Transcatheter occlusion of left atrial appendage for stroke prevention in patients with atrial fibrillation

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Abstract

Cardiac emboli in patients with atrial fibrillation are one of the major causes of ischemic stroke. Because the vast majority of these cardiac emboli descend from the left atrial appendage (LAA), the therapeutic strategy of percutaneous transcatheter occlusion of the LAA by means of a mechanical implant was a logical consequence. Three different devices have been developed and used in humans: PLAATO, WATCHMAN, and ACP. The PLAATO implant, a "soccer ball" shaped self-expanding nitinol cage has demonstrated stroke prevention capability in small, uncontrolled studies. The WATCHMAN implant, a "half rugby ball" shaped self-expanding nitinol cage, has demonstrated non inferiority compared to warfarin treatment in the randomized, controlled PROTECT AF trial. The ACP implant is also a self-expanding nitinol cage. However, its design is of fundamental difference compared to the other two implants. ACP consists of two parts connected by a short waist, which are an "icehockey puck" shaped body for the implant fixation in the appendage wall, and a flexible disc for sealing the appendage ostium. Due to the very flexible connecting waist between the two parts, ACP implant adapts itself to the LAA, which appears in significant individual structural variabilities. The currently unpublished initial experience with ACP in Europe is encouraging. Transcatheter occlusion of the LAA offers an appealing way to reduce the incidence of cardioembolic stroke in patients with atrial fibrillation. However, the concerns about procedural safety and the need for long-term follow up should be addressed before this potentially important technology is deployed widely.

Atrial fibrillation (AF) is an arrhythmia with high and irregular electrical activity of the atria, characteristically with an impulse frequency between 350 and 500 per minute. Under such conditions an effective contraction of the atria is impossible (1). In the group of arrhythmias AF contributing with 60% of all is most frequent. Epidemiological studies revealed that in industrialized countries up to 1.5% of the general population has AF. In Germany around 800.000 adults suffer from AF with a clear increase of incidence in elderly. Rapid changes of the age pyramid in the next future will result in a dramatic increase of the prevalence of AF (2). In the age group of 60-yrs and older the prevalence of AF is round about 4%, in the group of 70-yrs and older 7% (3), and according to Ezekowitz et al. (4) 17% in 85-yrs and older individuals.

In the Framingham-Study (5) the mortality rate of patients with AF was double of the control group individuals. As the major underlying cause of death in these patients cerebral embolism was identified, which increased from 1.5% in individuals between 50 yrs and 60 yrs of age to 30% in individuals between 80 yrs and 90 yrs. In this analysis patients undergoing heart surgery were not included. Data of the „Cardiovascular Health Study" confirms the high prevalence of AF also in the U.S. population of 4% to 6% in the age group of 60-yrs and older, and 10% in the age group of 75-yrs and older (6).

Figure 1 shows the prevalence of the age dependent AF rate (7). The prevalence of AF in the general population is 0.4% - 1% and 8% in individuals of 80 yrs and older. Using the so-called CHADS2-score the individual risk of development of ischemic stroke can be estimated. Because it is well known from meta-analysis that in patients with non-rheumatic AF 91% of all thrombi found in the left atrium are localized to the left atrial appendage (8), several therapeutic strategies of occlusion of the appendage by surgery or from the luminal side of left atrium by transcatheter techniques were hypothesized. Hellerstein was the first to show the feasibility of LAA resection in dogs (9). The first resection of the LAA for prophylaxis of recurrent arterial embolism in men was performed in 1949 by Madden (10), followed by Beal in 1950 (11). Johnson and coworkers performed atrial appendectomies in 437 patients during cardiac surgery. During follow-up no strokes were attributed to AF and no patients were found to have atrial clots on TEE (12). After the demonstration in dogs and human cadavers by Odell and coworkers (13) that thoracoscopic exclusion of the LAA using either a stapler or an endoloop is also feasible and effective, Blackshear and colleagues (14) evaluated left atrial appendage obliteration in 14 high-risk patients with AF with clinical risk factors for stroke and with an absolute contraindication to or failure of prior thrombosis prevention with warfarin. One fatal stroke occurred 55 months after surgery and one non-disabling stroke three months after surgery. For the LAA Occlusion Study (15, 16), 77 patients with risk factors for stroke were randomized to LAA occlusion or control (52 patients for LAA occlusion, 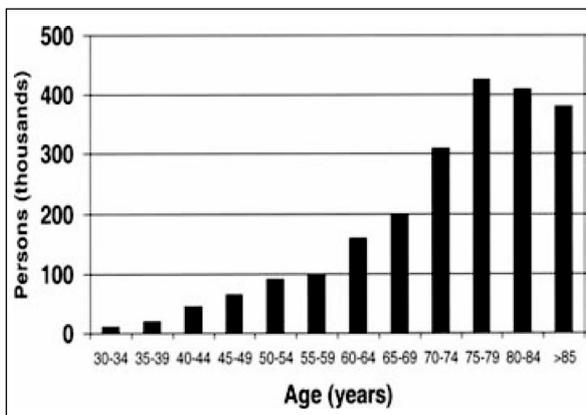25 patients in the control group) at the time of coronary artery bypass graft (CABG). In the LAA occlusion group, two (2.6%) patients had perioperative thromboembolic events: one an intraoperative ischemic stroke and the other a TIA occurring on the third postoperative day. The former patient was in AF and had echocardiographic evidence of a patent foramen ovale and bilateral carotid stenoses. After a mean follow-up of 13 ± 7 months, no further strokes or TIAs occurred in the LAA occlusion group (17). Nonetheless, surgical or thoracoscopic LAA closure, other than as an adjunctive procedure as recommended by ACC guidelines (18) in patients undergoing mitral valve surgery, has not been enthusiastically accepted because of its invasive nature. Thus, based on the surgical experience, the development of a less invasive percutaneous approach to close the LAA by implantation of a mechanical device was a logical consequence (19, 20).

The PLAATO system

The Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) (EV3, Inc., MN, Plymouth, USA) device was the first to be successfully deployed in humans (21) but was withdrawn from the market by the manufacturer in 2006. The PLAATO system consists of an implant and a delivery catheter. The implant is a self-expanding nitinol cage covered with an occlusive expanded polytetrafluoroethylene membrane. The expanded membrane has intimate contact with the inner wall of the appendage to achieve complete closure of the ostium. The diameter of the nitinol cage ranges from 15 to 32 mm. Small hooklets along the struts and passing through the membrane assist with device anchoring. The device was delivered through a custom 12 Fr transseptal sheath curved to point at the left atrial appendage.

Several reports demonstrate the efficacy in stroke prevention with PLAATO (Tab 1). However, in every patient cohort procedure related serious adverse events occurred, among those were vessel perforation during vascular access, and cardiac tamponade after transseptal puncture. Some patients experienced pericardial effusions which mostly were uneventful but also lead to pericardiocentesis and a prolonged hospital stay. The worst cases which happened in our series were a periprocedural death due to device embolization resulting in an acute occlusion of the left ventricular outflow tract. In another patient the implant anchoring seemed to be unstable in LA angiography, so that the device was explanted and the LAA of the patient oc-

Figure 1. Age Dependent Prevalence of Atrial Fibrillation.

Table 1: Currently published data for stroke prevention with the PLAATO system.

Author (Ref.#)	# pat.	FU	estimated annual stroke rate	actual annual stroke rate
Block (39, 40)	64	5 years	6.6%	3.3%
Park (41)	73	2 years	5.0%	0.0%
Ussia (42)	20	40±10 months	6.4%	0.0%
De Meester (43)	10	3±47 months	7.1%	0.0%
Ostermeyer (44)	111	9.8 months	6.3%	2.2%

cluded by open heart surgery on the catheter table (22). After these disastrous cases, our LAA occlusion program was stopped and an extensive revision of all 73 prior implantations was carried out. As a result we found a significant rotation of the device after release from the delivery system in some cases, resulting in a loss of contact between parts of the anchor rows and the LAA wall (unpublished observation). One further theoretical concern was the de novo formation of thrombi on the atrial surface of the implant which, to our knowledge, has never been reported on the basis of clinical data. Nevertheless, there are conflicting results concerning the formation of neo-endothelium on the device, which is the prerequisite of absent thrombogenicity. In a post mortem analysis, Omran and colleagues demonstrated a PLAATO device completely covered by neoendothelium on the atrial surface one year after implantation (23) whereas we could not find endothelialization of the luminal side 2.5 years after LAA occlusion (24).

The WATCHMAN system

The second device specifically designed for percutaneous transcatheter LAA exclusion is the Watchman Left Atrial Appendage System (Atritech Inc., Plymouth, Minnesota). This is a three-part system consisting of a transseptal sheath, a delivery catheter, and an implantable device. The implant is a selfexpanding nitinol frame structure with fixation barbs and a permeable polyester fabric that covers the atrial side, and is available in diameters from 21–33 mm. The device has been implanted since 2002 in Europe and since 2003 in the United States (25). Two patients experienced device embolization; both were successfully retrieved percutaneously. Five pericardial effusions (two of them needing percutaneous puncture) and one major air embolism occurred without long-term sequelae. The WATCHMAN Left Atrial Appendage System for

Embolic PROTECTion in Patients With Atrial Fibrillation (PROTECT AF) study was designed to demonstrate safety, efficacy, and non-inferiority against chronic warfarin therapy of the WATCHMAN device in patients with nonvalvular atrial fibrillation who are eligible for long-term anticoagulation (26, 27). Of 707 patients enrolled, 463 were randomly assigned to LAA closure and 244 to warfarin therapy. The device was implanted successfully in 91% of the patients in whom it was attempted. Patients were followed for an aggregate of 1065 patient-years. After 6 months, 355 (92%) of the patients with an implanted device could discontinue warfarin therapy. For the control group, plasma warfarin concentration was in the therapeutic INR range (between 2.0 and 3.0) 66% of the time. The rate of ischemic stroke was higher in the intervention group than in the control group. Five patients had periprocedural events, mainly air embolism. After the periprocedural time frame, ischemic stroke occurred in nine patients in the intervention group compared with six patients in the control group. In both groups, all ischemic strokes that had INR measurements available at the time of the event occurred at a subtherapeutic INR level. Hemorhagic strokes were less frequent in the intervention group than in the control group. Five of the six hemorhagic strokes in the control group were fatal and all occurred in patients with therapeutic INR levels. Device embolisation occurred in three patients; one was noted during the procedure and two were discovered by TEE on day 45. One device embolisation was removed percutaneously by use of a vascular snare; the other two patients underwent surgery, one of whom had concomitant aortic valve replacement. The endpoint data of adverse events are shown in table 2 (28). Nevertheless, this initial study shows substantial drawbacks: 12.3% of the patients had serious procedural complications and 2.2% of attempted implantations resulted in cardiovascular surgical intervention because of device-related complications. Therefore, a substantial learning curve associat-

Table 2: Results of the PROTECT-AF-Study: Adverse events.

	Intervention (n=463)	Control (n=244)
Serious pericardial effusion*	22 (4.8%)	0
Major bleeding[†]	16 (3.5%)	10 (4.1%)
Procedure related ischemic stroke	5 (1.1%)	0
Device embolisation	3 (0.6%)	0
Hemorrhagic stroke[‡]	1 (0·2%)	6 (2·5%)
Other[§]	2 (0·4%)	0

*Defined as the need for percutaneous or surgical drainage. [†]Major bleeding is defined as a bleeding event that required at least 2 units of packed red blood cells or surgery to correct. [‡]Of the seven hemorrhagic strokes, six resulted in death (intervention group, n=1; control group, n=5). [§]An oesophageal tear and a procedure-related arrhythmia.

ed with device implantation must be considered. The primary efficacy estimate of the PROTECT-AF-study is less precise due to the small number of participants and nearly 30% of patients receiving devices had a $CHADS_2$ score of 1 and, therefore, were candidates for aspirin therapy without warfarin even without LAA occlusion (29).

The AMPLATZER CARDIAC PLUG system

The AMPLATZER Cardiac Plug (ACP) is a transcatheter, self-expanding device constructed from a nitinol mesh and polyester patch (Fig. 2). The ACP consists of a lobe and a disc connected by a central waist. It is available in eight diameter sizes (16, 18, 20, 22, 24, 26, 28, and 30 mm). The lobe has stabilizing wires to improve device placement and retention. The device has threaded screw attachments at each end for connection to the delivery and loading cable. Radio-opaque markers at each end and at the stabilizing wires assist with fluoroscopic positioning. The ACP is a further development on the basis of the AMPLATZER double-disk septal occluder, which was designed for closure of atrial septal defects and patent foramen ovale. In principle, this device can also be used for occlusion of the LAA, but the results of a feasibility trial were disappointing as an embolization occurred in one out of 16 patients (30). The currently unpublished initial experience with ACP is encouraging. Its implantation is rather technically demanding, but the disadvantages and risks with the PLAATO system are apparently exterminated (Fig. 3). A multicenter prospective registry trial to evaluate the technical and short term success is approaching.
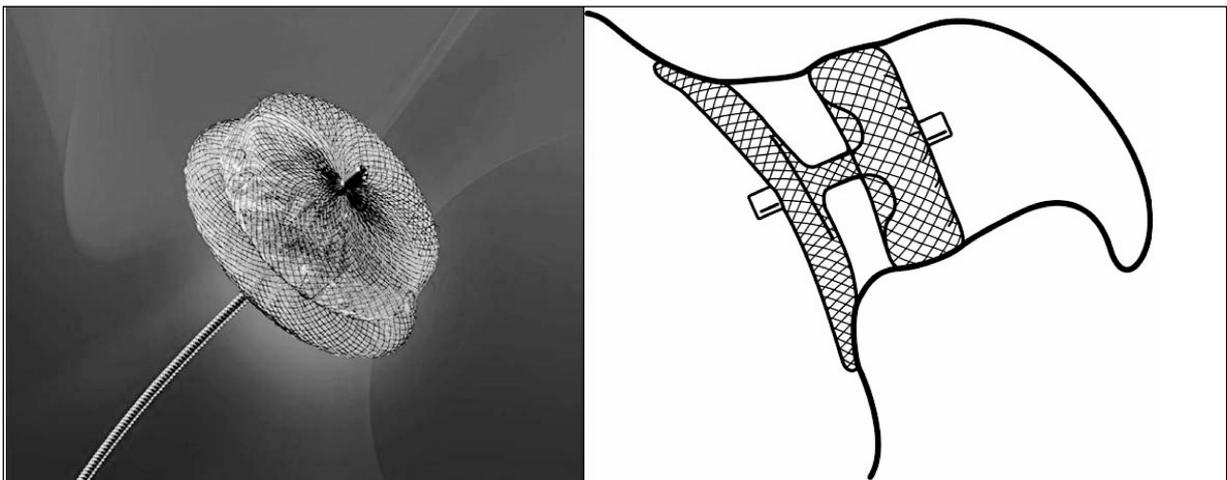

Figure 2. The AMPLATZER Cardiac Plug (ACP). On the right, the ideal position within the LAA is sketched. The lobe of the device is anchored in the "landing zone" 1-2 cm distal of the LAA orifice while the disc fully covers the outer shape and enables endothelialization from the surrounding atrial wall. These images were provided by and are property of AGA, Inc., Minneapolis, U.S.A.
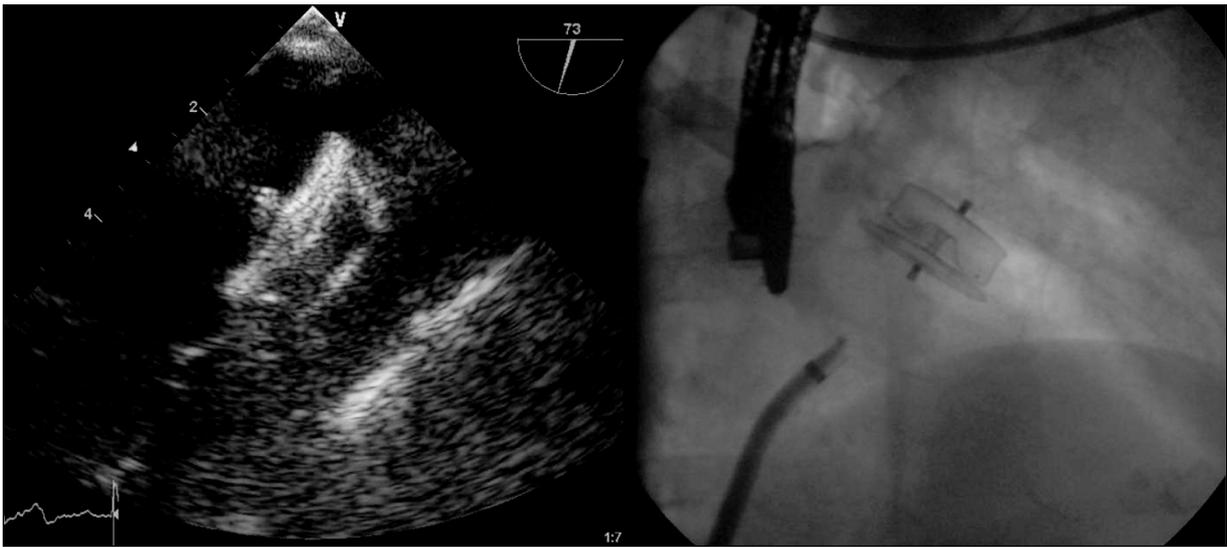
Figure 3. Images of the AMPLATZER Cardiac Plug (ACP) in situ: left) TEE; right) fluoroscopy after implantation.

Concerns about left atrial appendage closure

There are still controversies about the risks and benefit of LAA occlusion for prevention of embolic stroke. Adverse hemodynamic and physiological effects may result from LAA obliteration (31). A potential late complication of LAA occlusion is fluid retention. Human atrial appendages contain 30% of total cardiac atrial natriuretic factor (ANF) (32). Experimental data showed that bilateral appendectomy in dogs eliminates ANF release and blunts renal excretion of sodium and water during acute volume load (33). Clinically evident postoperative fluid retention after the maze procedure with bilateral appendectomy has been reported (34). Another study of the maze procedure observed diminished ANF secretion accompanied by increased need for postoperative diuretics and dopamine (35). However, when the right atrial appendage was preserved, this effect was abolished (36). There are clues, however, that in the natural course of permanent atrial fibrillation, atrial degeneration may at least lead to a decrease of ANF secretion (37). However, many cases of both surgical LAA exclusion with long term follow-up have not shown deleterious results to date. The pathophysiological consequences of implanting a foreign body into the LAA remain to be fully elucidated. Small iatrogenic atrial septal defects can be created after transseptal puncture. They usually disappear within 6 months of the procedure. Furthermore, every implanted foreign material bears the risk of infection (38).

Conclusion

Although AF is well recognized to confer a risk of stroke, this risk is not homogeneous. Chronic oral anticoagulation as the prophylactic measure of choice has a number of major limitations related to its narrow therapeutic range. Occlusion of the LAA orifice, therefore, offers a theoretically appealing way to reduce the incidence of stroke in patients who cannot be anticoagulated or developed stroke despite being on oral anticoagulation. Nevertheless, there are limitations to this approach in that it cannot be easily applied prophylactically to large numbers of patients. The concerns about procedural safety and the need for long-term follow up should be addressed before this potentially important technology is deployed widely.

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