# Left Atrial Appendage Closure with the Amplatzer Cardiac Plug in Patients with Atrial Fibrillation

*Ênio Eduardo Guérios[1,2], Michael Schmid[1], Steffen Gloekler[1], Ahmed A. Khattab[1], Peter M. Wenaweser[1], Stephan Windecker[1] e Bernhard Meier[1]*

*Cardiovascular Department - University Hospital Bern[1], Berna, Suíça; CONCEPT – Centro de Cardiopatias Congênitas e Estruturais do Paraná[2], Curitiba, PR - Brazil*

**Abstract**

**Background: Percutaneous left atrial appendage closure (LAAC) has emerged as an alternative to oral anticoagulation (OA) for prevention of thromboembolic stroke in patients with non-valvular atrial fibrillation (NVAF).**

**Objective: To describe the immediate results and short- to medium-term clinical follow-up (FU) of patients that underwent LAAC with Amplatzer Cardiac Plug (ACP) implantation in a single reference center.**

**Methods: Eighty-six consecutive patients with NVAF, contraindication to OA, and CHADS2 score=2.6±1.2 underwent LAAC with ACP implantation. Clinical and echocardiographic FU was performed at least four months after the procedure.**

**Results: All implants were guided by angiography alone. Procedural success was 99% (one patient suffered a cardiac tamponade requiring pericardiocentesis, and the procedure was waived). There were four major complications (the already mentioned cardiac tamponade, two transient ischemic attacks and one device embolization with percutaneous retrieval) and two minor complications (one pericardial effusion without clinical significance and one non-significant ASD evidenced at FU). There was one in-hospital death after six days, unrelated to the procedure. All other patients were discharged without OA. After 25.9 patient-years of FU (69 patients), there were no strokes and no late device embolization. The LAA was completely closed in 97% of the cases. Six patients showed evidence of thrombus formation on the device, which resolved after three months of OA.**

**Conclusion: LAAC is associated with high success, acceptable complication rates, and promising FU results, and may be considered a valuable alternative or complement to OA for stroke prevention in patients with NVAF. (Arq Bras Cardiol 2012;98(6):528-536)**

**Keywords: Atrial appendage; atrial fibrillation; prostheses and implants; arrhythmias cardiac / complications.**

## Introduction

With the general aging of the population, it is expected that the incidence and prevalence of atrial fibrillation (AF), the most common and epidemiologically most important cardiac arrhythmia, more than double by 2050 [1]. Stroke prevention is a primary goal in AF treatment, since 87% of strokes are believed to be thromboembolic, and patients with AF, whether permanent or paroxysmal, have a five-fold risk of stroke in comparison to a matched population in sinus rhythm[2]. This risk increases with age, from 1.5% / year in the 50-59-year-old age group to 23.5% in the 80-89-year-old age group[1,3]. Accordingly, oral anticoagulation for stroke prevention in AF patients has a class I, level of evidence A recommendation[4].

Oral anticoagulation with warfarin is effective when appropriately used but it requires regular monitoring because of its narrow therapeutic window and significant food and drug interactions. It also imposes life-style modifications[5]. These factors, on top of the potentially life-threatening bleeding complications, lead to under-utilization of oral anticoagulation, mainly in the elderly population, where it is most needed.

The fact that in patients with non-valvular atrial fibrillation (NVAF), over 90% of thrombus accumulation originates in the left atrial appendage (LAA,[6] , provided the rationale for occluding the LAA as an alternative treatment to oral anticoagulation for stroke prevention in these patients. In addition to surgical technique[7], percutaneous methods of LAA occlusion were developed, these being the dedicated Watchman (Boston Scientific - Atritech, Plymouth, MN) and the Amplatzer Cardiac Plug [ACP] (AGA Medical Corp., Minneapolis, MN) devices approved for clinical use. This report summarizes the largest up to date published single-center experience of ACP implantation for occlusion of the LAA. It describes the immediate results and the short- to medium-term clinical follow-up of the patients that underwent this procedure.

**Mailing Address: BernhardMeier MD •**
Bern University Hospital - 3010 Bern, Switzerland
E-mail: bernhard.meier@insel.ch
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## Methods

### Population

Between January, 2009 and September, 2011, 86 consecutive patients with permanent or paroxysmal NVAF, at least one additional risk factor for thromboembolic events, absence of thrombus in LAA, and contra-indication or aversion to chronic oral anticoagulation underwent percutaneous implantation of an ACP for LAA occlusion at Bern University Hospital, Switzerland. Table 1 depicts the clinical and pre-interventional echocardiographic and angiographic features of these patients.

### Description of the device

The ACP is a self-expandable nitinol device with a polyester patch within, formed by three parts: a cylindrical lobe with a fixed length of 6.5 mm, to which diameter (16 – 30mm, stepwise by 2mm) the prosthesis size refers; an occlusive disc, 4mm larger than the 16 – 22mm prosthesis, and 6mm larger than the 24 – 30mm devices; and a flexible central connector pine. There are six pairs of barbs attached to the lobe and directed to the disc, all identified by radiopaque marks, to enhance retention of the lobe in the LAA (Figure 1).

### Device implantation and follow-up protocol

Before intervention, a pre-evaluation TEE was performed to exclude thrombi in the LAA, oral anticoagulation was suspended, and an antibiotic prophylaxis with cefuroxime was given. All procedures were performed via femoral access, under local anesthesia, and were guided exclusively by angiography (biplane in most cases). Heparinization with 5000 units of heparin was given at the beginning of the procedure. Access to the left atrium was gained through transseptal puncture or passage through a preexisting patent foramen ovale (PFO) or atrial septal defect (ASD -Table 1). After angiography and measurement or estimation of the LAA diameter at the intended implantation site in at least 2 different projections (Figure 2), a device with a diameter at least 4 mm larger than the landing zone diameter was chosen for implantation. In patients with paroxysmal AF in sinus rhythm at the time of implantation, these measurements were taken during atrial diastole. Once the ACP was implanted and some compression of the lobe by the LAA wall was observed (Figure 3), device stability was tested by gently pulling and releasing the delivery cable (Minnesota wiggle maneuver). The lobe has to move in conjunction with the LAA while the disk moves freely with the wire. Control angiographies were performed in various projections (depicting the lobe separated from the disk) prior to device release. In case of unsatisfactory positioning or anchoring, the prosthesis was recaptured, preferentially except for the distal part of the lobe and redeployed in a different angle, or changed for a more suitably sized device. Once adequately positioned and fixed, the ACP was released and a final angiography was performed. Patients with a concomitant PFO or ASD had their defects closed by reloading the same delivery cable and sheath with an adequate septal occluder. Unless an arterial puncture had been performed simultaneously, patients themselves performed compression of the femoral vein. They were given clopidogrel 75 mg daily for 1 month and acetylsalicylic acid 100 mg for 3-4 months, or lifelong if there was significant coronary artery disease. A control TTE was performed before discharge. The patients received two additional doses of cefuroxime if discharged home the day after the intervention and one if discharged the same day. Endocarditis prophylaxis was recommended for a few months, and clinical control, a new TEE for device, and occlusion control were scheduled for 3-6 months after implantation (Figure 4).

**Table 1 - Baseline clinical and echocardiographic features**

| Characteristic | Studied population (n = 86) |
|---|---|
| Age (years) | 72.2 ± 10.1 |
| Male gender (%) | 65.1 |
| Permanent / paroxysmal AF (%) | 57.0 / 43.0 |
| **$CHADS_2$-Score** | 2.6 ± 1.2 (1 – 6) |
| C (%) | 17.4 |
| H (%) | 82.6 |
| A (%) | 52.3 |
| D (%) | 26.7 |
| S (%) | 37.2 |
| $CHA_2DS_2$-VASc Score | 3.6 ± 1.6 (1-7) |
| **Contraindication for oral anticoagulation (%)** | |
| Relevant bleeding or high risk of bleeding | 69.8 |
| Frequent falls | 8.1 |
| Labile INR | 4.7 |
| Aversion to oral anticoagulation | 15.1 |
| Other | 2.3 |
| LVEF (%) | 55.5 ± 9.9 (30 – 70) |

*AF- atrial fibrillation; C- congestive heart failure ; H- systemic hypertension; A- age≥75 years; D- diabetes mellitus; S- previous stroke ; INR- International Normalized Ratio ; LVEF- left ventricular ejection fraction*

### Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Categorical variables are reported as counts and percentages.

## Results

Table 2 compares the results obtained in this population to those achieved in the multicenter European experience with ACP implantation, the largest casuistic study published so far in which this device was used[8]. Procedural success was obtained in 85 of the 86 treated patients (99%). In the only unsuccessful case, the left atrium was accessed through a PFO, instead of a transseptal puncture, and the orientation of the PFO tunnel rigidified by an ASD Amplatzer occluder placed years earlier rendered the coaxialization of the delivery sheath in the LAA difficult. After repeat attempts at implantation of

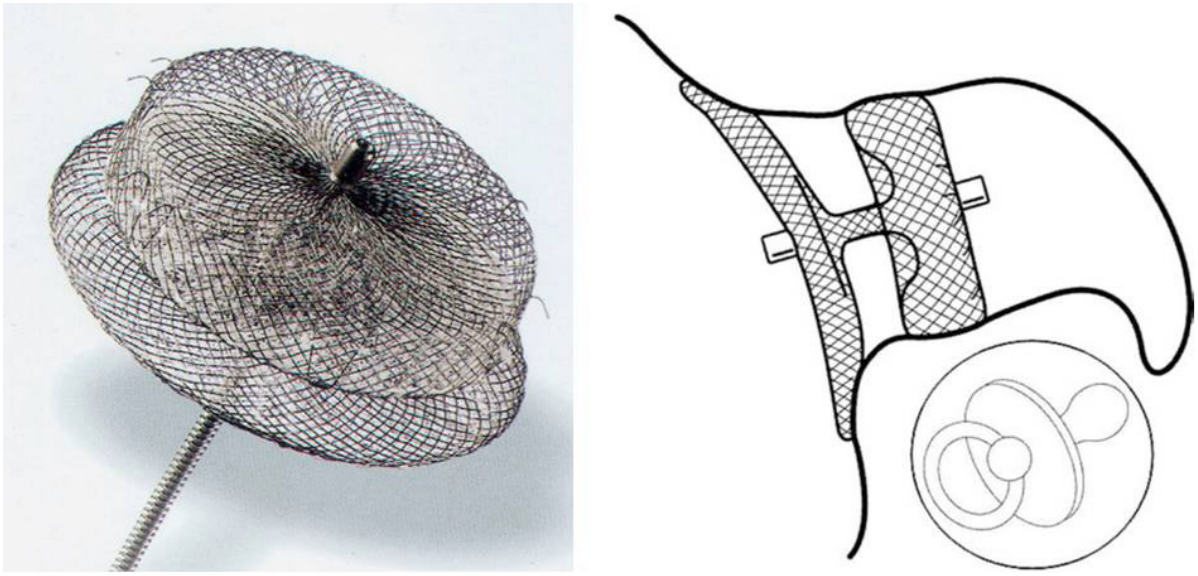

Figure 1 - *The Amplatzer Cardiac Plug (1a) and the "pacifier principle" (1b).*

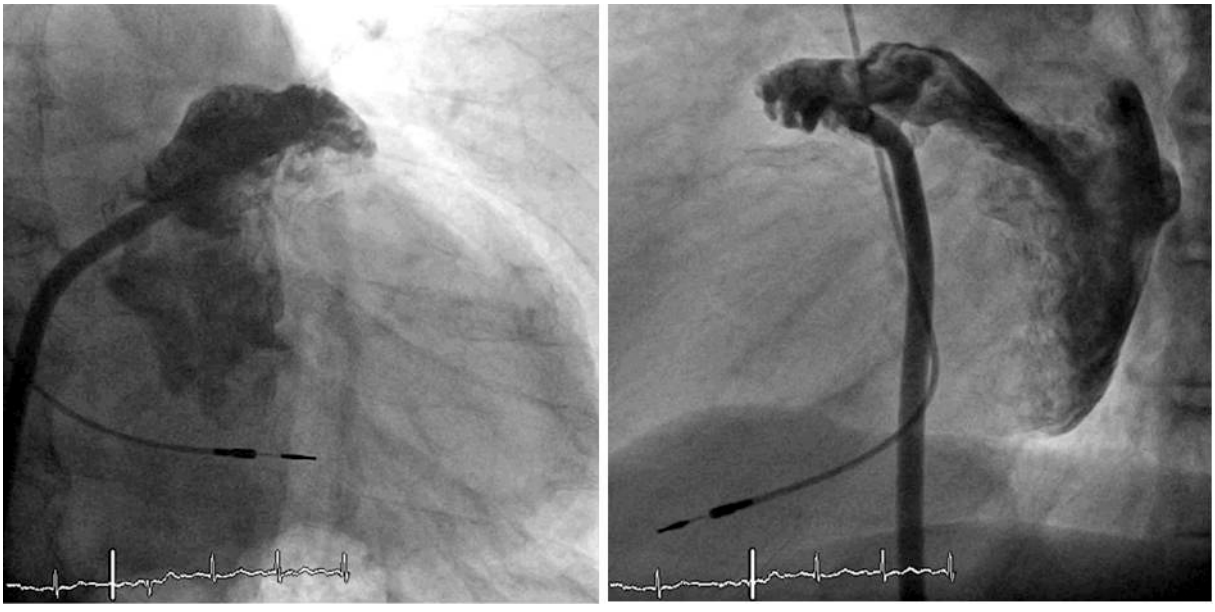

Figure 2 - *Angiography of the LAA, RAO projection (2a) and LAO projection (2b).*

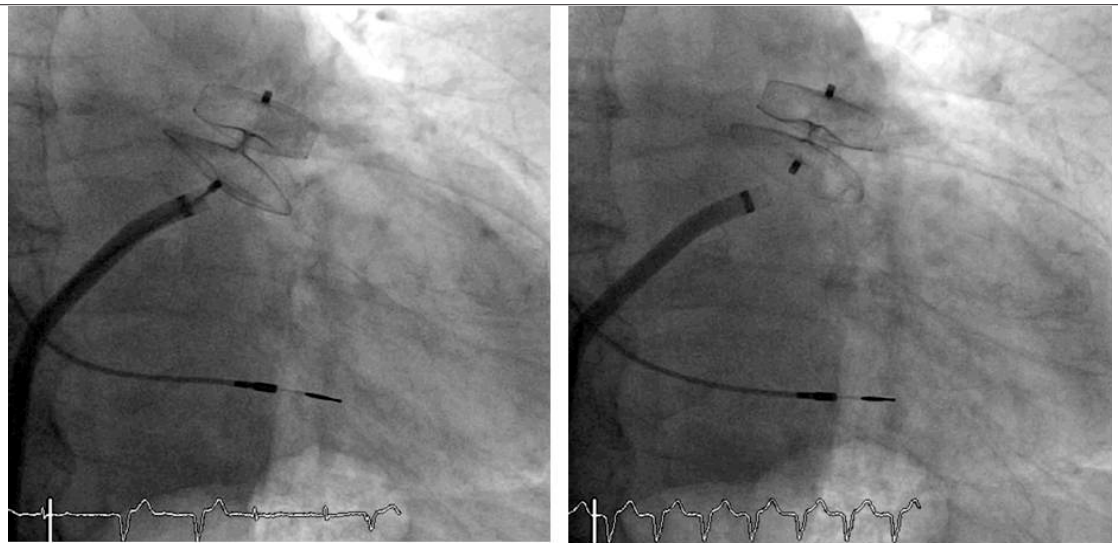

Figure 3 - *Implantation (3a) and release (3b) of the Amplatzer Cardiac Plug in the left atrial appendage.*

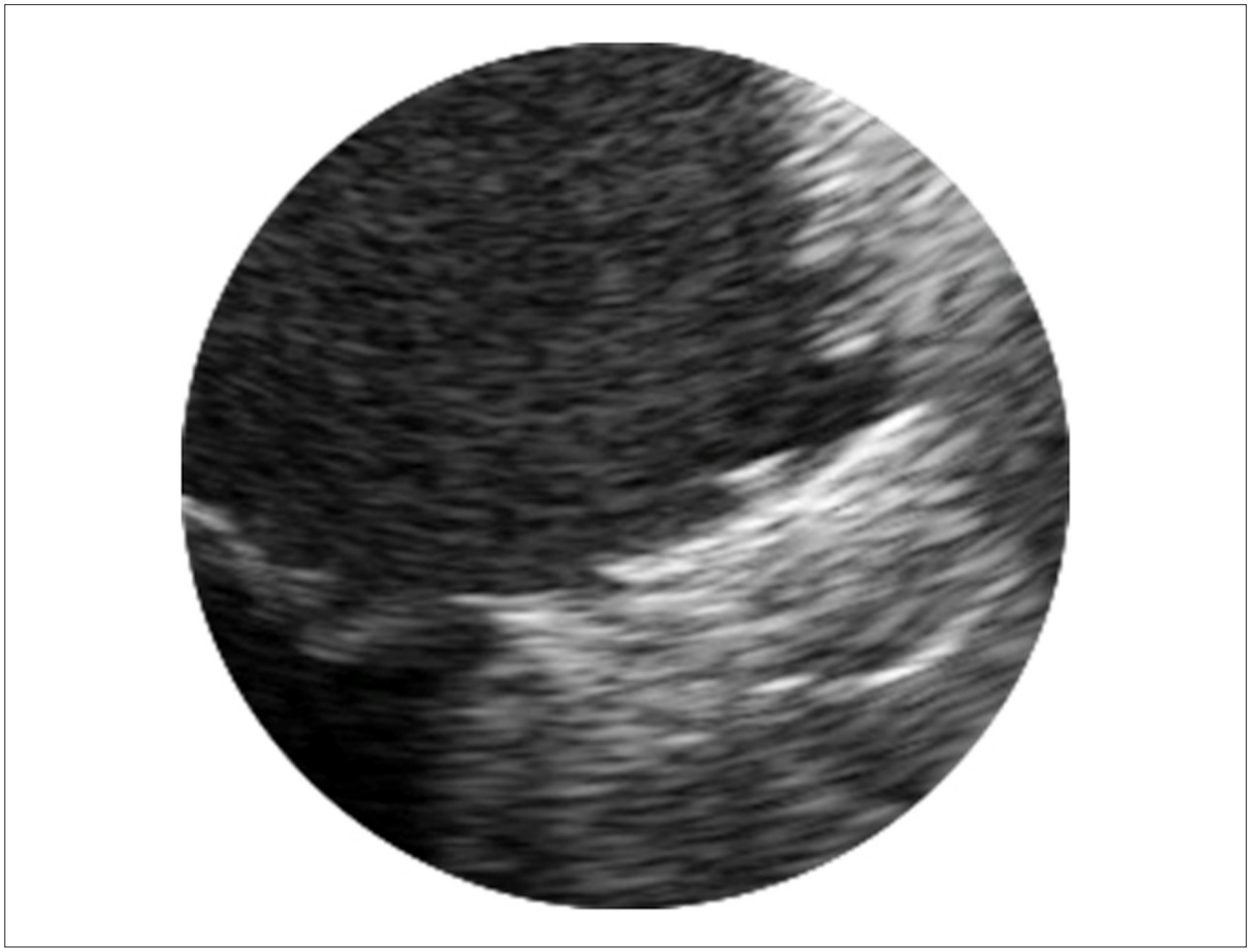

Figure 4 - *Control TEE four months after left atrial appendage occlusion with the Amplatzer Cardiac Plug.*

**Table 2 - Procedural results**

| | Studied population | Multicentric European Experience[8] |
|---|---|---|
| Number of patients | 86 | 143 |
| **Acess to left atrium** | | |
| Transseptal (n, %) | 56 (65.1) | 121 (84.6) |
| PFO (n, %) | 27 (31.4) | 17 (11.9) |
| ASD (n, %) | 3 (3.5) | 3 (2.1) |
| LAA orifice (angiography – mm) | 19.5 ± 4.3 | 19.7 ± 4.3 |
| Success (%) | 99 | 96 |
| ACP size (mm) | 23.1 ± 3.9 | 22.2 ± 3.6 |
| **Associated procedures** | | |
| PFO occlusion (n, %) | 27 (31.4) | 10 (7.0) |
| ASD occlusion (n, %) | 3 (3.5) | 1 (0.7) |
| PCI (n, %) | 22 (25.6) | n.a. |
| TAVI (n, %) | 5 (5.8) | n.a. |
| **Complications** | | |
| Periprocedural cerebral events (n, %) | 2 (2.3) | 3 (2.1) |
| Cardiac tamponade (n, %) | 1 (1.1) | 5 (3.5) |
| Pericardial effusion (n, %) | 1 (1.1) | 4 (2.8) |
| Device embolization (n, %) | 1 (1.1) | 2 (1.4) |

*PFO – patent foramen ovale ; ASD – atrial septal defect; LAA – left atrial appendage; ACP - Amplatzer Cardiac Plug; PCI - percutaneous coronary intervention; TAVI – transcatheter aortic valve implantation; n.a.- not available*

differently sized ACPs, a pericardial tamponade requiring emergency pericardial drainage ensued, and the LAA closure was waived. The PFO was closed and the patient was discharged the following day.

Eighty-seven devices were implanted in the 85 patients in whom success was achieved, as two patients received two devices each. In 81 of them adequate positioning and anchoring was obtained with the first device chosen. In the remaining four patients the initial prosthesis was changed for a more suitably sized one. In two cases this was a larger one and in two cases a smaller one. In two patients, both with a bilobulated LAA, an incomplete closure of the LAA was observed after device implantation. In one of them, an additional ACP was implanted, and in the other one the remaining part of the LAA was closed with an Amplatzer vascular plug, with a good final result in both cases. One ACP embolized into the aorta about 15 minutes after being released. This was observed during an incidental percutaneous coronary intervention (PCI) still ongoing, and the device was percutaneously retrieved and replaced by a smaller ACP. The patient was discharged the day after the procedure and the stable position of the second device was ascertained by echocardiography before dismissal. In addition to the pericardial tamponade described above, in one patient a small pericardial effusion with no hemodynamic compromise was observed, with total resolution during follow-up. One patient who underwent simultaneous PCI and TAVI developed acute renal failure with spontaneous recovery. There were two periprocedural cerebral events, one due to air embolism and the other most probably thromboembolic, both without clinical sequelae at the time of hospital discharge the following day.

Forty-eight patients (55.8%) underwent a simultaneous intervention (ASD or PFO closure, PCI, or TAVI, some in various combinations) at the time of LAA closure. The mean total administered volume of contrast medium was 253.5±114.3 ml, and the mean total fluoroscopy time 19±12 min.

One patient with a bleeding gastrointestinal tumor prohibiting anticoagulation died due to uncontrollable gastrointestinal bleeding six days after ACP implantation. Among the remaining 84 eligible patients, clinical and echocardiographic follow-up was obtained in 69 (82.1%). After 25.9 patient-years there were no strokes and no peripheral thromboembolizations. There were two late deaths, one due to respiratory failure secondary to bronchopneumonia. The other death was cardiac in a patient with known severe three-vessel coronary artery disease. In all but two patients, follow-up TEE demonstrated total occlusion of the LAA. In six patients, a non-mobile thrombus was detected on the device. All of them disappeared on repeat TEE done after reinstitution of oral anticoagulation for three months. In four patients, the presence of a fixed thrombus on the device could not be ruled out. Three of them remained on acetylsalicylic acid. In the fourth one warfarin was resumed and maintained for four months, with no change being observed in the control TEE after

this time. In one patient a persistent small, hemodynamically non-significant left-to-right shunt at the transseptal puncture site was observed during late follow-up.

## Discussion

Adequate levels of oral anticoagulation with warfarin proved effective to reduce stroke by 64% in NVAF patients[9]. This means that in a third of patients, the therapy is ineffective. Moreover, multiple studies, including the SPORTIF series, have shown that up to 29% of the international normalized ratios (INRs) are subtherapeutic, 15 – 20% are supratherapeutic[10], and that even in patients with optimal drug compliance, the INR is in its therapeutic range only about 60% of the time[11]. It must also be considered that the benefits of anticoagulation are not achievable without incurring the risk of bleeding. There is an annual risk of 3% for major bleeding and 9.6% for hemorrhagic complications in general with the use of warfarin[12]. Accordingly, its administration is contra-indicated in up to 44% of the patients with AF, especially those with recurrent major bleeding or previous cerebral bleeding[2]. Other issues to keep in mind are the difficult administration profile of the drug and the high rates of patient noncompliance due to the necessary life-style modifications. In clinical practice, therefore, the level of prescription of warfarin varies from 23% to 66% in high-risk patients and 8% to 49% in moderate risk patients[5].

New anticoagulant drugs proved to be as or more effective than warfarin, with a safety profile which is at least comparable. Dabigatran, an oral direct thrombin inhibitor, administered at a dose of 150mg twice daily, significantly reduced the rate of peripheral embolization, with similar rates of major bleeding. When given at a dose of 110mg twice daily, it showed similar rates of systemic embolism and significantly lower rates of major hemorrhage[13]. Rivaroxaban, an oral direct factor Xa inhibitor, given in a 20mg dose once daily, was non-inferior to warfarin in terms of peripheral embolism and bleeding complications as a whole, and was superior with regard to the occurrence of fatal and cerebral bleedings[14]. Apixaban, another oral direct factor Xa inhibitor, when 5mg twice daily was administered, was superior to warfarin with regard to both the prevention of cerebral and peripheral embolism and the occurrence of major bleeding complications[15]. These drugs, however, also have significant drug interactions (amiodarone, verapamil, quinidine) and some side effects, especially dyspepsia associated with dabigatran. Some are contraindicated in patients with liver or renal failure; they should be administered with caution in frail patients and in patients older than 75 years, due to enhanced bleeding risks; and there is currently no tested antidote that can be given in cases of major bleeding or emergency surgery[16-18]. Apart from these unfavorable characteristics and from their markedly higher cost when compared to warfarin, neither of these drugs is free of bleeding risk, especially in elderly patients and patients with previous major bleedings, and noncompliance, well illustrated by the high rates of drug discontinuity in the RE-LY (21% on dabigatran and 17% on warfarin group)[13,19] and ARISTOTELE (25% on apixaban and 27% on warfarin group) trials[15]. To overcome these limitations, non-pharmacologic therapeutic strategies for prevention of stroke in NVAF continue to be warranted.

The LAA, a remnant of the embryonic left atrium, is a (multi)lobulated structure of variable anatomy, made of trabecules of pectinate muscles that form crypts in between them. The asymmetric junction that connects it to the left atrium is usually narrower than its body, and is located typically anterior and inferior to the left superior pulmonary vein[2,20]. In AF, the LAA structure and the marked reduction of its flow velocities and ejection fraction provide a rich milieu for blood stasis and thrombus formation, making the LAA the most important source of cerebral and peripheral emboli. Accordingly, in a review of 23 studies in which the LAA was examined by autopsy, TEE, or direct intra-operative inspection, intracardiac thrombus was encountered in 17% of NVAF patients, 91% of which in the LAA[6]. That is why the LAA has been deemed "our most lethal attachment" [21], and its occlusion was proposed as a valuable alternative to anticoagulation for embolism prevention in patients with NVAF. LAA occlusion can be performed in three distinctive ways: surgical ligation or exclusion, concomitant to valvular surgery, coronary revascularization, or MAZE procedures; percutaneous epicardial exclusion, either thoracoscopic or via the pericardial sac, a new method that mimics surgical ligation; and percutaneous endovascular occlusion.

Despite the proven effectiveness of surgical occlusion of the LAA, and its inclusion in the guidelines for mitral valve surgery [22], its main limitation is high incomplete occlusion rates, varying from 10%-80%, depending on the employed technique and on the surgeon's experience. The highest success rate of complete occlusion is achieved with LAA excision, and the lowest, with exclusion by suture or staple ligation[7,23].

The familiarity, ease of implantation, and low thrombogenicity of the Amplatzer devices led to the first LAA closure series with an Amplatzer Septal Occluder in Bern, Switzerland. A study describing the results of such off-label procedures in 16 patients showed one device embolization and complete LAA occlusion in all remaining patients after a 5 patient-years follow-up[24]. However, a longer-time registry demonstrated that the use of septal occluders for LAA occlusion was associated with lower success and higher embolization rates when compared to the implantation of dedicated devices.*

The first dedicated device for LAA occlusion was the PLAATO System (ev3, Plymouth, MN, no longer available), first implanted in 2001[25]. It consisted of a self-expandable nitinol cage covered with a non-thrombogenic PTFE membrane. Short-term as well as 5-year results after PLAATO system implantation were good, with a 42% reduction of the stroke rate predicted by the $CHADS_2$ score (3.8% / year vs. 6.6% / year)[26,27].

The Watchman device is a self-expandable open-cage nitinol structure with fixation barbs, and a permeable polyester membrane over its atrial surface. Unlike the PLAATO system, the Watchman device should be implanted more distally into the LAA body, and warfarin should be administered for 6-12 weeks after device implantation[20,28]. The multicenter

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PROTECT-AF trial proved the non-inferiority of Watchman device implantation in comparison to chronic warfarin therapy in patients with NVAF, with a major event rate (stroke, systemic embolization, or cardiovascular or unexplained death) of 3.0 / 100 patient-years *versus* 4.9 / 100 patient-years, but at a cost of more complications in the group randomized to device implantation (7.7% vs. 3.7%)[29]. However, the incidence of procedure-related complications, mainly pericardial effusions and strokes secondary to air embolization, significantly decreased along the learning curve of the operators[30].

There are many structural differences between the Amplatzer Cardiac Plug and the Watchman device. The most important refers to the occlusive disc. The Watchman device is basically a plug that should be precisely implanted to avoid both its protrusion into left atrium as well as the creation of a cul de sac where thrombus may form. The ACP consists of two parts joined by a central pin. Being short, the ACP can be implanted in a shallow position in the LAA, as only the proximal 2 cm are needed for its occlusion. The occlusive disk permits the complete closure of the LAA orifice ("pacifier principle"[24] Figure 1), surpassing the problems that the myriad of LAA anatomical variations, mostly distally located, may impose. The flexibility of the central pin allows a misalignment between the disc and the lobe of the ACP after implantation, adapting the prosthesis to the LAA axis rather than distorting it[31]. Also, the more anatomic surface that derives from the occlusive disc implantation results in a rheology that is closer to normal and also in a more predictable endothelization[32]. Another significant difference between the devices is the fabric covering of the Watchman device, which is permeable to blood, hence the recommendation to continue warfarin therapy for six weeks after implantation. The ACP, on the other side, seems to permit cessation of anticoagulation immediately after its implantation[8]. Moreover, the kit used for implanting the ACP features a double-curved sheath, facilitating coaxial intubation of the LAA, and it is compatible with other Amplatzer devices, making simultaneous closure of atrial shunts straightforward by simply reloading the sheath with an additional device[33]. These features associated with the familiarity with the Amplatzer technique make ACP implantation user-friendlier in comparison to the Watchman device.

Regardless of the implanted device, however, percutaneous LAA occlusion is not a risk-free intervention, given the intrinsic structural vulnerability of the LAA and the possibility, albeit low, of device embolization, or embolization of preexisting thrombi not adequately identified by TEE or preliminary contrast medium injection into the LAA. Therefore, the procedure must only be indicated after assessing the risk of stroke (estimated by the $CHADS_2$ and the $CHA_2DS_2$-VASc scores[34,35]), risk of bleeding (estimated by the HAS-BLED score[36]), risk of the intervention and quality of life.

The mean $CHADS_2$ score of 2.6 of the studied cohort projects a yearly occurrence of 5.2% of embolic events[4,34]. No events were observed during the follow-up period. In addition, the total complication rate in this high-risk patient series was lower than that reported in the multicentric European experience with the ACP[8] (table 2), as well as in the PROTECT-AF trial[29] but higher than CAP registry with the Watchman device[30]. Similarly to all interventional procedures, the learning curve plays an essential role in LAA closure.

The empirical post-implantation medication protocol, namely dual antiplatelet therapy with no further oral anticoagulation, was adopted based on the legendary low thrombogenicity of the Amplatzer septal ocluder devices[37]. It can be argued, however, that the thrombogenic potential of a device occluding a septal defect in sinus rhythm is lower than that related to one in fibrillating LA[8]. Hence, the late echocardiographic finding of device-associated thrombi in some patients came as no surprise, taking into account the high $CHADS_2$ score of this population, and being aware of previous reports showing similar findings[38]. Retrospectively reviewing the images of these procedures it could be noted that, in 70% of them, the disk of the occluder was implanted somewhat inside the LAA rather than at its ostium, as would be ideal. However, these thrombi were firmly attached to the device. They generally disappeared after temporary reinstitution of oral anticoagulation, with no embolic events. The frequency of this finding in the growing experience with ACP implantation may suggest, however, a need to adapt post-implant medication protocols.

In summary, these data allow for concluding that ACP implantation for LAA occlusion is associated with high success and acceptable complication rates, and promising follow-up results. As with every interventional procedure, however, the clinical benefits that derive from the intervention depend on careful patient selection, on having passed the learning curve, and on well-defined, adequate pre- and post-implantation protocols.

### Potential Conflict of Interest

The author Ahmed A. Khattab states he serves an attorney-in-fact for ST. JUDE -AGA. Author Bernhard Meier states he receives consulting and lecturing fees from ST. JUDE - AGA.

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### Study Association

This study is not associated with any post-graduation program.

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