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Faculty of Medicine

Department of Cardiology

Contribution to the Study of Percutaneous Left Atrial Appendage Occlusion

Mathieu Lempereur, MD

Supervisors: Professor Dr Patrizio Lancellotti and Professor Dr Victor Legrand

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A Hadrien, Elliot et Eloïse

The left atrial appendage is our most lethal and disabling attachment!

W. Dudley Johnson, European Journal of Cardio-thoracic Surgery. 2000.[1]

If you want to get out of medicine the fullest enjoyment, be students all your lives.

David Riesman

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First Author

- **Lempereur M**, Aminian A, Freixa A, Gafoor S, Shakir S, Omran H, Berti S, Santoro G, Kefer J, Landmesser U, Nielsen-Kudsk JE, Cruz-Gonzalez I, Kanagaratnam P, Nietlispach F, Ibrahim R, Sievert H, Schillinger W, Park JW, Gloekler S, Tzikas A. Left Atrial Appendage Occlusion in Patients with Atrial and Previous Major Gastrointestinal Bleeding (From the Amplatzer Cardiac Plug Multicenter Registry). Am J Cardiol. 2017;120(3):414-420.

- **Lempereur M**, Aminian A, Dulgheru R, De Potter T, Oury C, Lancellotti P. Role of imaging in left atrial appendage occlusion. International Journal of Cardiovascular Practice. 2017;2(2):33-43.

- **Lempereur M**, Aminian A, Saw J. Rebuttal with regards to "Device-associated thrombus formation after left atrial appendage occlusion: A systematic review of events reported with the Watchman, the Amplatzer Cardiac Plug and the Amulet". Catheterization and Cardiovascular Interventions. 2017. Catheter and Cardiovas Interv. 2017. doi: 10.1002/ccd.27135. [Epub ahead of print]

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- Spencer R, DeJong P, Fahmy P, **Lempereur M**, Tsang M, Gin K, Lee P, Nair P, Tsang T, Jue J, Saw J. Changes in Left Atrial Appendage Dimensions Following Volume Loading During Percutaneous Left Atrial Appendage Closure. JACC Cardiovasc Interv. 2015;8(15):1935-41.

List of Abbreviations

Abbreviations	**Terms**
AC	anticoagulation
ACP	Amplatzer Cardiac Plug
AF	atrial fibrillation
ASA	acetylsalicylic acid
CCTA	cardiac computed tomography angiography
CE	Conformité Européenne
CI	confidence interval
CKD	chronic kidney disease
CT	computed tomography
DAPT	dual antiplatelet therapy
DAT	device-associated thrombus
EF	ejection fraction
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FO	fossa ovalis
FU	follow-up
GI	gastrointestinal
HR	hazard ratio
IAS	interatrial septum
ICB	intracranial bleeding
ICE	intracardiac echocardiography
IQ	interquartile
IQR	interquartile range
IV	intravenous
IVC	inferior vena cava
IVH	intravenous heparin
LA	left atrium

List of Abbreviations

LAA	left atrial appendage
LAAO	left atrial appendage occlusion
LAO	left anterior oblique
LCx	left circumflex
LWMH	low molecular weight heparin
MGIB	major gastrointestinal bleeding
NOAC	non-vitamin K oral anticoagulant
NVAF	nonvalvular atrial fibrillation
OAC	oral anticoagulation
OR	odds ratio
PET	polyethylene terephthalate
PFO	permanent foramen ovale
RA	right atrium
RAO	right anterior oblique
RR	relative risk
SVC	superior vena cava
TIA	transient ischemic attack
TOE	transoesophageal echocardiography
TSP	transseptal puncture
VKA	vitamin K antagonist
WM	WATCHMAN

Summary

LAA occlusion appears today as a valid alternative to long-term oral anticoagulation (OAC) in selected patients with nonvalvular atrial fibrillation (AF) at high thromboembolism risk in case of relative or absolute contraindications to OAC.

In the first publication, we underlined the importance of multimodality imaging in the understanding of 3D aspects and anatomy of the left atrial appendage (LAA) and surrounding structures for LAA occlusion (LAAO) procedures. Performant imaging is essential for procedural planning, during each step of the procedure, and for device surveillance after implantation. With the use of multimodality imaging, including 2D/3D echocardiography, fluoroscopy, and cardiac computed tomography, the safety and efficacy of the procedure can be increased.

The second part of this dissertation aimed to analyze the incidence, risk factors, treatment and prognosis of device-associated thrombosis (DAT), which is a potential complication after LAAO. DAT appeared to be an infrequent complication of percutaneous LAAO, with an overall incidence of DAT estimated at 3.9%. It occurred mainly early after the procedure (median time from procedure to diagnosis: 1.5 months) and was associated with a low rate of neurological complications. In the majority of cases, diagnosis was made during follow- up imaging with transoesophageal echocardiography (TOE). The treatment consisted mostly of anticoagulation, either with low molecular weight heparin or with OAC and was highly effective with complete thrombus resolution achieved in 95% of cases. Further studies are needed to evaluate the optimal management of DAT.

The third goal of this work was to analyze the efficacy and safety of LAAO in the subgroup of patients with previous major gastrointestinal (GI) bleeding. We found that, in these patients, the overall procedural safety of LAAO with the Amplatzer Cardiac Plug was high, although it was associated with an increased risk of periprocedural major bleeding. The efficacy of LAAO for stroke reduction was high and similar in patients with or without previous major GI bleeding, with similar overall survival in both groups. During the total follow-up (FU) period (periprocedural period and from day 8 to the end of FU), the procedure was associated with a reduction in the rate of bleeding events compared to the expected rate based on the HAS-BLED score. However, as compared to patients without previous major GI bleeding, this diminution in bleeding risk was less pronounced in patients with previous MGIB, as more major bleeding events were observed in the periprocedural period.

Further trials are needed to assess the best use and indication of LAA occluders, evaluation of LAAO vs. non-vitamin K oral anticoagulants, evaluation of results in specific subgroups of patients, and evaluation of the optimal antithrombotic regimen after implantation. Team approach, multimodality imaging and patient-tailored management will likely have a key role in LAAO in the future.

Résumé

L'occlusion percutanée de l'auricule gauche peut aujourd'hui être considérée comme une approche alternative valable à l'anticoagulation (AC) au long cours chez certains patients souffrant de fibrillation auriculaire (FA) non-valvulaire à haut risque thromboembolique et présentant une contre-indication absolue ou relative à l'anticoagulation.

Dans la première publication, nous soulignons l'importance de l'imagerie multimodale dans la compréhension de l'organisation tridimensionnelle et l'anatomie de l'auricule gauche et des structures avoisinantes en cas de fermeture percutanée de l'auricule gauche. La place de l'imagerie est fondamentale pour la planification de la procédure, durant chaque étape de l'intervention et pour la surveillance des dispositifs lors du suivi. Par l'utilisation de plusieurs modalités d'imagerie combinées, incluant l'échocardiographie bi- et tridimensionnelle, la fluoroscopie et le scanner cardiaque, la sécurité et l'efficacité de cette procédure peuvent être améliorées.

La seconde partie de cette dissertation vise à analyser l'incidence, les facteurs de risque, le traitement et le pronostic de la thrombose associée au dispositif (TAD), qui est une complication reconnue en cas de fermeture percutanée de l'auricule gauche. La TAD se présente comme une complication peu fréquente, avec une incidence globale estimée à 3,9%. Elle se produit essentiellement assez tôt après la procédure (temps médian post-procédural de 1,5 mois) et est associée à un faible taux de complication neurologique. Dans la majorité des cas, le diagnostic est réalisé durant le suivi programmé au moyen d'une échocardiographie transoesophagienne. Le traitement consiste en l'administration d'anticoagulants, sous forme d'héparine de bas poids moléculaire ou d'anti-vitamine K, et est très efficace, permettant la résolution du thrombus dans 95% des cas. La réalisation d'études complémentaires est nécessaire pour évaluer la prise en charge optimale en cas de TAD.

Le troisième objectif de ce travail est d'analyser l'efficacité et la sécurité de l'occlusion de l'auricule gauche dans le sous-groupe de patients présentant des antécédents d'hémorragie digestive sévère. Dans cette population, nous avons observé une bonne sécurité de la procédure, néanmoins associée à un risque accru de complications hémorragiques durant la période péri-procédurale. L'efficacité de la procédure en matière de réduction du risque d'accident vasculaire était élevée et similaire chez les patients avec ou sans antécédents d'hémorragie digestive sévère, avec une survie globale similaire dans les deux groupes. Durant la période de suivi totale, l'intervention était associée à une réduction du risque hémorragique en comparaison au risque attendu basé sur le score HAS-BLED. Cependant, la diminution du risque hémorragique était moins marquée chez les patients avec antécédents d'hémorragie digestive sévère, en raison de la survenue de plus d'évènements hémorragiques chez ces patients durant la période péri-procédurale.

La réalisation d'études complémentaires est nécessaire pour déterminer les indications optimales d'occlusion percutanée de l'auricule gauche, pour évaluer cette procédure en comparaison avec les anticoagulants directs, pour analyser les résultats de cette intervention chez différents sous-groupes cliniques de patients et pour distinguer le meilleur traitement antithrombotique dans les suites de l'implantation d'un dispositif de fermeture. Une approche multidisciplinaire, l'imagerie multimodale et la prise en charge personnalisée des patients vont probablement avoir une place importante dans cette technique dans le futur.

1 General Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting 1-2% of the general population. The major complication associated with AF is represented by thromboembolic events, especially ischemic stroke. Oral anticoagulation (OAC) has been the mainstay of therapy, reducing the relative risk of stroke by nearly two-thirds. However, this treatment is associated with a risk of major bleeding and is contraindicated in some high-risk patients. Based on the fact that >90% of thrombi originate from the left atrial appendage (LAA), nonpharmacologic approaches to exclude the LAA from the systemic circulation have been developed. Among those, percutaneous LAA occlusion (LAAO) has become a valid alternative to OAC in some patients with high thromboembolism risk and contraindications to long-term OAC. Currently, this prophylactic treatment is limited to a specific subgroup of patients. Clinical trials are underway to evaluate long-term efficacy and safety of this technique as well as defining the best periprocedural management.

In the first part of this dissertation, the role of imaging in this technique is discussed: multimodality imaging has proven to be effective in increasing the safety and efficacy of the procedure. In the second part of this dissertation, device-associated thrombus formation is analyzed in terms of epidemiology, treatment and complications. In the third part, results of this procedure in the subgroup of patients with history of major gastro-intestinal (GI) bleeding are presented.

2 Atrial fibrillation

2.1 Epidemiology of atrial fibrillation: prevalence and incidence

AF is the most common cardiac arrhythmia and is characterized by chaotic atrial electrical activity which results in irregularly irregular ventricular contractions and ineffective contraction of the atria. AF is strongly associated with structural heart disease and co-morbid cardiovascular conditions.[2,3]
AF is estimated to affect 1 to 2% of the general population. The prevalence of AF increases with age.[4] In the ATRIA study, 70% of patients were at least 65 years old.[5] The prevalence is projected to increase to 14-17 million by 2030 in the European Union[6,7] due to a growing proportion of elderly individuals secondary to an ageing population and due to improved survival of patients with conditions that predispose to AF.[8]

2.2 Cardiovascular mortality and morbidity associated with AF

Symptoms and complications linked to AF can broadly be divided in rhythm disturbance (palpitations, reduced cardiac output…) and in thromboembolic complications (ischemic stroke, peripheral embolization…). AF is associated with a number of severe complications including a two-fold increased risk of all-cause mortality in women and a 1.5-fold increase in men.[9–11] It is also associated with a four- to fivefold increased risk of stroke[12] and two- to threefold increased risk of heart failure[13].

2.3 Stroke and AF-related stroke

Globally, stroke is the second leading cause of death behind heart disease and is the first cause of serious long-term disability.[14,15] In case of AF, the atria contract irregularly which leads to stasis and dysfunction. These factors can lead to clot formation and eventually to thromboembolism.[16] AF is a major cause of stroke, increasing ischemic stroke risk by four- to fivefold, and is responsible for 15% of all strokes and 30% of strokes in patients age >80 years[4,17]. 70% of all strokes in patients with AF are cardioembolic in nature. The main source of these cardioembolic events lies within the LAA.[16]
Cardiac sources of emboli account for >25% of all ischemic strokes while nonvalvular AF remains the most common cause of cardioembolic stroke.[18]

2.3.1 Severity of AF-related stroke

Strokes due to cardioembolism are in general severe and prone to early and long-term recurrence. Strokes associated with AF are indeed more severe with 50% greater risk of disability or handicap and > 50% greater risk of death compared to non-AF related strokes.[19,20] Stroke is the third leading cause of death in patients with AF. Two thirds of patients with AF are at high risk of stroke and 35% of those patients will have a stroke in their lifetime.[4,21]

2.3.2 Clinical risk stratification for stroke prediction

There are several clinical risk scores to evaluate the risk of thromboembolic complications in patients with nonvalvular AF (NVAF). These risk models are derived from large studies of patients and include some clinical risk predictors.[22] The most widely used scores are the $CHADS_2$ and the CHA_2DS_2-VASc scores, which are developed below. Of note, there are other, less well established risk factors for stroke that may be taken under consideration while evaluating thromboembolism risk in patients: unstable international normalized ratio (INR) and low time in therapeutic range in patients treated with vitamin K antagonists (VKA); chronic kidney disease (CKD); previous bleed or anemia; alcohol excess; markers for decreased therapy adherence; elevated high-sensitivity troponin; and elevated N-terminal pro-B-type natriuretic peptide.[23]

2.3.2.1 $CHADS_2$ score

The $CHADS_2$ score includes five common clinical stroke risk factors derived from the non-warfarin arms of the historical trial cohorts and was tested and validated in other cohorts.[24,25]. This score includes Congestive heart failure (any history), Hypertension (prior history), Age ≥75 years, Diabetes mellitus, prior ischemic Stroke, transient ischemic attack, or systemic embolic event (Table 2-1). This score was used to define low-, moderate- and high-risk patients, so that 'high-risk' patients could be treated with OAC. However, this score has several limitations: the score tends to categorize a large proportion of the AF population into the intermediate-risk strata and many potential risk factors have not been included in the score.[26]

2.3.2.2 CHA_2DS_2-VASc score

The CHA_2DS_2-VASc score is an attempt to improve risk stratification and to move towards a risk-factor-based approach rather than a categorization of patients in risk strata. The CHA_2DS_2-VASc score is a refinement of the $CHADS_2$ score and adds some risks factors: any arterial vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65 to 74 years, and female sex are added to the $CHADS_2$ score. It also emphasizes the importance of age greater than 74 years[27] (Table 2-1). Thus, the 2006 Birmingham/National Institute for Health and Clinical Excellence (NICE) stroke risk stratification schema was refined into a risk factor-based approach by reclassifying and/or incorporating additional new risk factors where relevant. This schema was then compared with existing stroke risk stratification schema in a real-world cohort of patients with AF (n=1,084) from the Euro Heart Survey for AF. The CHA_2DS_2-VASc score was shown to provide some improvement in predictive value for thromboembolism over the $CHADS_2$ schema. It shows low event rates in low-risk subjects and allows the classification of only a small proportion of subjects into the intermediate-risk category.[28]

The rates of stroke or other thromboembolism at 1 year based on the $CHADS_2$ and CHA_2DS_2-VASc Scoring System are shown in Table 2-2.[24,29,30]

Table 2-1. $CHADS_2$ and CHA_2DS_2-VASc risk stratification scores

$CHADS_2$ acronym		**CHA_2DS_2-VASc acronym**	
Congestive HF	1	**C**ongestive HF	1
Hypertension	1	**H**ypertension	1
Age ≥75 years	1	**A**ge ≥75 years	2
Diabetes mellitus	1	**D**iabetes mellitus	1
Stroke/TIA/TE	2	**S**troke/TIA/TE	2
		Vascular disease	1
		Age 65–74 years	1
		Sex **c**ategory (female)	1
Maximum score	*6*	*Maximum score*	*9*

Abbreviations:
HF: heart failure; TIA: transient ischemic attack; TE: thromboembolism.
Definitions of risk factors:
Congestive heart failure: signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction (<40%); Hypertension: resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment; Diabetes mellitus: fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin; Vascular disease: previous myocardial infarction, peripheral artery disease, or aortic plaque.

Table 2-2. Stroke risk stratification with the $CHADS_2$ and CHA_2DS_2-VASc scores

$CHADS_2$ acronym	Unadjusted ischemic stroke rate (% per year) *	**CHA_2DS_2-VASc acronym**	Unadjusted ischemic stroke rate (% per year) *
0	0.6%	0	0.2%
1	3.0%	1	0.6%
2	4.2%	2	2.2%
3	7.1%	3	3.2%
4	11.1%	4	4.8%
5	12.5%	5	7.2%
6	13.0%	6	9.7%
		7	11.2%
		8	10.8%
		9	12.2%

* These stroke rates were not adjusted for possible use of aspirin.[31]

3 Prevention of stroke and thromboembolic complications

3.1 Pharmacologic approaches

Stroke prevention with anticoagulation is among the main pillars of AF management and has an impact on prognosis. Several randomized placebo-controlled trials have demonstrated that OAC is highly effective in preventing thromboembolism with AF, with landmark meta-analysis showing 64% stroke reduction and 26% mortality reduction with warfarin[32,33].

Thus, OAC therapy is currently the first line of treatment in patients with AF and 1 or more risk factors. This therapy can prevent most ischemic strokes and can prolong life.

3.1.1 Anticoagulants

The net clinical benefit of OAC therapy is almost universal. OAC should be used in most patients with AF, with the exception of patients at very low stroke risk. Based on current evidence, anticoagulation guidelines have become more stringent: the European Society of Cardiology recommends anticoagulation for CHA_2DS_2 -VASc ≥2 (IA). Anticoagulation should be considered in case of CHA_2DS_2-VASc=1, if the risk factor is not female sex (IIaB).[23]

3.1.1.1 Bleeding risk associated with long-term anticoagulant therapy

All anticoagulants increase the risk of bleeding. The risk of major bleeding in patients treated with anticoagulants varies with the degree of anticoagulation (anticoagulant agent and dosing, INR level in case of warfarin). Patient characteristics and comorbidities are also very important factors.[34,35] Of note, some of these risk factors are modifiable and the risk of bleeding should be minimized by addressing modifiable risk factors (uncontrolled hypertension, alcohol excess, use of concomitant non-steroidal anti-inflammatory drugs…). The assessment of bleeding risk is part of the clinical assessment before starting long-term anticoagulation in NVAF patients. This risk should be weighed against the risk of thromboembolic complications in a risk-benefit assessment. The evaluation of bleeding risk should help identifying modifiable bleeding risk factors in order to correct these factors. A number of bleeding risk scores have been developed, mainly in patients on VKAs. These include HAS-BLED[36], ORBIT (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation)[37], $HEMORR_2HAGES$ risk index[35], and more recently, the ABC (age, biomarkers, clinical history) bleeding score[38]. The $HEMORR_2HAGES$ score has been developped to quantify the bleeding risk in elderly patients with AF. In a meta-analysis by Caldeira et al., this score had a better specificity but less sensitivity than the HAS-BLED score to predict bleeding events.[39] Due to its ease of use and to a good diagnostic accuracy compared to other risk scores, the HAS-BLED risk score is the most widely used score in clinical practice.

It is important to note that stroke and bleeding risk factors overlap in the case of AF: a patient with a high risk of stroke related to AF has a high probability of having a high risk for bleeding complications related to anticoagulation. For example, older age is one of the most important predictors of both ischemic stroke and bleeding in AF patients.[40]

3.1.1.1.1 HAS-BLED risk score

The most commonly employed bleeding risk models for patients with AF is the HAS-BLED risk score. This risk score is based upon seven risk factors for bleeding and has been recommended within the European Society of Cardiology guidelines for assessing the risk of bleeding in AF management.[41]

The HAS-BLED score is a practical score that has been developed to estimate the 1-year risk for major bleeding (intracranial, hospitalization, hemoglobin decrease >2 g/L, and/or transfusion) in a cohort of real-world patients with AF. This score was derived from a cohort of 3,978 patients with atrial fibrillation in the Euro Heart Study.[36] Along with historical bleeding risk factors (OAC, alcohol use, and hypertension), all potential bleeding risk factors identified from the univariate analyses of the derivation cohort with a P value <0.10 (age >65 years, female sex, diabetes mellitus, heart failure, COPD, valvular heart disease, kidney failure, prior major bleeding episode, and clopidogrel use), were used in the multivariate logistic regression analyses. Variables in the score are described in Table 3-1. Thus, it was possible to elaborate a new bleeding risk score termed HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly). With this score, the annual bleeding rate increased with increasing risk factors and the predictive accuracy in the overall population using significant risk factors in the derivation cohort (*c*-statistic=0.72) was consistent when applied in several subgroups. The *c*-statistics were similar in subgroups, except when patients were receiving antiplatelet agents alone or no antithrombotic therapy. This clinical score has been validated in additional cohorts of patients with AF.[42,43] The risk of major bleeding within 1 year in patients based on the HAS-BLED score is given in Table 3-1.

Table 3-1. Clinical characteristics comprising the HAS-BLED bleeding risk score and risk of bleeding estimated by the HAS-BLED score.

HAS-BLED Letter	Clinical characteristic	Points
H	Hypertension (ie, uncontrolled blood pressure)	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding tendency or predisposition	1
L	Labile INRs (for patients taking warfarin)	1
E	Elderly (age greater than 65 years)	1
D	Drugs (concomittant aspirin or NSAIDs) or excess alcohol use (1 point each)	1 or 2
HAS-BLED score (total points)	**Bleeds per 100 patient-years**	
0	1.13	
1	1.02	
2	1.88	
3	3.74	
4	8.70	
5	12.50	
6 to 9	Insufficient data	

Abbreviations: INR: international normalized ratio; NSAIDs: nonsteroidal anti-inflammatory drugs.
Definitions of risk factors: Hypertension: systolic blood pressure >160 mmHg; Abnormal renal function: presence of chronic dialysis, renal transplantation, or serum creatinine ≥200 micromol/L; Abnormal liver function: chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (eg, bilirubin more than two times the upper limit of normal, plus one or more of aspartate transaminase, alanine transaminase, and/or alkaline phosphatase more than three times the upper limit normal); Bleeding predisposition: chronic bleeding disorder or previous bleeding requiring hospitalization or transfusion; Labile INRs: unstable INRs, excessively high INRs, or <60 percent time in therapeutic range.
Based on initial validation cohort from Pisters, R. A novel-user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138:1093.

3.1.1.2 Vitamin-K antagonists anticoagulants and limitations

VKA include multiple drugs, with the most widely used agents being warfarin and acenocoumarol. VKA act by inhibiting the synthesis of vitamin K-dependent clotting factors (Factors II, VII, IX, and X, anticoagulant proteins C and S). They are used in a variety of clinical settings and are highly effective in reducing the risk of venous and arterial thromboembolism in many settings. There is a large body of clinical experience proving the efficacy and safety of these agents.[32]

However, their use may be challenging because their therapeutic range is narrow and dosing is affected by many factors including drug interaction, diet interaction and genetic variation. There is a high variability intra- and inter-patients. The dose needed to reach the therapeutic range varies between individuals and may vary in the same patient due to diet variation, drug interaction… Thus, there is a need for frequent monitoring and dosage adjustment. The time spent with a prothrombin time (PT)/international normalized ratio (INR) in the therapeutic range influences directly the safety and efficacy of the treatment. Time above the therapeutic range increases the risk of bleeding, while time spent below the therapeutic range increases the risk of thromboembolic complications, which these agents were administered to prevent. Time spent in the therapeutic range varies between countries and healthcare systems but has been shown to be frequently of only 50% to 60%.[44,45] Moreover, only two-thirds of patients who are appropriate for OAC therapy actually receive the treatment.[46] On the long run, the rate of discontinuation of treatment can be as high as 50% at 3 years, despite ongoing AF.[47]

3.1.1.3 Non-vitamin K antagonist anticoagulants

The inherent limitation of VKAs have stimulated the development of other options for anticoagulation. Thrombin (factor IIa), which has a central role in coagulation, is the final enzyme of the clotting cascade that produces fibrin; it is formed by the proteolytic cleavage of prothrombin by factor Xa. Anticoagulants that directly target the enzymatic activity of thrombin and factor Xa have been developed, respectively direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (apixaban, edoxaban, rivaroxaban). They block major procoagulant activities involved in the generation of a fibrin clot.

These agents have a predictable effect without the need for regular anticoagulation monitoring. Some of them are given once daily, others twice daily. Dose reduction may be indicated in some clinical indications (low body weight, poor renal function, elderly...).

3.1.1.3.1 Efficacy and Safety of NOAC

Each agent has been evaluated in large randomized controlled studies vs. dose-adjusted warfarin.[48–51] In a meta-analysis based on the high-dose treatment groups of the pivotal studies of non-vitamin K antagonist oral anticoagulants (NOAC) vs. warfarin, NOACs significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR: 0.81; 95% CI: 0.73–0.91; $p<0.0001$), mainly driven by a reduction in hemorrhagic stroke (RR: 0.49; 95% CI: 0.38–0.64; $p<0.0001$).[52] There was a 10% mortality reduction in patients randomized to NOAC therapy (RR: 0.90; 95% CI: 0.85–0.95; $p<0.0003$). The rate of intracranial hemorrhage was reduced by ~50% (RR: 0.48; 95% CI: 0.39–0.59; $p<0.0001$), while gastrointestinal bleeding events were more frequent (RR: 1.25; 95% CI: 1.01–1.55; $p<0.04$).

Long-term therapy with warfarin or novel oral anti-coagulation (NOAC) is associated with lifetime major bleeding risks of 1.6% to 3.6% per year in recent clinical trials[49–51,53]. Although intra-cranial hemorrhage and hemorrhagic stroke rates are consistently lower with NOAC, the overall risk of major bleeding was not diminished with dabigatran or rivaroxaban compared with warfarin[49,53]. Apixaban and edoxaban were the only agent that showed a reduction of major bleeding but the study population were not perfectly comparable ($CHADS_2$ score, quality of INR adjustment…) [50,51].

'Real-world' use of NOAC has been assessed in observational studies. Available data confirmed the good efficacy and relative safety of NOAC in unselected patients in daily care.[54–56] Discontinuation rates were lower compared to patients treated with VKA.

3.1.2 Antiplatelet agents

3.1.2.1 Aspirin monotherapy

Aspirin monotherapy for the prevention of thromboembolic events in patients with AF with one 'clinically relevant non-major' risk factor (CHA_2DS_2-VASc score =1) was still a class IB recommendation in the 2010 ESC guidelines on the management of AF.[57]

This recommendation has now changed: antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk (class IIIA).[23] Aspirin treatment in this indication is consistently and substantially less effective in reducing thromboembolic risk compared to warfarin in all AF patients with a $CHADS_2$ score ≥1.[32,58–60] This difference in efficacy was shown in an individual patient meta-analysis of six prevention trials: patients treated with warfarin were significantly less likely to experience an ischemic stroke (2.0 vs. 4.3 per 100 patient-years, hazard ratio: 0.55, 95% CI: 0.45-0.71).[61]

Moreover, antiplatelet therapy significantly increases bleeding risk, especially dual antiplatelet therapy (2.0% vs. 1.3% with antiplatelet monotherapy; p<0.001).[62] Indeed, it has been demonstrated in several studies that bleeding rates on aspirin are similar to those on OAC.[63–66] Of note, in a recent meta-analysis only taking into account trials with target INR in the usually recommended range (2–3) and including the recently published WARCEF trial[67], major bleeding risk was substantially lower on aspirin than on VKA targeting current usual INR range. The authors conclude that, although antiplatelet agents increase the risk of spontaneous intracranial bleeding (ICB), they have a substantially lower bleeding risk than OAC with a VKA.[68]

Overall, the risk-benefit ratio of aspirin monotherapy for stroke prevention in AF patients is unfavourable and this treatment cannot be recommended in this indication, even though it is still found in routine clinical practice.

3.1.2.2 Dual antiplatelet therapy

The safety and efficacy of dual antiplatelet therapy (DAPT) has been studied in two large randomized trials in patients with one or more risk factor for stroke: ACTIVE W (DAPT vs. warfarin) and ACTIVE A (DAPT vs. aspirin alone in patients ineligible for VKA treatment). The ACTIVE W trial was stopped prematurely because warfarin anticoagulation significantly lowered the annual rate of the primary end point (first occurrence of stroke, systemic embolization, myocardial infarction, or vascular death) compared to combined antiplatelet therapy (3.9 vs. 5.6 percent, relative risk: 0.69, 95% CI: 0.57-0.85). There was also a trend toward a lower risk of major bleeding with warfarin.[64] In the ACTIVE A trial, patients treated with DAPT had a significantly lower annual rate of the primary combined end point (first occurrence of stroke, systemic embolization, myocardial infarction, or vascular death) (6.8 vs. 7.8 percent, RR: 0.89, 95% CI: 0.81-0.98), which was primarily driven by a reduction in stroke (2.4 vs. 3.3 percent, RR: 0.72, 95% CI: 0.62-0.83). DAPT had a significantly increased incidence of major bleeding (2.0 vs. 1.3% per year, RR: 1.57, 95% CI: 1.29-1.92).[62]

An analysis of data from the two ACTIVE trials has shown that there was a small non-significant benefit to combination therapy: adding clopidogrel to aspirin therapy prevented 0.57 ischemic stroke equivalent (95% CI: -0.12 to 1.24) per 100 patient-years of treatment.[69]

It is important to note that DAPT and OAC have similar bleeding risks. Thus, a patient who is not a good candidate for OAC because an excessive estimated bleeding risk is also not a candidate for DAPT. In case of LAAO, it should be noted that DAPT is generally only indicated for 1 to 6 months, and followed by aspirin monotherapy for a variable period of time (from no treatment to lifelong therapy). Thus, the exposure to DAPT post-LAAO is only temporary and reduces the cumulative risk of major bleeding events.

4 Nonpharmacologic approaches to stroke prevention in atrial fibrillation

Even though OAC is the main pillar of stroke prevention in AF patients, a significant proportion (30% to 50%) of eligible patients do not receive OAC due to absolute contraindications or perceived risks of bleeding[70]. This challenge has led to nonpharmacologic approaches for stroke prevention in nonvalvular AF.

4.1.1 Rationale for LAA closure

In case of AF, the irregularly irregular rhythm in the atrium leads to dysfunction and blood stasis. This can provoke clot formation and, eventually thromboembolism. Thus, as explained above, 70% of all strokes in AF patients have a cardioembolic origin. Transoesophageal echocardiography (TOE), autopsy, and surgical reports confirmed that >90% of non-rheumatic AF-related left atrial thrombi were isolated to or originated from the LAA. Blackshear et al. analyzed 23 studies evaluating the left atrium and LAA in valvular and nonvalvular AF patients. In this analysis, in case of NVAF, thrombi were isolated to or originated in the LAA in 91% of cases.[71] In case of valvular AF, the rate of thrombi localized in the LAA dropped to only 57% ($p<0.0001$). In a cohort of 272 NVAF patients, a TOE study showed that 8% had a left atrial thrombus with 100% of clots localized in the LAA.[72]

Thus, mechanical approaches to exclude the LAA from systemic circulation were explored, and early attempts by surgical removal or ligation of LAA developed over 60 years ago. The first report of LAA occlusion in an animal model was by Hellerstein et al. in 1947 while the first-in-man reported resection of the LAA was by Madden in 1949.[73] These procedures were limited by the invasiveness and by significant rates of incomplete exclusion that were associated with increased stroke risks.[74,75]

Minimally invasive approaches have been developed over the past 2 decades and can be broadly divided into endocardial and epicardial devices (Table 4-1).

Table 4-1. LAA closure devices

Device name	**Company**	**Design**
Endocardial Devices		
PLAATO	*Appriva Medical Inc.*	Single-lobe occluder; nitinol cage; ePTFE membrane; hooks
WATCHMAN	*Boston Scientific*	Single-lobe occluder; nitinol frame; PET membrane; hooks
ACP	*St-Jude Medical/Abbott*	Lobe and disk (polyester mesh in both); nitinol mesh structure; stabilizing wires
Amulet	*St-Jude Medical/Abbott*	Lobe and disk (polyester mesh in both); nitinol mesh structure; stabilizing wires
WaveCrest	*Coherex Medical*	Single-lobe occluder; nitinol frame; polyurethane foam and ePTFE membrane; retractable anchors
Occlutech LAA Occluder	*Occlutech*	Single-lobe occluder; nitinol wire mesh; stabilizing loops; nanomaterial covering
Sideris Transcatheter Patch	*Custom Medical Devices*	Frameless detachable latex balloon covered with polyurethane
LAmbre	*Lifetech*	Lobe and disk; nitinol; PET membrane; distal barbs anchors
PFM	*Pfm Medical*	Dual disk (distal anchor, variable middle connector, proximal disk); nitinol frame
Ultrasetp	*Cardia*	Lobe and disk; nitinol frame; Ivalon covering; distal anchors
Epicardial Devices		
Lariat	*SentreHeart*	Endocardial and epicardial approach: magnetically-assisted snare over balloon in LAA
Atriclip	*AtriCure*	Surgical approach: parallel clip with polyester mesh
Aegis	*AEGIS Medical Innovations*	Epicardial subxiphoid approach: electrodes guide navigation to LAA and tissue capture evaluation
Cardioblate Closure System	*Medtronic*	Epicardial approach: silicone band covered by polyester fabric

ACP: Amplatzer Cardiac Plug; ePTFE: expanded polytetrafluoroethylene; LAA: left atrial appendage; PET: polyethylene terephthalate.

4.1.2 Left atrial appendage

4.1.2.1 Embryology of LAA

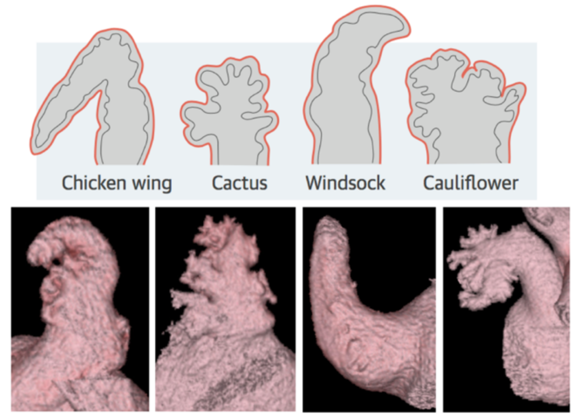
The LAA is the remnant of the original embryonic left atrium. It begins its development during the 3rd week of gestational life and originates from the wall of the left side of the primary left atrium, whereas the remaining portion of the left atrium derives from the branches of the primordial pulmonary veins.[76,77] Trabeculations formation starts at around the fifth week of embryonal development in the atria. They are secondary to cellular protrusion into the lumen.[78]

4.1.2.2 Anatomy of LAA

Compared to the right atrial appendage, the LAA is considerably smaller. It tends to have a small, tubular shape whereas the right atrial appendage has a wide triangular shape. The morphology of the LAA is extremely complex and heterogeneous. Individual LAA morphology is unique and may sometimes be referred to as a fingerprint. There are significant variations in LAA shape, size and relationship with adjacent cardiac and extra-cardiac structures.

In more than two-thirds of the cases, LAA is composed of 2 or more lobes that may be located in different planes.[79] Early transoesophageal echocardiography (TOE) anatomical studies described numerous shapes of LAA: narrow, tubular and hooked structure.[80] Currently used classification of LAA morphology is based on the general shape of the LAA. The four classical shapes are windsock (single dominant lobe without obvious bend), chicken wing (obvious bend in the body of the LAA), cactus (dominant central lobe with multiple secondary lobes) and cauliflower (short body with numerous secondary lobes and more complex internal characteristics).[81]

Figure 4-1. Variations in LAA shapes and usual classification of LAA morphologies.



Adapted from Wunderlich NC, Beigel R, Swaans MJ, et al. Percutaneous interventions for left atrial appendage exclusion: Options, assessment, and imaging using 2D and 3D echocardiography. *JACC Cardiovasc Imaging*. 2015;8:472–488 and Di Biase L, Santangeli P, Anselmino M, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. *J Am Coll Cardiol*. 2012;60:531–538.

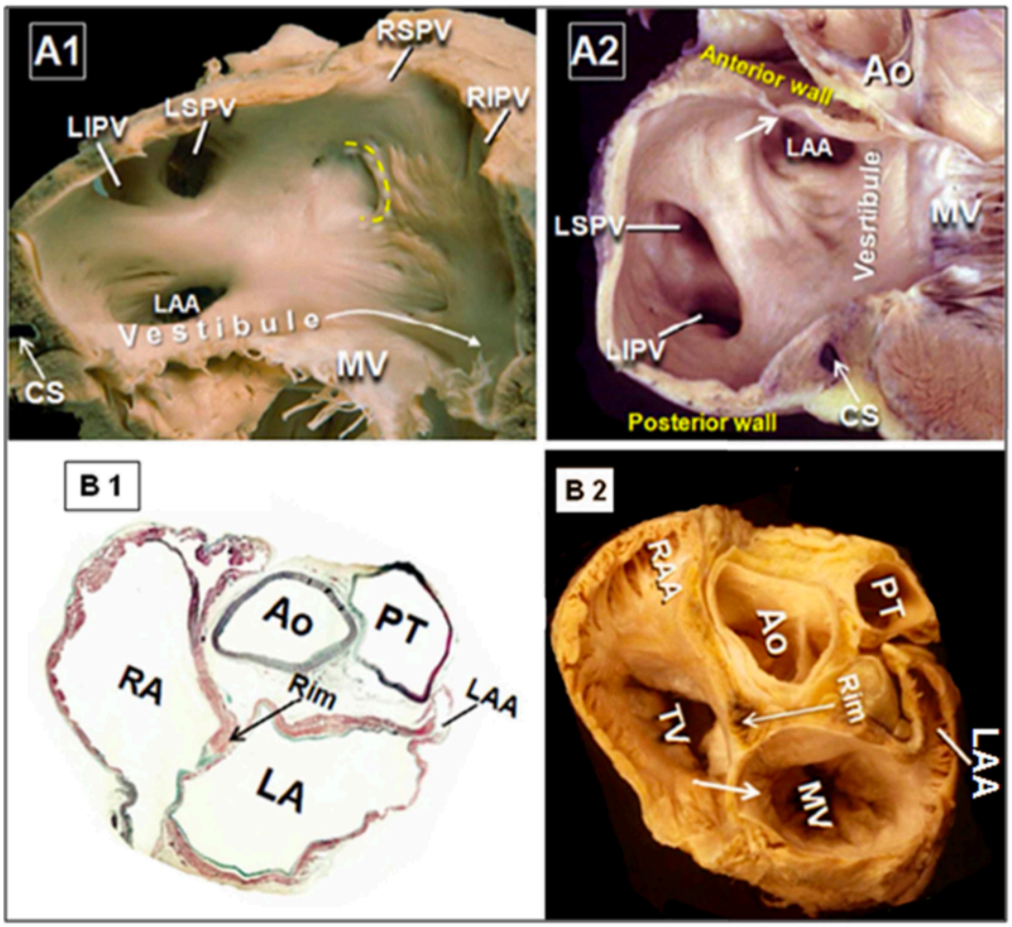
Most LAA are orientated superior-anteriorly and extend between the anterior and the lateral wall of the LA. The appendage overlaps the base of the pulmonary trunk, the main stem of left coronary artery, or its circumflex artery branch and the great cardiac vein at different levels.[77,82] In some cases, the tip may be directed inferiorly or posteriorly. In rare cases, the tip of the LAA passes behind the arterial pedicle to sit in the transverse pericardial sinus.

The border between the LAA and the LA body is described as the os. The shape of the LAA ostium is typically elliptical; other shapes have been less frequently described (round, triangular or water-drop shapes).[81,82] On heart specimen, the ostium had a mean long-diameter of 17.4±4mm and a short diameter of 10.9±4.2mm.[82]

The left lateral ridge represents the separation between the LAA orifice and the left pulmonary veins. In some hearts, there is a funnel-like zone between the left lateral ridge and the ostium, which is termed the limbus of the appendage. The precise relationship between the LAA orifice and the venous orifices as well as the distance between these orifices vary.[83] The endocardial aspect of the LAA is lined with muscle bundles of varied thicknesses made by the pectinate muscles. Theses muscles bundles are orientated in a "whorl-like" fashion throughout the LAA, with thin-walled myocardium between the pectinate muscles.[84]

Figure 4-2. Anatomy of the left atrial appendage and left atrial structures.

(A1)



Dissection of the posterior wall of the left atrium (LA) close to the posterior interatrial groove. The septal aspect of the LA shows the crescentic line of the free edge of the flap valve (yellow dotted line) against the rim of the oval fossa. The orifices of the right superior and inferior pulmonary veins (RSPV and RIPV) are adjacent to the plane of the septal aspect of the LA. (A2) Sagittal section of the heart showing the anterior wall of the LA behind the ascending aorta can become very thin at the area near the vestibule of the mitral valve (arrow). (B1) Histological section with Masson trichrome taken through the short axis of the heart to show the thin flap valve and the muscular rim of the fossa. (B2) Short axis through the interatrial septum (arrow). Ao, aorta; CS, coronary sinus; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; MV, mitral annulus; PT, pulmonary trunk; RA, right atrium; RAA, right atrial appendage; TV, tricuspid annulus.
Reproduced from Cabrera JA, Saremi F, Sánchez-Quintana D. Left atrial appendage: anatomy and imaging landmarks pertinent to percutaneous transcatheter occlusion. *Heart*. 2014;100:1636–50.

Figure 4-3. Relevant Anatomy Surrounding the Left Atrial Appendage.

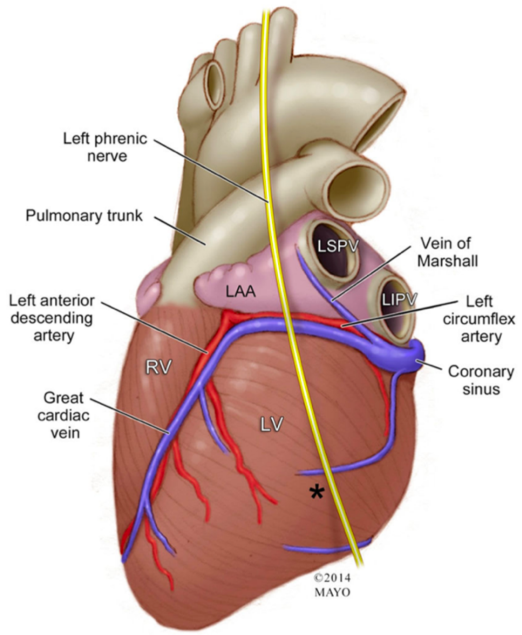


Illustration of the human heart emphasizing the left atrial appendage (LAA) and its closely related structures. The LAA is directed antero-superiorly and covers the left circumflex artery and great cardiac vein. The pulmonary trunk is abutting the LAA. The vein of Marshall traverses through the LAA and left superior pulmonary vein.
Reproduced from DeSimone C V, Gaba P, Tri J, et al. A Review of the Relevant Embryology, Pathohistology, and Anatomy of the Left Atrial Appendage for the Invasive Cardiac Electrophysiologist. *J Atr Fibrillation*. 8:81–87.

4.1.2.3 Physiology

LAA is thought to have several functions, including acting as a reservoir during left ventricular systole. The LAA is more compliant than the LA main chamber. Thus, in case of increase in LA pressure and/or volume observed in physiologic (i.e. during exercise) or pathologic conditions (i.e. heart failure), the LAA enlarges and acts as a blood reservoir. This may contribute to the modulation of LA pressure and elicit adaptive responses to maintain the homeostasis and maintain the cardiac output.[85,86] The LAA has also a significant role in endocrine regulation.[87] The left and right atrial appendages contain around 30% of the heart's pool of atrial natriuretic factor (aNF).[86] This potent endocrine modulator leads to multiple effects including change in heart rate, natriuresis, diuresis. Interaction between the LAA and autonomic nervous system has also been shown.[86] Thus, pressure and/or volume status can be sensed via the cells of the appendage, allowing the LAA to play a critical role in cardiac homeostasis and regulation of body volume status.

4.1.2.4 Anatomopathologic implications

In AF patients, LAA structure and function have several characteristics that make LAA a prothrombotic milieu favouring thrombus formation. The elements of the Virchow's triad are found in this setting: blood stasis in this blind-ended pouch with trabeculations and electromechanical dysfunction[88,89], endothelial dysfunction (secondary to fibrosis and inflammation)[90] and prothrombotic state (linked to the activation of coagulation cascade)[91, 92].

A post-mortem study on explanted hearts in patients with AF showed that the LAA volume was increased by a factor 3 compared to patient in normal sinus rhythm. They also reported that the endocardial surface was smoother and associated with more endocardial fibroelastosis. These findings suggest that LAA remodeling occurs frequently in chronic AF and may contribute to the increased risk of thrombus formation and systemic embolism.[93]

Different studies have evaluated a correlation between the thromboembolism risk and LAA morphological or structural features. LAA morphology has been shown to be a significant determinant of LAA flow velocity, suggesting an underlying mechanism for the association between LAA morphology and embolic events.[94] Patients with chicken wing LAA morphology were shown to less likely develop an embolic event even after controlling for comorbidities and $CHADS_2$ score.[95] This was confirmed in a recent meta-analysis.[96] Large LAA neck diameter and LAA depth as well as extensive LAA trabeculations may also be predictors of thromboembolic events.[97]

Anatomical studies demonstrated that LAA is quite compliant. As such, LAA volume and sizes may vary with pressure and volume loading conditions. This physiologic property may have technical implications as LAA dimensions may vary with loading conditions. Typically, a minimal left atrial pressure of 10-15 mmHg is mandatory before final device sizing assessment. Intraprocedural volume loading with saline, aiming for a LA pressure >12 mmHg, showed an increase in LAA dimensions in a small study.[98]

4.1.3 Surgical approaches

There are several techniques available to close the LAA which involve either excluding the LAA from the circulation, or excising the LAA altogether. The common techniques include simple neck ligation, purse-string technique, endocardial suturing, envagination and double suture technique, surgical amputation and closure, and surgical stapler. New surgical techniques have emerged in recent years with the development of new devices (Atriclip, TigerPaw, Endoloop snare, LigaSure TM vessel sealing system). These techniques have been developed to reduce the risk of complication and increase the rate of permanent complete closure.[99] Literature comparing the surgical technique is scarce. An analysis by Kanderian et al. showed that the rate of successful LAA closure was only 40% of the patients, with best rates with LAA excision.[74] The implication of incomplete LAA closure is important as the risk of thrombosis is increased in case of partially closed LAA due to the fact that blood is more stagnant.[74] The most serious complication of surgical LAA occlusion would be the occlusion or injury of the circumflex artery, with potential myocardial infarction and increased morbi-mortality of the procedure.[82]

In most studies, LAA occlusion/exclusion was performed during other open heart surgery, and more recently in combination with surgical ablation of AF[100] or as a stand-alone thoracoscopic procedure[101]. The evidence for the efficacy of surgical LAA exclusion for stroke prevention is currently inconclusive.[16] Some studies have shown a potential benefit, while others did not show any impact. In a series of 437 patients who underwent prophylactic LAA excision during open-heart surgery, there was no increase in the rate of bleeding or mortality and TOE follow-up did not demonstrate any clot in the LA.[1] The first randomized controlled trial included 77 patients who underwent coronary artery bypass graft surgery and had risk factors for stroke (LAAOS I). Patients were randomized to LAA occlusion versus no occlusion. 66% patients had a successful occlusion and there was no increased bleeding in the LAA occlusion group. After a follow-up of 13 months, the rate of thromboembolic events was 2.6% (2 peri-operative thromboembolic events in the occlusion group). Of note, this study was not designed to evaluate stroke outcomes.[102] LAAOS II randomized 51 patients with AF to LAA occlusion or no occlusion. After a follow-up of 1 year, there was no difference in the primary composite endpoint of death, MI, stroke, noncentral nervous system embolism and major bleeding (RR: 0.71, 95% CI: 0.19-2.66, p=0.61).[103] In a study by Garcia-Fernandez et al., 58 patients who had undergone LAA exclusion during mitral valve surgery were compared to 147 patients who did not undergo LAA exclusion. The occurrence of embolic events post-surgery was significantly lower in patients who had LAA ligation (3.4% vs. 17%, p=0.01) and the absence of LAA ligation was found to be an independent predictor of the occurrence of an embolic event in logistic regression analysis (Odds Ratio: 6.7, 95%CI: 1.5-31.0, p=0.02).[75] Another study on 136 patients who underwent mitral valve surgery did not show any difference in the rate of thromboembolic events after a follow-up of 3.6 years.[104] In a large propensity score-matching analysis including 9,792 patients who underwent prophylactic exclusion of the LAA during coronary artery bypass grafting and valve surgery, LAA closure was significantly associated with an increased risk of early postoperative AF (adjusted OR: 3.88; 95% CI: 2.89–5.20; p<0.001), but it did not influence the risk of stroke (adjusted HR: 1.07; 95%: 0.72–1.58; p=0.74) or mortality (adjusted HR: 0.92; 95% CI: 0.75–1.13; p=0.43).[105]

In conclusion, the strength of evidence for surgical LAA occlusion is currently poor. Thus, guidelines are based on the consensus opinion of experts (Level of Evidence C). The 2012 Heart Rhythm Society (HRS) guidelines recommend LAA closure when patients undergo surgical ablation of symptomatic AF (Class IIa).[106] Surgical excision of LAA may be considered in patients with AF undergoing cardiac surgery (Class IIb).[2] During mitral valve surgery, LAA excision may also be considered in patients with recurrent embolic events despite adequate anticoagulation (Class IIb).[107] Further trials are therefore needed to evaluate the efficacy and safety of surgical LAA exclusion. A large randomized controlled trial is currently ongoing and aims to recruit 4,700 patients in AF undergoing heart surgery (LAAOS III, NCT0156165).

4.1.4 Epicardial approach: Lariat

The catheter-based Lariat (SentreHEART Inc., Redwood City, California) LAA closure is a complex hybrid procedure that requires both an endocardial and epicardial approach. Lariat is Food and Drugs Administration (FDA)-approved (and CE-marked) for suture and knot tying during surgical applications, but not specifically for stroke prevention with AF. Lariat consists of a snare with a pre-tied suture that is magnetically guided epicardially over the LAA. There are 3 components: a 15-mm compliant occlusion balloon catheter (EndoCATH); 0.025- and 0.035-inch magnet-tipped guidewires (FindrWIRZ); and a 12-F Lariat suture delivery device[108].

The procedure was well described by Bartus et al.[108] with 4 key steps: 1) pericardial and transseptal access; 2) placement of the endocardial magnet- tipped guidewire in the apex of the LAA with balloon identification of the LAA ostium; 3) connection of the epicardial and endocardial magnet-tipped guidewires; and 4) snare capture of the LAA with closure confirmation and release of the pre-tied suture for LAA ligation.

The first published single-center experience with the Lariat procedure included 89 patients in Poland[108]. The mean age was 62 years, $CHADS_2$ score was 1.9, and CHA_2DS_2-VASc was 2.8. Technical success was 96%. There were 2 epicardial-related complications (right ventricular puncture and superficial epigastric artery laceration) and 1 transseptal complication (hemopericardium). Major post-operative adverse events included 2 severe pericarditis, 1 late pericardial effusion, 2 unexplained sudden deaths, and 2 late strokes. Of the 65 patients undergoing TOE at 1 year, complete LAA closure was observed in 98%. More recently, Price et al.[109] published the multicenter retrospective U.S. experience of 154 patients who underwent the Lariat procedure. Technical success was 94%, but procedural success (without procedural complication) was only 86%. Major adverse in-hospital events included: significant pericardial effusion (requiring intervention) 10.4%; bleeding requiring transfusion 4.5%; and emergent cardiac surgery 2.0%. At median 112 days follow-up, death, myocardial infarction or stroke occurred in 2.9%. TOE follow-up was performed in 63 patients revealing residual leak in 20%, and presence of thrombus in 4.8%. In summary, this study showed that even though technical success was acceptable, the Lariat procedure resulted in worrisome pericardial effusion and bleeding, thus requiring further evaluation.

In a recent systematic review, the use of the Lariat device for LAA exclusion was associated with a significant risk of adverse events (urgent need for cardiac surgery in 2.3% of cases, 7/309 procedures; death in 0.3% of cases, 1/309 procedures).[110] Thus, further controlled investigations into the safety and efficacy of this procedure are recommended in order to define the role of the Lariat LAA exclusion in the prevention of thromboembolic complication in AF.

4.1.5 Percutaneous LAA occlusion

The first percutaneous LAA device manufactured was the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) device (Appriva Medical

Inc., Sunnyvale, California) with the first human implant in 2001.[111] Despite promising early result, the device was withdrawn from the market for commercial reasons. The second dedicated LAA device to be manufactured was WATCHMAN, which was acquired by Boston Scientific (Natick, Massachusetts, USA) in 2011. The WATCHMAN device was the only device studied in randomized controlled trial: the PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial[112] and the PREVAIL (Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation vs. Long-Term Warfarin Therapy) trial[113]. These trials randomized warfarin-eligible patients to OAC vs. device therapy.

The dedicated Amplatzer Cardiac Plug (ACP) (Abbott/St. Jude Medical, St Paul, Minnesota, USA) was specifically designed to occlude the proximal segment of the LAA and is the third LAA device to be manufactured. The second-generation ACP is called the Amulet (Abbott/St. Jude Medical) and has some technical improvements. These devices have been mostly evaluated in registries of patients with contraindications to long-term OAC therapy.[114] Other devices are currently under development and being evaluated in clinical trials (LAmbre, WaveCrest, Occlutech LAA occluder, Ultrasept…) (Table 4-1).

5 Percutaneous LAA occlusion with the WATCHMAN, the Amplatzer Cardiac Plug and the Amulet

5.1 Commercially available devices for percutaneous LAA occlusion in Belgium

5.1.1 WATCHMAN device

The WATCHMAN LAA Closure Technology (Boston Scientific) consists of a self-expanding nitinol frame covered with permeable (160 μm) polyethylene terephthalate (PET) membrane (Figure 5-1).[115] There are 10 active fixation anchors at the nitinol frame perimeter, designed to engage LAA tissue for device stability. The PET membrane covers ~50% of the proximal outer nitinol frame, which blocks thrombus embolization from the LAA and promotes healing and endothelialization. The device's spherical contour accommodates most LAA anatomy. There are 5 sizes available, delivered through dedicated 14-F sheaths with 12-F inner diameter and 75 cm working length. There are 3 dedicated access sheaths: double-curve, single-curve, and anterior-curve. The standard work-horse is the double-curve sheath (>90% cases), which allows easier access into superiorly directed distal lobes. The first-generation WATCHMAN device received the Conformité Européene (CE) mark in 2005 to prevent thrombus embolization from the LAA and reduce the risk of life-threatening bleeding events in patients with nonvalvular AF who are eligible for anticoagulation therapy. In 2012, the CE Mark indication was expanded to include patients who have a contraindication to anticoagulation therapy. The latest generation of the WATCHMAN, the WATCHMAN FLX™ Left Atrial Appendage Closure (LAAC) Device, has a closed-end design and can be fully recaptured and repositioned. This device received CE mark in 2015 and the first implantation occurred in Europe. Due to higher-than-expected rate of device-related embolisms, sales of the device have been suspended and the device is currently in a phase of re-design and evaluation.

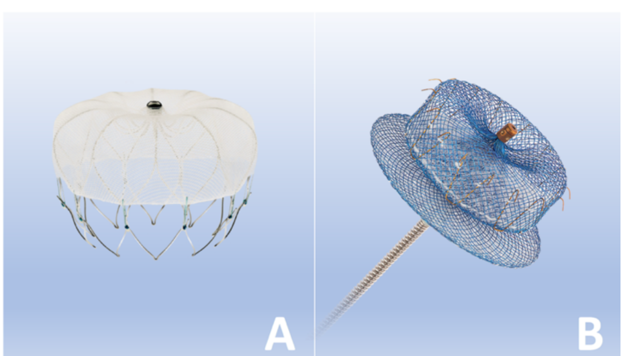
WATCHMAN sizing is based on the maximum LAA diameter, which should be 17 to 31 mm to accommodate available devices. An 8-20% compression ratio based on the widest measurement is recommended by the manufacturer, while most implanters will aim for the higher compression range (close to 20%). Given that the WATCHMAN is almost as long as it is wide, the depth of the distal (implant) lobe has to be as deep as the diameter of the device chosen.

5.1.2 Amplatzer Cardiac Plug and Amulet devices

Early adopters of percutaneous LAA closure in Europe attempted non-dedicated Amplatzer devices after the PLAATO device was discontinued as there was no other available option[116,117]. However, the incidence of embolization was high (12%), although the efficacy endpoints were similar to dedicated devices for successfully-implanted devices[117]. The dedicated Amplatzer Cardiac Plug (ACP) (Abbott/St. Jude Medical) was specifically designed to occlude the proximal segment of the LAA and is the third LAA device to be manufactured.

The ACP or Amulet (second generation ACP) devices are self-expanding nitinol devices made of a distal lobe, designed to anchor the device in the LAA, connected by a short mobile waist to a proximal disc, covered by polyester patches and intended to seal the LAA orifice (Figure 5-1)[118]. The lobe is implanted ~10 mm inside of the LAA orifice and serves as the key anchoring mechanism, supported by 6 pairs of stabilizing wires distally. The disk deployed in the left atrium is pulled under traction against the LAA orifice by the waist connecting to the lobe, which helps to seal the orifice. Both the lobe and disk have polyester mesh that is sewn in by hand. There are 8 sizes according to the lobe dimension, accommodating LAA diameters of 12.6 to 28.5 mm. The Amulet (Abbott/St. Jude Medical), has a wider lobe, longer waist, recessed proximal end screw, and more stabilizing wires. These features improve the stability of Amulet and theoretically may reduce thrombus formation on the atrial side of the device. Amulet also comes in 8 sizes and accommodates larger LAAs (up to 32 mm). ACP has to be manually loaded onto the delivery cable, but the Amulet comes pre-loaded on the delivery cable for ease of setup. ACP received the CE mark in December 2008, and Amulet received it in January 2013. The workhorse sheath is the TorqVue 45°x45°, which has a 3-dimensional distal tip, allowing anterior and superior angulation for coaxial positioning at the landing zone. The access sheath size varies according to the device size, although some operators routinely use the largest sheath. ACP sizing depends on the widest landing zone. It is recommended to oversize the device by 2-4 mm for the ACP and 3-6 mm for the Amulet from the widest measured landing zone.

Figure 5-1. WATCHMAN and Amulet devices.



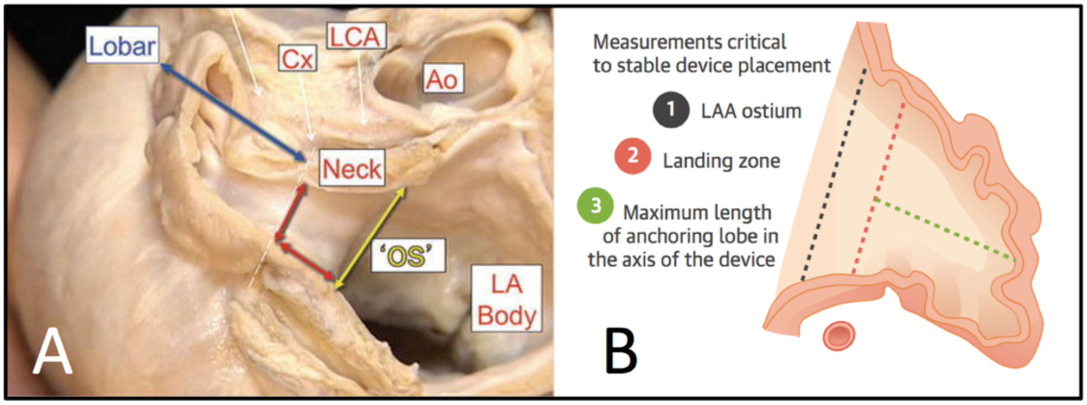
Panel A: WATCHMAN device. Panel B: Amulet device.

5.2 Technique

5.2.1 Pre-procedural imaging

Baseline assessment of the LAA days to weeks prior to the procedure is a recommended standard of practice for percutaneous LAA occlusion. This evaluation will gather information about presence of thrombus, LAA morphology and size, other cardiac structures and will exclude contraindications for LAA closure. TOE is the preferred modality but alternative (in case of contraindications to TOE) or complementary imaging by cardiac computed tomography angiography (CCTA) is increasingly performed.[119,120] The orifice diameter, the landing zone diameter and the depth of the LAA can be measured. This will orient device selection and ensure that LAA closure is feasible. For WATCHMAN, the widest LAA ostium (anatomic orifice measured from the circumflex artery inferiorly to a point superiorly 1 to 2 cm within the pulmonary vein ridge) at 0°, 45°, 90°, and 135° and the available depth of the LAA (from ostium to apex of LAA) are measured. For ACP, measurements at both the short axis (30° to 60°) and the long axis (120° to 150°) of the landing zone and orifice are important. The LAA orifice represents the line from the pulmonary vein ridge to the circumflex artery (echocardiographic orifice). The landing zone is measured at 10 mm within the orifice at an angle that is perpendicular to the neck axis. The LAA depth is measured from the orifice to the back wall along the neck axis. For Amulet, the landing zone is ~12 to 15 mm from the orifice due to the wider lobe. Many authors judge the presence of thrombus as an absolute contraindication for LAA closure. If thrombus is detected during the pre-procedural work-up, anticoagulation should be initiated or intensified for at least 3-4 weeks with repeated imaging to confirm thrombus resolution before proceeding with LAA occlusion[2]. LAA morphology and dimensions can be identified in the pre-procedural study. The orientation of the LAA may help operators in selecting the type of access sheath. Characteristics of the inter-atrial septum (IAS) will be assessed as some features may be associated with a difficult transseptal puncture (TSP). For instance, the presence of thick or aneurysmal IAS will be evaluated.

Figure 5-2. Components of LAA and measurements of critical locations.



Panel A: The LAA is usually described as having two components: the ostium (or "os") and the lobar region, separated by the neck which represents the junction between these two regions. The ostium diameter is measured from the limbus (the left lateral ridge separating the LAA from the lower pulmonary venous trunk) to the mitral valve annulus.
Panel B: This panel demonstrates the critical locations where measurements need to be made for optimal sizing of the LAA occlusion device. The "landing zone" is located at the neck which is defined by the course of the circumflex coronary artery and is used as a reference for placement of LAA occlusion devices.
Ao: Aorta; Cx: left circumflex artery; LA: left atrium; LCA: left coronary artery.
Adapted from Saw J, Kar S, Price MJ. Left Atrial Appendage Closure. Mechanical Approaches to Stroke Prevention in Atrial Fibrillation. Springer International Publishing; 2016 and Wunderlich NC, Beigel R, Swaans MJ, et al. Percutaneous interventions for left atrial appendage exclusion: Options, assessment, and imaging using 2D and 3D echocardiography. JACC Cardiovasc Imaging. 2015;8:472–488.

5.2.2 Per-procedural imaging

Interventions are performed with fluoroscopy while TOE allows guidance during the different procedural steps. TOE guidance during TSP is an important step as a puncture in the optimal infero-posterior region of the fossa ovalis may greatly facilitate further steps of LAA occlusion. Live TOE guidance improves safety of the TSP and increases the likelihood of an optimal TSP location. Wire and pigtail catheter position can also be identified more easily with TOE and procedure time may be shortened with guidance. Sheath positioning is visualized with TOE and fluoroscopy, ensuring a good coaxial alignment and access to the culprit (or implant) lobe. LAA morphology and sizing will be estimated by both imaging in several incidences. Successful implantation is evaluated based on pre-specified criteria; different for each device and ensuring complete seal and good stability. The presence of complications is best assessed by TOE (e.g., pericardial effusion, mitral valve impingement, left pulmonary vein occlusion).

It is generally recommended that LAA closures be performed with TOE guidance for accurate device positioning and safety, typically accompanied by general anaesthesia. However, there are a few centers adept with intracardiac echocardiography (ICE) that prefer procedural ICE instead, obviating the need for general anaesthesia. However, obtaining adequate LAA images can be challenging, and some overcome this problem by advancing the ICE probe into the left atrium through another transseptal puncture. There are also limited centers that rely on fluoroscopy alone[117]; however, these are typically very experienced centers for LAA closure, and this is not advised for the average operator.

The role of imaging in LAAO is extensively described in Publication N°1.

5.2.3 Venous access

Right femoral venous access is preferred because it allows more direct transseptal access than the left femoral vein does. Access site should be well prepared with the scalpel, and subcutaneous tissues separated by forceps to ease advancement of large 12- to 14-F sheaths. Manual compression, "figure-of-8" suture, or pre-closing with the 6-F Perclose ProGlide Suture-Mediated Closure System (Abbott Vascular, Temecula, California) are commonly used for haemostasis.

5.2.4 Transseptal puncture

Transseptal puncture should be inferiorly and posteriorly located in the fossa ovalis for both WATCHMAN and ACP/Amulet implantation, which is well gauged with the bicaval and short-axis TOE views, respectively. ICE is also useful to guide transseptal puncture. Very experienced operators sometimes use anatomic landmarks on fluoroscopy alone to guide punctures. Intravenous heparin is administered before or immediately following transseptal puncture to maintain an activated clotting time (ACT) >250 s. It is important to ensure that adequate filling pressure is present within the LA cavity (~15 mm Hg) to avoid underestimation of the dimension of the LAA landing zone.[121]

5.2.5 Fluoroscopic LAA measurements

Following transseptal puncture, a 5-F marker pigtail is advanced into the LAA and cineangiograms are performed in multiple projections to ascertain the LAA anatomy and measurements. Caudal projections are usually better in visualizing the mid-distal LAA for the WATCHMAN device, whereas RAO cranial projections are better in visualizing ostium and proximal LAA for ACP.

5.2.6 Access sheath advancement

A long (260-cm) J-tipped stiff 0.035-inch wire (e.g., Amplatz Super Stiff J-tip 3-mm curve) should be advanced into the left upper pulmonary vein as a rail for sheath access. The appropriately-sized access sheath is then safely advanced to the left upper pulmonary vein ostium. To allow easier access, the venous access should be well-dilated, and the sheath gently rotated during advancement to ensure coaxial approach while crossing the interatrial septum. For the WATCHMAN device, the 14-F access sheath is advanced deep into the LAA using a pigtail (5- to 6-F) before device introduction. RAO 20° to 30° caudal 20° to 30° angulation typically allows good visualization of the distal lobes for sheath advancement and device deployment. The access sheath is safely navigated over the pigtail into the distal segment of the LAA, until the corresponding radio-opaque marker band for the device size is aligned with the LAA ostium. Once in position, the pigtail is removed, and often a moderate degree of catheter torque is required to maintain sheath position in the distal lobe. For ACP/Amulet, the appropriately-sized sheath/dilator is usually advanced to the left upper pulmonary vein orifice, and then the sheath is withdrawn slightly and turned counterclockwise to fall into the LAA ostium. A J-tip wire or pigtail may be used to facilitate engagement to minimize traumatizing the thin left atrium. Usually an RAO cranial projection is used for ACP sheath positioning and implantation.

5.2.7 Watchman implantation steps

WATCHMAN sizing is based on the maximum LAA ostium diameter, which should be 17 to 31 mm to accommodate available devices. Oversizing is recommended by 8% to 20% based on the widest measurement, which generally corresponds to 2- to 4-mm oversizing. The prepped delivery system containing the compressed device is then introduced into the access sheath. The delivery system is advanced until both the distal marker bands of the delivery system and access sheath are aligned. The device is then unsheathed slowly without forward advancement of the device, preferably inducing apnoea for the patient to allow stable deployment. When the device is fully unsheathed, the device position is evaluated on fluoroscopy and TOE. If it is too distal, the device may be partially recaptured and the access system withdrawn slightly, then the unsheathing process is reattempted. If the device is too proximal (or sizing or position is suboptimal), the device can be fully recaptured, and a new device and delivery system can be reattempted through the existing 14-F sheath. Before device release, the 4 “PASS” criteria should be met: 1) Position (device distal or at LAA ostium, protrusion of shoulder by <40% to 50% of device depth is acceptable); 2) Anchor (testing stability by retracting the deployment knob and letting go, to assess return to original position); 3) Size (device shoulder compressed 8% to 20% of original size on TOE); and 4) Seal (assess TOE for any residual flow, must be <5 mm before release). When these criteria are met, the device may be released with counterclockwise rotation of the core wire for 3 to 5 turns. Final angiography and TOE assessment are then performed.

5.2.8 ACP/Amulet implantation steps

ACP sizing depends on the widest landings zone on fluoroscopy or TOE. A standard recommendation is to upsize the device by 2 to 4mm for ACP and 3 to 6mm for the Amulet device from the widest measured landing zone. This degree of oversizing improves stability of the device and proper anchoring of the lobe. However, caution should be exercised if the landing zone is very elliptical to avoid dramatic oversizing (>5 mm) in the narrowest dimension. The prepped device is advanced to the tip of the access sheath, which is positioned at the landing zone of the LAA. The first step of deployment is unsheathing by withdrawal of the delivery sheath to deploy the “ball”. If the position is adequate on TOE and fluoroscopy, the remainder of the lobe is then deployed. If the angle and position of the lobe at the landing zone is optimal, then the disk can be deployed. This manoeuvre requires slight traction of the delivery cable during further unsheathing of the disk, to separate the lobe from the disk adequately and to ensure that the disk is deployed in the left atrium. The position and angulation of the fully unsheathed device is confirmed on TOE and fluoroscopy. If unsatisfactory at any point prior to release, the disk and lobe can be resheathed into the “ball” configuration, as long as the 2 platinum markers on the device do not enter the radio-opaque band on the sheath. If the device positioning/size is inadequate, or if the platinum markers enter beyond the radio- opaque band, then the device has to be entirely removed, and the sheath replaced. Prior to device release, 5 signs should be present to ensure proper deployment: 1) tire-shape of the lobe (ensuring adequate compression of the lobe and engagement of stabilizing wires); 2) separation of the lobe from the disk (ensuring good seal of disk); 3) concavity of the disk (ensuring good seal by traction of the disk from the lobe); 4) axis of the lobe (should be perpendicular to the neck axis at landing zone, to ensure proper contact of lobe walls and stabilizing wires); and 5) lobe is adequately within the circumflex artery on TOE (i.e., lobe should be deep enough such that the width of the lobe is two-thirds or more within the circumflex artery). If there is uncertainty about device stability, a gentle “pull” of the disk may be performed, but vigorous wiggle testing is contraindicated. Alternatively, the device can be observed for several minutes for stability prior to release. The presence of residual leak is assessed on TOE. Contrast injections can be performed through the delivery sheath to assess optimal positioning after ensuring that the system is deaired. Once a satisfactory position is achieved, the device is released with counterclockwise rotation of the delivery cable.

Detailed procedural techniques are described in Additional Publication N°1: Percutaneous Left Atrial Appendage Closure. Procedural Technique and Outcomes.

5.3 Complications

Complications can broadly be divided in acute, peri-procedural complications (usually from procedure to day 7) and mid- to long-term complications (after day 7) (Table 5-1).

5.3.1 Acute complications

The majority (> 90 %) of complications related to LAA closure are procedure-related, occurring within 7 days of the index procedure.[122] The acute complications with WATCHMAN and ACP appear comparable. The rate of acute complications has been shown to decrease significantly in most recent studies. This is most likely explained by multiple factors including device design optimization, technique standardization and increasing experience of operators.
With good technical skills and procedural planning, the risk of procedural ischemic stroke is <0.5%, serious pericardial effusion 1% to 2%, and device embolization 0.5% to 1%[123]. Ischemic strokes may be related to procedural air embolism (inadequate device preparation or poor technique) or thrombus in LAA or on equipment. Baseline imaging to exclude pre-existing thrombus, adequate procedural anticoagulation, and meticulous and proficient techniques are important to minimize thromboembolism. Pericardial effusion causing hemodynamic compromise requires emergent pericardiocentesis, and possibly pericardial window or surgical intervention for cardiac perforation. Device embolization is typically managed by percutaneous retrieval if feasible. A large arterial sheath through the femoral artery that is >2-F larger than the implanting access sheaths is often required to retrieve the embolized device, in conjunction with loop-snare and bioptome. An embolized device trapped in the left ventricle is more challenging to retrieve but can be successfully performed. Sometimes, surgical removal is required, especially if the device is trapped by papillary muscles or trabeculations.

5.3.2 Mid- and long-term complications

Longer-term potential issues include thrombus on device and residual leak; thus, follow-up TOE or CCTA 1 to 6 months post-procedure is typically performed (and is sometimes repeated at 1 year).
A residual leak is defined as residual flow into the LAA after LAA closure. In the substudy of the PROTECT-AF trial, peri-device leaks were classified as none, minor (< 1 mm), moderate (1– 3 mm), and severe (> 3 mm).[124] Residual leaks occur in a fair proportion of WATCHMAN implantations, with some degree of leak seen in 32% of cases in PROTECT-AF at 12-month follow-up (36.8% >3 mm, and 63.2% ≤3 mm). In terms of clinical significance, there was no difference in thromboembolic events found during follow-up between the four subgroups in the PROTECT-AF trial. In the ACP multicentre registry TOE analysis, a peri-device leak was found in 73 patients (11.6%). The leak was trivial, mild, and significant in 27 (4.3%), 34 (5.4%), and 12 (1.9%) patients, respectively. Another study of residual leaks after ACP implantation indicated that peri-device leaks were frequently small.[125] The clinical significance of these leaks and recommended management needs to be further evaluated. Currently, in cases of residual leak >5 mm, patients may be continued on long-term anticoagulation[112]; there are also case reports of performing another LAA closure with a different device for large residual leaks[126].

Device-associated thrombus formation is discussed in Chapter 8. Formation of thrombus on the atrial side of devices can occur in 2% to 5% of cases. These occurrences are purported to occur predominantly on nonendothelialized device protrusions, such as the threaded insert with WATCHMAN and the proximal end screw with ACP, especially if implants are too deep. Thus, avoiding deep implantations creating cul-de-sacs, especially avoiding uncovered proximal LAA trabeculations, has been advised. New device designs have also been pursued to address these concerns. Although there is no consensus on management, such thrombotic complications are usually managed with anticoagulation (OAC or low-molecular-weight heparin) for 2 to 12 weeks, with repeat TOE to assess for thrombus resolution before cessation of anticoagulation. Reported thromboembolic stroke event rates related to device thrombus are low.

Table 5-1. Possible complications of percutaneous LAA closure.

Complications	**Short-term**	**Mid- to Long- term**
Cardiac perforation*	+	(+)
Pericardial effusion with tamponade†	+	(+)
Device embolization	+	+
Device thrombosis	+	+
Stroke/TIA (thromboembolism, air embolism)	+	+
Vascular complications (haematoma, bleeding, AV fistula formation)	+	(+)

* Cardiac perforation: pericardial effusion resulting in surgical intervention/repair—due to transseptal puncture, or LAA closure device which can perforate the LAA ± pulmonary artery (acute or after >7 days).

†Pericardial effusion with tamponade: pericardial effusion resulting in percutaneous treatment/drainage or pericardial window. LAA, left atrial appendage; TIA, transient ischemic attack; AV, arteriovenous.

Adapted from De Backer O, Arnous S, Ihlemann N, et al. Percutaneous left atrial appendage occlusion for stroke prevention in atrial fibrillation: an update. *Open Heart*. 2014;1:e000020.

5.4 Outcomes

Several studies have evaluated the efficacy and safety of the LAA occlusion devices for stroke prevention with AF. The majority are early experience registries, with only 2 randomized controlled trials published to date. Recently, 2 large registries have been published describing 'real-life' results, the EWOLUTION Registry (WATCHMAN) and the Amulet Observational Registry.

5.4.1 WATCHMAN device

The WATCHMAN device was studied in the multicenter PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial[112], where 707 patients with nonvalvular AF and $CHADS_2 \geq 1$ were randomized to the WATCHMAN device (n=463) or to continued warfarin therapy (n=244) in a 2:1 ratio. WATCHMAN was successfully implanted in 90.9% of cases. Warfarin was continued for 45 days with WATCHMAN and then switched to clopidogrel for 4.5 months (if there is no leak >5 mm on TOE at 45 days), with aspirin lifelong after implantation. Warfarin was discontinued in 86% of patients at 45 days and in 92% at 6 months. The composite primary efficacy of stroke, systemic embolism, and cardiovascular death event rates met noninferiority criteria at 1,065 and 1,588 patient-years of follow-up. However, the primary adverse procedure-related events and major bleeding were higher with the WATCHMAN device (5.5% vs. 3.6% annually; RR: 1.53; 95% CI: 0.95-2.70)[122,127].

Due to early safety concerns in PROTECT-AF, the FDA mandated a second randomized trial to confirm the late PROTECT-AF and CAP (Continued Access Protocol) registry safety results for approval of the device. Thus, the PREVAIL (Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation vs. Long-Term Warfarin Therapy) trial was conducted, which randomized 407 patients in a 2:1 ratio to WATCHMAN or warfarin. Inclusion criteria was $CHADS_2 \geq 2$, or $CHADS_2 = 1$ if 1 or more of the following was present: female sex; ≥75 years of age; left ventricular ejection fraction 30% to 34.9%; age 65 to 74 years with diabetes or coronary artery disease; or age ≥65 years with documented congestive heart failure.[113] Successful implantation improved to 95.1%. The safety endpoint met the pre-specified noninferiority criterion.

The ASAP (ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology) study[128] evaluated 150 patients with nonvalvular AF and $CHADS_2 \geq 1$ who were ineligible for warfarin. Patients were treated with thienopyridine for 6 months and lifelong aspirin after WATCHMAN implantation. With a mean follow-up duration of 14 months, all-cause stroke and systemic embolism was 2.3% per year. The observed ischemic stroke rate was 77% lower than expected based on the $CHADS_2$ score of 2.8 in the cohort.

The initial CAP (Continued Access Protocol) registry showed lower procedural-related events compared with the early PROTECT-AF results, with procedural-related stroke of 0%, and serious pericardial effusion of 2.2% with the WATCHMAN device[122]. There was a demonstrable learning curve with improvement in technical success rate and reduction in complications with increasing experience. The implant success rate improved from 91.3% in PROTECT-AF to 95.0% in the subsequent CAP registry (p=0.033) (which included only investigators who previously implanted WATCHMAN in PROTECT-AF), in conjunction with significant reduction in procedural time (56 min vs. 50 min, $p < 0.001$), there was also significant decline in procedure- or device-related safety event rates when comparing the first and second halves of PROTECT-AF and CAP, with 10.0%, 5.5%, and 3.7% of patients, respectively, experiencing events within 7 days of procedure (p=0.006).[122]

After 3.8 years of follow-up among patients with nonvalvular AF at elevated risk for stroke included in PROTECT-AF, LAA closure with WATCHMAN implantation met criteria for both noninferiority and superiority, compared with warfarin, for preventing the combined outcome of stroke, systemic embolism, and cardiovascular death, as well as superiority for cardiovascular and all-cause mortality.[129] At a mean follow-up of 3.8 years (2,621 patient-years), the primary event rate was 2.3 events per 100 patient-years in the device group vs 3.8 in the warfarin group (HR: 0.61; 95% CI: 0.38-0.97; p= 0.04). Patients in the device group demonstrated lower rates of both cardiovascular mortality (1.0 events per 100 patient-years for the device group vs. 2.4 events per 100 patient-years with warfarin; HR: 0.40; 95% CI: 0.21-0.75; p = 0.005) and all-cause mortality (3.2 events per 100 patient-years for the device group vs. 4.8 events per 100 patient-years with warfarin; HR:0.66; 95% CI: 0.45-0.98; p = 0.04).

In a meta-analysis including 2,406 patients with 5,931 patient-years of follow-up from the PROTECT AF and PREVAIL trials, and their respective registries (CAP registry and CAP2 registry), patients receiving LAA occlusion with the Watchman device had significantly fewer hemorrhagic strokes (0.15 vs. 0.96 events/100 patient-years; HR: 0.22; p = 0.004), cardiovascular/unexplained death (1.1 vs. 2.3 events/100 patient-years; HR: 0.48; p = 0.006), and nonprocedural bleeding (6.0% vs. 11.3%; HR: 0.51; p = 0.006) compared with warfarin. All-cause stroke or systemic embolism was similar between both strategies (1.75 vs. 1.87 events/100 patient-years; HR: 1.02; 95% CI: 0.62 to 1.7; p = 0.94). There were more ischemic strokes in the device group (1.6 vs. 0.9 events/100 patient-years; HR: 1.95; p = 0.05), but once procedure-related strokes were excluded, the rates of ischemic stroke were no longer significantly different between the device and warfarin (HR: 1.56; 95% CI: 0.78 to 3.09; p=0.21). [130]

The most recent data come from a large registry in which the indications for LAAO are based on ESC Guidelines. Peri-procedural outcomes of up to 30 days from the EWOLUTION registry were published in 2016.[131] This multicentre registry included 1,021 high-risk AF patients implanted with the WATCHMAN device in 47 centres. The mean age was 73.4±9 years, the average CHA_2DS_2-VASc score was 4.5±1.6, and the average HAS-BLED score was 2.3±1.2. 73% of patients were deemed unsuitable for oral anticoagulation therapy by their physician. The device was successfully deployed in 98.5% of patients while successful procedural closure of LAA (no flow or minimal residual flow) was achieved in 99.3% of implantations. 28 subjects experienced 31 serious adverse events (SAEs) within 1 day of the procedure. The overall 30-day mortality rate was 0.7%. The most common SAE occurring within 30 days of the procedure was major bleeding requiring transfusion. 1 year results of the EWOLUTION registry showed a good efficacy of the procedure with only 1.1% of ischemic stroke rate which translates to a RR reduction of 84% when compared to the estimated risk based on historical data.[132]

With the satisfactory long-term results of PROTECT-AF and improved safety results of PREVAIL and CAP, the FDA approved the use of the WATCHMAN device in the USA in March 2015 for patients with nonvalvular AF and high-risk of stroke who have an appropriate rationale to seek a non-pharmacologic alternative to warfarin.

5.4.2 ACP and Amulet devices

Since the launch of the ACP in 2008, over 10,000 devices have been implanted worldwide.[133] The ACP was evaluated in several small retrospective registries, mostly involving single-center experiences in Europe, Canada, Asia, and Latin America.[117,134–142] In aggregate, >1,100 patients were included in these registries, showing good safety profile (serious pericardial effusion ~1.7%, device embolization ~1.1%, ischemic stroke ~0.4%), and procedural success (~96.4%).

Tzikas et al. published the results of the ACP multicentre registry, which included 1,047 patients treated in 22 centres.[143] The mean age was 75±8 years, CHA_2DS_2-VASc score of 4.5±1.6, and HAS-BLED score of 3.1±1.2. About 27.2% were on (N)OAC prior to implantation. Implantation success was 97.3%, and in 93.3% of cases, the first device selected was implanted. With follow-up TOE, the closure rate (<3 mm residual flow) was 98.1%. The rate of periprocedural major adverse events (7-day death, ischemic stroke, systemic embolism, and procedure- or device-related complications requiring major cardiovascular or endovascular intervention) was

4.97% (mortality: 0.76%, pericardial tamponade: 1.24%, device embolization: 0.77%, stroke: 0.86%). Follow-up was complete in 1,001/1,019 (98.2%) of successfully implanted patients (average 13 months, total 1,349 patient-years). The annual rate of systemic thromboembolism was 2.3% (31/1.349 patient-years), which is a 59% risk reduction. The annual rate of major bleeding was 2.1% (28/1.349 patient-years), which is a 61% risk reduction.

Several sub-group analyses were performed based on data from the ACP multicentre registry. In case of patients with previous intracranial bleeding, LAAO seemed to be a safe procedure and was associated with a significant reduction in stroke/TIA (annual rate of 1.4%, 75% relative risk reduction) and a remarkably low frequency of major bleeding during follow-up (annual rate of 0.7%, 89% relative risk reduction).[144] Among patients with CKD, procedural safety was similar and LAAO showed a significant reduction of stroke/TIA (2.3%, 62% relative risk reduction) and of bleeding (2.1%, 60% relative reduction), which was persistent in all stages of CKD.[145] In elderly patients (age≥75 years), LAAO was associated with similar procedural success although older patients had a higher incidence of cardiac tamponade (0.5% vs. 2.2%; p<0.04). At follow-up, stroke and major bleeding rates were similar among groups.[146]

The Amulet Observational Study is a large prospective real-world registry which included 1,088 patients implanted with the Amulet device. The average age was 75 ±8.5 years, the average CHA_2DS_2-VASc score was 4.2±1.6, and the average HAS-BLED score was 3.3±1.1. 82.8% of patients were considered to have an absolute or relative contraindication to long-term anticoagulation and 72.4% had had a previous major bleeding. Successful device implantation rate was very high (99.0%). Periprocedural major events rate was 3.2%. TOE follow-up showed adequate occlusion of the appendage in 98.2% of patients.[147]

The Amulet IDE trial is an ongoing prospective, randomized, multicenter trial, designed to evaluate the safety and effectiveness of the Amulet. Patients are randomized in a 1:1 ratio between the Amulet or a WATCHMAN LAA closure devices. The estimated primary completion date of the trial is in February 2020 (ClinicalTrials.gov Identifier: NCT02879448).

5.5 Indications

Patients with AF and a high thromboembolic risk (CHA_2DS_2-VASc score >2) but contraindication to systemic anticoagulation represent the most widely accepted clinical indication for LAA occlusion nowadays. Currently, the ESC guidelines on AF management state that LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (Class IIb recommendation with Level of Evidence B).[41]

In case of a bleeding event in AF patients treated with (N)OAC, anticoagulation should be paused to control active bleeding. However, contraindications to long-term OAC after a bleeding episode are rare and reinitiation of OAC after the event is often clinically justified[148–150], after correction of the bleeding causes or triggers. Most of these triggers can indeed be eliminated, such as GI ulcers, intracranial aneurysms and uncontrolled hypertension.

LAAO remains a prophylactic procedure and should be limited to patients with a favourable risk-benefit ratio. Careful selection of patients is mandatory and implies a multidisciplinary team approach. Estimated risk of thromboembolism, estimated risk of complications linked to OAC and different available options have to be discussed with the physicians involved with patient management. This multidisciplinary team may include cardiologists, neurologists, imaging specialists, neurosurgeons, gastroenterologists, nephrologists, etc. The benefit of the procedure increases with time, as the protection from embolic complications progressively outweighs the risk associated with the procedure. Clinical decisions must also consider the expected life expectancy of patients.

The majority of procedures performed in Europe adhere to the ESC guideline as reported by Tzikas[114] and Boersma[151]. In the ACP multicentre registry, among ~1,000 LAA closures, 74% were for patients with major bleeding or at high bleeding risk. Other indications included coronary stenting (23%), drug interaction (18%), stroke on warfarin (16%), renal or hepatic disease (13%), labile international normalized ratio (7%), and risk of falls (7%).[114] In the EWOLUTION registry, 62% of patients implanted with the WATCHMAN were deemed unsuitable for OAT by their physician, based on factors such as co-morbidities, the inability to adhere to OAT, and bleeding history or high bleeding risk. 31.2% of all subjects had a history of major bleeding and 40% of patients had a moderate-to-high risk of bleeding (HAS-BLED score ≥3).[151]

Thus, LAAO appears nowadays as being a valid alternative in selected AF patients with contraindications for long-term anticoagulant treatment and high thromboembolism risk. In most patients, contraindication to OAC is mainly related to the risk of any repeated bleeding and its clinical consequences (e.g. history of a major bleeding event such as intracranial or life-threatening bleeding, the source of which cannot be eliminated). Clinical indications are described below and include history of major bleeding, high bleeding risk, embolic event while on optimal OAC, pharmacological contraindications to OAC, and other less robust indications such as noncompliance issues and patient preferences (Table 5-2).

5.5.1 History of Major Bleeding

5.5.1.1 History of Intracranial Bleeding

Intracranial bleeding (ICB) is judged by many as the most serious complications of oral anticoagulation therapy as it is associated with a very high rate of mortality and disability.[152,153] It is also associated with a high recurrence rate and severe clinical consequences in case of recurrence.[152] The cumulative risk of ICB recurrence is 1% to 5% per year.[154–156] Anticoagulation medication after the initial ICB can triple the risk of subsequent hemorrhagic events.[155] The risk of ICB recurrence is highest during the first year after the initial event but this risk remains high afterwards, particularly in case of lobar ICB.[156,157]

The risk factors for ICB recurrence include the following factors: 1) lobar location of the initial ICB; 2) older age; 3) hypertension; 4) greater number of microbleeds (particularly microbleeds in lobar brain locations) on gradient echo magnetic resonance imaging; 4) on-going OAC therapy; 5) history of ischemic stroke (in particular in case of the small-vessel "lacunar" type, which shares a common pathogenesis with ICB).[152,156,158–162]

Therefore, in patients with a history of ICB and presenting with high thromboembolism risk related to AF, there is regularly uncertainty about the initiation or re-initiation of the anticoagulant therapy. In case of spontaneous ICB, risks of recurrent ICB and ischemic stroke after ICB appear similar, which can provoke uncertainties about the use of antithrombotic drugs.[163] The AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage recommend the avoidance of long-term anticoagulation with warfarin as a treatment for nonvalvular atrial fibrillation after warfarin-associated spontaneous lobar ICH because of the relatively high risk of recurrence (Class IIa; Level of Evidence B).[164] To date, no prospective studies have investigated the risk-benefit ratio of the initiation of OAC after intracranial hemorrhage[165]. In the large randomized clinical trials comparing NOAC agents with VKA agents, patients with a history of ICB were excluded. The decision to reinitiate OAC in patients with AF has to weigh risk factors of recurrence of ICB and risk of thromboembolic complications. Thus, a multidisciplinary approach is recommended with involvement of physicians taking charge of the different area of expertise: neurologists, neurosurgeons, neuroradiologists, and cardiologists. The ESC Guidelines on the management of AF recommend the evaluation of the presence of factors supporting withholding OAC and factors supporting reinitiation of OAC.[41] Factors supporting withholding OAC include the following elements: bleeding occurred on adequately dosed NOAC or in setting of treatment interruption or underdosing, older age, uncontrolled hypertension, cortical bleed, severe intracranial bleed, multiple microbleeds (e.g. >10), cause of bleed cannot be removed or treated, chronic alcohol abuse, need for dual antiplatelet therapy after PCI.

Recently published data analyzing the safety and efficacy of LAAO in patient with history of ICB in the ACP Multicenter registry showed that LAAO seemed to be a safe procedure (similar procedural outcomes) and was associated with a significant reduction in stroke/TIA (annual stroke/TIA rate of 1.4%, 75% relative risk reduction) and a remarkably low frequency of major bleeding during follow-up (annual major bleeding rate of 0.7%, 89% relative risk reduction).[144] A smaller study also showed good safety and efficacy results of LAAO in patients with AF and a history of ICB.[166] LAAO should therefore be considered as an alternative to chronic OAC in patients with prior ICB.

5.5.1.2 History of Major Gastrointestinal Bleeding

Major gastrointestinal (GI) bleeding events are associated with a high risk of recurrence, particularly in patients on antithrombotic therapy[167], and are not always reversible or amenable to any efficient treatment.[168,169] GI bleeding remains also the most common extracranial hemorrhagic complication in patients receiving antithrombotic therapy and a frequent reason to discontinue OAC.[170–172] Conversely, a large proportion of patients do not resume anticoagulation after a GI bleeding event[173–175], even though resuming OAC may reduce the risk of stroke more than it increases the risk of recurrent GI bleeding, resulting in a net clinical benefit.[150,176] Patients with previous major GI bleeding (MGIB) might therefore be good candidates for percutaneous LAAO, as this would allow anticoagulation cessation, reducing the risk of bleeding recurrence, while keeping cardioembolic protection.
Results of the analysis of LAAO with the ACP in patients with previous major GI bleeding are discussed in Chapter 9.

5.5.1.3 History of Major Intraocular Bleeding

Following the criteria established by the International Society on Thrombosis and Hemostasis[177], only substantial intraocular bleedings (i.e., hyphema, vitreous hemorrhage, subretinal hemorrhage, and suprachoroidal hemorrhage) are considered as major bleeding events. A recent meta-analysis showed that NOACs did not increase the risk of substantial intraocular bleeding compared with other anticoagulants (VKAs and/or LMWH). The rate of these serious events was in deed very low (<0.4%) but they were reported in studies that were underpowered for this purpose.[178] Although rare[179], severe intraocular bleeding is a serious adverse event for patients treated with antithrombotic agents. Substantial intraocular hemorrhages can cause severe visual acuity impairment and require surgery for complete resolution in some cases.[180] As for patients with history of ICB, LAAO should be considered in patients with history of intraocular bleeding, even though data supporting this technique in this patient subgroup is limited.[166]

5.5.1.4 History of Other Major Bleeding

Other type of bleeding can represent an indication in case of severe event and/or high estimated recurrence rate on antithrombotic treatment (pericardial bleeding, retroperitoneal bleeding, spontaneous spleen bleeding, spinal cord bleeding, large hematoma…).

5.5.1.5 History of Recurrent Significant Minor Bleeding

In case of recurrent minor bleeding events which are estimated clinically significant (e.g. recurrent epistaxis requiring medical attention), LAA occlusion may be considered.

5.5.2 High Risk of Bleeding

Long-term therapy with warfarin or NOAC is associated with lifetime major bleeding risks of 1.6% to 3.6% per year.[41] Intracranial hemorrhage rate is consistently lower with NOAC but overall risk of major bleeding is not consistently diminished.

As described in the *EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion*[181], an individual risk benefit evaluation has to be performed, recognizing that the primarily recommended strategy would be the use of OAC. Patients with high risk of bleeding can be divided in 4 groups. The first group of patients associated with a high bleeding risk can be identified by the HAS-BLED score. Patients with high HAS-BLED score (HAS-BLED≥3) should be evaluated as to whether long-term OAC exposes them to an unacceptable bleeding risk. This risk has to be individually assessed and modifiable risk factors for bleeding have to be reduced as much as possible.[31,182] Adaptation of the degree of anticoagulation has also to be considered (appropriate use of NOACs associated with lower bleeding risk). The second group of patients include patient in whom triple antithrombotic therapy for a prolonged period of time would be associated with a significant increase in the bleeding risk. Patients with AF and high thromboembolic risk (CHA_2DS_2-VASc score >2) and severe coronary artery disease treated with one or more stents should be considered. This is particularly relevant in patients with left main stent, with multivessel stents or patient with history of MI at very high risk of cardiovascular events who would benefit from long term DAPT with ticagrelor, as shown in the PEGASUS-TIMI 54 trial[183]. The third group includes patients with high bleeding risk but for whom the risk is underestimated by the HAS-BLED score or other bleeding risk score. For instance, patients with high risk of falls or recurrent falls with significant injury, patients with cancer, patients with frailty, patients with blood cell dyscrasia, patients with IC amyloid angiopathy and patients with chronic inflammatory bowel disease are not well characterized by standard risk scores. The rate of anticoagulation in these patients is likely to be decreased and patients could potentially benefit from an alternative treatment such as LAAO. Finally, in patients with severe renal failure (creatinine clearance <15-30 mL/min) and high stroke risk, the risk-benefit ratio of anticoagulation by VKA or NOACs is questionable given the elevated risk of bleeding.[184,185] Moreover, the use of NOAC is controversial in the setting of severe renal failure.[186] A recent study by Kefer et al. showed that LAAO using the ACP had a similar procedural safety among CKD patients with a significant reduction of stroke/ TIA and of bleeding rates. [145]

5.5.3 Thromboembolic Event Occurring Despite Optimal Anticoagulation

Despite optimal anticoagulation, there is a residual stroke risk of 2% to 5%.[187] In this clinical scenario, options include increasing the international normalized ratio (INR) target to 2.5-3.5 or switching from VKA to one of the NOAC when it occurs while taking warfarin[188], or adding an antiplatelet agent to OAC when the embolic event occurred at elevated INR level or while taking NOACs. LAAO can also be discussed as an alternative treatment especially when embolism occurred at elevated INRs or while already taking NOACs or in case of contraindication to NOAC. The combination of OAC and LAAO may also be discussed in case of embolic event occurring in patients with optimal OAC and no other plausible cause (high-risk mobile aortic arch atheroma, severe carotid disease…). Available data regarding this management are scarce and clinical decision must be discussed in a multidisciplinary team.

LAAO may also be discussed after documentation of LAA thrombus despite adequate OAC therapy.

5.5.4 Pharmacological Considerations

The use of NOAC in patient with severe liver or renal dysfunctions is contraindicated. In some rare cases, the risk of drug interaction is seemed too high to ensure a safe and stable anticoagulation status.

5.5.5 Other Indications

Even with the relatively well-tolerated NOAC, the proportion of patients discontinuing NOAC during study follow-up was 15% to 25%[49,50,63,189]. Patients with demonstrated poor adherence or noncompliance to chronic OAC treatment could be considered for LAAO in case of high thromboembolism risk and no possible means to increase treatment compliance (psychiatric disorders…).

In case of patients refusing NOAC after explanations and physician advices, LAAO can be considered after thorough explanations about the risks and benefits of the procedure vs. OAC. Physicians have to explain the patients that available data are limited to only two studies with the WATCHMAN comparing it with warfarin[112,113] , that serious complications related to the procedure itself can occur, and that long-term outcome after LAA occlusion was shown to be equivalent to anticoagulation with warfarin (and superior in some aspects after 4-year follow-up)[129]. It is important to note that other devices have only been evaluated in observational studies. Moreover, even though NOAC have at least equivalent and probably improved efficacy with lower rate of intracranial hemorrhage, there is currently no study comparing NOAC vs. LAAO. The decision regarding the procedure in this scenario, which constitutes a small minority of current cases, should be made by a well-informed patient. Of note, most health care systems do not support this procedure based only on patient preferences and do not fund the device in this case.

Table 5-2. Indications for percutaneous LAAO.

1. **Contraindications to OAC**
   - History of IC bleeding
   - History of major GI bleeding
   - History of major intraocular bleeding
   - History of other major bleeding (e.g. pericardial, spinal cord)
   - History of recurrent significant minor bleeding (e.g. recurrent significant epistaxis)

2. **High bleeding risk**
   - High HAS-BLED score (HAS-BLED≥3)
   - Requirement of prolonged additional dual antiplatelet therapy for stenting
   - High risk of bleeding not well defined by bleeding risk score:
     - High risk of falls or recurrent falls with significant injury
     - Patients with cancer
     - Patients with chronic inflammatory bowel disease
     - Blood cell dyscrasia
     - Diffuse IC amyloid angiopathy
   - Severe renal failure or hemodialysis

3. **Thromboembolic event or documented presence of thrombus in the LAA occurring despite optimal anticoagulation**

4. **Pharmacological considerations**
   - Severe liver or renal dysfunction
   - High risk of drug interaction

5. **Other indications**
   - Documented poor adherence or noncompliance to treatment
   - Intolerance to treatment
   - High-risk occupation with increased risk of injury
   - Patient preferences

GI: gastrointestinal; IC: intracranial

5.6 Antithrombotic treatment following LAAO and Follow-up

5.6.1 Antithrombotic treatment post-LAA occlusion

Following LAA closure with percutaneous devices, thrombosis may appear on the surface of the device. The implantation of thrombogenic devices in patients with non valvular AF, who are at high risk of thrombosis in the left atrium, requires antithrombotic therapy in order to prevent on-device thrombus formation. Ideally, antithrombotic therapy should be pursued until complete occluder endothelialization.

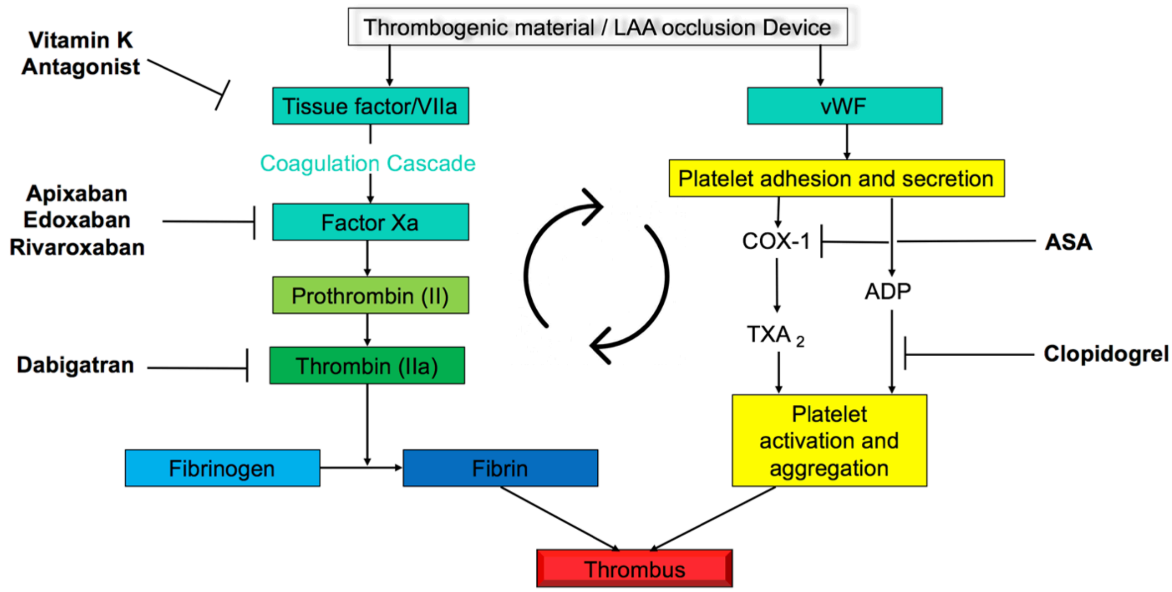
In the largest randomized-controlled trials comparing either LAA closure with the WATCHMAN device or warfarin therapy in patients eligible to long-term OAC, the PROTECT-AF[122] and PREVAIL[113] studies, it was recommended to give aspirin (81-325 mg) indefinitely with warfarin for 45 days. Warfarin was switched to clopidogrel (75mg) after demonstration of absence of device-related thrombus and significant peri-device leak (jet width ≤5 mm) on control TOE. Clopidogrel was continued up to 6 months post-procedure. In 'real-life' conditions, many patients treated with LAA closure are not eligible to long-term OAC. An EHRA/EAPCI expert consensus statement on catheter-based LAA occlusion recommended antithrombotic regimen based on bleeding risk profile in patients treated with WATCHMAN.[181] Thus, in case of WATCHMAN implantation in patients with high bleeding risk, the authors recommend treatment with clopidogrel for 1-6 months with ASA indefinitely (Figure 5-4). The safety of antiplatelet treatment was initially derived from animal studies that have analyzed endothelialization of cardiac devices[190], on previous experience with the PLAATO device[191], and on current practice after percutaneous PFO or ASD closure device implantation.[192]

In the ACP or Amulet experience, it is common practice to treat patients with DAPT following implantation: aspirin (80-100 mg daily) and clopidogrel 75 mg daily for 1-3 months and then only aspirin 80-100 mg daily for at least another 3 months. With this therapeutic regimen, the reported rate of DAT in the ACP multicentre registry was 4.4%.[143] In a recent smaller study, 104 patients implanted with the ACP or Amulet were treated with ASA monotherapy with a low rate of DAT or stroke post-implantation after a median follow-up of 2.3 years.[193] Further studies will have to evaluate the need for long-term aspirin therapy.

In the Ewolution registry, which reflects 'real-life' results after WATCHMAN implantation, 62% of patients were deemed unsuitable for OAC by their physician (bleeding history or high bleeding risk, co-morbidities, inability to adhere to OAC).[151] In this registry, after device implantation, as much as 59% of patients were on DAPT, while 27% of patients were on OAC. Subgroup analysis of serious adverse events through 7 days, did not show any difference between patients that were OAC eligible or ineligible (respectively 5.2% vs. 3.4%, p=0.180) or between patients on OAC after implant or not (respectively 4.4% vs. 4.0%, p=0.807). However, it will be important to assess mid and long-term results as DAT and its related complications are usually diagnosed later after the implantation (mean delay of 45 days from implantation to diagnosis).

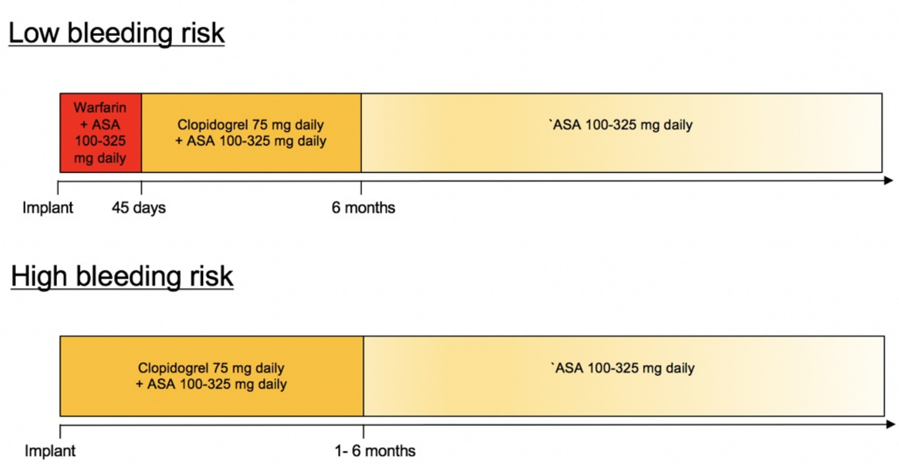
In the ASAP Study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology), 150 patients that were judged ineligible for OAC were administered 6 months of clopidogrel or ticlopidine and lifelong aspirin following the Watchman implant with favorable safety results as compared to PROTECT AF data (ischemic stroke rate of 1.7% vs. 2.2%, respectively).[128] The rate of DAT was 4.0% and there were 5 bleeding complication during the first 6 months, translating in an estimated annual bleeding rate of 6.6%. The use of antiplatelet therapy after WATCHMAN implantation appears to be a good alternative in patients with high bleeding risk. This treatment should ideally be evaluated in randomized trials. A large trial is currently ongoing to evaluate the safety and efficacy of antiplatelet therapy after LAAO in patients contraindicated for long-term OAC (ASAP TOO: ClinicalTrials.gov Identifier: NCT02928497).

Figure 5-3. Pathophysiology of atherothrombosis and therapeutic targets.



ADP, adenosine diphosphate; ASA, aspirin; COX-1, cyclooxygenase; TXA2, thromboxane A2; vWF, von Willebrand factor. Adapted from Shivu GN, Ossei-Gerning N. Rivaroxaban in patients with a recent acute coronary syndrome event: integration of trial findings into clinical practice. Vasc Health Risk Manag. 2014;10:291–302 and Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Nat Rev Cardiol. 2015;12:30–47.

Figure 5-4



Timeline of antithrombotic treatment after LAA occlusion with the Watchman device based on bleeding risk as recommended by the EHRA/EAPCI consensus statement. ASA, aspirin.
Adapted from Meier B, Blaauw Y, Khattab AA, et al. EHRA/ EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. EuroIntervention. 2015;10:1109–1125 and Price MJ, Reddy VY, Valderrabano M, et al. Bleeding outcomes after left atrial appendage closure compared with long-term warfarin: a pooled, patient-level analysis of the Watchman randomized trial experience. JACC Cardiovasc Interv. 2015;8:1925–1932.

5.6.2 Follow-up post-LAAO

We routinely perform Chest X-ray and transthoracic echocardiography before patient discharge to ensure the absence of device embolization and pericardial effusion. Post-procedural TOE and/or CCTA can be performed 1-3 months post-implantation. Imaging will assess presence of DAT and peri-device leaks and will rule out any complication (e.g., device embolization, pericardial effusion). Results of post-implantation imaging are used in many centers to modify antithrombotic treatment (i.e. switch form warfarin to dual antiplatelet therapy (DAPT) or from DAPT to aspirin alone). During follow-up, further imaging is indicated in case of clinical events potentially related to device complication.

6 Goal and Work Plan

The first aim of this thesis was to assess the role of imaging in LAA occlusion. Imaging is involved in patient and device selection, post-implantation follow-up, and most importantly in procedure guidance. Thus, we analyzed strengths and weaknesses of available imaging modalities, in order to determine the best modalities and best technique for each task. We emphasized the importance of multimodality imaging and developed the role of imaging in each step of LAAO management. We also described new interesting imaging techniques.

The second objective of this dissertation was to analyze and evaluate the diagnosis, predisposition, management, and complications related to device-associated thrombosis (DAT), which is a known complication after LAAO. Indeed, data about DAT are scarce and there are no large trials evaluating this complication. Furthermore, prevention and management of DAT remain a matter of controversy. We sought to provide a systematic review of reported cases of LAAO device thrombosis by focusing on the most commonly implanted devices.

Finally, we sought to analyze the efficacy and safety of LAAO in the subgroup of patients with prior major GI bleeding. History of major GI bleeding is indeed a frequent indication for LAAO as this procedure is thought to protect from thromboembolic complications without the need for systemic anticoagulation. This alternative may be promising in patients with a high risk of recurrent GI bleeding or in case of GI bleeding secondary to an irreversible cause. We analyzed data from the ACP multicenter registry, which included more than 1,000 patients treated with the ACP.

7 Part one: Role of Imaging in Percutaneous Left Atrial Appendage Occlusion

7.1 Publication N°1: Role of Imaging in Percutaneous Left Atrial Appendage Occlusion

7.1.1 Introduction

Percutaneous LAA occlusion is now a valid alternative to long-term oral anticoagulation in patients with nonvalvular atrial fibrillation at high thromboembolism risk, especially for patients who are considered ineligible for anticoagulation. The most frequently used occluders worldwide include the WATCHAMN (Boston Scientific) and the Amplatzer Cardiac Plug or Amulet (Abbott/ St. Jude Medical) devices. Imaging is a key part of LAA occlusion. Different imaging modalities coexist and have specific advantages.

7.1.2 Summary

Multimodality imaging is key in the understanding of 3D aspects of the LAA and surrounding structures anatomy. Imaging is essential for procedural planning, during each step of the procedure and for device surveillance after implantation. Multimodality imaging, including 2D/3D echocardiography, fluoroscopy, and cardiac computed tomography may increase the safety and efficacy of the procedure.

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Role of Imaging in Left Atrial Appendage Occlusion

Mathieu Lempereur [1,*], Adel Aminian [2], Raluca Dulgheru [1], Tom De Potter [3], Cécile Oury [1], Patrizio Lancellotti [1,4,*]

[1] MD, University Hospital of Liège, GIGA Cardiovascular Sciences, Imaging Cardiology Liège, Liège, Belgium

[2] MD, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium

[3] MD, Arrhythmia Unit, Cardiovascular Center, OLV Hospital, Aalst, Belgium

[4] MD, Gruppo Villa Maria Care and Research, Anthea Hospital, Bari, Italy

** Corresponding author: Patrizio Lancellotti and Mathieu Lempereur, Department of Cardiology, University Hospital Sart Tilman, B - 4000 Liège, Belgium. Tel: + 32.4.366.71.94, Fax: + 32.4.366.71.95. E-mail: plancellotti@chu.ulg.ac.be and mathieu.lempereur@chu.ulg.ac.be*

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Cardiac computed Tomography Angiography

Abstract

Percutaneous left atrial appendage (LAA) occlusion is now a valid alternative to long-term oral anticoagulation in patients with non-valvular atrial fibrillation at high thromboembolism risk, especially for patients who are considered ineligible for anticoagulation. The most frequently used occluders worldwide include the WATCHAMN (Boston Scientific, Natick, MA, USA) and the Amplatzer Cardiac Plug or Amulet (St. Jude Medical/Abbott, St Paul, MN, USA) devices. Multimodality imaging is key in the understanding of 3D aspects of the LAA and surrounding structures anatomy. Imaging is essential for procedural planning, during each step of the procedure and for device surveillance after implantation. Multimodality imaging, including 2D/3D echocardiography, fluoroscopy, and cardiac computed tomography can increase the safety and efficacy of the procedure.

INTRODUCTION

Left atrial appendage (LAA) occlusion is increasingly recognized as a valid non-pharmacologic therapy for stroke prevention in high-risk patients with non-valvular atrial fibrillation (AF), especially in cases where long-term oral anticoagulation (OAC) therapy is contraindicated. Two randomized-controlled trials, the PROTECT AF and PREVAIL studies, have shown the safety and efficacy of this procedure in patients randomized to either LAA closure with the WATCHMAN device (Boston Scientific, Natick, MA, USA) or warfarin therapy [1, 2]. Two large registries in patients who were mostly contra-indicated or deemed unsuitable to long-term anticoagulation and treated with the Amplatzer Cardiac Plug (ACP) (St. Jude Medical/Abbott, St Paul, MN, USA) (ACP multicenter registry) [3] or the WATCHMAN (Ewolution registry) [4] have confirmed safety and efficacy of this procedure in this population. Currently, the European Society of Cardiology (ESC) guidelines for the management of AF recommend that LAA closure may be considered in patients with high-risk of stroke and contraindications to long-term OAC (class IIb, level of evidence B) [5]. The 2014 American (ACC/AHA/HRS) guidelines on management of AF have not made any recommendation on this procedure [6]. Food Drug Administration approval in the USA for the WATCHMAN device was obtained in March 2015 for patients with non-valvular AF and high-risk of stroke who have an appropriate rationale to seek a non-pharmacologic alternative to warfarin.

Imaging is a key part of LAA occlusion as it portends patient selection, device selection, procedural guidance and post-implantation surveillance. Different imaging modalities are currently used for each of these steps, as multimodality imaging in this procedure has the potential to improve procedure safety and efficacy. Close collaboration and excellent communication between the operator and the imaging specialist are essential. The implanting team has to understand the various steps of the procedure, its complexity and 3D anatomy of the LAA and surrounding structures. This review will focus on the role of imaging in LAA closure with the most commonly used devices, the WATCHMAN and the ACP/Amulet. After explaining the role of imaging in the different steps of the procedure, specific aspects will be developed with emphasis on transoesophageal echocardiography (TOE) and cardiac computed tomography angiography (CCTA).

Characteristics of the ACP/Amulet and Watchman Devices

The ACP or Amulet (second generation ACP) devices are self-expanding nitinol devices made of a distal lobe, designed to anchor the device in the LAA, connected by a short mobile waist to a proximal disc, covered by polyester patches and intended to seal the LAA orifice [7]. ACP sizing depends on the widest landing zone. It is recommended to oversize the device by 2-4 mm for the ACP and 3-6 mm for the Amulet from the widest measured landing zone. The WATCHMAN device is a self-expanding nitinol frame structure with fixation barbs and a permeable polyester fabric cover [8]. WATCHMAN sizing is based on the maximum LAA diameter, which should be 17 to 31 mm to accommodate available devices. A 8-20% compression ratio based on the widest measurement is recommended by the manufacturer, while most implanters will aim for the higher compression range (close to 20%). Given that the WATCHMAN is almost as long as it is wide, the depth of the distal (implant) lobe has to be as deep as the diameter of the device chosen.

ROLE OF IMAGING IN PROCEDURAL STEPS

Pre-Procedural Planning

Baseline assessment of the LAA days to weeks prior to the procedure is a recommended standard of practice for percutaneous LAA occlusion. This evaluation will gather information about presence of thrombus, LAA morphology and size, other cardiac structures and will exclude contra-indications for LAA closure. TOE is the preferred modality but alternative (in case of contraindications to TOE) or complementary imaging by CCTA is increasingly performed [9, 10]. Many authors judge the presence of thrombus as an absolute contra-indication for LAA closure. If thrombus is detected during the pre-procedural work-up, anticoagulation should be initiated or intensified for at least 3-4 weeks with repeated imaging to confirm thrombus resolution before proceeding with LAA occlusion [6]. LAA morphology and dimensions can be identified in the pre-procedural study. The orifice diameter, the landing zone diameter and the depth of the LAA can be measured. This will orient device selection and ensure that LAA closure is feasible.

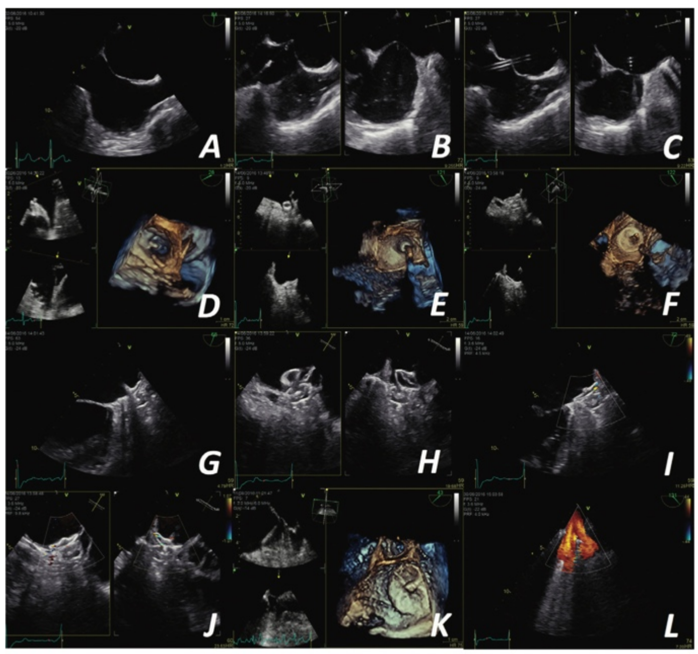

Figure 1: Step-by-step 2D/3D Transoesophageal (TOE) Guidance for Left atrial Appendage (LAA) Occlusion with an Amulet Device.
A: Step 1: The transseptal needle is pulled down with imaging guidance in the bicaval view (from superior to inferior positioning).
B: Step 2: Bicaval and short-axis views allowing visualization of the needle tenting on the fossa ovalis. The goal is to puncture in the infero-posterior region of the fossa ovalis. The use of X-plane or Bi-plane view is recommended.
C: Step 3: Gentle advancement of the guide through the interatrial septum (IAS) is tracked in X-plane or Bi-plane view.
D: Step 4: The pigtail catheter is advanced inside the LAA. Real-time 3D TOE with zoom is the preferred modality for guidance.
E: Step 5: Positioning and deployment of the device lobe inside the LAA is followed on 3D TOE.
F: Step 6: Real-time 3D TOE with zoom shows the deployment of the disc at the level of the LAA orifice. The saddling of the disc in the LAA orifice can be imaged with 3D zoom mode.
G: Step 7: Position of the device lobe inside the LAA in relationship with the left circumflex (LCx) artery is assessed. 60 to 90^0 views on 2D will image the LCx artery.
H: Step 8: A tug test is performed to test device stability inside the LAA.
I and J: Step 9: Once the final position is considered appropriate, residual peri-device leaks are looked for with 2D color flow mode with adapted velocities at 45^0, 60^0, 90^0 and 135^0. Bi-plane views with color-flow can also be used (panel J).
K: Step 10: On 3D zoom, the anatomic relationship between the disc of the device, the left pulmonary veins and the mitral valve are evaluated.
L: Step 12: Color flow Doppler of the left pulmonary veins is performed together with pulsed-wave Doppler to exclude any compression on the pulmonary veins by the device.

High quality figures are available as online supplements.

The orientation of the LAA may help operators in selecting the type of access sheath. Characteristics of the inter-atrial septum (IAS) will be assessed as some features may be associated with a difficult transseptal puncture (TSP). For instance, the presence of thick or aneurysmal IAS will be evaluated.

Procedural Guidance

Interventions are performed with fluoroscopy while TOE allows guidance during the different procedural steps (Fi 1). TOE guidance during TSP is an important step as a puncture in the optimal infero-posterior region of the fossa ovalis may greatly facilitate further steps of LAA occlusion. Live TOE guidance improves safety of the TSP and increases the likelihood of an optimal TSP location. Wire and pigtail catheter position can also be identified more easily with TOE and procedure time may be shortened with guidance. Sheath positioning is visualized with TOE and fluoroscopy, ensuring a good co-axial alignment and access to the culprit (or implant) lobe. LAA morphology and sizing will be estimated by both imaging in several incidences. It is important to ensure that adequate filling pressure is present within the LA cavity to avoid underestimation of the dimension of the LAA landing zone [11]. Successful implantation is evaluated based on pre-specified criteria; different for each device and ensuring complete seal and good stability. The presence of complications is best assessed by TOE (e.g., pericardial effusion, mitral valve impingement, left pulmonary vein occlusion).

Post-Procedural Device Surveillance

We routinely perform Chest X-ray and transthoracic echocardiography (TTE) before patient discharge to ensure the absence of device embolization and pericardial effusion. Post-procedural TOE and/or CCTA can be performed 1-3 months post-implantation. Imaging will assess presence of device-associated thrombus (DAT) and peri-device leaks and will rule out any complication (e.g., device embolization, pericardial effusion). Results of post-implantation imaging are used in many centers to modify antithrombotic treatment (switch form warfarin to dual antiplatelet therapy (DAPT) or from DAPT to aspirin alone). Further imaging is indicated in case of clinical events potentially related to device complication (Table 1).

ROLE OF IMAGING IN SPECIFIC SITUATIONS OR INDICATIONS

Sizing

Correct sizing is of utmost importance for the optimization of the efficacy and safety of the procedure. Proper sizing will allow complete closure of the LAA with good device stability. Undersizing may increase peri-device leakage and increases the risk of device instability leading to dislodgement and embolization. Oversizing increases the risk of pericardial effusion, cardiac perforation and cardiac tamponade, long-term erosion and device instability. Thus, precise knowledge of LAA orifice dimensions is crucial for the selection of the occluder size. The measurements should be performed when the LAA size is the largest, at the end of the ventricular systole and under normal LA filling conditions. Performing multiple measurements in different views and ideally with multiple imaging modalities is necessary in order to select the proper device type and appropriate device size for LAA closure. Depending on the device used, specific measurements will be performed. The short-axis view enables measurements of maximal LAA diameters while the long-axis view allows measurement of the LAA depth. With the probe in mid-oesophageal position, TOE imaging planes from 0-135° are obtained to perform measurements. 3D TOE may also be useful to find maximal and mean diameters. On CCTA, 3D multiplanar reconstruction (MPR) is typically used. Given the orientation of LAA, standard orthogonal views are indeed inadequate. 2D oblique measurements are used after manipulation of cross-sectional orthogonal views. After identification of the LAA orifice in a plane showing the circumflex artery and the pulmonary vein ridge, an orthogonal plane is obtained to ensure good co-axial alignment. The orthogonal "end-on" view allows measurements of LAA dimensions at selected area of interest (Fi 2).

Table 1: Role of Imaging Modalities in Left Atrial Appendage Occlusion

Evaluation	Fluoroscopy	TOE	ICE	CCTA
Pre-procedural planning				
Absence of thrombus in the LAA	NA	++	NA	++
LAA morphology, orientation and size (length and diameters)	NA	++	NA	++
Inter-atrial septum assessment	NA	++	NA	+
Per-procedural guidance				
Absence of thrombus in the LAA	-	++	++	NA
Transseptal puncture	+	++	++	NA
Wires, catheters and sheath positioning	++	++	+	NA
Implantation success	+	++	++	NA
Peri-device leak	-	++	++	NA
Pericardial effusion	-	++	++	NA
Interaction of the device with other cardiac structures	-	++	++	NA
Embolization	++	+	+	NA
Post-procedural device surveillance				
Implantation success	NA	++	NA	++
Peri-device leaks	NA	++	NA	++
Device-associated thrombosis	NA	++	NA	++
Embolization	NA	+	NA	++
Pericardial effusion	NA	++	NA	+

++: very useful; +: useful; -: inappropriate; NA: not applicable
Abbreviations: LAA: left atrial appendage; ICE: intracardiac echocardiography; TOE: transoesophageal echocardiography
High quality figures are available as online supplements.

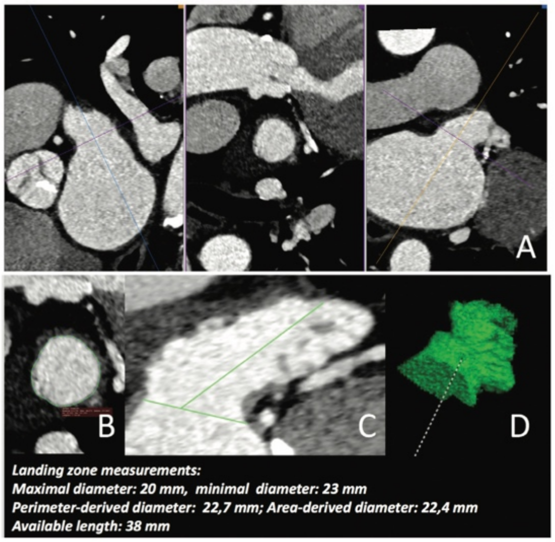

Figure 2: Cardiac Computed Tomography Evaluation of a Patient Before Left atrial Appendage (LAA) Closure with a WATCHMAN Device.

A: Multiplanar reconstruction is required for analysis as axial views are inadequate for assessing LAA dimensions given the shape and orientation of LAA. Measurements are made during the phase that corresponds best to maximal LAA end-diastolic filling (LV end-systolic filling). In multiplanar reformat (MPR) images, planes are aligned to the direction of the main lobe of the LAA. The orthogonal plane giving the LAA cross-section is moved to the level of the proximal left circumflex (LCx) artery.

B: Orthogonal (axial) cross-section ("end-on" view). Measurements of the maximal and minimal diameters, the area and perimeter of the LAA landing zone can be obtained.

C: The maximal length or depth of the LAA is measured from the landing zone to the distal tip of the main lobe (implant lobe) of the LAA in the longitudinal view (use largest value in coronal or sagittal view).

D: Volume rendered three-dimensional image obtained by cardiac computed tomography of the LAA showing a Windsock shape.

Perimeter-derived diameter is the most reproducible parameter for sizing an LAA occluder. It provides mean and maximum diameters of the landing zone and may improve correct device selection, resulting in less over- or undersizing [12-14].

For the ACP/Amulet, the size of the device is mostly based on the landing zone diameter, where the lobe will be anchored. The "anatomical" ostium is the plane that joins the left superior pulmonary vein rim (the ligament of Marshall) superiorly with the inferior junction of LA/LAA at the level of the left circumflex artery. The landing zone can be found 10 mm (for ACP) and 12 mm (for Amulet) below this segment, perpendicular to the major axis of the LAA, usually at the junction between the neck and the body of the LAA. The depth of the appendage is measured from the landing zone to the most distal tip of the main lobe of the appendage (Fig 3).

For the WATCHMAN device, the LAA anatomical orifice diameter is measured on TOE at 0°, 45°, 90° and 135°. The "effective" LAA orifice is defined as the plane connecting the pulmonary vein ridge superiorly (1-2cm within the left upper superior pulmonary vein ridge) to the inferior junction of the LA and the LAA at the level of the circumflex artery. The widest dimension should be used for sizing. Maximal length or depth of LAA is defined as the linear distance from the center of the landing zone to the distal tip of the main lobe of the appendage (Fig 4).

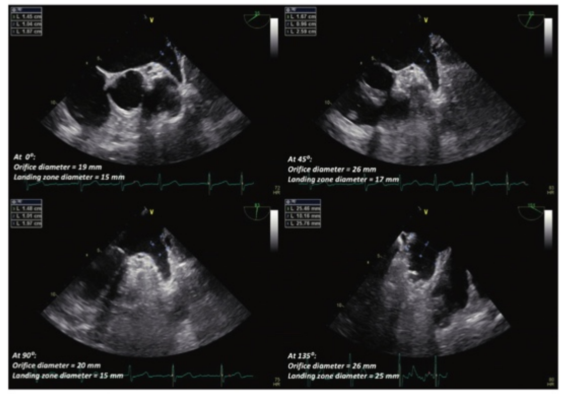

Figure 3: TOE evaluation of a patient before left atrial appendage (LAA) closure by the Amulet device. Images are acquired in the mid-oesophageal view focused on the LAA at 0^0, at 45^0 at 90^0 and at 125-135^0. Measurements are performed in a frame that gives the largest LAA, usually in end-systole. The orifice of the LAA is measured in each of these views. The landing zone (the part of the LAA in which the lobe of the Amulet device will be fixed) is measured in each of these views at 10-12 mm from the LAA orifice. The depth is measured in the main lobe of the LAA.

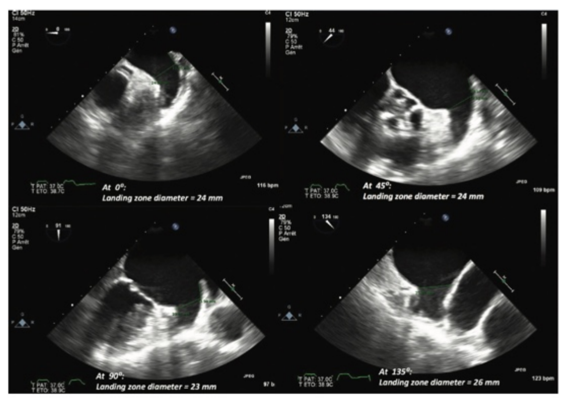

Figure 4: TOE images with measurements of the landing zone for left atrial appendage (LAA) closure with the WATCHMAN device at 0°, 45°, 90° and 135° views.

The shape of the LAA ostium is typically elliptical; other shapes have been less frequently described [13, 15]. Markedly oval-shaped orifices or landing zones are associated with a significant difference between maximal and minimal diameters, which can be confounding and may lead to over- or under-sizing. Manufacturers' recommendations for sizing are based on maximal diameter on TOE. The elliptical shape of LAA short-axis has led to the development of more flexible devices (last generation devices), allowing for more successful occlusion. The LAA usable depth is measured in the long-axis view from the LAA orifice to the LAA apex. On TOE, the angle of choice depends on LAA orientation. Angles of 0°, 45° or 90° are typically used. In case of more

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laterally orientated LAA, angle of 90° or more are necessary. On CCTA, the depth is best assessed on 3D MPR. The required depth is different between devices: ACP/Amulet devices need 10-12 mm to accommodate the lobe, WATCHMAN requires an equivalent depth as the diameter of the device.

In a study by Saw et al., fluoroscopy, 2D TOE and CCTA showed good correlations for LAA measurements. CT provided the largest measurements, followed by TOE and fluoroscopy [16]. In another study, LAA dimensions measured by CCTA correlated with the diameters obtained with fluoroscopy and intracardiac echocardiography (ICE), but they were slightly larger than the others [17]. A particular value of CCTA may be the detection and subsequent avoidance of gross sizing error by 2D TOE that occurred in a small proportion of cases (3.4%) in a single-center registry [18]. In most studies, CCTA most often predicts the appropriate device size [10, 17, 19]. The use of real time 3D TOE for the visualization and quantitative analysis of LAA parameters is more frequent and has several advantages. RT3D-TEE allows better spatial visualisation of the LAA and more comprehensive evaluation of the device and surrounding structures during the procedure. The use of MPR mode in 3D TOE allows correct identification and direct planimetric measurement of the LAA orifice area (Fig 5).

The measurements correlate well with those obtained with cardiac CT and are associated with a lower observer variability and higher accuracy and reliability than 2D TOE. Indeed, 2D TOE tends to significantly underestimate the maximal LAA orifice diameter compared to 3D TOE. There is a closer correlation between 3D TOE measurements and LAA closure device size than 2D TOE or angiographic measurements. After implantation, the device can be visualized more completely with 3D TOE [14, 20-23]. LAA is thought to have several functions, including acting as a reservoir during left ventricular systole. As such, LAA volume and sizes may vary with pressure and volume loading conditions. Typically, a minimal left atrial pressure of 10-15 mmHg is mandatory before final device sizing assessment. Intraprocedural volume loading with saline, aiming for a LA pressure >12 mmHg, showed an increase in LAA dimensions in a small study [11].

Morphology and Orientation

The morphology of the LAA is extremely complex and heterogeneous. Individual LAA morphology is unique and may sometimes be referred to as a fingerprint. In more than two-thirds of the cases, LAA is composed of 2 or more lobes that may be located in different planes [24]. Early TOE anatomical studies described numerous shapes of LAA: narrow, tubular and hooked structure [25]. Currently used classification of LAA morphology is based on the general shape of the LAA. The four classical shapes are windsock (single dominant lobe without obvious bend), chicken wing (obvious bend in the body of the LAA), cactus (dominant central lobe with multiple secondary lobes) and cauliflower (short body with numerous secondary lobes and more complex internal characteristics) [13]. Different studies have evaluated a correlation between the thromboembolism risk and LAA morphological or structural features. LAA morphology has been shown to be a significant determinant of LAA flow

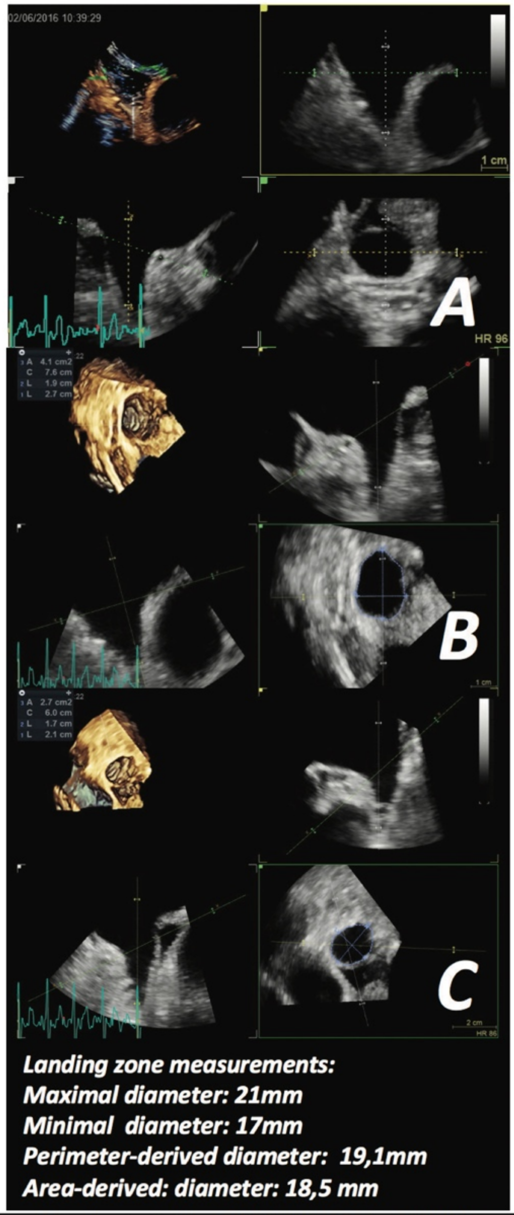

Figure 5: Step-by-step Real-time 3D TOE Evaluation for Left Atrial Appendage (LAA) Closure Device Sizing.
Step 1: In the frame with the largest LAA dimensions (usually end-systole), the first plane is positioned to transect the left circumflex (LCx) artery (this plane cuts the LAA showing the inferior and the superior walls of the LAA) and aligned to be parallel to the long-axis of the LAA.
Step 2: The second orthogonal plane is aligned with the long-axis of the LAA (Panel A).
Step 3: The third plane, the axial plane (green), is moved to be at the intersection of the LCx artery and the ridge of the left upper pulmonary vein. At this point the diameters of the LAA orifice can be measured (Panel B).
Step 4: The axial plane (green) is moved into the LAA to the estimated landing zone. The diameters of the landing zone can be measured in this view. (Panel C). For the WATCHMAN, this plane should transect the LCx artery and a point lower than the ridge but above the trabeculated parts of the LAA. For the Amulet-ACP, this plane is moved 10-12 mm into the LAA from the LAA ostium.
In our example, the measurements were made before Amulet implantation. The area-derived and perimeter-derived diameters were respectively 18.5 and $19.1cm^2$.

velocity, suggesting an underlying mechanism for the association between LAA morphology and embolic events [26]. Patients with chicken wing LAA morphology were shown to less likely develop an embolic event even after controlling for comorbidities and $CHADS_2$ score [27]. This was confirmed in a recent meta-analysis [28]. Large LAA neck diameter and LAA depth as well as extensive LAA trabeculations may also be predictors of thromboembolic events [29].

Accurate assessment of the anatomic LAA characteristics is crucial before an LAA occlusion procedure as variations in LAA anatomy may impact device selection and procedure strategy. Understanding LAA morphology can help anticipating the complexity of the procedure and the need for the use of some unusual techniques. For example, the presence of a chicken wing morphology with an early and severe bend constitutes one of the most difficult anatomical settings for LAA occlusion. A particular implanting strategy has been described with the ACP-Amulet device and consists of deploying the distal lobe of the device inside the chicken-wing bend ('Sandwich' technique) [30]. However, in some very complex chicken wing configuration or in case of very shallow LAA, the anatomy may be judged as inappropriate for LAA closure. Determination of LAA orientation also has procedural implications. Most LAA are orientated superior-anteriorly. For this reason, most LAA occlusion procedures are performed with the so called double-curve sheaths (double-curve access sheath for WATCHMAN, Boston Scientific; TV45x45 for ACP/Amulet, Saint-Jude Medical/Abbott). In cases of LAA oriented infero-posteriorly, a single-curve may be preferred [13].

Images obtained by volume rendered (VR) 3D CCTA can also be useful to plan the procedure. With manipulation of VR images, it is possible to determine the best corresponding fluoroscopic views to guide LAA occlusion during the procedure. The choice of the fluoroscopic views during the procedure relies on the LAA anatomy and on the device selected for the occlusion. The right anterior oblique (RAO) view with cranial projection (RAO 20-30°, cranial 20-30°) identifies the left lateral ridge and shows the orifice and proximal segment of the LAA best, which is particularly useful for ACP/Amulet implantation. On TOE, this view corresponds usually to the 45° view. The RAO view with caudal projection (RAO 20-30°, Caudal 20-30°), corresponding to the 135° view on TOE, can separate the possible anterior and posterior lobes and shows the body and distal segment of the LAA, which is useful for sheath placement in the distal lobe and for WATCHMAN deployment. As in transcatheter aortic valve implantation, CCTA can help planning the precise fluoroscopic implant angle.

Transseptal Puncture

Transseptal puncture is performed under fluoroscopy. Left anterior oblique view (30°) is preferred as the transseptal needle is located perpendicular to the septum in this view when oriented at about 45° medially and posteriorly (clockwise, 4-6 o'clock orientation). After a first drop from the superior vena cava to the right atrium (RA) wall, the second drop confirms needle position in the fossa ovalis. TOE is useful for the transseptal puncture guidance as it allows targeting the infero-posterior region of the septum to perform the puncture (Figure 6).

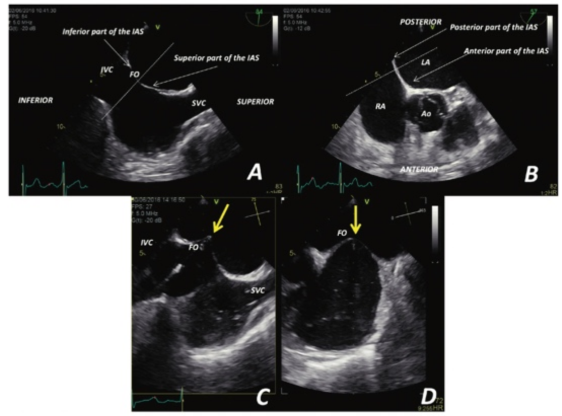

Figure 6: A: Bicaval view (90⁰) with the superior vena cava (SVC) on the right and inferior vena cava (IVC) on the left. The fossa ovalis (FO), the site of puncture, is imaged with its superior (close to the SVC) and inferior (close to the IVC) aspects. `
B: Short-axis view (45°) showing the aorta as a landmark. The FO is also visualized with its anterior (close to the aortic valve (Ao)) and posterior (close to the atrial roof) aspects.
C: Using bi-plane imaging with a 3D-TOE probe, the bicaval view shows the tenting of the FO (arrow) that results from impinging of the Brokenbrough needle into the FO.
D: The orthogonal plane (short-axis) is set through the tenting point to image the tenting on the FO from the antero-posterior aspect of the FO. The optimal area for puncture for LAA occlusion is the infero-posterior region of the interatrial septum.
Abbreviations: IAS: inter-atrial septum; LA: left atrium; RA: right atrium; SVC: superior vena cava.

Simultaneous TOE images demonstrate tenting of the inter-atrial septum (IAS) due to pressure from the needle prior to the puncture. In the upper oesophageal position, the bicaval view (90-110°) assesses the height of the puncture, while the short-axis view (30-60°) gives information about the antero-posterior position and allows puncture to be away from the aorta. As mentioned, ideal puncture location lies in the infero-posterior region of the IAS as it facilitates coaxial orientation of the access sheath for accessing the LAA. TOE can identify features that may be associated with complex transseptal puncture (thick IAS, very enlarged LA, aneurysmal IAS) and can therefore change procedural strategy (use of radiofrequency transseptal needle, increased transseptal needle curve…).

Successful Implantation

After implantation, evaluation of the success of the implantation and the absence of complications are of utmost importance. TOE remains the gold-standard imaging modality for assessing the success of the implantation but fluoroscopy is complimentary. For the WATCHMAN, the PASS criterion should be achieved: Position (device is distal to or at the ostium of the LAA), Anchor (device is stable, fixation anchors engaged, tug test stability), Size (device is compressed 8-20% of original size), Seal (device spans ostium, all lobes of LAA are covered, peri-device leak <5mm). For the ACP/Amulet device, 5 criteria are used to assess implantation adequacy: (1) tire-shape of the lobe, (2) separation of the lobe from the disc, 3) concavity of the disc, (4) axis of the lobe is perpendicular to the neck axis at landing zone, (5) lobe (at least 2 thirds) lies adequately within the circumflex artery. The disc should cover completely the anatomical orifice of the LAA. Gentle traction is applied to the disc and maintained for 30 seconds to confirm stability. The absence of significant peri-device leaks is assessed by TOE in all incidences (by color flow Doppler with Nyquist limit < $50cm.s^{-1}$) (Fig 7, panel A).

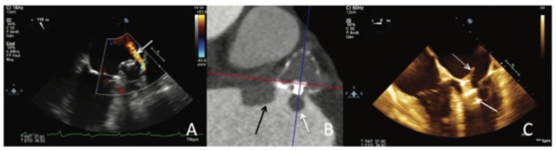

Figure 7: Evaluation of Implantation Success and Complications After LAA Occlusion.
A: Perprocedural Color flow Doppler TOE imaging showing peri-device leak (arrow) after WATCHMAN implantation.
B: Contrast-enhanced CT images revealing an atrial-side device thrombus on a WATCHMAN device at the fabric insert (white arrow) and adjacent to the device (black arrow).
Reproduced with permission from Cardiac CT angiography for device surveillance after endovascular left atrial appendage closure; Saw et al.; European Heart Journal Cardiovascular Imaging; 2015;16:1198-206. doi: 10.1093/ehjci/jev067. Oxford University Press.
C: Delayed embolization of an Amplatzer Cardiac Plug. TOE image showing entrapment of the device (arrow) in the anterior mitral apparatus with flail leaflet (dotted arrow).

CCTA can also detect peri-device leaks and identify the underlying mechanism. Different aetiologies explain peri-device leaks. In WATCHMAN cases, leaks are mostly eccentric and secondary to an edge effect. For ACP/Amulet cases, higher proportion of off-axis lobes were found in cases of patent LAA [31, 32] and leaks were more frequent when lobe compression was ≤ 10% [33]. In the presence of peri-device leak ≥5mm, resuming or pursuing antithrombotic therapy or further intervention may be considered. However, the clinical impact of peri-device leak is unknown with no clear relationship with adverse events [3, 4, 34].

Thrombus

The rationale for LAA closure development was that around 90% of thrombi in the LA originated in the LAA in patients with non-valvular AF after evaluation by autopsy, TOE or operation [35]. In AF patients, LAA structure and function have several characteristics that make LAA a prothrombotic milieu favouring thrombus formation. The elements of the Virchow's triad are found in this setting: blood stasis in this blind-ended pouch with trabeculations and electromechanical dysfunction [36, 37], endothelial dysfunction (secondary to fibrosis and inflammation) [38]. and prothrombotic state (linked to the activation of coagulation cascade) [39, 40]. The presence of thrombus is usually considered as an absolute contra-indication for LAA closure, even though several cases of LAA occlusion with Amulet have been described [41, 42]. The standard of best practice recommends anticoagulation treatment for at least 3-4 weeks in case of detection of thrombus in the LAA [6]. Control imaging after this period to confirm thrombus resolution is recommended before procedure planning. Left atrial (LA) thrombus on TOE is recognized as an echo dense mass, with smooth contours and synchronous movement with adjacent heart wall during heart cycle. TOE is considered the gold standard modality in detecting LA or LAA thrombi. In one intraoperative study, TOE was compared with direct visualization of LA contents at surgery and had a sensitivity and specificity of 100% and 99%, respectively [43] 3D TOE can help discriminate pectinate muscles from thrombus in cases with diagnostics doubts [44]. In case of uncertainty about the presence of a thrombus in the LAA, the use of ultrasound contrast can be helpful [45].

Studies with mutlidetector CT have reported good sensitivity and specificity for CCTA for LAA thrombus detection [46, 47]. Recent meta-analysis demonstrated that CT shows a good diagnostic accuracy in detecting LA/LAA thrombus with high sensitivity and specificity [48, 49]. This technique has a high negative predictive value for excluding LAA thrombus. Adaptation to CCTA protocols may improve LAA thrombus detection: delayed imaging (2-phase scan with delayed image acquisition at least 30 seconds after contrast bolus), dual-enhanced scan (single scan after 2-bolus contrast), dual-energy source and prone position [50, 51]. When delayed imaging was performed, the diagnostic accuracy significantly improved across different studies [49]. Hence, CCTA, particularly when delayed imaging is performed, may be a reliable alternative for the detection of LA or LAA thrombi. Thrombus appears in this setting as round-shaped or oval filling defects (Fig 7, panel B).

The presence of DAT is assessed during post-procedural device surveillance. DAT is not rare, with an overall reported rate of 3.9% in a recent review [52]. Diagnosis is most of the time performed during routine follow-up imaging, as most cases remain asymptomatic. Management consist mostly on short-term anticoagulation. Recently, Main et al. have proposed consensus echocardiographic diagnostic criteria for DAT diagnosis: echo density on the LA aspect of the device (1) not explained by imaging artefact; (2) inconsistency with normal healing/device incorporation; (3) visible in multiple TOE planes, (4) in contact with the LAA occluder device; and (5) exhibiting independent motion [53]. CCTA is also able to detect DAT or thrombus on the adjacent LA wall [32].

Complications

Device embolization is a well-known and feared complication of LAA closure with an average reported rate of less than 4% [54], and less than 1% in recent registries [3, 4]. In a systematic review by Aminian et al., two-thirds of reported cases were acute, with 60% of those cases occurring during the procedure. Most cases were asymptomatic [55]. Device embolization may be diagnosed by fluoroscopy, chest X-ray, TTE, TOE or CCTA (Fig 7, panel C). Pericardial effusion incidence is decreasing with last generation of devices, standardization and better understanding of the procedure [2]. Pericardial effusion occurs mostly during the procedure and is best diagnosed by echocardiography. Pericardiocentesis is rarely necessary and can be echo-guided.

ALTERNATIVE AND FUTURE IMAGING MODALITIES

Intracardiac Echocardiography (ICE)

With a successful ICE-guided LAA closure reported rate ≥ 97%, ICE has proved to be a valid alternative imaging modality for LAA occlusion in experienced centers [56-59]. The main advantage of ICE utilization is that it avoids the need for general anaesthesia or deep sedation, which can be associated with additional complications (aspiration, delirium…), lead to longer procedure-time and to additional resource utilization. Of note, a recent small study showed the feasibility of LAA closure using conscious sedation with TOE guidance [60] whereas another study described the use of an ICE-TOE probe through the oesophageal route without general anaesthesia for the monitoring of ACP device implantation [61]. ICE currently lacks multiplanar capabilities and may provide suboptimal imaging of LAA, even though the ability to move the probe in different positions may compensate these shortcomings. Furthermore, location of the ICE probe within the LA cavity improves imaging of the LAA. The main disadvantages of ICE remain the additional cost and a significant learning curve. Several ICE catheters are commercially available including the AcuNav ultrasound catheter (Siemens Medical Solutions, USA, Inc., Mountain View, CA, USA) and the ViewFlex Xtra catheter (St. Jude Medical/Abbott). Both systems are available in 8-10 Fr size and can be steered in 4 directions (anterior, posterior, left, and right). They also have color flow and spectral Doppler capabilities. The catheters are inserted from the ipsilateral or contralateral femoral vein via large venous sheaths and advanced from the inferior vena cava to the working position. The ICE probe can be positioned in the RA, the coronary sinus [56], the pulmonary artery [62] or the LA via a single-transseptal approach or after a second transseptal puncture [57]. Once the desired position is achieved, the probe can be set in that position with a lock mechanism. ICE can provide detailed imaging of the LAA in multiple views with serial and real-time assessment of the procedures steps (Fig 8).
ICE guidance is able to achieve tasks typically performed by TOE: evaluation of the presence of thrombus [63]; transseptal puncture guidance [64] measurement of LAA dimension for device sizing [17]; verification of the delivery sheath position; evaluation of device stability and peri-device leaks and continuous monitoring to detect procedural complications [56].

Integrated/Synchronized X-Ray and Echocardiography (Fusion Imaging)

LAA occlusion procedures under fluoroscopic and echocardiographic guidance with image fusion technology have been described with good results [65]. The EchoNavigator ®-system (Philips, Best, The Netherlands) is based on a fast and automated image based algorithm that localizes and tracks the TOE probe. Since the 3D dataset generated by the TOE probe has a known spatial relationship to the TOE probe, once the algorithm has recognized the TOE probe and its orientation, TOE images and X-Ray are co-registered and synchronized in real-time (Fig 9) [66].

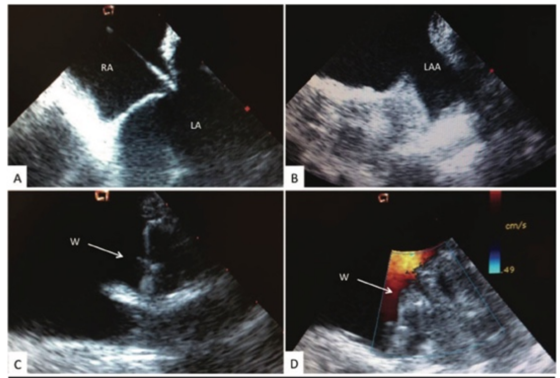

Figure 8: Intracardiac Echocardiography (ICE) Guidance for Left Atrial Appendage (LAA) Occlusion. (A) Interatrial septal puncture (ICE probe in the right atrium); (B) visualization of the LAA and anatomy assessment (ICE probe in the left atrium); (C) device position assessment; (D) check for peri-device flow/leak with color Doppler flow imaging.
Abbreviations: LA: left atrium; RA: right atrium; W: WATCHMAN device.
Reproduced with permission from Intracardiac versus transesophageal echocardiography for left atrial appendage occlusion with watchman; Frangieh et al.; Catheterization and Cardiovascular Interventions; 2016. doi: 10.1002/ccd.26805. Wiley Periodicals, Inc.

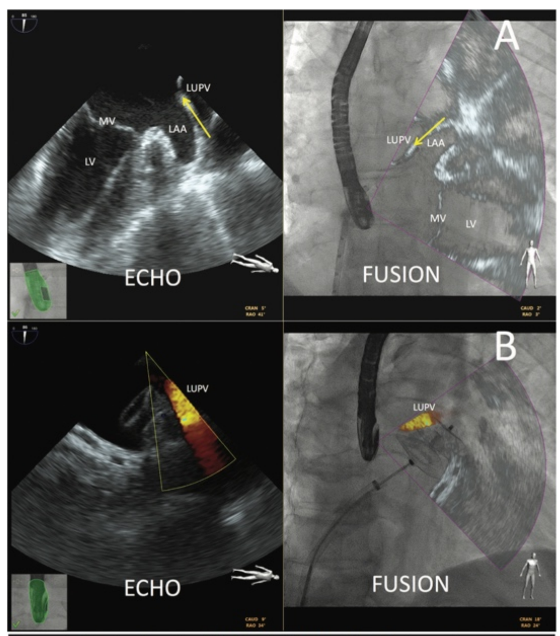

Figure 9: Fusion Imaging Obtained with the EchoNavigator ®-system.
A: Fusion of the TOE image (left) with the fluoroscopy image (right) showing the left atrial appendage (LAA) and surrounding structures. This imaging modality allows identification of the position of the Coumadin ridge (yellow arrow) and facilitates positioning of the sheath in the LAA.
B: Fusion of the Color flow Doppler TOE image (left) with the fluoroscopy image showing the absence of obstruction to flow in the left upper pulmonary vein (LUPV). The stability of the device (Amulet) is tested with application of slight tension on the delivery cable (wiggle test).
Abbreviations: LSPV: left superior pulmonary vein; LV: left ventricle; MV: mitral valve.

The system allows the simultaneous display of up to 3 different echo views: 1) the C-arm gantry view, in which the echo view is oriented in the same anatomic alignment as the x-ray view and automatically updated by each movement of the C-arm gantry; this image is then fused with the X-ray view and both images are concordant in size and orientation; 2) the « echo » view, which is the standard TOE projection showing up on the echo machine; and 3) a free image that can be rotated or cropped by the operator at the table site by using a sterile mouse pad. This view allows the operator to manipulate the real-time images without the need to request further TOE projections. There is also a marker feature that allows setting markers on anatomical location of interest on the echo image that are automatically displayed on the X-Ray image. This imaging modality seems useful for the transseptal puncture and for sheath and device positioning. This technology has the potential to improve the interaction between the operator and the imager. Whether this imaging modality may increase safety, accuracy, and efficacy of LAA occlusion has yet to be demonstrated. Of note, a preliminary study showed a significant reduction in radiation dose and fluoroscopy time with the use of the EchoNavigator®-system [67].

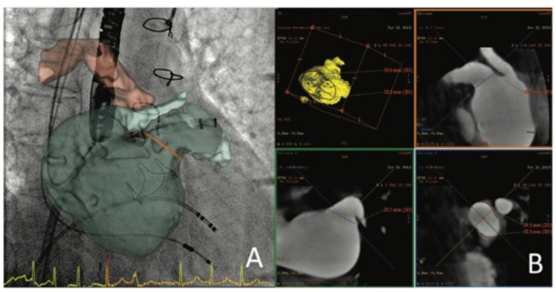

Figure 10: Images Obtained After Rotational Angiography.
A: RAO 20° view. The left atrium (LA) and left atrial appendage (LAA) are cut away along the viewing angle (i.e. 20° from frontal), the posterior wall of the structures is visible (green). A line is drawn at the position where the LAA neck is measured (orange). The bronchi (blue) are segmented to verify positioning of the 3D model. The Watchman Delivery System (WDS) is positioned in the LAA, with the device still in the sheath. Markers on the WDS allow verification of adequate LAA length.
B: 3D reconstruction of LAA (left upper corner). The LA is cut away; viewing angle is from inside the LA into the LAA ostium. Right lower corner shows cross-section at the LAA ostium with measurements. Both other images show level where cross-section was created (blue lines).

Rotational Angiography

Rotational angiography (3DRA) is an innovative method that allows per-procedural reconstruction of tomographic slices of a volume of interest in a manner similar to CT, using singe plane radiographic equipment [68, 69]. These slices can be used to perform measurements in any plane of the 3D volume, or to make a 3D reconstruction of a structure of interest and integrate it with fluoroscopy or other 3D mapping technologies. In the setting of LAA closure, the technology can be leveraged to create near-real time 3D models of the LAA. These models provide anatomical guidance by overlaying the model on the live 2D fluoroscopy image. Using tools typically provided by the manufacturer of the X-Ray equipment, the 3D model can be appropriately sized and positioned on the 2D image, and rotates automatically with the angle of the imaging tube to provide the correct visualization (Fig 1). In addition, a multiplanar reconstruction can be made through any arbitrary angle, such that a planar slice can be created at the base of the appendage perpendicular to the long-axis of the appendage in that position. This slice can be used to measure the exact dimensions of the base of the LAA without imaging imperfections that may be present with TOE in certain anatomies (Fig 2 or Fig 3 or both). Preliminary data suggest this workflow may offer more accurate selection of the most appropriate LAA occluder size (unpublished data).

CONCLUSIONS

Imaging has a key role in every step of LAA occlusion: pre-procedural planning, procedural guidance and post-implantation surveillance. Several imaging modalities are available and offer complementary information, allowing good understanding of the LAA anatomy and its relationship to the surrounding structures. Multimodality imaging should be used to improve procedural safety and efficacy of LAA occlusion.

CONFLICTS OF INTEREST

Dr. Lempereur, Dr. Dulgheru, and Dr Lancellotti have no disclosure. Dr. Aminian is proctor for St Jude Medical/Abbott and Boston Scientific. Dr. De Potter is proctor for Boston Scientific.

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8 Part Two: Device-Associated Thrombus Formation after Left Atrial Appendage Occlusion

8.1 Publication N°2: Device-Associated Thrombus Formation after Left Atrial Appendage Occlusion: A Systematic Review of Events Reported with the Watchman, the Amplatzer Cardiac Plug and the Amulet

8.1.1 Introduction

Device-associated thrombosis (DAT) is a rare but known complication after LAAO with an incidence that ranges between 0 and 17% according to different reports. Management and clinical consequences of this complication are however a matter of controversy and remain to be further studied. In addition, there is currently no consensus about the antithrombotic treatment and echocardiographic surveillance after LAAO.

We therefore sought to provide a systematic review of reported cases of LAAO device thrombosis by focusing on the three most commonly implanted devices: WATCHMAN, ACP, and Amulet. We analyzed and discussed the diagnosis, predisposition, management, and complications related to this event.

8.1.2 Summary

Objectives: This study aimed to provide a systematic review of DAT after LAAO with the Watchman, Amplatzer Cardiac Plug, and Amulet devices.

Background: DAT is known as a complication of LAAO but data about its clinical impact is scarce.

Methods: A systematic review of studies evaluating the incidence, treatment and clinical implications of DAT from January 2008 to September 2015 was conducted.

Results: A total of 30 studies describing DAT events were included in the analysis. The overall incidence of DAT was 3.9% (82 DAT for 2,118 implanted devices). The median time from procedure to diagnosis of DAT was 1.5 months (IQR: 0–2.9). Most cases were diagnosed with TOE. The treatment consisted of low molecular weight heparin (LMWH) in 45.5% of cases, and oral anticoagulation (OAC) or other treatment modalities in 54.5%. Complete thrombus resolution was achieved in 95.0% of cases (100% with LMWH and 89.5% with OAC). Treatment duration varied greatly with a median treatment duration of 45 days (IQR: 14–135). Clinical events related to DAT consisted of neurologic events namely two transient ischemic attacks (2.4%) and four ischemic strokes (4.9%).

Conclusions: DAT is an infrequent complication of percutaneous LAAO. It occurs mainly early after the procedure and is associated with a low rate of neurological complications. In the majority of cases, diagnosis is made during follow- up imaging with TOE. Anticoagulation treatment seems to be safe and highly effective. Further studies are needed to evaluate the optimal management of DAT.

Catheterization and Cardiovascular Interventions 00:00–00 (2017)

Original Studies

Device-Associated Thrombus Formation after Left Atrial Appendage Occlusion: A Systematic Review of Events Reported with the Watchman, the Amplatzer Cardiac Plug and the Amulet

Mathieu Lempereur,[1*] MD, **Adel Aminian,**[2] MD, **Xavier Freixa,**[3] MD, PhD, **Sameer Gafoor,**[4,5] MD, **Joelle Kefer,**[6] MD, PhD, **Apostolos Tzikas,**[7] MD, PhD, **Victor Legrand,**[1] MD, PhD, **and Jacqueline Saw,**[8] MD

Objectives: This study aimed to provide a systematic review of device-associated thrombosis (DAT) after left atrial appendage occlusion (LAAO) with the Watchman, Amplatzer Cardiac Plug, and Amulet devices. Background: DAT is known as a complication of LAAO but data about its clinical impact is scarce. Methods: A systematic review of studies evaluating the incidence, treatment and clinical implications of DAT from January 2008 to September 2015 was conducted. Results: A total of 30 studies describing DAT events were included in the analysis. The overall incidence of DAT was 3.9% (82 DAT for 2118 implanted devices). The median time from procedure to diagnosis of DAT was 1.5 months (IQR: 0–2.9). Most cases were diagnosed with transesophageal echocardiogram (TEE). The treatment consisted of low molecular weight heparin (LMWH) in 45.5% of cases, and oral anticoagulation (OAC) or other treatment modalities in 54.5%. Complete thrombus resolution was achieved in 95.0% of cases (100% with LMWH and 89.5% with OAC). Treatment duration varied greatly with a median treatment duration of 45 days (IQR: 14–135). Clinical events related to DAT consisted of neurologic events namely two transient ischemic attacks (2.4%) and four ischemic strokes (4.9%). Conclusions: DAT is an infrequent complication of percutaneous LAAO. It occurs mainly early after the procedure and is associated with a low rate of neurological complications. In the majority of cases, diagnosis is made during follow-up imaging with TEE. Anticoagulation treatment seems to be safe and highly effective. Further studies are needed to evaluate the optimal management of DAT. © 2017 Wiley Periodicals, Inc.

Key words: left atrial appendage closure; thrombosis; complication

Additional Supporting Information may be found in the online version of this article.

[1]University Hospital of Liège, Liège, Belgium
[2]Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium
[3]Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain
[4]Swedish Heart and Vascular, Seattle, WA, USA
[5]CardioVascular Center Frankfurt, Frankfurt, Germany
[6]Cliniques Universitaires Saint-Luc, Brussels, Belgium
[7]AHEPA University Hospital, Thessaloniki, Greece
[8]Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada

*Correspondence to: Mathieu Lempereur, MD; Cardiology University of Liège Hospital, C.H.U. du Sart-Tilman B35, 4000 Liège, Belgium. E-mail: mathieu.lempereur@chu.ulg.ac.be

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INTRODUCTION

Percutaneous left atrial appendage (LAA) closure is increasingly recognized as an alternative to long-term oral anticoagulation (OAC), mainly in patients with contraindications to OAC such as patients with history of severe bleeding or at high bleeding risk. Currently, LAA occlusion (LAAO) was given a class IIb recommendation for patient with nonvalvular atrial fibrillation (AF) with high stroke risk and contraindications to long-term OAC in Europe [1]. In USA, the Watchman device (WM) (Boston Scientific, Plymouth, Minnesota, USA) was recently approved by the US Food and Drug Administration as an option for high-risk AF patients with appropriate rationale for nonpharmacologic alternative to warfarin.

Percutaneous LAAO has been widely adopted, with >10,000 of each of WM and Amplatzer Cardiac Plug (ACP) (St. Jude Medical, Minneapolis, Minnesota, USA) devices implanted worldwide [2]. However, several major complications have been reported including pericardial tamponade and device embolization [3]. Device-associated thrombosis (DAT) is a rare but known complication after LAAO with an incidence that ranges between 0 and 17% according to different reports. Management and clinical consequences of this complication are however a matter of controversy and remain to be further studied. In addition, there is currently no consensus about the antithrombotic treatment and echocardiographic surveillance after LAAO.

We sought to provide a systematic review of reported cases of LAAO device thrombosis by focusing on the three most commonly implanted devices: WM, ACP, and Amulet (2nd generation ACP) (St. Jude Medical, Minneapolis, Minnesota, USA). We analyzed and discussed the diagnosis, predisposition, management, and complications related to this event.

MATERIALS AND METHODS

DAT was defined as the detection of thrombus adherent to the luminal (left atrial) side of the device by any imaging modality and irrespective of clinical findings or complications. The English scientific literature was searched using PubMed for eligible studies with the following list of keywords: left atrial appendage occlusion AND thrombosis, left atrial appendage occlusion AND thrombus, left atrial appendage closure AND thrombosis, left atrial appendage closure AND thrombus, left atrial appendage closure, left atrial appendage occlusion, LAA closure, LAA occlusion, Watchman, Amplatzer Cardiac Plug, or Amulet. The search included references from January 1, 2008 until September 30, 2015, by limiting to human and English language literature. We focused our analysis on the WM and Amplatzer devices. All main registries and trials including WM and Amplatzer devices were searched for cases of DAT. All review articles were excluded but their references were searched for all potential cases as well as references of case reports, trials and registries. Redundant data were excluded. Periprocedural events were not included in this analysis. One report with thrombus inside the occlusion device was excluded [4], as we only included cases with thrombus adherent to the left atrial side of the implanted device. The resultant reports were reviewed by two independent investigators (ML, AA) with careful analysis of the timing and modality of diagnosis, treatment at time of diagnosis, complication, treatment and resolution rate of DAT, when available. The rate of DAT was expressed as the number of events divided by the number of implanted devices. The rate of DAT for all devices, WM and ACP/Amulet were based on available reported cases from case series, registry and randomized trials (we excluded individual case reports when calculating the overall incidence of DAT). We excluded studies with no reported imaging follow-up (FU) or with missing imaging FU data. For the timing of event, duration of anticoagulation and rate of thrombus resolution, case reports, and registries or trials with no reported event or with missing data were not included in the analysis. Correlation between the number of imaging FU performed and the incidence of DAT was also evaluated.

Statistical Analysis

Parametric data were expressed as mean ± standard deviation. Nonparametric data were described as median ± interquartile range. Nonparametric independent data were compared using a Mann–Whitney test and rank correlation between nonparametric data was evaluated using a Spearman test. *P* value of 0.05 was considered as significant. Statistical analyses were performed using MedCalc for Windows, version 15.11.0 (MedCalc Software, Ostend, Belgium).

RESULTS

Search and Synthesis of the Literature

We found 525 citations on PubMed after the first literature search (Fig. 1). Of these, 210 citations were not related to LAAO and were excluded. Of the remaining 315 citations, 95 articles were excluded because of review articles, 104 citations were excluded because they consisted in original studies or case report not relevant to DAT events, and 66 citations were excluded because they reported other technique (e.g., epicardial

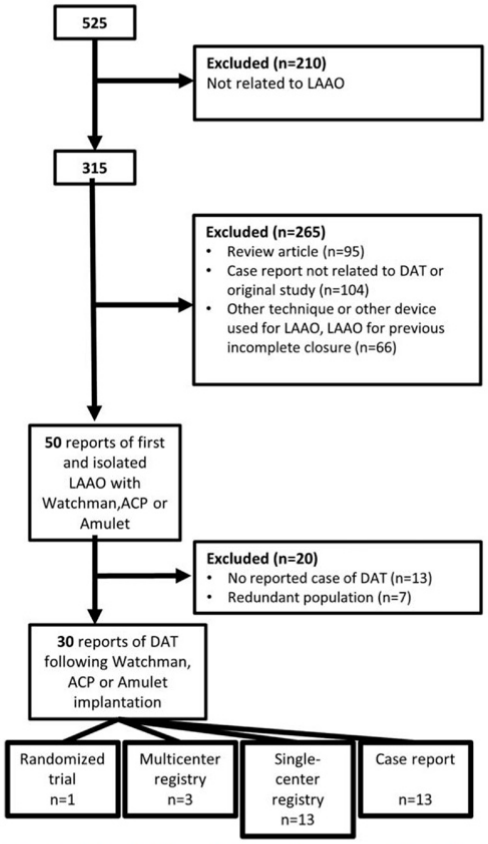

Fig. 1. Search criteria and flow diagram of the literature selection process.

approach) or other device [e.g., PLAATO (Appriva Medical, Sunnyvale, CA)] used for LAAO, or LAAO for previous incomplete closure. Of the remaining 50 citations, 20 citations were excluded either because of an absence of reported DAT ($n = 13$, Supporting Information File 1) or because of a redundant study population ($n = 7$). Of note, the ACP multicenter registry was excluded due to concerns of substantial "double-reporting" as many series reporting DAT were also included in this registry [5]. After excluding the above, a remaining 30 studies reporting DAT were included, consisting of 1 multicenter randomized trial, 3 multicenter registries, 13 single-center registries, and 13 case reports (10 ACP, 3 WM). Ten studies with no reported event of DAT but available FU data were included in the analysis for the estimation of DAT incidence (Supporting Information File 1). Studies reporting DAT are summarized in Table I (registries and trials) and Supporting Information File 2 (case reports).

Incidence of Device Thrombosis

The reported incidence of DAT per implanted device varied from to 0 to 17.6% in the various studies. In larger series ($n \geq 100$), the incidence varied from 0 to 8.2%. In previously reported large analyses ($n \geq 450$), the incidence was reported at 4.4% for the ACP [5] and 4.2% for the WM [21]. In total, there were 82 cases of DAT identified out of 2118 of LAAO cases from reported case series (individual case reports were excluded when calculating the overall incidence of DAT). Thus, in our pooled analysis, the mean incidence of DAT after LAA closure was 3.9% for all devices (82/2118), 3.4% for WM (40/1184), 4.6% for ACP/Amulet (35/757), 4.8% for ACP (34/707), and 2.0% for Amulet (1/50) (Fig. 2; Supporting Information File 3). The reported incidence of DAT at 6 weeks postimplantation was similar for WM and ACP/Amulet (2.0 vs. 2.6%, respectively, $P = 0.60$) (Supporting Information File 4). Overtime, the reported incidence of events in the literature did not seem to change significantly, with significant variations between studies (Fig. 3; Supporting Information File 5). We found a significant correlation between the incidence of DAT and the number of FU performed [Spearman's coefficient of rank correlation (rho) = 0.414, $P = 0.03$) (Supporting Information File 6).

Clinical Implications and Treatment Strategies

Although most DAT were asymptomatic, 7.3% of patients with DAT (6/82) presented with neurological events (2 TIAs and 4 strokes). Overall, only 0.28% of implanted LAAO patients presented with neurological events presumably related to DAT (6/2118).

The management of DAT following diagnosis varied in the studies, and data was missing for most cases. Treatment of DAT consisted generally of starting LMWH, intravenous (IV) heparin or OAC, or intensification of pre-existing antithrombotic regimen (e.g., higher doses of OAC, or higher target INR). In three case reports, surgical treatment was performed, due to the presence of a very large thrombus in two cases and because of refusal of OAC in one patient (Supporting Information File 2) [23–25].

Overall, complete thrombus resolution under treatment was achieved in the vast majority of cases (95.0%, 38/40 cases). Partial resolution was also reported in rare cases (2/40 cases) but late FU data was not available in these cases [9, 19]. Recurrence rate was low with only two reported cases at one and 3 months after cessation of intensified antithrombotic regimen but the number and duration of imaging FU after thrombus resolution are unknown [8, 26]. Treatment regimen for DAT included starting LMWH in

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TABLE I. Registries and Studies with Reported Events of DAT

Reference	Study design	Device	Number of cases/ implanted devices	Follow-up duration	Timing and diagnosis modality	Treatment at time of thrombosis	Treatment type and duration	Complications	Thrombus resolution after antithrombotic treatment
ACP/Amulet									
Guerios et al. [6]	Single-center registry ($n = 86$, 85 implanted)	ACP	6/85 (7.1%)	25.9 patient-years	Unknown	Unknown	3 months of OAC	None	Complete resolution in 100% of cases
Lopez-Minguez et al. [7]	Single-center registry ($n = 35$, 34 implanted)	ACP	5/34 (14.7%)	21.1 ± 10.1 months	Case 1: 1st week Case 2: 2nd month Case 3: 3rd month Case 4. 3rd month Case 5: 6th month	Case 1: None Cases 2-5: Unknown	Case 1: Antiplatelet and LMWH for 2 weeks Case 2: LMWH added for 2 weeks Case 3: LMWH added for 2 weeks Case 4: IV heparin Case 5: 2 weeks of LMWH	Case 4: TIA (no treatment at first because of hematoma)	Complete
Plicht et al. [8]	Single-center registry ($n = 34$, 34 implanted)	ACP	6/34 (17.6%)	12-month FU TEE was performed in 74% of patients	−3 cases before discharge TEE (3.6 ± 1.7 days after the procedure) (Cases 1,2 and 3) −3 cases at 3-month FU TEE (Cases 4, 5 and 6)	DAPT	Case 1: IV heparin Case 2: IV heparin: partial resolution: dabigatran: partial resolution: VKA Case 3: VKA Cases 4,5,6: VKA or IV Heparin: resolution	None	-Complete resolution -Recurrence at 3 months in 1 of the patient with thrombus diagnosed before discharge: VKA: resolution at 12 months
Freixa et al. [9]	Single-center registry ($n = 25$, 24 implanted)	Amulet	1/24 (4.2%)	TEE FU at 1.46 months (IQR 1.2–2.3 months) in 87.5% of patients	Case 1: 2 months (FU TEE)	DAPT	Case 1: long-term dalteparin	None	Progressive regression
Wiebe et al. [10]	Single-center registry ($n = 60$, 57 implanted)	ACP	2/57 (3.5%)	1.8 y (1.0–2.8) (median years, range) 103.2 patient-years	Case 1: 1 month (routine TEE) Case 2: 6 months (routine TEE)	Case 1: DAPT Case 2: ASA	Case 1: LMWH – duration unknown: good evolution at FU Case 2: LMWH – duration unknown, thrombus seen at FU, OAC started, control pending	No embolic symptoms	Case 1: Complete resolution Case 2: Unknown

TABLE I. *Continued*

Reference	Study design	Device	Number of cases/ implanted devices	Follow-up duration	Timing and diagnosis modality	Treatment at time of thrombosis	Treatment type and duration	Complications	Thrombus resolution after antithrombotic treatment
Minguez et al. [11]	Multicenter registry ($n = 167$, 158 implanted)	ACP	13/158 (8.2%)	22 ± 8.3 months 290 patients- year	Unknown	Unknown	If thrombus occurred, subcutaneous enoxaparin in a therapeutic dose was added for 2 weeks, clopidogrel was prolonged and the TEE was repeated to check for disappearance.	Unknown	Unknown
WATCHMAN									
Sick et al. [12]	Multicenter registry ($n = 75$, 66 implanted)	WM	4/66 (6.1%)	24 ± 11 months	A: TIA at 6 months B: Modality unknown, 6 and 12 months, no details	Unknown	6 months of warfarin	1 TIA at 6 months	Complete
Bai et al. [13]	Single-center registry ($n = 58$)	WM	1/58 (1.7%)	25.9 ± 13.4 months	Case 1: 21.6 months postprocedure	DAPT	Warfarin (duration unknown)	None	Unknown
Meincke et al. [14]	Single-center registry ($n = 59$)	WM	3/59 (5.2%)	6.3 ± 0.5 months	Case 1: 6 weeks Cases 2 and 3: 12 weeks postimplantation FU TEE	Unknown	Minimum 4 weeks of LMWH	None	Complete
Ledwoch et al. [15]	Single-center registry ($n = 36$, 34 implanted)	WM	1/34 (2.9%)	12 months FU	6-months FU	Unknown	4 weeks of LMWH	None	Complete
ACP and WATCHMAN									
Chun et al. [16]	Single-center registry ($n = 80$, 78 implanted)	ACP ($n = 40$), WM ($n = 38$)	4/78 (5.1%) (3 WM, 1 ACP)	364 days (interquartile range 283–539 days)	6 weeks FU TEE	1 on DAPT (1/59 patients, 1.7%) 3 on OAC (3/19; 15.8%)	6 weeks of intensified antithrombotic therapy: if on OAC, target 2.5-3.5, if on DAPT, LMWH added	None	Complete resolution in 100% of cases
Faustino et al. [17]	Single-center registry ($n = 22$, 22 implanted)	ACP ($n = 20$) WM($n = 2$)	1/22 (4.5%) (1 ACP)	12 ± 8 months FU	1-month FU TEE	DAPT	LMWH for up to six months with strict echo monitoring	None	Complete

TABLE I. *Continued*

Reference	Study design	Device	Number of cases/ implanted devices	Follow-up duration	Timing and diagnosis modality	Treatment at time of thrombosis	Treatment type and duration	Complications	Thrombus resolution after antithrombotic treatment
Gafoor et al. [18]	Single-center registry ($n = 53$, 49 implanted)	ACP ($n = 27$) WM ($n = 26$)	1/49 (2.0%)	12 months FU 129 patient-years	6-months FU Modality unknown	Unknown	VKA for 4 weeks	None	Complete
Matsuo et al. [19]	Single-center registry ($n = 179$, 177 implanted)	WM ($n = 167$), ACP ($n = 10$)	9/177 (5.1%) A. 2 peri-operative thrombus B. 45-d FU: 7/165 (4.2%)	6-month FU in 145 patients	A. TEE during procedure B. 45-days FU TEE	A. IV heparin B. 4 under aspirin and clopidogrel, 1 under aspirin mono therapy, 1 on OAC, and 1 patient taking OAC and aspirin	A. Device exchanged for a new one B. Remained on OAC	None	A. NA B. 5/7 (71.2%) resolution at 6-months
Saw et al. [20]	Single-center registry ($n = 45$)	ACP ($n = 18$) WM ($n = 18$) Amulet ($n = 9$)	1/45 (2.2%) (1 WM)	1.2 ± 1.1 year	Routine CCTA 78 days postprocedure	DAPT	Warfarin 3 months	None	Complete
NO DETAILS ON TIMING OF DIAGNOSIS AND TREATMENT MODALITY									
Reddy et al. [21] PROTECT AF	Randomized trial ($n = 542$, $n = 478$ devices implanted)	WM	20/478 (4.2%)	Median FU of 2.5 years (range, 0 to 4.7 years)	Unknown	Unknown	Unknown	3 ischemic stroke (1/3 had a mobile/ pedunculated thrombus)	Unknown
Reddy et al. [22] ASAP	Multicenter registry ($n = 150$)	WM	6/150 (4.0%)	14.4 ± 8.6 months	A: FU TEE: 5 (mean 164 ± 135 days postimplant) B: Stroke 341-days postimplantation	NA	A: 4 received 4 to 8 weeks of LMWH, and 1 received no treatment B: Treatment unknown	A: None B: 1 ischemic stroke	Unknown

AC: anticoagulation; ASA: acetyl salicylic acid; CCTA: cardiac computed tomography angiogram; CT: computed tomography; DAPT: dual antiplatelet therapy; EF: ejection fraction; FU: follow-up; IQ: interquartile; IQR: interquartile range; IVH: intravenous heparin; LMWH: low molecular weight heparin; NA: not applicable; PFO: permanent foramen ovale; TEE: transesophageal echocardiogram; TIA: transient ischemic attack; TTE: transthoracic echocardiogram; VKA: vitamin K antagonist.

45.5% of cases and starting OAC in 36.4%, among patients not previously on OAC. In other cases (18.1%), intensification of antithrombotic regimen included intensifying warfarin dosage with target INR of 2.5–3.5 if patients were already on warfarin, switching to intravenous heparin (IVH) among patients on OAC, starting OAC or IVH (no details available), or starting combined therapy (IVH followed by OAC). Among available data on treatment efficacy, LMWH was associated with 100% rate of DAT resolution (10/10), while OAC success rate was reported at 89.5% (17/19) ($P = 0.3855$) (Supporting Information File 7).

Treatment duration varied greatly with reported minimal duration of 2 weeks and maximum duration to 6 months or even long-term anticoagulation in two cases [1 case with long-term OAC [19], 1 case with long-term dalteparin [9]]. The median duration of antithrombotic treatment in our analysis was 45 days (IQR: 14–135), with shorter treatment duration for LMWH [14.0 days (IQR: 14.0–14.0)] compared to OAC [90.0 days (IQR: 90.0–180.0)], $P \leq 0.0001$.

Regarding the use of NOACs, successful use of apixaban (5 mg bid for 6 months) was reported in one case [27] and dabigatran was used in two cases with only partial resolution for both at mid-term FU (later FU data not available) [8, 26].

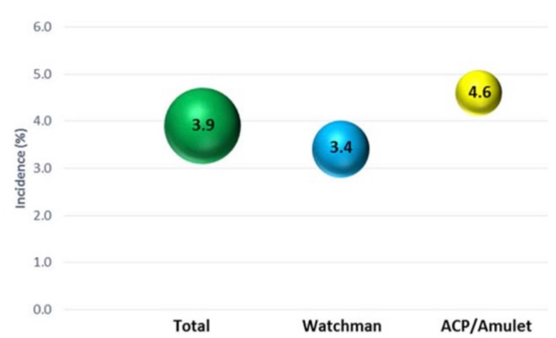

Fig. 2. Incidence of DAT (%) for all devices, Watchman and ACP/Amulet with relative size based on the sample size. [Color figure can be viewed at wileyonlinelibrary.com]

Timing and Modality of Diagnosis

The median time from procedure to diagnosis of DAT was 1.5 months (IQR: 0–2.9) ($n = 55$). Most cases were found on routine FU imaging in asymptomatic patients (94%). In three reported cases, transesophageal echocardiogram (TEE) was performed in the context of a neurologic event (stroke 341 days postimplantation [22] or transient ischemic attack 3 or 6

TABLE II. Potential Risk Factors for Device-Related Thrombosis

Characteristics	Risk factors
Patient characteristics	High $CHADS_2$ score [8]
	High CHA_2DS_2-VASc score [8]
	High platelet count [8]
	Early discontinuation of antithrombotic medication [9, 29]
	Poor treatment compliance or under-target INR [12, [27, 30]]
Echocardiogram findings	Low ejection fraction [[8], [24]]
	Spontaneous echo or dense smoke in LA [4, 13, 24, 27, 31]
	Markedly enlarged LA [24, 31]
Procedure results	Deep implantation [32]
	Incomplete LAA occlusion [33]
	Poor inferior disc-apposition (ACP) [34]
Device	Thrombus on screw, on connector pin or at fabric insert site [7, 23, 30, 35]

LA: left atrium; LAA: left atrial appendage.

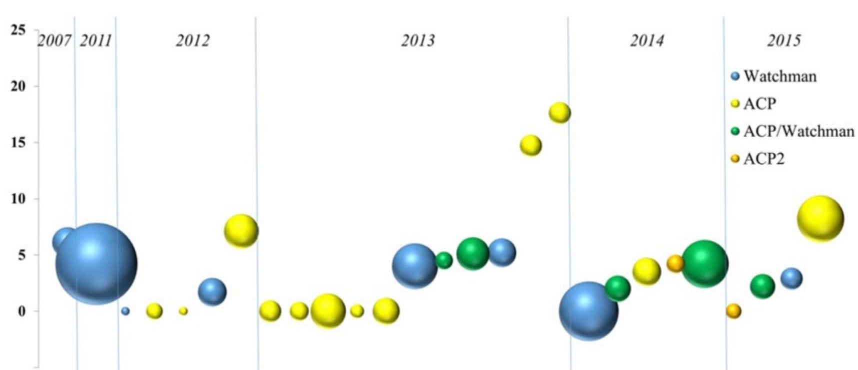

Fig. 3. Chronological incidence of DAT (%) by study for the WM, ACP, ACP/WM, or Amulet, with relative bubble size based on the sample size. [Color figure can be viewed at wileyonlinelibrary.com]

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months postimplantation [7, 12]). The diagnosis was based in most cases by TEE FU imaging. Some cases were found on routine CT [20, 26], one case was suspected on transthoracic echocardiogram (TTE) [24], and one case was only discovered during coronary artery bypass graft surgery, as it was not seen on previous TTE or TEE [28].

Predisposing Factors for DAT

Predisposing factors were rarely described in the reports. However, known risk factors included in particular the presence of a high profile proximal pin connector, spontaneous contrast in the LA cavity, markedly enlarged atrium, high $CHADS_2$ or CHA_2DS_2-VASc score, or poor antithrombotic treatment compliance (Table II). One case of paraneoplastic syndrome was also reported [17].

Case Reports

Thirteen case reports were published from 2011 to 2015 (Supporting Information File 2). Thrombus characteristics were typically available for case reports only. Most thrombi reported in these cases were described as large or ≥10 mm (8/13) and were partly mobile in more than a third of cases (5/13). Thrombus originated from the connector pin in 3/13 cases (1 WM, 2 ACP).

DISCUSSION

Our study is the first systematic review of reported cases of WM and ACP/Amulet DAT.

In our review, the mean incidence for overall LAAO was 3.9%, and was 3.4% for WM device, and 4.6% for ACP or Amulet (Fig. 2). Interestingly, the reported incidence of DAT events in the literature remained constant over time (Fig. 3). The incidence of DAT varied greatly between studies. The cause of this variation could be related to many factors including technical issues, selection bias, learning curve or low sample size. One should also consider that the rate of device-thrombosis might be underreported. Indeed, in most trials with the WM device, it was not included in the end-points as it was considered an ‘imaging end-point’ and not a clinical end-point (i.e., PROTECT AF or CAP) [21]. So far, there is no data on DAT from the PREVAIL trial [33].

The incidence of thrombus formation is thought to be more frequent in the first few weeks after implantation and to decline with complete endothelialization of the device surface. Thus, thrombosis is usually diagnosed early after implantation, but cases of delayed thrombosis up to 3 years after implantation have been described [36]. As most cases of DAT were diagnosed on routine TEE imaging, an artifact of surveillance cannot be excluded. One could argue that in early cases, thrombus formation is probably related to delayed endothelialization [37], whereas late cases could be secondary to mechanical factors (e.g., uncovered lobe, significant residual flow in the LAA) or systemic patient factors [e.g., low ejection fraction (EF), spontaneous echo contrast].

Most cases of DAT were found on routine FU imaging although TEE was performed in the context of a neurologic event (stroke or TIA) in a few reported cases. Diagnosis was made in most cases based on FU TEE as it is the most widely used FU modality. CCTA has also been shown to be an effective surveillance modality [20]. It is important to note that the number of imaging FU performed was significantly correlated with the incidence of DAT.

Treatment at the time of diagnosis varied depending on the treatment regimen in place and the delay from implantation to diagnosis. Current antithrombotic recommendations after device implantation varied between the types of devices implanted (WM or ACP/Amulet), and between centers. In the main WM trials, which included patients eligible for OAC, treatment with warfarin was indicated for 45 days to facilitate device endothelialization, and was followed by 6 months of DAPT and then lifelong aspirin [38]. On the other hand, most studies with ACP/Amulet included patients with contraindications to OAC, thus the post-implantation protocol consisted of DAPT for 1–3 months followed by aspirin for ≥5 months, based on the experience of the participating centers [39]. Currently, different protocols are followed in different centers without consensus showing the variable and empirical management [40].

The occurrence of DAT appears to be complex and probably multifactorial. Systemic and local factors are likely involved in the development of this complication. In a prospective single-center trial comparing postimplantation antithrombotic therapy after WM and ACP implantations, the authors found significantly lower rates of thrombus formation in patients treated with DAPT compared to those treated with OAC [16]. Nonetheless, it is unlikely that antithrombotic regimen post-LAA implantation is an independent risk factor for device thrombosis, as no clear clinical signal has been observed from the registries. Plicht et al. [8] analyzed data from a series of 34 ACP implantation and showed that the risk factors for thrombus formation on the ACP were higher $CHADS_2$ and CHA_2DS_2VASc scores, higher platelet count, and lower left ventricular ejection fraction. From our analysis, thrombus formation seems also to be more frequent over the proximal connector pin, which is protruding and is the only part of the device uncovered by nitinol (ACP) or PET (WM), and could therefore represent a potential thrombogenic source. This potential risk factor has been taken into account for the design of newer-generation devices. Indeed, the latest generations of ACP (Amulet) and WM have lower profile proximal screws in order to minimize risks of thrombus formation [41]. The presence of spontaneous echo contrast in the LA is reported as a well-known risk factor for thrombus formation in the LA [42]. Discontinuation of antithrombotic treatment for medical reasons or secondary to poor patient compliance must also be considered. There was only one reported case associated with a residual leak and partially uncovered lobe but data on the quality of LAAO (complete or partial occlusion) were lacking. Deep implantation creating cul-de-sacs and leaving uncovered LAA trabeculations might also be a risk factor for thrombus formation and should be avoided when possible. Moreover, incomplete LAA closure may increase blood stagnation and velocity at the LAA ostium, which may paradoxically increase the risk of thromboembolic stroke [34, 43]. In a canine model, the disk of ACP could potentially jeopardize LAA neighboring structures and lead to delayed healing. Importantly, it seems that poor apposition at the inferior edge of the LA wall may be an indicator of prolonged healing response. This delay in surface healing could contribute to thrombus formation [32]. However, so far this has not been reported to occur in clinical practice. In a 2012 single-center registry including 86 patients with ACP implantation, careful reviewing of the 6 DAT cases showed that the disk of the occluder was implanted somewhat inside the LAA rather than at its ostium in 70% of the cases [6]. Understanding patient-related and procedure-related factors could help evaluate individual risk of DAT and tailor postimplantation antithrombotic therapy.

The treatment modality for DAT consisted generally of starting anticoagulation among patients not previously on OAC, or an intensification in the antithrombotic regimen associated with a repeat FU imaging. The specific treatment modality and duration varied greatly among studies. The use of LMWH or IV heparin for a short period of time was used and showed to be effective in most cases. Alternatively, a trial of OAC for 1–3 months was also common. Complete thrombus resolution was achieved in the majority of cases (95.0%, 38/40 cases with available data), as was previously shown in cases of LA thrombus not associated with device implantation [29]. Anticoagulation, whether with OAC or LWMH, seems to be very efficient and both treatment (OAC or LMWH) could be used as first line therapy. Recurrence rate was low and not associated with clinical events. Surgical treatment was very rare (3 case reports) and only performed in cases of very large thrombus or according to patient preferences. The potential role of new oral anticoagulants has yet to be defined, as it was used in only 3 cases (2 of which resulted in incomplete resolution of DAT). There is currently insufficient data to recommend the use of novel/direct OAC in the setting of DAT. Further prospective studies should be performed to assess the safety and efficacy this treatment regimen.

Repeat imaging for device surveillance is usually recommended after LAAO. Early detection of DAT can prompt early treatment in order to prevent serious thrombotic complications. Repeat TEE is commonly used to assess thrombus resolution before cessation of antithrombotic treatment, but CCTA has also proven to be an effective imaging modality.

Clinical events related to DAT were low and consisted of infrequent neurologic events, with no systemic embolic events reported. In the literature, reported thromboembolic stroke event-rates related to DAT ranged between 0.3 and 0.7%. In the PROTECT AF study, the device thrombus-associated annualized stroke rate was 0.3% per 100 patient-years [21, 22]. In the multicenter ACP registry, no embolic complications were reported in more than 1,000 patients and there was no association between DAT and stroke. Nevertheless, the rate of thrombosis was too small and the FU duration too short to conduct a robust analysis of this registry data. Of note, intensification of antithrombotic therapy to resolve the thrombus may increase the risk of bleeding complication.

Currently, the antithrombotic strategy after successful LAAO varies greatly as there is no consensus or guidelines on the optimal antithrombotic regimen and duration after LAAO. In the same way, there are no specific recommendations about the management of DAT.

Antithrombotic regimen and duration after LAAO could be tailored according to the risk of device-related thrombosis. This risk assessment should include patient-related characteristics (i.e., high CHA_2DS_2-VASC score), echocardiographic characteristics (i.e., low EF, spontaneous contrast), and closure results (i.e., incomplete closure, deep implantation) (Table II). Careful imaging FU is of utmost importance in order to adapt treatment duration and allow early detection of DAT. Finally, the evaluation of different antithrombotic strategies after LAAO should ideally be performed by randomized trials, although such studies would be difficult to perform given the low event-rates. In the meantime, large registries provide an important source of data regarding the optimal treatment strategy after LAAO. Further randomized controlled trial and dedicated prospective registries should ideally evaluate the incidence of DAT occurring with the commercially available LAA occluders.

Limitations

This review was performed based on available published data. The rate of DAT was possibly underestimated as these events could have been underreported and/or underdiagnosed due to inconsistent/incomplete routine postimplantation surveillance. We only analyzed available published data; most studies did not reveal their management of DAT, treatment duration and follow-up imaging after therapy. We note that definition of DAT is not standardized across studies and reports, which can therefore modify the analysis. We summarized the antithrombotic regimen used in these published series, but could not draw firm conclusions on recommendations on DAT treatment type and duration. Despite these limitations, our review sought to summarize and clarify the varied data available on DAT following successful LAAO, by systematic organization and aggregation of available information.

CONCLUSIONS

Our systematic review suggests that DAT is an infrequent complication of percutaneous LAAO. It occurs mainly early after the procedure and is associated with infrequent neurological complications. In the majority of cases, diagnosis is made during FU imaging with TEE. Although there is currently no consensus about the optimal management of DAT, anticoagulation is associated with a high rate of thrombus resolution. Further large multicenter prospective studies are needed to confirm the true prevalence of DAT and to evaluate risk factors, treatment efficacy, and associated complications.

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9 Part Three: Left Atrial Appendage Occlusion in Patients with Atrial Fibrillation and Previous Major Gastrointestinal Bleeding

9.1 Publication N°3: Left Atrial Appendage Occlusion in Patients with Atrial Fibrillation and Previous Major Gastrointestinal Bleeding (From the Amplatzer Cardiac Plug Multicenter Registry)

9.1.1 Introduction

A prior history of major GI bleeding represents a frequent clinical indication for LAAO, as some cases are associated with a high risk of recurrence, particularly in patients on antithrombotic therapy[167], and are not always reversible or amenable to any efficient treatment.[168,169] GI bleeding remains also the most common extracranial hemorrhagic complication in patients receiving antithrombotic therapy and a frequent reason to discontinue OAC.[170–172] Conversely, a large proportion of patients do not resume anticoagulation after a GI bleeding event[173–175] even though resuming OAC may reduce the risk of stroke more than it increases the risk of recurrent GI bleeding, resulting in a net clinical benefit.[150,176] Patients with previous major GI bleeding (MGIB) might therefore be good candidates for percutaneous LAAO, as this would allow anticoagulation cessation, reducing the risk of bleeding recurrence, while keeping cardioembolic protection. However, antithrombotic treatment is also necessary during the periprocedural period and for a variable period of time after the procedure, increasing thereby the risk of bleeding events. Thus, the aim of the present study was to assess the safety and efficacy of LAAO in patients with prior MGIB.

9.1.2 Summary

History of major GI bleeding may represent a frequent clinical indication for LAAO in patients with nonvalvular AF. This study aims to investigate the procedural safety and long-term outcome of patients with previous MGIB undergoing LAAO. Data from the Amplatzer Cardiac Plug multicenter registry on 1,047 patients were analyzed. Patients with previous MGIB as indication for LAAO were compared to patients without previous MGIB. A total of 151 patients (14.4%) with previous MGIB were identified. Peri-procedural major bleeding events were more frequent in patients with previous MGIB (4.0% vs. 0.8%, p=0.001). With an average follow-up of 1.3 years, the observed annual rate of stroke/TIA and major bleeding for patients with prior MGIB were 2.1% (61.4% relative reduction according to the CHA_2DS_2-VASc score) and 4.6 % (20.1% relative reduction according to the expected rate based on the HAS-BLED score), respectively. In conclusion, in patients with NVAF and previous MGIB, LAAO was associated with a low annual rate of stroke/TIA. Peri-procedural major bleeding events were more frequent in this specific population although the annual major bleeding rate showed a 20.1% relative risk reduction according to the HAS-BLED score.

Left Atrial Appendage Occlusion in Patients With Atrial Fibrillation and Previous Major Gastrointestinal Bleeding (from the Amplatzer Cardiac Plug Multicenter Registry)

Mathieu Lempereur, MD[a,*], Adel Aminian, MD[b], Xavier Freixa, MD, PhD[c], Sameer Gafoor, MD[d,e], Samera Shakir, MD[f], Heyder Omran, MD[g], Sergio Berti, MD[h], Gennaro Santoro, MD[i], Joelle Kefer, MD, PhD[j], Ulf Landmesser, MD[k], Jens Erik Nielsen-Kudsk, MD[l], Ignacio Cruz-Gonzalez, MD[m], Prapa Kanagaratnam, MD[n], Fabian Nietlispach, MD[f,k], Reda Ibrahim, MD[o], Horst Sievert, MD[d], Wolfgang Schillinger, MD[p], Jai-Wun Park, MD[q], Steffen Gloekler, MD[f], and Apostolos Tzikas, MD, PhD[r]

History of major gastrointestinal (GI) bleeding may represent a frequent clinical indication for left atrial appendage occlusion (LAAO) in patients with non−valvular atrial fibrillation (AF). This study aims to investigate the procedural safety and long-term outcome of patients with previous major GI bleeding (MGIB) who underwent LAAO. Data from the Amplatzer Cardiac Plug multicenter registry on 1,047 patients were analyzed. Patients with previous MGIB as indication for LAAO were compared with patients without previous MGIB. A total of 151 patients (14.4%) with previous MGIB were identified. Periprocedural major bleeding events were more frequent in patients with previous MGIB (4.0% vs 0.8%, p = 0.001). With an average follow-up of 1.3 years, the observed annual rate of stroke/transient ischemic attack and major bleeding for patients with previous MGIB were 2.1% (61.4% relative reduction according to the Congestive Heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65−74, and Sex (female) [CHA_2DS_2-VASc] score) and 4.6% (20.1% relative reduction according to the expected rate based on the Hypertension, Abnormal renal/liver function (1 point each), Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly (1 point each) [HAS-BLED] score), respectively. In conclusion, in patients with non-valvular atrial fibrillation and previous MGIB, LAAO was associated with a low annual rate of stroke/transient ischemic attack. Periprocedural major bleeding events were more frequent in this specific population although the annual major bleeding rate showed a 20.1% relative risk reduction according to the HAS-BLED score. **(Am J Cardiol 2017;120:414−420)**

Left atrial appendage occlusion (LAAO) is increasingly recognized as a valid alternative therapy in patients with non−valvular atrial fibrillation (AF) and contraindication to oral anticoagulation (OAC) therapy. A previous history of major gastrointestinal (GI) bleeding represents a frequent clinical indication for LAAO, as some cases are associated with a high risk of recurrence, particularly in patients on antithrombotic therapy,[1] and are not always reversible or amenable to any efficient treatment.[2,3] GI bleeding also remains the most common extracranial hemorrhagic complication in patients receiving antithrombotic therapy and a frequent reason to discontinue OAC.[4−6] Conversely, a large proportion of patients do not resume anticoagulation after a GI bleeding event[7−9] even though resuming OAC may reduce the risk of stroke more than it increases the risk of recurrent GI bleeding, resulting in a net clinical benefit.[10,11] Patients with previous major GI bleeding (MGIB) might therefore be good candidates for percutaneous LAAO, as this

[a]Department of Cardiology, University Hospital of Liège, Liège, Belgium; [b]Department of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium; [c]Department of Cardiology, Hospital Clinic of University of Barcelona, Barcelona, Spain; [d]Department of Cardiology, Cardiovascular Center Frankfurt, Frankfurt, Germany; [e]Department of Cardiology, Swedish Heart and Vascular, Seattle, Washington; [f]Department of Cardiology, University Hospital of Bern, Bern, Switzerland; [g]Department of Cardiology, University Hospital of Bonn, Bonn, Germany; [h]Department of Cardiology, Fondazione Toscana Gabriele Monasterio, Massa, Italy; [i]Department of Cardiology, Ospedale Careggi di Firenze, Florence, Italy; [j]Department of Cardiology, St-Luc University Hospital, Brussels, Belgium; [k]Department of Cardiology, University Hospital of Zurich, Zurich, Switzerland; [l]Department of Cardiology, Aarhus University Hospital, Skejby, Denmark; [m]Department of Cardiology, University Hospital of Salamanca, Salamanca, Spain; [n]Department of Cardiology, Imperial College Healthcare National Health Service Trust, London, United Kingdom; [o]Department of Cardiology, Montreal Heart Institute, Montreal, Quebec, Canada; [p]Department of Cardiology, Universitätsmedizin Göttingen, Göttingen, Germany; [q]Department of Cardiology, Coburg Hospital, Coburg, Germany; and [r]Department of Cardiology, American Hellenic Educational Progressive Association University Hospital, Thessaloniki, Greece. Manuscript received February 15, 2017; revised manuscript received and accepted April 25, 2017.

See page 419 for disclosure information.

*Corresponding author: Tel: +(32) 43667192; fax: +(32) 43667627.
E-mail address: mathieu.lempereur@chu.ulg.ac.be (M. Lempereur).

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Table 1
Baseline characteristics, risk scores, and bleeding history

Variable	All (n=1047)	Previous Major GI Bleeding		p value
		No (n=896)	Yes (n=151)	
Age (years)	74.9 ± 8.4	74.9 ± 8.5	75.2 ± 8.1	0.685
Men	648 (61.9%)	548 (61.2%)	100 (66.2%)	0.236
BMI (kg/m^2)	27.2 4.8	27.2	27.5	0.451
Heart Failure	274 (26.2%)	234 (26.1%)	40 (26.5%)	0.923
Hypertension	868 (82.9%)	734 (81.9%)	134 (88.7%)	0.039
Diabetes mellitus	307 (29.3%)	260 (29.0%)	47 (31.1%)	0.792
Coronary artery disease	367 (35.6%)	301 (34.2%)	66 (43.7%)	0.024
Previous myocardial infarction	164 (15.9%)	137 (15.6%)	27 (17.9%)	0.473
Previous percutaneous coronary intervention	228 (22.1%)	190 (21.6%)	38 (25.2%)	0.332
Carotid disease	87 (8.3%)	73 (8.1%)	14 (9.3%)	0.153
Previous stroke/TIA	404 (38.6%)	362 (40.4%)	42 (27.8%)	0.003
Permanent AF	595 (56.8%)	497 (55.5%)	98 (64.9%)	0.030
Paroxysmal/Persistent AF	449 (42.9%)	396 (44.2%)	53 (35.1%)	0.037
eGFR (MDRD) (ml/kg/1.73m^2)	66.0 ± 22.9	66.6 ± 22.3	61.6 ± 27.1	0.92
$CHADS_2$ score	2.8 ± 1.3	2.8 ± 1.3	2.58 ± 1.3	0.031
CHA_2DS_2-VASc score	4.5 ± 1.6	4.5 ± 1.6	4.29 ± 1.5	0.185
Annual risk of thromboembolism (%)	5.7 ± 2.8	5.7 ± 2.8	5.4 ± 2.6	0.0164
HASBLED score	3.1 ± 1.2	3.1 ± 1.2	3.29 ± 1.2	0.064
Annual risk of major bleeding (%)	5.4 ± 3.8	5.3 ± 3.7	5.9 ± 4.0	0.081
Previous major Bleeding	496 (47.4%)	345 (38.5%)	151 (100.0%)	<0.001
Previous Major bleeding while on warfarin	280 (28.8%)	187 (22.4%)	93 (67.4%)	<0.001
Intracranial bleeding	198 (18.9%)	187 (20.9%)	11 (7.3%)	<0.001
Other type of major bleeding	88 (8.4%)	86 (9.6%)	2 (1.3%)	0.001

Variables are expressed as mean ± SD or n (%).

AF = atrial fibrillation; BMI = body mass index; CHA_2DS_2-VASc = Congestive Heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65−74, and Sex (female); eGFR = estimated glomerular filtration rate; GI = gastrointestinal; TIA = transient ischemic attack.

would allow anticoagulation cessation, reducing the risk of bleeding recurrence, while keeping cardioembolic protection. However, antithrombotic treatment is also necessary during the periprocedural period and for a variable period of time after the procedure, thereby increasing the risk of bleeding events. The aim of the present study is therefore to assess the safety and efficacy of LAAO in patients with previous MGIB.

Methods

This study included 1,047 consecutive patients with non−valvular AF who underwent LAAO using the Amplatzer Cardiac Plug (ACP) in 22 centers between December 2008 and November 2013 and was included in the multicenter ACP registry. Details regarding the registry have been previously published.[12] For the purpose of this study, patients with previous MGIB as indication for LAAO were identified and compared with patients with other indications. Procedural success was defined as successful implantation of the ACP in the left atrial appendage (LAA). Periprocedural adverse events (occurring 0 to 7 days after the procedure or before hospital discharge, whichever last) included death, myocardial infarction, stroke, transient ischemic attack (TIA), systemic embolization, air embolization, device embolization, cardiac tamponade, and major bleeding. Report of adverse events during follow-up (FU) included death (cardiovascular or noncardiovascular), stroke, TIA, systemic embolism, and major bleeding. Antithrombotic medication was recorded on the date of admission and at last FU visit. The recommendation by the device manufacturer after LAAO was to give a low dose of aspirin (80 to 100 mg daily) and clopidogrel (75 mg daily) for 1 to 3 months and then only aspirin (80 to 100 mg daily) for at least another 3 months. However, the choice and the duration of antithrombotic therapy were individualized depending on the patient history, indication for LAAO, and physician preference. Device efficacy to prevent stroke, TIA, and systemic embolism was tested by comparing the actual event rate at FU with the predicted event rate by the Congestive Heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65−74, and Sex (female) [CHA_2DS_2-VASc] score. In a similar way, bleeding reduction was assessed by comparing the actual major bleeding events with the rate predicted by the Hypertension, Abnormal renal/liver function (1 point each), Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly (1 point each) [HAS-BLED] score. MGIB as indication of LAAO was defined as any GI bleeding treated with intervention or transfusion. Reporting of periprocedural major bleeding and major bleeding during FU were based on the Valve Academic Research Consortium-2 (VARC-2) criteria.[13] Thus, MGIB events included BARC type 3a and 3b bleeding events.[14]

Statistical analysis: Continuous variables are presented as means (±SD) and categorical variables are listed as frequencies and percentages. Continuous variables were tested

Table 2
Procedural characteristics and periprocedural complications

Variable	All (n=1047)	Previous Major GI Bleeding		p value
		No (n=896)	Yes (n=151)	
Procedural characteristics				
Procedural success	1019 (97.3%)	873 (97.4%)	146 (96.7%)	0.600
Size ACP (mm)	24.2 ± 3.7	24.2 ± 3.8	24.3 ± 3.5	0.740
First ACP selected implanted	970 (92.6%)	832 (92.9%)	138 (91.4%)	0.523
Combined intervention	216 (20.6%)	190 (21.2%)	26 (17.2%)	0.263
PFO closure	61 (5.8%)	56 (6.3%)	5 (3.3%)	0.154
ASD closure	11 (1.1%)	9 (1.0%)	2 (1.3%)	0.721
Coronary angiogram	107 (10.2%)	93 (10.4%)	14 (9.3%)	0.678
Coronary angioplasty	54 (5.2%)	49 (5.5%)	5 (3.3%)	0.267
TAVI	16 (1.5%)	15 (1.7%)	1 (0.7%)	0.348
AF ablation	18 (1.7%)	17 (1.9%)	1 (0.7%)	0.280
Via transseptal puncture	950 (90.7%)	806 (90.0%)	144 (95.4%)	0.034
Via PFO	97 (9.3%)	90 (10.0%)	7 (4.6%)	0.034
Peri-procedural complications				
Death	8 (0.8%)	5 (0.6%)	3 (2.0%)	0.062
Stroke	9 (0.9%)	9 (1.0%)	0 (0.0%)	0.216
TIA	4 (0.4%)	3 (0.3%)	1 (0.7%)	0.546
Device embolization	10 (1.0%)	7 (0.8%)	3 (2.0%)	0.159
Device snared	7 (0.7%)	6 (0.7%)	1 (0.7%)	0.992
Device removed surgically	2 (0.2%)	0 (0.0%)	2 (1.3%)	0.01
Major bleeding	13 (1.2%)	7 (0.8%)	6 (4.0%)	0.001
Minor bleeding	25 (2.4%)	24 (2.7%)	1 (0.7%)	0.133
Tamponade	16 (1.5%)	11 (1.2%)	5 (3.3%)	0.54
Air embolization	5 (0.5%)	4 (0.4%)	1 (0.7%)	0.722
Others complications	15 (1.4%)	11 (1.2%)	4 (2.6%)	0.174

Variables are expressed as mean ± SD or n (%).
AF = atrial fibrillation; ASD = atrial septal defect; PFO = patent foramen ovale; TAVI = transfemoral aortic valve implantation; TIA = transient ischemic attack.

using the independent samples *t* test and categorical variables using the chi-square test. A two-sided p value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS 22.0 software (SPSS Inc., Chicago, Illinois).

Results

A total of 151 patients (14.4%) with previous MGIB were identified. Baseline characteristics are described in Table 1. The CHA_2DS_2-VASc score was similar between groups (4.5 ± 1.6 vs 4.3 ± 1.5, p = 0.185) and there was a trend for a higher HAS-BLED score in patients with previous MGIB (3.1 ± 1.2 vs 3.3 ± 1.2, p = 0.064). In patients with previous MGIB, 67.4% had a history of major bleeding while on warfarin. The predicted annual stroke risk was similar according to the CHA_2DS_2-VASc score (5.7 ± 2.8% vs 5.4 ± 2.6%, p = 0.164), whereas there was a trend for a higher major bleeding risk according to the HAS-BLED score in patients with previous MGIB (5.3 ± 3.7% vs 5.9 ± 4.0%, p = 0.081). Baseline antiplatelet and OAC treatment was similar between groups.

Procedural success was achieved in 97.3% (1,019/1,047 patients) (Table 2) with no difference between the 2 groups. Periprocedural major bleeding events were more frequent in patients with previous MGIB (4.0% vs 0.8%, p = 0.001), with more documented GI bleeding (1.3% vs 0.0%, p = 0.01). Half of major bleeding events in patients with previous MGIB were related to femoral access site complications (Table 3). There was no death related to periprocedural major bleeding complications.

The average FU was 16.4 ± 12.2 months and was complete for 1,001 of 1,019 (98.2%) successfully implanted patients. There were no significant differences between groups in stroke, TIA, death, cardiovascular death, and major adverse event rates. Major bleeding events were more frequent in patients with previous MGIB (6.0% vs 2.1%, p = 0.006) (Table 4). Bleeding events during the periprocedural period (0 to 7 days), from day 8 to the end of FU, and total FU are summarized in Table 5. During the FU period (day 8 to the end of FU), patients with previous MGIB showed an increased rate of documented MGIB (1.4% vs 0.2%, p = 0.043) with no difference in terms of all-cause major bleeding events (2.8 vs 1.3%, p = 0.177). At last FU, there was no difference in antithrombotic treatment regimen and treatment duration between the 2 groups (Table 6).

The observed annual stroke/TIA rate (including periprocedural events) for patients with previous MGIB was 2.1 events per 100 patient-years (3.3% absolute reduction, 61.4% relative reduction according to the CHA_2DS_2-VASc score) as compared with 2.1 events per 100 patient-years for patients without previous MGIB (3.6% absolute reduction, 62.7% relative reduction) (Figure 1, panel A; Figure 2). The

Table 3
Types of major bleeding events

Major bleeding events	Previous Major GI Bleeding	
	No (n=896)	Yes (n=151)
Periprocedural (0-7 days)	7 (0.78%)	6 (3.97%)
Femoral artery (vascular closure)	5 (0.56%)	3 (1.99%)
Pulmonary artery perforation	1 (0.11%)	0
GI	0	2 (1.32%)
Other	1* (0.11%)	0
Unknown	0	1 (0.66%)
From day 8 to end of follow-up	11 (1.2%)	4 (2.65%)
GI	2 (0.22%)	2 (1.32%)
Frequent epistaxis	0	1 (0.66%)
Access site bleeding	1 (0.11%)	1 (0.66%)
Other	5[†] (0.56%)	0
Unknown	3 (0.33%)	0

Variables are expressed as n (%). One bleeding in case of NSTEMI while on DAPT, 1 subdural hematoma, and 1 severe blood dyscrasia.

DAPT = dual antiplatelet therapy; GI = gastrointestinal; IC = intracranial; NSTEMI = non-ST-segment elevation myocardial infarction; OAC = oral anticoagulation.

* IC bleed.

† One trauma causing subdural hematoma, 1 IC bleeding while on OAC for device thrombosis.

Table 4
Adverse events during total follow-up

Variable	All (n=1047)	Previous Major GI Bleeding		p value
		No (n=896)	Yes (n=151)	
TIA	13 (1.3%)	12 (1.4%)	1 (0.7%)	0.484
Stroke	16 (1.6%)	13 (1.5%)	3 (2.1%)	0.625
Major bleeding	27 (2.7%)	18 (2.1%)	9 (6.0%)	0.006
Death	80 (7.6%)	67 (7.5%)	13 (8.6%)	0.628
Cardiovascular death	24 (2.4%)	20 (2.3%)	4 (2.8%)	0.759
MAE (Stroke, TIA, Major bleeding, death)	107 (10.2%)	88 (9.8%)	19 (12.6%)	0.300

Variables are expressed as n (%).

MAE = major adverse events; TIA = transient ischemic attack.

observed annual major bleeding rate for patients with previous MGIB was 4.6 events per 100 patient-years (1.2% absolute reduction, 20.1% relative reduction according to the HAS-BLED score) as compared with 1.5 events per 100 patient-years for patients without previous MGIB (3.8% absolute reduction, 71.1% relative reduction) (Figure 3, panel B; Figure 4).

Discussion

The main findings of the present study can be summarized as follows:

1. In patients with previous MGIB, the overall procedural safety of LAAO with the ACP was high, although it was associated with an increased risk of periprocedural major bleeding.

Table 5
Bleeding events during the periprocedural period, from day 8 to the end of follow-up and total follow-up

Bleeding events	All (n=1047)	Previous Major GI Bleeding		p value
		No (n=896)	Yes (n=151)	
Periprocedural (0-7 days)				
Major bleeding	13 (1.2%)	7 (0.8%)	6 (4.0%)	0.001
Documented major GI bleeding	2 (0.2%)	0	2 (1.3%)	0.001
Minor bleeding	25 (2.4%)	24 (2.7%)	1 (0.7%)	0.133
From day 8 to end of follow-up				
Major bleeding	15 (1.5%)	11 (1.3%)	4 (2.8%)	0.177
Documented major GI bleeding	4 (0.4%)	2 (0.2%)	2 (1.4%)	0.043
Minor bleeding	17 (1.7%)	12 (1.4%)	5 (3.4%)	0.078
Minor/Major bleeding	32 (3.1%)	23 (2.6%)	9 (6.0%)	0.025
Total follow-up				
Major Bleeding	27 (2.7%)	18 (2.1%)	9 (6.0%)	0.006
Documented major GI bleeding	5 (0.5%)	2 (0.2%)	4 (2.6%)	<0.001

Variables are expressed as n (%).

GI = gastrointestinal.

Table 6
Antithrombotic medications at last follow-up and duration of antithrombotic treatment

Variable	All (n=1047)	Previous Major GI Bleeding		p value
		No (n=896)	Yes (n=151)	
Antithrombotic medications at last follow-up				
Aspirin	845 (86.0%)	727 (86.7%)	118 (82.5%)	0.187
Clopidogrel	242 (24.6%)	210 (25.0%)	32 (22.4%)	0.496
Warfarin	31 (3.2%)	29 (3.5%)	2 (1.4%)	0.193
NOAC	13 (1.3%)	12 (1.4%)	1 (0.7%)	0.480
LMWH	2 (0.4%)	2 (0.4%)	0	0.531
Duration of treatment (months)				
Aspirin	12.8 ± 18.2	13.3 ± 19.2	10.3 ± 11.6	0.141
Clopidogrel	3.8 ± 6.7	3.6 ± 6.1	4.8 ± 9.0	0.208
Warfarin	0.4 ± 3.0	0.5 ± 3.2	0.1 ± 0.67	0.012
NOAC	0.1 ± 1.7	0.1 ± 1.9	0.1 ± 0.91	0.889

Variables are expressed as n (%) or mean ± SD.

ASA = acetylsalicylic acid; LMWH = low molecular weight heparin; NOAC = non-vitamin K oral anticoagulants.

2. The efficacy of LAAO for stroke reduction was high and similar in patients with or without previous MGIB.
3. During the total FU period (periprocedural period and from day 8 to the end of FU), the procedure was associated with a reduction in the rate of bleeding events compared with the expected rate based on the HAS-BLED score. However, as compared with patients without previous MGIB, this diminution in bleeding risk was less pronounced in patients with

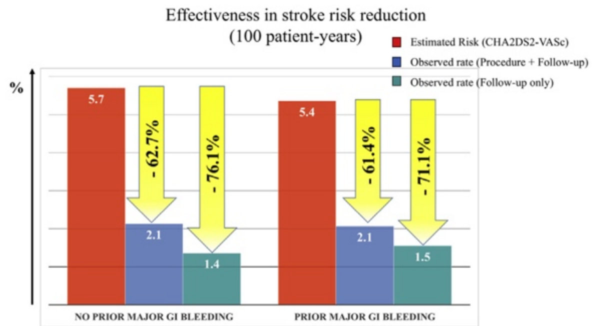

Figure 1. Effectiveness of LAAO in reduction of stroke/TIA based on annual rate predicted by CHA_2DS_2-VASc score. CHA_2DS_2-VASc = Congestive Heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65−74, and Sex (female).

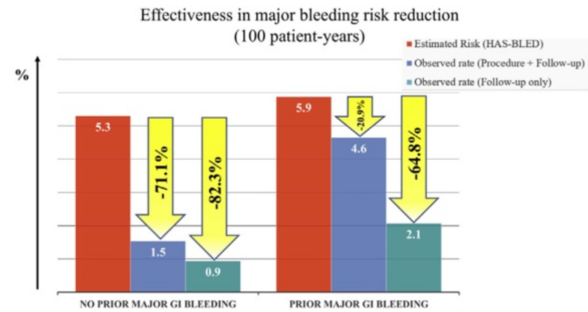

Figure 3. Effectiveness of LAAO in reduction of major bleeding based on annual rate predicted by HAS-BLED score. HAS-BLED = Hypertension, Abnormal renal/liver function (1 point each), Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly (1 point each).

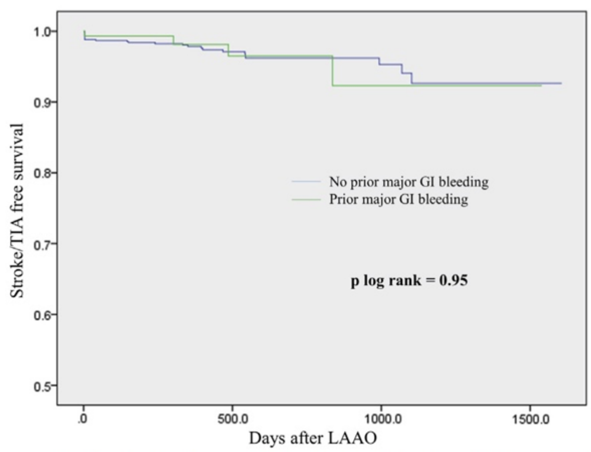

Figure 2. Stroke/TIA free survival after LAAO. Kaplan-Meier analysis showing the effect of previous major GI bleeding on stroke/TIA free survival.

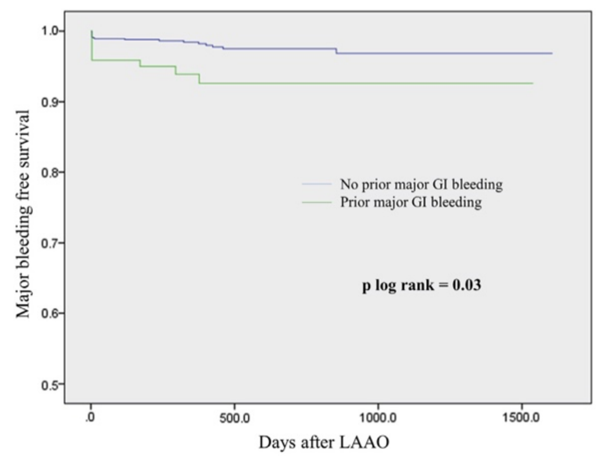

Figure 4. Major bleeding free survival after LAAO. Kaplan-Meier analysis showing the effect of previous major GI bleeding on major bleeding free survival.

previous MGIB, as more major bleeding events were observed in the periprocedural period

4. The overall survival was similar in both groups (Figure 5)

AF patients with a history of MGIB represent a common indication for LAAO. As these patients carry a high-bleeding risk profile and the potential risk of recurrent bleeding events during the periprocedural period and the weeks after the procedure, they deserve specific analysis. Of note, patients with previous MGIB showed an increased rate of major bleeding events during the periprocedural period (4.0% vs 0.8%, $p = 0.001$). However, during the FU period, we found no statistical difference in all-cause major bleeding events rates (2.8% vs 1.3%, $p = 0.177$) although more documented MGIB were observed (1.4% vs 0.2%, $p = 0.043$). In comparison, a landmark analysis from the Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation (PROTECT-AF) and Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation vs. Long-Term Warfarin Therapy (PREVAIL) randomized clinical trials showed an overall rate of major bleeding of 3.5 events per 100 patient-years in the group of patients assigned to LAA closure, with about half of bleeding events occurring within the first 7 days after randomization.[15] In the recently published EWOLUTION registry evaluating LAAO with the WATCHMAN device, 17 of 1,021 patients implanted experienced major bleeding requiring transfusion from procedure to 30 days, with 57.9% of events unrelated to device or procedure and MGIB present in 4 of 17 patients.[16]

We found a reduction in the rate of major bleeding events after comparing the observed and expected rates according to the HAS-BLED score. However, this reduction was less pronounced in patients with previous MGIB, particularly when events in the periprocedural period were taken into account. Even after periprocedural anticoagulation and antithrombotic therapy during several weeks or months, there was still a reduction in bleeding events in this high-risk group. Interestingly, patients with previous MGIB demonstrated higher rates of MGIB during the periprocedural period. This is most likely related to the more aggressive

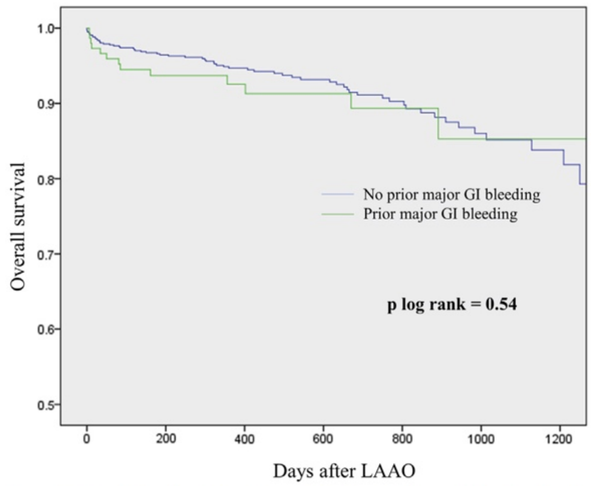

Figure 5. Overall survival after LAAO. Kaplan-Meier analysis showing the effect of previous major GI bleeding on overall survival.

antithrombotic treatment applied during this period, including heparinization and clopidogrel load. Of note, 50% of major bleeding events in patients with previous MGIB were related to femoral access site complications. Given the small number of events, this could represent a statistical bias but one could also argue that patients with history of MGIB have a higher general predisposition for bleeding.

As expected, the reduction in stroke/TIA at FU was in accordance with previous studies and close to 60% in both groups.[12,17,18] This can be explained by procedural success rate that was similar between groups with no difference in terms of antithrombotic treatment, except for a shorter duration of OAC with warfarin/dicoumarol in patients with previous MGIB.

The evaluation of the risk and benefit of resuming OAC therapy in AF patients with previous MGIB remains a clinical dilemma. If deemed feasible, restarting OAC early in high-risk patients has been shown to decrease mortality and thromboembolism with a net clinical benefit.[9,11] However, restarting OAC may be associated with an unacceptable risk of recurrent MGIB. Our study demonstrates that percutaneous closure of the LAA may provide a safe and effective alternative strategy to long-term OAC therapy in some groups of AF patients with high stroke risk and a formal contraindication to OAC therapy because of severe or recurrent GI bleeding (i.e., hereditary hemorrhagic telangiectasia).[19] This therapeutic option should ideally be discussed within a team including gastroenterologists and cardiologists, taking into account the risk of recurrence as well as the reversibility of the disease. Patient selection should include not only those with previous MGIB, but also patients with nonmajor but clinically significant GI bleeding, or GI intolerance for any antithrombotic treatments, because these situations are associated with a high rate of permanent treatment discontinuation.

Finally, the ideal antithrombotic regimen after implantation is still under debate. In most centers, dual antiplatelet therapy for 1 to 3 months followed by aspirin treatment for 3 months or longer still represents the cornerstone of antithrombotic regimen after LAAO. However, recent small studies have shown favorable results with less aggressive antithrombotic therapy (aspirin only after the procedure),[20] which would likely increase safety and efficacy of LAAO in the population of patients with MGIB history. This therapeutic regimen has yet to be evaluated in large randomized trials.

The present study has several limitations that should be acknowledged. This is a nonrandomized, retrospective, observational study, which included many large-volume centers. The major limitation for estimating the overall value of LAAO is the lack of a randomized control group and only a calculated stroke or bleeding risk. Another important limitation of our study is the lack of information on the type of previous MGIB and the type or combination of antithrombotic treatments received by the patient at the time of GI bleeding and before LAAO. Ideally, the definition of MGIB should be standardized across studies, as it is currently recommended by expert consensus.[21]

In conclusion, the efficacy of LAAO for stroke reduction was high and similar in patients with or without previous MGIB. Patients with previous MGIB had similar procedural outcome compared with those without previous MGIB, except for a small but significantly increased rate of periprocedural major bleeding, including an increased rate of periprocedural MGIB.

Disclosures

Tzikas, Sievert, Schillinger, and Meier are consultants, proctors, and have received research grants from St. Jude Medical. Omran, Berti, Santoro, Kefer, Nielsen-Kudsk, Cruz-Gonzalez, Nietlispach, Aminian, Freixa, and Ibrahim are consultants and proctors for St. Jude Medical. The other authors have no conflicts of interest to disclose.

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10 Conclusions and Perspectives

10.1 Discussion

10.1.1 Role of Imaging

In the first part of this thesis, we developed the role of imaging in percutaneous LAAO. Indeed, imaging plays already a key role in every step of LAA occlusion: pre-procedural planning, procedural guidance and post-implantation surveillance. The development of new imaging modalities, the integration of fusion imaging in the work-flow, and technical improvements will most likely increase the role of imaging in every step of the procedure and will eventually lead to improved safety and efficacy of LAAO. Even though LAAO is feasible with minimal imaging guidance by experienced operators, the use of multiple available imaging modalities brings up complementary information, allowing good understanding of the LAA anatomy and its relationship to the surrounding structures. Thus, multimodality imaging should be used to improve procedural safety and efficacy of LAA occlusion.

The role of each imaging modality in different steps of the procedure and determination of the best modality for different area of interests have yet to be determined. New imaging modalities will have to prove their advantages and the expected clinical improvements.

10.1.2 Device-associated thrombosis

Our systematic review of reported cases of WM and ACP/Amulet DAT showed that the mean incidence for LAAO was 3.9%. However, the incidence of DAT varied greatly between studies and the rate of device-thrombosis might be underreported in the literature. The incidence of thrombus formation is thought to be more frequent in the first few weeks after implantation and to decline with complete endothelialization of the device surface. Thus, thrombosis is usually diagnosed early after implantation. As most cases of DAT were diagnosed on routine TOE imaging, an artefact of surveillance cannot be excluded. It is important to note that the number of imaging follow-up performed was significantly correlated with the incidence of DAT.

Repeat imaging for device surveillance is usually recommended after LAAO. Early detection of DAT can prompt early treatment in order to prevent serious thrombotic complications.

Clinical events related to DAT were low and consisted of infrequent neurologic events, with no systemic embolic events reported. In the literature, reported thromboembolic stroke event-rates related to DAT ranged between 0.3 and 0.7%. In the PROTECT AF study, the device thrombus-associated annualized stroke rate was 0.3% per 100 patient-years.[122,127] In the multicenter ACP registry, no embolic complications related to DAT were reported in more than 1,000 patients and there was no association between DAT and stroke.[194] Nevertheless, the rate of thrombosis may have been too small and the FU duration too short to show a significant association between DAT and embolic events in this registry analysis. Of note, intensification of antithrombotic therapy to resolve the thrombus may increase the risk of bleeding complication but available data are scarce.

Currently, the antithrombotic strategy after successful LAAO varies greatly as there is no consensus or guidelines on the optimal antithrombotic regimen and duration after LAAO. In the same way, there are no specific recommendations about the management of DAT. Antithrombotic regimen and duration after LAAO could be tailored according to the risk of device-related thrombosis. This risk assessment should include patient-related characteristics (i.e., high CHA_2DS_2-VASC score), echocardiographic characteristics (i.e., low EF, spontaneous contrast), and closure results (i.e., incomplete closure, deep implantation).

Modification in antithrombotic therapy after LAAO may result in reduction of bleeding events. In the ACP multicenter registry, patients treated with LAAO alone on ASA only or with no antithrombotic treatment at last follow-up after ACP implantation showed better results than the other group of patients with an increased reduction in stroke-TIA and bleeding rates.[195] Conversely, in the EWOLUTION registry, which reflects ‘real-life’ results after WATCHMAN implantation, the incidence of serious adverse events within 30 days was significantly lower for subjects deemed to be ineligible for oral anticoagulation therapy (bleeding history or high bleeding risk, co-morbidities, inability to adhere to OAC) compared with those eligible for OAC (6.5 vs. 10.2%, p=0.042).[151] In the ASAP Study, 150 patients that were judged ineligible for OAT were administered 6 months of clopidogrel or ticlopidine and lifelong aspirin following the Watchman implant with favorable safety results as compared to PROTECT AF data (ischemic stroke rate of 1.7% vs. 2.2%, respectively).[128] The rate of DAT was 4.0% and there were 5 bleeding complication during the first 6 months, translating in an estimated annual bleeding rate of 6.6%. In a recent smaller study, 104 patients implanted with the ACP or Amulet were treated with ASA monotherapy with a low rate of DAT or stroke post-implantation after a median follow-up of 2.3 years.[193] Thus, reduction in the intensity and/or duration of the antithrombotic treatment may bring a clinical benefit in this high risk population. Further studies will have to evaluate the optimal antithrombotic regimen post-implantation as well as the need for long-term aspirin therapy. Further randomized controlled trial and dedicated prospective registries should ideally evaluate different antithrombotic strategies after LAAO and the incidence of DAT occurring with the commercially available LAA occluders.

NOACs have proven to be as effective and safer than warfarin for stroke prevention in AF patients in recent large randomized trials[14]. Since NOAC are easier to use and initiate in clinical practice, they may represent an interesting alternative to warfarin after LAAO. In a small pilot single-center registry, 18 patients received NOAC during the first 45 days after WATCHMAN implantation (dabigatran 2x110 mg/day in 16 patients and rivaroxaban 20 mg/day in 2 patients) with no case of DAT at 45 days TOE follow-up[15]. In a second single-center study, 98 patients underwent concomitant AF ablation and LAAO with WATCHMAN. Post-implantation treatment strategy consisted in the use of warfarin in 37 patients, dabigatran in 34 patients and rivaroxaban in 27 patients (61 patients on NOAC therapy). Incidental DAT was detected in 2 patients (both in the NOAC group) at 7 days and 6-weeks post-implantation. Both patients were asymptomatic and the thrombus resolved by continuing the same anticoagulation regimen[16]. In a recent large retrospective multicentre registry, 214 patients undergoing WATCHMAN implantation received NOACs (46% apixaban, 46% rivaroxaban, 7% dabigatran and 1% edoxaban) in either an uninterrupted (82%) or a single-held-dose (16%) strategy. TOE or chest computed tomography were performed between 6 weeks and 4 months post-implant to assess for the presence of DAT. As compared to a control group of 212 patients with uninterrupted warfarin, the authors found no significant difference in the rate of periprocedural complications (2.8 vs. 2.4%, p=0.99), DAT (1.4% vs. 0.9%, p=0.99) or post-procedure bleeding events (0.5% vs. 0.9%, p=0.6)[16]. In the EWOLUTION registry, 113 patients received NOACs after WATCHMAN implantation (dabigatran, rivaroxaban and apixaban) with a rate of DAT of 1.4% at 3 months[17]. Taken together, these results suggest that the use of NOACs may represent a safe and effective peri- and post-procedural alternative to warfarin for preventing DAT. These preliminary favourable results should be validated in a dedicated prospective randomized comparison of NOAC versus warfarin or DAPT after LAAO.

Further large multicenter prospective studies are needed to confirm the true prevalence of DAT, to evaluate associated complications, to assess treatment efficacy and role of NOAC, and to optimize antithrombotic regimen post-implantation.

10.1.3 LAAO in patients with previous major GI bleeding

AF patients with a history of MGIB represent a common indication for LAAO. As these patients carry a high-bleeding risk profile and a potential risk of recurrent bleeding events during the periprocedural period and the weeks following the procedure, they deserve specific analysis. Of note, patients with previous MGIB showed an increased rate of major bleeding events during the periprocedural period (4.0% vs. 0.8%, p=0.001). However, during the FU period, we found no statistical difference in all-cause major bleeding events rates (2.8% vs. 1.3%, p=0.177) although more documented MGIB were observed (1.4% vs. 0.2%, p=0.043). By comparison, a landmark analysis from the PROTECT-AF and PREVAIL randomized clinical trials showed an overall rate of major bleeding of 3.5 events per 100 patient-years in the group of patients assigned to LAA closure, with about half of bleeding events occurring within the first 7 days after randomization.[196] In the recently published EWOLUTION registry evaluating LAAO with the Watchman device, 17 out of 1,021 patients implanted experienced major bleeding requiring transfusion from procedure to 30 days, with 57.9% of events unrelated to device or procedure and MGIB present in 4/17 patients.[151]

We found a reduction in the rate of major bleeding events after comparing the observed and expected rates according to the HAS-BLED score. However, this reduction was less pronounced in patients with previous MGIB, particularly when events in the periprocedural period were taken into account. Thus, even after periprocedural anticoagulation and antithrombotic therapy during several weeks or months, there was still a reduction of bleeding events in this high-risk group. Interestingly, patients with previous MGIB demonstrated higher rates of MGIB during the periprocedural period. This is most likely related to the more aggressive antithrombotic treatment applied during this period, including heparinization and clopidogrel load. Of note, 50% of major bleeding events in patients with previous MGIB were related to femoral access site complications. Given the small number of events, this could represent a statistical bias but one could also argue that patients with history of MGIB have a higher general predisposition for bleeding.

The evaluation of the risk and benefit of resuming OAC therapy in AF patients with previous MGIB remains a clinical dilemma. If deemed feasible, restarting OAC early in high-risk patients has been shown to decrease mortality and thromboembolism rates with a net clinical benefit.[150,175] However, restarting OAC may be associated with an unacceptable risk of recurrent MGIB. Our study demonstrates that percutaneous closure of the LAA may provide a safe and effective alternative strategy to long-term OAC therapy in some groups of AF patients with high stroke risk and a formal contraindication to OAC therapy due to severe or recurrent GI bleeding (e.g. hereditary hemorrhagic telangiectasia)[197]. This therapeutic option should ideally be discussed within a team including gastroenterologists and cardiologists, taking into account the risk of recurrence as well as the reversibility of the disease. Patient selection should include not only those with previous MGIB, but also patients with non-major but clinically significant GI bleeding, or GI intolerance for any antithrombotic treatments, since these situations are associated with a high-rate of permanent treatment discontinuation.

Finally, the ideal antithrombotic regimen post-implantation is still under debate. In most centers, DAPT for 1-3 months followed by aspirin treatment for 3 months or longer still represents the cornerstone of antithrombotic regimen following LAAO. However, recent small studies have shown favorable results with less aggressive antithrombotic therapy (aspirin only post-procedure)[193], which would likely increase safety and efficacy of LAAO in the population of patients with MGIB history. This therapeutic regimen has yet to be evaluated in large randomized trials.

Further studies are needed to evaluate the safety and efficacy of LAAO in patients with prior major GI bleeding. Ideally, the definition of major GI bleeding should be standardized across studies, as it is currently recommended by expert consensus[198], and information on the type of prior MGIB, the type of GI bleeding after LAAO, and the type or combination of antithrombotic treatments received by the patient at the time of GI bleeding and after LAAO should be collected and analyzed.

10.2 Perspectives

Further larger trials are needed to assess the best use and indication of LAA occluders, including patients who are unsuitable for OAC or in patients who suffer a stroke on (N)OAC.

Anticoagulation with direct oral anticoagulant agents has become the standard and best available anticoagulation therapy in nonvalvular AF in the absence of contraindication. Randomized controlled trials comparing LAA occluders with NOACs are therefore necessary. One trial, PRAGUE-17, is currently ongoing and compares LAAO (with the Amulet or WATCHMAN device) to NOAC (apixaban, rivaroxaban, or dabigatran).[199] This study will include 396 patients and will be completed in 2020.

The best antithrombotic regimen after LAAO is still under debate. As most indications for LAAO are contraindications to long-term OAC, the assessment of the minimal antiplatelet therapy acceptable after LAA occlusion will be of great interest. The ASAP-TOO trial, which evaluates DAPT after WATCHMAN implantation, will give us some information on this matter. Registries of cases treated with DAPT or ASA alone post-implantation will also be helpful.

The predictive ability of current bleeding risk scores is only modest in patients with AF. As LAAO may be indicated in patients with high or very high risk of bleeding, development of accurate bleeding risk-prediction scores would be very useful in clinical practice, especially among the elderly.

Several other remaining issues should also be addressed in the future as additive effects of OAC and LAAO, comparisons between different LAA occlusion devices and cost-effective analyses.

LAA also plays a role in endocrine regulation, especially in controlling circulating blood volume. Implications of LAAO on the cardiovascular physiology have still to be studied. We intend to perform a study of endocrine regulators in cases of LAAO in association with other Belgian centers and hope this will help us understand long-term and systemic effects of LAAO.

10.3 Concluding remarks

LAA occlusion appears today as a valid alternative to long-term OAC in selected patients with NVAF at high thromboembolism risk in case of relative or absolute contraindications to OAC.

Determination of the optimal clinical indications requires a clinical expertise and a team approach. Results from future and ongoing studies and registries will help clinicians choose the best therapeutic approach, improving net clinical benefit. Team involved in patient care may include physicians from multiple specialisations and sub-specialisation.

We expect that improvements in imaging in all steps of the procedure, in the selection of devices, and in procedure planning as well as a patient-tailored post-implantation drug regimen will increase the risk-benefit ratio of LAAO and will probably confirm, if not expand, the current clinical indication.

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Annexes

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STATE-OF-THE-ART REVIEW

Percutaneous Left Atrial Appendage Closure

Procedural Techniques and Outcomes

Jacqueline Saw, MD, Mathieu Lempereur, MD

ABSTRACT

Percutaneous left atrial appendage closure technology for stroke prevention in patients with atrial fibrillation has significantly advanced in the past 2 decades. Several devices are under clinical investigation, and a few have already received Conformité Européene (CE)-mark approval and are available in many countries. The WATCHMAN device (Boston Scientific, Natick, Massachusetts) has the most supportive data and is under evaluation by the U.S. Food and Drug Administration for warfarin-eligible patients. The Amplatzer Cardiac Plug (St. Jude Medical, Plymouth, Minnesota) has a large real-world experience over the past 5 years, and a randomized trial comparing Amplatzer Cardiac Plug with the WATCHMAN device is anticipated in the near future. The Lariat procedure (SentreHEART Inc., Redwood City, California) has also gained interest lately, but early studies were concerning for high rates of serious pericardial effusion and major bleeding. The current real-world experience predominantly involves patients who are not long-term anticoagulation candidates or who are perceived to have high bleeding risks. This pattern of practice is expected to change when the U.S. Food and Drug Administration approves the WATCHMAN device for warfarin-eligible patients. This paper reviews in depth the procedural techniques, safety, and outcomes of the current leading devices. (J Am Coll Cardiol Intv 2014;7:1205–20) © 2014 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) is estimated to affect 1.5% to 2% of the general population, and the prevalence is projected to increase to 12.1 million by 2030 in the United States (1). Unfortunately, AF is a major cause of stroke, increasing ischemic stroke risk by 5-fold, and is responsible for 15% of all strokes and 30% of strokes in patients age >80 years (2,3). Strokes associated with AF are also more severe, with victims having a 50% greater likelihood of becoming disabled or handicapped and >50% likelihood of death (4,5). Accordingly, stroke prevention with anticoagulation is among the main pillars of AF management, and anticoagulation guidelines have become more stringent. The Canadian Cardiovascular Society recommends anticoagulation for $CHADS_2$ (congestive heart failure history, hypertension history, age ≥75 years, diabetes mellitus history, stroke or transient ischemic attack symptoms previously) ≥1 and the European Society of Cardiology recommends it for CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, age 65 to 74 years, diabetes mellitus, stroke/transient ischemic attack/thromboembolism, vascular disease, sex female) ≥1 (6,7).

Several randomized placebo-controlled trials have demonstrated that oral anticoagulation (OAC) is highly effective in preventing thromboembolism with AF, with landmark meta-analysis showing 64% stroke reduction and 26% mortality reduction with warfarin (8,9). However, a significant proportion (30% to 50%) of eligible patients do not receive OAC due to absolute contraindications or perceived risks of bleeding (10). Long-term therapy with warfarin or novel oral anticoagulation (NOAC) is associated with lifetime major

From the Division of Cardiology, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada. Dr. Saw is a proctor and consultant for St. Jude Medical and Boston Scientific. Dr. Lempereur has reported that he has no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ACP = Amplatzer Cardiac Plug

CCTA = cardiac computed tomography angiography

CE = Conformité Européene

FDA = Food and Drug Administration

ICE = intracardiac echocardiography

LAA = Left atrial appendage

NOAC = novel oral anticoagulation

OAC = oral anticoagulation

PET = polyethylene terephthalate

RAO = right anterior oblique

RR = risk ratio

TEE = transesophageal echocardiography

bleeding risks of 2.1% to 3.6% per year in recent clinical trials (11-13). Although intracranial hemorrhage is consistently lower with NOAC, the overall risk of major bleeding is not diminished with dabigatran or rivaroxaban compared with warfarin (12,13). Apixaban was the only agent that reduced major bleeding (11).

Other concerns and contraindications with OAC include patients with renal and liver dysfunctions (for NOAC), high risk of falls, noncompliance, and those requiring dual antiplatelet therapy after stenting. For warfarin, there are additional issues with drug and diet interaction, the need for monitoring, and a narrow therapeutic window with time in therapeutic range of only 50% to 60% (14,15). Even with the relatively well-tolerated NOAC, the proportion of patients discontinuing NOAC during study follow-up was 15% to 25% (11-13). There is also residual stroke risk of 2% to 5% annually despite optimal anticoagulation (16). These challenges have led to device-based therapies for nonvalvular AF.

Transesophageal echocardiography (TEE), autopsy, and surgical reports confirmed that >90% of nonrheumatic AF-related left atrial thrombi were isolated to, or originated from, the left atrial appendage (LAA) (17). Thus, mechanical approaches to exclude the LAA from systemic circulation were explored, and early attempts by surgical removal or ligation of LAA developed over 60 years ago were limited by the invasiveness and by significant rates of incomplete exclusion that were associated with increased stroke risks (18,19). Minimally invasive approaches have been developed over the past 2 decades and can be broadly divided into endocardial and epicardial devices (**Table 1**). This paper reviews contemporary percutaneous LAA closure, with in-depth discussions of the procedural techniques and clinical outcomes of leading devices.

INDICATIONS FOR PERCUTANEOUS LAA CLOSURE

The current indications for percutaneous LAA closure vary geographically. Recently, the European Society of Cardiology implemented a class IIB recommendation for patients with high stroke risk and contraindications to long-term OAC (7). The majority of procedures performed in Europe adhere to this guideline as reported by Tzikas (20). Among ~1,000 LAA closures, 74% were for patients with major bleeding or at high bleeding risk. Other indications included coronary stenting (23%), drug interaction (18%), stroke on warfarin (16%), renal or hepatic disease (13%), labile international normalized ratio (7%), and risk of falls (7%). In Canada, LAA closure is generally restricted to patients with $CHADS_2 \geq 1$ and contraindications to long-term OAC, under the Health Canada special access program. In the United States, the Lariat procedure may be performed for patients at high risk for stroke with or without contraindications to OAC, but WATCHMAN may only be implanted under the CAP2 (Continued Access Protocol 2) registry for patients eligible for OAC (up until early 2014), pending U.S. Food and Drug Administration (FDA) approval.

DEVICES FOR PERCUTANEOUS LAA OCCLUSION

PLAATO. The PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) device (Appriva Medical Inc., Sunnyvale, California) was the first percutaneous LAA device manufactured with the first human implant in 2001 (21). It consisted of a self-expanding nitinol cage (diameter 15 to 32 mm) with 3 anchors on each strut to stabilize the occluder. It was covered with nonthrombogenic polytetrafluoroethylene membrane to exclude blood flow into the remaining LAA. The PLAATO feasibility study involved 64 patients with AF and contraindications to OAC; the observed annual stroke risk was much lower than expected based on $CHADS_2$ score (3.8% vs. 6.6%) with 5-year follow-up (22). Despite this promising early result, the device was withdrawn from the market for commercial reasons.

WATCHMAN. The second dedicated LAA device to be manufactured was WATCHMAN, which was originally owned by Atritech Inc. (Plymouth, Minnesota) but acquired by Boston Scientific (Natick, Massachusetts) in 2011. The current second-generation WATCHMAN LAA Closure Technology consists of a self-expanding nitinol frame covered with permeable (160 μm) polyethylene terephthalate (PET) membrane (**Figure 1**). There are 10 active fixation anchors at the nitinol frame perimeter, designed to engage LAA tissue for device stability. The PET membrane covers ~50% of the proximal outer nitinol frame, which blocks thrombus embolization from the LAA and promotes healing and endothelialization. The device's spherical contour accommodates most LAA anatomy (case example, **Figure 2**). There are 5 sizes available (**Table 2**), delivered through dedicated 14-F sheaths with 12-F inner diameter and 75 cm working length. There are 3 dedicated access sheaths: double-curve, single-curve

TABLE 1 LAA Closure Devices

Device Name	Company	Design	Device Sizes	Approval Status
Endocardial Devices				
PLAATO	Appriva Medical Inc.	Single-lobe occluder; nitinol cage; ePTFE membrane; hooks	15, 18, 20, 23, 26, 29, and 32 mm (14-F sheath)	Removed from market
WATCHMAN	Boston Scientific	Single-lobe occluder; nitinol frame; PET membrane; hooks	21, 24, 27, 30, and 33 mm (14-F sheath)	CE mark
ACP	St. Jude Medical	Lobe and disk (polyester mesh in both); nitinol mesh structure; stabilizing wires	16, 18, 20, 22, 24, 26, 28, and 30 mm (9, 10, and 13-F sheaths)	CE mark
Amulet	St. Jude Medical	Lobe and disk (polyester mesh in both); nitinol mesh structure; stabilizing wires	16, 18, 20, 22, 25, 28, 31, and 34 mm (12- and 14-F sheaths)	CE mark
WaveCrest	Coherex Medical	Single-lobe occluder; nitinol frame; polyurethane foam and ePTFE membrane; retractable anchors	22, 27, and 32 mm	CE mark
Occlutech LAA Occluder	Occlutech	Single-lobe occluder; nitinol wire mesh; stabilizing loops; nanomaterial covering	15, 18, 21, 24, 27, 30, 33, 36, and 39 mm (12- and 14-F sheaths)	Clinical trial evaluation
Sideris Transcatheter Patch	Custom Medical Devices	Frameless detachable latex balloon covered with polyurethane		Clinical trial evaluation
LAmbre	Lifetech	Lobe and disk; nitinol; PET membrane; distal barbs anchors	16 to 36 mm (7- to 10-F sheaths)	Clinical trial evaluation
Pfm	Pfm Medical	Dual disk (distal anchor, variable middle connector, proximal disk); nitinol frame	(8- and 9-F sheaths)	Pre-clinical trial evaluation
Ultrasept	Cardia	Lobe and disk; nitinol frame; Ivalon covering; distal anchors	16, 20, 24, 28, and 32 mm (10-, 11-, and 12-F sheaths)	Clinical trial evaluation
Epicardial Devices				
Lariat	SentreHeart	Endocardial and epicardial approach: magnetically-assisted snare over balloon in LAA	14-F epicardial sheath	FDA approval CE mark
AtriClip	AtriCure	Surgical approach: parallel clip with polyester mesh	35, 40, 45, and 50 mm	FDA approval CE mark
Aegis	AEGIS Medical Innovations	Epicardial subxiphoid approach: electrodes guide navigation to LAA and tissue capture		Clinical trial evaluation
Cardioblate Closure System	Medtronic	Epicardial approach: silicone band covered by polyester fabric		Pre-clinical trial evaluation

ACP = Amplatzer Cardiac Plug; CE = Conformité Européene; ePTFE = expanded polytetrafluoroethylene; FDA = Food and Drug Administration; LAA = left atrial appendage; PET = polyethylene terephthalate; PLAATO = Percutaneous Left Atrial Appendage Transcatheter Occlusion.

(Figure 1), and anterior-curve. The standard workhorse is the double-curve sheath (>90% cases), which allows easier access into superiorly directed distal lobes. The fourth-generation device was evaluated in a European registry, and the fifth generation (WATCHMAN FLX) is awaiting first-in-man evaluation. The WATCHMAN device received the Conformité Européene (CE) mark in 2005 and is under FDA evaluation with anticipated approval in early 2015.

AMPLATZER CARDIAC PLUG. Early adopters of percutaneous LAA closure in Europe attempted non-dedicated Amplatzer devices after the PLAATO device was discontinued as there was no other option (23,24). However, the incidence of embolization was high (12%), although the efficacy endpoints were similar to dedicated devices for successfully-implanted devices (24). The dedicated Amplatzer Cardiac Plug (ACP) (St. Jude Medical, Plymouth, Minnesota) was specifically designed to occlude the proximal segment of the LAA and is the third LAA device to be manufactured.

ACP consists of self-expanding nitinol mesh forming a lobe and disk, connected by a central articulating waist (Figure 3). The lobe is implanted ~10 mm inside of the LAA orifice and serves as the key anchoring mechanism, supported by 6 pairs of stabilizing wires distally. The disk deployed in the left atrium is pulled under traction against the LAA orifice by the waist connecting to the lobe, which helps to seal the orifice (case example, Figure 4). Both the lobe and disk have polyester mesh that is sewn in by hand. There are 8 sizes according to the lobe dimension, accommodating LAA diameters of 12.6 to 28.5 mm (Figure 3). The second-generation ACP, Amulet (St. Jude Medical), has a wider lobe, longer waist, recessed proximal end screw, and more stabilizing wires. These features improve the stability of Amulet and theoretically may reduce thrombus formation on the atrial side of the device. Amulet also comes in 8 sizes and accommodates larger LAAs (up to 32 mm).

ACP has to be manually loaded onto the delivery cable, but the Amulet comes pre-loaded on the

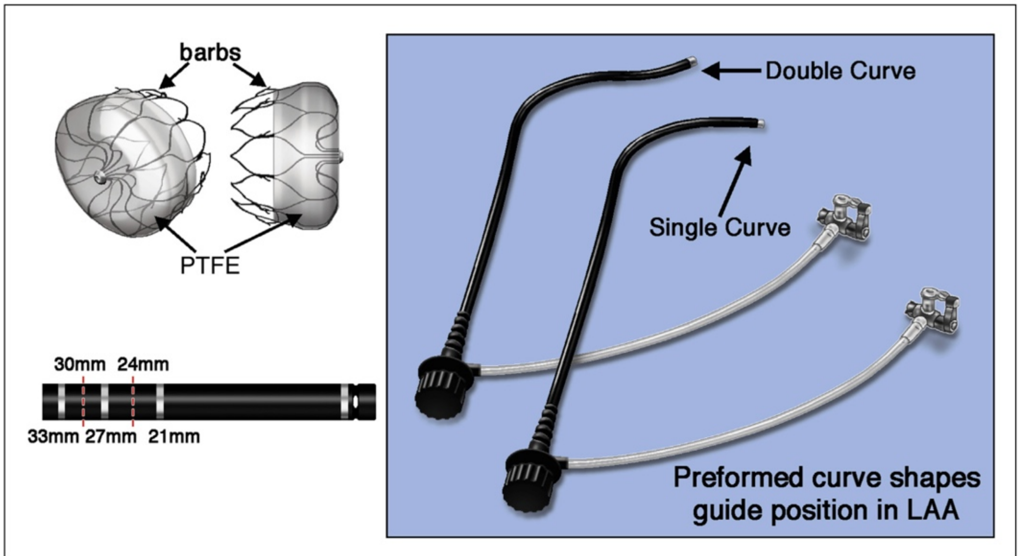

FIGURE 1 **WATCHMAN and 14-F Access Sheaths (Double- and Single-Curve)**

There are 3 radio-opaque marker bands (33, 27, and 21 mm) on the distal sheath, which should be aligned to the left atrial appendage (LAA) "ostium" according to the selected device. PTFE = polyethylene terephthalate.

delivery cable for ease of setup. Currently, the Amulet is undergoing redesign of the delivery system and will be relaunched in late-2014. ACP received the CE mark in December 2008, and Amulet received it in January 2013.

There were 3 ACP/Amulet delivery sheaths available; the workhorse is the TorqVue™ 45° × 45° (>95% of cases), which has a 3-dimensional distal tip, allowing anterior and superior angulation for coaxial positioning at the landing zone. The TVLA1 and TVLA2 sheaths are no longer being manufactured because of lack of demand. The access sheath size varies according to the device size (Figure 3), although some operators routinely use the largest sheath.

LARIAT. The catheter-based Lariat (SentreHEART Inc., Redwood City, California) LAA closure is a complex hybrid procedure that requires both an endocardial and epicardial approach. Lariat is FDA-approved (and CE-marked) for suture and knot tying during surgical applications, but not specifically for stroke prevention with AF. There is a recent surge in interest and procedural volume in the United States due to the availability of this device for patients who are not OAC candidates. Lariat consists of a snare with a pre-tied suture that is magnetically guided epicardially over the LAA. There are 3 components: a 15-mm compliant occlusion balloon catheter (EndoCATH); 0.025- and 0.035-inch magnet-tipped guidewires (FindrWIRZ); and a 12-F Lariat suture delivery device (25).

IMPLANTATION TECHNIQUES FOR WATCHMAN AND ACP

PRE-PROCEDURAL IMAGING. Baseline TEE is important to exclude pre-existing LAA thrombus and to assess for suitability for LAA closure, especially for sizing and device selection. A full 0° to 180° sweep is useful to appreciate the LAA anatomy and for accurate measurements. For WATCHMAN, the widest LAA ostium (anatomic orifice measured from the circumflex artery inferiorly to a point superiorly 1 to 2 cm within the pulmonary vein ridge) at 0°, 45°, 90°, and 135° and the available depth of the LAA (from ostium to apex of LAA) are measured. For ACP, measurements at both the short axis (30° to 60°) and the long axis (120° to 150°) of the landing zone and orifice are important. The LAA orifice represents the line from the pulmonary vein ridge to the circumflex artery (echocardiographic orifice) (Figure 5). The landing zone is measured at 10 mm within the orifice at an angle that is perpendicular to the neck axis. The LAA depth is measured from the orifice to the back wall along the neck axis. For Amulet, the landing zone is ~12 to 15 mm from the orifice due to the wider lobe.

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TABLE 2 WATCHMAN Studies and Key Results

Study (Ref. #)	Design	CHADS2, Mean ± SD	Procedural Success, %	Follow-Up Duration	Efficacy Events	Important Safety Issues With WM
PROTECT-AF (29,31)	RCT, N = 707: 2 WM; 1 warfarin	2.2 ± 1.2	90.9	1,065 pt-yrs (mean 1.8 yrs)	Primary endpoint: stroke, systemic embolism, CV death: 3.0% WM, 4.9% warfarin per 100 pt-yrs; RR: 0.62. Met noninferiority criteria.	Serious pericardial effusion 4.8%, procedural stroke 1.3%, device embolization 0.6%, major bleeding 3.5% (4.1% warfarin), hemorrhagic stroke 0.2% (2.5% warfarin).
				1,588 pt-yrs (mean 2.3 yrs)	Primary endpoint: 3.0% WM, 4.3% warfarin per 100 pt-yrs; RR: 0.71. Met noninferiority criteria.	
				2,621 pt-yrs (45 months)	Primary endpoint: 2.3% WM, 3.8% warfarin per 100 pt-yrs; RR: 0.6. Met noninferiority and superiority criteria.	Major bleeding 4.8% (7.4% warfarin), hemorrhagic stroke 0.6% (3.7% warfarin).
PREVAIL (32)	RCT, N = 407: 2 WM; 1 warfarin	2.6 ± 1.0	95.1	18 months	Stroke, systemic embolism, CV, and unexplained death at 18 months: 0.064 both groups, RR: 1.07. Did not meet noninferiority criteria (<90 pts at 18-month follow-up). Ischemic stroke or systemic embolism >7 days met noninferiority criteria: 0.0253 WM; 0.0201 warfarin.	7-day death, ischemic stroke, systemic embolism, and procedure complications met noninferiority criteria (2.2% WM). Pericardial effusion needing pericardiocentesis, window, or surgery 1.9%. Procedure stroke 0.4%. Device embolization 0.8%.
CAP (30)	Registry, N = 460	2.4 ± 1.2	95.0	Median 0.4 yr		Procedural stroke 0%, serious pericardial effusion 2.2%.
ASAP (33)	Registry, N = 150	2.8 ± 1.2	94.7	14 months	All-cause stroke and systemic embolism 2.3%/yr. Observed ischemic stroke rate was 77% lower than expected.	Serious procedure- or device-related events 8.7%. Pericardial effusion with tamponade 1.3%, device embolism 1.3%, device thrombus 4.0% (with 0.7% causing stroke).

ASAP = ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology; CAP = Continued Access Protocol; CHADS2 = congestive heart failure history, hypertension history, age ≥75 years, diabetes mellitus history, stroke or transient ischemic attack symptoms previously; CV = cardiovascular; PREVAIL = Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation vs. Long-Term Warfarin Therapy; PROTECT-AF = WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation; pt-yrs = patient-years; RCT = randomized controlled trial; RR = risk ratio; WM = WATCHMAN.

Of note, the LAA measurements are usually wider at the long axis view (corresponding to caudal projection on fluoroscopy) compared to the short axis (corresponding to the right anterior oblique [RAO] cranial).

Pre-procedural cardiac computed tomography angiography (CCTA) is also useful to examine LAA anatomy and dimension, given the superior spatial resolution and 3-dimensionality. Moreover, CCTA is good for ruling out LAA thrombi, especially when delayed imaging is acquired (negative predictive value 100%) (26). Thus, CCTA can become a noninvasive alternative to TEE in experienced CCTA centers and is increasingly routinely performed prior to LAA closures (27).

PROCEDURAL IMAGING. It is generally recommended that LAA closures with any current CE mark devices be performed with TEE guidance for accurate device positioning and safety, typically accompanied by general anesthesia. However, there are a few centers adept with intracardiac echocardiography (ICE) that prefer procedural ICE instead, obviating the need for general anesthesia. However, obtaining adequate LAA images can be challenging, and some overcome this problem by advancing the ICE probe into the left atrium through another transseptal puncture. There are also limited centers that rely on fluoroscopy alone (24); however, these are typically very experienced centers for LAA closure, and this is not advised for the average operator.

VENOUS ACCESS. Right femoral venous access is preferred because it allows more direct transseptal access than the left femoral vein does. Access site should be well prepared with the scalpel, and subcutaneous tissues separated by forceps to ease advancement of large 13- to 14-F sheaths. Manual compression, "figure-of-8" suture, or pre-closing with the 6-F Perclose ProGlide Suture-Mediated Closure System (Abbott Vascular, Temecula, California) are commonly used for hemostasis.

TRANSSEPTAL PUNCTURE. Transseptal puncture should be inferiorly and posteriorly located in the fossa ovalis for both WATCHMAN and ACP implantation, which is well gauged with the bicaval and short-axis TEE views, respectively. ICE is also useful to guide transseptal puncture. Very experienced operators sometimes use anatomic landmarks on fluoroscopy alone to guide punctures. Although there is a small study showing good procedural success with LAA closure through patent foramen ovale (28), it is generally advised and preferential to perform a separate transseptal puncture inferoposteriorly that

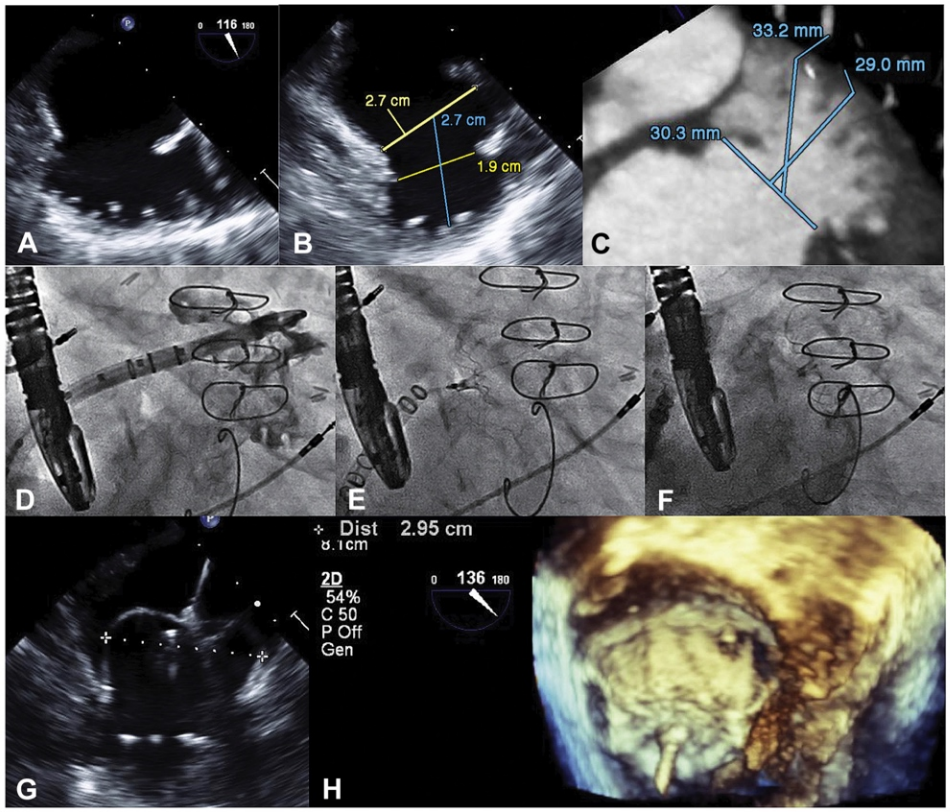

FIGURE 2 Example of WATCHMAN Implantation

(A) Transesophageal echocardiography (TEE) image at 116° showing left atrial appendage (LAA) with trabeculations in a fan shape. **(B)** TEE at 97° with measurements. **(C)** Pre-procedure cardiac computed tomography angiography showing complex LAA with protruding proximal pectinate ridge, widest dimension of 30.3 mm, and usable depth of 29 to 33.2 mm. **(D)** The 14-F double-curve sheath advanced deep over the marker pigtail. **(E)** The 33-mm WATCHMAN deployed. **(F)** Device released after ensuring PASS (position, anchor, size, seal) criteria were achieved. **(G)** TEE widest shoulder measurement of 29.5 mm representing 10.6% compression and no significant residual leak. **(H)** Three-dimensional TEE showing acceptable slight protrusion of the shoulder of the WATCHMAN into the left atrium, with polyethylene terephthalate fabric covering the device.

provides more direct vector orientation to access the LAA, which is more anterior and superior. Intravenous heparin is administered before or immediately following transseptal puncture to maintain an activated clotting time >250 s. It is also important to attain adequate mean left atrial pressure (~15 mm Hg) with fluid bolus for accurate measurements.

FLUOROSCOPIC LAA MEASUREMENTS. Following transseptal puncture, a 5-F marker pigtail is advanced into the LAA and cineangiograms are performed in multiple projections to ascertain the LAA anatomy and measurements. Caudal projections are usually better in visualizing the mid-distal LAA for the WATCHMAN device, whereas RAO cranial projections are better in visualizing ostium and proximal LAA for ACP. We typically perform ≥3 angiographic views, often aided by CCTA for angle selection. For the WATCHMAN device, we usually perform RAO (20° to 30°) caudal (20° to 30°), PA caudal (20° to 30°), and RAO (20° to 30°) cranial (10° to 20°) projections. For ACP, we usually perform RAO (30°) cranial (10°), RAO (30°) cranial (30°), and PA caudal (20° to 30°) projections.

ACCESS SHEATH ADVANCEMENT. A long (260-cm) J-tipped stiff 0.035-inch wire (e.g., Amplatz Super Stiff J-tip 3-mm curve) should be advanced into the left upper pulmonary vein as a rail for sheath access.

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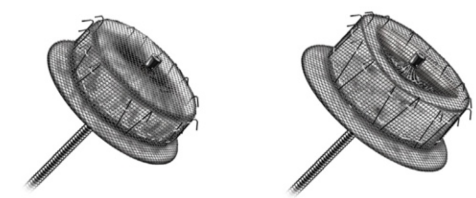
The appropriately-sized access sheath is then safely advanced to the left upper pulmonary vein ostium. To allow easier access, the venous access should be well-dilated, and the sheath gently rotated during advancement to ensure coaxial approach while crossing the interatrial septum.

For the WATCHMAN device, the 14-F access sheath is advanced deep into the LAA using a pigtail (5- to 6-F) before device introduction. RAO 20° to 30° caudal 20° to 30° angulation typically allows good visualization of the distal lobes for sheath advancement and device deployment. The access sheath is safely navigated over the pigtail into the distal segment of the LAA (Figure 2), until the corresponding radio-opaque marker band for the device size (Figure 1) is aligned with the LAA ostium. Once in position, the pigtail is removed, and often a moderate degree of catheter torque is required to maintain sheath position in the distal lobe.

For ACP, the appropriately-sized sheath/dilator is usually advanced to the left upper pulmonary vein orifice, and then the sheath is withdrawn slightly and turned counterclockwise to fall into the LAA ostium. A J-tip wire or pigtail may be used to facilitate engagement to minimize traumatizing the thin left atrium. Usually an RAO cranial projection is used for ACP sheath positioning and implantation.



Feature	ACP								Amulet							
Sizes (mm)	16	18	20	22	24	26	28	30	16	18	20	22	25	28	31	34
Disc Diameter	Lobe + 4 mm				Lobe + 6 mm				Lobe + 6 mm				Lobe + 7 mm			
Lobe Length	6.5 mm								7.5 mm				10 mm			
Waist Length	4 mm								5.5 mm				8 mm			
Sheath Diameter	9Fr	10Fr			13Fr				12Fr						14Fr	
Stabilizing Wires	6 pairs								6 pairs		8 pairs			10 pairs		

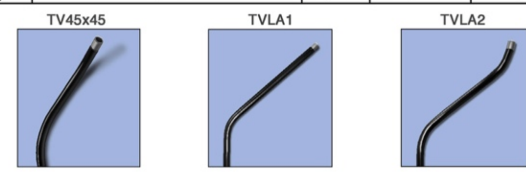


FIGURE 3 **ACP and Amulet Characteristics and Available Sheaths**

ACP = Amplatzer Cardiac Plug; Fr = French.

WATCHMAN SIZING AND IMPLANTATION STEPS. WATCHMAN sizing is based on the maximum LAA ostium diameter, which should be 17 to 31 mm to accommodate available devices. Oversizing is recommended by 9% to 25% based on the widest measurement, which generally corresponds to 2- to 4-mm oversizing. The prepped delivery system containing the compressed device is then introduced into the access sheath. The delivery system is advanced until both the distal marker bands of the delivery system and access sheath are aligned. The device is then unsheathed slowly without forward advancement of the device, preferably inducing apnea for the patient to allow stable deployment. When the device is fully unsheathed, the device position is evaluated on fluoroscopy and TEE. If it is too distal, the device may be partially recaptured and the access system withdrawn slightly, then the unsheathing process is reattempted. If the device is too proximal (or sizing or position is suboptimal), the device can be fully recaptured, and a new device and delivery system can be reattempted through the existing 14-F sheath.

Before device release, the 4 "PASS" criteria should be met: 1) position (device distal or at LAA ostium, protrusion of shoulder by <40% to 50% of device depth is acceptable); 2) anchor (testing stability by retracting the deployment knob and letting go, to assess return to original position); 3) size (device shoulder compressed 8% to 20% of original size on TEE); and 4) seal (assess TEE for any residual flow, must be <5 mm before release). When these criteria are met, the device may be released with counterclockwise rotation of the core wire for 3 to 5 turns. Final angiography and TEE assessment are then performed.

ACP SIZING AND IMPLANTATION STEPS. ACP sizing depends on the widest landing zone on fluoroscopy or TEE. A standard recommendation is to upsize the device by 3 to 5 mm for ACP and 2 to 4 mm for the Amulet device from the widest measured landing zone. This degree of oversizing improves stability of the device and proper anchoring of the lobe. However, caution should be exercised if the landing zone is very elliptical to avoid dramatic oversizing (>5 mm) in the narrowest dimension.

The prepped device is advanced to the tip of the access sheath, which is positioned at the landing zone of the LAA. The first step of deployment is unsheathing by withdrawal of the delivery sheath to deploy the "ball" (Figure 5). If the position is adequate on TEE and fluoroscopy, the remainder of the lobe is then deployed. If the angle and position of the lobe at the landing zone is optimal, then the disk can be

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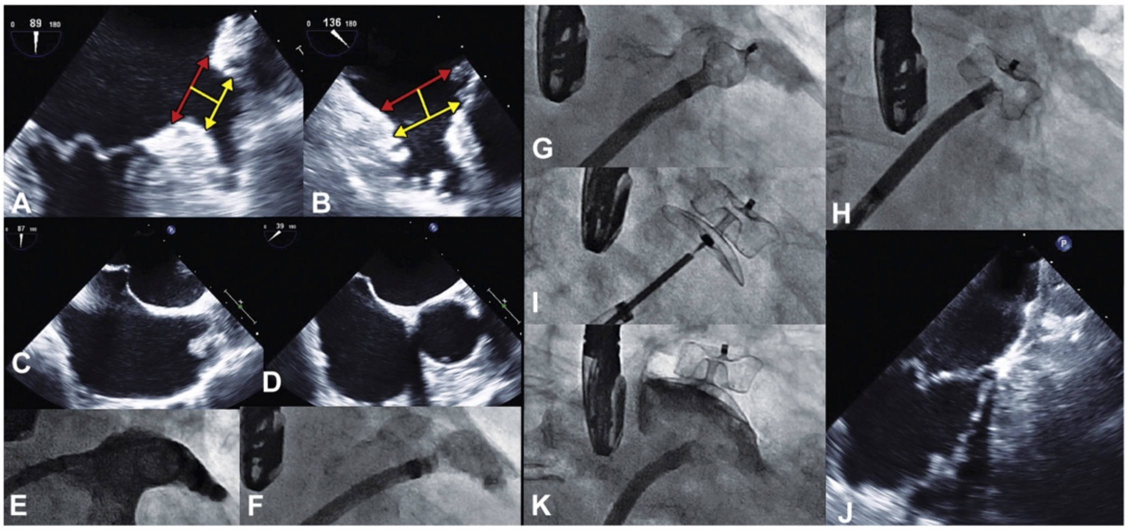

FIGURE 4 **ACP/Amulet Implantation**

(A) Short- and **(B)** long-axis baseline TEE views showing measurements of the orifice **(red arrows)** and the landing zone **(yellow arrows)** at 10 mm **(yellow line)** within the orifice. Transseptal puncture in an inferior position on bicaval TEE view **(C)** and posterior position on short-axis TEE view **(D)**. **(E)** Cineangiogram with marker pigtail in the LAA, and same measurements taken as with TEE. **(F)** TorqueVue 45 × 45 sheath is advanced with distal tip aligned with the landing zone. **(G)** First step of ACP/Amulet deployment is unsheathing to a "ball" configuration. **(H)** The remainder of the lobe is unsheathed and the position is checked on cineangiogram and TEE. **(I)** The disk is then unsheathed. **(J)** Device position is confirmed on TEE with color Doppler to assess leak. **(K)** Device is released and final cineangiogram performed. Abbreviations as in Figures 2 and 3.

deployed. This maneuver requires slight traction of the delivery cable during further unsheathing of the disk, to separate the lobe from the disk adequately and to ensure that the disk is deployed in the left atrium. The position and angulation of the fully unsheathed device is confirmed on TEE and fluoroscopy. If unsatisfactory at any point prior to release, the disk and lobe can be resheathed into the "ball" configuration, as long as the 2 platinum markers on the device do not enter the radio-opaque band on the sheath. If the device positioning/size is inadequate, or if the platinum markers enter beyond the radio-opaque band, then the device has to be entirely removed, and the sheath replaced.

Prior to device release, 5 signs should be present to ensure proper deployment (examples in Figure 6): 1) tire-shape of the lobe (ensuring adequate compression of the lobe and engagement of stabilizing wires); 2) separation of the lobe from the disk (ensuring good seal of disk); 3) concavity of the disk (ensuring good seal by traction of the disk from the lobe); 4) axis of the lobe (should be perpendicular to the neck axis at landing zone, to ensure proper contact of lobe walls and stabilizing wires); and 5) lobe is adequately within the circumflex artery on TEE (i.e., lobe should be deep enough such that the width of the lobe is two-thirds or more within the circumflex). If there is uncertainty about device stability, a gentle "pull" of the disk may be performed, but vigorous wiggle testing is contraindicated. Alternatively, the device can be observed for several minutes for stability prior to release. The presence of residual leak is assessed on TEE. Contrast injections can be performed through the delivery sheath to assess optimal positioning after ensuring that the system is deaired. Once a satisfactory position is achieved, the device is released with counterclockwise rotation of the delivery cable.

IMPLANTATION TECHNIQUES FOR LARIAT

A pre-operative CCTA is necessary to exclude large (>40 mm) appendages and other anatomic variants (e.g., posteriorly rotated LAA under the pulmonary artery, pericardial adhesions) that preclude the use of this device, which may occur in up to 20% of cases. TEE is performed pre-procedurally to exclude LAA thrombus and during the procedure to verify the anatomic position of the EndoCATH balloon at the LAA ostium.

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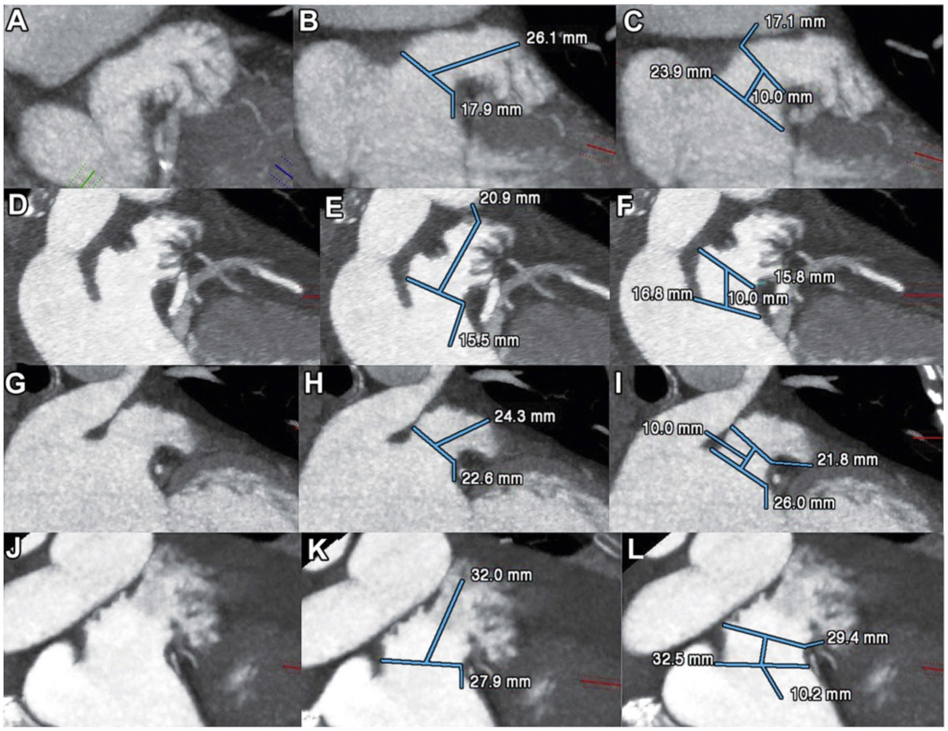

FIGURE 5 **Cardiac CCTA of LAA Demonstrating the 4 Most Common Shapes**

Measurements for WATCHMAN are shown in the **middle column** and ACP in the **right column**. **(A to C)** Cauliflower-shaped LAA; **(D to F)** windsock-shaped LAA with mid-distal trabeculations; **(G to I)** chicken wing LAA, with distal opacification of the LAA due to incomplete contrast-mixing (not thrombus); **(J to L)** cactus-shaped LAA with trabeculations extending from all directions from the main body. CCTA = cardiac computed tomography angiography; other abbreviations as in Figures 2 and 3.

The procedure was well described by Bartus et al. (25) with 4 key steps: 1) pericardial and transseptal access; 2) placement of the endocardial magnet-tipped guidewire in the apex of the LAA with balloon identification of the LAA ostium; 3) connection of the epicardial and endocardial magnet-tipped guidewires; and 4) snare capture of the LAA with closure confirmation and release of the pre-tied suture for LAA ligation.

Pericardial access requires an anterior approach through the subxiphoid area with a 17-gauge epidural needle, and fluoroscopic guidance in anteroposterior and lateral views. Following epicardial access, a 0.035-inch guidewire is advanced and left in the pericardial space while the transseptal puncture is performed. The EndoCATH back-loaded with the magnet-tipped 0.025-inch endocardial guidewire is advanced to the LAA apex through the transseptal catheter. The epicardial access is then sequentially dilated to insert the 14-F guide-cannula, and the 0.035-inch epicardial magnet-tipped guidewire is then placed through the epicardial sheath and directed toward the LAA to connect with the endocardial magnet. With the EndoCATH balloon inflated at the LAA ostium, the Lariat suture is then guided to the LAA along the epicardial magnet, and looped over the LAA to snare it. The snare is closed after confirmation on TEE and left atrial angiogram, and suture tightening and cutting is then performed. A pigtail catheter is usually left in the pericardial space for several hours post-procedure.

CLINICAL TRIALS EVALUATING SAFETY AND EFFICACY OF LAA OCCLUSION

Several studies have evaluated the efficacy and safety of these LAA occlusion devices for stroke prevention with AF. The majority are early experience registries, with only 1 randomized controlled trial published to date.

WATCHMAN. The WATCHMAN device was studied in the multicenter PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial (29), where 707 patients with nonvalvular AF and $CHADS_2$ ≥1 were randomized to the WATCHMAN device (n = 463) or to continued warfarin therapy (n = 244) in a 2:1 ratio. WATCHMAN was successfully implanted in 90.9% of cases. Warfarin was continued for 45 days with WATCHMAN and then switched to clopidogrel for 4.5 months (if there is no leak >5 mm on TEE at 45 days), with aspirin lifelong after implantation. Warfarin was discontinued in 86% of patients at 45 days and in 92% at 6 months.

The composite primary efficacy of stroke, systemic embolism, and cardiovascular death event rates met noninferiority criteria at 1,065 and 1,588 patient-years of follow-up. However, the primary adverse procedure-related events and major bleeding were higher with the WATCHMAN device (5.5% vs. 3.6% annually; risk ratio [RR]: 1.53; 95% confidence interval: 0.95 to 2.70) (**Table 2**) (30,31).

At 45-month (2,621 patient-years) follow-up (presented at Heart Rhythm Society 2013), the primary efficacy endpoint was significantly lower with the WATCHMAN device (2.3 events vs. 3.8 events per 100 patient-years; RR: 0.6), meeting both the noninferiority and superiority criteria. Hemorrhagic stroke (RR: 0.15), cardiovascular death (RR: 0.4), and all-cause mortality (hazard ratio: 0.66, $p = 0.0379$) were also significantly lower with the WATCHMAN device.

Due to early safety concerns in PROTECT-AF, the FDA mandated a second randomized trial to confirm the late PROTECT-AF and CAP registry safety results for approval of the device. Thus, the PREVAIL (Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation vs. Long-Term Warfarin Therapy) trial was conducted, which randomized 407 patients in a 2:1 ratio to WATCHMAN or warfarin. Inclusion criteria was $CHADS_2$ ≥2, or $CHADS_2$ = 1 if 1 or more of the following was present: female sex ≥75 years of age; left ventricular ejection fraction 30% to 34.9%; age 65 to 74 years with diabetes or coronary artery disease; or age ≥65 years with documented congestive heart failure. This study was recently published (**Table 2**) (32). Successful implantation improved to 95.1%. The safety endpoint met the pre-specified noninferiority criterion.

The ASAP (ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology) study (33) evaluated 150 patients with nonvalvular AF and $CHADS_2$ ≥1 who were ineligible for warfarin. Patients were treated with thienopyridine for 6 months and lifelong aspirin after WATCHMAN implantation. With a mean follow-up duration of 14 months, all-cause stroke and systemic embolism was 2.3% per year. The observed ischemic stroke rate was 77% lower than expected based on the $CHADS_2$ score of 2.8 in the cohort.

The CAP2 registry recently stopped enrolment in the United States in early 2014. The initial CAP registry showed lower procedural-related events compared with the early PROTECT-AF results, with procedural-related stroke of 0%, and serious pericardial effusion of 2.2% with the WATCHMAN device (30). With the promising long-term results of PROTECT-AF and improved safety results of PREVAIL and CAP, the FDA is anticipated to imminently approve WATCHMAN.

There was a demonstrable learning curve with improvement in technical success rate and reduction in complications with increasing experience. The implant success rate improved from 91.3% in PROTECT-AF to 95.0% in the subsequent CAP registry ($p = 0.033$) (which included only investigators who previously implanted WATCHMAN in PROTECT-AF), in conjunction with significant reduction in procedural time (56 min vs. 50 min, $p < 0.001$), there was also significant decline in procedure- or device-related safety event rates when comparing the first and second halves of PROTECT-AF and CAP, with 10.0%, 5.5%, and 3.7% of patients, respectively, experiencing events within 7 days of procedure ($p = 0.006$) (30).

AMPLATZER CARDIAC PLUG. Since the launch of the ACP in 2008, over 7,000 devices have been implanted worldwide. The ACP was evaluated in several small retrospective registries (**Table 3**), mostly involving single-center experiences in Europe, Canada, Asia, and Latin America (24,34–43). In aggregate, >1,100 patients were included in these registries, showing good safety profile (serious pericardial effusion ~1.7%, device embolization ~1.1%, ischemic stroke ~0.4%), and procedural success (~96.4%).

Recently, Tzikas (20) presented a pooled ACP experience of 20 European and Canadian centers inclusive of 969 patients at Transcatheter Cardiovascular Therapeutics 2013. The mean age was 74.9 years, CHA_2DS_2-VASc score of 4.4, and HAS-BLED (hypertension, abnormal liver function, abnormal renal function, stroke, bleeding, labile international normalized ratios, elderly [age >65 years], drugs, alcohol) score of 3.2. About 29% were on OAC prior to implantation. Implantation success was 97.2%, and in

93.2% of cases, the first device selected was implanted. With follow-up TEE, the closure rate (<3 mm residual flow) was 97.6%. The rate of periprocedural major adverse events (7-day death, ischemic stroke, systemic embolism, and procedure- or device-related complications requiring major cardiovascular or endovascular intervention) was 4.1% (mortality 0.6%, pericardial tamponade 1.2%, device embolization 0.2%, stroke 0.7%). The observed annual stroke rate was 2.1%, which was 63% lower than the expected 5.6% stroke rate based on CHA_2DS_2-VASc score, similar to other smaller registries (24,39,41).

The U.S. pivotal ACP randomized-controlled trial commenced enrollment in early 2013, randomizing AF patients with $CHADS_2 \geq 2$ to ACP versus anticoagulation (warfarin or dabigatran) in a 2:1 ratio. However, due to slow enrollment and imminent FDA approval of WATCHMAN, this study was discontinued in December 2013 after enrollment of ~80 patients. The study is being redesigned, and it is anticipated that the new randomized study will involve a noninferiority comparison to the WATCHMAN device.

LARIAT. The first published single-center experience with the Lariat procedure included 89 patients in Poland (25). The mean age was 62 years, $CHADS_2$ score was 1.9, and CHA_2DS_2-VASc was 2.8. Technical success was 96%. There were 2 epicardial-related complications (right ventricular puncture and superficial epigastric artery laceration) and 1 transseptal complication (hemopericardium). Major post-operative adverse events included 2 severe pericarditis, 1 late pericardial effusion, 2 unexplained sudden deaths, and 2 late strokes. Of the 65 patients undergoing TEE at 1 year, complete LAA closure was observed in 98%.

More recently, Price et al. (44) published the multicenter retrospective U.S. experience of 154 patients who underwent the Lariat procedure. The procedural time was 76.6 min and technical success was 94%, but procedural success (without procedural complication) was only 86%. Major adverse in-hospital events included: significant pericardial effusion (requiring intervention) 10.4%; bleeding requiring transfusion 4.5%; and emergent cardiac surgery 2.0%. At median 112 days follow-up, death, myocardial infarction or stroke occurred in 2.9%. TEE follow-up was performed in 63 patients revealing residual leak in 20%, and presence of thrombus in 4.8%. In summary, this study showed that even though technical success was acceptable, the Lariat procedure resulted in worrisome pericardial effusion and bleeding, thus requiring further evaluation.

COMPLICATIONS WITH PERCUTANEOUS LAA CLOSURE AND MANAGEMENT

The acute complications with WATCHMAN and ACP appear comparable. With good technical skills and procedural planning, the risks of procedural ischemic stroke is <0.5%, serious pericardial effusion 1% to 2%, and device embolization 0.5% to 1%. Ischemic strokes may be related to procedural air embolism (inadequate device preparation or poor technique) or thrombus in LAA or on equipment. Baseline imaging to exclude pre-existing thrombus, adequate procedural anticoagulation, and meticulous and proficient techniques are important to minimize thromboembolism. Pericardial effusion causing hemodynamic compromise requires emergent pericardiocentesis, and possibly pericardial window or surgical intervention for cardiac perforation. Pericarditis related to Lariat procedures is often managed with nonsteroidal anti-inflammatories or with steroids. Device embolization is typically managed by percutaneous retrieval if feasible. A large arterial sheath through the femoral artery that is ≥2-F larger than the implanting access sheaths is often required to retrieve the embolized device, in conjunction with loop-snare and bioptome. An embolized device trapped in the left ventricle is more challenging to retrieve but can be successfully performed (**Figure 7**). Sometimes, surgical removal is required, especially if the device is trapped by papillary muscles or trabeculations.

Longer-term potential issues include thrombus on device and residual leak; thus, follow-up TEE or CCTA ~3 to 6 months post-procedure is typically performed (and is sometimes repeated at 1 year). Formation of thrombus on the atrial side of devices can occur in 2% to 5% of cases with the 3 devices. These occurrences are purported to occur predominantly on nonendothelialized device protrusions, such as the threaded insert with WATCHMAN and the proximal end screw with ACP, especially if implants are too deep. Thus, avoiding deep implantations creating cul-de-sacs, especially avoiding uncovered proximal LAA trabeculations, have been advised. New device designs have also been pursued to address these concerns; for example, Amulet has a recessed proximal end screw. Although there is no consensus on management, such thrombotic complications are usually managed with anticoagulation (OAC or low-molecular-weight heparin) for 8 to 12 weeks, with repeat TEE to assess for thrombus resolution before cessation of anticoagulation. Reported thromboembolic stroke event rates related to device thrombus are low: 0.3% to 0.7% (30,33).

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TABLE 3 Procedural Success and Complications in ACP Registries

ACP Registries (Ref. #)	Enrollment Period	N	$CHADS_2$ Score, Mean ± SD	Procedural Success, %	Serious Pericardial Effusion, %	Embolization, %	Ischemic Stroke, %	Total Safety Events, %
Initial European registry (34)	December 2008–November 2009	143	NA	96	3.5	1.4	2.1	7
Asia-Pacific experience (35)	2009-2010	20	2.3 ± 1.3	95	0	0	0	1 air embolism, 1 thrombus
Latin America (36)	2009-2012	60	3.2 ± 1.1	100	6.6	1.7	0	8.3
Spanish experience (37)	2009-2011	35	2.4 ± 1.5	97.1	0	0	0	0
Polish experience (38)	2009-2012	21	CHA_2DS_2-VASc 4.4 ± 1.4	95.2	4.8	0	0	0
Iberia registry (42)	2009-2011	213	NA	92.5	1.4	1.9	0.5	5.6; 1.4 deaths
Bern experience (24)	2008-2012	120	CHA_2DS_2-VASc 3.4 ± 1.7	97.5	1.6	1.6	0.8	6.7 (2 TIA)
Canadian registry (39)	2009-2011	52	3.0 ± 1.0	98.1	0	1.9	0	1.9
Israel experience (40)	2009-2012	100	3.2 ± 1.2	100	1	0	0	1
Belgian registry (43)	2009-2012	90	CHA_2DS_2-VASc 4.4 ± 1.8	98.9	3.3	0	0	1.1 deaths
European post-marketing registry (41)	2009-2011	204	2.6 ± 1.3	96.6	2.4	1.5	0	2.9

CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, age 65 to 74 years, diabetes mellitus, stroke/transient ischemic attack/thromboembolism, vascular disease, sex female; NA = not available; TIA = transient ischemic attack; other abbreviations as in Tables 1 and 2.

Residual leaks occur in a fair proportion of WATCHMAN implantations, with some degree of leak seen in 32% of cases in PROTECT-AF at 12-month follow-up (36.8% >3 mm, and 63.2% ≤3 mm). However, residual leak was not associated with increased risk of subsequent thromboembolism (45), although the event rate was low and these findings were considered hypothesis generating. For ACP, leak >5 mm has not been documented; leak 3 to 5 mm occurs in 0% to 1% of cases (41), and leak <3 mm occurs in 0% to 16% of cases (35,37,39). The ACP's low incidence of leak is presumably related to the double-disk design. Residual leak has also been demonstrated with the Lariat procedure, with variable reported incidence from 2% to 22% at follow-up TEE (25,44). In cases of residual leak >5 mm, patients may be continued on long-term anticoagulation (29); there are also case reports of performing another LAA closure with a different device for large residual leaks (46).

SELECTION AND COMPARISON OF LEADING LAA DEVICES

LAA device choice often depends on the availability at the institution and country. Although there is no randomized comparative study, the technical success of the leading devices (WATCHMAN and ACP) appears quite comparable, 95% to 97%. The Lariat procedure appears to have lower technical success of 93%, with even lower procedural success of 83% (due to major complications). Most operators would prefer the endocardial route and relegate epicardial approach to unsuitable anatomy for endocardial closure (e.g., large LAA with diameter >31 to 32 mm but <40 mm, or unusual anatomy such as a short neck).

Although baseline TEE is commonly done, this technology is limited by spatial resolution and often does not provide full definition of the LAA. Baseline CCTA is very useful to fully appreciate the LAA complexity, which helps with device selection and optimizes fluoroscopic views. LAA can be broadly divided into 4 different shapes (47): chicken wing, cactus, windsock, and cauliflower (Figure 5). However, LAA anatomy is highly variable and may have a combination of these characteristics. We pay particular attention to the anatomy at intended landing zones evaluating for sphericity, pectinate ridges, trabeculations, diverticula, and additional lobes. Detailed measurements are taken at the orifice, intended landing zone, and available depth (Figure 5). Using 3-dimensional CT reconstruction, we select the optimal fluoroscopic angles for the different devices: ACP/Amulet requires optimized views for the proximal/neck of LAA, whereas WATCHMAN requires better visualization of the body and distal lobes. Examples of LAA anatomy ranging from easy to challenging closures with leading devices are shown in Figures 6 and 7.

In general, both leading devices can accommodate over 95% of LAA anatomy. The LAA size is an

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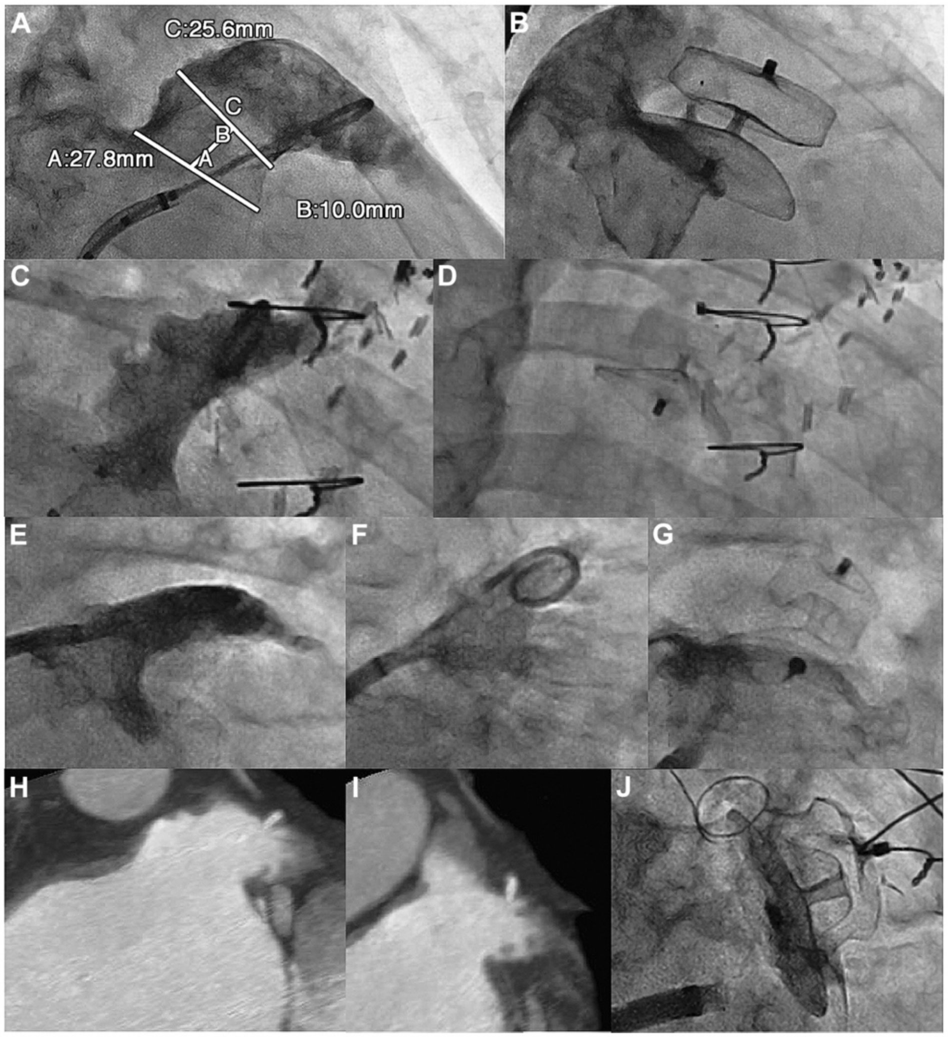

FIGURE 6 **Easy to Intermediate Challenging Anatomies for LAA Closures**

(A) Chicken wing LAA with moderately-angled (<90°) and gentle curve with apex of bend >15 mm from orifice, easily closed with the ACP 28-mm device **(B)**. **(C and D)** Windsock LAA easily closed with the Amulet device. **(E)** Cactus LAA with quite eccentric landing zone being narrow in the right anterior oblique cranial projection but much wider and showing marked filamentous trabeculations in the caudal projection **(F)**; this was moderately challenging for LAA closure with the Amulet device. **(H to J)** Early bifurcating bilobed LAA at ~10 mm from orifice, moderate difficulty closing with the Amulet device with lobe abutting against the carina. Abbreviations as in Figures 2 and 3.

important consideration for selection. According to the manufacturers, the WATCHMAN device can accommodate a maximum LAA ostium between 17 mm and 31 mm, whereas ACP can accommodate a maximum LAA landing zone of 12.6 to 28.5 mm (Amulet between 12.6 mm and 32 mm). The shape of the LAA may also influence device choice. WATCHMAN is a relatively spherical device that requires as much LAA depth as the device diameter does. This may limit implantation where there is inadequate depth. There is also a threshold as to the acceptability of shoulder protrusion into the left atrium with WATCHMAN (the PET membrane covers ~50% of the proximal part of the device, and thus

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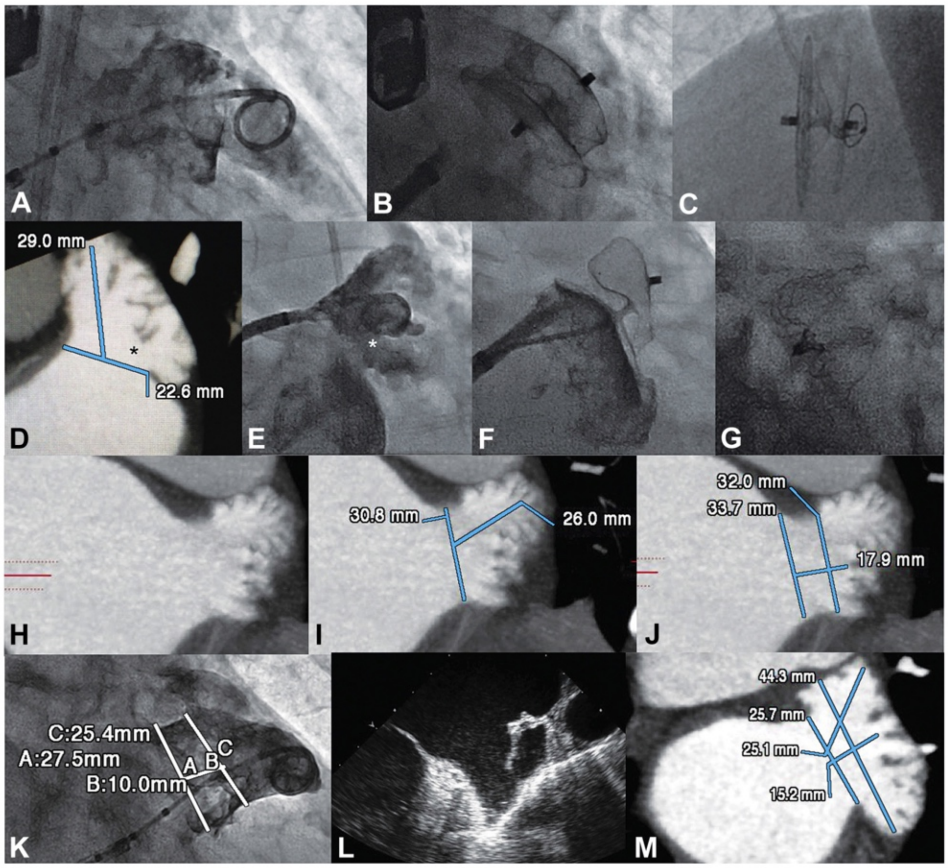

FIGURE 7 Examples of Challenging LAA Anatomies for Closure

(A to C) Early proximal (10 mm from orifice) acute sharp (>90°) chicken wing bend resulting in unstable ACP position at the intended landing zone. Device embolized the following day and was successfully retrieved by snare. Deeper placement of the ACP or WATCHMAN may result in stable position, but would compromise coverage of the ostium. **(D)** Cardiac computed tomography angiography and **(E)** fluoroscopy showing proximal (<10 mm from orifice) protruding pectinate ridge **(*)** precluding stable ACP positioning **(F)** with compression of the inferior portion of the ACP lobe, ultimately closed with a 30-mm WATCHMAN **(G)**. **(H to J)** Short-necked cauliflower LAA is not suitable for WATCHMAN, but should be amenable to closure with Amulet 34-mm device. **(K to L)** Fluoroscopy and transesophageal echocardiography images of a large early bifurcation lobe (~10 mm from orifice) resulting in unstable position of the largest 30-mm ACP device; the WATCHMAN or Amulet may be feasible here. **(M)** Challenging large (>44 mm) cauliflower LAA with a short neck, precluding the use of WATCHMAN or ACP devices or Lariat procedure. Abbreviations as in Figures 2 and 3.

the device should not protrude greater than this amount). The ACP, on the other hand, only requires a depth of ~10 mm (Amulet requires depth of 12 to 15 mm). Other important shape considerations are the presence of protruding pectinate ridges, location of additional lobes and trabeculations, and angulation at the landing zones. Challenging anatomies include proximal (≤10 mm from orifice) and severely sharp-angled (>90° bend) chicken wing configuration, certain cactus configuration, and limited depths. A mental visualization of how each device would optimally sit in the proximal LAA is helpful for device selection.

CONCLUSIONS

Percutaneous LAA closure is an emerging technology with several CE-marked devices available in many countries. The WATCHMAN device has the most supportive data and is anticipated to be approved imminently by the FDA. For ACP, there has been a large real-world experience in the past 5 years, and a randomized trial comparing ACP with WATCHMAN is anticipated in the near future. The Lariat procedure has also gained interest lately, but early studies were concerning for high rates of serious pericardial effusion and major bleeding. There are many other devices under investigation. The current real-world experience predominantly involves patients who are not long-term anticoagulation candidates (or perceived at high risk of bleeding). This pattern of practice is expected to change if the FDA approves the WATCHMAN device for warfarin-eligible patients. Before the pendulum swings completely in favor of LAA closure over OAC, several remaining issues should be addressed: longer-term follow-up efficacy data; comparative efficacy of LAA closure to NOAC; additive effects of OAC and LAA closure; noninferiority comparisons between different LAA devices; and updated cost-effective analyses for LAA closure.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Jacqueline Saw, Division of Cardiology, Vancouver General Hospital, University of British Columbia, 2775 Laurel Street, Level 9, Vancouver, British Columbia V5Z1M9, Canada. E-mail: jsaw@mail.ubc.ca.

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Cardiac CT angiography for device surveillance after endovascular left atrial appendage closure

Jacqueline Saw*, Peter Fahmy, Peggy DeJong, Mathieu Lempereur, Ryan Spencer, Michael Tsang, Kenneth Gin, John Jue, John Mayo, Patrick McLaughlin, and Savvas Nicolaou

Divisions of Cardiology and Radiology, Vancouver General Hospital, 2775 Laurel Street, Level 9, Vancouver, British Columbia, Canada V5Z1M9

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Aims Left atrial appendage (LAA) device imaging after endovascular closure is important to assess for device thrombus, residual leak, positioning, surrounding structures, and pericardial effusion. Cardiac CT angiography (CCTA) is well suited to assess these non-invasively.

Methods and results We report our consecutive series of non-valvular atrial fibrillation patients who underwent CCTA post-LAA closure with Amplatzer Cardiac Plug (ACP), Amulet (second generation ACP), or WATCHMAN devices. Patients underwent CCTA typically 1–6 months post-implantation. Prospective cardiac-gated CCTA was performed with Toshiba 320-detector or Siemens 2nd generation 128-slice dual-source scanners, and images interpreted with VitreaWorkstation^{TM}. GFR <30 mL/min/1.73 m^2 was an exclusion. We assessed for device thrombus, residual LAA leak, device embolization, position, pericardial effusion, optimal implantation, and device lobe dimensions. Forty-five patients underwent CCTA at median 97 days post-LAA closure (18 ACP, 9 Amulet, 18 WATCHMAN). Average age was 75.5 ± 8.9 years, mean CHADS2 score 3.1 ± 1.3, and CHADS-VASc score 4.9 ± 1.6. All had contraindications to oral anticoagulation. Post-procedure, 41 (91.1%) were discharged on DAPT. There was one device embolization (ACP, successfully retrieved percutaneously) and one thrombus (WATCHMAN, resolved with 3 months of warfarin). There were two pericardial effusions, both pre-existing and not requiring intervention. Residual leak (patency) was seen in 28/44 (63.6%), and the mechanisms of leak were readily identified by CCTA (off-axis device, gaps at orifice, or fabric leak). Mean follow-up was 1.2 ± 1.1year, with no death, stroke, or systemic embolism.

Conclusion CCTA appears to be a feasible alternative to transoesophageal echocardiography for post-LAA device surveillance to evaluate for device thrombus, residual leak, embolization, position, and pericardial effusion.

Keywords left atrial appendage closure • cardiac CTA • Amplatzer cardiac plug • WATCHMAN • Amulet

Introduction

Percutaneous endovascular left atrial appendage (LAA) closure is increasingly performed worldwide for patients with atrial fibrillation (AF), especially those with contraindications to long-term oral anticoagulation (OAC). This is supported by guidelines from the European Society of Cardiology, which had implemented a class IIB recommendation for LAA closure in AF patients with high stroke risk and contraindications to long-term OAC.[1] The majority of procedures performed in Europe adhere to this guideline as reported by Tzikas of ~1000 patients who underwent LAA closure with the Amplatzer Cardiac Plug (ACP) (St Jude Medical, Maple Grove, MN, USA) device,[2] with 74% performed in patients with major bleeding or at high bleeding risk. Other reported indications were coronary stenting requiring dual antiplatelet therapy (DAPT; 23%), drug interaction (18%), stroke on warfarin (16%), renal or hepatic disease (13%), labile INR (7%), and risk of falls (7%). In Canada, LAA closure may be performed under the Health Canada special access program for patients with CHADS2 $\geq$1 and contraindications to long-term OAC. In the USA, the WATCHMAN (Boston Scientific Corporation, Natick, MA, USA) device is anticipated to receive FDA approval in early 2015 for patients who are eligible for OAC.

Given the projected more than doubling of the prevalence of AF to 15.9 million by 2050,[3] and since ~50% of patients eligible for OAC

* Corresponding author. Tel: +1 604 875 5547; Fax: +1 604 875 5563, E-mail: jsaw@mail.ubc.ca

are not receiving OAC in the community,[4,5] percutaneous LAA closure is expected to increasingly play a dominant role in stroke prevention for AF. Following LAA closure, routine surveillance with transoesophageal echocardiogram (TEE) is usually performed at 1–6 months post-procedure to evaluate for device-associated thrombus and residual leak into LAA (patency). The implications of these findings include the necessity to institute short-term anticoagulation (heparin or OAC) to dissolve device thrombus, and consideration of resumption of OAC or repeat LAA closure with a different device in the setting of large residual leak, respectively.

We have reported our preliminary experience of using cardiac computed tomography angiography (CCTA) as an alternative to TEE for post-procedural surveillance with the ACP device.[6] We showed that CCTA provided accurate assessment of the position and function of ACP compared with transthoracic echocardiography (TTE). Moreover, CT linear attenuating coefficient (degree of attenuation, Hounsfield) measurements allowed the detection of residual flow (patency) into the LAA. With the added advantage of non-invasiveness, we proposed that CCTA is a valid alternative to TEE for post-LAA closure surveillance, and this has become the routine imaging modality of choice for this indication at our institution. In this study, we report our experience with our consecutive series of patients who underwent endovascular LAA closure followed by CCTA for surveillance.

Methods

We report our consecutive series of patients who underwent CCTA for post-procedural surveillance after endovascular LAA closure with the ACP, Amulet (2nd generation ACP), or WATCHMAN devices at Vancouver General Hospital. All patients underwent baseline pre-planning imaging, typically with TEE at 4–8 weeks prior to their LAA closure procedure. Since November 2013, we also routinely performed baseline CCTA in addition to baseline TEE prior to LAA closures. GFR <30 mL/min/1.73 m^2 was an exclusion for CCTA. Indications for LAA closure were high stroke risk, non-valvular AF patients with contraindications for long-term OAC, with CHADS2 ≥1 and CHADS-VASc ≥2 (in accordance to the Canadian Cardiovascular Society and American College of Cardiology AF guidelines for OAC).[3,7]

Endovascular LAA closures were performed under TEE guidance and general anaesthesia. Transseptal punctures were performed inferoposteriorly at the fossa ovalis with SL1 (St Jude Medical) transseptal sheath and either BRK-1™ XS (St Jude Medical) or NRG® radiofrequency (Baylis Medical, Burlington, MA, USA) transseptal needles. Volume loading to achieve mean left atrial pressure ~15 mmHg and intravenous heparin was given to maintain ACT >250 s. A 5F marker pigtail was advanced into the LAA and cineangiograms taken for measurements. For ACP/Amulet, the widest landing zone was measured at ~10 mm inside the orifice for ACP and ~12 mm for Amulet. For WATCHMAN, the widest anatomic orifice (from circumflex artery inferiorly to a point 1–2 cm inside the tip of the pulmonary vein ridge superiorly) was recorded. Corresponding measurements on TEE were recorded after volume loading (and also on baseline CCTA if available). Device sizing was based on the widest landing zone dimensions and we typically upsize by 3–5 mm for ACP, 2–4 mm for Amulet, and 9–25% for WATCHMAN. The LAA shape was categorized into four major shapes using baseline CCTA and fluoroscopic images.[8]

The appropriately sized TorqueVue 45 × 45 delivery sheath or the WATCHMAN double-curve (or single-curve) sheath was advanced into the LAA typically using a pigtail as a rail. Our steps for LAA device deployment were previously described.[9] We strive to achieve the recommended five signs of proper deployment for ACP/Amulet: (i) tire-shaped lobe, (ii) separation of the lobe from the disc, (iii) concavity of the disc, (iv) axis of the lobe should be perpendicular to the neck axis at landing zone, and (v) width of the lobe is ≥2/3 within the circumflex artery. For WATCHMAN, the PASS (position, anchor, size, and seal) criteria were achieved prior to release. The presence of residual leak was assessed on TEE and cineangiograms after device release. The presence and degree of peri-device leak were measured on TEE with the Nyquist limit set low (<50 cm/s).

Post-procedure, patients were admitted overnight for observation. Antithrombotic regimen post-LAA closure typically consisted of DAPT (aspirin + clopidogrel) for 1–3 months, followed by aspirin alone indefinitely. Patients were followed clinically at 1–3 months and annually post-procedure. Patients routinely underwent post-procedural TTE the next day and at 1 month. In this cohort, CCTA was typically performed at 1–6 months for surveillance. One patient had CCTA performed the day post-procedure due to concern of device embolization on TTE. A subset of patients also underwent TEE post-procedure for follow-up, typically at 1–6 months.

Prospective systolic-triggered ECG synchronized cardiac-gated CCTA was performed with Aquilion One 320-detector (Toshiba Medical Systems Corporation, Tokyo, Japan) or Siemens 2nd generation 128-slice dual-source CT (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) scanners, and the digital images were interpreted with the VitreaWorkstation™ (Vital, Toshiba Medical Systems Group Company, The Netherlands). Our CT protocol for pre-planning and post-procedural LAA closures is described in *Table 1*. Our approach

Table 1 Vancouver General Hospital CT protocol for pre-planning and post-procedure for LAA closures with the Toshiba or Siemens scanners

Prospective cardiac-gated scans	Values
Tube potential	100 kV for BMI <30 120 kV if BMI >30
Tube current	300–500 mA with ECG tube current modulation
Scan direction	Cranial to caudal
Scan volume	Heart to diaphragm (14–16 cm)
Size	Images reconstructed to 0.5 and 0.6 mm with 40% overlap, 512 × 512 mm matrix, FOV 25cm
Detector collimation	320 × 0.5 mm Toshiba or 128 × 0.6 mm Siemens
Cardiac phase reconstruction	Relative triggering 30–40% of RR interval or absolute triggering 250 ms after R wave
Contrast bolus tracking	Sure Start (Toshiba) or Cardiac Definition (Siemens)
IV contrast injection (5 cc/s)	50–80 cc Optiray contrast, followed by 50 cc 30% contrast/70% saline mixture, and final 30 cc saline chaser
Heart rate	No restriction
Beta-blocker and nitrates	Not required

BMI, body mass index.

to digital post-processing reconstructions and interpretations of the pre-planning and post-procedural CCTA images has been previously described.[10] The processed images were assessed for atrial-side device thrombus, residual contrast leak (patency) into the LAA, device embolization, device positioning, pericardial effusion, the presence of the five signs of proper implantation, the presence of peri-device gap, and device lobe dimensions. Lobe compression (%) was calculated as: [(manufacturer device diameter − measured diameter)/manufacturer device diameter] × 100%. Residual leak (patency) into the LAA was assessed by measurements of the linear attenuation coefficient (Hounsfield unit, HU) in the LAA distal to the device and comparison of contrast density to surrounding cardiac chambers.

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of patients. Continuous variables were summarized as mean ± standard deviation, or median and inter-quartile range. Categorical variables were summarized as frequency and percentage. Categorical variables were compared using a χ^2 test or Fisher exact test, and continuous variables using the Student *t*-test or Mann–Whitney test. Statistical analyses were performed with the SPSS software (IBM SPSS version 20, New York).

Results

Forty-five patients with non-valvular AF underwent routine CCTA at a mean of 141.6 ± 130.5 days (median 97 days) post-LAA closure (18 ACP, 9 Amulet, 18 WATCHMAN) for device surveillance at our hospital. Baseline characteristics are described in *Table 2* and the indications for LAA closure in *Table 3*. The average age was 75.5 ± 8.9 years. The mean CHADS2 score was 3.1 ± 1.3, and CHADS-VASc score was 4.9 ± 1.6. The mean radiation dose for these patients with our standard post-LAA CCTA protocol was 5.3 ± 3.7 mSv. All patients had contraindications to long-term OAC: 42 (93.3%) had a history of major bleeding, 1 (2.2%) had oesophageal varices from chronic liver disease, 1 (2.2%) had high risk of falls due to seizures, and 1 (2.2%) had non-healing venous ulcers on warfarin requiring skin grafting. Eleven (24.4%) were on anticoagulation prior to LAA closure, including four who were found to have thrombus in the LAA on baseline pre-planning TEE (requiring OAC with subsequent proven thrombus resolution prior to LAA closure), and two on short-term, low-molecular weight heparins because of systemic embolization and pulmonary embolism prior to LAA closure.

Procedural success with device release was 100% (devices implanted are listed in *Table 4*), and there were no procedural stroke or major bleeding. There was one clinically insignificant trans-septal puncture-related pericardial effusion that did not require intervention. Post-procedure, 41 (91.1%) were discharged on DAPT [21 for 1 month (2 stopped aspirin or clopidogrel after a week because of bleeding), and 20 for 3 months]; only 1 patient was discharged on

Table 2 Baseline characteristics

Baseline characteristics	*n* = 45
Age (years)	75.5 ± 8.9
Sex (women)	20 (44.5%)
Height (cm)	167.8 ± 11.8
Weight (kg)	75.4 ± 19.3
BMI	26.6 ± 5.5
AF paroxysmal	14 (31.1%)
AF chronic	31 (68.9%)
History stroke/TIA	20 (44.4%)
CAD	18 (40.0%)
CHF	21 (47.7%)
Diabetes mellitus	13 (28.9%)
Hypertension	38 (84.4%)
Previous bioprosthesis	3 (6.7%)
Liver disease	6 (13.3%)
Renal failure (GFR $<$60 mL/min/1.73 m^2)	21 (46.7%)
LVEF (%)	52.8 ± 13.4
LVEF ≤40%	9 (20.0%)

Table 3 Indications for LAA closure and baseline antithrombotic agents

Indications for LAA closure	*n* = 45
CHADS2 score	3.1 ± 1.3
CHADS-VASc score	4.9 ± 1.6
HASBLED score	4.2 ± 1.0
Previous major bleeding	42 (93.3%)
Intracranial bleed	17 (37.8%)
Intraocular bleed	2 (4.4%)
Gastrointestinal bleed	21 (46.7%)
Retroperitoneal bleed	3 (6.7%)
Genitourinary bleed	1 (2.2%)
Transfusions	22 (48.9%)
High fall risk (seizure)	1 (2.2%)
Other reasons: oesophageal varices, non-healing venous ulcers	2 (4.4%)
Baseline antithrombotic	
None	16 (35.6%)
Aspirin	16 (35.6%)
Clopidogrel	3 (6.7%)
Aspirin + clopidogrel	1 (2.2%)
Warfarin	7 (15.6%)
Novel OAC	2 (4.4%)
Heparin	2 (4.4%)

Table 4 LAA device and size implanted

Device implanted	*n* = 45
Amplatzer Cardiac Plug (ACP)	18
Mean size	25.6 ± 3.4 mm
Amulet (second generation ACP)	9
Mean size	22.7 ± 3.2 mm
WATCHMAN	18
Mean size	27.5 ± 4.3 mm

warfarin (concomitant pulmonary embolism requiring short-term OAC), 2 on aspirin alone, and 1 on clopidogrel alone (*Table 5*).

There was one device-associated thrombus (2.2%) with WATCHMAN (*Figure 1*) found on routine CCTA follow-up at 78 days post-implant while on DAPT (planned DAPT for 3 months post-LAA closure) that was successfully treated with 3 months of warfarin without clinical sequelae. There was no residual LAA leak in this patient. There was one device embolization (2.2%) with ACP demonstrated on CCTA done 1 day post-implant, as the post-TTE showed device in a high posterior position (*Figure 2*); this was successfully retrieved percutaneously without consequence. Two patients had pericardial effusion (4.4%) on post-CCTA, which were both present pre-LAA closure that did not require intervention.

Residual leak (patency) was seen in 28/44 (63.6%) of the follow-up CCTA and was not significantly different with the various devices: ACP 12/17 (70.6%), Amulet 6/9 (66.7%), and WATCHMAN 10/18 (55.6%) (P = NS). Of note, only 6/44 (13.6%) had peri-device leak into the LAA on TEE at the end of the procedure. Of 23 patients who had both TEE and CCTA for post-procedural follow-up, CCTA patency was present in 12/23 (52.2%, of which 7/12 had TEE peri-device leak), and any TEE peri-device leak was present in 8/23 (34.8%). The radiodensity of the LAA was evaluated for contrast patency. Patent LAA (residual leak) had mean 352.2 ± 136.4 Hounsfield unit (HU) compared with mean 65.2 ± 17.4 HU in occluded LAA ($P < 0.0001$). In fact, all occluded LAA had radiodensity <100 HU, and contrast opacification <25% of the left atrium (*Figure 3*).

Table 5 Antithrombotic regimen post-LAA closure

Antithrombotic regimen post-LAA	*n* = 45
ASA + clopidogrel: 1 month	21 (46.7%)[a]
ASA + clopidogrel: 3 months	20 (44.4%)
ASA + clopidogrel: 6 months	1 (2.2%)
Warfarin	1 (2.2%)
ASA alone	2 (4.4%)
Clopidogrel alone	1 (2.2%)

[a]One stopped clopidogrel and one stopped aspirin after 1 week due to bleeding.

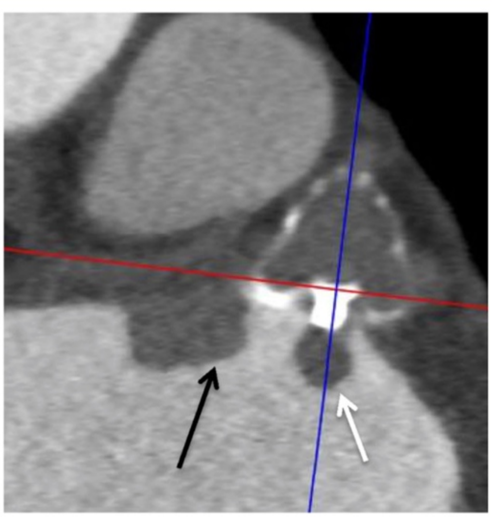

Figure 1 Contrast-enhanced CT images revealed an atrial-side device thrombus on a WATCHMAN device at the fabric insert (white arrow) and adjacent to the device (black arrow).

We evaluated the five signs of proper deployment with the ACP and Amulet devices on follow-up CCTA. The device lobe was tire shaped, and there was separation of the lobe and disk in all 26/26 of cases. The disc was concave in 22/26 (84.6%) of cases. In 24/26 (92.3%) cases, the lobe was at least 2/3 within the circumflex artery. However, only 12/26 (46.2%) of cases had good alignment of the lobes (*Figure 4*). Of the 14/26 (53.8%) of ACP/Amulet cases where the lobes were off-axis at the landing zone on CCTA, only 1/14 appeared to be off-axis on procedural TEE.

We evaluated potential contributing causes of residual leak into the LAA on CCTA. For ACP/Amulet, patent LAA had significantly higher proportion of off-axis lobes (13/18, 72.2%) compared with occluded LAA (1/8, 12.5%), $P = 0.007$. Furthermore, the mean maximum lobe compression on CCTA was 9.2 ± 6.8% in the patent LAA group and 16.1 ± 7.6% in the occluded LAA group ($P = 0.011$). The mean minimum lobe compression was not different in the patent LAA and occluded LAA groups (5.4 vs. 6.5%, P = NS). For WATCHMAN, the mean maximum and minimum lobe compressions on CCTA were not different between the patent LAA and occluded LAA groups, 14.8 vs. 14.2% (P = NS) and 9.2 vs. 8.9% (P = NS), respectively. However, all WATCHMAN devices with patent LAA on CCTA had demonstrable ostial peri-device gaps that led to contrast opacification of the LAA (*Figure 5*). Furthermore, one patient also had fabric leak through the WATCHMAN device at 90 days post-implant (*Figure 6*). Residual leaks were observed in all four major LAA shapes and were not statistically different [chicken-wing 11/18 (61.1%), windsock 9/14 (64.3%), cactus 5/7 (71.4%), cauliflower 3/6 (50.0%)].

A second repeat post-CCTA was performed in eight patients (ACP or Amulet) with LAA patency at a mean of 327.1 ± 170.4 days post-implant. Six (75.0%) had persistent leak, all had off-axis lobes and ostial gaps (all <5 mm). Two repeat CCTA showed subsequent occluded LAA, both initial LAA patency were presumed predominantly related to fabric leak as the first CCTAs were performed at 37 days (slight off-axis lobe) and 57 days (good lobe alignment) post-implant in these cases.

The mean duration of follow-up was 1.2 ± 1.1 years in this cohort. There was no occurrence of death, stroke, or systemic embolism. One patient had a transient ischaemic attack with transient speech disturbance, and investigations did not show new cerebral infarction, device thrombus, or leak. As mentioned, one patient had device-associated thrombus, which resolved with warfarin without clinical sequelae. Follow-up bleeding (non-procedural) occurred in 4/45 (8.9%) of patients; 1 minor bleed while on warfarin, 2 occurred 1 week post-procedure while on DAPT (lower GI bleeds requiring discontinuation of one antiplatelet agent), and 1 required transfusion for unexplained haemoglobin drop to 76 mg/dL while on DAPT (planned 3-month therapy).

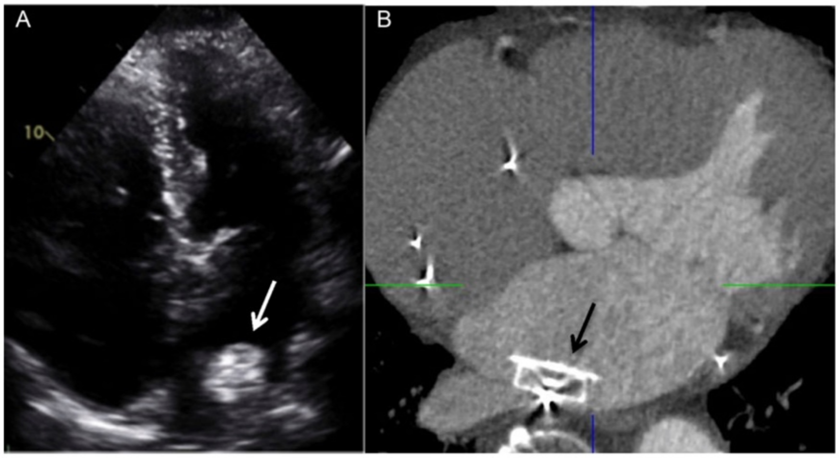

Figure 2 Embolized ACP device in the left atrium that was lodged posteriorly, seen on (*A*) TTE (white arrow) and confirmed on (*B*) contrast-enhanced four-chamber CT image (black arrow).

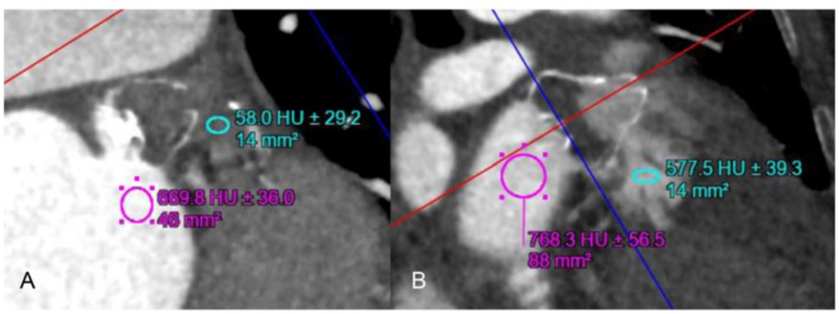

Figure 3 Linear attenuation coefficient measured in Hounsfield units on contrast-enhanced CT images of the LAA after WATCHMAN closures showing (*A*) complete occlusion of the LAA (no residual contrast patency, 58.0 HU) and (*B*) patent LAA (residual contrast patency, 577.5 HU).

Discussion

Our study showed that CCTA is a useful, non-invasive post-procedural surveillance test for endovascular LAA closure devices in patients with contraindications for OAC, with safe long-term clinical outcomes. We were able to evaluate for atrial-side device thrombus, residual leak (patency) into the LAA, device embolization, device position, pericardial effusion, the presence of the five signs of proper deployment, and device lobe and compression dimensions.

We found that endovascular LAA devices were well visualized on CCTA in the LAA, with high spatial resolution that enabled assessment of device angles and positions. The presence of pericardial effusion and atrial-side device thrombus can be readily identified on CCTA. Embolized devices in the heart chambers can also be clearly visualized on CCTA, as in our case of ACP embolization into the left atrium that was successfully retrieved percutaneously. CCTA is also useful to visualize embolized devices in the left ventricle and assess if they are trapped by papillary muscles and trabeculations, which may be relevant when considering percutaneous retrieval.

The linear attenuation coefficient within the LAA can also be readily measured in Hounsfield units and ascertained for residual LAA patency from contrast leak. In fact we found that all occluded LAA have an attenuation of <100 HU and <25% of the contrast opacification of the left atrium. These thresholds have become our criteria to evaluate for LAA patency after percutaneous closure.

Using CCTA, we found that a large proportion of patients (63.6%) had residual LAA patency after ACP, Amulet, and WATCHMAN closures. This is contrary to reports based upon TEE follow-up that showed much lower incidence of residual leak with ACP, up to 11.9% in the report by Tzikas.[2] Other series have shown that leak

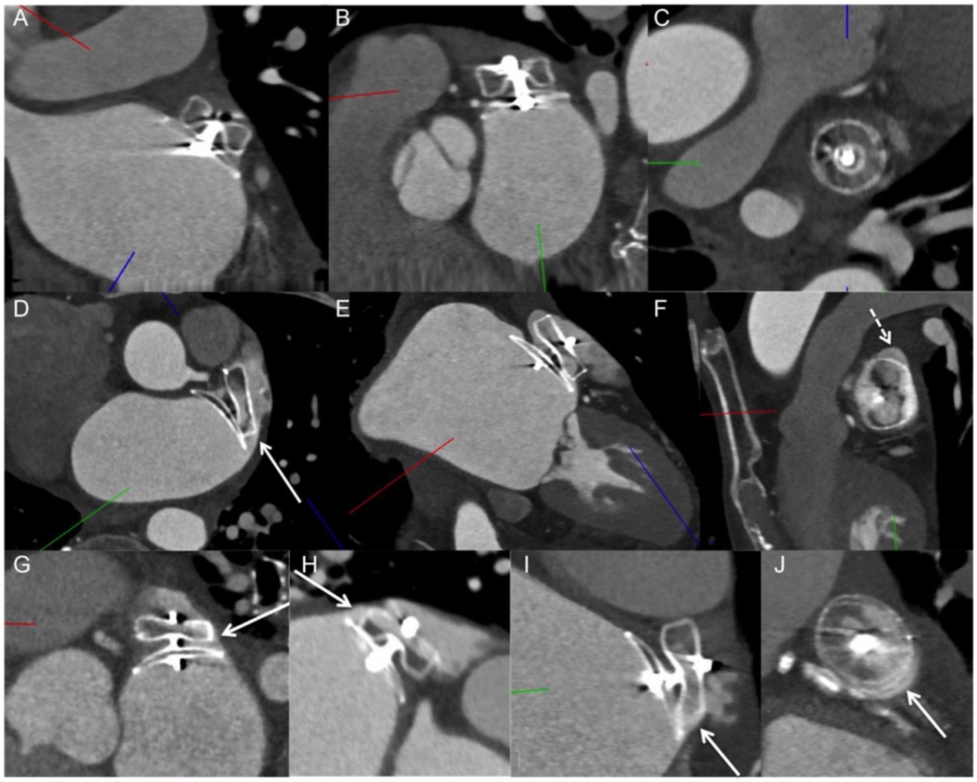

Figure 4 Contrast-enhanced CT images: (*A–C*) Amulet case with good alignment of lobe perpendicular to the neck of the LAA, with complete occlusion of the LAA. (*D–F*) ACP case with off-axis lobe (not perpendicular to the LAA neck) (white arrow in D) and superior gap (dashed arrow in F) causing residual contrast patency of LAA. (*G*) Example of ACP case with off-axis on the right side (arrow) with contrast leak through that edge, whereas there was no lobe leak on the left side. (*H*) Example of ACP case with off-axis lobe and contrast leak through the superior edge (arrow) (bottom half of lobe with no contrast opacification). (*I*) ACP lobe off-axis inferiorly (arrow) with contrast leaking through the edge and gap (arrow in *J*).

>5 mm has not been documented with ACP; leak of 3–5 mm was reported in 0–1% of cases,[11] and leak <3 mm was reported in 0–16%.[12–14] The clinical significance of residual leak with the ACP device has not been explored. With the WATCHMAN device, residual leak was shown to occur in a significant proportion of patients on TEE follow-up, with some degree of leak seen in 32% of cases in the PROTECT-AF study at 12-month follow-up (36.8% >3 mm and 63.2% ≤3 mm). In this study, residual leak was not associated with increased risk of subsequent thromboembolism;[15] however, the event-rate was low and these findings were considered hypothesis generating. CCTA appears to be a much more sensitive modality to detect residual leak compared with TEE, and the clinical significance of CCTA-detected residual leak into LAA after closure with the ACP/Amulet or WATCHMAN devices is unknown and needs further study.

With the superior resolution of CCTA, we were able to clearly evaluate the five signs of proper deployment as defined by the instructions for use for the ACP/Amulet devices on CCTA. Interestingly, we identified a large proportion of cases where the alignment of the device lobe was suboptimal as assessed on CCTA, even though they were deemed to be well aligned based upon the final procedural TEE images. This highlights the challenges with TEE in depicting the three-dimensional LAA structure; alternatively, the devices may have shifted in position since implantation. In addition, a larger proportion of patients with residual patent LAA had suboptimal alignment (off-axis at the landing zone) compared with patients with occluded LAA. A schematic explaining the mechanism of lobe off-axis leak with this device is depicted in *Figure 7*. Given that the polyester fabric sewn into the lobe is thin and proximally located within the lobe, contrast can readily diffuse through the edges of the lobe when malapposed at the landing zone. Thus, achieving proper alignment is not only important to minimize device embolization, but also promote complete LAA occlusion with this device. The use of CT co-registration during percutaneous LAA closure to improve ACP/Amulet device alignment at the landing zone may be useful.

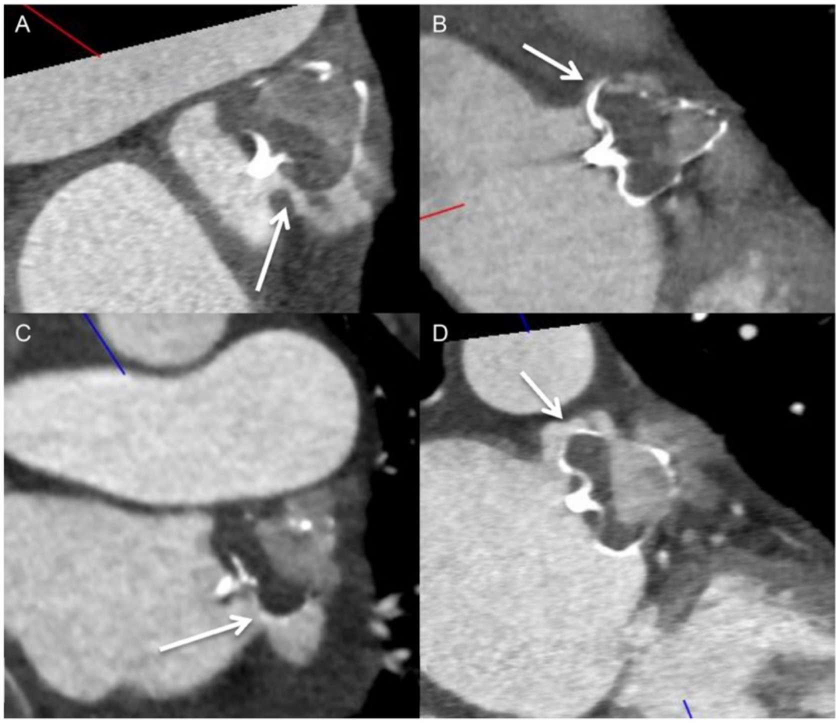

Figure 5 Contrast-enhanced CT images of four different examples of WATCHMAN implanted devices with ostial peri-device gaps with residual contrast patencies of the LAA.

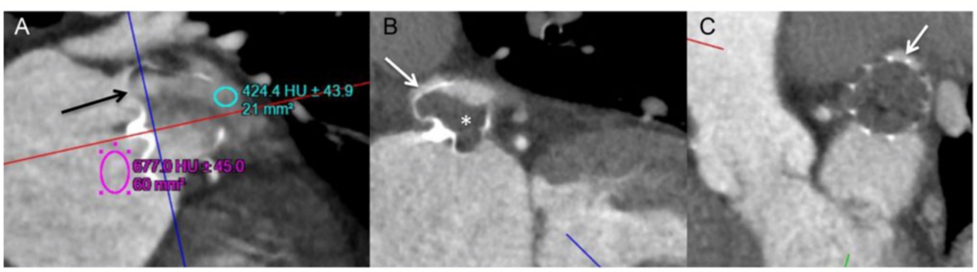

Figure 6 Contrast-enhanced CT images: (*A*) example of fabric leak through an incompletely endothelialized WATCHMAN device, with contrast seeping through the fabric at the proximal shoulder of the device (black arrow). (*B* and *C*) In comparison, this WATCHMAN device had no contrast opacification of the proximal shoulder of the device (*), but instead contrast into the LAA came through the superior gap (white arrows in B and C).

For the ACP/Amulet device, we found that patients with residual LAA patency had lower mean maximum lobe compression (9.2%) compared with patients with occluded LAA (16.1%) on CCTA. Moreover, those with residual leak were also more likely to have sub-optimal alignment (off-axis lobe) (72.2%) compared with those without leak (12.5%). Thus, achieving adequate lobe compression and optimal lobe alignment appear to reduce residual leak. This was similarly described by Jaguszewski *et al.*[16] in their smaller 24-patient ACP series, where they found residual contrast patency in 62%, and also found that occluded LAA had greater lobe compression (>10%) and perpendicular lobe axis.

For the WATCHMAN device, when deployment was optimal according to the instruction for use PASS criteria, we found that device compression measurements were not different among

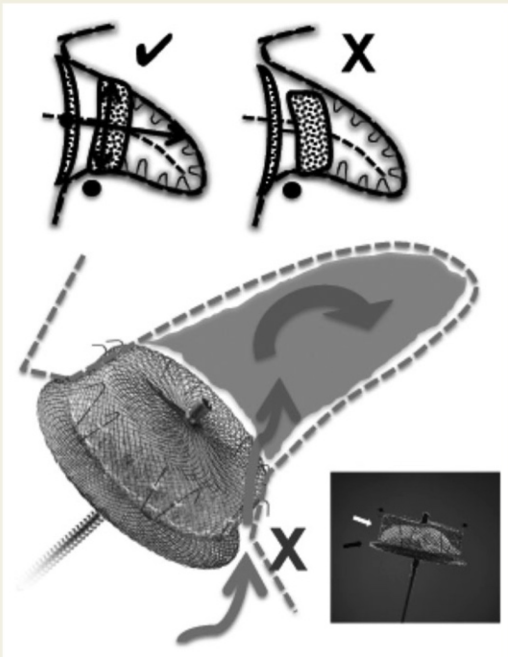

Figure 7 Schematic showing how an off-axis ACP/Amulet lobe results in contrast diffusing through the side edge of the lobe (not covered by polyester fabric, which is a thin layer sewn to the proximal part of the lobe). Proper alignment of the lobe entails perpendicular apposition of the lobe against the wall of the LAA at the neck (✓); poor alignment with the lobe is off-axis at the LAA neck (X).

patients with occluded or patent LAA on CCTA. On the other hand, all WATCHMAN patients with residual LAA patency had peri-device gaps at the LAA ostia. This highlights the importance of minimizing peri-device leaks during the procedure, which will presumably correspond to lower incidence of contrast patency on CCTA. In addition, one patient had fabric leak at 90 days post-implantation, which contrasts with other WATCHMAN patients without fabric leak, highlighting the variability in timing of complete endothelialization in humans. In canine models, complete endothelialization was shown to occur within 28–45 days; however, the endothelialization process appears to be accelerated in dogs.[17,18]

In summary, from our experience, it appears that there are three underlying important mechanisms of residual LAA contrast patency after endovascular closure: (i) off-axis lobe with the ACP/Amulet device, enabling contrast diffusion across non-fabric covered sides of the lobe; (ii) ostial peri-device LAA gaps, especially important with the WATCHMAN device as it is a single-lobe occluder without a disc that covers the echocardiographic orifice; (iii) fabric leak through non-endothelialized portion of the devices. Since two of our ACP patients with fabric leak on their initial CCTA (performed <60 days post-implant) were subsequently found to have occluded LAA on repeat CCTA, it would be preferable to scan patients at least 3 months post-LAA closure with endovascular devices to minimize demonstrating leaks due to incomplete endothelialization.

The mean radiation dose with our standard post-LAA CCTA protocol was only 5.3 mSv, which is considered low and equivalent to annual background radiation dose of 3–5 mSv. To put in context, the potential risk of fatal cancer with 10 mSv exposure is only 1 : 2000. In addition, the 2011 position statement from the Radiologic Society of North America and the American Association of Physicists in Medicine stated that the risks of medical imaging at effective doses <50 mSv for single procedures are too low to be detectable and may be non-existent. Thus, the radiation dose incurred by our post-surveillance CCTA protocol is low and acceptable.

Limitations

Our study is limited by being a small retrospective series of patients who underwent CCTA after endovascular LAA closure, with low clinical events. Only a subset of patients had both TEE and CCTA post-procedure. Furthermore, the clinical significance of CCTA residual LAA contrast patency is unknown.

Conclusions

CCTA is a feasible, non-invasive post-procedural surveillance imaging modality after endovascular LAA closure to evaluate for atrial-side device thrombus, residual leak (and mechanisms of leak), device embolization, device position, and pericardial effusion. Thus, CCTA may a suitable alternative to TEE for post-LAA closure surveillance; however, the clinical significance of residual LAA patency on CCTA should be further explored in larger studies.

Conflict of interest: None declared.

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Changes in Left Atrial Appendage Dimensions Following Volume Loading During Percutaneous Left Atrial Appendage Closure

Ryan J. Spencer, MD, Peggy DeJong, MD, Peter Fahmy, MD, Mathieu Lempereur, MD, Michael Y.C. Tsang, MD, Kenneth G. Gin, MD, Pui K. Lee, MD, Parvathy Nair, MD, Teresa S.M. Tsang, MD, John Jue, MD, Jacqueline Saw, MD

ABSTRACT

OBJECTIVES This study sought to determine whether volume loading alters the left atrial appendage (LAA) dimensions in patients undergoing percutaneous LAA closure.

BACKGROUND Percutaneous LAA closure is increasingly performed in patients with atrial fibrillation and contraindications to anticoagulation, to lower their stroke and systemic embolism risk. The safety and efficacy of LAA closure relies on accurate device sizing, which necessitates accurate measurement of LAA dimensions. LAA size may change with volume status, and because patients are fasting for these procedures, intraprocedural measurements may not be representative of true LAA size.

METHODS Thirty-one consecutive patients undergoing percutaneous LAA closure who received volume loading during the procedure were included in this study. After an overnight fast and induction of general anesthesia, patients had their LAA dimensions (orifice and depth) measured by transesophageal echocardiography before and after 500 to 1,000 ml of intravenous normal saline, aiming for a left atrial pressure >12 mm Hg.

RESULTS Successful implantation of LAA closure device was achieved in all patients. The average orifice size of the LAA at baseline was 20.5 mm at 90°, and 22.5 mm at 135°. Following volume loading, the average orifice size of the LAA increased to 22.5 mm at 90°, and 23.5 mm at 135°. The average increase in orifice was 1.9 mm ($p < 0.0001$). The depth of the LAA also increased by an average of 2.5 mm after volume loading ($p < 0.0001$).

CONCLUSIONS Intraprocedural volume loading with saline increased the LAA orifice and depth dimensions during LAA closure. Operators should consider optimizing the left atrial pressure with volume loading before final device sizing. (J Am Coll Cardiol Intv 2015;8:1935–41) © 2015 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) is thought to account for 15% to 20% of all ischemic strokes and, due to an increasingly aging population, is growing in prevalence. Studies predict that by the year 2050, there will be between 12 and 16 million patients with AF in the United States alone (1). AF is associated with a 4- to 5-fold increase risk of ischemic stroke, this being its most devastating complication (2). Although warfarin and the novel oral anticoagulants reduce the risk of ischemic stroke in many patients with AF, they carry significant risks of bleeding and may not be tolerated by all. Accordingly, alternative treatment strategies for reducing the bleeding complications associated

From the Division of Cardiology, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada. Dr. Gin is on the advisory boards of Bayer, Pfizer, and Boehringer Ingelheim. Dr. Saw has received unrestricted research grant support from the Canadian Institutes of Health Research, University of British Columbia Division of Cardiology, AstraZeneca, Abbott Vascular, St. Jude Medical, Boston Scientific, and Servier; speaker honoraria from AstraZeneca, St. Jude Medical, Boston Scientific, Bayer, and Sunovion; consultancy and advisory board honoraria from AstraZeneca, St. Jude Medical, Boston Scientific, and Abbott Vascular; and proctorship honoraria from St. Jude Medical and Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

ACP = Amplatzer Cardiac Plug

AF = atrial fibrillation

CT = computed tomography

IV = intravenous

LAA = left atrial appendage

TEE = transesophageal echocardiography

with lifelong anticoagulation have been widely sought.

Two randomized controlled trials have shown the safety and efficacy of percutaneous left atrial appendage (LAA) closure, and this procedure has emerged as an alternative for patients with AF and significant stroke risk, who are at increased risk of bleeding (3,4). Percutaneous LAA closure has obvious benefits, including removing the need for ongoing adherence to anticoagulation, eliminating monitoring, decreasing medication interactions, and reducing ongoing bleeding risk. Minimizing periprocedural complications of percutaneous LAA closure is critical in order to offer a favorable risk-benefit ratio to patients. These include access site complications, pericardial effusion and tamponade, residual leak around the device, and embolization of the implanted device. Appropriate sizing of the currently available implantable devices is paramount for both procedural success and to reduce periprocedural complications. Choosing the correctly sized device relies on accurate measurement of LAA size.

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The 2 most widely implanted LAA closure devices are the WATCHMAN (Boston Scientific, Natick, Massachusetts) and the Amplatzer Cardiac Plug (ACP)/ Amulet (St. Jude Medical, Plymouth, Minnesota). Choosing the correct device size is important to achieve proper apposition of the device and its hooks against the LAA wall. An undersized device may result in embolization or residual leak, whereas aggressive oversizing may cause tamponade, or device embolization due to inadequate engagement of the hooks. Hence, accurately measuring the LAA size is integral to safe percutaneous LAA closure. Both transesophageal echocardiography (TEE) and computed tomography (CT) have been used pre-procedurally to measure the depth and orifice diameter of the LAA, and been shown to correlate reasonably well (5). Although CT is usually undertaken in a euvolemic state, pre-procedural and intra-procedural TEE involves at least 6 h of fasting. This may affect the volume status of the patient, which in turn may affect LAA size. Previous studies in animals and patients in sinus rhythm have shown the LAA to be more compliant than the left atrium (6,7), supporting a hypothesis that clinically significant increases in LAA size may occur with volume loading. A single canine study demonstrated small increases in LAA size after volume loading (8), leading to speculation that LAA measurements used for percutaneous closure may be affected by volume status and the fasting state (5).

We hypothesized that volume loading during the procedure (to overcome the fluid restriction pre-procedure) affects LAA dimensions, and thus we routinely administer intravenous (IV) normal saline before sizing measurements. Our study aims to assess the impact of an intravenous fluid bolus on LAA size, and thus determine whether there is clinical utility in optimizing fluid status before measuring maximum LAA dimensions.

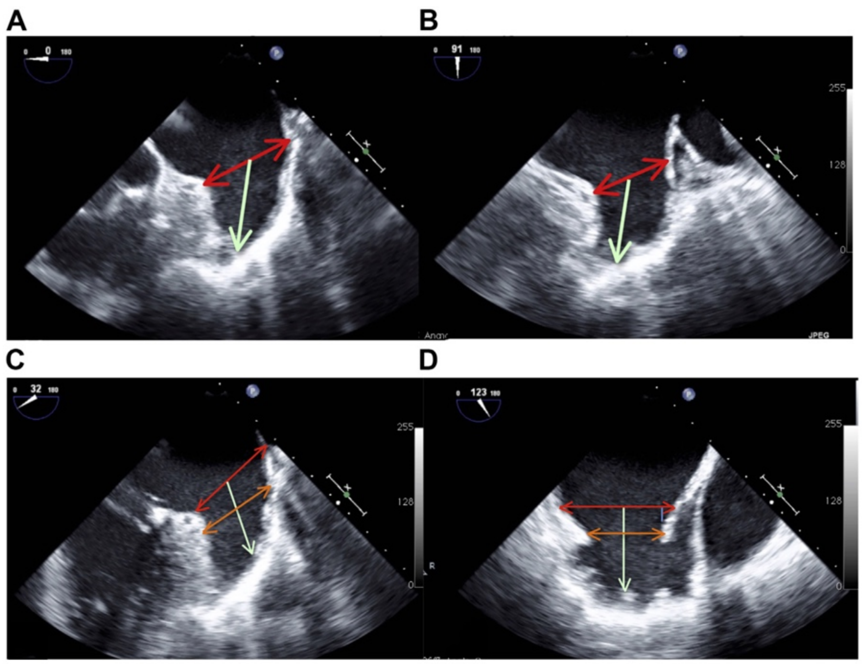
METHODS

Thirty-one consecutive patients who underwent percutaneous LAA closure (with either the ACP or WATCHMAN devices) at our center between March 2014 and May 2015 were included in this study. All patients received IV normal saline targeting a left atrial pressure of >12 mm Hg. Indications for LAA closure were nonvalvular AF with contraindications to long-term anticoagulation, with CHADS2 ≥1 and CHADS-VASc ≥2 (in accordance with the American College of Cardiology and the Canadian Cardiovascular Society AF guidelines for oral anticoagulation) (9,10). All patients underwent general anesthesia after a minimum of 6 hours of fasting.

A Philips IE33 echocardiography machine and X7-2t TEE probe (Philips, Andover, Massachusetts) were used to obtain baseline measurements of the LAA orifice diameter and depth before normal saline administration. Measurements were taken as per the manufacturer's guidelines. For ACP/Amulet, the widest landing zone was measured at ~10 mm inside the orifice for ACP and ~12 mm for Amulet. For WATCHMAN, the widest anatomic orifice (from the circumflex artery inferiorly to a point 1 to 2 cm inside the tip of the pulmonary vein ridge superiorly) and the LAA depth were recorded (**Figure 1**). For the purpose of this study, we measured the LAA orifice and depth at 90° and 135°, because these usually produce the largest dimensions; and utilized the WATCHMAN orifice definition to measure the orifice diameter (**Figures 1 and 2**). Measurements were taken when LAA width was greatest, which usually occurs at end-systole.

Following baseline measurements, a 500- to 1,000-ml IV bolus of normal saline was infused. One liter was given unless the patient had known left ventricular dysfunction or there were pre-operative concerns of volume overload, in which case 500 ml was given instead. We proceeded with transseptal puncture during the saline infusion, and the left atrial pressure was measured after transseptal access was achieved. After the infusion was completed, and the left atrial pressure was >12 mm Hg, we then repeated the LAA

FIGURE 1 Measuring the Orifice and Depth of the LAA for Percutaneous Closure



(A and B) A WATCHMAN device requires measuring from a point adjacent to the circumflex artery to the widest point 1 to 2 cm down from the tip of the pulmonary vein ridge at 0°, 45°, 90°, and 135°. **(C and D)** Similar measurements are required for the ACP/Amulet devices although the orifice is defined as the tip of the pulmonary vein ridge, and an extra measurement, 10 to 12 mm down from the orifice, is also required. ACP = Amplatzer Cardiac Plug; LAA = left atrial appendage; **(A and B): Red** = WATCHMAN ostium measurement zone; **green** = WATCHMAN depth measurement; **(C and D): Red** = echocardiographic orifice; **orange** = ACP landing zone; **green** ==ACP depth measurement.

measurements on TEE. Saline infusion occurred during typical procedural steps and did not delay procedural completion. Given that mechanical ventilation may reduce pre-load, we ensured that the left atrial pressure was >12 mm Hg in addition to volume loading alone, before repeating TEE measurements.

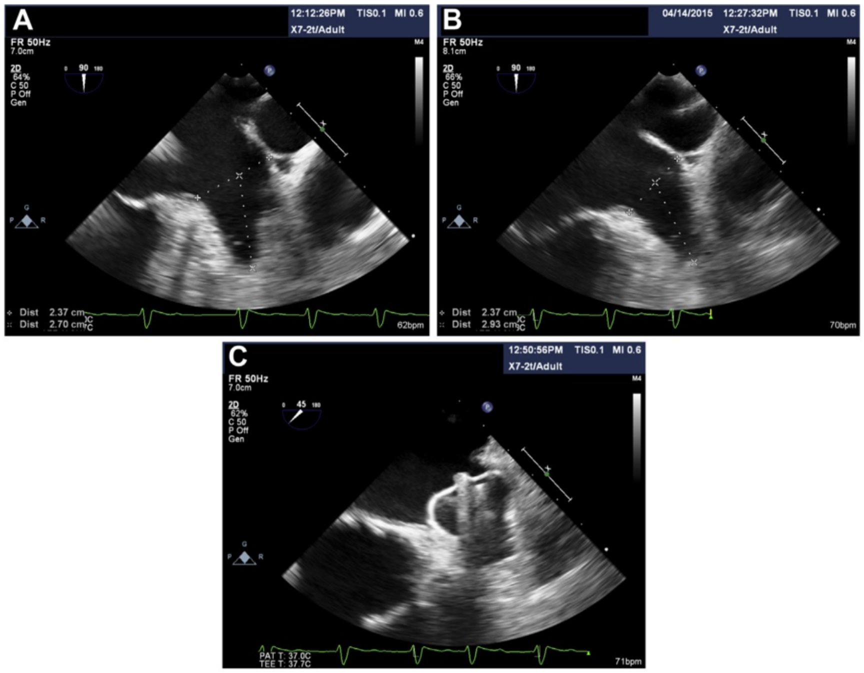
Device size selection was based on the widest orifice/landing zone dimensions measured post-fluid bolus, incorporating an upsize by 3 to 5 mm for ACP and 9% to 25% for WATCHMAN. Patients then underwent LAA closure with either a WATCHMAN or ACP/Amulet, according to our previously described protocol (11). In an effort to reduce bias and improve accuracy, all LAA TEE images were reread utilizing a commercially available offline workstation (Xcelera, Philips, Andover, Massachusetts) by 1 of 3 echocardiographers (R.S., M.T., J.J.) blinded to the stage of the procedure. Only these blinded measurements were used in this study.

STATISTICAL ANALYSIS. Descriptive statistics were used to describe the baseline characteristics of patients. Continuous variables were summarized as mean ± SD or median and interquartile range. Categorical variables were summarized as frequency and percentage. Continuous variables were compared using the paired Student *t* test. Statistical tests were 2-sided, and a p value <0.05 was considered significant. Statistical analyses were performed with the SPSS software (IBM SPSS version 20, Armonk, New York).

RESULTS

All 31 patients had underlying nonvalvular AF with contraindications to anticoagulation. The average age of the patients was 77 ± 7 years, and the mean CHADS2 score was 3.0 ± 1.4. Baseline characteristics are described in Table 1. All patients achieved mean left atrial pressure >12 mm Hg (28 of 31, or 90.3%, had a left atrial pressure of at least 15 mm Hg) after volume loading. Left atrial pressures were not obtained before volume loading, because all baseline TEE

FIGURE 2 **LAA Measurements Made Before Closure With a WATCHMAN Device**



(A) Measurements made before the fluid bolus. **(B)** Measurements post-fluid bolus. **(C)** Final image after WATCHMAN deployment showing occlusion of the LAA. LAA = left atrial appendage.

measurements were taken before transseptal puncture to minimize procedural time. All patients had 90° pre- and post-bolus images available for blinded analysis. Four patients had post-bolus 135° images that were either obscured by the delivery catheter or not stored, leaving 31 90° measurements and 27 135° measurements for analysis.

The average orifice size of the LAA at baseline was 20.5 ± 4.5 mm at 90°, and 22.5 ± 4.4 mm at 135°. Following volume loading, the average orifice size of the LAA increased to 22.5 ± 4.0 mm at 90°, and 23.5 ± 4.7 mm at 135° (**Figure 3A**). The average depth of the LAA at baseline was 24.5 ± 5.4 mm at 90°, and 22.7 ± 5.6 mm at 135°. After volume loading, the average depth of the LAA was 26.1 ± 5.0 mm at 90°, and 25.0 ± 5.3 mm at 135° (**Figure 3B**). The average increase in orifice was 1.9 mm ($p < 0.0001$), and increase in depth was 2.4 mm ($p < 0.0001$) (**Table 2**). Twenty-nine of the 31 patients had an increase in width measurements after volume loading. Analysis by sex and by age quartiles did not detect any significant interactions.

All patients proceeded to successful LAA closure with no periprocedural stroke or major bleeding. No pericardial effusions or congestive heart failure occurred. Four of the 31 patients were noted to have small peridevice leaks (<3 mm) on their procedural TEE. Thirty of the 31 patients were discharged the day after the procedure. One device embolization occurred with a 24-mm ACP device. This was discovered when routine transthoracic echocardiography the morning after the procedure suggested an unusual location of the device in the left atrium. This device was successfully retrieved percutaneously with no complication. This patient was delirious and

TABLE 1 **Baseline and Procedural Characteristics**

Age, yrs	76.7 ± 6.7
Male	55%
CHADS2 score	3.0 ± 1.4
Final LA pressure after volume, mm Hg	17.6 ± 3.5
IV normal saline given, ml	855 ± 227

Values are mean ± SD or %.
IV = intravenous; LA = left atrial.

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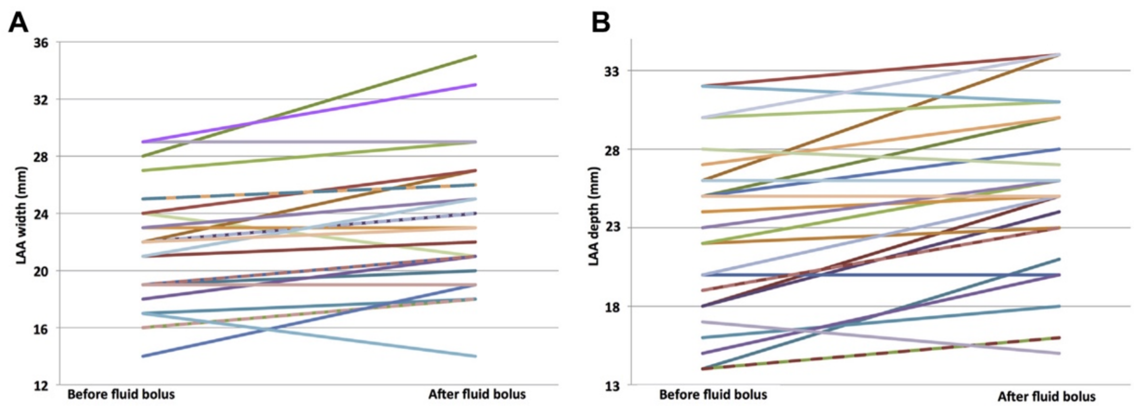
FIGURE 3 Graph Showing Change in LAA Orifice Width and Depth



(A) Graph showing change in LAA orifice width (measured at 135°) after infusion of normal saline bolus. n = 27 (data were not recorded for 4 patients at 135°). Each **line** represents 1 patient (**long-dashed line** represents 3 patients; **short-dashed lines** represent 2 patients). **(B)** Graph showing change in LAA depth (measured at 135°) after infusion of normal saline bolus. n = 27 (data were not recorded for 4 patients at 135°). Each **line** represents 1 patient, **dashed lines** represent 2 patients. LAA = left atrial appendage.

combative during the evening after the procedure and required 4-point restraints. The aggressive physical movements in the setting of slight device malapposition were felt to be contributing factors leading to embolization, as opposed to inaccurate device sizing.

DISCUSSION

In this study, we found that LAA width and depth consistently increased by an average of ~2 mm after volume loading during general anesthesia. These results support the hypothesis that LAA size can vary with volume loading. This size difference, although relatively small, still represents an ~10% increase in the LAA dimensions following fluid bolus. This is clinically relevant when considering the appropriate device size for a given patient, because this 10% size increase typically corresponds to upsizing of the currently available devices by an entire size. For example, the WATCHMAN device comes in 5 sizes (21, 24, 27, 30, and 33 mm) and a device 10% to 20% larger than the measured orifice width is typical chosen. A 2-mm increase in the measured orifice width is likely to result in selecting a device that is 1 size larger than if measurements without volume loading were used. Theoretically, this more accurate sizing will result in better device stability and potentially lower residual LAA leak. Although the clinical significance of residual leak has not yet been established, many believe that large residual LAA leaks can contribute to higher stroke risk, as was seen with surgical LAA closure (12,13).

Although the fasting state may represent the natural state for many patients in the early hours of the day, the optimal values when choosing a closure device are the largest possible LAA dimensions. Establishing the physiological maximum width of the LAA enables the operator to select the largest device that can be accommodated by the LAA, which is likely to have the least risk of leak, embolization, and perforation. Overzealous oversizing should be avoided because this increases the risk of perforation, and may also lead to device embolization if the hooks fail to engage the LAA wall properly. Therefore, selecting a device that remains 8% to 20% compressed when the LAA is at its maximal size is of paramount importance. Our strategy of volume loading of 500 to

TABLE 2 LAA Width and Depth Measurements Before and After Volume Loading

	Before Fluid Bolus	After Fluid Bolus	p Value
90° width, mm	20.5 ± 4.5	22.5 ± 4.0	<0.001
90° depth, mm	24.5 ± 5.4	26.1 ± 5.0	<0.01
135° width, mm	22.5 ± 4.4	23.5 ± 4.7	<0.001
135° depth, mm	22.7 ± 5.6	25.0 ± 5.3	<0.001

Values are mean ± SD.
LAA = left atrial appendage.

1,000 ml during the procedure and aiming for a left atrial pressure >12 mm Hg is simple to adhere to and tolerated by all patients. This strategy maximizes the measurements for device selection.

Our findings suggest that a similar volume loading strategy may be useful for the baseline pre-procedural TEE (days to weeks before the procedure) in order to optimize LAA measurements. Because most echocardiographic laboratories require patients to fast for TEE, the measured dimensions may be similarly affected, and consideration should be given to volume loading before measuring LAA dimensions. The difference in volume status may also explain the small differences between CT angiography and TEE measurements seen in previous studies (5), because most patients are not required to restrict fluids before CT.

STUDY LIMITATIONS. These findings should be viewed in the context of the study's limitations. Our sample size was relatively small, and although a significant difference was found, caution is required when studying such small groups. Accurate echocardiographic measurement of the LAA is challenging, and obtaining identical views before and after volume loading is not always possible. Although the differences seen were small, they were consistent across the group of patients studied, and are supported by previous studies (6–8). In an effort to reduce possible bias, TEE measurements were made by echocardiographers experienced in assessing LAA size for percutaneous closure, who were blinded to the fluid status of the patient. Because we were unable to measure pre-bolus left atrial pressure, it is possible that a few patients may have started with an adequate volume status, potentially explaining the smaller LAA size change seen in some patients. From a practical perspective, because all patients fasted before the procedure and were likely to receive IV fluid after induction of anesthesia, delaying LAA measurements until after fluid administration and achievement of adequate LA pressure seems prudent. Of note, significant contrast administration during the procedure has the potential to increase LAA dimensions and could have confounded our repeat LAA measurements; however, these measurements were typically performed before contrast administration. Finally, we were not able to assess the effect of volume loading on clinical outcomes, as there was no comparative group who did not undergo volume loading.

CONCLUSIONS

Given the importance of pre-implantation LAA measurements for accurate device sizing and the increase in LAA dimensions observed with volume loading in this study, operators should consider ensuring that patients are adequately volume loaded before making final measurements and device sizing choices during percutaneous LAA closure. The clinical outcomes of this simple intervention should be further explored in larger prospective studies focusing on procedural safety and efficacy.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Jacqueline Saw, Division of Cardiology, 2775 Laurel Street, Level 9, Vancouver General Hospital, Vancouver, British Columbia V5Z1M9, Canada. E-mail: jsaw@mail.ubc.ca.

PERSPECTIVES

WHAT IS KNOWN? The safety and efficacy of percutaneous LAA closure relies on accurate device sizing, which necessitates accurate measurement of LAA dimensions. LAA size may change with volume status, and as patients are fasting for these procedures, intraprocedural measurements may not be representative of true LAA size.

WHAT IS NEW? This study provides evidence that volume loading during percutaneous LAA closure increases the orifice width and depth of the LAA by ~2 mm, which can significantly impact device size selection.

WHAT IS NEXT? Further studies evaluating procedural outcomes in patients undergoing LAA closure with and without periprocedural volume loading and optimizing left atrial pressure, will help clarify the clinical impact of volume loading.

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KEY WORDS left atrial appendage, left atrial appendage closure, transesophageal echocardiography, WATCHMAN

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REBUTTAL

WILEY

Rebuttal with regards to "Device-associated thrombus formation after left atrial appendage occlusion: A systematic review of events reported with the Watchman, the Amplatzer Cardiac Plug and the Amulet"

M. Lempereur, MD[1] | A. Aminian, MD[2] | J. Saw, MD[3]

[1]Division of Cardiology, University Hospital of Liège, Liège, Belgium
[2]Division of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium
[3]Division of Cardiology, University of British Columbia, Vancouver General Hospital, Vancouver, British Columbia, Canada

Correspondence
M. Lempereur, MD, University Hospital of Liège, 4000 Liège, Belgium.
Email: matlempereur@gmail.com

We thank Koniari et al. for their interest and comments on our article. We agree that allergic reaction to nitinol is an important aspect to consider, as nitinol is widely used in interventional cardiology devices (coronary stents, atrial septal defect (ASD) or patent foramen ovale (PFO) occluders, left atrial appendage (LAA) occluders, TAVI) and could potentially lead to adverse clinical consequences. Nitinol is a nickel-titanium alloy and nickel is a potential sensitizer which can give rise to hypersensitivity-associated events. However, with conflicting reports in the setting of percutaneous coronary intervention [1–3], there is currently little evidence that nickel allergy has a cause-effect relationship with adverse cardiovascular clinical events. There are indeed reported cases of symptoms of allergic reaction to metal in case of PFO or ASD closure, mainly related to the occurrence of postimplantation chest discomfort or palpitations but without any evidence of an associated increase in the occurrence of device-associated thrombosis (DAT) [4–6]. Moreover, in a large registry including 418 patients implanted with an Amplatzer ASD or PFO device, the rate of DAT was 0% at 1 month TEE follow-up [7].

As reported in our article, DAT after LAA occlusion is most likely multifactorial with risk factors including patient, device and anatomic characteristics. The possibility that nickel allergy may result in DAT cannot be firmly excluded. However, this is most likely a rare etiology as reported in PFO/ASD devices [7–9]. Furthermore, in reported cases of DAT, the presence of postimplantation allergic reaction was not described. To the best of our knowledge, in the rare cases where an LAA occluder had to be explanted, there was no available histologic finding implicating an allergic reaction. The Amplatzer Cardiac Plug and the Amulet (St. Jude Medical/Abbott, St Paul, MN, USA) are composed of nitinol wire with an inner ultra-thin membrane of expanded polytetrafluoroethylene, which seems to be less thrombogenic than the metallic framework of other devices used in PFO occlusion [7,10]. The WATCHMAN device (Boston Scientific, Natick, MA, USA) consists of a nitinol frame also covered with permeable polyethylene terephthalate membrane.

Therefore, we believe that nickel hypersensitivity testing may be considered in patients with an allergic history before device implantation, and nickel hypersensitivity may be relevant in DAT cases with no other identified risk factors. Further documentation of metal allergy and complimentary investigations in the setting of DAT should be considered in future studies on LAA occlusion.

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STRUCTURAL DISEASE

Anticoagulation Management After Watchman Implantation

Current indications for antiplatelet agents and NOACs after Watchman implantation.

BY MATHIEU LEMPEREUR, MD, AND ADEL AMINIAN, MD

Left atrial appendage (LAA) occlusion is increasingly being recognized as a valid nonpharmacologic therapy for stroke prevention in high-risk patients with nonvalvular atrial fibrillation (AF), especially in cases when long-term oral anticoagulation therapy (OAT) is contraindicated. Currently, the European Society of Cardiology guidelines for the management of AF recommend that LAA closure may be considered in patients at high risk for stroke and contraindications to long-term OAT (class IIb, level of evidence B).[1] The US Food and Drug Administration approved the Watchman device (Boston Scientific Corporation) in March 2015 for patients with nonvalvular AF who have a high risk of stroke and when there is an appropriate rationale to seek a nonpharmacologic alternative to warfarin.

After LAA closure with the Watchman device, thrombosis may appear on the surface of the device. The implantation of thrombogenic devices in patients with nonvalvular AF who are at high risk of thrombosis in the left atrium requires antithrombotic therapy to prevent on-device thrombus formation (Figure 1). Ideally, antithrombotic therapy should be pursued until complete occluder endothelialization occurs. Based on the post-implantation treatment protocols from the PROTECT AF and PREVAIL trials, the vast majority of Watchman implantations described in the literature were accompanied by warfarin anticoagulation for 45 days, followed by dual antiplatelet therapy (DAPT) for 6 months post-procedure and aspirin thereafter.

In a recent review, the rate of device-associated thrombosis (DAT) after LAA occlusion with Watchman was 3.4%.[2] Although most patients diagnosed with DAT are asymptomatic at the time of diagnosis, DAT can be associated with thromboembolic events (mostly neurologic). Moreover, in cases of DAT, intensification of antithrombotic therapy was required to resolve the thrombus, which may increase the risk of a bleeding complication. Therefore, antithrombotic treatment after LAA occlusion is currently recommended. Predisposing factors for development of DAT are multifactorial and include patient characteristics, echocardiographic findings, procedural results, and device-related factors. Further studies are needed to evaluate the clinical impact of these predisposing factors.

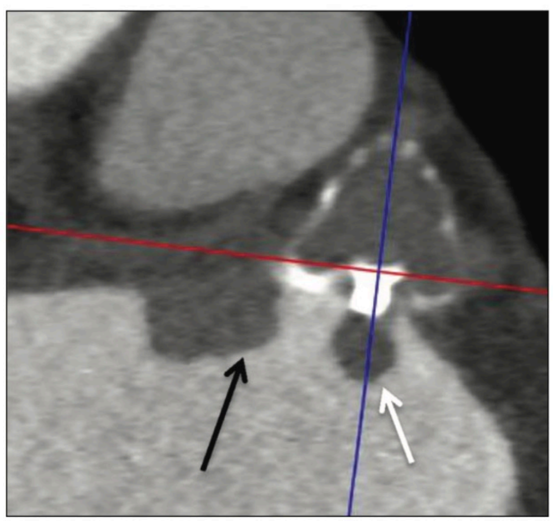

Figure 1. Contrast-enhanced CT images revealing an atrial-side device thrombus on a Watchman device at the fabric insert (white arrow) and adjacent to the device (black arrow). Reprinted from Saw J, Fahmy P, DeJong P, et al. Cardiac CT angiography for device surveillance after endovascular left atrial appendage closure. Eur Heart J Cardiovasc Imaging. 2015;16:1198–1206, by permission of Oxford University Press.

Currently, the optimal antithrombotic regimen and its duration after Watchman implantation is still under debate and might be patient-specific. Anticoagulation remains the standard therapy in patients with low bleeding risk, whereas the use of antiplatelet agents may be indicated in some clinical settings when the risk of thromboembolism is balanced by the risk of bleeding. The role of non–vitamin K antagonist oral anticoagulants (NOACs) has yet to be determined.

USE OF ANTIPLATELET AGENTS AFTER WATCHMAN IMPLANTATION

Anticoagulation represents the most potent therapy after LAA occlusion to prevent thrombus formation (Figure 2). It is the therapy of choice for thromboembolism prevention in AF and has proven to be effective for treating DAT. In the largest randomized controlled trials comparing either LAA closure with the Watchman device or warfarin therapy in patients eligible for long-term OAT (the PROTECT AF and PREVAIL studies[3,4]), it was recommended to give aspirin (81–325 mg) indefinitely with warfarin for 45 days. Warfarin was switched to clopidogrel (75 mg) after an absence of device-related thrombus and significant peridevice leak (jet width ≤ 5 mm) on control transesophageal echocardiography (TEE). Clopidogrel was continued for up to 6 months postprocedure. The rate of DAT was 4.2% in PROTECT AF and bleeding complications occurred in six patients in the first 45 days, translating to an estimated annual bleeding rate of 10.5%.[5] However, compared to the warfarin treatment group, LAA closure significantly reduced bleeding beyond the procedural period, particularly once adjunctive pharmacotherapy was discontinued.[6]

In real-world conditions, many patients treated with LAA closure are not eligible for long-term OAT. A European Heart Rhythm Association/European Association of Percutaneous Cardiovascular Interventions (EHRA/EAPCI) expert consensus statement[7] on catheter-based LAA occlusion recommended an antithrombotic regimen based on the bleeding risk profile in patients treated with Watchman. Thus, when Watchman is implanted in patients with a high bleeding risk, the authors recommend treatment with clopidogrel for 1 to 6 months and aspirin indefinitely (Figure 3). The safety of antiplatelet treatment was initially derived from animal studies that analyzed endothelialization of cardiac devices,[8] from

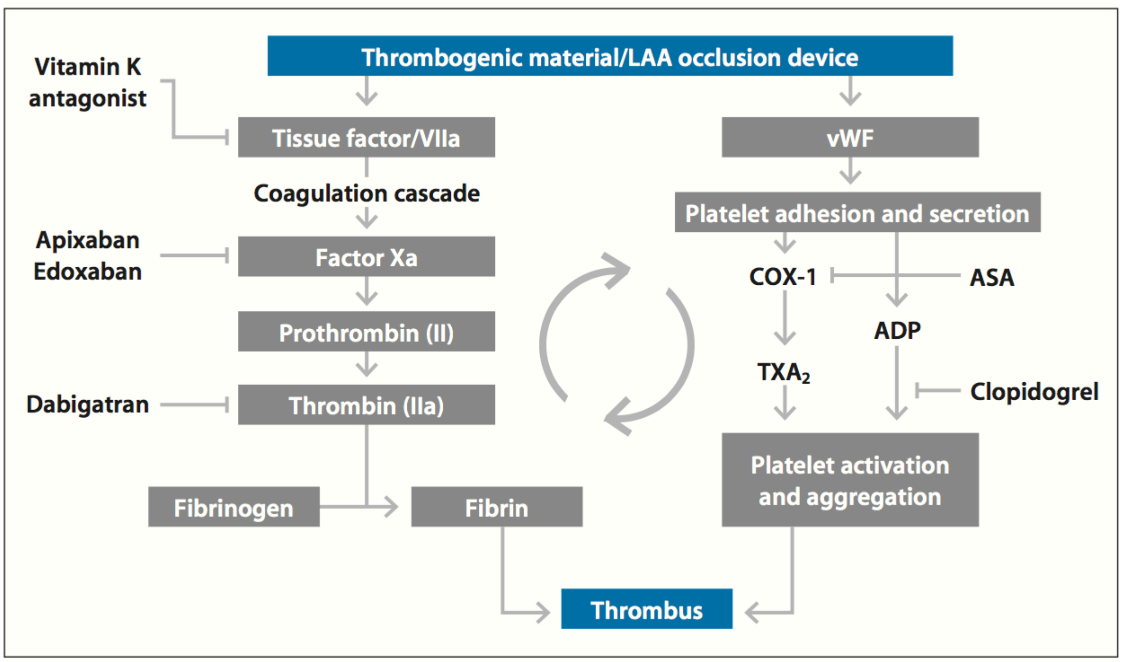

Figure 2. Pathophysiology of atherothrombosis and therapeutic targets. ADP, adenosine diphosphate; ASA, aspirin; COX-1, cyclooxygenase; TXA_2, thromboxane A2; vWF, von Willebrand factor. Adapted from Shivu GN, Ossei-Gerning N. Rivaroxaban in patients with a recent acute coronary syndrome event: integration of trial findings into clinical practice. Vasc Health Risk Manag. 2014;10:291–302 and Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Nat Rev Cardiol. 2015;12:30–47.

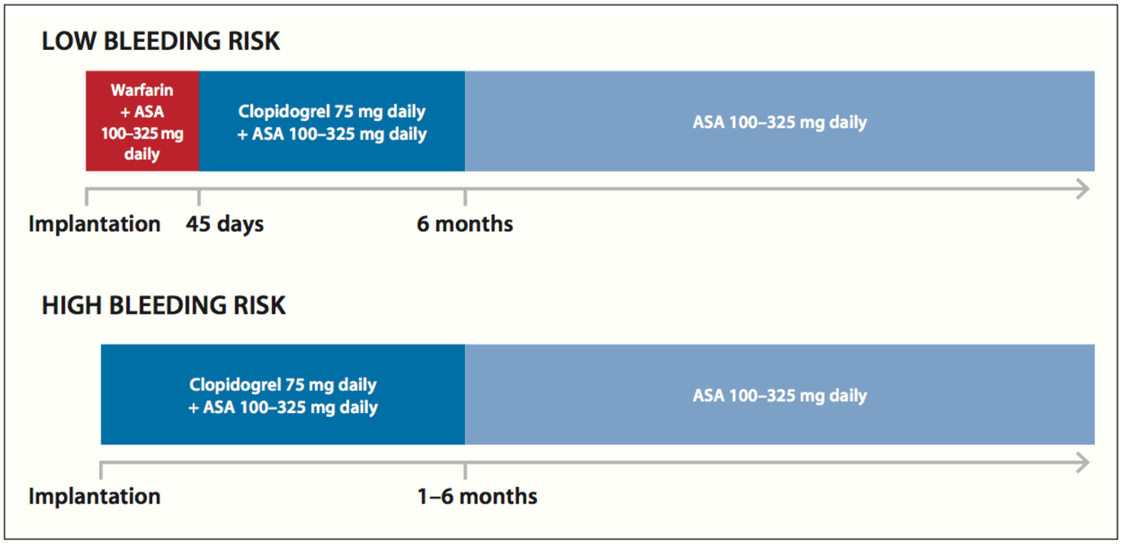

Figure 3. Timeline of antithrombotic treatment after LAA occlusion with the Watchman device based on bleeding risk as recommended by the EHRA/EAPCI consensus statement. ASA, aspirin. Adapted from Meier B, Blaauw Y, Khattab AA, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. EuroIntervention. 2015;10:1109–1125 and Price MJ, Reddy VY, Valderrabano M, et al. Bleeding outcomes after left atrial appendage closure compared with long-term warfarin: a pooled, patient-level analysis of the Watchman randomized trial experience. JACC Cardiovasc Interv. 2015;8:1925–1932.

previous experience with the PLAATO device,[9] and from current practice after percutaneous patent foramen ovale or atrial septal defect closure device implantation.[10]

In the EWOLUTION registry, which reflects real-world results after Watchman implantation, 62% of patients were deemed unsuitable for OAT by their physician due to bleeding history or high bleeding risk, comorbidities, or an inability to adhere to OAT.[11] In this registry, after device implantation, as many as 59% of patients were on DAPT, and 27% of patients were on OAT. Subgroup analysis of serious adverse events through 7 days did not show any difference between patients who were OAT eligible or ineligible (5.2% vs 3.4%; *P* = .18) or between patients on OAT after implantation or those who were not (4.4% vs 4%; *P* = .807). However, it will be important to assess mid- and long-term results because DAT and its related complications are usually diagnosed later after the implantation (mean delay of 45 days from implantation to diagnosis).

In the ASAP study, 150 patients who were deemed ineligible for OAT were placed on 6 months of clopidogrel or ticlopidine and lifelong aspirin after Watchman implantation and showed favorable safety results as compared to PROTECT AF data (ischemic stroke rate of 1.7% vs 2.2%, respectively).[12] The rate of DAT was 4%, and there were five bleeding complications during the first 6 months, translating to an estimated annual bleeding rate of 6.6%. In a trial studying the Amplatzer cardiac plug (ACP; Abbott Vascular), it was common practice to treat patients with DAPT after device implantation as follows: aspirin 80 to 100 mg and clopidogrel 75 mg daily for 1 to 3 months and then only aspirin 80 to 100 mg daily for at least another 3 months. With this therapeutic regimen, the reported rate of DAT in the ACP multicenter study was 4.4%.[13] In a recent smaller study, 104 patients implanted with the ACP were treated with aspirin monotherapy and demonstrated a low rate of DAT or stroke postimplantation after a median follow-up of 2.3 years.[14] Further studies will have to evaluate the need for long-term aspirin therapy.

The use of antiplatelet therapy after Watchman implantation appears to be a good alternative in patients with a high bleeding risk. This treatment should ideally be evaluated in randomized trials. A large trial is currently ongoing to evaluate the safety and efficacy of antiplatelet therapy after LAA closure in patients contraindicated for long-term OAT (ASAP TOO, NCT02928497).

USE OF NOACs AFTER WATCHMAN IMPLANTATION

As previously stated, in the PROTECT AF and PREVAIL randomized clinical trials, warfarin with a target international normalized ratio between 2 and 3 was typically given for 45 days after LAA occlusion with Watchman, thereby representing the most studied drug in this setting and the standard medical treatment for the prevention of DAT.

However, the use of warfarin is complicated by its narrow therapeutic window, the need for repeated blood testing, and drug-drug and drug-food interactions. NOACs have proven to be safer than and as effective as warfarin for stroke prevention in AF patients in recent large randomized trials.[15] Because NOACs are easier to use and initiate in clinical practice, they may represent an interesting alternative to warfarin after LAA occlusion with Watchman.

In a small, pilot, single-center registry, 18 patients received NOAC therapy during the first 45 days after Watchman implantation (dabigatran 110 mg twice daily in 16 patients and rivaroxaban 20 mg per day in two patients), and there were no cases of DAT at 45 days on TEE follow-up.[16] In a second single-center study, 98 patients underwent concomitant AF ablation and LAA occlusion with Watchman. The postimplantation treatment strategy consisted of the use of warfarin in 37 patients, dabigatran in 34 patients, and rivaroxaban in 27 patients (61 patients on NOAC therapy). Incidental DAT was detected in two patients (both in the NOAC group) at 7 days and 6 weeks postimplantation. Both patients were asymptomatic, and the thrombus resolved by continuing the same anticoagulation regimen.[17]

In a recent large, retrospective, multicenter registry, 214 patients who underwent Watchman implantation received NOACs (46% apixaban, 46% rivaroxaban, 7% dabigatran, and 1% edoxaban) in either an uninterrupted (82%) or a single-held dose (16%) strategy. TEE or chest CT was performed between 6 weeks and 4 months postimplantation to assess for the presence of DAT. As compared to a control group of 212 patients with uninterrupted warfarin, the investigators found no significant difference in the rate of periprocedural complications (2.8% vs 2.4%; $P > .99$), DAT (1.4% vs 0.9%; $P > .99$), or postprocedural bleeding events (0.5% vs 0.9%; $P = .6$).[18] In the EWOLUTION registry, 113 patients received NOACs after Watchman implantation (dabigatran, rivaroxaban, and apixaban) and a DAT rate of 1.4% at 3 months.[19]

Taken together, these results suggest that the use of NOACs may represent a safe and effective peri- and postprocedural alternative to warfarin for preventing DAT. These favorable preliminary results should be validated in a dedicated prospective randomized comparison of NOAC versus warfarin therapy after Watchman implantation.

CONCLUSION

The optimal antithrombotic regimen and its duration after Watchman implantation has yet to be determined. This treatment could be tailored according to the individual patient's risk of DAT and bleeding, and antiplatelet agents could be used for patients with a high bleeding risk. In patients eligible for OAT, preliminary data have shown that NOACs may represent an interesting alternative to Warfarin after Watchman implantation. Larger clinical trials are needed to confirm the safety and efficacy of NOACs over warfarin in this setting. ■

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Mathieu Lempereur, MD
Department of Cardiology
University Hospital of Liège
Liège, Belgium
+32 4 366 71 92; mathieu.lempereur@chu.ulg.ac.be
Disclosures: None.

Adel Aminian, MD
Centre Hospitalier Universitaire de Charleroi
Charleroi, Belgium
Disclosures: Consultant and proctor for Boston Scientific Corporation.

Real-time fusion of echocardiography and fluoroscopy allowing for successful implantation of a Watchman device without contrast injection

Adel Aminian[1], MD, Mathieu Lempereur[2], MD, Mohammed Ben Yedder[1], MD, Philippe Dubois[1].

[1]Centre Hospitalier Universitaire de Charleroi

Charleroi, Belgium.

[2]University Hospital of Liège, Liège, Belgium

Short title: Successful Watchman device implantation without contrast injection

Corresponding author:

Adel Aminian, MD, Centre Hospitalier Universitaire de Charleroi, Chaussée de Bruxelles 140, 6042 Charleroi, Belgium, Tel : +3271922217, Email : adaminian@hotmail.com

Text word count: 449

A 84-year old man with paroxysmal atrial fibrillation (AF) was scheduled for percutaneous left atrial appendage (LAA) closure. The patient had a high thromboembolic risk based on a CHA2DS2-VASc score of 5 (previous stroke, age > 75 years and hypertension) and a prior history of ulcerative colitis with recurrent episodes of major gastrointestinal bleeding under oral anticoagulant therapy. Due to the presence of severe chronic kidney disease (eGFR 28 ml/min/1.73m2), an attempt was made to perform the procedure without contrast injection using the Echonavigator system (Philips Healthcare, Best, The Netherlands), which allows for real-time fusion of 3D transesophageal echocardiography (TEE) and fluoroscopic images (1). Following transseptal puncture, adequate LA filling pressure (14 mmHg) was confirmed and procedural 3D TEE measurements showed a maximal and mean diameter of the landing zone of 25.3 mm and 23.5 mm, respectively. It was decided to implant a 27 mm Watchman device (Boston Scientific, Natick, MA). The Watchman access sheath was advanced over a 5 French pigtail catheter into the LAA cavity. Thanks to the projection of TEE images on the fluoroscopic screen (« fused image »), we could precisely position the 27 mm marker of the access sheath at the level of the landing zone without contrast injection (figure 1a). The Watchman device was then released by careful retraction of the access sheath and the correct final position was confirmed by both standard TEE and fused images, without peri-device leak (figures 1b and c, movie 1). Total procedure duration was 45 minutes. Prevalence of chronic kidney disease is high in patients undergoing LAA occlusion, approaching 40% (2). This case illustrates a potential role of fusing echocardiography and fluoroscopy images during LAA closure with the Watchman device in patient with advanced renal failure in whom contrast injection may be contraindicated. Since the Echonavigator system relies on optimal 3D-TEE visualization of the LAA, difficult image acquisition or poor visualisation of LAA distal lobes during sheath placement may represent potential technical limitations of this approach.

DISCLOSURES

Dr Adel Aminian is consultant and proctor for Boston Scientific.

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FIGURES LEGEND

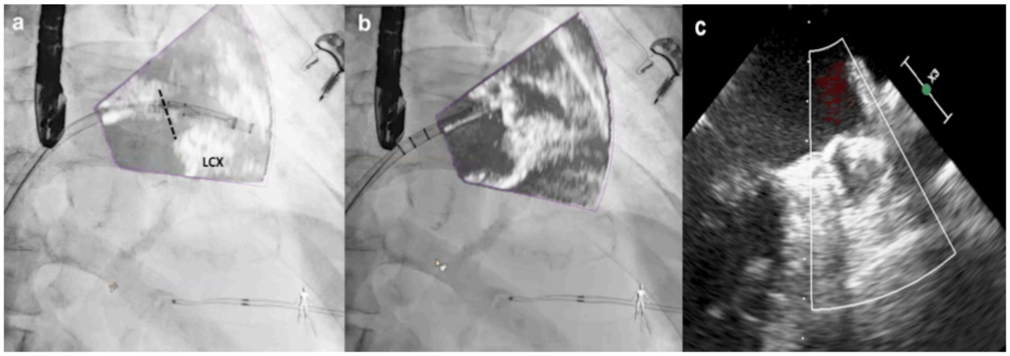
Figure 1a. Placement of the Watchman access sheath into the LAA. By using TEE and X-ray fusion, the 27 mm marker of the access sheath is placed at the level of the LAA ostium (Black dotted-line). LCX= Left Circumflex Artery.

Figure 1b and c. Correct final position of the Watchman device in the LAA confirmed by both standard TEE and fused images.

Movie 1: TEE and X-ray fusion during Watchman implantation.

KEYWORDS

Atrial Fibrillation, LAA Closure, Other imaging modalities.


a
LCX
b
c

<u>Transcatheter Left Atrial Appendage Occlusion for Stroke Prevention in Patients with Atrial Fibrillation : Results from the Belgian Registry.</u>

Joelle KEFER (1) MD PhD, Adel AMINIAN (2) MD, Paul VERMEERSCH (3) MD PhD, Tom DE POTTER (4) MD, Francis STAMMEN (5) MD, Edouard BENIT (6) MD, Werner BUDTS (7) MD PhD, Luc MISSAULT (8) MD DSc, Benny DRIEGHE (9)MD, Ian BUYSSCHAERT (10) MD PhD, Kristoff CORNELIS (11) MD, Jean-Manuel HERZET (12) MD, Antoine GUEDES (13) MD PhD, Nadia DEBBAS (14) MD PhD, Maximo RIVERO (15) MD, Mathieu LEMPEREUR (16) MD PhD, Stijn LOCHY (17) MD, Ruben CASADO-ARROYO (18) MD, Christophe LARUELLE (19) MD, Philippe DEBRUYNE (20) MD, Thierry LEDENT (21) MD.

(1) Cliniques Universitaires Saint-Luc, Brussels, BELGIUM; (2) CHU Charleroi, Charleroi, Belgium, (3) Middelheim ZNA, Antwerp, BELGIUM; (4) OLV ziekenhuis, Aalst, BELGIUM; (5) AZ Delta Roeselare, Roeselare, BELGIUM; (6) Jessaziekenhuis, Hasselt, BELGIUM; (7) Gasthuisberg UZ Leuven, Leuven, BELGIUM; (8) AZ Sint-Jan, Brugge, BELGIUM; (9) UZ Gent, Gent, BELGIUM; (10)ASZ Aalst, Aalst, BELGIUM; (11) Marie Middelares, Gent, BELGIUM; (12) CHR Citadelle, Liège, BELGIUM; (13) CHU UcL Namur, Yvoir, BELGIUM; (14) CHU St-Pierre, Bruxelles, BELGIUM; (15) Ziekenhuis oost-limburg, Genk, BELGIUM; (16) CHU Liège, Liège, BELGIUM; (17) UZBrussel, Brussels, BELGIUM; (18) Erasme ULB, Bruxelles, BELGIUM; (19) St-Luc Bouge, Bouge, BELGIUM; (20) Imelda ziekenhuis, Bonheiden, BELGIUM; (21) CHU Tivoli, La Louvière, BELGIUM.

Short running title : The Belgian Left Atrial Appendage Occlusion Registry

Corresponding author: Joelle Kefer, MD, PhD

Cliniques Universitaires Saint-Luc

Division of Cardiology

Avenue Hippocrate, 10-2881

1200 Brussels

Phone: +3227642815

E-mail: joelle.kefer@uclouvain.be

J. Kefer, W. Budts and A. Aminian are proctors for StJude Medical ; A.Aminian is proctor for Boston Scientific. The other authors have no conflict of interest to declare

Total word count : 5041

ABSTRACT

Aims. This study aimed at assessing the safety and efficacy at mid-term follow-up of left atrial appendage occlusion (LAAO) using different devices, in real life in Belgium.

Methods and results. Between June 2009 and November 2016, 457 consecutive patients (63% males, 75±12 yrs, CHA_2DS_2-VASc 4±0.6, HASBLED 3.5±0.7) undergoing LAAO were included. Technical success was 97.1%. There were 19 periprocedural major adverse events (4.1%) including three deaths (0.6%), nine tamponades (1.9%), four major bleedings (0.8%) and two device embolizations (0.4%).

Among patients successfully implanted with a complete follow-up (672 patient-years, median follow-up 1273 days), the actual annual stroke rate was 1.2%, lower than the expected stroke risk (4%, 70% reduction). The observed bleeding rate was 2%, while the calculated risk was 3.7% (46% reduction).

Kaplan-Meier analysis showed a similar overall survival (93±2% and 87±3% versus 91±3% and 87±4%; p = 0.35) and event-free survival (92±2% and 84±3% versus 88±3% and 80±5%; p = 0.17) at 1 and 2 years, for the ACP/Amulet versus the Watchman groups of patients, respectively.

Conclusions. The data of the Belgian left atrial appendage occlusion registry suggest that the procedure is effective and relatively safe in a real world setting, using either the Watchman or the ACP/Amulet device.

CLASSIFICATION

Stroke, Bleeding, Specific device closure/technique, Atrial fibrillation

CONDENSED ABSTRACT

Between June 2009 and November 2016, 457 consecutive patients (63% males, 75±12 yrs, CHA_2DS_2-VASc 4±0.6, HASBLED 3.5±0.7) undergoing LAAO were included. There were 19 periprocedural major adverse events (4.1%) including three death (0.6%). Among patients successfully implanted with a complete follow-up (672 patient-years), the actual annual stroke rate was 1.2%, lower than the expected stroke risk (4%). The observed bleeding rate was 2%, while the calculated risk was 3.7%. Overall (90±2% versus 87±4%) and event-free (88±2% versus 80±5%) survival were similar between ACP/Amulet vsWatchman device (p=NS for both).

ABBREVIATIONS LIST

LAAO : Left Atrial Appendage Occlusion

AF : Atrial Fibrillation

OAC : Oral AntiCoagulant

ACP : Amplatzer Cardiac Plug

TIA : Transient Ischemic Attack

MAE : Major Adverse Event

TEE : TransoEsophageal Echocardiography

NS : not significant

DAPT : Dual AntiPlatelet Therapy

NOAC : New Oral AntiCoagulant

INTRODUCTION

Transcatheter percutaneous left atrial appendage occlusion (LAAO) is an alternative therapeutic option for stroke prevention in patients with atrial fibrillation (AF). (1-4). LAAO has been demonstrated to be non inferior to warfarin in two randomized-controlled trials that included only patients without contraindications to oral anticoagulants (OACs) (5-6). Large observational studies described the safety and short-term outcome after using only one device (7-8-9-10-11-12-13-14). Until now, there are no randomized trial comparing the results of the currently available prostheses. Real world data on long-term safety and efficacy of LAAO using different device technologies are limited (15-16). The aim of our study was to collect the baseline, procedural and follow-up characteristics of patients undergoing LAAO in Belgium, to assess the safety and efficacy of the procedure in the real world of patients not candidates for long term OAC, and allowing a comparison of the different types of devices used.

METHODS

Between June 2009 and November 2016, consecutive patients undergoing LAAO in 21 centres in Belgium, were prospectively included in the registry. Demographics, baseline characteristics, indications for LAAO, CHA_2DS_2-VASc and HAS-BLED scores, antithrombotic medication, procedural details, periprocedural adverse events and clinical follow-up were prospectively collected in a dedicated database. The protocol was approved by the Ethics Committee of the Université Catholique de Louvain. Three different devices, available in the country, were implanted according to the operator preference : the Amplatzer cardiac plug (ACP), the Amulet (St.Jude Medical, for both) and the Watchman (Boston Scientific). The results of the 90 first patients implanted with the ACP device were previoulsy reported (10).

Definitions of success

According to the Munich consensus document (17), device success was defined as successful implantation of the device in correct position. Technical success is a device success with no large leak and no device-related complications. Device-related complications are embolization, erosion, interference with surrounding structures, thrombus, fracture, infection, perforation or allergy. Procedural success is a technical success without any major periprocedural complications.

Periprocedural complications

Periprocedural complications (occuring during 0-7 days after procedure or before hospital discharge, whichever last) included death, myocardial infarction, stroke, transient ischaemic attack (TIA) according to VARC criteria (18), systemic embolism, air embolism, device embolization, major bleeding according to the BARC 3 and 5 criteria (19) and cardiac tamponade.

Periprocedural major adverse events (MAE) included death, stroke, systemic embolism and complication requiring major surgical or endovascular intervention (major bleeding, tamponade, device migration treated by snare or surgery) occurring between 0-7 days post procedure or before hospital discharge, whichever latest.

Clinical follow-up

Patients survival and clinical events during the follow-up were determined by review of medical records or phone contact of patients implanted successfully. Adverse events during follow-up included death (cardiovascular or non-cardiovascular), stroke, TIA, systemic embolism, major bleeding, tamponade, myocardial infarction, and device-related complications. Antithrombotic medication was recorded at discharge and at last follow-up visit.

Efficacy on stroke, TIA, systemic embolism and bleeding prevention

LAAO efficacy on thromboembolism and bleeding prevention was tested by comparing the actual event rate with the predicted event rate by the CHA_2DS_2-VASc or HAS-BLED score, respectively (20-21). Event reduction was calculated as follows (estimated % - actual% event rate)/estimated % event rate.

Echocardiography

Patients underwent a transoesophageal echocardiography (TEE) during the procedure allowing to grade the potential residual leak after implantation. Despite the fact that several definitions were proposed over time (3-8-9-10), in the current study, according to the Munich consensus document, residual leak was graded using the width of the Doppler colour jet as none (absence of colour jet), mild (1-5 mm) or large (> 5 mm) for all devices.

Statistical analysis

Continuous variables are presented as mean ± 1 standard deviation. Categorical variables are presented as counts and percentages. Continuous variables were tested using the independent samples t-test and categorical variables using the Fischer's exact test.

Univariate and multivariate analysis were done using the Cox proportional-hazards method. Variables with a $p < 0.10$ at the univariate analysis were included in the backward stepwise multivariate analysis. Estimates for freedom from the composite of death and MAE were obtained by the Kaplan-Meier estimation method. A p value < 0.05 was considered statistically significant. Analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Patients

A total of 457 patients were included in the database and constituted the total cohort of the study. Baseline characteristics are listed in Table 1. The distribution of the CHA_2DS_2-VASc and HAS-BLED scores is detailed in Figure 1. The mean CHA_2DS_2-VASc (4.6 ± 1.6) and HAS-BLED (3.2 ± 1) score were not significantly different between patients treated by ACP/Amulet (Group 1) and those undergoing a Watchman implantation (Group 2 ; 4.5 ± 1.7 and 3.1 ± 1, respectively ; p=NS). Patients of Group 1 experienced more frequently a previous major bleeding but had less diabetes mellitus than in Group 2.

Indications for the procedure in Belgium were mainly previous major bleeding (gastro-intestinal and cerebral in 136 and 134 patients, respectively). The other reasons for LAAO were recurrent minor bleeding in 27%, recurrent stroke under anticoagulant in 11% and other cause in 18% of cases.

Procedure

Procedures were performed in 21 centers reporting by themselves their complete data since the beginning (first implants were not excluded from the study). Only three centers performed more than 50 procedures, while six others started the LAAO program in 2016. The device implanted was ACP in 174 patients, Amulet in 144 and Watchman in 139 cases. One hundred and sixty eight patients (37%) were in sinus rythm at the time of implantation. An additional procedure was combined in 22% of cases : 93 coronary angiography, 11 atrial fibrillation ablation and 1 interatrial septal defect closure. The outcome of the patients was similar between patients with and those without a combined intervention. Device success was achieved in 97.5% : 11 device failures were reported due to inappropriate anatomy : 4 with the ACP device, 0 with the Amulet and 7 with the Watchman. Large residual leak was observed after two Watchman implantations (0.4% of the total cohort); the technical success was achieved in 97.1%.

Periprocedural complications

The rate of periprocedural major adverse events (MAE) was 4.1%. (Table 2). Three procedural deaths occured (0.6%), all related to tamponades treated by surgery but ultimately, resulting in death. Additional tamponades were observed in 9 cases : 4 of them were successfully treated by a percutaneous pericardiocentesis and 5 required surgery. There were significantly more MAE with the ACP device than after Amulet implantation (4.5% versus 0.7%, p=0.04), explained by the learning curve (centers started with the ACP and moved to Amulet when it became available). Two devices embolizations were reported : one was totally asymptomatic, discovered at day 1 and successfully retrieved by snare. The other one required a surgical removal of implant with good outcome. Major bleedings occured only in Group 2 (4 versus 0, p=0.008) : two groin hematoma and two recurrent bleedings (one from the lung, the otherone from gastrointestinal angiodysplasia) still recurrent despite stop of anticoagulants after LAAO. Dual antiplatelet therapy (DAPT) was used in three of them, while the last one was under aspirin alone. This is the only statistically significant difference between group 1 and 2, but it is numerically not clinically relevant. There were no periprocedural stroke, TIA nor myocardial infarction in our cohort. Procedural success was achieved in 96.6 % of cases. Medications at discharge were mainly DAPT, prescribed in 72% of cases (Figure 2a). Any form of anticoagulant therapy was more frequently used after Watchman (24%) than after ACP/Amulet implantation (3%). Eighty-eight percent of patients were left untreated by any anticoagulant at discharge after LAAO.

Follow-up

The follow-up was complete in 417 of 444 patients with successful LAAO (94%). The mean duration of follow-up was 589 days, the median value was 8.4 months (interquartile range 136-841 days) resulting in a total of 672 patients-years. There were 10 strokes (8 ischemic, 2 hemorrhagic), 7 TIAs, 3 fatal bleedings, 9 major bleedings reported during the follow-up period, with no difference between groups (Table 3). Among the 49 deaths observed during this period, 14 were from an identified cardiovascular disease (Table 4). Only one death was procedure-related due to a delayed device embolization at 1 month after an uneventful ACP implantation, treated by emergent surgery but resulting in death. The vast majority of deaths were related to the co-morbidities of patients and occurred at a mean time of 594 (median 406) days after the procedure.

Overall survival of the total cohort was 89 ± 2% (Figure 3). Kaplan-Meier analysis showed a similar overall and event-free survival, for the Watchman versus the ACP/Amulet groups of patients, respectively (Figure 4).

With univariate analysis, CHA_2DS_2VASc score, HASBLED score, congestive heart failure and alcohol abuse/use of drugs were associated with death at follow-up, while by multivariate analysis, serum creatinine level, vascular disease and previous major bleeding were independent predictors of mortality at follow-up (Table 5).

The actual annual rate (periprocedural and follow-up period) of stroke was 1.2%, and of thromboembolism was 2.2%, while the expected annual thromboembolism risk was calculated by the CHA_2DS_2-VASc score at 4%, which translates into 45% risk reduction (Figure 5).

The observed annual major bleeding rate (periprocedural and follow-up period) was 2% and the annual risk of bleeding estimated by the HASBLED score was 3.7% (46% reduction).

Medication at last follow-up was limited to acetylsalicylic acid in 65% of patients, while only

10% of them were under anticoagulant therapy (Figure 2b). In details, medication used in patients of Group 1 *vs* Group 2 was OAC (5 *vs* 6), NOAC (10 *vs* 15), aspirin (207 *vs* 63), DAPT (38 *vs* 13), clopidogrel (9 *vs* 4), association (1 *vs* 5), and nothing (14 *vs* 10 patients, respectively).

DISCUSSION

The main findings of this paper are :

1. The efficacy of LAAO on stroke prevention is very high in the real life settings.
2. The bleeding rate after LAAO, especially the hemorrhagic stroke rate (0.2%/year), was lower than expected.
3. The procedure of LAAO is relatively safe in Belgium, with a rate of periprocedural MAE at 4.1%.
4. The outcome of patients undergoing LAAO in the real life was similar regardless the type of device used

Efficacy on stroke reduction

Two randomized trials (3, 6) showed the non inferiority of LAAO using the Watchman device as compared with warfarin. The ACP multicenter registry (9) showed a thromboembolism rate after LAAO at 2.3% among patients with a CHA_2DS_2-VASc score at 4.5. The thromboembolism rate after Watchman implantation in the ASAP registry including patients contra-indicated for OAC (22) was at 2.3% (mean CHA_2DS_2-VASc score at 4.4). The effectiveness on cardioembolic events reduction was similar in our study : the observed stroke rate was 1.2%, the thromboembolism rate was 2.2%, which translates into a 45% risk reduction for patients at a mean CHA_2DS_2-VASc score at 4.0.

Impact on bleeding

The bleeding rate observed after LAAO in Belgium was 2%, while the expected bleeding rate was 3.7%. Only two hemorrhagic strokes were observed during the follow-up period (hemorrhagic stroke rate 0.2%/year), despite the fact that 29% of our population experienced an intracranial bleeding before the procedure. The rate of major bleeding in the new oral anticoagulants (NOACs) trials were 4.5% in the ROCKET (23), 2.7% in the RELY (24) and 2.1% in the ARISTOTLE trial (25), while the rate of hemorrhagic stroke were 0.3, 0.1 and 0.2%/year, respectively. In the Belgian LAAO registry, 90% of patients were left untreated by any form of OAC at last follow-up, explaining potentially the lower rate of bleeding as compared with NOAC trials, despite that the latters included patients at a lower risk profile than in our real life study.

Procedural safety

The rate of MAEs (4.1%) in our study is lower than in the initial ACP European registry (4) or the PROTECT AF study (3), reporting 7.3 and 7.7 % of MAEs respectively, and is similar than in the more recent publications (6,7,9), such as the CAP (3.7%), multicenter ACP registry (4.9%) and PREVAIL study (4.2%). The Belgian LAAO registry included all the procedures performed in all the centers (the first implants were not excluded). There was a wide range of number of implants per center (3 had more than 50 procedures while 10 others less than 10). In our study, all the first cases in each institution were performed with an on-site proctor, explaining better results, compared to the initial experience (3-4). Periprocedural mortality was similarly low at 0.6% and 0.7% in the Belgian and in the EWOLUTION registries, respectively.

As an elective and preventive procedure, these upfront risks must be taken into account for LAAO indication and must be weighed against serious bleeding issues when using (N)OAC.

Devices comparison

To the best of our knowledge, the Belgian LAAO registry is the national registry with the highest number of patients, comparing the three devices ACP, Amulet and Watchman. Betts et al. (16) reported the experience in the United Kingdom among 371 patients treated with Watchman, ACP, Lariat or Coherex wavecrest device, followed during a mean period of 24 months: they stated that the procedure is safe and successfull regardless of the technology used but without side by side comparison of the devices. Oreglia et al. (26) reported the Italian experience among 110 patients using the Watchman, ACP or Amulet devices, but also, without comparison between devices. Our study compared baseline, procedural and follow-up data on 457 patients treated with ACP, Amulet or Watchman, followed during a mean period of 20 months. Except for major bleedings during the periprocedural period, we showed that the outcome was similar after LAAO, using either the Watchman or the ACP/Amulet device.

LIMITATIONS

This registry has an observational design limited by several factors :

- the centers included by themselves their data with no corelab, especially for the neurological evaluation in case of stroke and TIA
- the follow-up is limited to the clinical evaluation without non invasive imaging information

CONCLUSIONS

The Belgian LAAO registry showed that the procedure is relatively safe, reduces the thromboembolism and the bleeding rates as compared with the expected risks calculated by the CHA_2DS_2-VASc and HAS-BLED score, respectively. It is important to emphasize that the observed rate of cerebral hemorrhage was very low at 0.2%/year in our registry, despite one third of this real life population of patients having experienced a prior intracranial bleeding before the procedure. The overall and event-free survival was similar after LAAO in Belgium, regardless the type of the device used (ACP, Amulet or Watchman). These data may support further studies, using either one of these prostheses, evaluating NOAC versus LAAO to compare the impact on the clinical outcome and the cost-effectiveness of these two strategies among AF patients at high risk for stroke.

IMPACT ON DAILY PRACTICE

The data of the Belgian left atrial appendage occlusion registry suggest that the procedure is safe and effective in a real world setting, for atrial fibrillation-related thromboembolism prevention using either the Watchman or the ACP/Amulet device.

FUNDING

This investigator-initiated study did not receive financial support

CONFLICT OF INTEREST

J. Kefer, W. Budts and A. Aminian are proctors for StJude Medical ; A.Aminian is proctor for Boston Scientific. The other authors have no conflict of interest to declare

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FIGURE LEGENDS

Figure 1. Distribution of the CHA_2DS_2-VASc (panel A) and the HAS-BLED (panel B) scores observed in the total cohort (in blue), Group 1 (in red), and Group 2 (in green).

Figure 2. Medications given at discharge (panel A) and at last follow-up (panel B). DAPT = dual antiplatelet therapy ; OAC = oral anticoagulant ; NOAC = new oral anticoagulant ; (N)OAC = any form of anticoagulant.

Figure 3. Panel A : Kaplan-Meier analysis showing the overall survival of the total cohort. Panel B : comparison of the overall survival between Group 1 and Group 2.

Figure 4. Panel A : Kaplan-Meier analysis showing the event-free survival of the total cohort. Panel B : comparison of the event-free survival between Group 1 and Group 2.

Figure 5. Effectiveness of LAAO in reduction of thromboembolism and bleeding based on annual rate predicted by CHA_2DS_2-VASc and the HAS-BLED score.

Blue = observed event rate; Pink = expected event rate.

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TABLES

Table 1. Baseline characteristics

Characteristics		All N = 457	ACP N = 174	Amulet N = 144	Group 1 ACP+Amulet N = 318	Group 2 Watchman N = 139	*p* value
Age (yrs)	mean ± sd	75 ± 12	74 ± 7	77 ± 8	75 ± 7	75 ± 8	0.74
Gender	M/F	288/169	112/62	82/62	194/124	94/45	0.20
Congestive heart failure	n (%)	110 (24)	38 (22)	37 (26)	75 (24)	35 (25)	0.72
Hypertension	n (%)	357 (78)	131 (75)	121 (84)	252 (79)	105 (75)	0.39
Diabetes	n (%)	123 (27)	43 (25)	33 (23)	76 (24)	47 (34)	0.03
Vascular disease	n (%)	172 (38)	64 (37)	52 (36)	116 (36)	56 (40)	0.46
Previous stroke/TIA	n (%)	203 (44)	75 (43)	71(49)	146 (46)	57 (41)	0.35
Previous major bleeding	n (%)	365 (80)	138 (79)	126 (87)	264 (83)	101 (73)	0.01
Permanent AF	n (%)	267 (58)	96 (55)	86 (60)	182 (57)	85 (61)	0.94
Serum creatinine (mg/dl)	mean ± sd	1.2 ± 0.7	1.1 ± 0.4	1.4 ± 1	1.3 ± 0.8	1.2 ± 0.5	0.78
$CHADS_2$ score	mean ± sd	2.8 ± 1.3	2.7 ± 1.3	3 ± 1.2	2.8 ± 1.3	2.7 ± 1.3	0.75
CHA_2DS_2-VASc score	mean ± sd	4 ± 0	4.5 ± 1.6	4.7 ± 1.5	4.6 ± 1.6	4.5 ± 1.7	0.96
HAS-BLED score	mean ± sd	3.5 ± 0.7	3.3 ± 1.2	3.1 ± 0.9	3.2 ± 1	3.1 ± 1.1	0.86

ACP = Amplatzer cardiac plug ; TIA : transient ischemic attack ; AF = atrial fibrillation

Table 2. Periprocedural complications

Characteristics		All N = 457	ACP *N = 174*	Amulet *N = 144*	Group 1 *ACP+Amulet* *N = 318*	Group 2 *Watchman* *N = 139*	*p* value
MAE peri-procedural	n (%)	19 (4.1)	8 (4.5)	1 (0.7)*	9 (2.8)	10 (7.2)	0.04
Death	n (%)	3 (0.6)	1 (0.6)	1 (0.7)	2 (0.6)	1 (0.7)	1
Stroke	n (%)	0	0	0	0	0	1
Systemic embolism		1 (0.2)	0	0	0	1 (0.7)	0.30
Device embolization	n (%)	2 (0.4)	2 (1.1)	0	2 (0.6)	0	1
Major bleeding	n (%)	4 (0.8)	0	0	0	4 (2.9)	0.008
Tamponade	n (%)	9 (1.9)	5 (2.9)	0	5 (1.6)	4 (2.9)	0.46

ACP = Amplatzer cardiac plug ; MAE : major adverse event ;
* = p<0.05 for the comparison between ACP and Amulet

Table 3. Adverse events during follow-up

		All N = 417	ACP *N = 161*	Amulet *N = 132*	Group 1 *ACP+Amulet* *N = 293*	Group 2 *Watchamn* *N = 124*	*p* value
MAE follow-up	n (%)	75 (17.9)	39 (24.2)	16 (12.1)	55 (18.7)	20 (16.1)	0.57
Stroke	n (%)	10 (2.4)	5 (3.1)	3 (2.2)	8 (2.7)	2 (1.6)	0.72
TIA	n (%)	7 (1.7)	5 (3.1)	1 (0.7)	6 (2)	1 (0.8)	0.67
Major bleeding	n (%)	9 (2.1)	2 (1.2)	3 (2.2)	5 (1.7)	4 (3.2)	0.46
Death	n (%)	49 (11.7)	27 (16)	9 (7)	36 (12)	13 (10)	0.73

ACP = Amplatzer cardiac plug ; TIA : transient ischemic attack

Table 4. Causes of death at follow-up

Cause of death at follow-up	Number
Total	*49*
Cardiovascular	*23*
Heart failure	6
Sudden death	4
Stroke	1
Myocardial infarction	1
Device embolization	1
Mesenteric infarction	1
Unknown	9
Non cardiovascular	*26*
Sepsis	14
Liver cirrhosis	3
Cancer	6
Acute abdomen	1
ARDS	1
Suicide	1

Table 5. Univariate and multivariate analysis for predictors of survival according to Cox models

	Univariate analysis		Multivariate analysis	
parameter	HR (95% CI)	*p* value	HR (95% CI)	*p* value
age	1,03 (0,99-1,07)	0.16		
permanent atrial fibrillation	0,99 (0,56-1,75)	0.97		
serum creatinine level	1,43 (1,21-1,71)	<0,001	1,36 (1,12-1,64)	0,002
congestive heart failure	2,48 (1,40-4,4)	0,002		
hypertension	1,28 (0,64-2,59)	0,48		
age ≥ 75 yrs	1,26 (0,70-2,25)	0,44		
diabetes	1,08 (0,59-1,9)	0,81		
previous stroke/transient ischemic attack	0,84 (0,47-1,49)	0,55		
vascular disease	2,96 (1,64-5,34)	<0,001	2,36 (1,26-4,40)	0,007
age (between 65 and 74)	1,10 (0,61-1,97)	0,76		
sex category (female gender)	1,32 (0,75-2,33)	0,34		
total CHA2DS2VASc score	1,23 (1,04-1,45)	0,01		
previous major bleeding	2,72 (1,53-4,84)	0,001	2,14 (1,16-3,95)	0,016
alcohol/drug	1,91 (1,06-3,45)	0,032		
total HASBLED score	1,38 (1,09-1,74)	0,006		

TIA : transient ischemic attack

Figure 1

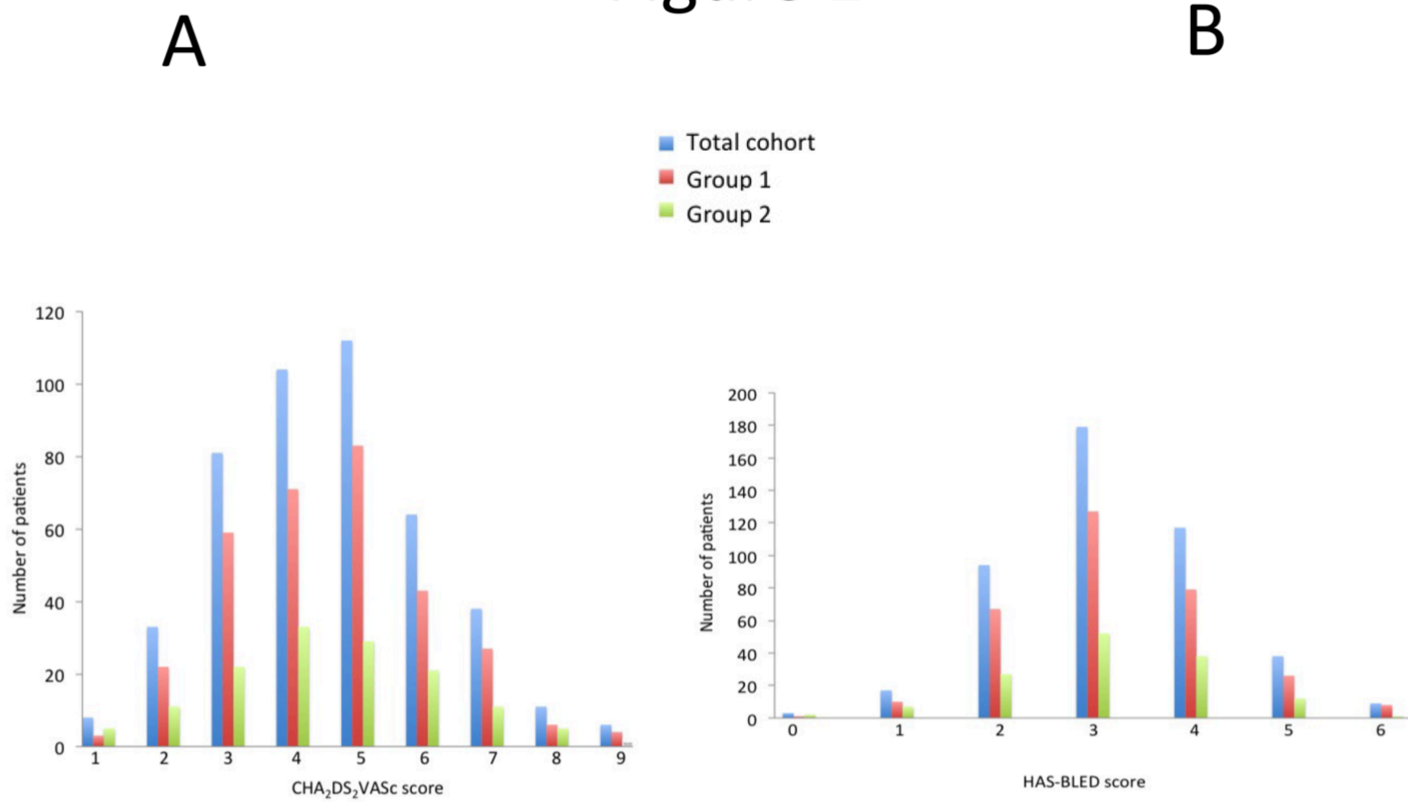

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Figure 2.

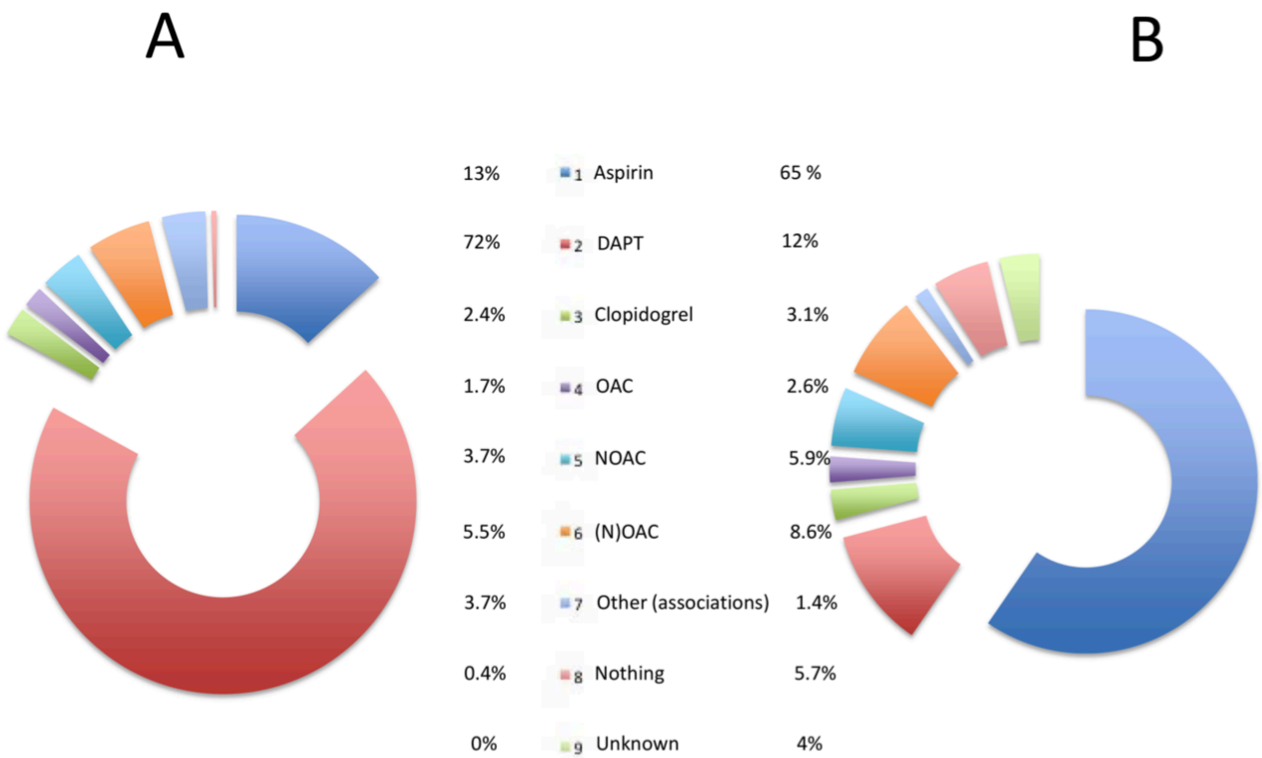

A
B
13% 1 Aspirin 65 %
72% 2 DAPT 12%
2.4% 3 Clopidogrel 3.1%
1.7% 4 OAC 2.6%
3.7% 5 NOAC 5.9%
5.5% 6 (N)OAC 8.6%
3.7% 7 Other (associations) 1.4%
0.4% 8 Nothing 5.7%
0% 9 Unknown 4%

Figure 3.

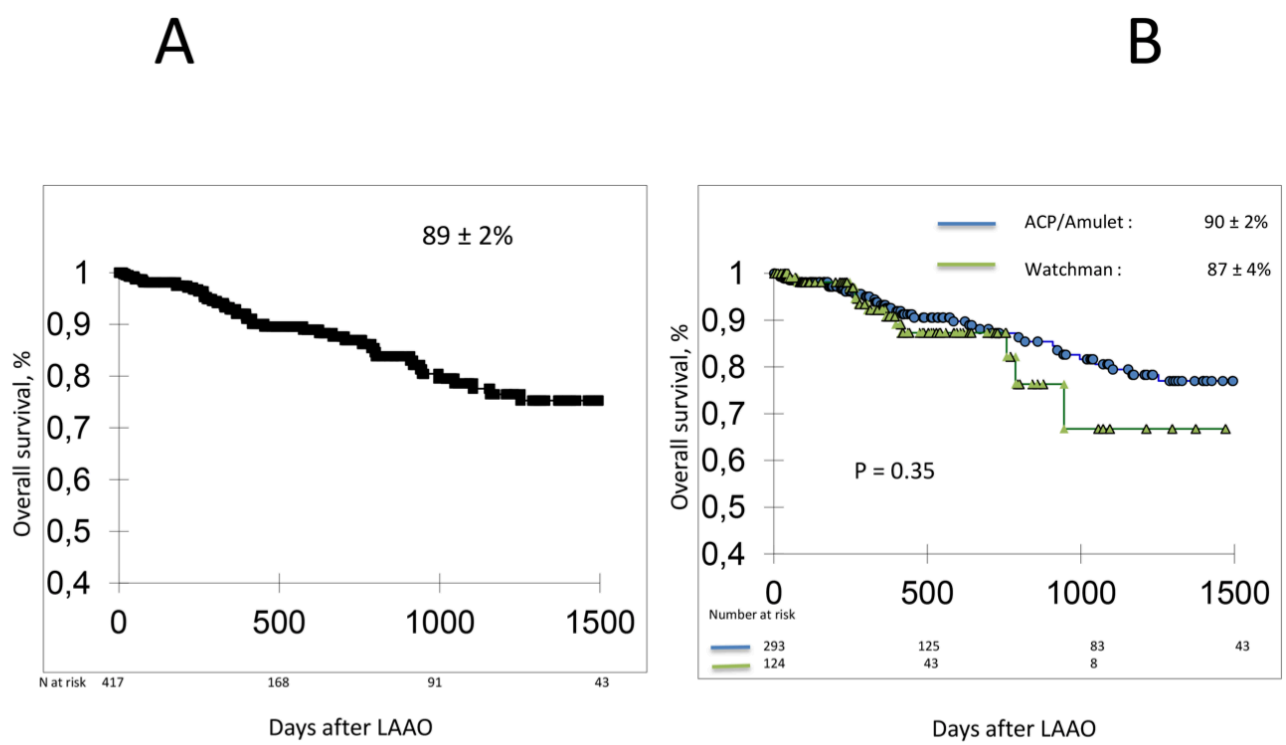

A
B
89 ± 2%
Overall survival, %
1
0,9
0,8
0,7
0,6
0,5
0,4
0
500
1000
1500
N at risk 417 168 91 43
Days after LAAO
ACP/Amulet : 90 ± 2%
Watchman : 87 ± 4%
P = 0.35
Number at risk
293 125 83 43
124 43 8

Figure 4.

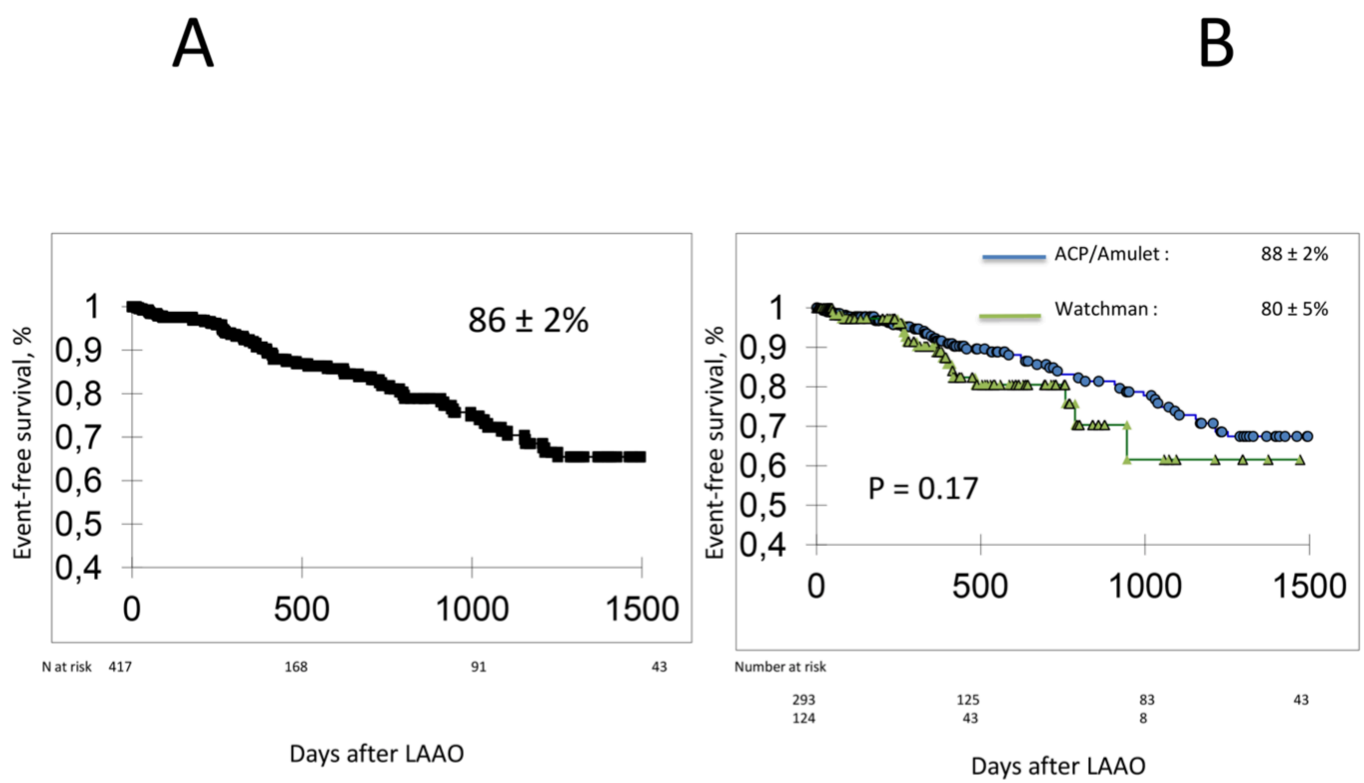
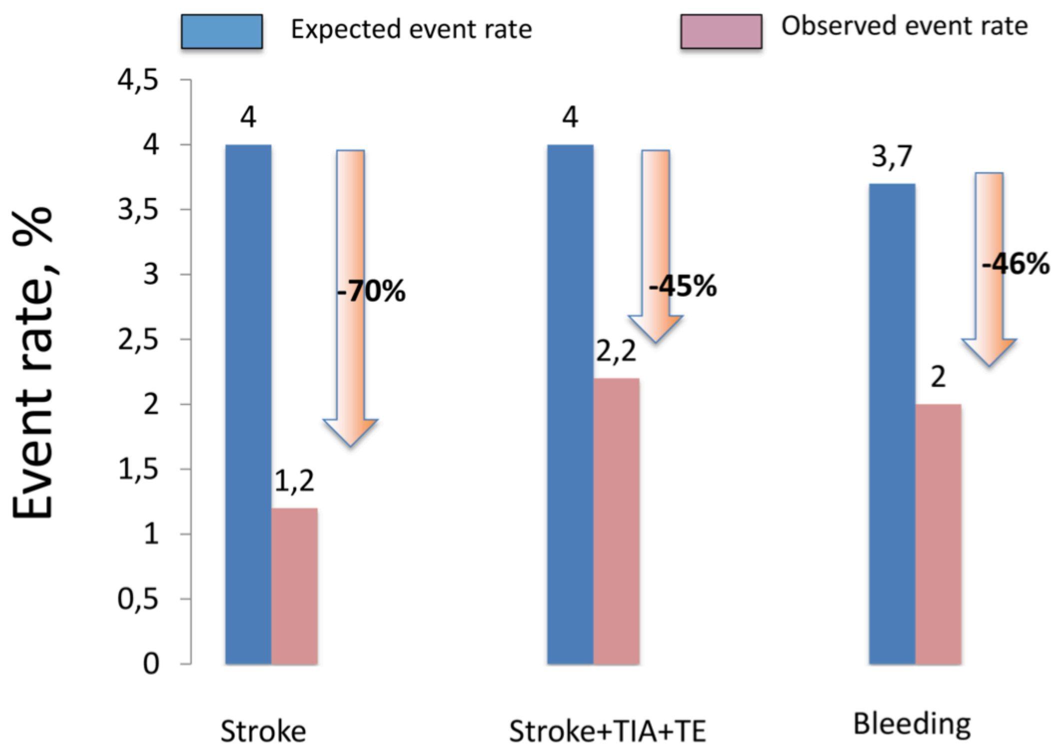

A
B
Event-free survival, %
1
0,9
0,8
0,7
0,6
0,5
0,4
0
500
1000
1500
86 ± 2%
N at risk 417 168 91 43
Days after LAAO
ACP/Amulet : 88 ± 2%
Watchman : 80 ± 5%
P = 0.17
Number at risk
293 125 83 43
124 43 8
Days after LAAO

Figure 5.


Expected event rate
Observed event rate
Event rate, %
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
4
1,2
-70%
4
2,2
-45%
3,7
2
-46%
Stroke
Stroke+TIA+TE
Bleeding