor strokes, one cardiac tamponade requiring surgery (adjudicated as related to the implant procedure), one probable cerebral fatal haemorrhage, and one myocardial infarction. The annualized stroke/transient ischaemic attack (TIA) rate was 3.8%, less than the anticipated rate with the $CHADS_2$ scoring system of 6.6%/year.[15]

In 2006, however, the manufacturer withdrew the device due to the costs projected for clinical approval.

AMPLATZER® devices

The ease of use and low thrombogenicity of the AMPLATZER® devices for closure of the patent foramen ovale and atrial septal defects led to the investigation of the AMPLATZER® technique for percutaneous obliteration of the LAA. On 10 April 2002, the world's first percutaneous LAA occlusion in an awake patient was performed in Bern, Switzerland, resulting in a publication on the first 16 patients treated at four centres.[16] All but two procedures were done under local anaesthesia of the groin only. There was one technical failure (device embolization) requiring surgery. All other patients left the hospital a day after the procedure without complications. There were no problems or embolic events during an overall follow-up of 5 patient-years and all LAA were completely occluded without evidence of thrombosis at the atrial side of the device at the latest follow-up echocardiography. This promising experience led to the development of a dedicated Amplatzer LAA occlusion device.

The AMPLATZER Cardiac Plug® (AGA Medical, Corp., North Plymouth, MN, USA, *Figure 1*, *Table 1*) is made of flexible braided nitinol mesh and a polyester patch, and consists of a distal lobe connected by a central waist to a proximal disc, designed to provide occlusion of the LAA neck with full cross-sectional orifice coverage. As other devices, the Cardiac Plug has the ability to be repositioned, if necessary. The lobe of the AMPLATZER Cardiac Plug® is designed to conform to the inner wall of the LAA neck with a depth of about 10 mm and to provide secure device placement. Positional adaptability is achieved through a waist that acts as an articulating, compliant connection between the disc and lobe allowing the disc to self-orient to the proper left atrial wall, simulating a pacifier in a toddler's mouth with 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 (*Figure 2*). The Cardiac Plug is available in eight sizes from 16 to 30 mm, requiring a delivery sheath from 9 to 13 French. Device upsizing by 2–4 mm above the LAA neck diameter is recommended. Two special features of the AMPLATZER Cardiac Plug® contribute to

Table 1 Comparison between the AMPLATZER Cardiac Plug® system and the WATCHMAN® device for transcatheter left atrial appendage exclusion

	AMPLATZER Cardiac Plug®	WATCHMAN®
Manufacturer	AGA Medical, Corp., North Plymouth; MN, USA	Atritech, Inc., North Plymouth, MN, USA
Approval	CE-Mark (2008)	CE-Mark (2005), FDA (2009)
Material and design	Nitinol mesh and polyester patch (lobe, waist, and disc)	Nitinol frame with fixation barbs and polyester fabric
Available sizes	8 sizes (16–30 mm)	5 sizes (21–33 mm)
Fixation	Passive and active (hooks)	Passive
Delivery sheath tip	Double bend (three-dimensional)	Simple bend
Delivery sheath size	9–13 French	12 French
Ultrasound guidance	Recommended but not indispensable	Recommended but not indispensable
Device retrieval	Possible before release	Possible before release
Oral anticoagulants	Usually not given	At least 45 days afterwards[a]
Initial dual antiplatelet therapy	Yes	Yes (after withdrawal of oral anticoagulant)[a]
Long-term antiplatelet therapy	No	Recommended[a]

[a]According to protocol of the PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) study.[5]

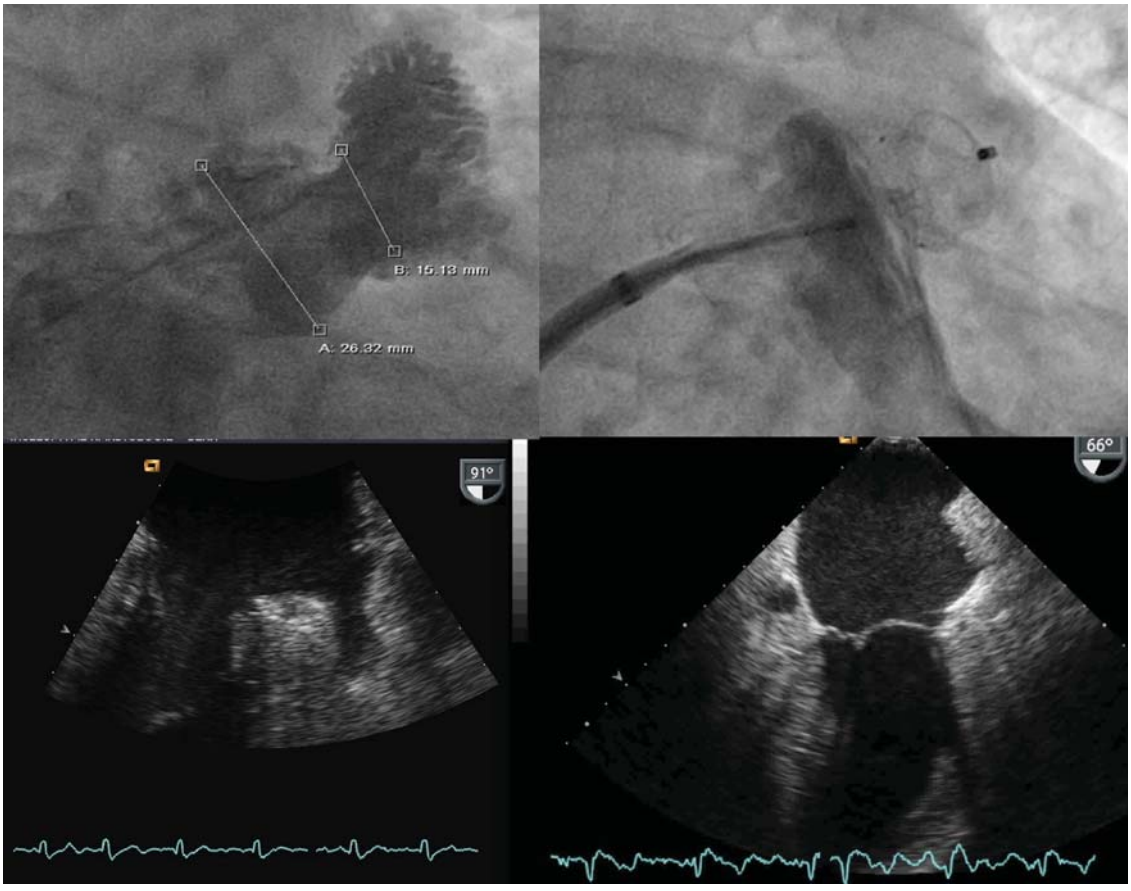

Figure 2 Top: left atrial appendage (LAA) angiography (left) and 20 mm AMPLATZER Cardiac Plug in the LAA before release (right). Bottom: pre-procedure (left) and 2-month follow-up (right). transoesophageal echocardiography of the LAA showing complete occlusion according to the pacifier principle.

the ease, safety, and reliability of device placement: first, the $2\times45^{\circ}$ bending of the tip of the delivery sheath and its soft tip make it steerable in a three-dimensional plane facilitating parallel engagement of the LAA and meanwhile decreasing the risk of free-wall perforation and pericardial effusion. Second, the backward-bent hooks on the lobe afford active fixation of the device in the LAA.

The device received CE-Mark approval in December 2008 and meanwhile about 300 AMPLATZER Cardiac Plugs® have been implanted worldwide. Among these patients, there were no implantation failures reported but two device embolizations, two pericardial effusions requiring drainage, and two thromboembolic events. Currently, a prospective, post-market, open-label AMPLATZER Cardiac Plug® European Registry of 100 patients with paroxysmal, persistent, or permanent AF is being conducted in eight centres. The recommended antiplatelet therapy is low-dose acetylsalicylic acid for 6 months and clopidogrel 75 mg for 1 month. A follow-up TOE at 1 and 6 months is recommended.

WATCHMAN® system

The WATCHMAN® device (Atritech, Inc., North Plymouth, MN, USA, *Figure 1*, *Table 1*), the third device line introduced, was first implanted on 12 August 2002, in Seigburg, Germany.[17] It comprise of 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 five sizes from 21 to 33 mm expanded diameter. Different to the PLAATO® system, the WATCHMAN® device is released more distal to the LAA orifice. Device embolization was frequent in initial studies, which led to redesign of the barbs to achieve better fixation. The PROTECT-AF multicentre, prospective, randomized, controlled, unblinded study examined the efficacy and safety of percutaneous closure of the LAA in patients with non-valvular AF who were deemed eligible for warfarin therapy.[5] The study was designed to assess the non-inferiority of the device against chronic warfarin therapy. The 707 patients had at least one of the following: previous stroke, TIA, congestive heart failure, diabetes, hypertension, or were $\geq$75 years. They were randomized in a 2:1 manner to percutaneous LAA occlusion and subsequent discontinuation of warfarin or warfarin treatment with target INR 2–3. Efficacy was assessed by a primary composite endpoint of stroke, cardiovascular death, and systemic embolism. Serious adverse events that constituted the primary endpoint for safety included major bleeding, pericardial effusion, and device embolization. At 1065 patient-years of follow-up, the primary efficacy event rate was 3.0 per 100 patient-years (95% credible interval CrI 1.9–4.5) in the intervention group and 4.9 per 100 patient-years (2.8–7.1) in the control group (rate ratio 0.62, 95% CrI 0.35–1.25). The probability of non-inferiority of the intervention was $>$99.9%. Primary safety events were more frequent in the intervention group than in the control group (7.4 per 100 patient-years, 95% CrI 5.5–9.7, vs. 4.4 per 100 patient-years, 95% CrI 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.[18] Among 449 attempted implantations, the device was successfully placed in 408 patients (91%). Overall, 12% of patients had serious procedural complications, including pericardial effusion requiring drainage or surgery in approximately 5% and acute ischaemic stroke due to air or thromboembolism in 1%. Four patients had to have the device removed because of device embolization (three patients: one removed percutaneously using a vascular snare and two were surgically removed) or post-implantation sepsis. In total, 2% of attempted implantations resulted in cardiovascular surgical intervention because of device-related complications. These events were not part of the study's primary effectiveness analysis. In addition, the rate of serious pericardial effusion was 50% higher at less experienced centres indicating a substantial learning curve associated with device implantation. The FDA advisory panel voted, on 23 April 2009, 7 to 5 to recommend approval of the WATCHMAN® device. The vote to recommend approval came with conditions, including 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 left atrial appendage exclusion, gold or fool's gold

The role of the LAA in the pathogenesis of stroke among AF patients is well documented and beyond challenge, therefore its exclusion seems reasonable and research efforts in this direction remain on the right track. However, since oral anticoagulants have proven effectiveness for reducing the incidence of stroke among these patients, albeit with certain caveats, the widespread application of transcatheter LAA exclusion devices must be preceded by several landmarks: (i) insuring user-friendliness of the procedure. This is already fulfilled to a great extent, as only a femoral vein puncture under local anaesthesia is needed. The transseptal puncture, which is not specific for the procedure, may be a hindering step in in-experienced centres. Directable delivery sheaths, best met by the AMPLATZER® sheath with its double bend, enable aligned engagement of the LAA orifice. (ii) A low potential for complications, particularly device embolization and thrombus formation on the device. The AMPLATZER Cardiac Plug® has an excellent record regarding low thrombogenicity based on the 300 000 Amplatzer devices implanted in the past 15 years. (iii) Effectiveness of the procedure compared with oral anticoagulation. The PROTECT-AF using the WATCHMAN® device provides first evidence that transcatheter LAA exclusion is non-inferior to chronic warfarin therapy. Whether this can be confirmed regarding warfarin successors at the doorstep remains to be seen. Transcatheter LAA exclusion is no fool's gold. Further evidence may even prove it high-carat gold.

Conflict of interest: B.M. received research grants and speaker fees from AGA Medical.

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