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Abstract: Atrial fibrillation is a frequent cause of stroke; in the elderly, more than 20% of strokes are attributed to this common arrhythmia. Anticoagulation with warfarin reduces the risk of stroke by 60%; however, a large proportion of patients with atrial fibrillation do not receive this treatment because of relative/absolute contraindications. Moreover, patients often discontinue warfarin for a variety of reasons and chronic warfarin administration rates remain suboptimal. Although the compliance with anticoagulation may improve with novel anticoagulants and bleeding risk can be somewhat reduced when compared with warfarin, there is still a progressive increase in bleeding complications over time. Accordingly, new approaches for stroke prevention in these patients are being explored and tested. In transoesophageal echocardiographic (TEE) studies, more than 90% of thrombi were found in the left atrial appendage (LAA) in non-valvular atrial fibrillation, and transcatheter LAA closure is developed and examined as a novel approach to reduce the risk of stroke in these patients. The PROTECT-AF study provides first evidence from a randomized clinical trial that a strategy of LAA occlusion using the Watchman device can be non-inferior to anticoagulation with warfarin for a combined endpoint in patients with non-valvular atrial fibrillation (mean CHADS(2) score 1.8). In successfully occluded patients fulfilling TEE criteria (86%), warfarin was stopped after 45 days, followed by aspirin and clopidogrel for 6 months after randomization and subsequently aspirin. The PREVAIL trial is further evaluating this concept. Limited data are available for another LAA occlusion system, the Amplatzer Cardiac Plug (ACP) device, for which the ACP trial has been initiated. Left atrial appendage occlusion needs to be performed with meticulous care by experienced operators because periprocedural complications such as pericardial effusion or stroke have been documented. With increased operator experience and technical improvements of the device, these complications can be minimized.

DOI: https://doi.org/10.1093/eurheartj/ehr393

Originally published at:
Landmesser, U; Holmes, D R (2012). Left atrial appendage closure: a percutaneous transcatheter approach for stroke prevention in atrial fibrillation. European Heart Journal, 33(6):698-704.
DOI: https://doi.org/10.1093/eurheartj/ehr393

Left atrial appendage closure – a percutaneous transcatheter approach for stroke prevention in atrial fibrillation

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Total word count: 4739

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Subject codes: Left atrial appendage closure; atrial fibrillation; stroke

Abstract

Atrial fibrillation is a frequent cause of stroke; in the elderly more than 20 % of strokes are attributed to this common arrhythmia. Anticoagulation with warfarin reduces the risk of stroke by approximately 60 %, however, a large proportion of patients with atrial fibrillation does not receive this treatment because of relative/absolute contraindications. Moreover, patients often discontinue warfarin for a variety of reasons and chronic warfarin administration rates remain suboptimal. Although the compliance with anticoagulation may improve with novel anticoagulants and bleeding risk can be somewhat reduced as compared to warfarin, there is still a progressive increase in bleeding complications over time. Accordingly, new approaches for stroke prevention in these patients are being explored and tested.

In transesophageal-echocardiographic studies more than 90 % of thrombi were found in the left-atrial appendage (LAA) in non-valvular atrial fibrillation, and transcatheter left-atrial appendage closure is developed and examined as a novel approach to reduce risk of stroke in these patients. The PROTECT-AF study provides first evidence from a randomized clinical trial that a strategy of LAA occlusion using the Watchman device can be non-inferior to anti-coagulation with Warfarin for a combined endpoint in patients with non-valvular atrial fibrillation (mean $CHADS_2$-score 1.8). In successfully occluded patients fulfilling TEE criteria (86%) warfarin was stopped after 45 days; followed by aspirin and clopidogrel for 6 months after randomization and subsequently aspirin. The PREVAIL trial is further evaluating this concept. Limited data are available for another LAA occlusion system, the Amplatzer Cardiac Plug device, for which the ACP-trial has been initiated. LAA occlusion needs to be performed with meticulous care by experienced operators because periprocedural complications such as pericardial effusion or stroke have been documented. With increased operator experience and technical improvements of the device these complications can be minimized.

Introduction

Stroke remains a main cause of morbidity and mortality from cardiovascular disease with an annual incidence of ≈795 000 patients with a new or recurrent stroke and an estimated prevalence of 7 million patients in the US (1). In high-income countries, about 80% of strokes are caused by focal cerebral ischemia due to arterial occlusion, and the remaining about 20 % are caused by cerebral hemorrhages (1). The incidence of stroke increased markedly with advancing age; the percentage of strokes attributable to atrial fibrillation increases steeply from about 1.5% at 50 to 59 years of age to more than 20 % at 80 to 89 years of age, making atrial fibrillation a primary risk factor of stroke in these patients (1). Moreover, strokes related to atrial fibrillation have been observed to be associated with a higher mortality and morbidity as compared to non-atrial fibrillation strokes, emphasizing the need for more effective stroke prevention in these patients (2).

Stroke prevention in patients with atrial fibrillation has largely been based on the use of anticoagulation with warfarin, that reduces the risk of stroke by approximately 60 % (3), and more recently on the use of novel anticoagulants in some patients, such as the direct thrombin-inhibitor dabigatran (4). Therapy with warfarin or the novel oral anticoagulants, e.g. the direct thrombin inhibitor dabigatran or the selective factor Xa inhibitors apixaban and rivaroxaban, comes with a significant life-time risk of major bleedings ranging from 1.4 - >3 % per year in clinical trials (4-8), that have excluded patients with a high risk of bleeding. A recent analysis of the RE-LY trial has suggested that in patients with atrial fibrillation at risk for stroke, the lower and the higher dose of dabigatran compared with warfarin had a lower risk of both intracranial and extracranial bleeding in patients aged <75 years. In those aged ≥75 years, intracranial bleeding risk is lower but extracranial bleeding risk is similar or higher with both doses of dabigatran compared with warfarin (8). The cumulative incidence of major hemorrhage for patients > or = 80 years of age has been estimated to be as high as 13.1 per 100 person-years, and these patients are not frequently enrolled in randomised clinical trials (9).

A significant proportion of patients with atrial fibrillation, ranging from 30-50 % do not receive anticoagulation due to relative or absolute contraindications or due to patient- and/or physician-pertinent barriers limiting the use of anticoagulation in clinical practice, including the perceived risk or fear of treatment-induced bleedings (10, 11). Moreover, the persistent use of anticoagulation with Warfarin prescribed for secondary prevention after stroke was observed to decline to 45 % after 2 years in a recent analysis from a large Swedish stroke registry (12).

For these reasons, device-based therapies are currently being developed for stroke prevention in non-valvular atrial fibrillation and potentially offer an alternative approach for stroke prevention in these patients that will be the focus of the present review article.

Left atrial appendage closure – the rationale

The trabecular left atrial appendage (LAA) is the remnant of the original embryonic left atrium and develops during the third week of gestation, whereas the main smooth walled left atrial cavity develops later (13). The LAA has been the site in the left atrium where more than 90 % of thrombi were detected in patients with non-valvular atrial fibrillation in transesophageal studies (14). The LAA has therefore been considered by some our ”most lethal human attachment “ (15).

The LAA is actively contracting and has a characteristic pattern of emptying in sinus rhythm, that can be detected by both transesophageal echocardiography or cardiac MRI studies (16).

In patients with atrial fibrillation, however, blood flow velocity in the LAA frequently decreases, resulting in stasis, and increasing the probability of thrombus formation (16, 17). Thrombi have been detected by transesophageal echocardiography in approximately 15 % of patients with atrial fibrillation (14, 18). Of note, in immunohistochemical studies, immunoreactive von Willebrand factor (vWF), a platelet adhesion molecule, was increased in overloaded human left atrial appendages, that likely can predispose to thrombus formation (19), in addition to the anatomical and structural factors favoring thrombus formation in the LAA. In the SPAF III (Stroke Prevention in Atrial Fibrillation III) trial including patients with non-valvular atrial fibrillation, TEE was performed in 786 study participants, and thrombi detected in the LAA as well as a reduced LAA peak flow velocity were identified as independent predictors of an increased thromboembolic risk (20). In the same study, detection of complex aortic plaques by TEE was also associated with an increased thromboembolic risk, indicating that causes of stroke are likely multifactorial in elderly patients with atrial fibrillation and that LAA closure is unlikely to prevent all ischemic strokes in these patients (20). The frequent detection of left atrial thrombi in the LAA as well as the observed association of LAA thrombi with an increased thromboembolic risk do not yet, however, prove a causal relationship between LAA thrombi and stroke. The concept, that exclusion of left atrial appendage from the circulation reduces the risk of stroke in patients with non-valvular atrial fibrillation is therefore being examined in clinical studies as a potential novel approach to prevent cardioembolic strokes in these patients as described in detail below.

Development of transcatheter left atrial appendage occlusion

The first technology developed for percutaneous transcatheter LAA occlusion was the ***Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device***, a self-expanding nitinol cage covered with a polymeric membrane (21). The device was manufactured with anchors to prevent embolization, and it was made in a variety of sizes (21). Ostermayer et al. reported the early experience with this device in two prospective, multi-center observational studies, where a successful device implantation was achieved in 108 out of 111 patients. This report suggested that transcatheter LAA occlusion is feasible and can be performed with an acceptable risk in patients with atrial fibrillation and a contraindication for anticoagulation therapy (22). One patient (0.9%) experienced two major adverse events within 30 days (i.e. need for cardiovascular surgery and in-hospital neurological death, likely due to cerebral hemorrhage after anticoagulation had been instituted for a thrombosis). Three other patients underwent in-hospital pericardiocentesis due to a hemopericardium, of which two patients were the first patients at a new site in which pericardial hemorrhage occurred during the attempt to enter the LAA after transseptal puncture (22). No device migration or mobile thrombus was noted on the device at 1 and 6 months after device implantation (22). Two patients experienced stroke during an average follow-up of 9.8 months, i.e. the annual stroke rate was 2.2. % (22). The estimated annual stroke rate for these patients was 6.3% (using the $CHADS_2$ score), assuming that patients were taking aspirin (22).

Bayard et al. described the experience of the following European PLAATO study including 180 elderly patients with atrial fibrillation and contraindications for anticoagulation (23). LAA occlussion was successful in 162/180 patients (90 %) (23). Two patients (1.1 %) died within 24 hours. In one patient (82-year-old), the cause of death was thought to be exarcerbation of chronic heart failure secondary to severe coronary disease following anaesthesia. The second patient (74-year-old) was operated for pericardial tamponade after attempted device implantation and died due to hemorrhagic shock after rupture of iliac artery, when removal of the device, that had embolised during resuscitation, was attempted with a snare catheter (23). Including the above event there were six patients (3.3 %) with pericardial tamponade, that had to be drained surgically in two patients (23). The reported incidence of strokes (2.3 %/year) in patients with the PLAATO device and aspirin was lower as compared to the expected annual stroke risk according to the $CHADS_2$ score (6.6 %/year) in a mean follow-up of 9.6 months (23). This study was halted prematurely during the follow-up phase for financial considerations. Bloch et al. reported the long-term experience in the US and Canada from a mean follow-up of 3.75 years in 64 patients of the PLAATO study, suggesting a lower annual stroke rate compared to that predicted from the $CHADS_2$ score (24). Although the clinical development program for this device has been halted, there are lessons that can be learned. There were certain limitations of the PLAATO device, e.g. it was rather rigid and required therefore 20-50 % oversizing as compared to the LAA-orifice to achieve a stable position. In contrast, more recent LAA occlusion devices, i.e. the Watchman device and the Amplatzer Cardiac Plug (ACP) device, are more flexible and need only 10-20 % oversizing to achieve a stable position in the LAA. That is important since the LAA has typically an oval orifice (25-27). Furthermore, the flatter shape of the more recent devices as compared to the PLAATO device allows also for occlusion of LAAs that have a short proximal portion and an early separation into lobes, which could not be completely occluded by the PLAATO device due to the necessity of a deeper implantation. Notably, in approximately 80 % the LAA is multilobulated (26). Indeed, the LAA has a very individual anatomy, almost like a finger print, with a different number of lobes (1-4), substantial differences in length and orifice size, that makes a flatter LAA occlusion device more appropriate for occlusion of a significant proportion of left atrial appendages (25-27).

The feasibility and early experience using the ***WATCHMAN Left Atrial Appendage System*** (Atritech Inc., Plymouth, Minnesota), a self-expanding nitinol device for percutaneous implantation to seal the LAA, was reported in 2007 (28). In this feasibility study complete LAA sealing was observed in 54 of 58 patients (93 %) by transesophageal echocardiography at 45 days, and no strokes were reported during a mean follow-up of 740 days (28). Importantly, the Watchman device is the first LAA occlusion device that has been evaluated in a prospective, controlled, randomized trial, the Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) clinical trial (29).

In this multicenter non-inferiority trial performed in 59 centers in the US and Europe comparing long-term treatment with warfarin versus LAA occlusion with the Watchman device, patients were elegible if they had non-valvular atrial fibrillation and at least one of the following: previous stroke or transient ischaemic attack, congestive heart failure, diabetes, hypertension, or age > 75 years, i.e. a $CHADS_2$-score ≥ 1. 707 eligible patients were randomly assigned in a 2:1 ratio to percutaneous closure of the LAA and subsequent discontinuation of warfarin (n=463) or long-term warfarin therapy with INR between 2.0 and 3.0 (control; n=244). In patients randomised to the percutaneous device closure arm, the device was successfully implanted in 408 of 463 patients (88%) and warfarin therapy was terminated after 45 days in most of these patients (349 of 408 patients [86 %] meeting TEE criteria of either complete closure of LAA or minimal residual peri-device flow; jet<5 mm in width) and these patients were then treated with aspirin and clopidogrel for 6 months after randomisation, followed by long-term aspirin monotherapy (29). The trial results demonstrated that the probability of non-inferiority of the device was greater than 99.9% with regard to the primary efficacy end point (occurrence of ischemic or hemorraghic stroke, cardiovascular or unexplained death, or systemic emboli within up to 3 years) based on an analysis of 1065 patient-years of follow-up. Patients receiving the device had fewer haemorrhagic strokes than the controls. In a safety analysis of the primary endpoint including only patients of the intervention group who were successfully treated and who discontinued warfarin therapy the primary efficacy event rate was 1.9 per 100 patient years as compared with 4.6 per 100 patient-years in control patients who received long-term warfarin (29).

The primary safety endpoint consisting of events related to excessive bleeding (eg, intracranial or gastrointestinal bleeding) or procedure-related complications (serious pericardial effusion, device embolisation or procedure-related stroke) was significantly greater in the device group (7.4 vs. 4.4 per 100 patient-years) (29). The most frequent primary safety event in the intervention group was serious pericardial effusion (defined as the need for percutaneous or surgical drainage), which occurred in 22 (4·8%) patients. 15 of these patients were treated with pericardiocentesis, and 7 underwent surgical intervention, there was no fatality due to pericardial effusion (29). As described below, pericardial effusion rates declined with increasing operator experience. Device embolisation occurred in three patients; one was noted during the procedure and two were observed by TEE on day 45-FU; one device was removed using a vascular snare; the other two patients underwent surgery. There were five patients with a procedure-related stroke, of which three had no long-term residual deficit, whereas two patients were discharged to nursing homes and subsequently died. After the periprocedural timeframe, ischaemic stroke occurred in nine patients in the intervention group (1.3 events/100-patient-years) compared with six patients in the control group (1.6 events/100 patient-years) (29).

A recent analysis of the non-randomised Continued Access Protocol (CAP) registry including 460 subsequent patients after the PROTECT-AF study had been completed, documented a significant improvement in the safety of the Watchman left atrial appendage closure, a result of increased experience of the operators (all operators had participated in the PROTECT-AF trial) as well as technical improvements in the device (30). In this group, serious periprocedural pericardial effusion were observed in 10 patients (2.2. %) and no procedure-related strokes were reported. These findings clearly suggest in line with the experience with the PLAATO device that increasing experience of the operators reduces the risk of periprocedural complications. In addition, another recent analysis from the PROTECT-AF study has shown that the small iatrogenic ASDs that are frequently observed after transseptal procedure with a large-diameter transseptal sheath of 12 F have a very high spontaneous closure rate and are not associated with an increased rate of stroke or systemic embolization during long-term follow-up (31).

A second prospective, randomised trial using the Watchman device, i.e. the PREVAIL trial, is currently under way and will provide further information for the LAA occlusion procedure.

Another device designed for LAA occlusion is the ***Amplatzer Cardiac Plug (ACP***), that is CE-marked in Europe and consists of a body for device fixation in the LAA and a disc for sealing of the LAA from the circulation (Figure 3C). An investigator-initiated retrospective data collection to evaluate the procedural feasibility and safety up to 24 hr after implantation of the ACP device has recently been reported (32) as well as a small registry from the Asia-Pacific experience (33). Park et al. reported that LAA occlusion using the ACP device was successfully performed in 132 of 137 patients (96%)(32). There were serious complications in 10 patients (7 %), of which three patients had an ischemic stroke; two patients experienced device embolization (that could be percutaneously recaptured) and five patients had a clinically significant pericardial effusion (32). As a note of caution it should be added that these data are self reported and non-adjudicated. A pivotal trial for the Amplatzer Cardiac Plug device, the ACP trial (http://www.acptrial.com), with a similar study design as the PROTECT-AF trial has been initiated and is recruiting patients.

Safeguarding the procedure

In Europe, the Watchman device and the Amplatzer Cardiac Plug are at present already widely used, in particular in patients with non-valvular atrial fibrillation who have an absolute or relative contraindication to anticoagulation and a relevant risk of an ischemic stroke (i.e. CHADS2 score >1). As described above two prospective, randomized trials are currently recruiting patients, i.e. the PREVAIL and ACP trial, that will provide important data on the efficacy and safety of LAA occlusion in atrial fibrillation using the Watchman or ACP device. The above observations clearly suggest that LAA occlusion needs to be performed by experienced operators.

The observation that operator experience reduces the rates of periprocedural complications suggests that in centers were the technique is started, this needs to be done together with an experienced operator. Moreover, the follow-up of patients is very important to optimize the procedure. For both devices, there has been the observation that in a small percentage of patients thrombus may form on the device in the first weeks/months after implantation, suggesting that transesophageal echocardiography follow-up after the procedure is important to detect this abnormality. In the majority of patients the detected thrombus disappears after short-term anticoagulation (30, 34, 35). In a follow-up report for the Watchman device, a device-associated thrombus was described in 20 of 478 successfully implanted patients (4.2%) (30). Of these patients, 17 patients were either asymptomatic or endothelialized with anticoagulation. This suggests a device-related thrombus-associated annualized stroke rate of 0.3% per 100 patient-years (30). The experience from histological analyses of the Watchman device suggests that in the long-term there is device endothelization which should minimize the risk of device-related thrombus formation (36).

Furthermore, in the PROTECT-AF study all patients were treated for 45 days after device implantation with warfarin. Therefore, the safety and efficacy of LAA closure without short-term warfarin treatment is not known and more experience and data are needed in patients with an absolute contraindication for warfarin therapy.

For the Amplatzer Cardiac Plug device less data on periprocedural complications are available (32). The Amplatzer PFO and ASD devices have a very low risk of device-related thrombus formation (37), however, these devices are frequently implanted in patients without atrial fibrillation. For the Amplatzer Cardiac Plug device, thrombus-formation on the device has been reported in some individual cases (34, 35), which could be resolved by short-term anticoagulation, suggesting that the TEE follow-up is important for this device as well. More follow-up data are needed for this device, both from registries and clinical trials such as the ACP trial.

Conclusions and Perspective

As described above, the available data suggest that LAA occlusion reduces the risk of stroke in patients with non-valvular atrial fibrillation, and the PROTECT-AF study provides the first evidence from a randomized clinical trial that this therapeutic device intervention (as performed with warfarin for 45 days in successfully occluded patients fulfilling TEE criteria; aspirin and clopidogrel for 6 months followed by aspirin) is non-inferior to anti-coagulation with Warfarin using the combined endpoint (29). The rate of ischemic strokes was numerically higher in the device intervention group, that could be attributed to five periprocedural strokes (mainly air embolism). The recent Continued Access Protocol (CAP) registry suggests that the complication rates during LAA occlusion likely improve with increasing operator experience, since no procedure-related strokes were reported in 460 consecutive patients (30).

If these findings are substantiated by further randomized trials, one may speculate that the benefit of a device-based approach could be more pronounced in clinical practice than that observed in clinical trials, given the observation that even in patients after an ischemic stroke the persistent use of a prescribed anticoagulation therapy with Warfarin in clinical practice after 2 years was lower than 50 % (12). However, the compliance with anticoagulation may also improve with the novel anticoagulants. Therefore, more detailed information on the persistent use of the novel anticoagulants as well as on the complication rate of LAA occlusion when it is more widely used in clinical practice will be of interest in this respect.

Disclosures

Dr Holmes has received research grant support from Atritech, Inc. In addition, the Watchman LAA closure technology has been licensed to Atritech, and both Mayo Clinic and Dr Holmes have contractual rights to receive future royalties from this license. To date, no royalties have been received.

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Figures

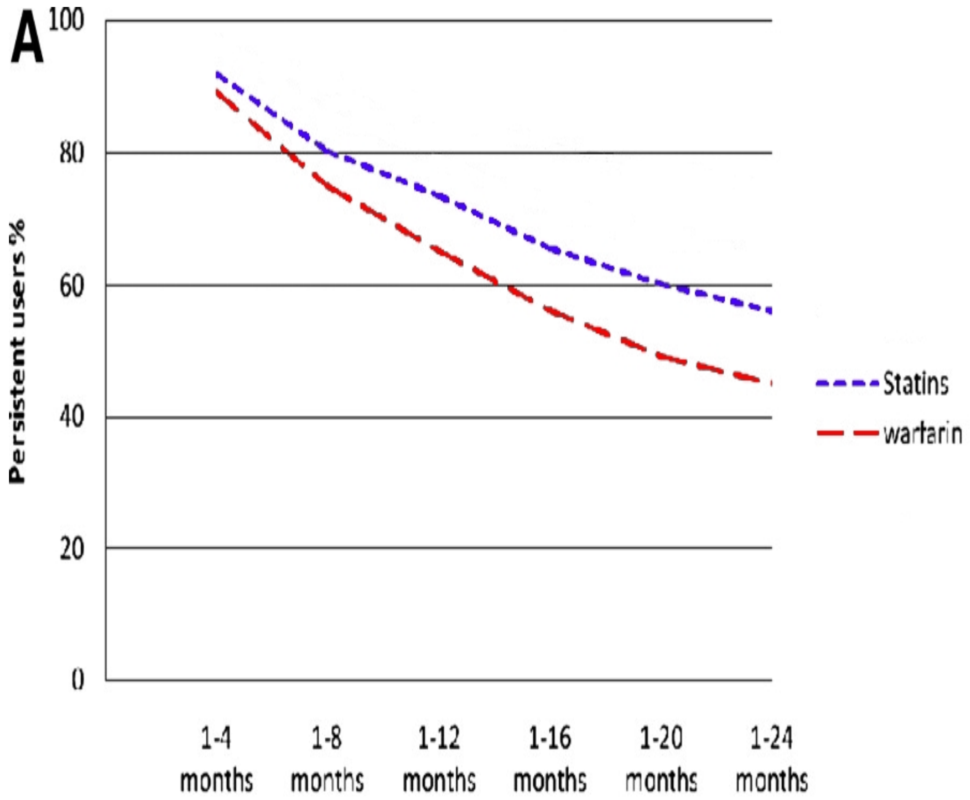


Figure 1

The analysis of a recent study examining the persistent use of a prescribed anticoagulation in a cohort of stroke survivors (21 077 survivors) is shown, indicating that the persistent use of anticoagulation with warfarin declined to 45 % after 2 years (adopted and modified from (12)).

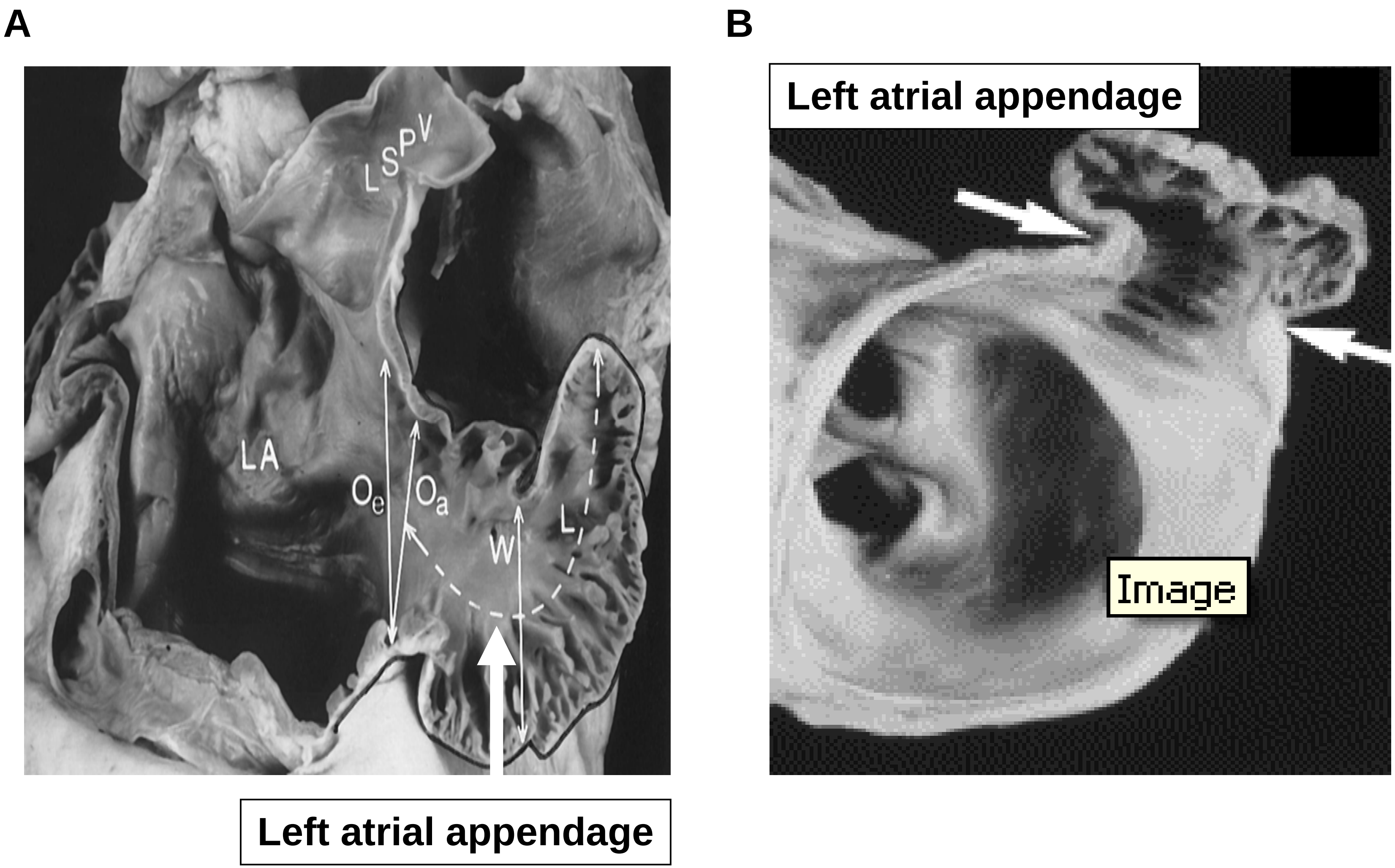
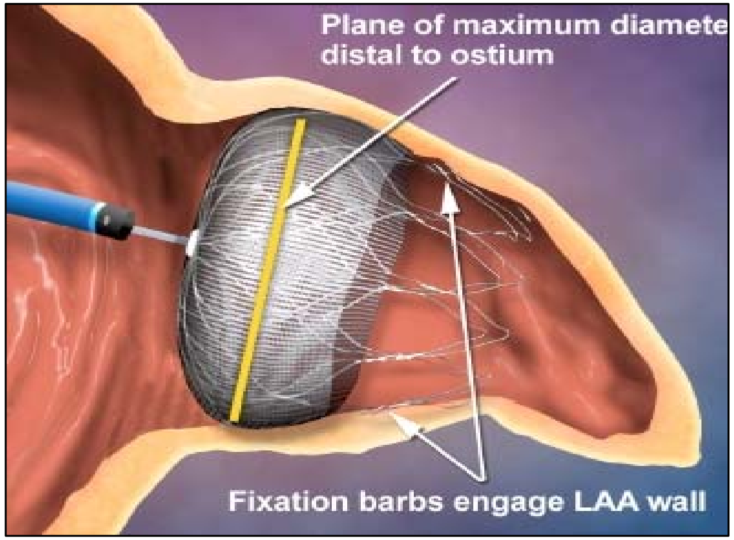

A
LSPV
LA
Oe
Oa
W
L
Left atrial appendage
B
Left atrial appendage
Image

Figure 2

Anatomical specimens showing the variable anatomy of the left atrial appendage (LAA), i.e. a single-lobed (A) LAA and a bilobed LAA (B), the most frequent variant of LAA anatomy. Both specimens illustrate the difference between the trabecular left atrial appendage and the smooth walled left atrial cavity, that have diverse embryonic origins. The echocardiographic orifice (Oe) is often larger than the anatomic orifice (Oa). (Adapted and modified from (26, 38). LA, left atrium; LSPV, left superior pulmonary vein.

A

B


Plane of maximum diamete
distal to ostium
Fixation barbs engage LAA wall

C

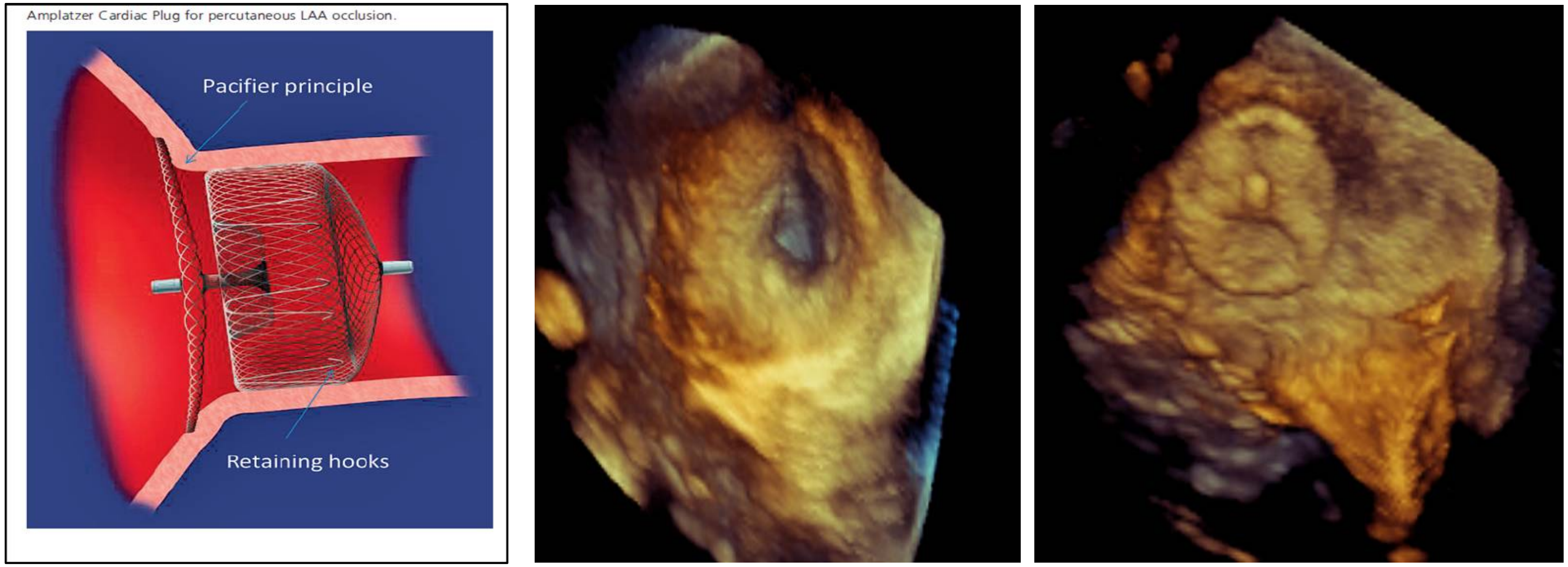

Amplatzer Cardiac Plug for percutaneous LAA occlusion.
Pacifier principle
Retaining hooks

Figure 3

Devices for percutaneous transcatheter left atrial appendage closure that have been examined in clinical studies. **A**, The PLAATO® device (ev3 Endovascular, Inc., North Plymouth, MN) was the first transcatheter LAA occlusion device implanted percutaneously in patients with atrial fibrillation. **B**, The WATCHMAN® Left Atrial Appendage System (Atritech Inc., Plymouth, Minnesota) is the first LAA occlusion device examined in a prospective, randomized clinical trial vs. anticoagulation with warfarin. The WATCHMAN LAA System consists of a parachute-shaped device with a self-expanding nitinol frame structure with a permeable polyester membrane over the atrial side and mid-perimeter fixation barbs to secure it in the LAA. **C**, The AMPLATZER® Cardiac Plug (ACP) device (AGA Medical Corporation, Golden Valley, MN) consists of two bodies, i.e. a distal anchoring lobe and a proximal sealing disc linked via a flexible central waist. On the right panel, 3D transesophageal images are shown before and after LAA occlusion.