



Cardiac Plug I and Amulet Devices: Left Atrial Appendage Closure for Stroke Prophylaxis in Atrial Fibrillation

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Abstract

Percutaneous left atrial appendage (LAA) occlusion has emerged as an exciting and effective modality for stroke prophylaxis in patients with non-valvular atrial fibrillation who are deemed too high risk for anticoagulation with warfarin or newer anticoagulants. The Amplatzer devices have been used in LAA occlusion for more than a decade, starting with off label use of an atrial septal occluder device for LAA occlusion. This was followed by introduction of a dedicated Amplatzer cardiac plug (ACP) 1 for LAA occlusion, and more recently, the second generation Amulet device, with reported better stability enhancing features, has been introduced. Both these devices are widely used outside the United States, however in the US only the WATCHMAN device has been FDA approved. Unlike the WATCHMAN device, where the evidence is continuously building as the data from two pivotal randomized controlled trials are emerging, most of the evidence for ACP devices is from pooled multicenter registry data. In this article, we review the device design, implantation techniques and the most recently published evidence for both the Amplatzer cardiac plug 1 and the newer Amulet device. Our goal is to summarize the most recent literature and discuss the current role of the Amplatzer devices in the exciting and rapidly growing field of percutaneous LAA occlusion.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia to affect the population, with some estimates placing its prevalence up to 2% in the general population.¹ Stroke is the most common morbidity associated with atrial fibrillation, especially in the elderly where up to a third of strokes may be attributed to atrial fibrillation.^{2,3} Data from the European Community Stroke project showed that strokes associated with atrial fibrillation have a significantly worse outcome both in terms of quality of life and mortality.⁴

Hence, stroke prophylaxis is a cornerstone of management of atrial fibrillation. Anti-coagulation with warfarin has been the benchmark of stroke prevention in atrial fibrillation. Current use of warfarin as a stroke prevention agent in patients with AF is associated with a decreased rate of residual stroke or systemic embolism (1.6% per year).⁵ However, over the past few years, newer oral anti-coagulants (NOAC) – factor Xa inhibitors and direct thrombin inhibitors have emerged as exciting alternatives to warfarin to achieve the same goal.⁶ The most recent guidelines recommend anti-coagulation therapy for everyone with non-valvular atrial fibrillation with prior

stroke, transient ischemic attack (TIA), or a CHA₂DS₂-VASc score of 2 or greater (CHA₂DS₂-VASc indicates Congestive heart failure, Hypertension, Age \geq 75 years (doubled), Diabetes mellitus, prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex).^{7,8} However, all forms of anticoagulation increase the risk of both intracranial and extra cranial bleeding, and approximately 30% to 50% of patients with AF are ineligible to receive anticoagulation.⁹

The left atrial appendage (LAA) is an out-pouching structure in the adult left atrial chamber and persists as a remnant of the embryonic left atrium. In atrial fibrillation, the LAA acts as a site of blood stasis which is thought to significantly increase the risk of thrombogenesis and subsequent systemic embolization of a clot commonly leading to ischemic strokes.¹⁰ Current estimates put the risk of thrombus formation at 15% in patients with non-valvular atrial fibrillation and the LAA as the site for clot formation in >90% of these cases.^{11,12}

The surgical approach of excluding the left atrial appendage from the circulation has been previously explored, and it was fraught with high rates of incomplete closure, which in turn led to increased stroke risk.¹³ Percutaneous left atrial appendage occlusion devices offer a viable alternative to oral anticoagulants in patients who are deemed high risk for bleeding or are otherwise ineligible to receive anti-coagulation. In the following sections we extensively review evidence behind two generations of one such device, designed exclusively for the minimally invasive endocardial approach towards closure of the left atrial appendage. The device includes the first generation Amplatzer cardiac plug (ACP) and an improved second generation

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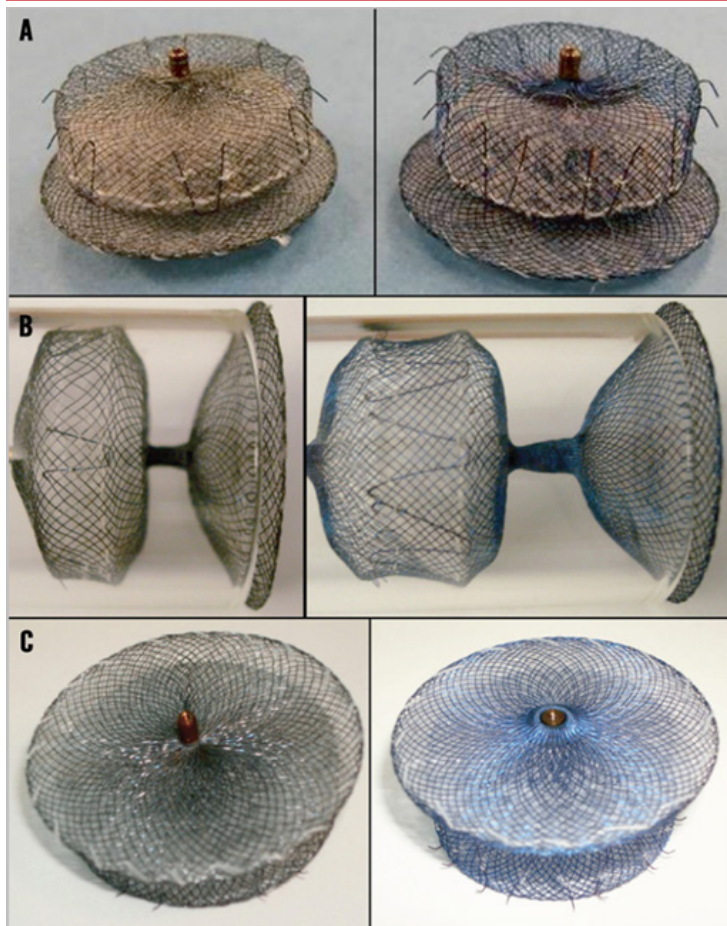


Figure 1:

Comparison between the ACP 1 and the ACP 2. Comparison between the ACP 1 (left) and the ACP 2 (right) highlighting the greater diameter of the ACP 2, distal lobe (A and B) and waist (B), the increased number of stabilizing wires (A) and the inversion of the disc endscrew (C). (Adapted DIRECTLY from Friexa et al)¹⁴ PERMISSIONS PENDING

Amulet device.¹⁴ In this review we summarize the indications, device design, implantation technique, current literature on outcomes and future scope of the Amplatzer devices.

Device Design

Amplatzer Cardiac plug (ACP) 1

The system consists of a delivery catheter, a deployment wire and the self-expanding plugging device made of nitinol mesh with two polyester patches sewn to a lobe in the distal part and a disc in the proximal segment which are connected via an articulated waist. The design is aimed at sealing the body and ostium of the LAA, respectively, using the “pacifier effect.” The lobe is usually implanted 10 mm inside the LAA body, and the anchoring mechanism is aided by six pairs of stabilizing wires. The device is available in 16, 18, 20, 22, 24, 26, 28 and 30 mm (with 9, 10 and 13 F sheaths) corresponding to LAA diameters of 12.6 to 28.5 mm. The device has to be manually loaded into the delivery cable before implantation.

Amulet

The Amulet or ACP 2 is the second generation of the ACP device which retains the basic structure of ACP 1 with some significant improvements.¹⁴ The device has a pre-loaded system eliminating the need for manual loading and also has stiffer stabilizing wires. It is also available in larger disc diameters, longer lobe and waist length,

thus usually implanted approximately 12 mm inside the LAA cavity. Larger sizes of 31mm and 34mm are also available, comprised of more stabilizing wires. The inner wire allows re-evaluation of the device orientation thereby allowing more room for post-deployment adjustment. The Amulet device, as of this writing, is undergoing a modification of its delivery systems with a plan of a relaunch soon¹⁵ (Figure 1).

Guidelines for Percutaneous LAA Occlusion

There is a wide variation in the indications for Percutaneous LAA occlusion, depending on the region of the world and the existing regulatory framework. The recent AHA/ACC atrial fibrillation guidelines do not mention percutaneous LAA occlusion, as the WATCHMAN device was just recently approved by the food and drug administration (FDA).⁷ All device implantations in the United States have been experimental in patients considered high risk for bleeding with anticoagulation. The Amplatzer Cardiac Plug device is currently not approved for use in the USA on a commercial basis. However, the European Society of Cardiology in its focused update to atrial fibrillation guidelines in 2012 offered a class IIb recommendation for percutaneous LAA closure (Level of evidence B) in patients with high stroke risk who are otherwise ineligible for long term oral anticoagulation.⁸ There are no specific data on comparability of different percutaneous devices; hence there are no specific guidelines to prefer one device over the other. The ACP received the CE mark in December 2008, and the Amulet received it in January 2013. In a recent pooled analysis of multicentric registries evaluating the ACP device, the most common indications for LAA occlusion were previous major bleeding (47%), high bleeding risk (35%), stroke on Warfarin (16%), and coronary stents (22%). Notably, most patients had >1 indication.¹⁶

Implantation Technique

Baseline Imaging For Planning The Procedure

Trans-Esophageal Echocardiography

Almost all operators prefer to define LAA anatomy via a prior TEE. This is paramount for excluding any pre-existing LAA thrombus and also to aid in selection of the right device size. It is highly recommended to measure the LAA at both the long axis (120 to 150 degrees) and the short axis (30 to 60 degrees). The echocardiographic orifice is defined as the line from the pulmonary vein ridge to the circumflex artery. The deployment zone (“landing zone”) for the ACP 1 is approximately 10mm inside the orifice at a right angle to the neck axis. However, for the Amulet, the deployment

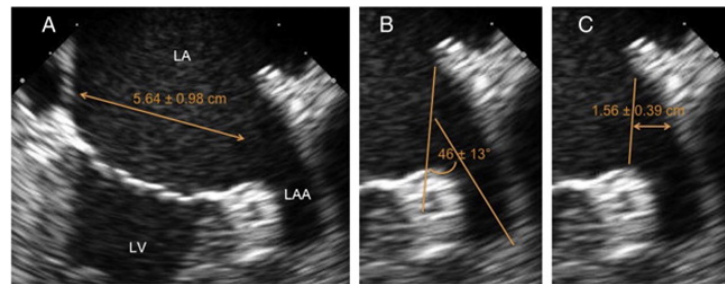


Figure 2:

Transesophageal echocardiogram assessment of the LAA. Evaluation of the septum-LAA ostium distance (A), angle of the appendage (B), and distance from the ostium to the first bend of the appendage (C). LA: left atrium; LAA: left atrial appendage; LV: left ventricle. (Adapted with permission from Krishnaswamy et al)¹⁹

Table 1: Summary of procedural events in studies reporting implantation of Amplatzer Cardiac Plug 1 device

Author	Region	Duration	Number	Procedural success, %	Ischemic Stroke, %	Embolization rate, %	Severe Pericardial effusion, %
Park et al ²⁸	Europe	2008-09	143	96	2.1	1.4	3.5
Lam et al ²⁹	Asia-Pacific	2009-10	20	95	0	0	0
Damonte et al ⁴⁰	L. America	2009-12	60	100	0	1.7	6.6
Lopez-Minguez et al ³⁰	Europe	2009-11	35	97	0	0	0
Streb et al ³¹	Europe	2009-12	21	95	0	0	4.8
Bethencourt et al	Europe	2009-11	213	93	0.5	1.9	1.4
Nielsenspach et al ²²	Europe	2008-12	120	98	0.8	1.6	1.6
Urena et al ³²	Canada	2009-11	52	98	0	1.9	0
Plicht et al ³³	Europe	2009-11	20	100	0	0	5
Meerkin et al ³⁴	Israel	2009-12	100	100	0	0	1
Santoro et al ³⁵	Europe	2009-12	134	93	0	0	2.4
Kefer et al ⁴¹	Europe	2009-12	90	99	0	0	3.3
Park et al ⁴²	Europe	2009-11	204	97	0	1.5	2.4
Gloeckler et al ¹⁷	Europe	2012-13	50	98	0	4	6

zone is approximately 12-15 mm from the orifice (figure 2).¹⁷

Cardiac Computed Tomography

Cardiac CT is emerging as a promising alternative imaging modality. It has an added advantage of a better 3 dimensional resolution.¹⁸ However, the experience in pre-procedural imaging is limited, as of this writing. Cardiac CT may play a vital role in determining the relationship between the LAA and surrounding crucial structures including the left superior pulmonary vein and the left aortic sinus (figure 3). Efforts are currently underway to develop cardiac CT protocols for adjunctive imaging prior to the procedure to aid in procedural planning.¹⁹ Autopsy studies have demonstrated that the LAA ostium can be located at different levels relative to the left superior pulmonary vein ostium.²⁰ There is also ongoing work on the role of Cardiac CT in post-procedural surveillance.²¹ However, at present TEE is the modality of choice for pre-procedural planning in most centers, with cardiac CT at best being a useful adjunct.

Imaging during the procedure

TEE remains the intra-procedural modality of choice for most operators reporting implantation of ACP devices with a few exceptions.²² The procedure is performed both under local and general anesthesia depending on the institutional preferences. It is generally recommended that all ACP device implantations should be done under TEE guidance in the setting of general anesthesia, with the exception of centers that are highly experienced with this technique.

Accessing the LAA

The femoral vein is the access site, right being preferred over the left, in most of the reported studies for ACP device implantation. The rationale is that approach from the right side provides a more direct access for trans-septal puncture than the left femoral approach. After obtaining the access, the next step is trans-septal puncture to gain access to the left atrial cavity. However, some operators have also used a patent foramen ovale or a preexisting atrial septal defect to gain access to the left atrium, thereby eliminating the need for trans-septal puncture.²² The trans-septal puncture is usually made at the postero-inferior atrial septum at the fossa ovalis under TEE guidance. Following the puncture, a pigtail catheter is placed in the LAA and angiographic measurements are performed, preferably in

RAO cranial projections to visualize the orifice and proximal part of the appendage.²³

Access Sheath Placement And Device Implantation

A stiff wire is passed and placed in the left upper pulmonary vein over which the sheath (appropriately sized) is passed up to the vein ostium. The ACP devices are usually upsized by approximately 4 mm for ACP 1 and 3 mm for Amulet for proper anchoring and stability.

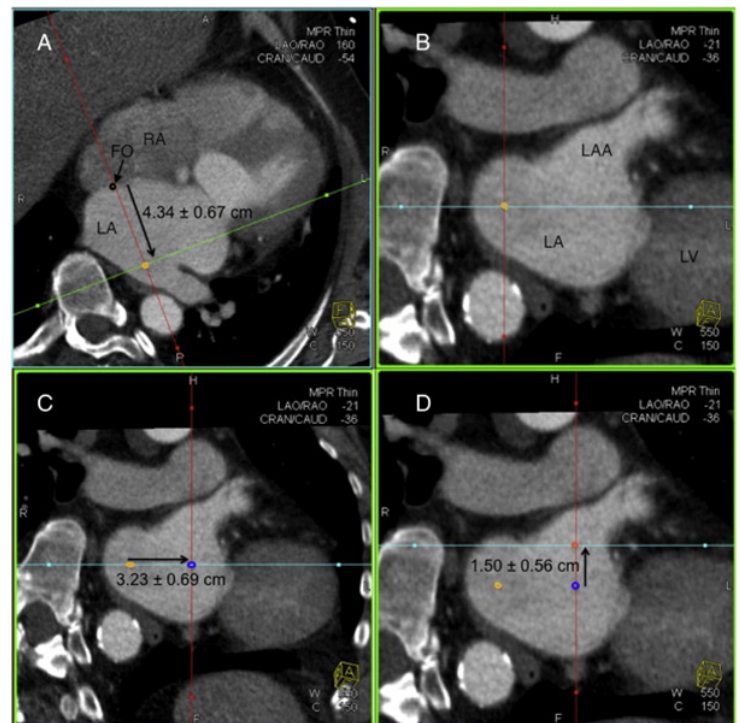


Figure 3: Systematic evaluation of distance along three planes from the fossa ovalis to the left atrial appendage ostium. Lateral distance from the FO (black dot) to the lateral margin (yellow dot) is measured in the axial (A) image using the coronal view (B) as a reference for the plane of the LAA ostium; (C) subsequent anterior distance to the plane of the LAA ostium (yellow dot to blue dot) and (D) subsequent superior distance to the LAA ostium (blue dot to red dot) are measured in the coronal view. FO: fossa ovalis; LA: left atrium; LAA: left atrial appendage; LV: left ventricle; RA: right atrium (Adapted with permission from Krishnaswamy et al)¹⁹

Table 2: Summary of procedural events in studies reporting implantation of Amplatzer Cardiac Plug 1 device

Author	Region	Duration	N	Procedural success, %	Ischemic Stroke, %	Embolization rate, %	Severe Pericardial effusion, %
Freixa et al ³⁸	Europe-Canada	2012-2013	25	96	0	0	0
Lam et al ²⁴	Europe	2013	17	100	0	0	6
Gloekler et al ¹⁷	Europe	2012-13	50	94	0	6	6

The device is advanced to the “landing zone” inside the LAA, and the device is ready to be deployed (figure 4). The following criteria have been defined in the literature to ensure adequate deployment:

- (1) adequate alignment of the device lobe in the LAA and adequate compression of the lobe to LAA wall;
- (2) concave shape of the disk for good seal;
- (3) separation of lobe and the disk;
- (4) right angle of lobe to the neck axis at the “landing zone”;
- (5) lobe position at least two-thirds distal to left circumflex.²⁴

Once these criteria are met on TEE imaging, the device is released by twisting the delivery cable counterclockwise.

Evidence On Outcomes

Amplatzer Cardiac Plug 1 Device

The Amplatzer cardiac plug (ACP) 1 and the second generation Amulet devices are among the two most commonly used percutaneous LAA occlusion devices in the world (the other being the WATCHMAN device). The data from randomized controlled trials (RCTs) are only available for the WATCHMAN device.²⁵⁻²⁷ Most of the data for the ACP devices is derived from small registries maintained at centers outside the United States^{17,22,28-35} [table 1]. A prospective randomized multicenter controlled trial is presently underway to compare this device head-to-head to long-term OAC with warfarin or dabigatran in a 2:1 randomization strategy.³⁶ Most promising data for the ACP devices are derived from a pooled analysis of 1047 consecutive patients from 22 centers in Europe, Asia, Latin America and Canada recently published by Tzikas et al.¹⁶ They reported pooled procedural success as 97.3% with 5% periprocedural major adverse events. Mean follow up was 13 months (1349 patient years), and one year all-cause mortality was reported at 4.2%. The stroke rate is reported at 0.9%, TIA's at 0.9% (9 each) and systemic embolism was 2.3% (31 events). Since, the data are derived from pooled estimates from individual registries, there was no control group.

Sub-group analysis from another systematic review evaluating the safety and efficacy of percutaneous LAA devices demonstrated a stroke rate of 0.9% [95% CI:(0.7-2.4)] after implantation of an Amplatzer Cardiac plug device. The periprocedural adverse event rate was reported as 23.5% [95% CI: (15.9-33.2%)] for ACP devices.³⁷

Santoro et al have recently reported up to 4 years of follow up data on a group of 134 patients implanted with an ACP 1 device, representing 238 patient years of follow up. They report an ischemic stroke rate of 0.8/100 person-years, thromboembolic event rate of 2.5/100 person-years and all-cause mortality of 2.5% over the follow up period.³⁵

Amulet Device

Unlike the ACP 1 device, there are very few studies evaluating the newer Amulet device [table 2]. Lam et al reported a case series of 17 patients with follow up data available up to 90 days.²⁴ They reported a procedural success of 100% and no procedural complication except for 1 case of pericardial effusion. A larger case series of 25 patients reported by Freixa et al reported a procedural success of 96% without

any complication at up to 3 months of follow up³⁸. A recent report by Gloeckler et al compares the last consecutive 50 ACP 1 cases with the first 50 consecutive Amulet cases in a non-randomized manner.¹⁷ The study gives an interesting insight into the efficacy and safety of the newer Amulet device versus the ACP 1, wherein patient population and operating conditions, including the procedure specialists, are similar between the two groups. The devices were similar in efficacy and safety per their analysis. The authors conclude that, at least in the early experience, the Amulet offers no significant benefit over the ACP 1 device except for a non-significant reduction in rates of pericardial effusion.

Conclusion

Left atrial appendage occlusion by percutaneous strategy is a rapidly growing discipline in the field of structural cardiac interventions. The technology involving multiple devices has a potential to modify the risk of stroke in patients with non-valvular atrial fibrillation. The Amplatzer cardiac plug 1 and the second generation Amulet devices seem promising from the limited non randomized controlled trial data available from centers mostly outside the United States. In light of the promising results for the most commonly used WATCHMAN device from two randomized studies, it seems obvious that similar studies are also needed to assess the efficacy and safety of the Amplatzer devices. However some additional key questions remain unanswered before these devices

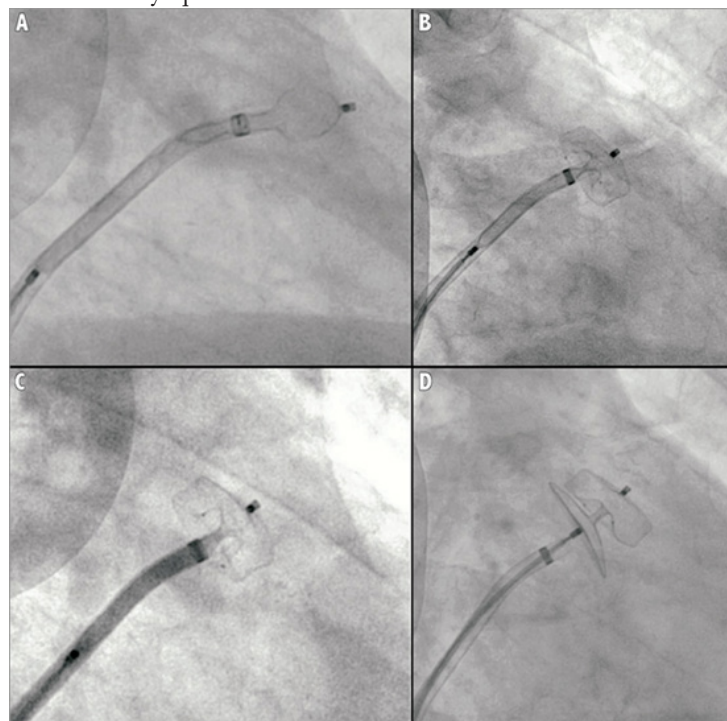


Figure 4: A) Angiography of Amplatzer Cardiac Plug – lobe “ball” shape; B) Deployment of Amplatzer Cardiac Plug – lobe; C) Angiography of Amplatzer Cardiac Plug – lobe positioned RAO 40° – caudal 20°; D) Deployment of Amplatzer Cardiac Plug – disc. (Adapted DIRECTLY from Berti et al²³) PERMISSIONS PENDING

gain widespread commercial use in the United States. These include regulatory framework, training requirements, role of learning curve and most importantly selection of patient cohorts who are most likely to benefit from these devices. Also relevant are the data on superiority versus non-inferiority of new devices to warfarin.³⁹ The answers to these questions can only be derived from more data on the outcomes after implantation of these devices. Considering the recent approval of the WATCHMAN device by FDA, it is unlikely that the Amplatzer devices will see a head-to-head comparison with the WATCHMAN device in any randomized study. It will be interesting to see the results from the presently ongoing ACP trial for definite assessment of safety and efficacy outcomes in ACP devices. The need of the hour currently is to standardize the outcome measures and possibly also create a nationwide registry of percutaneous LAA occlusion devices including the Amplatzer, so that more high quality data may be generated.

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