



Complications From Left Atrial Appendage Exclusion Devices

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and has been identified as an independent risk factor for stroke. Prevention of thromboembolic events has been based on oral anticoagulation (OAC) using Vitamin K antagonists (VKA). However, long-term OAC medication is limited by an increased bleeding risk and a low patient compliance. Relying on the observation that the majority of cardiac thrombi originate from the left atrial appendage (LAA) different devices aiming for LAA closure have been proposed. This review will discuss contemporary LAA closure devices with special emphasis on procedure related complications.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and an independent risk factor for stroke. The prevalence of AF is approximately 1.5–2% in the general population, ranging from <0.5% at 40–50 years to 5–15% at 80 years, and is expected to double within the next 50 years as a consequence of aging societies.^{1–7} All types of AF (paroxysmal, persistent and permanent) increase the risk of ischemic stroke to a similar degree (five-fold).^{8,9}

The CHA₂DS₂-VASc score has been proposed to stratify AF patients for ischemic stroke risk (Table 1, ESC¹²) with a low risk categorized as a CHA₂DS₂-VASc score of 0, intermediate risk as a score of 1, and high risk as a score ≥ 2 .¹⁰

In patients with AF and a CHA₂DS₂-VASc score ≥ 1 , long-term oral anticoagulation (OAC) is recommended irrespective of the rhythm management strategy.¹² However, in many patients, OAC can not be administered due to either a high bleeding risk (as defined by an HAS-BLED bleeding risk score ≥ 3),¹¹ life-threatening bleeds, perceived frailty and/or high risk of falls, especially in very elderly patients. As a result, approximately 50% of patients eligible for OAC using Vitamin K antagonists (VKA) are not treated.¹² In addition, optimal medical treatment in patients with both, a high bleeding risk and a high stroke risk remains unclear. Therefore, alternative treatment options to reduce strokes in non-valvular AF (NVAF) are warranted.

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Rationale For Left Atrial Appendage Closure

Atrial fibrillation leads to loss of effective atrial contractions, promoting blood stasis and thrombus formation in the left atrial appendage (LAA).¹³ Therefore, the LAA has been identified as the main source of cardiac thrombi (>90%) in ischemic strokes associated with NVAF^{14–17} and has been termed the ‘most lethal human attachment’.¹⁸

The LAA is a trabeculated, embryological remnant of the left atrium (LA) with a multilobed structure positioned anteriorly in the atrioventricular sulcus close to the left circumflex artery, the left phrenic nerve, and the left pulmonary veins.¹⁹ Recently, the shape of the LAA has been correlated with different degrees of thromboembolic risk: the “chicken wing” LAA morphology has been associated with a lower stroke risk compared to the other three main morphologies described (“cactus”, “windsock”, and “cauliflower”).²⁰ These findings were corroborated by Khurram et al.: the presence and extent of LAA trabeculations and a small LAA orifice were independently associated with thromboembolic events.²¹ In addition, also the burden of silent cerebral ischemia evaluated through magnetic resonance or computed tomography resulted significantly related to LAA morphology in AF patients undergoing transcatheter ablation.²²

The pivotal role of the LAA in the genesis of ischemic strokes along with the recently published PROTECT AF trial (Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF)²³ has led to an update of the current AF guidelines¹²: percutaneous LAA closure has been introduced as a non-pharmacological option in NVAF patients with a high bleeding risk (level of recommendation: IIb).

Techniques For LAA Occlusion And Complications

Currently, three different strategies can be pursued to exclude the LAA from systemic circulation. They can be grouped into either

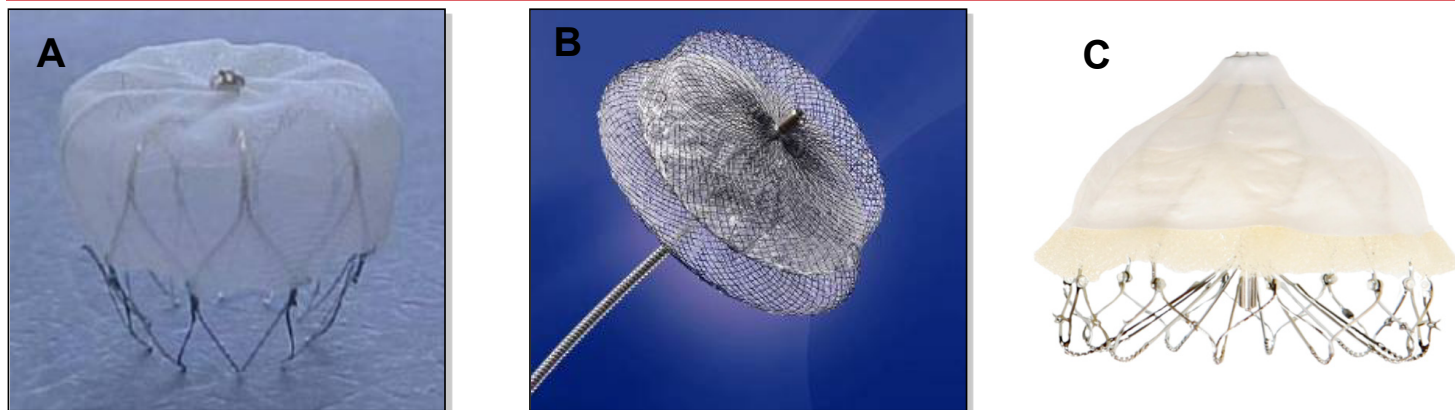


Figure 1:

Endocardial left atrial appendage occlusion devices: A) WATCHMAN (Boston Scientific, Maple Grove, MN); B) Amplatzer Cardiac Plug (ACP) (St. Jude Medical, Minneapolis, MN); C) Wavecrest™ System (Coherex Medical, Salt Lake City, UT).

interventional/percutaneous (endocardial, epicardial) or surgical approaches. The completeness of LAA closure as well as specific complications may be variable among different techniques. This review will focus on percutaneous LAA closure device-related complications, which will be described separately according to each different strategy.

Interventional/Percutaneous LAA Closure

Percutaneous Endocardial LAA Closure

General considerations

The endocardial LAA closure approach via the femoral vein is based on a transseptal LA access.²⁴ A large delivery sheath is exchanged after transseptal puncture followed by LAA visualization using angiography and transesophageal echocardiography (TEE), to define the individual LAA anatomy. Thereafter, an adequate sized device (Fig.1) is released in the LAA landing zone after confirmation of the correct position again using TEE and fluoroscopy.

The first, randomized trial comparing percutaneous LAA occlusion (WATCHMAN, Boston Scientific, Maple Grove, MN) to OAC with warfarin, was the PROTECT AF trial (Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF).²³ Importantly, this study demonstrated noninferiority of percutaneous LAA closure to OAC. However, the PROTECT AF trial was characterized by a high risk of procedure related complications in

the intervention group (n=463 patients, 4.8% cardiac tamponades, 3.5% major bleeding, 1.1% stroke, 0.6% device embolization, 0.2% hemorrhagic stroke).²³

In general, complications linked to percutaneous LAA closure can be divided into:

- a. Access related
- b. Device implantation related
- c. Antithrombotic treatment related.

All types of complications are discussed in detail below along with device specific considerations (Table 2).

Access-Related Complications

Vascular complications such as groin hematoma, femoral arterial pseudoaneurysm or femoral arteriovenous fistula, retroperitoneal bleed, sometimes requiring transfusions and surgical interventions are the most common complications in interventional cardiology (0.6-13%).²³⁻²⁵ Patients undergoing percutaneous LAA closure are particular at risk due to the use of large delivery sheaths. Moreover, elderly patients often present with frail and tortured vascular anatomy.

Device Implantation

Different types of complications can be related to the transseptal LA access (Table 2). Large delivery sheaths increase the risk of air embolism and subsequent peri-procedural stroke/transient ischemic attack (TIA) or ST-segment elevation, and pericardial effusion with or without cardiac tamponade has been described.²⁶ Implantation of LAA occlusion devices is associated with a learning curve that is inversely related to the complication rate of the transseptal puncture approach: the rate of serious pericardial effusion is higher in less-experienced centers and tends to decrease with the growing experience of the operators performing the procedure.²⁷ Potential implantation-related complications may occur during the procedure and include device migration, dislodgement or embolization (Fig. 2) and cardiac perforation. In addition, traumatic damage to adjacent structures, including the pulmonary artery, left pulmonary veins and the circumflex coronary artery are possible.^{28,29}

In complex LAA anatomies, a mismatch between device size and LAA ostium may cause incomplete LAA occlusion and residual peri-device blood flow (Fig. 3). Severity of these leaks has been classified as minor (<1mm), moderate (1 mm to 3 mm) or major (>3 mm) but a sub-study of the PROTECT AF demonstrated no adverse impact on clinical outcome even if the gap was 3mm.³⁰ Interestingly, the role of sinus rhythm during LAA device implantation is undetermined and may need evaluation in a larger patient cohort. In our recent study

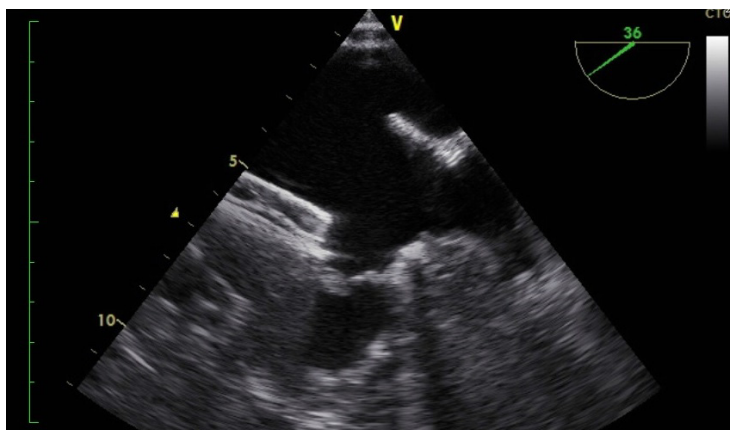


Figure 2: Two-dimensional transesophageal echocardiography (TEE) revealing the dislocation of a 30mm-Amplatzer Cardiac Plug (ACP) device from LAA into the LA, 6 weeks after the implantation. LSPV= left superior pulmonary vein; LAA= left atrial appendage; LA= left atrium.

the only both delayed tamponades were linked to sinus rhythm.³¹ In theory, sinus rhythm with enhanced LAA contractions could promote mechanical trauma.

Iatrogenic atrial septal defects following transseptal LA access usually disappeared within 6 months of the procedure or can persist in a very small proportion of patients but without any haemodynamic impairment.²⁸

Post Implantation Antithrombotic Treatment

Postprocedural management is not well standardized and several antithrombotic treatment algorithms have been proposed. Importantly, it has to be remembered that LAA closure is often performed in patients with contraindication to OAC. All current strategies strive for antithrombotic treatment, which allows device endothelialization without thrombus formation (Fig. 4) but, at the same time, increases the bleeding risk.

Post-procedural dual antiplatelet therapy (DPI) with aspirin (ASA) and clopidogrel has been suggested but the duration is unclear, ranging from 1 to 6 months in different studies. A consensus about the most appropriate post-procedural antithrombotic medication is still lacking.

In the PROTECT AF trial,²³ patients were initially treated with warfarin for 45 days post-WATCHMAN implantation. This was followed by DPI for 6 months and thereafter by “stand alone” ASA therapy. Nevertheless, during follow-up, device related thrombus was observed in 4.2% of the patients.

A similar rate (4%) of device-related thrombus has been reported in the “ASA Plavix Registry” (ASAP).³² In this registry a WATCHMAN device was implanted as in PROTECT-AF but the target population was different. All patients in ASAP had a contraindications to OAC and after implantation, DPI was administered for 6 months followed by ASA alone. This treatment strategy resulted in a 77% reduction of expected stroke rate: stroke occurred in 4 patients (ischemic stroke in 3 patients and hemorrhagic stroke in 1 patient) with a low rate of peri-procedural pericardial effusion (5 patients, 2 requiring

percutaneous drainage).³²

A significantly higher rate of device thrombi has been reported in 34 patients undergoing Amplatzer Cardiac Plug (ACP) implantation: despite DPI, thrombi on ACP were identified 6/34 (17.6%) patients (in 3 patients before discharge and in the other 3 patients at the 3-months follow-up) and Plicht et al. identified CHADS₂ and CHA₂DS₂-VASc scores, platelet count, and ejection fraction as risk factors.³³ (Table 2).

Interesting data has been recently reported from our group³¹: in 80 patients undergoing percutaneous LAA occlusion with either Watchman or ACP device, a short-term 6-week DPI followed by stand-alone therapy was administered in 76% of the patients, while the remaining patients continued preexisting OAC. After 6 weeks, OAC or DPI was discontinued and patients were switched to stand-alone aspirin. The overall rate of thrombus formation was comparable to previous study (5%), but interestingly, significantly lower rates of thrombus formation were observed in patients taking DPI compared to those treated with OAC (1.7% vs. 15.8%, $p=0.042$), without any differences in device distribution.³¹ These results may suggest that short term (6 weeks) DPI may be preferable to OAC in preventing thrombus formation on LAA closure devices. Nevertheless, further studies enrolling larger numbers of patients are needed to verify the safety of this suggested post-implantation antithrombotic therapy.

Device Specific Complications

Currently, four percutaneous transcatheter devices have been investigated for LAA occlusion³⁴: the Percutaneous LAA Transcatheter Occlusion (PLAATO) System (eV3, Plymouth, MN); the WATCHMAN device (Boston Scientific, Maple Grove, MN); the Amplatzer Cardiac Plug (ACP) (St. Jude Medical, Minneapolis, MN) and the Wavecrest™ System (Coherex Medical, Salt Lake City, UT). (Fig. 1; Table 2).

The PLAATO System

The PLAATO system was the first device developed specifically for LAA occlusion. It consists of a self-expandable nitinol cage covered with an occlusive expanded polytetrafluoroethylene membrane with small anchors along the struts.³⁵⁻³⁶ Acute successful LAA occlusion has been reported as higher than 90%,³⁷⁻³⁸ while the annual stroke rate was 2.2%,³⁷ with a 65% relative risk reduction compared to a CHADS₂ score predicted stroke rate of 6.3%.³⁹ Even after a long-term follow-up (5 years), the annual stroke rate was 3.8%, lower than the 6.6%/year expected with the CHADS₂ score.³⁹ In the recently published North American PLAATO long-term experience (follow-up of 3.75 years in 64 patients) only one adverse event was attributed to the device (1 cardiac tamponade requiring surgery). The other observed complications were the following: 7 deaths, 5 major strokes, 3 minor strokes, 1 probable cerebral hemorrhage/death, and 1 myocardial infarction.³⁹ Despite initially encouraging results, the PLAATO device is no longer available due to commercial reasons.

The WATCHMAN System

The WATCHMAN system (Fig. 1A) is a self-expanding, nitinol device available in 5 sizes (ranging from 21 to 33mm) that has been studied in two randomized clinical trials, the PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF)²³ and the PREVAIL (Prospective Randomized EVALuation of the Watchman LAA closure device In patients with atrial fibrillation vs. Long-term warfarin therapy)²⁷ and in one registry, the CAP (The Continued Access to PROTECT AF),⁴⁰ which investigated patients outcomes after the end of enrolment of



Figure 3:

TEE image of incomplete LAA occlusion 6 weeks after percutaneous deployment of a WATCHMAN device (30 mm). A persistent peri-device flow (white arrow) with a blood jet size of 4.5 mm is evidenced by Color Doppler. TEE= transesophageal echocardiography; LAA= left atrial appendage.

Table 1: Stroke risk factors defined by CHA₂DS₂-VASc the scoring system

CHA ₂ DS ₂ -VASc score		
	Risk Factor	Score
C=	Congestive heart failure/LV dysfunction	1
H=	Hypertension	1
A ₂ =	Age ≥ 75years	2
D=	Diabetes mellitus	1
S ₂ =	Stroke/TIA/thrombo-embolism	2
V=	Vascular disease	1
A=	Age 65–74	1
Sc=	Sex category (i.e. female sex)	1
	Maximum score	9

LV= left ventricular. Vascular disease= Prior myocardial infarction, peripheral artery disease, aortic plaque. Modified from Reference ¹

PROTECT AF trial. The PROTECT AF²³ is the first trial which prospectively enrolled a large number of patients (707) with NVAF to compare LAA closure using the WATCHMAN device with long-term OAC. The trial demonstrated that the percutaneous LAA closure with WATCHMAN was noninferior to OAC in preventing stroke, cardiovascular death, and systemic embolism. Patients receiving the device had fewer hemorrhagic strokes than the controls but a higher rate of adverse events, mainly due to peri-procedural complications.

Approximately 5% of patients had pericardial effusions (n=22) requiring drainage: 15 patients were treated with pericardiocentesis and 7 with surgical intervention. There were 3 device embolizations, one during the procedure and 2 during follow-up while procedure-related stroke occurred in 5 patients (Table 2). However, in the WATCHMAN group, there was a 29% reduction in stroke and 38% reduction in death compared with the warfarin control group.

A further analysis including patients undergoing WATCHMAN implantation from PROTECT AF and from a subsequent nonrandomized registry (CAP Registry) has been recently published⁴⁰ showing increased implantation success rates along with decreased complications. Importantly, the rate of pericardial effusion was decreased (2.2% vs. 4.8% in PROTECT AF) and no procedure-related strokes were observed (0% vs 0.9% in PROTECT AF) (Table 2). The significant reduction of major safety events may indicate increased operators' experience having accomplished the procedural learning curve. Preliminary data of the PREVAILE trial is in line with the CAP data.²⁷ This second prospective, randomized study using the Watchman device also showed significantly increased success device implantation rates (95.1% vs. 94.3% in CAP and 90.9% in PROTECT AF) with a 49% reduction of safety events (4.6% vs. 8.7% in PROTECT AF; p=0.004).^{27,34} The rates of procedure-related stroke were significantly reduced compared to PROTECT AF (p=0.019) as well as the pericardial effusions requiring intervention (1.9% in PREVAILE vs. 4.0% of patients in PROTECT AF, 52% reduction) (Table 2). The decreased rate of safety events can be explained by increased overall experience. Interestingly, after appropriate training implantation success was comparable for new vs experienced operators: 93.2% vs. 96.3% (p=0.282). Also, the rate of major complications was consistently low in both groups.²⁷

Amplatzer Cardio Plug System

Another self-expanding endocardial device for LAA occlusion is

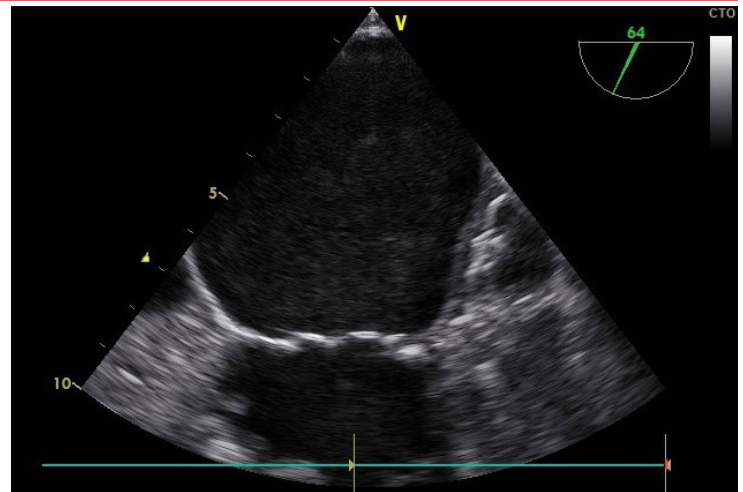


Figure 4: Post-procedural TEE after 6 weeks demonstrating device-related thrombus (arrows) completely covering a 24 mm WATCHMAN device adequately occluding LAA. TEE= transesophageal echocardiography; LAA= left atrial appendage; LA= left atrium; MV= mitral valve; LV= left ventricle.

the ACP, which is made of a disc for sealing the LAA and a body for device fixation in the LAA,⁴¹ connected by a central body (Fig. 1B). It is available in 8 different sizes (from 16 to 30mm). Initial European⁴² and Asia-Pacific⁴³ experience reported similar high implantation success rates (96% and 95%) (Table 2).

Device repositioning and complete LAA closure may be facilitated by the design.³¹

Serious complications were observed in 10 (7%) patients (3 ischemic stroke, 2 device embolizations and 5 significant pericardial effusions) and 3 patients in the Asia-Pacific registry (1 catheter-related thrombus formation during procedure leading to stop the implant, 1 coronary artery air embolism and 1 TEE-attributed esophageal damage), respectively.^{42, 43}

Thrombus formation on the ACP has been reported.⁴⁴ A recent study⁴⁵ investigated risk factors associated to this complication: despite dual antiplatelet therapy, thrombi on ACP were identified with TEE in 6 (17.6%) patients (in 3 patients before discharge and in the other 3 patients at the 3-months follow-up) (Table 2). CHADS₂ and CHA₂DS₂-VASc scores, platelet count, and ejection fraction resulted risk factors for such thrombus formation.³³ However, this data has not been replicated³¹ and more information is required.

Wavecrest System

The Wavecrest LAA occlusion system (Fig. 1C) recently received CE mark and has been introduced in the Europe. The device consists of a self-expanding Nitinol frame covered by ePTFE with a polyurethane rim and a distal face. This system has been designed to facilitate device deployment by allowing non-traumatic repositioning maneuvers at the LAA orifice. Two injection ports (distal and proximal) allow fluoroscopic assessment of adequate device positioning within the landing zone and device stability before release. The Wavecrest device has 20 interlocking anchors, which engage the surrounding tissue to complete the implant deployment. The cover material (ePTFE) has been clinically used before (PLAATO device) and is expected to minimize thrombus formation. There is currently no published human data available. In our own experience 12 patients were treated successfully without major complication. However, more data is certainly required to fully assess its role in LAA closure.

There are currently no studies directly comparing the three different

LAA occluders and only one paper from our group,³¹ prospectively compared procedural data and outcome of 80 patients who underwent percutaneous LAA occlusion with either a Watchman (n=40) or an ACP device (n=40). There was no statistical difference in patients characteristics and procedure and fluoroscopy times between the two groups. The acute success rate was very high for both the LAA closure systems (95 and 100%), despite of different devices designs. Also the number of serious complications was comparable (5%): 1 air embolization and 1 delayed cardiac tamponade in each group, while minor complications occurred in 6.8% of patients (4 cases of groin hematoma, 1 case of false arterial aneurysm). At 6-weeks TEE follow-up, 1 asymptomatic ACP dislocation into the LA was observed and the device was successfully retrieved percutaneously without surgical intervention.⁴⁵ Our study³¹ investigated alternative antithrombotic treatment regimens in high-risk patient: after device implantation, either preexisting OAC or dual platelet inhibition (DPI; Aspirin 100 mg/d + clopidogrel 75mg/d) was continued for 6 weeks; thereafter, OAC or DPI was discontinued and patients were switched to stand-alone aspirin. Interestingly, lower rates of thrombus formation were observed in patients taking DPI compared to those treated with OAC (1.7% vs 15.8%, p= 0.042), without any differences in device distribution.³¹

Percutaneous Epicardial

An alternative approach to percutaneous LAA occlusion is evolving and is based on a combined epicardial/endothelial technique (LARIAT®, SentreHEART Inc., Redwood City, California, USA). This approach ligates the LAA with an epicardial suture. After obtaining percutaneous epicardial access, a magnet-tipped endocardial wire is introduced into the pericardial space. In addition, a transseptal puncture is performed introducing a 20-mm compliant occlusion balloon catheter (EndoCATH, SentreHEART, Inc., Palo Alto, CA) with a second magnet-tipped endocardial wire into the LAA. Both magnets are approximating the LAA. Then the LARIAT snare delivery system is advanced epicardially over the LAA, guided

by the endocardial balloon catheter positioned inside the LAA. After correct placement verification, the snare is closed and the suture is tightened to ligate and exclude the LAA. This can result in complete LAA closure without any device “left inside the LAA”.

First experience⁴⁶ reported encouraging results with complete closure in 81 of the 85 patients who successfully underwent LAA ligation with LARIAT device, and residual LAA flow ≤ 3mm only in 4 patients. No complications due to the device were observed, but there were 3 access-related complications during pericardial access and transseptal catheterization. Major complications included 2 severe pericarditis, 1 late pericardial effusion, 2 unexplained sudden death, and 2 late strokes probably non-embolic.⁴⁶

The major limitation of this technique is the need for an epicardial access. Most of the complications are related to the epicardial puncture and include possible cardiac perforation, pericardial effusion or tamponade and severe pericarditis. In some patients, the presence of pre-existing pericardial adhesions may complicate catheter manipulation. In addition, successful ligation could not be achieved inadvertent LAA anatomy (LAA size > 40 mm, posteriorly rotated LAA or lobes superiorly orientated).⁴⁷

The major advantage of this approach refers to the fact that there remains no permanent device within systemic circulation. Therefore no OAC or DPI is required after the procedure to prevent thrombus formation during endothelialization.

However, some case-reports described acute and delayed adverse events: “reopening” of the LARIAT closure device,⁴⁸ LA thrombus⁴⁹⁻⁵⁰ and LA laceration (3/6 patients: 50%) progressing to cardiac tamponade, requiring surgery.⁵¹

These preliminary results demonstrated feasibility of this concept but further studies are needed to validate its future clinical role in LAA closure.

Conclusions And Perspective:

Percutaneous LAA closure is able to reduce the risk of stroke in NVAF and represents a treatment option for high-risk patients. The

Table 2: Complications associated with percutaneous endocardial LAA closure

	PLAATO	WATCHMAN			ACP			ACP vs WATCHMAN		
	Ostermayer, 2005 ⁴³	Bayard, 2010 ⁴⁴	Block, 2009 ⁴⁵	Protect AF ²⁹	CAP ⁴⁶	PREVAIL ⁴²	Park, 2011 ⁴⁸	Asia-Pacific experience ⁴⁹	Plicht, 2013 ³⁹	Chun, 2013 ³⁷
Patients, n	111	180	64	463	460	407	143	20	34	80 (40 vs 40)
Acute implantation success rate, %	97	90	93.85	90.9	94.3	95.1	96	95	100	95-100
Serious complications rate, %	NA	NA	18 (all late but PE)	39 (8.7)	23 (4.1)	12 (4.4)	10 (7%)	2 (10%)	1	4 (5%): 2 Watchman, 2 ACP
Device embolization, n (%)	0	2 (1.1%)	0	3 (0.6%)	0	NA	2 (1%)	0	0	1 ACP (1.2%)
Air embolism, n	0	0	0	3 (0.6%)	0	NA	2 (1%)	1 (5%)	0	2 (2.5%): 1 Watchman, 1 ACP
Thrombus formation, n	0	0	0	20 (4.2%) ⁴⁶	0	NA	NA	1 (5%)	6 (17.6%)	4 (5.1%) : 3 Watchman (7.9%) vs 1 ACP (2.5%)
Serious pericardial effusion	2 (1.8%)	6 (3.3%)	1 (1.5%)	22 (4.8%)	10 (2.2%)	1.9%	5 (4%)	0	1 (2.9%)	2 (2.5%): 1 Watchman, 1 ACP
Procedural stroke	0	NA	0	5 (0.9%)	0 (0%)	NA	3 (2%)	0	0	0
Procedural-related death	0	2(1.1%)	0	0	0	0	0	0	0	0
Access-related complications	1 perforation R femoral artery; 1 Right leg deep vein thrombosis 2 (1.8%)	NA	NA	2 hematoma, 1 arterio-venous fistula 3 (0.6%)	1 pseudoaneurysm	NA	NA	NA	NA	4 hematoma, 1 pseudoaneurysm (6.8%)

initially high procedural complication rate decreased with growing operator experience after accomplishing the learning curve and is now associated with an acceptable safety profile. Moreover, novel devices and designs are currently under evaluation, which may contribute to perform safer LAA closure in future. The important topic of optimal post-procedural antithrombotic treatment requires further investigation.

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