Fibrillation auriculaire chez des patients à haut risque: Du diagnostic précoce à la prévention thromboembolique

Atrial fibrillation in high-risk patients: From early diagnosis to thromboembolic prevention

Thèse

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RÉSUMÉ

La fibrillation auriculaire (FA) est la plus fréquente des arythmies cardiaques. La FA est associée à un risque accru d'accident vasculaire cérébral, d'insuffisance cardiaque et de mortalité, constituant un problème de santé publique majeur. L'avènement de nouvelles technologies permettant une surveillance électrocardiographique a démontré une haute prévalence de FA subclinique ou silencieuse chez les patients âgés à haut risque. Récemment, plusieurs efforts et essais thérapeutiques ont été dirigés vers une identification et un traitement plus précoces de la FA chez ces patients. L'anticoagulation orale a bien prouvé son efficacité dans la prévention thromboembolique chez les patients qui présentent un haut risque thromboembolique, mais au prix d'une augmentation significative des événements hémorragiques, un risque qui s'élève régulièrement chez les patients âgés et avec une comorbidité importante.

Au cours des dernières années, des nouvelles alternatives non-pharmacologiques dans la prévention thromboembolique ont été développées. La fermeture percutanée de l'auricule gauche, site de formation de la majorité (~90%) des thrombus, est progressivement devenue une alternative valable à l'anticoagulation chez des patients avec FA non valvulaire à haute risque hémorragique. L'expérience des opérateurs et les innovations technologiques ont permis une amélioration remarquable des résultats en ce qui concerne la sécurité et l'efficacité. Cependant, quelques questions restent sans réponse. Les préoccupations les plus débattues suite à la fermeture de l'auricule gauche sont la prise en charge de l'anticoagulation postprocédure et la prévention/gestion de la thrombose de dispositif.

Les objectifs de ce travail de recherche sont : (i) évaluer la charge arythmique silencieuse chez des patients à haut risque à l'aide de l'utilisation de nouveaux systèmes d'enregistrement électrocardiographique prolongé, et (ii) analyser l'impact hémodynamique et thrombogénique de la fermeture percutanée de l'auricule gauche avec les dispositifs actuels et émergents.

ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia. AF is associated with an increased risk of stroke, heart failure and mortality, posing a major public health problem. The advent of new technologies for continuous electrocardiographic monitoring has demonstrated a high incidence of subclinical or silent AF in elderly high-risk patients. Recently, several therapeutic efforts and studies have been directed towards earlier identification and treatment of AF in these patients. Oral anticoagulation has proven to be effective in preventing thromboembolism in patients at high thromboembolic risk, albeit at the expense of a significant increase in hemorrhagic events; a risk that increases steadily in elderly patients with high comorbidity burden.

In recent years, novel non-pharmacological alternatives have been developed for thromboembolic prevention. Percutaneous left atrial appendage (LAA) closure, site of origin of the vast majority (~ 90%) of thrombi, has progressively become a valid alternative to anticoagulation in patients with non-valvular AF at high bleeding risk. Increasing operators' experience and technological innovations have led to remarkable improvements in the safety and efficacy of the procedure. However, some issues remain unanswered or controversial. Two of the most debated concerns are post-procedural antithrombotic management and device-related thrombosis (DRT) following LAA closure.

The aims of the present research study are: (i) to evaluate the silent arrhythmic burden in high-risk patients using novel prolonged continuous electrocardiographic monitoring systems, and (ii) to assess the hemodynamic and thrombogenic impact of percutaneous LAA closure using current and emerging devices.

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LIST OF ABBREVIATIONS

ACP: Amplatzer Cardiac Plug

AF: Atrial fibrillation

APT: Antiplatelet therapy

AT: Atrial tachycardia

AVB: Atrioventricular block

CEM: Continuous ECG monitoring

$CHADS_2$: Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack

CHA_2DS_2-VAS_C: Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category

CT: Cardiac computed tomography

DAPT: Dual antiplatelet therapy

DOAC: Direct oral anticoagulants

DRT: Device-related thrombosis

ECG: Electrocardiographic

ESVEA: Excessive supraventricular ectopic activity

F1+2: Prothrombin fragments 1+2

HAS-BLED: Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol

HAVB: High-degree atrioventricular block

LA: Left atrium

LAA: Left atrial appendage

LAAC: Left atrial appendage closure

LBBB: Left bundle branch block

MAE: Major adverse event

NSVT: Non-sustained ventricular tachycardia

OAC: Oral anticoagulation

PET: polyethylene terephthalate

PPM: Permanent pacemaker

RBBB: Right bundle branch block

SAPT: Single antiplatelet therapy

SCAF: Subclinical atrial fibrillation

TAT: thrombin-antithrombin III complex

TAVR: Transcatheter aortic valve replacement

TEE: Transesophageal echocardiography

“Medicine is a science of uncertainty and an art of probability”

William Osler (1849-1919)

ACKNOWLEDGMENTS

"Difficult roads often lead to beautiful destinations"

Zig Ziglar (1926 – 2012)

The debts of gratitude incurred in a work of this nature are countless. My deep gratitude goes first to Josep Rodés-Cabau, my mentor, the person who opened the door for me without even knowing me, who trusted in me since the very beginning and taught me the beauty of research and the distinctive value of a rigorous scientific method. It has been a tremendous privilege and pleasure to be one of your fellows, and hopefully only the beginning of a lasting relationship and friendship.

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I want to thank my fellow labmates in the IUCPQ. It has been a pleasure to share these years with you. It has been much more than just a team-work, but a true family during this journey, who have become lifelong friends.

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Last, but most importantly, my biggest gratitude goes to my wife Ana, whom this work is dedicated. It has been a long journey, which I would have never accomplished without your unconditional support and loving understanding. A road filled with challenges and joys along the way, that has led to the beautiful destination of our growing family.

FOREWORD

The research works embedded in this PhD Thesis were carried out in the research group of Structural Heart Disease Interventions at the Quebec Heart and Lung Institute (IUCPQ, Laval University, Québec, City, Québec), led by Dr Josep Rodés-Cabau.

Throughout the research project, the student received a research grant from the Fundación Alfonso Martin Escudero (Madrid, Spain), effective between January 2017 and December 2018; and Dr Rodés-Cabau holded the Research Chair "Fondation Famille Jacques Larivière" for the Development of Structural Heart Disease Interventions.

This thesis is composed by 6 research articles, which have been published in high-impact peer-review cardiovascular journals.

The first article included in this thesis is entitled: **"Prolonged Continuous ECG Monitoring Prior to Transcatheter Aortic Valve Replacement. The PARE Study**". It has been published in **JACC: Cardiovascular Interventions**, and the student is the first author. The study evaluated the prevalence of subclinical atrial fibrillation and other cardiac arrhythmias in elderly patients with aortic stenosis screened for transcatheter aortic valve replacement at the IUCPQ. The student was the first author, and Dr Josep Rodés-Cabau, the senior author. Drs François Philippon and Isabelle Nault participated in the conception and design of the study, as well as in the interpretation of the data. All other authors approved the manuscript and contributed with their critical review of the manuscript.

The second article entitled: "**Percutaneous Left Atrial Appendage Closure: Current Devices and Clinical Outcomes**" was published in **Circulation: Cardiovascular Interventions**. This review analyzed the temporal trends in procedural complications since the beginning of the percutaneous left atrial appendage closure era, as well as the available evidence on mid- and long-term outcomes following left atrial appendage closure. The

student was the first author of this article and participated in the review of the literature, drafting and revision of the manuscript, under the supervision of Dr Josep Rodés-Cabau.

The third article of this thesis is entitled: **"Percutaneous Left Atrial Appendage Closure with the Ultraseal Device: Insights from the Initial Multicenter Experience".** This work was presented as an oral communication at the Transcatheter Cardiovascular Therapeutics meeting in September 2018 (TCT 2018, San Diego, USA) with simultaneous publication in **JACC: Cardiovascular Interventions**. It was also presented as an oral communication at the meeting from the Spanish Society of Cardiology (Seville, Spain, October 2018). This study included the initial worldwide experience with the Ultraseal LAAC device, with 15 centers from Canada and Europe. The student was responsible for the collection of the data at the IUCPQ, the management, analysis and interpretation of the data from the worldwide centers, and drafting of the manuscript. Dr Josep Rodés-Cabau was the principal investigator and senior author of the study, and supervised each of the steps. All other authors contributed with their comments and constructive review of the manuscript.

The fourth article, which was entitled: "**Hemodynamic Impact of Percutaneous Left Atrial Appendage Closure in Patients with Paroxysmal Atrial Fibrillation**" was published in the **Journal of Interventional Cardiac Electrophysiology**, and evaluated non-invasively the acute hemodynamic impact of percutaneous left atrial appendage occlusion. The student is the first author of the study, and participated in the conception of the study, analysis and interpretation of the data, and drafting of the manuscript, under the supervision of Dr Josep Rodés-Cabau. All other authors approved and revised the manuscript.

The fifth article of this thesis is entitled: "**Short-Term Oral Anticoagulation Versus Antiplatelet Therapy Following Transcatheter Left Atrial Appendage Closure**" and has been published in **Circulation: Cardiovascular Interventions**. This work compared the activation of the coagulation system following left atrial appendage occlusion between patients receiving antiplatelet therapy or 45-day oral anticoagulation therapy after the

procedure at our institution. The student was responsible for the collection and interpretation of the data, drafting and revision of the manuscript. The statistical analysis was performed by Mélanie Côté, with all steps supervised by the senior author, Dr Josep Rodés-Cabau. All other authors approved the manuscript and revised it for relevant intellectual content.

The last and sixth article presented in this thesis was entitled: "**Recurrence of Device-Related Thrombus After Percutaneous Left Atrial Appendage Closure**". It was published in the **Circulation** Journal. The student was the first author, developed the database for the study, and was responsible for the collection, analysis and interpretation of the data, as well as drafting of the manuscript. Dr Josep Rodés-Cabau supervised all of these steps. All other authors approved the manuscript and contributed with their critical review of the manuscript.

INTRODUCTION

1.1. ATRIAL FIBRILLATION

1.1.1. Epidemiology

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide[1-4] with an incidence projected to double to more than 12 million in the United States by 2050 and 17.9 million in Europe by 2060 (**Figure 1**).[1, 2] It is noteworthy that this prevalence is largely underestimated due to underdiagnosis in elderly asymptomatic patients or when associated with only transient symptoms. Of note, age is the most important risk factor for AF. Compared to individuals aged 50 to 59, the risk of occurrence is 4.98-, 7.35- and 9.33-fold higher in patients aged 60-69 years, 70-79 years and 80-89 years, respectively.[5] Two other traditional cardiovascular risk factors, diabetes (odds ratio: 1.4 for men, 1.6 for women) and hypertension (odds ratio: 1.5 for men, 1.4 for women) have been identified as independent risk factors for AF.[6]

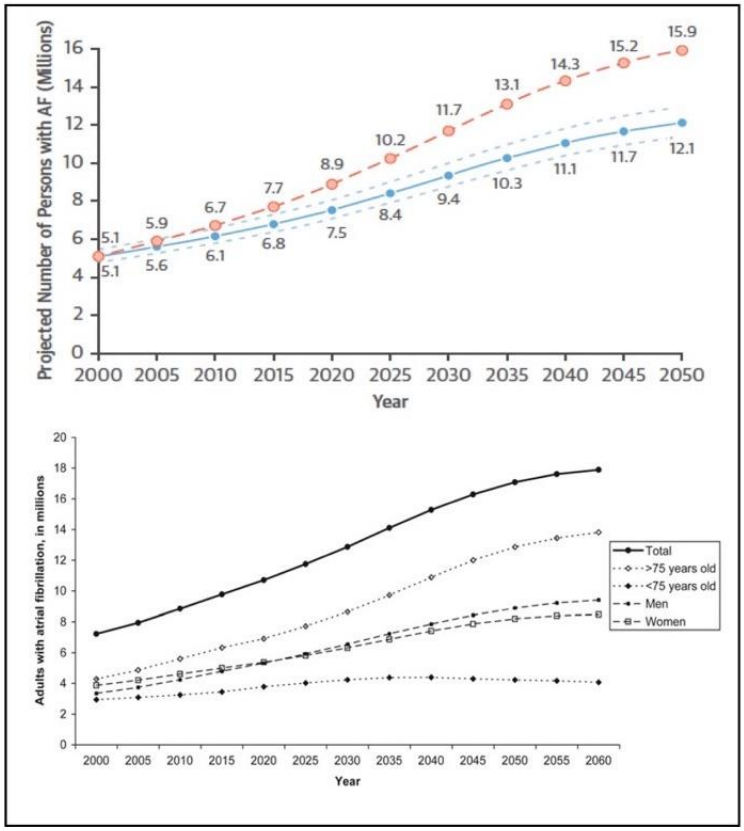

Figure 1. Projected number of persons with atrial fibrillation in the United States (top) and in Europe (bottom).

The solid curve in the top figure indicates assuming no further increase in age-adjusted incidence, and the dotted curve assuming a continued increase in incidence as observed between 1980 and 2000. From Miyasaka et al.[1] and Krijthe et al.[2] with permission.

AF represents a major public health concern, significantly increasing the risk of stroke, morbidity, mortality and healthcare costs.[7] Indeed, AF has been associated with an increased risk of frailty (HR: 4.1), heart failure (HR: 1.2 – 23.2), hospitalization (HR: 1.1), sudden death (HR: 3.3) and increased risk of cardiac and total mortality (HR: 1.7 – 2.1).[3, 8-10] AF has substantial socioeconomic implications mainly derived from AF-related hospitalisations, with exponential increase in hospital costs by 24% to 468% over the last decade.[4, 11] Hence, AF constitutes a growing epidemic with enormous economic and public health burden. A compelling clinical need exists for improved healthcare measures including novel screening technologies to optimize early identification of asymptomatic individuals, and enhancement of stroke prevention measures to decrease AF-related healthcare expenses.

1.1.2. Atrial fibrillation and stroke

AF confers a 5-fold increase in the risk of stroke,[12] and 17-fold increase in patients with rheumatic valve disease.[13] Importantly, AF-related strokes are associated with greater morbidity - >50% greater disability, handicap and recurrence -, mortality and costs compared with non-cardioembolic strokes.[12] The risk of ischemic stroke in non-valvular AF patients averages 5% per year (8% in patients aged 75 years-old or older). About 15-20% of all ischemic strokes are attributed to AF.[14] This proportion increases steadily with age, accounting for up to 40% of strokes in patients over the age of 80 years.[15, 16] Noteworthy, the prevalence of AF increased by 22% and by 38% among patients admitted in the United States for acute ischemic stroke and transient ischemic attack respectively between 2003 and 2014.[17] Up to 50-70% of all strokes in AF patients are thought to be cardioembolic, the main source of these cardioembolic events lying within the left atrial appendage (LAA, >90% of cases in non-rheumatic AF, 57% in rheumatic AF).[18]

1.1.3. Pathophysiology: Thrombogenic mechanisms in atrial fibrillation

Thrombogenesis in AF is a complex and multifactorial process, with several mechanisms promoting a prothrombotic or hypercoagulable state. Interestingly, the triad postulated by Rudolf Virchow in 1856 to explain thrombus formation - endothelial or endocardial

damage; abnormal blood stasis; abnormal blood constituents - is also fulfilled in AF (**Figure 2**).[19]

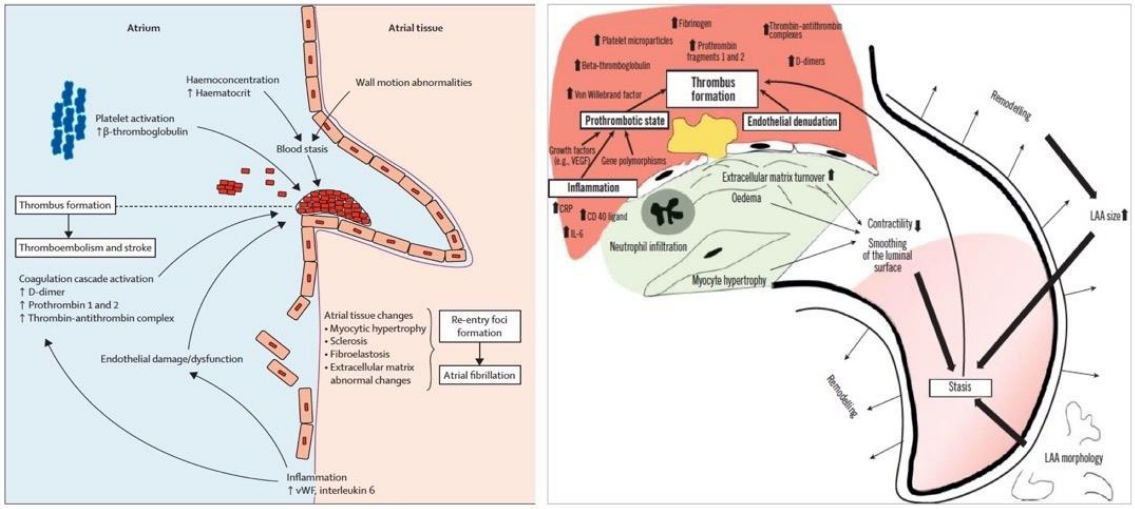

Figure 2. Virchow's triad components for thrombogenesis in atrial fibrillation.
From Watson et al.[19] and Glikson et al.[20] with permission.

Abnormalities of the vessel wall. The LAA is the most common site of intra-atrial thrombus formation. Because of AF, the atrial wall and endocardium experience progressive dilatation, endocardial denudation with thrombotic aggregation, myocytic hypertrophy, and edematous or fibro-elastic infiltration of the extracellular matrix. Importantly, the disruption of the extracellular matrix observed in AF patients (with abnormal concentrations of matrix metalloproteinases) may not only lead to conduction defects potentially perpetuating AF, but also induce fibrosis and infiltration of the endocardium, thus promoting thrombogenesis. Altogether, such cardiac stunning underscores the importance of an adequate thromboembolic stroke prevention strategy even after restoration of sinus rhythm.[19]

Abnormal blood stasis. The structural changes associated with AF along with the loss of atrial systole, contribute to the increased stasis in the left atrium and diminished flow velocities within the LAA. This phenomenon is even more remarkable in the presence of mitral stenosis, with greater left atrial dilatation and further stasis. Of note, atrial size has been identified as an independent risk factor for stroke.[21] In normal sinus rhythm, a

quadriphasic pattern of blood flow can be noted in the LAA, with none or minimal blood stasis. In AF, this pattern disappears and spontaneous echo contrast can be visualized by transesophageal echocardiography, which is thought to be linked to an interaction between fibrinogen and erythrocytes, being a risk factor for both thrombus formation and thromboembolism.[22]

Abnormal blood constituents. Platelets and coagulation cascade, along with other blood constituents (inflammatory cytokines and growth factors), constitute the chief intravascular promoters of thrombogenesis in AF patients. AF constitutes a prothrombotic state itself, with increased fibrin turnover and abnormally high levels of prothrombotic markers (prothrombin fragments 1+2, thrombin-antithrombin complex).[19] Furthermore, in non-valvular AF, there is a significant correlation between prothrombin fragments 1+2, fibrinopeptide A, thrombin-anti-thrombin complex and the presence of spontaneous echo contrast at transesophageal echocardiography.[23] Similarly, AF patients exhibit greater levels of D-dimer and β-thromboglobulin, the former potentially predicting the presence of LAA thrombus, and subsequent thromboembolic events.[24] Von Willebrand factor, a well-established marker of endothelial dysfunction, has been demonstrated to be a predictor of stroke and vascular events, improving clinical risk stratification for stroke.[25] However, its non-specificity may probably hamper its applicability in AF. The potential role of platelets in the hypercoagulable state associated with AF remains controversial. Platelets seem to interact with the endocardium, proteins of the coagulation cascade, and inflammatory cells to increase the thrombogenecity in AF. CD40 ligand is present on the platelet surface only after activation and then cleaved, generating the soluble biologically active fragment sCD40L. In AF, sCD40L is slightly elevated, but the stimulus for this is unclear.[26] P-selectin and CD63, well-validated markers of platelet activation, have been related to the embolic status of patients with non-valvular AF.[27] Finally, abnormal changes in systemic inflammation have been suggested to drive the prothrombotic state in AF. Levels of interleukin-6 and C-reactive-protein are abnormally elevated in AF, which could increase platelet production and sensitivity to thrombin. Likewise, vascular endothelial growth factors have been shown to alter in AF, acting as potent stimulants for tissue factor

expression, which in turn acts as a cofactor to factor VIIa, a well-known trigger to thrombin formation.[19]

1.1.4. Diagnosis

The diagnosis of AF requires documentation by 12-lead electrocardiography or a single-lead ECG tracing showing absolutely irregular RR intervals and no discernible, distinct P waves (**Figure 3**). By accepted convention, an episode lasting at least 30 seconds is diagnostic.[28]

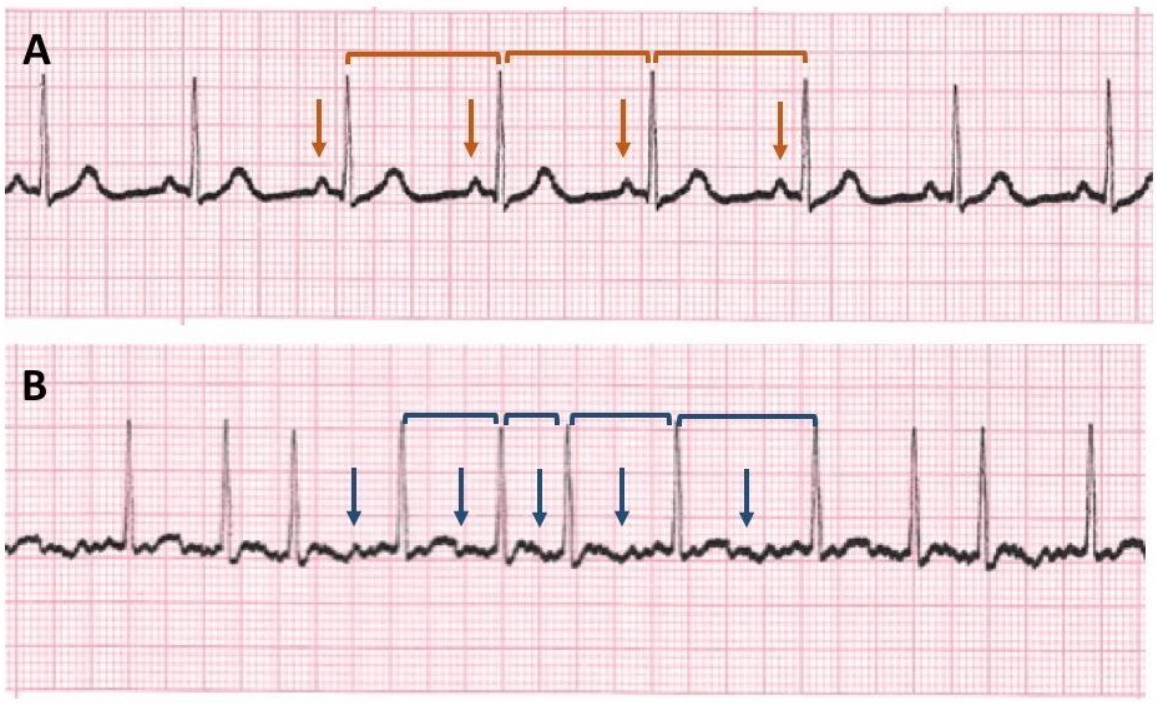

Figure 3. Atrial fibrillation ECG findings.

(A) Electrocardiogram in sinus rhythm. Orange arrows indicate normal p waves and regular RR intervals (orange bracket).

(B) Electrocardiogram in atrial fibrillation. Blue arrows indicate abnormal atrial fibrillation waves and irregular RR intervals (blue bracket).

Five patterns of AF have been described according to the clinical presentation, duration, and termination of AF episodes (**Table 1**).

Table 1. Classification of atrial fibrillation

AF pattern	Definition
First diagnosed AF	AF not diagnosed before, irrespective of the duration or symptoms
Paroxysmal AF	Self-terminating, in most cases within 48 hours (for up to 7 days)
Persistent AF	Lasting longer than 7 days, including episodes terminated by cardioversion
Long-standing persistent AF	Lasting for ≥1 year when it is decided to adopt a rhythm control strategy
Permanent AF	Accepted by the patient (and physician). Rhythm control interventions are not pursued in those patients.

AF: Atrial fibrillation. From Hindricks et al.[28]

Undiagnosed AF is frequent, particularly among elderly patients. Data from the GLORIA-AF (Global Registry on Long-Term Antithrombotic Treatment in Patients with AF) registry showed that AF may be asymptomatic or minimally symptomatic in up to 70% of patients.[29] Of note, subclinical AF (SCAF) has been associated with a greater risk of stroke given the potential delay in oral anticoagulation (OAC) prescription in the absence of symptoms.[30] Opportunistic screening for SCAF has proved cost-effective in elderly populations >65 years of age.[31] Current guidelines recommend opportunistic AF screening (during routine interactions with the healthcare system) by pulse palpation or ECG rhythm strip in patients ≥65 years (I-B), with systematic screening (at some predefined time point outside routine medical care) considered to detect AF in patients aged ≥ 75 years, or those at high stroke risk (IIa-B).[28] However, recent data from the ARIC (Atherosclerosis Risk in Communities), which identified a 2.5% prevalence of SCAF in elderly populations using 2 weeks continuous ambulatory ECG monitoring, casted doubts on the role of pulse palpation or single lead ECG for screening, since the majority of SCAF cases (75%) were intermittent and had low AF burden (≤10%).[32] In fact, effectiveness of screening has been

strongly related to its duration, with longer continuous ECG monitoring having a higher diagnostic yield to detect SCAF.

With newer ambulatory monitoring technologies enabling extended continuous electrocardiographic monitoring,[33, 34] a high prevalence of previously unknown AF has been detected in high-risk populations – elderly,[35] with comorbid disorders,[36] or in patients undergoing transcatheter aortic valve replacement (TAVR) (**Table 2, Figure 4**).[37] Prompt identification of SCAF, classically undiagnosed, and early initiation of directed therapies, including OAC or non-pharmacologic stroke prevention therapies, is essential to optimize our management of patients with AF.

Table 2. Types of ambulatory cardiac monitoring devices

Type of recorder	Monitoring duration	Continuous recording	Unique features	Sensitivity
Holter monitor	24-48 hs	Yes	-Short term -Data on arrhythmic burden	44-60 %
Patch monitor	1-3 weeks	Yes	-Intermediate term -Improved patient compliance without leads	N/A
External loop recorder	1 month	Yes	-Good correlation between symptoms and arrhythmias	39-68 %
Mobile cardiac telemetry	1 month	Yes	-Real-time central monitoring -Relatively expensive	N/A
Implantable loop recorder	≤3 years	Yes	-Improved patient compliance -AF needs confirmation by ECG	45-88 %
Smartphone monitor	Indefinite	No	-Inexpensive long-term -Dependent on patient compliance	98.5 %
Pacemaker or ICD	Indefinite	Yes	-Good documentation of burden -AF needs confirmation by electrogram tracing (in the absence of an atrial lead)	96-98 %

AF: Atrial fibrillation; ECG: electrocardiogram; ICD: implantable cardioverter defibrillator. Adapted from Calkins et al.[38]

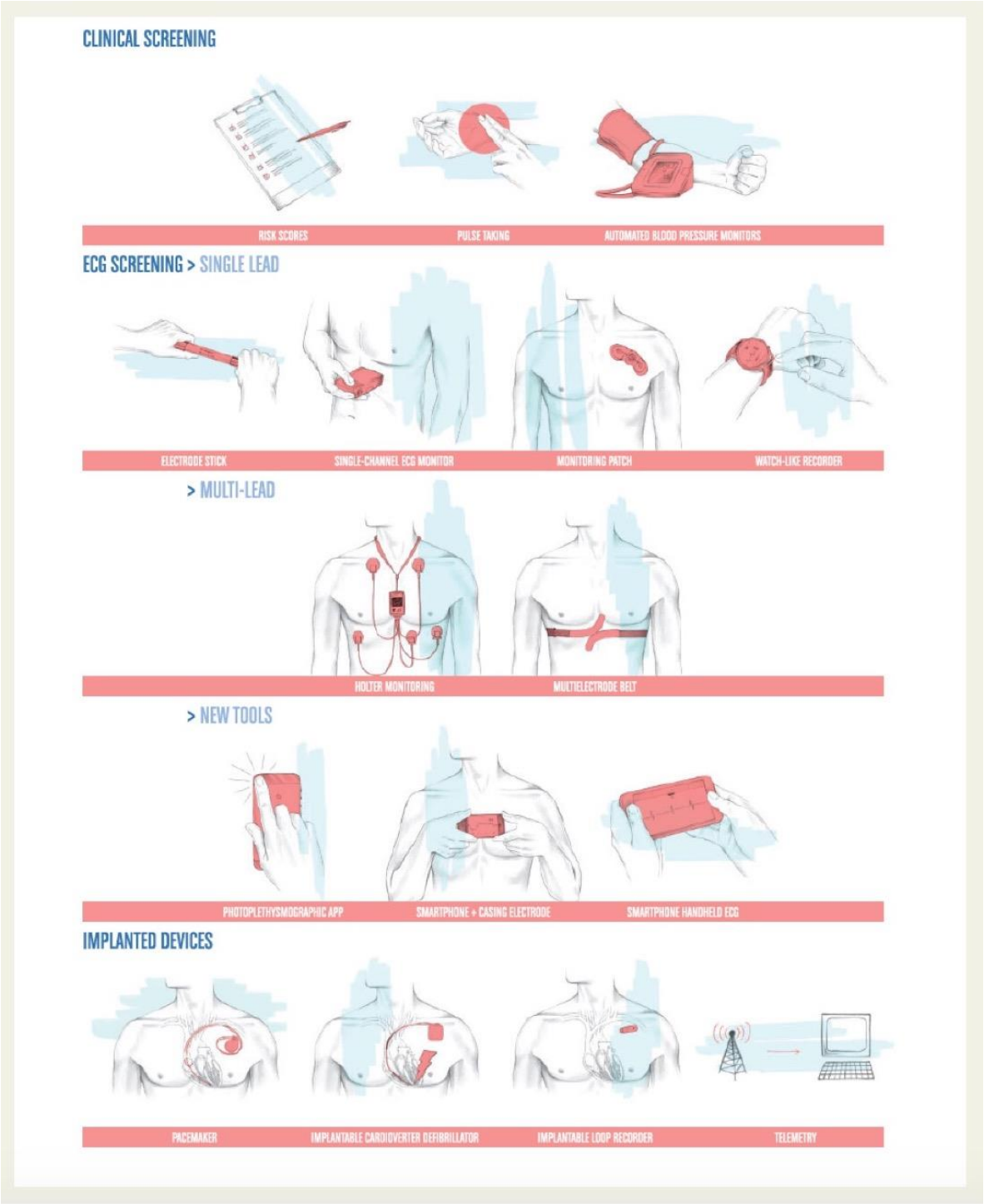

Figure 4. Screening tools for atrial fibrillation diagnosis.

From Mairesse et al.[39] with permission.

1.1.5. Clinical risk stratification for stroke prevention

The prevention of AF-related ischemic stroke is based on a balance between benefit and harm from a specific strategy using probability calculation tools. In fact, stroke and bleeding risk factors often overlap, posing a major clinical challenge for decision making. Since the first stroke risk-stratification schemes developed in the late 1990s, the $CHADS_2$ score (congestive heart failure, hypertension, age >75 years, diabetes and previous stroke [doubled]), with a C-statistic of 0.82, emerged in 2001 as the simplest and most precise predictor of stroke.[40] Although widely used for many years, the $CHADS_2$ score showed several shortcomings (age treated as a binary variable, exclusion of important risk factors, and poor ability to identify low-risk patients who do not benefit from stroke prevention therapy). To overcome this limitations, Lip et al.[41] created in 2010 a new risk-scoring scheme by adding additional risk factors (female gender, vascular disease, and age categories [65-74 years, and ≥75 years]): the extended CHA_2DS_2-VAS_C score. Given its superiority over $CHADS_2$ score in quantifying stroke risk, the CHA_2DS_2-VAS_C score is the recommended stroke risk prediction tool for patients with nonvalvular AF by the European Society of Cardiology and American College of Cardiology / American Heart Association guidelines, since 2010 and 2014 respectively. Thresholds for OAC recommendation vary slightly between guidelines (**Table 3**).

The European and American guidelines for the management of AF advise OAC for patients with AF and a CHA_2DS_2-$VAS_C \geq 2$ (class I recommendation, level A).[28, 42] Patients with a CHA_2DS_2-VAS_C =1 (which represent about 10-15% of patients), constitute a gray area of uncertainty. However, a net clinical benefit from OAC has recently been shown even in the presence of 1 non-sex-related risk factor,[43] and latest guidelines recommend the possibility of stroke prevention in those patients, taking patient values and preferences into consideration (IIa-B and IIb-C for European and American guidelines, respectively). Finally, Canadian guidelines recommend OAC in all AF patients aged > 65 or with $CHADS_2$ score ≥ 1.[44] Importantly, most elements of these scores are dynamic, requiring periodic risk reassessment.

Table 3. Stroke risk prediction algorithms and antithrombotic recommendations

	2019 AHA/ACC/HRS[42]	2020 ESC[28]	2018 CCS[44]
	CHA_2DS_2-VAS_C		CHADS-65
Congestive heart failure	1		1
Hypertension	1		1
Age ≥ 75 years	2		1
Diabetes Mellitus	1		1
Stroke, TIA, embolism	2		1
Vascular Disease	1		-
Age 65-74 years	1		1
Female Sex	1		-
0	No (IIa)	No (III)	No (conditional)*
1	NOAC > VKA (IIb)	NOAC > VKA (IIa)	NOAC (strong)
≥ 2	VKA > NOAC (I)	NOAC > VKA (I)	NOAC (strong)

*ASA for patients aged <65 years with a $CHADS_2$ score=0 with arterial vascular disease (coronary, aortic, or peripheral)
ACC: American College of Cardiology; AHA: American Heart Association; ASA: Aspirin; CCS: Canadian Cardiovascular Society; ESC: European Society of Cardiology; HRS: Heart Rhythm Society; NOAC: novel oral anticoagulant; OAC: Oral anticoagulant; TIA: transient ischemic attack; VKA: vitamin K antagonist.

Several bleeding risk scores have been developed to date, albeit generally with a modest predictive ability (**Table 4**). The most commonly used risk score for assessing the risk of bleeding in AF patients is the HAS-BLED score, which takes into account seven factors: hypertension >160 mmHg, abnormal renal or liver function (creatinine >200 µmol/l, dialysis or kidney transplant, cirrhosis or bilirubin >2x normal or AST/ALT >3x normal), stroke, bleeding, labile INR (time in therapeutic range <60%), >65 years old and consumption of anti-inflammatory or anti-platelet drugs or alcohol.[45] A score ≥ 3 represents a high risk of bleeding which may translate into close monitoring, but in general should not result in withholding OAC. Other bleeding risk scores include the ORBIT (older age ≥75 years, reduced hemoglobin or anemia, bleeding history, insufficient kidney function, treatment with antiplatelets), the ATRIA (anemia, severe renal disease, age, any prior hemorrhage, diagnosed hypertension), or the $HEMORR_2HAGES$ (hepatic or renal dysfunction, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding risk, hypertension, anemia, genetic factors, excessive fall risk, stroke).[46-49]

Table 4. Bleeding risk scores

ATRIA		HAS-BLED		ORBIT		HEMORR$_2$HAGES	
Anemia	3	**H**ypertension-uncontrolled	1	**O**lder age (>75yo)	1	**H**epatic or renal disease	1
Severe renal disease	3	**A**bnormal renal or liver function	1 or 2	**R**educed hemoglobin, hematocrit or anemia	2	**E**thanol abuse	1
Age	2	**S**troke	1	**B**leeding history	2	**M**alignancy	1
Any prior hemorrhage	1	**B**leeding history	1	**I**nsufficient kidney function	1	**O**lder age	1
Hypertension	1	**L**abile INR	1	**T**reatment with anti-platelets	1	**R**educed platelet count or function	1
		Elderly	1			**R**ebleeding risk	2
		Drugs or alcohol	1 or 2			**H**ypertension	1
						Anemia	1
						Genetic factors	1
						Excessive fall risk	1
						Stroke	1
Maximum score: 10		Maximum score: 9		Maximum score: 7		Maximum score: 12	
High risk ≥5		**High risk ≥3**		**High risk ≥4**		**High risk ≥4**	

The HAS-BLED score is the most often used to estimate bleeding risk given its ease of use and having proven to be superior to other scores in predicting bleeding risk.[50, 51] Interestingly and unlike other scores, HAS-BLED includes modifiable risk factors that can easily be addressed such as uncontrolled high blood pressure, concomitant treatment with an antiplatelet therapy (which can generally be withdrawn after one year of an acute coronary syndrome), alcohol abuse or poor anticoagulation control. Furthermore, its predictive value for bleeding has been validated in several scenarios (e.g. direct OAC, bridging therapy in patients undergoing percutaneous coronary intervention).[52, 53] However, some important limitations should be acknowledged. First, it has modest risk discrimination ability, with C statistics ranging from 0.50 to 0.80.[54] Second, because of the parallel nature of bleeding and stroke risk scores, many of the risk factors encountered in HAS-BLED overlap with those included in stroke risk scores, lacking ability to discriminate bleeding risk from stroke risk. Third, in a recent substudy of the Amulet Observational Study (Abbott, Plymouth, Minnesota), HAS-BLED did not predict major bleeding events in patients undergoing left atrial appendage closure (LAAC) treated by antiplatelet therapy, especially in those with a history of previous gastrointestinal bleeding.[55]

More recently, the biomarker-based ABC-bleeding risk score (age, biomarkers [GDF-15, cTnT-hs, hemoglobin], clinical history [prior bleeding]) has been proposed with the potential to overcome some of the limitations of previous scores by including tailored blood biomarker guidance, while avoiding risk factors overlap (other than age) with other ischemic stroke risk scores.[56] However, ABC-bleeding failed to show long-term advantage over HAS-BLED score in a recent "real-world" validation study (the latter performing better in identifying low-bleeding risk patients [HAS-BLED 0-2]), and will require further validation in larger populations outside of clinical trials.[57] Overall and most importantly, most bleeding risk factors should be perceived as potentially correctable factors to be revisited periodically, rather than contraindicate OAC initiation or continuation per se.

1.2. PHARMACOLOGICAL STRATEGIES FOR STROKE PREVENTION

Oral anticoagulation therapy is the mainstay of treatment for stroke prevention in patients with AF, providing a stroke risk reduction >60%, and a 26% reduction in all-cause mortality compared with control or placebo.[58] Within the last decade, the introduction of four direct OAC and the development of minimally invasive non-pharmacologic strategies have emerged as alternative therapeutic options for AF stroke prevention.

1.2.1. Vitamin k antagonist anticoagulants

For more than 50 years and until 2009, vitamin K antagonists were the only available OAC class, with a large body of evidence supporting effectiveness of warfarin in thromboembolic prevention.[58-60] Vitamin K antagonists act by inhibiting the enzyme vitamin K epoxide reductase, thereby inhibiting carboxylation activation of coagulation factors II, VII, IX and X, and proteins C and S (**Figure 5**). Vitamin K antagonists are metabolized by C-P450 enzymes, and interact with a broad range of drugs and foods, requiring regular international normalized ratio (INR) monitoring and dose adjustment. The pharmacological characteristics of vitamin K antagonists – warfarin, phenprocoumon, acenocumarol – particularly their narrow therapeutic window requiring close coagulation monitoring, frequent dose adjustments,[61] and drug and food interactions, have led to

reluctance to prescription among physicians (<50% prescription prevalence even in high-risk patients),[62, 63] and high discontinuation rates.[64-68]

1.2.2. Non-vitamin k antagonist anticoagulants

Direct Factor Xa inhibitors – apixaban, rivaroxaban and edoxaban – as well as the direct thrombin inhibitor dabigatran, have been developed to overcome the limitations of vitamin K antagonists therapy. The formers are competitive, selective and potent direct inhibitors of the Factor Xa, that determine a strong inhibition of Factor-Xa binding to its active site both when free and when pro-thrombin (Factor II) bound. Dabigatran is a potent, competitive direct thrombin inhibitor that binds specifically and in a reversible manner both clot-bound and free thrombin, inhibiting thrombin-induced platelet aggregation (**Figure 5**). Importantly, direct Factor Xa inhibitors are not pro-drugs and do not require activation, whereas Dabigatran is administered as a pro-drug (dabigatran etexilate) which is rapidly activated by carboxylesterases, with no hepatic metabolism by cytochrome P450.

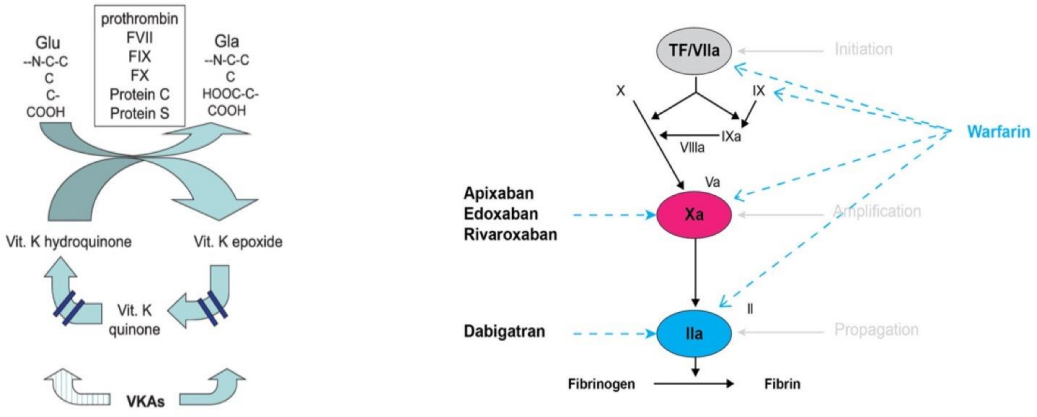

Figure 5. Mechanism of action of vitamin K antagonists (left) and direct oral anticoagulants (right).

Glu: glutamic acid; Gla: γ-carboxyglutamic acid. With permission from De Caterina et al.[69] and Nutescu et al.[70]

Of note, these therapies yielded favorable safety and efficacy profiles compared with warfarin in 4 large randomized controlled trials (**Table 5**),[71-74] with consistent reduction in intracranial and fatal/life-threatening bleeding compared to warfarin,[75] emerging as the preferred choice for stroke prevention in AF patients, particularly in those newly started on OAC.[28, 76] In a meta-analysis including data from all four direct OAC studied in the pivotal phase 3 clinical trials (vs warfarin), direct OAC significantly reduced stroke or systemic embolic events by ~20% compared with warfarin (RR 0.81, 95% CI 0.73-0.91, p<0.0001), all-cause mortality by 10% (0.90, 0.85-0.95, p=0.0003) and intracranial hemorrhage by ~50% (0.48, 0.39-0.59, p<0.0001), but slightly increased the risk of gastrointestinal bleeding (RR 1.25, 1.01-1.55, p=0.04).[75] Despite slight increase in OAC use linked to the advantageous characteristics of direct OAC over vitamin K antagonists (improved efficacy/safety ratio, predictable anticoagulant effect with no need for routine monitoring, fewer drug and food interactions), up to 40% of AF patients at high stroke risk still fail to receive appropriate thromboembolic prophylaxis in contemporary practice.[77]

Importantly, there seems to be no "class effect" of direct OAC, since the potential risk of bleeding from different direct OACs is not necessarily the same. The AVERROES (Apixaban versus Aspirin to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) showed similar rates of major bleeding (1.4% vs 1.2% per year, p=0.57) and intracranial hemorrhage (0.4% vs 0.4%, p=0.69) between apixaban and aspirin, the former being much more effective in stroke prevention (1.6% vs 3.7% per year, HR=0.45, p<0.001).[78] In the recently published ELDERCARE AF trial (Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients), which randomized once-daily 15-mg dose of edoxaban or placebo in nearly 1,000 very elderly Japanese patients (mean age 87±4 years) unsuitable for direct OAC (mean creatinine clearance 36±14 ml/min, low body weight 51±11 kg, 1/3 on non-steroidal anti-inflamatory drugs, >50% on antiplatelet agents), low-dose edoxaban did not increase the risk of intracranial bleeding (0.3% vs 0.6%), although it tripled the rate of gastrointestinal bleeding (2.3% vs 0.8%) compared to placebo.[79] Altogether, the efficacy and safety of direct OAC is generally consistent across different studies regardless of having received prior vitamin K antagonists, but care should be taken to avoid gastrointestinal bleedings.

Table 5. Randomized data on Pharmacological Stroke Prevention Therapies in AF

First author / Trial, year (Ref)	Type	No	Findings
VKA			
Van Walraven, 2002[59]	RCT-PLMA	4,052	Compared with ASA, warfarin resulted in: • 45% ↓ in any stroke (95% CI: 29% to 57%) • 52% ↓ in ischemic stroke (95% CI: 37% to 63%) • 71% ↓ in bleeding events (95% CI: 21% to 141%)
Hart, 2007[58]	MA	2,900	Compared with no treatment, warfarin resulted in: • 64% ↓ in stroke (95% CI: 49% to 74%)
		3,647	Compared with ASA, warfarin resulted in: • 37% ↓ in stroke (95% CI: 23% to 48%)
		4,876	Compared with no treatment, antiplatelets resulted in: • 19% ↓ in stroke (95% CI: -1% to 35%
DOAC			
RE-LY, 2009[71]	RCT	18,113	Compared with warfarin, high-dose dabigatran resulted in: • 34% ↓ in stroke / embolism (95% CI: 18% to 47%) • 74% ↓ in ICH (95% CI: 51% to 86%) • 12% ↓ in all-cause death (95% CI: 0% to 13%)
ARISTOTLE, 2011[72]	RCT	18,201	Compared with warfarin, apixaban resulted in: • 21% ↓ in stroke / embolism (95% CI: 5% to 34%) • 49% ↓ in ICH (95% CI: 25% to 65%) • 11% ↓ in all-cause death (95% CI: 1% to 20%)
ROCKET AF, 2011[73]	RCT	14,264	Compared with warfarin, rivaroxaban resulted in: • 21% ↓ in stroke/ embolism (95% CI: 4% to 34%) • 33% ↓ in ICH (95% CI: 7% to 53%)
ENGAGE AF-TIMI 48, 2013[74]	RCT	21,105	Compared with warfarin, high-dose edoxaban resulted in: • 21% ↓ in stroke/ embolism (95% CI: 1% to 37%) • 20% ↓ in ICH (95% CI: 1% to 37%) • 14% ↓ in cardiac mortality (95% CI: 3% to 23%)

Adapted from Alkhouli et al[80] with permission.

ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ASA: aspirin; CI: confidence interval; DOAC: direct oral anticoagulants; ENGAGE AF-TIMI 48: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction 48; HR:hazard ratio; ICH: intracranial hemorrhage; MA: meta-analysis; OAC: Oral anticoagulation; PLMA: patient-level meta-analysis; RCT: randomized controlled trial; RE-LY: Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; VKA: vitamin K antagonists

1.2.3. Antiplatelet agents

1.2.3.1. Single antiplatelet therapy

Aspirin monotherapy has been shown to be less effective than warfarin for stroke prevention in AF patients,[58] and its benefit compared with no therapy remains

controversial. A meta-analysis by Hart et al.[58] showed a 19% nonsignificant reduction in stroke with aspirin vs no therapy (95% CI: 1.0 to 35.0), but a large observational study in Sweden showed a higher incidence of ischemic stroke and thromboembolic events with aspirin monotherapy compared with no antithrombotic therapy.[81] Overall, bleeding rates on aspirin monotherapy are non-inferior to those on OAC,[82] and should not be recommended for stroke prevention in AF patients.

1.2.3.2. Dual antiplatelet therapy (DAPT)

The ACTIVE W and ACTIVE A (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) randomized trials evaluated the potential benefit of adding clopidogrel to aspirin for stroke prevention in AF patients. The ACTIVE W trial (DAPT vs warfarin) was stopped prematurely due to a significantly lower annual rate of stroke, systemic embolism, myocardial infarction or vascular death with warfarin compared to DAPT (3.9% vs 5.6%, RR: 0.69, 95% CI, 0.57-0.85).[83] In the ACTIVE A trial (DAPT vs aspirin in patients ineligible for OAC), DAPT was associated with a lower rate of stroke, systemic embolism, myocardial infarction or vascular death (RR: 0.89, 95% CI, 0.81-0.98) but at the expense of increased major bleeding (RR: 1.57, 95% CI, 1.29-1.92).[84] Overall, a pooled analysis of these trials showed that the addition of clopidogrel translated into a modest net clinical benefit in patients unsuitable for OAC (0.57 ischemic stroke prevented [95% CI: 0.12-1.24] per 100 patients-year of treatment).[85] However, bleeding risk on DAPT is similar to that on OAC, and should be avoided as stroke prevention therapy in AF patients.

1.3. NON-PHARMACOLOGICAL STRATEGIES FOR STROKE PREVENTION

1.3.1. Rationale for left atrial appendage closure

Despite the benefits and increasing use of direct OAC, close to one in ten patients have a contraindication to OAC and 2% have an absolute contraindication (major intracranial pathology or end-stage liver disease).[86, 87] In contemporary clinical practice, up to 40% of patients at high risk for stroke do not receive OAC due to fear of serious bleedings, and approximately 20% of patients discontinued direct OAC therapy in randomized clinical trials.[77] The pivotal role of the LAA in AF-related thrombogenesis constitutes the rationale for mechanical LAAC, as an alternative stroke-prevention therapy for AF patients deemed not suitable for OAC.

Autopsy and surgical data suggest that LAA is the most common source of thrombus formation in AF,[18, 88] since the fibrillating LAA creates a favorable milieu for blood stagnation and thrombus formation. Furthermore, transesophageal echocardiography suggests that most AF-related strokes result from LAA thromboembolism.[89] A meta-analysis from Blackshear et al.[18] pointed out that 91% of thrombi in nonvalvular AF patients were located in the LAA. In a recent, large-scale study including >1,400 patients with nonvalvular AF or atrial flutter undergoing transesophageal echocardiography before electrical cardioversion, the localization of atrial thrombosis was inside the LAA in 100% of the cases, and 4.6% of the patients (0.28% of the overall study population) had concomitant extra-LAA thrombus (3.4% in the right atrial appendage and 1.2% in the left atrial cavity) (**Figure 6**).[90] The low prevalence of extra-LAA thrombus observed in this study reinforces the potential role of LAAC for preventing thromboembolic events.

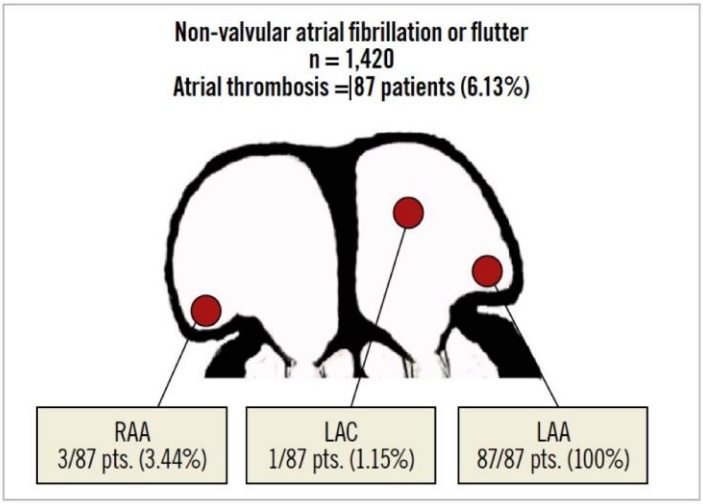

Figure 6. Localization of left atrial thrombi in patients with non-valvular atrial fibrillation or flutter.
From Cresti et al[90] with permission.

Finally, there may also be a role for LAAC as an adjunctive therapy to OAC in patients with recurrent stroke despite optimal OAC, after exclusion of other plausible causes (by cerebral computed tomography, echocardiography, carotid Doppler). Although this strategy may apply to a limited proportion of LAAC candidates (<5%), recent data suggest feasibility and safety of such an approach at 2-year follow-up.[91, 92]

1.3.2. Embryology, anatomy and function of the LAA

Embryologically, the LAA is a remnant of the primary atrial tube which develops during the third week of fetal cardiac development, whereas the remaining smooth left atrium derives from the primordial pulmonary veins. At week 4, right-handed looping of the primary endocardial tube takes place, bringing the caudal and cranial ends in close proximity. At this stage, the appendages and the atrium differentiate (balloon outward) laterally from the superolateral wall of the primary heart, whereas the ventricles balloon out in a more anterior-posterior fashion. The outpouching of the superior and left sided aspect of the primary atrial tube finally constitutes the LAA, with subsequent trabeculae formation around the fifth week of gestation.[93]

The LAA varies in size, shape and in its relationship with surrounding structures (**Figure 7**). There are three components: an ostium (or os), neck and body. The ostium connects the left atrium and the LAA, generally running at an oblique angle to the mitral valve annulus, and is the distance from the limbus to the mitral annulus. The neck is the narrowest part of the LAA and overlays the left circumflex artery. The body is the most variable part, often multilobulated (range: 1 to 4), with 2 lobes in up to 54% of the patients.[94] The LAA is an anterolateral structure that extends parallel to the left pulmonary veins, with the tip directed anteriorly and cranially, overlapping the pulmonary trunk and adjacent to the origin of the left descending coronary artery. The superior aspect is related to the pulmonary trunk, separated by the transverse sinus. The inferior aspect is closely related to the left circumflex artery and the great cardiac vein, that run beneath the neck of the LAA and along the atrioventricular groove and the mitral valve. Anteriorly, the lobes run parallel to the obtuse margin of the left ventricle and the left phrenic nerve courses posterolaterally. The posterior and superior aspects of the ostium are well-delimitated by a ridge separating the ostium from the left upper pulmonary vein, which corresponds epicardially to the ligament (or vein) of Marshall. The left phrenic nerve courses posterolaterally.[95]

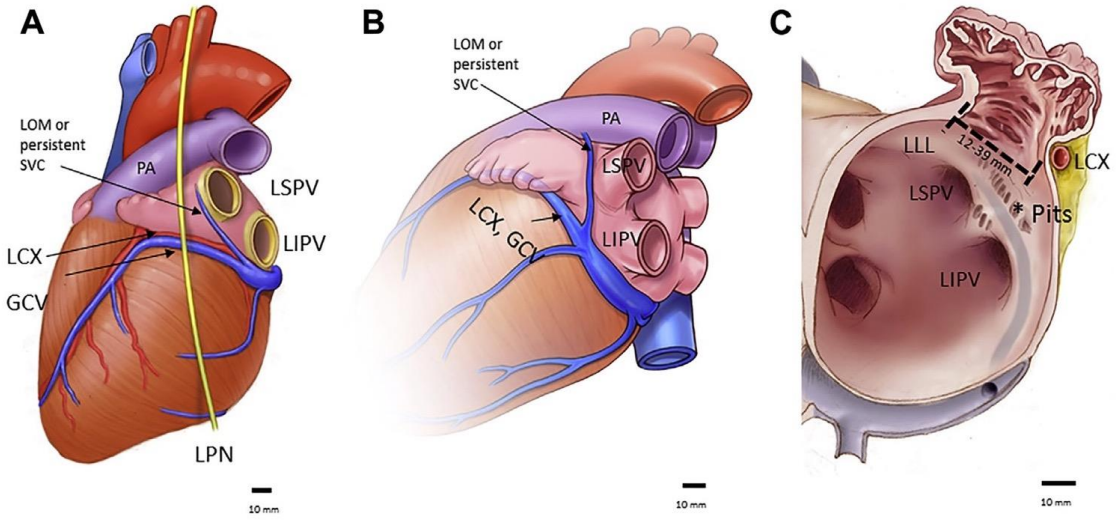

Figure 7. The left atrial appendage and surrounding structures.

From Naksuk et al.[95] with permission.
GCV: Great cardiac vein; LAA: Left atrial appendage; LCX: Left circumflex; LIPV: Left inferior pulmonary vein; LLL: Left lateral ridge; LOM: Ligament of Marshall; LPN: Left phrenic nerve; LSPV: Left superior pulmonary vein; PA: Pulmonary artery; SVC: Superior vena cava

Several LAA shapes and variants have been described (**Figure 8**): chicken wing (dominant lobe with a bend in the middle part, folding back on itself with a secondary lobe or twig), windsock (one dominant lobe larger than the distal portion of the LAA), cactus (dominant central lobe with secondary lobes extending superiorly and inferiorly) and cauliflower (complex, irregular, multilobed anatomy with no dominant lobe). In a study by Biase et al.[96] using computed tomography and cardiac magnetic resonance, the chicken wing morphology was the most common (48%) and less thrombogenic anatomy, followed by cactus (30%), windsock (19%) and cauliflower (3%), the latter associated with the highest risk of embolic event.

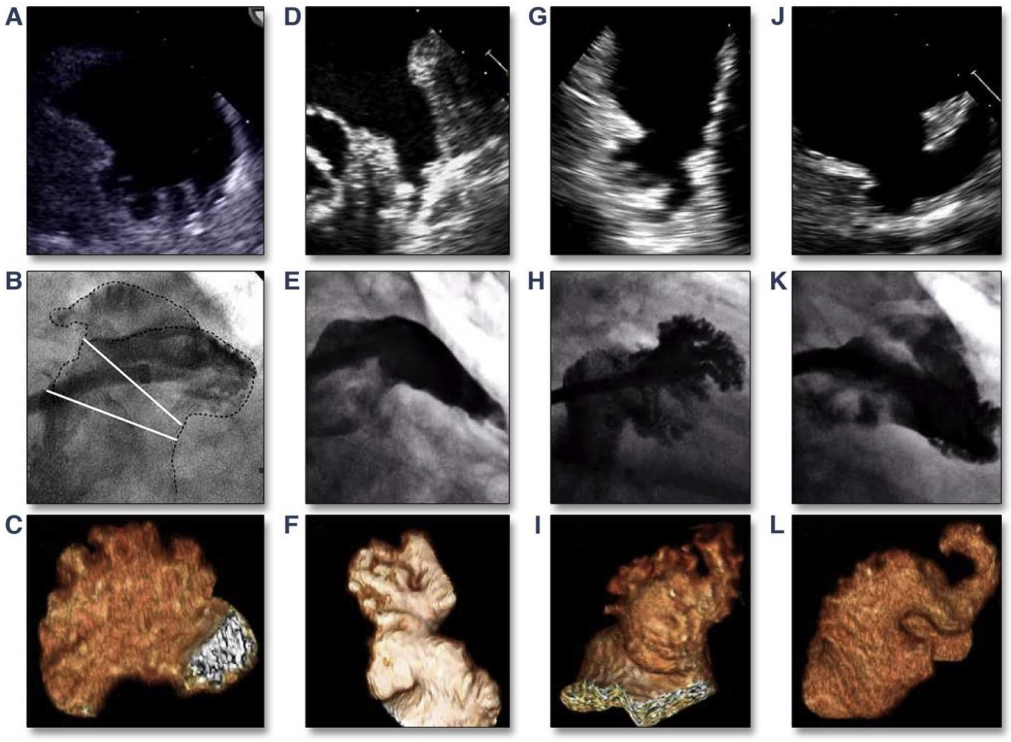

Figure 8. Multimodality imaging morphological classification of the LAA assessed by transesophageal imaging (top), angiography (middle) and computed tomography (bottom).
Cauliflower (A-C), windsock (D-F), cactus (G-I), chicken wing (J-L). From Beigel et al.[97] with permission.

The LAA has several physiologic unique functions, mainly reservoir, neurohormonal and electrical. First, the LAA is the most compliant structure within the left atrial chamber, acting as a reservoir and decompression chamber during left ventricular systole and in conditions of left atrial pressure and/or volume overload (eg. exercice, atrial arrhythmias or heart failure).[98] In patients with AF and/or increased filling pressures, LAA remodeling takes place, resulting in reduced contractile function and distensibility, and greater risk of thrombus formation. Second, the LAA is responsible for about 30% of all atrial natriuretic peptide production, modulating the left atrial pressure by activating stretch receptors, with effects on heart rate, diuresis and natriuresis.[99] Finally, chronic AF may result into remodeling, inflammation and fibrosis of both the left atrium and the LAA, leading to focal triggers and re-entry arrhythmias, thus constituting a vicious cycle.[100]

1.3.3. Indications for LAA closure

OAC therapy remains the standard of care for patients with nonvalvular AF and a CHA_2DS_2-VAS_C score ≥2. However, long-term OAC may chronically expose patients to increased risk of hemorrhagic complications, a concerning issue among frail, elderly patients, with prior bleeding history or predisposition, considered poor candidates for OAC. Over the last 2 decades, LAAC has emerged as a valid alternative to OAC for patients with contraindication to long-term OAC. Current American and European guidelines state that percutaneous LAAC may be considered for high-risk AF patients who are deemed unsuitable for OAC and consider surgical LAA excision for AF patients undergoing cardiac surgery (**Table 6**).[28, 42]

Table 6. Society guideline recommendations for left atrial appendage closure

Guide	Recommendation	Grade	LOE
2019 AHA/ACC/HRS[42]	Percutaneous LAAC may be considered in patients with AF at increased risk of stroke who have contraindications to long-term OAC	IIb	B
	Surgical LAAC may be considered in patients with AF undergoing cardiac surgery, as a component of an overt heart team approach to the management of AF	IIb	B
2020 ESC[28]	Percutaneous LAAC may be considered in patients with AF and contraindications for long-term anticoagulant treatment	IIb	B
	Surgical excision of the LAA may be considered in patients with AF undergoing cardiac surgery	IIb	C

ACC: American College of Cardiology; AF: Atrial fibrillation; AHA: American Heart Association; ESC: European Society of Cardiology; HRS: Heart Rhythm Society; LAAC: Left atrial appendage closure; LOE: Level of evidence; OAC: Oral anticoagulation

Additionally, the latest consensus statement on catheter-based LAAC considers potential indications for transcatheter LAAC in the following 5 scenarios:[20]

Patients with a contraindication for OAC. Those patients represent the most accepted clinical indication and the vast majority of patients currently undergoing LAAC. Whereas no specific definition for "absolute" contraindication to OAC exists, conditions generally contraindicating long-term OAC include risk for major or life-threatening bleeding (intracranial/intraspinal bleeding, severe gastrointestinal bleeding, untreatable pulmonary or urogenital bleeding) or severe side effects under vitamin K antagonists or direct OAC. Although no randomized data targeting this specific group of patients is available so far, safety and efficacy of this strategy have been widely demonstrated in several observational studies and registries, and are currently being evaluated in ongoing randomized trials (ASAP-TOO, NCT0292828497; CLOSURE-AF, NCT03463317).

Patients with nonvalvular AF eligible for long-term OAC. This is the only group of patients that has prospectively been evaluated in two randomized trials (PROTECT-AF and PREVAIL) so far. Based on these 2 studies, the FDA approved LAAC with the Watchman device in March 2015 for patients at increased risk of stroke deemed suitable for warfarin, with a rationale to seek a non-pharmacologic alternative to warfarin. Nevertheless, given the large body of evidence and clinical experience with OAC, LAAC should not be offered as a primary, mere alternative to OAC in patients with no significant increased bleeding risk, but only in those who categorically refuse OAC despite accurate explanation.

Patients with elevated bleeding risk under chronic OAC. Several observational studies have evaluated safety and efficacy of LAAC in high-bleeding risk patients with good results, including patients with high HAS-BLED score (≥3), with previous intracranial bleeding or major gastrointestinal bleeding (eg. diffuse angiodysplasia) or end-stage renal disease (in whom most direct OAC are contraindicated).[101-104]

Specific subgroups. LAAC may be considered in patients who experience an ischemic event despite adequate OAC (or OAC not efficient),[91, 92] in patients who undergo electrical isolation of the LAA as part of a left-sided ablation (which exhibit a higher risk of thrombus formation or thromboembolism), or in combination with AF ablation, to avoid an additional procedure with transseptal puncture.[105] However, data in these groups are still limited and require further investigation.

1.3.4. Surgical left atrial appendage closure

Since the first ever surgical LAA excision performed by Madden in 1949,[106] several surgical techniques have been developed. However, it was not until Cox et al.[107] described the Cox-Maze III procedure (requiring complete excision of the LAA in addition to a specific pattern of surgical incisions within both atria) in the late 1980s, that surgical LAAC gained popularity among the surgical community. Broadly, surgical LAAC can be obtained during concomitant cardiac surgery either by exclusion (LAA isolation from circulation) or excision (amputation and removal) of the LAA.[108] Exclusion can be achieved either endo- or epicardially by various suturing methods (simple neck ligation, purse-string technique, running or mattress sutures with and without felt pledgets) or using device-enabled approaches (non-cutting surgical staplers or other epicardial clipping systems such as the Endoloop snaring, LigaSure, TigerPaw or AtriClip [AtriCure, Westchester, OH]). Conversely, excision is performed epicardially by amputating the LAA using the cut-and-sew method or cutting staplers.

Data examining surgical LAA exclusion techniques have been inconclusive, mainly from small, retrospective studies with limited follow-up. In a landmark study using transesophageal echocardiography, Kanderian et al.[109] reported an overall rate success of LAA closure of 40%, with surgical excision exhibiting a higher success rate compared to exclusion (73% vs 23%, respectively). A meta-analysis by Dawson et al.[110] reported similar low success rates of complete LAA occlusion (55-66%), and the first randomized controlled trial (Left Atrial Appendage Occlusion Study, LAAOS) had to be stopped prematurely due to high failure rates.[111] Of note, incomplete surgical LAAC has been associated with increased LAA thrombosis and risk of stroke.[112-114] Surgical excision techniques have yielded higher success rates, although at the expense of increased rates of residual stumps (> 10 mm) and bleeding complications.[108, 109] A comparison of the efficacy of the different surgical closure techniques is outlined in **Table 7**.

Table 7. Comparison of surgical left atrial appendage closure techniques

Study, yr	Design	S-LAAC	Technique	Success rate, %*	FU, months	Stroke, %
Katz, 2000[115]	Retrospective	50	Ligation	64	64	2
Garcia-Fdez, 2003[116]	Retrospective	58	Double suturing	90	69	3.4
Healey, 2005[111]	RCT	52	Epicardial suture Stapler	45 72	13	2.6
Kanderian, 2008[109]	Retrospective	137	Excision Suture exclusion Stapler	73 23 0	8	13**
Nagpal, 2009[117]	RCT	22	Resection	82	In-hospital	4.5
Whitlock, 2013[118]	RCT	26	Amputation and closure	100	12	3.8
Zapolanski, 2013[119]	Retrospective	808	Double ligation	95	10	3.6
Kim, 2013[120]	Retrospective	631	Ligation, excision	-	1	0.9
Lee, 2014[121]	Retrospective	119	Amputation	-	37	0.8
Melduni, 2017[122]	Retrospective	461	Amputation, suturing, stapler	-	109	7.1
Elbadawi, 2017[123]	Retrospective	2519	NR	-	In-hospital	2.0
Friedman, 2018[124]	Retrospective	3892	Any technique	-	31	4.2
Yao, 2018[125]	Retrospective	4295	Any technique	-	25	2.4
Caliskan, 2018[125]	Prospective	291	AtriClip	100	36	1.7

*As assessed by intraoperative transesophageal echocardiography, defined as absence of Doppler flow and residual stump <1cm
**Stroke or transient ischemic attack
FU: follow-up; NR: not reported; RCT: randomized controlled trial; S-LAAC: surgical left atrial appendage closure

Recently, promising results have been shown with the AtriClip device, the only device-enabled exclusion system currently available (**Figure 9**). In a study including 291 patients undergoing epicardial LAAC with the AtriClip device, Caliskan et al.[126] reported a complete closure rate of 100% without any safety events at 36 months, and excellent durability by computed tomography up to 8 years post-LAAC, with no significant stump or residual communication. The AtriClip device has received CE mark and US FDA 510K approval for LAA ligation. The ATLAS (AtriClip LAA Exclusion Concomitant to Structural Heart Procedures, NCT02701062) randomized trial is currently enrolling surgical patients without preoperative AF, but with high CHA_2DS_2-VAS_C and HAS-BLED scores. The LAAOS III (Left Atrial Appendage Occlusion Study III, NCT01561651) trial will randomly assign 4,700 AF patients undergoing cardiac surgery to concomitant surgical LAAC or not, and will provide valuable data on the efficacy of surgical LAAC in these patients.[127]

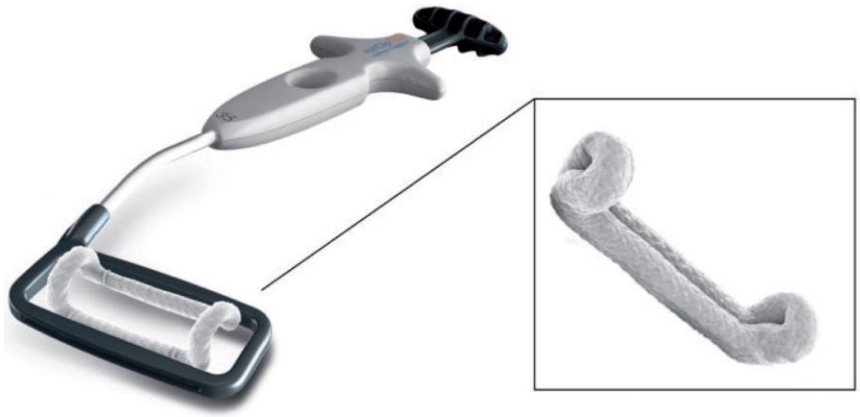

Figure 9. The AtriClip device.

1.3.5. Percutaneous left atrial appendage closure

1.3.5.1. Devices

The first-in-human percutaneous LAAC was performed by Sievert in August 2001 using the PLAATO device (Appriva Medical, Sunnyvale, CA).[128] From then on, several percutaneous approaches have been developed.[129] Transcatheter LAAC therapies can be classified into endocardial or epicardial devices.

Endocardial devices

Watchman. The Watchman device (Boston Scientific, Natick, Massachusetts), was the second dedicated LAAC device and is the only device studied in randomized trials to date.[130, 131] It consists of a parachute-shaped self-expanding nitinol cage, with 10 active-fixation barbs and a 160 μm permeable polyester (polyethylene terephthalate membrane [PET]) fabric (**Figure 10A-C**). It is available in 5 sizes (from 21 to 33 mm diameter) to accommodate LAA ostia from 17-31 mm. The device is delivered through a 14-F sheath, available in three different preformed curve shapes (anterior, double, single), although the double curve is used in most (>90%) cases. Device size is selected according to the maximum LAA ostium diameter, and an oversizing by 10-20% is generally recommended. The Watchman device received CE-mark approval in 2005 and FDA approval in 2015. The Watchman FLX device is an evolution of the Watchman device with the following iterations: 10-20% shorter length, five different sizes (20 to 35 mm) for LAA ostia measuring from 15 to 32 mm, increased number of struts (18 vs 10 in the first-generation Watchman) and anchors (12 in two rows), atraumatic closed distal end to minimize risk of LAA perforation and fully covered to minimize device leaks.

Amplatzer Cardiac Plug and Amulet. The Amplatzer Cardiac Plug (ACP) (Abbott Vascular, Santa Clara, CA) device is a self-expanding nitinol device with a distal lobe and a proximal disk (**Figure 10D-G**). The second-generation of ACP, the Amulet device, included the following modifications: the device comes preloaded in 8 different sizes (16-34 mm) fitting LAA sizes from 11-31 mm, the proximal disc is larger (6-7 mm greater than the lobe vs 4-6 mm for ACP) and the distal lobe is longer (7.5-10 mm), with more stabilizing wires (6-10 pairs vs 6 pairs for ACP). Appropriate sizing is determined by the

maximum landing zone at 10-12 mm from the ostium, with a general oversizing of 2 to 4 mm. The Amulet device is implanted through a 12-14F double-curved TorqVue 45ºx45º sheath. The ACP and Amulet devices received CE mark in 2008 and 2013, respectively. In the United States, the device is for investigational use only. An investigational device exemption trial comparing the efficacy and safety of the Amulet device with the Watchman device is currently ongoing (Amulet-IDE, NCT02879448).

Other endocardial devices. Three other devices have received CE Mark in Europe (the Coherex WaveCrest system, Biosense Webster, Irvine, CA; the LAmbre LAAC System, Lifetech Scientific Co Ltd, Shenzhen, China; and the Ultraseal LAAC device, Cardia Inc, Eagan, MN) and several other are in various phases of clinical investigation in Europe and the United States. Further in-depth discussion on the different LAAC devices in the clinical investigation pipeline is provided in Chapter 2.

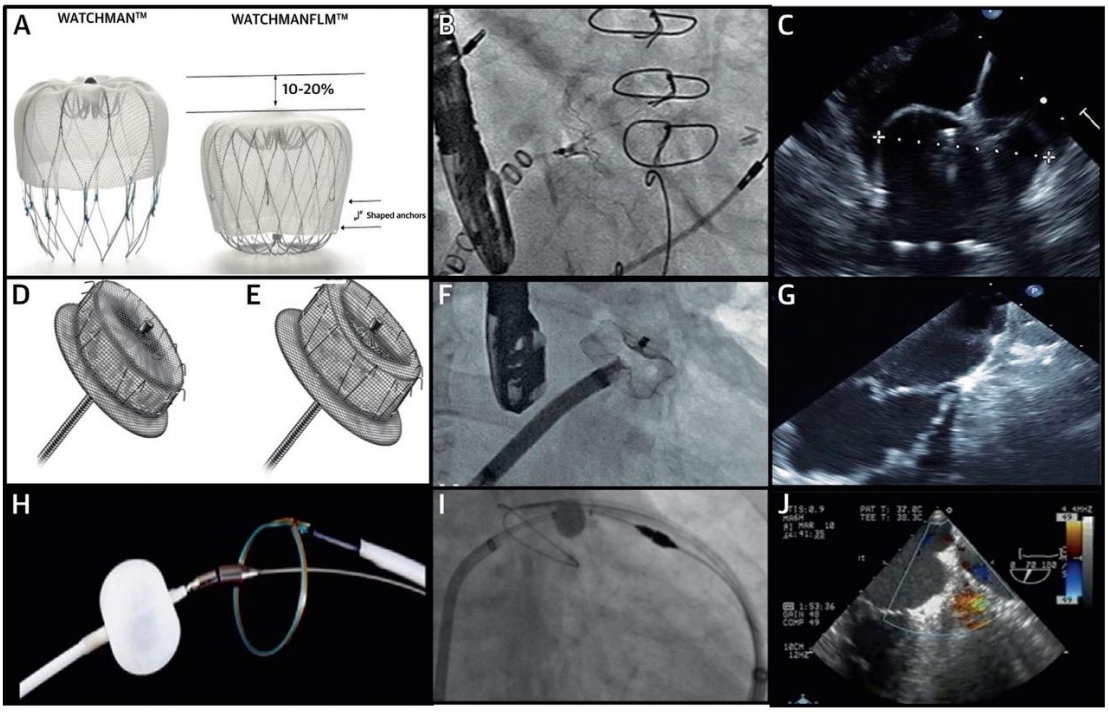

Figure 10. Most commonly used percutaneous LAAC devices.

The Watchman device (A-C), the ACP and Amulet devices (D-G), and the LARIAT system (H-J). From Turagam et al.[132] with permission.

Epicardial LAAC devices

LARIAT. The LARIAT system (SentreHEART, Redwood, California) allows LAA ligation by combining endocardial and epicardial approaches. After transseptal puncture, a magnetic-tipped wire is placed at the LAA apex, with balloon identification of the ostium. A second magnetic wire is then advanced epicardially. Upon magnetic wires apposition, a lasso-like suture is advanced and cinched around the LAA (**Figure 10H-J**). The LARIAT device received CE-mark in 2015 and FDA approval in 2006 for surgical soft tissue approximation, but not yet for stroke prevention. The largest series with the LARIAT system to date included 712 patients from 18 US centers, with 95% success rate and 5.3% periprocedural complications (3.4% significant pericardial effusion, 1.3% major bleeding, 0.5% arterial injury, 0.1% procedural death).[133]

1.3.5.2. Implantation technique

Pre-procedural imaging is essential for planning the implantation strategy, for procedural device guidance, and post-procedural surveillance. Transesophageal echocardiography and/or cardiac computed tomography angiography can be used for pre-procedural work-up, to determine anatomical feasibility of the procedure, rule out LAA thrombus, and provide accurate LAA measurements for device selection.[134] LAA device sizing differs between manufacturers, but in general, it is based on the maximum diameter of the landing zone, with 3- to 6-mm device oversizing. For Watchman, the ostium is measured from the circumflex artery to a superior point 1-2 cm within the pulmonary vein ridge, whereas for Amulet, both the ostium (from the inferior edge of the LAA to the left superior pulmonary vein ridge) and the landing zone (10-12 mm inside) should be measured.

The procedure can be performed under general anesthesia and transesophageal echocardiography guidance, or under local anesthesia and intracardiac echocardiography guidance, with the patient awake. Through right femoral venous access, a transseptal system is advanced (traditional SL-1 sheath and Brockenbrough-1 needle, or alternatively radiofrequency needle especially useful for hypermobile or thick septum). A pressure transducer should be connected to the needle to allow continuous pressure monitoring and

confirm left atrial crossing after puncture. Since the LAA is anterolateral and superior, the puncture should be performed in a posterior and inferior location (confirmed through X-plane imaging showing both the bicaval and transesophageal short-axis views), to enable coaxial alignment of the sheath and delivery system. After interatrial septal puncture, the sheath and dilator are advanced over the needle into the left atrium and the needle is removed. With the transseptal sheath across the septum, a stiff wire is advanced into the left upper pulmonary vein (with a slight clockwise movement of the sheath) to enable safe exchange of the transseptal sheath for the LAAC delivery access sheath. Once the LAAC access sheath has crossed into the left atrium, the dilator and wire can be removed. A pigtail catheter is inserted into the LAA via the access sheath (some operators may prefer to advance it through the transseptal sheath in a previous step, and advance the access sheath directly into the LAA), and angiographies of the LAA are performed in RAO/CAU and RAO/CRA views to measure both the ostium and landing zone.

For Watchman, the access sheath (outer 14 F) is advanced over the pigtail catheter into the LAA tip as far as possible, considering that the distal marker band is 5 mm proximal from the tip. There are three more proximal markers, which correspond with the 21, 27 and 33 mm devices, for final device sizing selection (**Figure 11**). The pigtail catheter is then exchanged for the delivery catheter (which contains the device), which is advanced slowly to prevent air embolism, while maintaining counterclock torque of the sheath. When the distal marker of the delivery catheter and the distal marker of the access sheath align, the access sheath is slightly pulled back to lock both catheters together. While fixing the proximal end of the cable, the access sheath is slowly unsheathed and the device is unfolded. Before device release, the "PASS" release criteria must be confirmed: position (device distal to or at the ostium of the LAA), anchor (stability checked using tug test), size (compression 8-20%) and seal (no color Doppler seen).

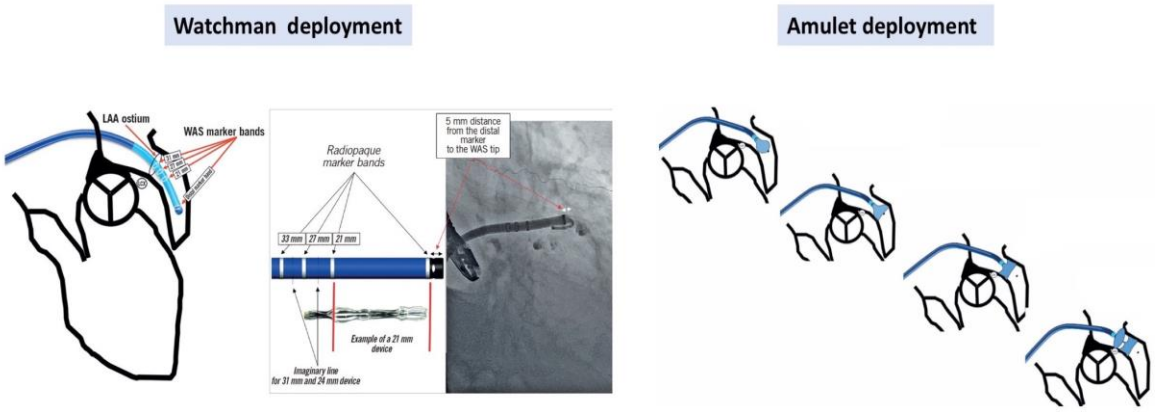

Figure 11. Step-by-step implantation of the Watchman (left) and Amulet (right) devices.
From Glikson et al.[20] with permission.

For Amulet, the TorqVue delivery sheath is advanced into the left atrium or the LAA directly. The delivery cable is advanced after loading the Amulet device in the loading catheter. Visualizing the landing zone in a RAO/CRA view, the delivery sheath is gently retracted to expose the distal portion of the device (ball position). At this point, counterclock rotation of the sheath may be needed for a more coaxial alignment. While maintaining the sheath in place, the delivery cable is pushed forward enabling device triangle configuration and anchoring into the LAA, and with further cable advancement the distal lobe is completely unfolded. Finally, device deployment is completed by unsheathing the device disk (**Figure 11**). As with Watchman, specific-device release criteria must be fulfilled before release: appropriately device lobe compression; slightly separation between the lobe and the disk; concave, tire-shape of the disk; axis of the lobe in line with the LAA neck, and at least 2/3 of the lobe distal to the left circumflex artery.[20]

1.3.5.3. Procedural complications and management

The most serious complications related to transcatheter LAAC procedures include procedure-related stroke, death, pericardial effusion/tamponade and device embolization. Other complications include vascular-access related complications, acute renal injury, device-related complications (device erosion, thrombus, fracture, interference or infection), or transesophageal echocardiography-related complications (esophageal trauma).[135] Despite higher rates of procedural complications in the very early experience, a positive learning curve has been observed, with significant reduction of complication rates to <2% (**Table 8**).[136]

Table 8. Major procedural complications from the PROTECT-AF and PREVAIL randomized trials, and largest LAAC registries

Study, yr	Device	Tamponade, %	Stroke, %	Embolization, %	Mortality, %
PROTECT-AF, 2009[130]	Watchman N=463	4.8	1.1	0.6	0
CAP Registry, 2011 [137]	Watchman N=460	1.4	0	0.2	0
PREVAIL, 2014[131]	Watchman N=269	1.9	0.4	0.7	0
EWOLUTION, 2016[138]	Watchman N=1019	0.3	0.1	0.2	0.1
ACP Registry, 2016[139]	ACP N=1047	1.2	0.9	0.8	0.8
Amulet Registry, 2017[140]	Amulet N=1088	1.2	0.2	0.1	0.2
PRAGUE-17, 2020[141]	Amulet: 111 Watchman: 70	1.0	0	0.5	0.5

Pericardial effusion is the most common complication, accounting for up to 40% of all procedural complications. The rate of periprocedural pericardial effusion has declined over time with operator experience, from 4.8% in the early PROTECT-AF trial, to 1.2% in the latest Amulet registry.[130, 140] According to the Munich consensus, effusions requiring percutaneous or surgical drainage should be considered clinically significant.[135] Most

pericardial effusions occur early (90% within 24 hours of the procedure), mainly related to manipulation of guidewires, catheters or delivery sheath, transseptal puncture or device deployment; although no definitive cause may be identified in up to 1/3 of the cases.[137] Preventive measures such as baseline exclusion of preexisting pericardial effusion, echocardiography guidance during transseptal puncture or pigtail-guided advancement of the delivery sheath into the LAA should always be kept in mind. Early identification and treatment is paramount, with availability of pericaridocentesis kit and surgical back-up if needed. Reversal of anticoagulation may also be considered after achieving pericardial drainage.

Periprocedural stroke is a rare but serious complication, with a reported incidence <0.5%. Most often, these events occur early and are transient, particularly if related to air embolism. However, they may also be related to thrombus, whether preexisting in the LAA or de novo on the equipment in the presence of incomplete heparinization. Careful flushing of all catheters and meticulous device preparation is of utmost importance, along with maintaining adequate activated clotting time >250 seconds immediately after the transseptal puncture. In the presence of air embolism, air should be aspirated and 100% oxygen administrated, whereas in the presence of thrombus, full heparinization is mandatory, and thrombus aspiration through a large-bore sheath may be considered.

Device embolization remains one of the most worrisome complications, with reported rates between 0-2%. Whereas slightly higher rates of embolization were initially suggested with first-generation Amplatzer devices compared with Watchman (0.78% vs 0.26%, p<0.001), the risk of device embolization seems to have been reduced with the latest-generation Amulet device (<0.2%).[142] Most embolizations occur early during the procedure, most often to the left ventricle or the aorta. Appropriate device sizing selection using multimodality imaging and careful stability assessment before release may help avoiding this complication. Retrieval route and technique are often determined by the location of the embolized device: embolizations to the aorta are easier to retrieve percutaneously, whereas embolizations to the left ventricle may be much more challenging and often require surgical retrieval. Finally, procedural death is very rare, occurring in less than 0.1% of cases.

1.3.5.4. Safety and efficacy

Watchman. To date, two randomized trials with a non-inferiority design (PROTECT-AF [Watchman LAA System for Embolic Protection in Patients with AF] and PREVAIL [Watchman LAAC Device in Patients with AF Versus Long-Term Warfarin Therapy]) have assessed the safety and efficacy of LAAC with the Watchman device in comparison with vitamin K antagonists in patients eligible for OAC (**Table 9**).[130, 131] Both trials randomized 707 and 407 patients respectively, with nonvalvular AF and a $CHADS_2$ score ≥ 1, to LAAC or warfarin in a 2:1 fashion. Postprocedural antithrombotic therapy included 45 days of warfarin, followed by aspirin and clopidogrel for 6 months (in the absence of residual leak >5mm), and lifelong aspirin. Watchman was non-inferior to warfarin (3% vs 4.3%, RR: 0.62, 95% CI: 0.35 to 1.25) for the combined primary efficacy endpoint of stroke, cardiovascular death and systemic embolism. Superiority was driven mainly by lower rates of hemorrhagic stroke (0.2% vs 1.1% per year) and death (1.0% vs 2.4% per year) in the Watchman arm, although differences in hemorrhagic stroke rates have been questioned given the higher hemorrhagic stroke rates seen in the warfarin arm (1.1%) compared to the 0.4-0.5% observed in the ROCKET-AF and ENGAGE AF-TIMI-48 trials, and possible uneven adjudication of hemorrhagic strokes noted by FDA reviewers.[143] However, adverse events were higher in the device group (7.4% vs 4.4%, RR: 1.69, CI: 1.01 to 3.19), mainly driven by procedural complications (4.8% pericardial effusion).[130] The PREVAIL trial was designed to address some safety concerns, meeting the second non-inferiority criterion and safety endpoint of stroke or systemic embolism >7days after LAAC, albeit not meeting the primary efficacy non-inferiority of stroke, systemic embolism and cardiovascular death.[131] Despite not meeting the first criterion for non-inferiority and considering the results of both randomized trials altogether, the FDA deemed the Watchman device safe, and approved its use in 2015.

Five-year patient level meta-analysis of the PROTECT-AF and PREVAIL trials showed the non-inferiority of the Watchman device compared to warfarin (HR: 0.82, p=0.27) for the composite endpoint of stroke, systemic embolism and cardiovascular death. Differences in hemorrhagic stroke, mortality and major bleeding favored Watchman (HR: 0.20, p=0.0022,

HR: 0.73, p=0.035, HR: 0.48, p=0.0003, respectively). However, the rate of ischemic stroke or systemic embolism was numerically (but not statistically significantly) higher in the device arm (HR: 1.71, p=0.080) (**Figure 12**).[144]

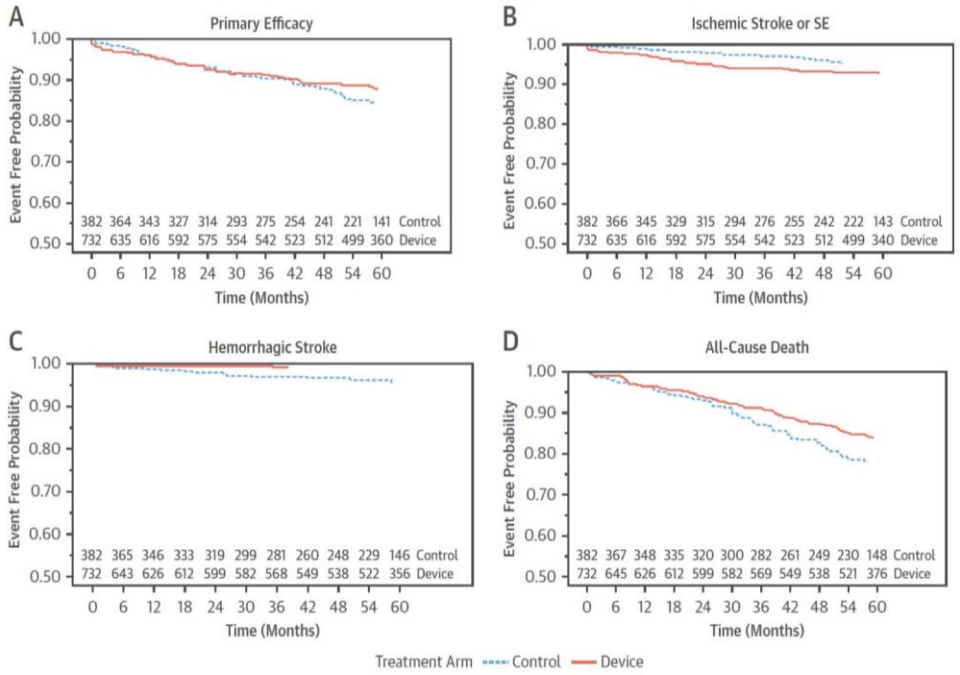

Figure 12. 5-year efficacy outcomes of the PROTECT-AF and PREVAIL trials.
(A) Freedom from composite endpoint of stroke, systemic embolism and cardiovascular death. (B) Freedom from ischemic stroke or systemic embolism. (C) Freedom from hemorrhagic stroke. (D) Freedom from all-cause mortality. From Reddy et al.[144]

Recently, two large registries have demonstrated the safety and efficacy of the Watchman device in real-world practice (**Table 9**). The prospective EWOLUTION registry (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the Watchman LAAC Technology) included 1,021 patients undergoing LAAC with the Watchman device in 13 countries. Sixty-two percent of patients had a contraindication to OAC. Implantation success was 98.5%, with a low rate of procedure-related adverse events at 7 and 30 days (2.8% and 3.6%, respectively).[138] Single- or dual-antiplatelet therapy was used in 67% of patients, OAC in 27% and no antithrombotic therapy was used in 6%. At two-year follow-up, the mortality rate was 16.4%, with an ischemic stroke rate of 1.3/100 patient-years, conferring an 83% relative risk reduction versus historical data.[145] Similarly,

the US post-approval registry included 3,822 patients treated with Watchman, with high procedural success (95.6%) and low complication rates (1.4%).[146]

The results of the PINNACLE FLX study with the new-generation FLX were presented in Heart Rhythm Society 2020 meeting. The single-arm IDE trial enrolled 400 patients (mean CHA_2DS_2-VAS_c: 4.2), and the post-procedural regimen included direct OAC plus aspirin for 45 days, followed by dual antiplatelet therapy for 6 months and then lifelong aspirin. Implant success was 98.8%, with 100% effective LAAC at 1 year. The primary safety endpoint (death, ischemic stroke or embolism, device/procedure-related events within 7 days) was 0.5%, with a device thrombosis rate of 1.8% at 1 year.

Table 9. Overview of the largest randomized trials and registries using Watchman and Amulet

Study, yr	Patients	$CHADS_2$/ $CHADSVAS_C$	Ineligible OAC, %	FU, months	Implant success, %	7-day SAE	Ischemic stroke/SE
PROTECT-AF, 2009[130]	463	2.2±1.2 / 3.4	0	18±10	88	8.7	2.5/100PY
PREVAIL, 2014[131]	269	2.6±1.0 / 3.8±1.2	0	12±6	95	4.2	2.3%
5-year RCTs, 2017[144]	732	2.3±1.1 / 3.6±1.4	0	4,343 PY	95	-	1.6/100PY
EWOLUTION, 2019[145]	1,021	2.8±1.3 / 4.5±1.6	62	24	99	2.8	1.3/100PY
Post-FDA Mark, 2017[146]	3,822	-	-	-	96	1.4	-
ACP Registry, 2016[139]	1,047	2.8±1.3 / 4.5±1.6	73	13	97	5	2.3%
Amulet Registry, 2018[147]	1,088	- / 4.2±1.6	83	12	99	3.2	2.9%
PRAGUE-17, 2020[141]	201	4.7±1.5	0	20	96.8	2.0	2.6%
PINNACLE FLX, 2020	400	4.2	0	12	98.8	0.5	2.6%

FU: Follow-up; OAC: Oral anticoagulation; PY: Patient years; SAE: Severe adverse event; SE: Systemic embolism

Amplatzer Cardiac Plug and Amulet. The ACP and Amulet devices are the second most frequently used LAAC devices after Watchman, and the most commonly implanted in Europe, with large European registries supporting their safety and efficacy, especially among patients deemed ineligible for OAC (**Table 9**). Tzikas et al.[139] reported in 2016 the largest multicenter experience with the first-generation ACP device, including 1,047 patients from 22 centers. Seventy-three percent of the patients had a contraindication to OAC due to prior bleeding or high bleeding risk. Procedural success occurred in 97.3% and periprocedural adverse events in 5% (1.2% cardiac tamponade, 1.2% major bleeding, 0.9% stroke, 0.8% device embolization, 0.8% procedure-related death). At 13 months' follow-up, the annual rates of systemic thromboembolism and major bleeding were 2.3% and 2.1% respectively, with a 59% relative risk reduction of stroke based on the CHA_2DS_2-VAS_c score, and a 61% annual reduction of bleeding risk as compared the risk predicted by the HAS-BLED score. The results of the second-generation Amplatzer Amulet registry, which enrolled 1,088 patients (83% with contraindications to OAC) in 61 centers showed even higher implantation success (99.0%) and lower periprocedural adverse event rate (3.2%: 1.2% pericardial tamponade, 0.2% death, 0.2% stroke, 0.1% device embolization), with adequate (< 3 mm jet) LAA occlusion at 3 months in 98.2% of patients.[140] Three-quarters of the patients were discharged on single- or dual-antiplatelet therapy, with an annual ischemic stroke rate of 2.9% (57% lower risk of stroke as compared to that predicted by the CHA_2DS_2-VAS_c score), and an 8.4% all-cause mortality at one year.[147]

More recently, Osmanick et al.[141] reported the results of the PRAGUE-17 trial (LAAC vs Novel Anticoagulation Agents in Atrial Fibrillation), the first randomized trial comparing percutaneous LAAC (n=201, 61% Amulet) with direct OAC (n=201, primarily apixaban in 95.5%) in 402 high-risk patients (mean CHA_2DS_2-VAS_C: 4.7 ±1.5). All patients had a history of prior bleeding, history of cardioembolic event on OAC, and/or a CHA_2DS_2-$VAS_C \geq 3$ and HAS-BLED score >2. LAAC was successful in 90% of patients assigned to LAAC (96.8% of attempted procedures), with 4.5% major LAAC-related complications. At a median 19.9 months' follow-up, the annual rates of the primary outcome (composite of stroke, transient ischemic attack, systemic embolism, cardiovascular death, bleeding or procedure/device-related complication) were 10.99% in the LAAC group vs 13.42% in the

DOAC group (p=0.44, p=0.004 for noninferiority). There were no differences in stroke, significant bleeding or cardiovascular death between the two groups.

Late (30-day) complications. Most studies conducted to date have focused mainly on early complications (≤7 days, **Table 9**), failing to report 30-day outcomes. In the EWOLUTION registry, the total 30-day severe adverse event rate was 7.9%, with a 30-day procedure/device-related adverse event rate of 3.6%, unrelated to baseline CHA_2DS_2-VAS_C or comorbidities.[138] Major bleeding requiring transfusion was the most common adverse event (11.0% and 15.1% related and unrelated to the device/procedure, respectively), with low rates of death (0.7%) and stroke (0.1%). Likewise, in the Amulet Observational registry (although did not specifically report 30-day outcomes), half of the major bleeding occurred within the first month after LAAC (during dual antiplatelet therapy), whereas the remaining complications were uniformly distributed over follow-up.[147] Vuddanda et al.[148] evaluated the rate of 30-day readmissions after percutaneous LAAC using 2016 US nationwide real-world data. Among 5,480 LAAC procedures (94% endocardial), the rates of 30-day unplanned readmission were 8.3% and 19.5% (p<0.001) for endocardial and epicardial LAAC, respectively. As with EWOLUTION and Amulet registries, the most common cause of readmission was gastrointestinal bleeding after endocardial LAAC (16%) and pericarditis/pericardial effusion after epicardial LAAC (34%). Similar findings were reported in another nationwide analysis presented by Wu et al. at the American College of Cardiology 2020 meeting, with a 7.3% 30-days readmission post-LAAC with Watchman, with most common cause being gastrointestinal bleeding (35%). Lastly, in the PRAGUE-17 randomized trial, up to 2.7% of significant complications (55% of overall complications) in the device arm occurred late, 104±57 days after LAAC. Among these late device-related complications, there was one death (secondary to a delayed pericardial tamponade), 2 uneventful pericardial effusions, 1 device malposition and 1 device-related thrombosis. Although PRAGUE-17 included up to 40% centers without previous LAAC experience, these findings still underscore the upfront risk of such an invasive procedure and the importance of operator's experience to minimize risk of early and late complications. A comprehensive review of the results from recent major LAAC studies is provided in Chapter 2.

1.3.5.5. Post-procedural management

Despite the growing body of data on safety and efficacy of percutaneous LAAC, some concerns remain, particularly regarding optimal post-procedure antithrombotic therapy and device-related thrombus (DRT).

Antithrombotic therapy after LAAC. The type and duration of antithrombotic regimen after LAAC have evolved empirically, with none of the non-warfarin strategies having been studied in a randomized fashion so far. Kar et al.[149] showed in a preclinical study that it takes from 30 days to 3 months to achieve a full endothelization of LAAC devices after implantation. Rodés-Cabau et al.[150] previously demonstrated, in a mechanistic study, that percutaneous LAAC is associated with a significant activation of the coagulation system (particularly prothrombin fragment 1+2 and thrombin-antithrombin complex), but not platelet activation. This coagulation activation reaches a peak at 7 days' post-procedure, progressively returning to baseline levels at 1 and 6 months. Considering these findings, devices may be exposed to potentially thrombogenic circulating blood during this early period, and short-term post-procedural antithrombotic therapy is recommended for preventing DRT.

Most of the current LAAC recipients have a contraindication to OAC or are at high bleeding risk. Accordingly, and based on early experiences with the PLAATO device,[128] and other transcatheter procedures (atrial septal defect or patent foramen ovale closure), the most widely adopted antithrombotic strategy, particularly in Europe, has been DAPT for 1 to 6 months, modifying the regimen upon surveillance imaging results (generally aspirin indefinitely, in the absence of DRT or significant residual leak >5mm). The safety and feasibility of this strategy with the Amplatzer device family (ACP/Amulet) has been widely studied in multiple registries, and the European Heart Rhythm Association/European Association of Percutaneous Cardiovascular Interventions expert consensus statement recommends treatment with clopidogrel for 1-6 months and aspirin indefinitely in patients with high bleeding risk.[20]

For Watchman recipients, the post-LAAC antithrombotic protocol described in the two landmark randomized trials (warfarin for 45 days, followed by 6-month DAPT and aspirin lifelong) has been the most commonly used regimen so far. More recently, different studies have assessed the efficacy of alternative strategies (direct OAC, DAPT) post-Watchman device implantation with favorable results. The ASAP (ASA Plavix Feasibility Study with Watchman) registry used DAPT in 150 patients ineligible to OAC, with an annual thromboembolic rate of 2.3%, and a 4% incidence of DRT.[151] In the EWOLUTION registry, 60% received DAPT and 7% single antiplatelet therapy post-Watchman respectively, with an overall rate of DRT of 2.3%, and no significant differences between different regimens.[145] Enomoto et al.[152] evaluated, in a restrospective study, the safety of direct OAC post-Watchman in 214 patients, with no differences in terms of DRT, or procedural- and post-procedural bleeding compared with warfarin. These findings led to changes in the device labeling, now allowing 3-month DAPT or direct OAC post-Watchman when the standard regimen is not feasible. Finally, the use of single antiplatelet therapy has been suggested for patients at extremely high bleeding risk, with initial encouraging results.[153] However, a larger French study raised concerns about this strategy, as they observed much higher rates of DRT in patients receiving single antiplatelet therapy or no antithrombotic therapy post-LAAC, compared to those treated with OAC or DAPT.[154]

Surveillance imaging: Leaks and device-related thrombus.

Device surveillance with either transesophageal echocardiography or computed tomography is recommended 6 to 12 weeks following LAAC to rule out DRT or peri-device leak, and repeat imaging may be considered at 12 months.[20] The Munich consensus established a threshold of 5mm for relevant leaks based on surgical LAAC data,[135] although previous studies used the 3- to 5-mm cut-off arbitrarily. In the absence of anomalous findings (DRT or relevant leak), OAC or DAPT may be de-escalated to lifelong single antiplatelet therapy.

Contrary to their surgical counterparts, most of the published studies on transcatheter LAAC failed to find any association between peri-device leak and clinical events. In a sub-study of the PROTECT-AF trial, any degree of residual leak was identified in one-third of cases at 12 months (of which 37% >3mm), whereas in the contemporary EWOLUTION registry, the rate of relevant leak >5mm was only 1%.[138] In the ACP registry, any leak occurred in 12.5% of patients (0.6% >5mm), with no leaks greater than 5mm in the latest Amulet registry.[139, 140] Interestingly, several mechanisms of peridevice leak have been described for different LAAC devices. In the case of endocardial devices such as Amulet or Watchman, a circular plug tends to occlude a noncircular LAA orifice, potentially leaving an uncovered gap between the edge of the device and the atrial wall when the plug is off axis (eccentric edge effect), whereas most residual leaks in epicardial devices such as Lariat are central, as a result of the of the gunny suck effect created by the suture (concentric) (**Figure 13**). Although the presence of any peri-device leak was not associated with thromboembolic events during follow-up, it has been suggested that patients with large residual large peri-device leaks (>5mm) may be continued on long-term OAC.[130]

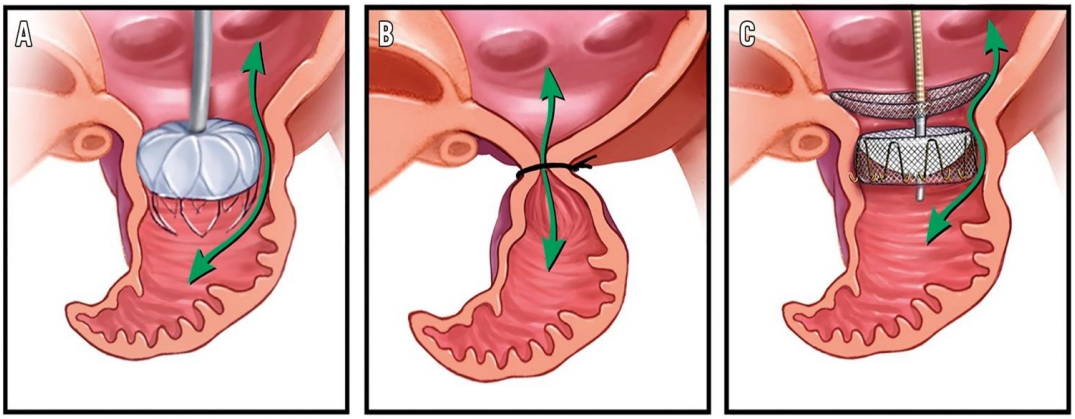

Figure 13. Likely mechanisms for peri-device leaks for endocardial (A and C) and epicardial (B) LAAC devices.
From Raphael et al.[155] with permission.

The incidence of DRT following LAAC has ranged from 0% to 17%, with wide variations depending on device type, technical issues, post-procedural antithrombotic therapies, and timing and frequency of control transesophageal echocardiography post-LAAC.[156] DRT is

generally defined as a homogeneous echo-dense mass visible in multiple planes, adherent to the atrial surface of the LAAC device (**Figure 14**). In the presence of DRT, anticoagulation with whether OAC or low-molecular weight-heparin for 8 to 12 weeks is advised, and repeat imaging performed to document thrombus resolution. Additional delayed imaging at 3-6 months may be considered to ensure lack of recurrence.

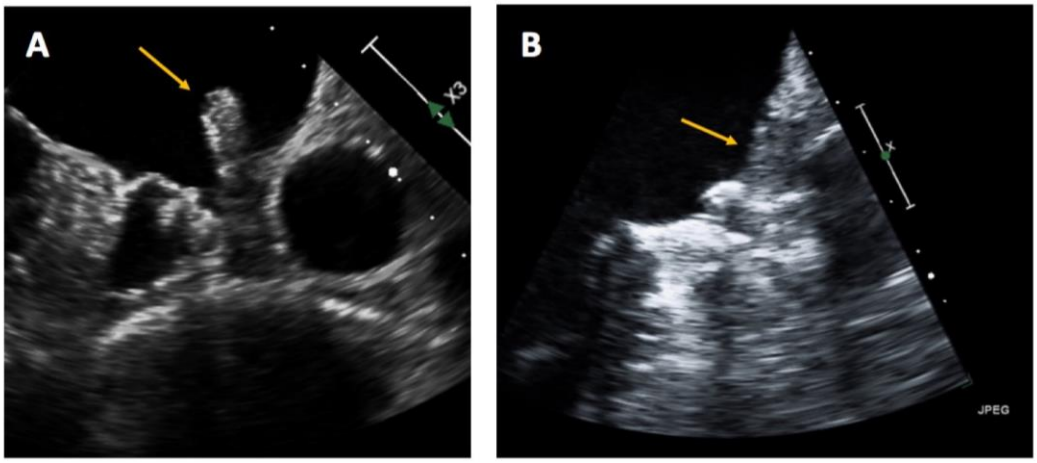

Figure 14. Illustration of a pedunculated (A) and a large, laminar (B) device-related thrombus attached to the Watchman device on transesophageal echocardiography.

Importantly, DRT has been associated with 3- to 5-fold increased risk of stroke and systemic embolism (**Figure 15**).[154, 157] In a study by Dukkipati et al.[157] including 1,739 patients from the 4 prospective FDA trials (PROTECT-AF, PREVAIL, and their subsequent continued registries), DRT was seen in 3.7%, and was associated with >3-fold higher risk of stroke and systemic embolism, but not with an increased mortality. Prior history of stroke or vascular disease, permanent AF, lower ejection fraction and larger LAA emerged as predictors of DRT. In a French study by Fauchier et al.[154] including 469 patients, the incidence of DRT was 7.2% at 13 months, being associated with a 4.39-higher risk of ischemic stroke or transient ischemic attack. Similar findings were found in the multicenter Amulet observational study (n=1,088) with a DRT rate of 1.7%/year, with DRT patients exhibiting a 5.27-higher risk of stroke or transient ischemic attack compared with non-DRT patients.[158] Interestingly, most DRT developed near a cul-de-sac formed by the superior disc edge and the pulmonary vein ridge, suggesting suboptimal device implantation as a potential contributor to DRT.

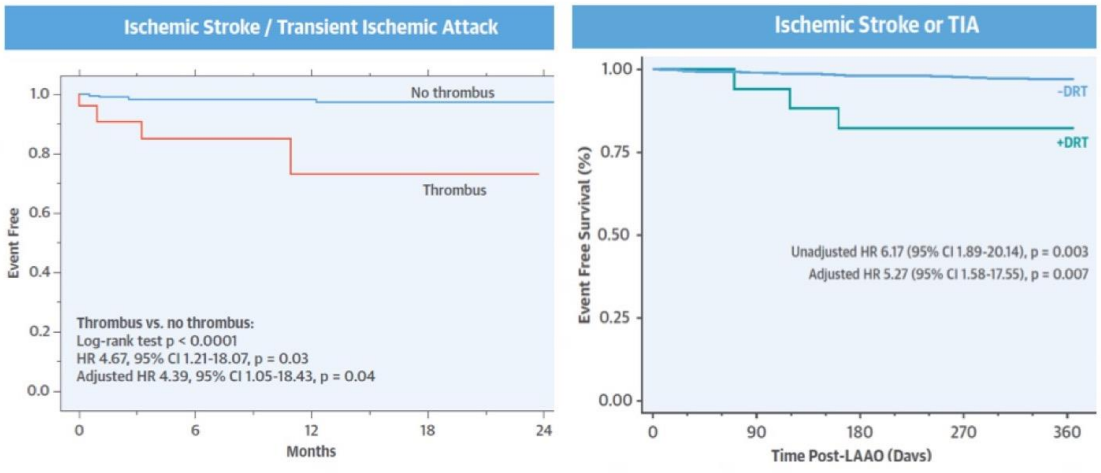

Figure 15. Kaplan-Meier curves for thromboembolic events according to the presence of thrombus on the device.

From Fauchier et al[154], Aminian et al.[158] with permission.

Despite the growing body of data regarding the safety and efficacy of LAAC, many unanswered questions remain, particularly regarding the optimal post-implantation antithrombotic therapy and the prevention and management and DRT. Whether technological iterations and new devices and biomaterials may have a clinical impact on DRT is unknown. Also, there is a paucity of mechanistic data on the effect of different antithrombotic strategies on coagulation system activation after LAAC. Finally, no study to date has yet evaluated the incidence of recurrent DRT following LAAC.

HYPOTHESIS AND OBJECTIVES

I. HYPOTHESIS

I.I. General hypothesis

The subclinical arrhythmic burden among high-risk elderly populations is largely underestimated, and the incidence, related factors and recurrence of DRT following percutaneous LAAC in patients with non-valvular AF differ among different devices and post-procedural antithrombotic strategies.

I.II. Specific hypothesis

1. A significant proportion of arrhythmias, particularly subclinical AF, in high-risk elderly patients such as those undergoing transcatheter heart valve interventions already exist prior to the procedure, not being related to the procedure itself.

2. Increased LAAC experience of operators and continuous device iterations are associated with improved in-hospital and late clinical outcomes.

3. Use of novel emerging LAAC devices with different biomaterials may help to improve procedural outcomes and mitigate DRT.

4. Percutaneous LAAC does not exert deleterious hemodynamic effects despite exclusion of ~10% of the left atrium.

5. The activation of the coagulation system following LAAC can be significantly reduced with short-term OAC rather than with antiplatelet therapy; identification of factors associated with a greater coagulation activation may enable tailored antithrombotic management post-LAAC.

6. The time course and optimal antithrombotic management of DRT are poorly understood, and very scarce data exist on DRT recurrence rate.

II. OBJECTIVES

II.I. General objectives

The main objectives of my PhD project are: (i) to determine the prevalence of pre-existing silent arrhythmic events in elderly patients undergoing TAVR, and (ii) to assess the hemodynamic, biological and clinical impact and potential complications of percutaneous LAAC using currently available and emerging devices, with a particular focus on DRT.

II.II. Specific objectives

1. To determine the prevalence of arrhythmic events in TAVR candidates using novel prolonged continuous electrocardiographic monitoring systems.

2. To evaluate whether newer iterations of transcatheter LAAC devices and increasing operator experience correlate with lower peri- and post-procedural complication rates in AF patients currently undergoing percutaneous LAAC.

3. To determine the safety, efficacy and device-related events of LAAC using the Ultraseal bulb-and-sail device through a first multicenter worldwide experience.

4. To assess the acute hemodynamic impact of percutaneous LAAC in patients with paroxysmal AF.

5. To compare the degree of activation of coagulation markers after LAAC in patients receiving short-term OAC versus those on antiplatelet therapy post-LAAC with the Watchman device; determine the factors associated with an increased prothrombotic status after LAAC.

6. To determine the incidence and impact of recurrent DRT following LAAC, as assessed by transesophageal echocardiography or computed tomography surveillance imaging.

CHAPTER 1. Prolonged Continuous ECG Monitoring Prior to Transcatheter Aortic Valve Replacement. The PARE Study

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1.1. RÉSUMÉ

L’objectif était de déterminer l'incidence d'événements rythmiques préexistants inconnus chez 106 patients atteints de sténose aortique sévère et sans pacemaker préalable évalués pour implantation d’une valve aortique transcathéter (TAVR). Un dispositif de surveillance électrocardiographique continue (1 semaine) a été installé dans les 3 mois précédant le TAVR. Suite à une évaluation multidisciplinaire, 90 patients ont subi un TAVR électif. Des arythmies diagnostiquées *de novo* ont été observées chez 51 patients (48.1%), conduisant à un changement de traitement chez 14/51 (27.5%) patients. Une fibrillation/tachycardie auriculaire a été détectée chez 8/79 patients (10.1%), et des arythmies ventriculaires chez 31 patients (29.2%). Des bradyarythmies significatives ont été observées chez 22 patients (20.8%), entraînant un changement de traitement et implantation d’un pacemaker permanent chez 8/22 (36.4%) et 4/22 (18.2%) patients, respectivement. Les troubles de conduction préexistants (bloc de branche droit) et l'insuffisance rénale chronique ont été associés à une charge plus élevée d’événements rythmiques.

1.2. ABSTRACT

Background: Scarce data exist on the arrhythmic burden of transcatheter aortic valve replacement (TAVR) candidates (pre-procedure).

Objectives: To determine, using continuous ECG monitoring (CEM) pre-TAVR, the incidence and type of unknown pre-existing arrhythmic events (AEs) in TAVR candidates, and to evaluate the occurrence and impact of therapeutic changes secondary to the detection of AEs pre-TAVR.

Methods: Prospective study including 106 patients with severe aortic stenosis and no prior permanent pacemaker (PPM) screened for TAVR. A prolonged (1-week) CEM was inserted within the 3 months pre-TAVR. Following heart team evaluation, 90 patients underwent elective TAVR.

Results: New AEs were detected by CEM in 51 patients (48.1%), leading to a treatment change in 14/51 (27.5%) patients. Atrial fibrillation/tachycardia was detected in 8/79 patients (10.1%) without known atrial fibrillation/tachycardia, and non-sustained ventricular arrhythmias in 31 patients (29.2%). Significant bradyarrhythmias were observed in 22 patients (20.8%), leading to treatment change and PPM in 8/22 (36.4%) and 4/22 (18.2%) patients, respectively. The detection of bradyarrhythmias increased up to 30% and 47% among those patients with pre-existing 1st-degree atrioventricular block and right bundle branch block (RBBB), respectively. Chronic renal failure, higher valve calcification, and left ventricular dysfunction determined (or tended to determine) an increased risk of AEs pre-TAVR (p=0.028, p=0.052, p=0.069, respectively). New-onset AEs post-TAVR occurred in 22.1% of patients, and CEM pre-TAVR allowed early arrhythmia diagnosis in one-third of them.

Conclusions: Prolonged CEM in TAVR candidates allowed identification of previously unknown AEs in nearly one-half of the patients, leading to prompt therapeutic measures (pre-TAVR) in about one-fourth of them. Pre-existing conduction disturbances (particularly RBBB) and chronic renal failure were associated with a higher burden of AEs.

1.3. INTRODUCTON

Transcatheter aortic valve replacement (TAVR) has emerged as a viable alternative for the treatment of elderly patients with severe aortic stenosis.[159-161] However, the occurrence of arrhythmic events (either brady- or tachyarrhythmia) remains the most frequent complication of TAVR.[162, 163] Whereas most arrhythmic events post-TAVR are directly related to the procedure/valve prosthesis, few data exist on the occurrence of pre-existing arrhythmias in TAVR candidates. A study using 24-hour continuous ECG monitoring (CEM) within the days prior to the TAVR procedure showed that a significant proportion of silent arrhythmias were already present before the procedure.[37] However, it is well-known that 24-hour continuous monitoring has a low sensitivity, and ECG monitoring >24 hours has shown a much higher sensitivity for detecting arrhythmias.[164] In addition to determining the real impact of the TAVR procedure on arrhythmic events, the detection of arrhythmias pre-procedure may help to implement specific treatment measures (e.g. pacemaker implantation, anticoagulation therapy) that can improve the global care of TAVR candidates, reduce hospitalization length and improve clinical outcomes post-TAVR. The objectives of this study were (1) to determine the incidence and type of arrhythmic events in TAVR candidates as assessed by prolonged CEM pre-TAVR, and (2) to evaluate the occurrence and impact of therapeutic changes secondary to the detection of arrhythmic events pre-TAVR.

1.4. METHODS

1.4.1. Study Design and Patients. The PARE study (Prolonged Continuous ECG Monitoring Prior to Transcatheter Aortic Valve Implantation, NCT03561805) was a prospective, single-center study, approved by the institutional ethics committee, and all patients provided signed informed consent to participate in the study. Patients with severe symptomatic aortic stenosis referred for TAVR who did not have a pre-existing permanent pacemaker (PPM) were included. There was no restriction regarding the type of valve and approach used for the TAVR procedure. Patients underwent a prolonged -1 week- CEM using the CardioSTAT® device (Icentia, Quebec City, Canada) within the 3 months prior to the TAVR procedure. Patients requiring urgent TAVR precluding one week ECG monitoring within the 3 months pre-TAVR were excluded. All types of arrhythmic events

were recorded, as well as the specific therapeutic measures implemented upon the occurrence of the arrhythmic event. Following the TAVR procedure, the patients were monitored (telemetry) until hospital discharge. All arrhythmic events during the hospitalization period were recorded. Clinical follow-up was also performed at 30 days.

1.4.2. The CardioSTAT® device. The CardioSTAT® is a single-use, wire-free, wearable heart monitoring patch, that provides continuous ECG recording of a single lead tracing up to 14 days. CardioSTAT comes in the form of a thin flexible strip designed to be worn on the upper part of the torso and features conventional gel electrodes allowing a low impedance between the skin and the electrode in order to obtain an optimal signal. The device has been clinically validated, showing excellent correlation with the standard Holter ECG monitoring.[165] The monitoring period in the present study was of 7 days. Patients were asked to report any symptom potentially related to arrhythmic events (eg. palpitations, dizziness, dyspnea, or exercise intolerance) by pressing a symptom trigger button located on the front of the device. Once the registration was complete, the patient returned the device personally or by mail. The data were analyzed at the service center by a certified technologist and a report was sent electronically to the cardiac electrophysiologist (I. N.) for validation and final reporting. The time delay between the end of the monitoring and data interpretation was no longer than 7 days.

1.4.3. Outcomes. The primary outcomes were (i) the incidence and type of arrhythmic events, and (ii) the therapeutic changes related to the diagnosis of arrhythmic events prior to the TAVR procedure. Secondary outcomes were incidence and duration of AF, incidence of high-degree atrioventricular block (HAVB), incidence of severe bradycardia, percentage of patients with an indication of PPM, and percentage of patients with an indication for anticoagulation therapy.

Significant arrhythmias were defined according to current guidelines. Excessive supraventricular ectopic activity (ESVEA) was defined as ≥30 premature supraventricular contractions/hour (≥720 PSC/24 hours) or episode of premature supraventricular

contractions runs ≥20 beats.[34] Paroxysmal AF was defined as irregular RR intervals with absent P waves lasting at least 30 seconds, and atrial tachycardia (AT) as sudden rapid regular atrial rhythm with identifiable p waves.[28] Non-sustained ventricular tachycardia (NSVT) was defined as ≥3 consecutive complexes originating in the ventricles at a rate >100 bpm.[166] Severe bradycardia was defined as heart rate <40 bpm.[167] HAVB was defined as any of the following: second-degree atrioventricular block (AVB) type 2 (Mobitz II), 2:1 AVB, or ≥2 consecutive P waves that do not conduct to the ventricle. Complete heart block (CHB) was defined as P waves with a constant rate with dissociated ventricular rhythm (no association between P waves and R waves) or fixed slow ventricular rhythm in the presence of atrial fibrillation.[163, 168] PPM implantation was indicated in the presence of HAVB or CHB.[168] Clinical events were defined according to the Valve Academic Research Consortium-2.[169]

1.4.4. Statistical analysis. Data on CEM prior to TAVR was limited to a single study with ECG monitoring duration limited to 24 hours, which identified newly diagnosed arrhythmias in about 16% of patients.[37] Assuming that extending the duration of CEM to 7 days would significantly increase the detection of arrhythmic events (to ≥25% of patients), the sample size of this observational study was estimated at 100 patients. Qualitative variables were reported as counts and percentages and continuous variables as mean ± SD or median (interquartile range), depending on variable distribution. Categorical variables were compared using the chi-square or Fisher exact test as appropriate, and the Student's t-test or Wilcoxon rank sum test for continuous variables. The factors associated with newly diagnosed arrhythmic events were determined using a multivariable logistic regression analysis. Parameters with a p value <0.15 in the univariable analysis were modeled in a multivariable analysis using a stepwise procedure in a logistic regression model. After stepwise elimination, three variables were retained in the model: chronic renal failure, left ventricular systolic dysfunction (ejection fraction <50%), and valvular calcification (Agatston score). A p value <0.05 was considered significant for all statistical tests. All data were analyzed using the statistical package STATA version 14.0 (StataCorp LP, College Station, Texas).

1.5. RESULTS

Of 142 patients with severe symptomatic aortic stenosis and no prior PPM screened for TAVR in our institution, 27 patients were excluded due to the need of urgent TAVR, and 9 patients were excluded due to inadequate ECG recording (n=7) or monitor not returned appropriately (n=2), leading to a study cohort of 106 patients with completed 7-day CEM (**Figure 1.1**). The main baseline characteristics of the study population are summarized in **Table 1.1**. Mean age of the patients was 80 ± 8 years, and 58.5% were male, with a mean Society of Thoracic Surgeons Predicted Risk of Mortality of 4.8 ± 2.7%. Twenty-seven patients (25.5%) had a history of prior AF (either paroxysmal or permanent), and any pre-existing first-degree AVB and intraventricular conduction disturbances were present in 20 (22.5%) and 28 (26.4%) patients, respectively.

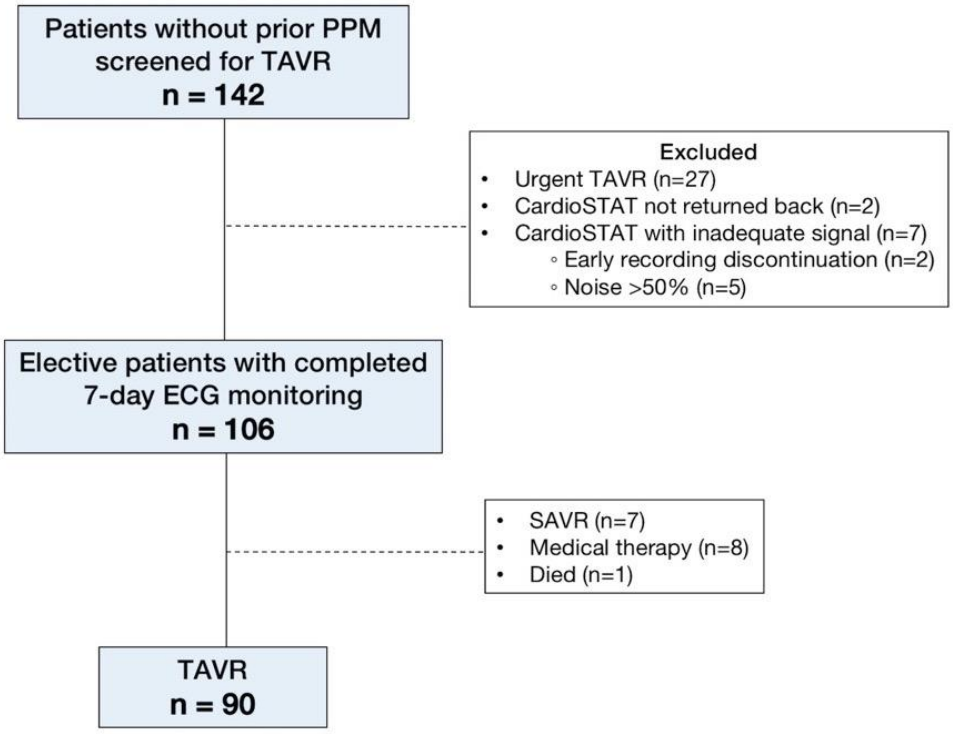


Figure 1.1. Patient Flowchart.

The overall population included 142 patients who did not have a prior pacemaker, screened for TAVR. Patients requiring an urgent procedure and those in whom ECG recording was insufficient or not returned back (n=36) were excluded. Among the 106 TAVR candidates with complete 7-day ECG monitoring, 90 patients ultimately underwent elective TAVR.
PPM: permanent pacemaker implantation; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

Table 1.1. Clinical characteristics according to the occurrence of arrhythmic events during 7-day CEM

	Overall	New AE	No AE	p value
	N=106	**N =51**	**N = 55**	
Baseline variables				
Age, years	80±8	81±6	80±9	0.206
Male	62 (58.5)	31 (60.8)	31 (56.4)	0.644
Hypertension	91 (85.8)	45 (88.2)	46 (83.6)	0.497
Previous coronary disease	58 (54.7)	30 (58.8)	28 (50.9)	0.413
Atrial fibrillation/flutter	27 (25.5)	18 (35.3)	9 (16.4)	0.025
COPD	29 (27.4)	14 (27.5)	15 (27.3)	0.984
eGFR<60mL/min	51 (48.1)	30 (58.8)	21 (38.2)	0.034
CHA_2DS_2-VAS_C	4.3 ± 1.3	4.4 ± 1.2	4.2 ± 1.3	0.357
STS-PROM, %	4.8 ± 2.7	4.5 ± 2.4	5.0 ± 2.9	0.301
Electrocardiographic variables				
PR interval, ms	180 ± 41	183 ± 54	179 ± 27	0.626
QRS duration, ms	105 ± 28	109 ± 29	101 ± 25	0.125
First degree atrioventricular block*	20 (22.5)	11 (29.0)	9 (17.7)	0.206
Right bundle branch block	15 (14.2)	10 (19.6)	5 (9.1)	0.121
Left bundle branch block	9 (8.5)	4 (7.8)	5 (9.1)	1.000
Intraventricular conduction delay	4 (3.8)	3 (5.9)	1 (1.8)	0.350
Echocardiographic variables				
LVEF <50%	27 (25.5)	17 (33.3)	10 (18.2)	0.074
Mean AV gradient, mmHg	42 ± 16	43 ± 17	40 ± 15	0.306
AV area, cm^2	0.72 ± 0.22	0.69 ± 0.19	0.74 ± 0.23	0.232
Computed tomography variables				
Aortic annular area, mm^2	429 ± 119	441 ± 119	419 ± 119	0.414
Aortic annular perimeter, mm	75 ± 10	74 ± 12	75 ± 8	0.709
Agatston calcium score, AU	2,164±1,376	2,394±1,612	1,947±1,081	0.107
Baseline treatment				
Anticoagulation	22 (20.8)	14 (27.5)	8 (14.6)	0.102
Beta-blockers	53 (50.0)	25 (49.0)	28 (50.9)	0.846
Calcium channel blockers	30 (28.3)	17 (33.3)	13 (23.6)	0.268
Digoxin	2 (1.9)	2 (3.9)	0 (0)	0.229
Amiodarone	3 (2.8)	1 (2.0)	2 (3.6)	1.000

Values are expressed as n (%), mean (±SD) or median (IQR). *Patients in sinus rhythm (n=89). AV: aortic valve; CHA_2DS_2-VAS_C: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality.

1.5.1. Incidence and type of arrhythmic events during 7-day CEM.

The main ambulatory CEM findings are displayed in **Table 1.2**. Arrhythmic events were diagnosed in 51 (48.1%) patients, with a median number of 2 episodes (1 to 6) per patient. In 14 patients (13.2% of the overall population; 27.5% of the 51 patients with newly diagnosed arrhythmias), the arrhythmic events led to therapeutic changes.

Newly diagnosed tachyarrhythmic events were found in 37 patients (34.9%), most of them (97.3%) asymptomatic. Among the 79 patients without a prior history of AF, paroxysmal AF/AT was identified in 8 patients (10.1%), leading to a treatment change in 5 of them (oral anticoagulation in 4, antiarrhythmic agent in 1). Of the patients with newly diagnosed paroxysmal AF, the median AF burden was 0.2% (IQR: 0.1-0.3%), with a median duration of AF episodes of 2.1 (IQR: 1.3-10.7) minutes. NSVT occurred in 31 patients (29.2%), with no episodes of sustained ventricular tachycardia.

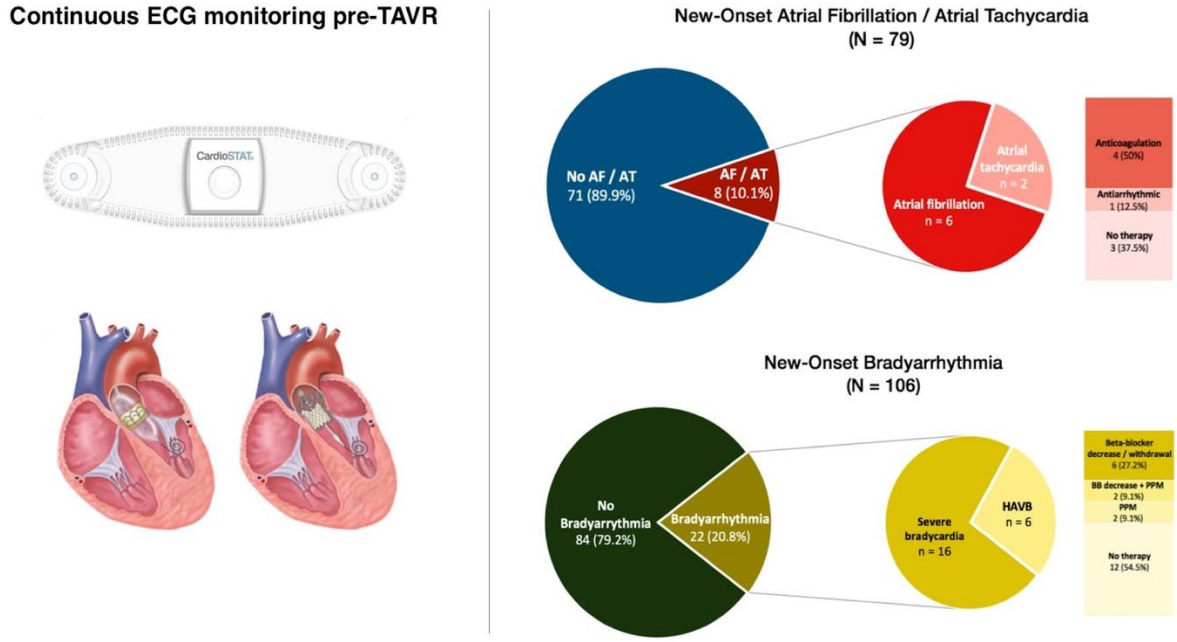
Twenty-two patients (20.8%) experienced significant bradyarrhythmias, most of them asymptomatic (90.9%): severe bradycardia in 16, HAVB and severe bradycardia in 4, and HAVB in 2 patients. Bradyarrhythmic events led to a treatment change in 10 patients (9.4% of the cohort study, 45.5% of the patients with bradyarrhythmias): change in medical therapy in 6, and PPM in 4 patients with HAVB while awake (two of them with concomitant medical therapy modification). Among those patients treated with PPM, 2 presented symptoms associated with HAVB (shortness of breath), none of them experiencing dizziness or syncope. (**Central Illustration**).

Table 1.2. New-onset arrhythmic events observed during 1-week continuous ECG monitoring with Cardiostat before transcatheter aortic valve replacement

	Patients with completed 7-day CEM N = 106
Duration of Cardiostat, days	7 (6-7)
Global arrhythmic burden	
Patients with new AE	51 (48.1)
Patients with new AE requiring therapeutic changes	14 (13.2)
Number of AE recorded per patient	2 (1-6)
Noise (%)	9.8 (5.2-19.3)
Mean HR (bpm)	68 ± 10
Tachyarrhythmias	
Time in tachycardia HR>100 bpm, %	1.6 (0.4 – 6.1)
Patients with tachyarrhythmic events	37 (34.9)
Symptomatic tachyarrhythmias	1/37 (2.7)
Atrial arrhythmias*	8/79 (10.1)
Atrial tachycardia (>30 sec)	2/79 (2.5)
Atrial fibrillation (>30 sec)	6/79 (7.6)
Duration of AF episodes	
≥ 30 sec	6 (100)
≥ 6 min	2 (33.3)
≥ 30 min	1 (16.7)
Ventricular arrhythmias	31 (29.2)
Non-sustained VT (≥3 beats, >100 bpm)	31 (29.2)
≥ 3 beats	28 (26.4)
> 6 sec	3 (2.8)
Sustained VT (>30 sec)	0 (0)
Tachyarrhythmias requiring therapeutic changes	5 (4.7)
Anticoagulation therapy	4 (3.8)
Antiarrhythmic therapy	1 (0.9)
Bradyarrhythmias	
Time in bradycardia HR<60 bpm, %	16.4 (2.6 – 49.2)
Patients with bradyarrhythmic events	22 (20.8)
Symptomatic bradyarrhythmias	2/22 (9.1)
HAVB	2 (1.9)
HAVB + severe bradycardia	4 (3.8)
Severe bradycardia	16 (15.1)
Bradyarrhythmias requiring therapeutic changes	10 (9.4)
Change in medical therapy	6 (5.7)
Change in medical therapy + PPM pre-TAVR	2 (1.9)
PPM pre-TAVR	2 (1.9)

AE: Arrhythmic events; AF: Atrial fibrillation; CEM: Continuous ECG monitoring; HAVB: High-degree atrioventricular block; HR: Heart rate; PPM: Permanent pacemaker; PSC: Premature supraventricular contraction; TAVR: Transcatheter aortic valve replacement; VT: ventricular tachycardia

*Only patients without prior atrial fibrillation/tachycardia in the denominator



Central Illustration. New-onset arrhythmic events pre-TAVR and associated therapeutic changes

Patients with newly diagnosed AF/AT (n=79 patients with no prior history of AF/AT; top) using the CardioSTAT device within the 3 months prior to the TAVR procedure. Patients with newly diagnosed significant bradyarrhythmia (bottom).

AF: atrial fibrillation; AT: atrial tachycardia; BB: beta-blocker; HAVB: High-degree atrioventricular block; PPM: permanent pacemaker; TAVR: transcatheter aortic valve replacement

1.5.2. Factors associated with arrhythmic events. Clinical characteristics of the study population according to the occurrence of arrhythmic events as assessed by 7-day CEM are presented in **Table 1.1**. Patients with arrhythmic events had more frequently a history of chronic kidney disease (58.8% vs 38.2%, p=0.034), a trend towards a higher prevalence of left ventricular dysfunction (33.3% vs 18.2%, p=0.074) and increased aortic valve calcification (Agatston score: 2394±1612 vs 1947±1081 Agatston units, p=0.107). By multivariable logistic regression analysis, the factors determining an increased risk of arrhythmic events were chronic renal failure (odds ratio, 2.67; 95% confidence interval: 1.11-6.41, p=0.028), and a higher Agatston calcium score (odds ratio, 1.04; 95% confidence interval: 1.00-1.08, p=0.052 for each increase of 100 Agatston units) and left ventricular dysfunction (odds ratio, 2.50; 95% confidence interval: 0.93-6.69, p=0.069)

exhibited a tendency towards an increased risk of arrhythmic events as assessed by 7-day CEM.

The occurrence of significant bradyarrhythmic events during 7-day CEM according to the presence of pre-existing conduction disturbances at baseline ECG are shown in **Figure 1.2**. The presence of first-degree AVB (p=0.047) and RBBB (p=0.008), but not LBBB or nonspecific intraventricular conduction disturbances (p=0.910 and p=0.831, respectively), were associated with a higher incidence of bradyarrhythmic events at CEM.

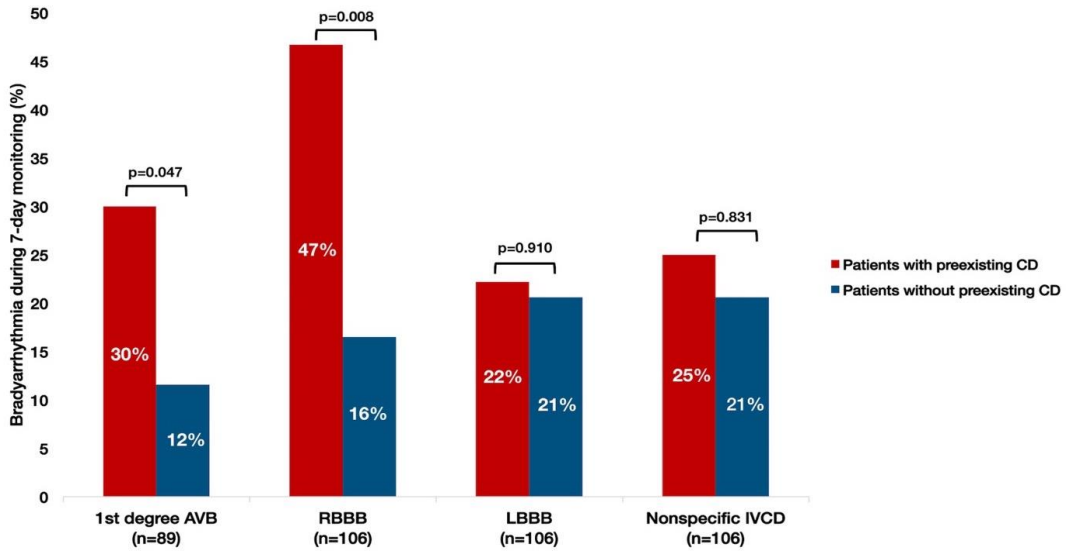


Figure 1.2. Incidence of bradyarrhythmic events during 7-day ambulatory cardiac monitoring pre-TAVR according to pre-existing conduction disturbances at baseline electrocardiogram

Occurrence of relevant bradyarrhytmic events during 7-day ECG monitoring pre-TAVR according to baseline ECG. Pre-existing 1st-degree AVB and RBBB, but not LBBB/IVCD, associated with a higher incidence of arrhythmic events.
AVB: atrioventricular block; CD: conduction disturbances; IVCD: intraventricular conduction disturbances; LBBB: left bundle branch block; RBBB: right bundle branch block

1.5.3. Arrhythmic events post-TAVR. Among the 106 TAVR candidates that underwent 7-day CEM, 7 and 8 patients were finally referred to surgical valve replacement and conservative management (frailty condition and/or excessive co-morbidity burden) following heart team evaluation, respectively (**Figure 1.1**). One additional patient, with pre-existing first-degree AVB and a nonspecific intraventricular conduction disturbance died before the TAVR procedure from sudden death. This led to a total of 90 patients who finally underwent elective TAVR. The main procedural and 30-day outcomes of TAVR are outlined in **Table 1.3**. At 30-days, there was one non-cardiac death (1.1%), and one stroke (1.1%) in another patient with history of AF and no relevant arrhythmic events detected on pre-procedural 7-day CEM. Nineteen patients (21.1%) developed new-onset persistent LBBB post-TAVR, and new-onset AF post-TAVR occurred in 3 patients (3.3%). Significant bradyarrhythmias requiring PPM following TAVR occurred in 17 patients (18.9%). Fifteen patients (16.7%) presented HAVB/CHB post-TAVR, one patient had alternant RBBB and LBBB, and another patient had sinus node dysfunction.

In one-third of the patients with new-onset arrhythmic events post-TAVR (AF, bradyarrhythmic events requiring PPM), significant arrhythmic events had already been diagnosed during pre-procedural 7-day CEM (**Figure 1.3**). Frequent episodes of silent ESVEA (not meeting the criteria for AF) were identified during CEM pre-TAVR in one of the 3 patients with new-onset AF post-TAVR. Similarly, significant bradyarrhythmias had been previously detected with CEM pre-TAVR in 5 out of 17 (29.4%) patients requiring a PPM within 30 days post-TAVR and in 9 out of 21 (42.9%) patients receiving a PPM due to severe bradyarrythmias either before or after the procedure. Among those patients with pre-existing first-degree AVB or RBBB, and concomitant severe bradyarrhythmias during CEM pre-TAVR, 66.7% and 50.0%, respectively, required PPM implantation before or after TAVR.

Table 1.3. Procedural and 30-day outcomes in patients undergoing TAVR, overall and according to the occurrence of AEs during 7-day continuous electrocardiographic monitoring pre-TAVR

	Overall	New AE	No AE	p value
	N=90	N =41	N =49	
Procedural findings				
Valve type				
Balloon-expandable valve	58 (64.4)	29 (70.7)	29 (59.2)	0.254
Self-expandable valve	32 (35.6)	12 (29.3)	20 (40.8)	
Approach				
Transfemoral	55 (61.1)	22 (53.7)	33 (67.4)	0.185
Non-transfemoral	35 (38.9)	19 (46.3)	16 (32.7)	
Valve size, mm	26.6±2.7	26.5±2.7	26.7±2.7	0.663
Valve-in-valve	5 (5.6)	2 (4.9)	3 (6.1)	1.000
Pre-dilatation	9 (10.0)	6 (14.6)	3 (6.1)	0.180
Post-dilatation	17 (18.9)	8 (19.5)	9 (18.4)	0.890
Procedural success	88 (97.8)	40 (97.6)	48 (98.0)	0.898
30-day outcomes				
All-cause death	1 (1.1)	0 (0)	1 (2.0)	1.000
Cardiovascular death	0 (0)	0 (0)	0 (0)	-
Stroke	1 (1.1)	0 (0)	1 (2.0)	1.000
Myocardial infarction	2 (2.2)	1 (2.4)	1 (2.0)	1.000
Major or life-threatening bleeding	6 (6.7)	2 (4.9)	4 (8.2)	0.685
Arrhythmic events				
New-onset atrial fibrillation*	3 (4.5)	2 (7.7)	1 (2.4)	0.555
Severe bradyarrhythmias requiring PPM	17 (18.9)	8 (19.5)	9 (18.4)	0.890
HAVB /CHB	15 (16.7)	7 (17.1)	8 (16.3)	0.925
Alternant RBBB + LBBB	1 (1.1)	1 (2.4)	0 (0)	0.456
Sick sinus syndrome	1 (1.1)	0 (0)	1 (2.0)	1.000

No patient was lost to follow-up.
*Patients with no history of atrial fibrillation (n=67)
CHB: Complete heart block; HAVB: High-degree atrioventricular block; LBBB: Left bundle branch block; PPM: Permanent pacemaker; RBBB: right bundle branch block

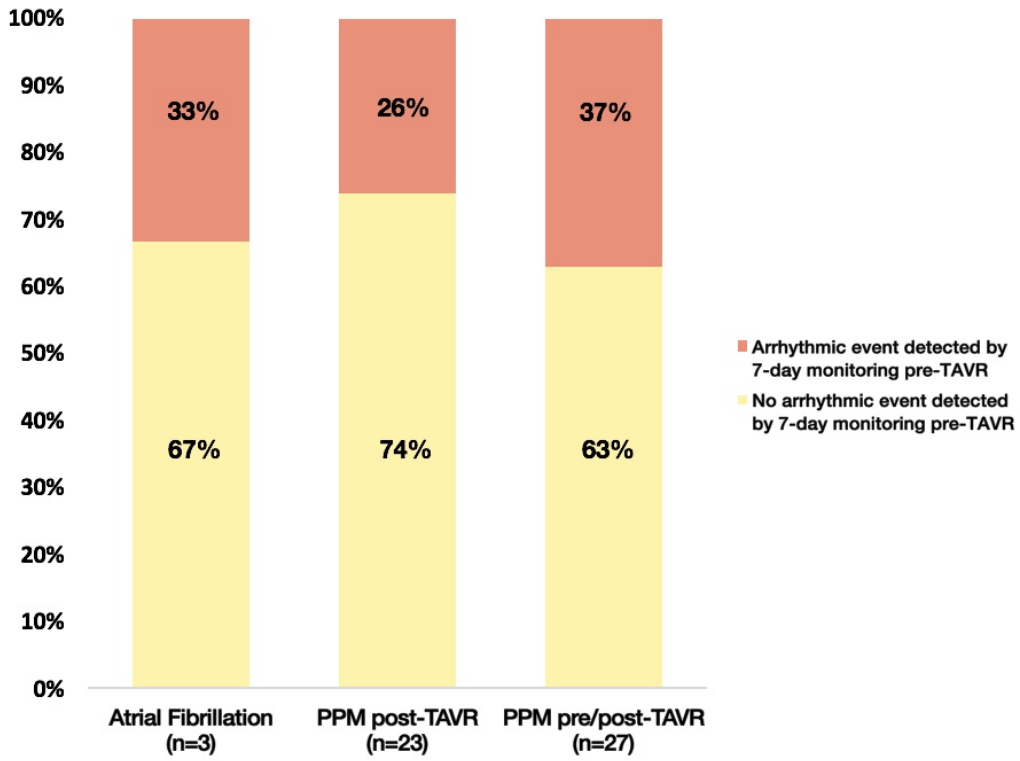


Figure 1.3. New-onset atrial fibrillation and need for pacemaker according to the occurrence of previously unknown arrhythmic events during 7-day cardiac monitoring pre-TAVR

Continuous ECG monitoring pre-TAVR identified early arrhythmic events in 33% of the patients with new-onset atrial fibrillation post-TAVR, and in 29% and 43% of the patients requiring a pacemaker post-TAVR or pre/post-TAVR, respectively.
PPM: permanent pacemaker; TAVR: transcatheter aortic valve replacement

1.6. DISCUSSION

The results of this first study evaluating the usefulness of pre-procedural prolonged CEM in patients with severe aortic stenosis screened for TAVR can be summarized as follows: (i) 1 out of 10 patients exhibited subclinical episodes of AF/AT, and a therapeutic change (anticoagulation and/or antiarrhythmic therapy) was implemented in close to 2/3 of such patients (ii) significant bradyarrhythmias were detected in ~20% of patients (HAVB in about one-fourth of the cases), with treatment changes and PPM required in approximately one-half and one-fifth of them, respectively; (iii) pre-TAVR CEM allowed early arrhythmia diagnosis in about one-third of the patients with new-onset arrhythmic events post-TAVR.

A high arrhythmic burden has been shown in elderly patients with calcific aortic valve stenosis.[37, 170] Progressive pathophysiological changes such as calcium deposit on the conduction system, along with increased left ventricular overload resulting in left ventricular hypertrophy/fibrosis and left atrium overload have been suggested to play a role in the pathogenesis of dysrhythmias in this population.[171, 172] Urena et al.[37] identified previously unknown arrhythmias in 16% of TAVR candidates who had 24-hour ECG monitoring the day before the procedure (paroxysmal AF/AT in 10.5% of patients without known AF/AT, NSVT in 6.0%, significant bradyarrhythmias in 6.4% patients without prior PPM), resulting in therapeutic changes in 43% of such patients. Nevertheless, the efficacy of arrhythmic detection by monitoring devices depends on the duration and method of ECG monitoring, and 24-hour ECG Holter exhibits moderate sensitivity (44-66%) compared to longer event recorders (>90%).[34, 164] Notably, the use of 7-day CEM in the present study translated into a higher diagnostic yield for the detection of previously unknown arrhythmias (overall 48.1%; paroxysmal AF/AT in 10.1%, NSVT in 29.2%, significant bradyarrhytmias in 20.8%).

The prevalence of silent AF in the elderly has ranged between 1.5% and 14%, depending on type and duration of ECG monitoring.[34] Of note, asymptomatic AF detection increases in higher-risk populations (e.g. history of stroke, patients with structural heart disease) and extended duration of ECG monitoring (≥7 days), and it has been associated with a worse prognosis given the potential delay in anticoagulation prescription in the absence of

symptoms.[173]. Importantly, the occurrence of ESVEA has been strongly associated with an increased risk of incident AF, stroke, and mortality.[34] In the present study, the prevalence of newly diagnosed ESVEA and paroxysmal AF were 32.9% and 7.6% respectively, but was not associated with an increased risk for stroke (occurring in one single patient with prior history of AF). Interestingly, new-onset AF post-TAVR occurred in 3 patients, of whom one had ESVEA during preprocedural 7-day CEM. Whereas ESVEA has been considered a surrogate marker for paroxysmal AF, future studies are needed to evaluate whether intensive risk factor or therapeutic modification in these patients could improve outcomes or mitigate the progression from supraventricular ectopy to AF.

Whether to initiate anticoagulation in patients with device-detected AF remains controversial. In the present study, anticoagulation treatment was initiated in four patients with newly diagnosed episodes of AF and high stroke risk (mean CHA_2DS_2-VAS_c score: 5.5). Although a device-detected threshold of >5.5 hours has been suggested for anticoagulation initiation for patients with long-term CEM (i.e. cardiac implantable electronic devices),[34] it seems prudent to offer a much lower threshold for patients undergoing CEM of shorter duration when the bleeding risk is low, and current guidelines recommend that patients with AF should be given oral anticoagulants, irrespective of paroxysmal (≥30 seconds) or persistent AF.[28] Of note, integration of AF burden and CHA_2DS_2-VAS_c score is crucial in the decision to prescribe anticoagulation, with recent studies suggesting an increased risk of thromboembolic events in patients with CHA_2DS_2-VAS_c score ≥5, regardless of device-detected AF duration.[174] Further trials are needed to determine the minimal duration of AF needed to warrant anticoagulation initiation.

A high prevalence of ventricular arrhythmias has been classically described in patients with severe aortic stenosis.[172] The prevalence of pre-existing NSVT in TAVR recipients, defined according to current guidelines, has been established between 6.0% and 9.6% in previous studies using short 24-hour ECG monitoring before the procedure, [37, 175] and up to 13% (episodes >6 seconds) within the year post-TAVR by implantable CEM.[170] A higher rate of NSVT was observed in the present study (29.2%), mainly attributable to extended ECG recording, although most episodes (90%) lasted less than 6 seconds (none sustained), and

did not lead to pre-TAVR therapeutic measures. One patient with mild left ventricular dysfunction, newly diagnosed AF and NSVT during pre-TAVR CEM, died before the procedure, although no definite arrhythmic cause could be confirmed at the time of sudden death. Larger studies are needed to assess the potential association between pre-existing ventricular arrhythmias and sudden cardiac death in patients undergoing TAVR.

The prevalence of pre-existing significant bradyarrhythmias - severe bradycardia or HAVB - in TAVR candidates was higher (20.8%) than previously reported (5.5% in overall patients and 6.4% in patients without prior PPM) (6). This translates into a number needed to screen of 5 TAVR candidates to diagnose 1 previously unknown significant bradyarrhythmia (18 patients to diagnose 1 HAVB before TAVR). Of note, therapeutic intervention was required in one-half of the patients with bradyarrhythmias during 7-day CEM before the procedure. Additionally, and in accordance with previous studies,[37] CEM pre-TAVR allowed prompt identification of previously unknown bradyarrhythmias in approximately 1/3 of patients requiring PPM post-TAVR (possibly not related to the procedure but already preexistent in this high-risk population), although CEM seemed to fail reducing the global rate of PPM post-TAVR. Indeed, the rate of significant bradyarrhythmias requiring PPM after TAVR in the present study was high (18.9%), which may be explained by several factors. First, unlike our study, most studies to date did not exclude patients with prior PPM when reporting post-TAVR PPM rates (denominator including patients with an intracardiac device at baseline), leading to a systematic underestimation of the real incidence of PPM post-TAVR[176]. Second, the Sapien 3 valve (Edwards Lifesciences, Irvine, CA) - for which higher rates of PPM have been reported compared to Sapien XT valves - was used in 58% of the TAVR procedures, which may have influenced the rate of PPM in the present study[177]. Indeed, the reported PPM rates with the Sapien 3 valve have been higher than 10%, almost double than the rates generally observed with previous-generation balloon-expandable valves[162]. This phenomenon may be due either to its design (bulkier skirt aimed to reduce paravalvular regurgitation, longer stent frame) or because of a potential learning curve effect with the new-generation valve likely related to valve positioning issues (too low –ventricular- positioning in the initial experience with this valve type). Of note, a trend towards a reduction in the need for PPM

was observed throughout the study period, from 23.1% to 7.7% when comparing the first with the second half of Sapien 3 valve implantations (p=0.124).

Chronic kidney disease was the strongest predictor of new-onset arrhythmic events during preprocedural ambulatory CEM. It is well-known that patients with chronic renal disease are predisposed to heart rhythm disorders, including AF (16-21% in patients not dependent on dialysis, 15-40% in patients on dialysis), ventricular arrhythmias and sudden cardiac death, with annual rates of sudden death in non-dialysis patients comparable to that of post-infarction patients.[178] Several mechanisms have been proposed to explain this relationship: common risk factors, long-standing abnormalities predisposing to arrhythmogenic conditions, myocardial ischemia, volume shifts or left ventricular hypertrophy and dysfunction. Also, there was a trend toward increased pre-TAVR arrhythmic burden in patients with left ventricular dysfunction, as previously shown by Urena et al.[37] and in several previous studies evaluating patients with aortic stenosis.[179, 180] Likewise, calcium deposition at the level of the conduction system in patients with calcific aortic stenosis could translate into prolonged His-ventricular intervals and HAVB[181], partially explaining the observed trend toward increased pre-existing unknown arrhythmias in patients with severe valve calcification.

Patients with pre-existing first-degree AVB or RBBB exhibited higher rates of new-onset bradyarrhythmic events during the 7-day CEM pre-TAVR, although the relatively small sample size and number of bradyarrhythmic events observed precluded the assessment of independent predictive factors. Of note, the presence of first-degree AVB and RBBB have been associated with increased risk of PPM (4- to 11-fold, and 3- to 47-fold, respectively), the latter being the strongest and most consistent predictor of PPM post-TAVR in the literature.[163] This raises the question whether this subset of patients may particularly benefit from pre-TAVR screening strategy with long-term CEM to improve detection of severe subclinical bradyarrhythmias before TAVR, although larger studies are warranted to further evaluate these findings.

Study limitations. This was a single-center study, and potential variations in the arrhythmic burden related to geographic patterns cannot be ruled out and may limit generalizability of our findings. Second, a significant portion (one-fourth) of the study patients had previously documented atrial fibrillation, although none of those patients had a prior PPM. Third, the single-lead design of the ambulatory CEM used in the present study, did not allow the assessment of the incidence of new-onset LBBB before the TAVR procedure. Finally, the relatively limited sample size of the study precluded the evaluation of the predictive factors associated with newly diagnosed tachyarrhytmic and bradyarrhythmic events (analyzed separately).

1.7. CONCLUSIONS

In conclusion, nearly half of elderly patients with severe symptomatic aortic stenosis presented newly diagnosed arrhythmic events during 7-day CEM pre-TAVR. Paroxysmal AF/AT and significant bradyarrhythmias were observed in one-tenth and one-fifth of patients, respectively, with pharmacological or invasive intervention required in about half of them. These findings support the usefulness of CEM for the early diagnosis and treatment of arrhythmic events in TAVR candidates. Also, they open the door to further studies evaluating the possibility of tailored CEM pre-TAVR in selected populations with certain baseline clinical features (eg. chronic renal failure, left ventricular dysfunction, higher valve calcification) or pre-existing conduction disturbances (first-degree AVB, RBBB).

1.8. PERSPECTIVES

What is known? TAVR candidates are at risk of developing cardiac arrhythmias.

What is new? Pre-TAVR prolonged continuous ECG monitoring detects previously unknown arrhythmic events in nearly 50% of the patients, and allows prompt therapy implementation in nearly one-fourth of them.

What is next? Further studies are needed to evaluate the role of tailored continuous ECG monitoring in selected high-risk populations (pre-existing conduction disturbances [RBBB], chronic renal failure, or increased valve calcification).

1.9. ACKNOWLEDGMENTS

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CHAPTER 2. Percutaneous Left Atrial Appendage Closure: Current Devices and Clinical Outcomes

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2.1. RÉSUMÉ

Le traitement anticoagulant oral chronique est le traitement standard pour prévenir les événements thromboemboliques chez les patients atteints de fibrillation auriculaire (FA). Cependant, l'anticoagulation orale a été associée à un risque accru de saignements et, malgré les améliorations liées à l'introduction des anticoagulants oraux directs, plus d'un tiers des patients atteints de FA ne sont toujours pas traités. Au cours de la dernière décennie, la fermeture percutanée de l'auricule gauche est apparue comme une alternative valable au traitement anticoagulant pour la prévention des accidents vasculaires cérébraux et des embolies systémiques chez les patients atteints de FA. Dans ce manuscrit, nous fournissons une mise à jour des dispositifs actuels de fermeture de l'auricule gauche transcathéter, et on examine les résultats associés à la fermeture de l'auricule gauche, avec attention spéciale sur les résultats procéduraux et tardifs, et en pointant vers les directions futures.

2.2. ABSTRACT

Chronic oral anticoagulation therapy is the standard therapy for preventing thromboembolic events in patients with atrial fibrillation (AF). However, oral anticoagulation has been associated with an increased risk of bleeding events, and despite the improvements linked to the introduction of direct oral anticoagulants, more than one third of AF patients still remain untreated. Over the past decade, percutaneous left atrial appendage closure has emerged as a valid alternative to anticoagulation therapy for the prevention of stroke/systemic embolism in patients with AF. In this manuscript, we provide an updated overview of current transcatheter left atrial appendage closure devices, and review the results associated with left atrial appendage closure, focusing on procedural and late outcomes, and pointing to future directions.

2.3. INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia. It affects more than 33 million individuals worldwide, and its prevalence is projected to double by 2050.[182] AF is associated with a 5- and 2-fold increased risk of stroke and mortality, respectively.[7] Furthermore, AF-related strokes are associated with higher morbidity, mortality and healthcare costs compared to non-cardioembolic strokes.[12]

The mainstay of stroke prevention remains oral anticoagulation (OAC), with vitamin K antagonists and, more recently, direct oral anticoagulants (DOAC) reducing the risk of ischemic stroke and all-cause mortality in patients with AF. However, more than one third of AF patients at high risk for stroke still fail to receive effective stroke prophylaxis in contemporary practice.[77] While the introduction of DOAC has overcome some of the limitations of warfarin therapy, persistent barriers including costs, ongoing bleeding risks with no reversal agent for most DOACs, noncompliance and high discontinuation rates may preclude a broader use of DOAC in clinical practice.[74]

The left atrial appendage (LAA) is a remnant of the embryonic left atrium, and is considered the main reservoir for left atrial thrombi in >90% of patients with non-valvular AF.[18] In recent years, percutaneous left atrial appendage closure (LAAC) has rapidly grown worldwide as an appealing alternative for the prevention of thromboembolisms in patients at high risk for stroke, with a specific focus on patients ineligible for OAC. Whereas no specific recommendation on LAAC was given in the 2014 American guidelines,[7] the 2016 European guidelines for the management of AF provided a Class IIb recommendation for percutaneous LAAC in patients with AF and contraindications for long-term OAC,[183] based on data from the PROTECT-AF and PREVAIL trials, the only LAAC randomized trials to date.[130, 131, 184, 185] Although none of these studies included patients ineligible for OAC, most of the "real-world" registries conducted to date have focused on this target population, which currently represents the majority of LAAC recipients. This review provides an updated overview of current transcatheter LAAC devices, and reviews the main clinical data from LAAC randomized trials and registries, focusing on procedural and late

outcomes, as well as on future directions. Details about LAA imaging and LAAC closure techniques are beyond the focus of this review.

2.4. DEVICE CHARACTERISTICS AND TECHNICAL ASPECTS

2.4.1. Plaato

The first-in-human percutaneous LAAC with a dedicated device was performed by professor Sievert in 2001 using the PLAATO device (Appriva Medical, Sunnyvale, California). The device consisted of a self-expanding nitinol metal cage, available in different sizes (15-32 mm). Despite favorable initial clinical results,[128, 186] the device was withdrawn from the market in 2006.

2.4.2. Watchman and Watchman FLX

The WATCHMAN device (Boston Scientific, Natick, Massachusetts), was the second dedicated LAAC device, and remains the only device studied in randomized clinical trials to date.[130, 131] It consists of a self-expanding nitinol 10-strut frame, with a 160 μm permeable polyethylene terephthalate membrane (PET) fabric cap facing the left atrium (**Table 2.1, Figure 2.1A**). The open distal end is fixed by 10 active fixation anchors in one row. The device is available in 5 sizes: 21, 24, 27, 30 and 33 mm. The transseptal access sheath has a 14F outer diameter and is available in three different preformed curve shapes: anterior curve, double curve (used in >90% of procedures) and single curve. Three proximal radio-opaque markers correspond to the approximate level of deployment for 21, 27 and 33 device sizes, respectively.

The transseptal puncture is performed under fluoroscopic and preferably transesophageal echocardiography (TEE; bicaval view followed by short-axis view) guidance in the inferoposterior portion of the fossa ovalis. Following transseptal puncture, a long extra-stiff J tipped 0.035-inch wire is advanced into the left upper pulmonary vein and the transseptal sheath is exchanged over the wire for the access sheath. After dilator and guidewire removal, a 5-6F pigtail catheter is advanced through the access sheath into the left upper pulmonary vein. Using TEE and fluoroscopic guidance, both the access sheath and pigtail are repositioned into the LAA.

Appropriate WATCHMAN device sizing is determined by the maximum LAA ostium diameter (measured from the circumflex artery to 1-2 cm within the pulmonary vein ridge at 0º, 45º, 90º and 135º), and depth (from ostium to the tip of LAA). An oversizing of the device by at least 10-20% (corresponding to 2 to 4 mm) is generally recommended. A fluoroscopic right (20-30º) and caudal projection (20º-30º), which usually opens the mid-distal portion of the LAA, is the preferred one for the deployment of the WATCHMAN device.[187]

Following accurate LAA assessment, the delivery system is advanced into the access sheath until the distal markers of the delivery catheter and the access sheath align. The device is then deployed with a slow unsheathing movement. Following device deployment, the four "PASS" criteria are checked prior to device release: (1) position (adequate coverage of the ostium with < 50% shoulder), (2) anchor (gentle tug-test without change of the device position), (3) size (8-20% device compression) and (4) seal (<5 mm residual leak). If the device is too distal it may be partially recaptured, but if it is too proximal full recapture is required. Upon satisfactory position, the device is released by unscrewing the connector wire.

The second-generation WATCHMAN FLX device (Boston Scientific) is fully covered by the PET cap in order to minimize peri-device leaks (**Table 2.1, Figure 2.1B**).[188] It is 10-20% shorter than the previous generation device, and is available in five sizes (20, 24, 27, 31, and 35 mm) for LAA ostia measuring from 15 to 32 mm. The increased number of struts (18) and anchors (12 in two rows), combined with a higher radial strength, provide improved tissue fixation. Whereas a greater compression (10-27%) was initially allowed, an increased risk of device embolization was observed with excessive oversizing.

The WATCHMAN device received Conformité Européenne (CE)-mark approval in 2005, and FDA approval in 2015 for patients with non-valvular AF at high risk for stroke. The WATCHMAN FLX device obtained CE-mark approval in 2015, but was withdrawn from

the European market in March 2016 due to an increased number (6 of 207, 2.9%) of implant embolization reports both during the procedure and postprocedure. A new generation design is currently being developed.

2.4.3. Amplatzer Cardiac Plug and Amulet

The AMPLATZER Cardiac Plug (ACP) (Abbott Vascular, Santa Clara, CA) is a self-expanding nitinol mesh with a distal lobe and a proximal disk with polyester fabric, connected by an articulated waist (**Table 2.1, Figure 2.1E**).[186] The length of the ACP device is shorter than its diameter and may therefore accommodate to shorter LAAs. The lobe has 6 pairs of stabilizing wires and is aimed to be implanted at 10 mm within the LAA orifice, whereas the disk is meant to seal the LAA ostium at the left atrial side. There are 8 different sizes according to the lobe dimensions, ranging from 16 to 30 mm (for landing zone measures between 12.6 and 28.5 mm).

The Amulet device (Abbott Vascular, Santa Clara, CA) is the latest generation device, based on a similar design to the ACP device but with modifications to both facilitate implantation and reduce peri-procedural complications (**Table 2.1, Figure 2.1F**).[186] The device comes preloaded in 8 different sizes (from 16 to 34 mm), fitting LAA sizes from 11 to 31 mm (landing zone measurements), with a minimum LAA depth of 12 mm. Compared to the ACP device, the distal lobe is 2-3 mm longer and the diameter of the proximal disk is 6-7 mm greater than the distal lobe diameter, with more stabilizing wires (6-10 pairs) and a longer waist, conferring altogether improved stability. Furthermore, the proximal end screw was recessed to minimize device thrombosis. Similar to the WATCHMAN FLX device, less oversizing is needed considering its more stable design.[189]

The ACP and Amulet devices are implanted through 9-13F and 12-14F sheaths, respectively. Currently, only the TorqVue 45ºx45º delivery sheath is available. The main procedural steps are similar to those previously described for the WATCHMAN device. Device sizing is based on the widest diameter of the landing zone. An oversizing of 3-5 mm for ACP and 2-4 mm for Amulet is generally recommended. TEE measurements at both

short axis (30-60º) and long-axis (120-150º) of the landing zone and orifice (from the circumflex artery to the pulmonary vein ridge) are used for appropriate LAA assessment. The landing zone is measured at 10 mm and 12-15 mm from the orifice for the ACP and Amulet devices, respectively. A right (30º) and cranial (10-20º) angiographic view for depicting the ostium and proximal LAA segments are usually recommended for device deployment.[187]

The device is advanced to the distal delivery sheath and placed at the landing zone. The delivery sheath is retracted, with exposure of the distal portion in the "ball position", allowing safe manipulation of the sheath to the desired landing zone. After optimal positioning, deployment of the remainder lobe and the disk is completed by advancing the delivery cable while unsheathing the device disk. Five signs of device stability are checked before device release: (1) tire-shaped lobe ensuring good compression, (2) optimal lobe orientation perpendicular to the LAA neck, (3) concave-shaped disk, (4) separation between the lobe and the disk ensuring adequate seal, and (5) the lobe should be ≥ 2/3 within the circumflex artery. After a subtle tug test, the device is released.[189]

The ACP and Amulet devices received CE mark in 2008 and 2013, respectively. A US study comparing the Amulet and WATCHMAN devices is currently ongoing (*NCT02879448*).

Table 2.1. Percutaneous LAAC Devices

Device	Manufacturer	Specific requirements / Possible advantages	Design	Sizes (mm)	Sheath	Approval status (year)
ENDOCARDIAL LAAC DEVICES						
PLAATO	Appriva Medical (Sunnyvale, CA)	First-in-human endocardial LAAC device	Single-lobe; nitinol cage; ePTFE membrane; hooks	15, 18, 20, 23, 26, 29, 32	14 F	Discontinued (2006)
WATCHMAN	Boston Scientific (Natick, MA)	Ostium: 17-31 mm Depth: ≥ width of ostium Spherical contour accommodating most LAA anatomies Long-term data from RCT	Single-lobe; nitinol 10-strut frame; 160 μm PET membrane; 10 anchors	21, 24, 27, 30, 33	14 F	CE Mark (2005) FDA (2015)
WATCHMAN FLX	Boston Scientific (Natick, MA)	Shorter profile, extended sizing range, increased stability	Single-lobe; nitinol 18-strut frame; extended PET membrane; closed distal end; 12 anchors	20, 24, 27, 31, 35	14 F	CE Mark (2015) Withdrawn (2016)
ACP	Abbott Vascular (Santa Clara, CA)	Landing zone: 12.6-28.5 mm Depth: ~10 mm Fits in short LAA or LAA with multiple proximal lobes Double sealing system	Lobe and disk; central waist; nitinol mesh; polyester patch; 6 pairs of stabilizing wires	16 18, 20, 22 24, 26, 28, 30	9 F 10 F 13 F	CE Mark (2008)
Amulet	Abbott Vascular (Santa Clara, CA)	Landing zone: 11.0-31.0 mm Depth: ~12-15 mm Fully preloaded, wider diameters, low-profile endscrew to reduce thrombus, increased stability.	Lobe and disk; wider lobe; longer waist; recessed proximal endscrew; 6-10 pairs of stabilizing wires	16, 18, 20, 22, 25 28, 31, 34	12-14 F 14 F	CE Mark (2013)
WaveCrest	Biosense Webster (Diamond Bar, CA)	Small LAA anatomies (no delivery sheath placement into the LAA required) Repositionable at any time prior to release	Single-lobe; nitinol frame; LA-facing ePTFE layer; LAA-facing foam layer; 10 bi-directional anchors and 10 single-anchors	22, 27, 32	12 F	CE Mark (2013)

Occlutech	Occlutech (Helsingborg, Sweden)	Uncommon anatomies (180º angle rotation of the steerable sheath during positioning)	Single-lobe; nitinol wire mesh; nano-spun polyurethane covering; closed stabilizing loops	15, 18, 21 24, 27, 30, 33, 36, 39	12 F 14 F	CE Mark (2016)
LAmbre LAA closure system	Lifetech Scientific (Shenzhen, China)	Low profile Fully retrievable and repositionable Special device for multilobed, small or "chicken wing" anatomies	Lobe (umbrella) and disk (cover); nitinol; double PET membrane; double stabilization mechanism (8 distal hooks, 8 proximal U-shaped anchors)	Single-lobe anatomy: 16-36 Double-lobe anatomy: 16-26	8-10 F	CE Mark (2016) CFDA (2017)
Ultraseal	Cardia (Eagan, MN)	Fits in complex LAA anatomies due to the multidirectional articulating join	Lobe (bulb) and disk (sail); nitinol frame; polyvinylacetate foam; 12 distal hooks	16 18, 20, 22, 24, 26 28, 30, 32	10 F 11 F 12 F	Clinical evaluation
Sideris Patch	Custom Medical Devices (Athens, Greece)	Bioabsorbable No risk of perforation	Frameless bioabsorbable balloon-deliverable device; latex balloon; polyurethane foam tailored patch; nylon loop suture	≤25	13 F	Clinical evaluation
Pfm	Pfm Medical (Köln, Germany)	Barbless anchor reducing risk of perforation	Dual disk; nitinol; primary distal anchor, middle connector and proximal occluder with secondary anchor	15-25	10-12 F	Pre-clinical evaluation
			EPICARDIAL LAAC DEVICES			
LARIAT	SentreHEART (Redwood City, CA)	Unsuitable anatomies for endocardial devices (LAA diameter > 31 but < 40 mm, short neck) Universal size	Endo-epicardial approach; EndoCATH occlusion balloon; FindrWIRZ magnet-tipped guidewires; epicardial snare with a pre-tied Teflon-coated suture	One-size (40 Lariat; 45 next generation Lariat+)	13.5 F epicardial 8.5 F transseptal	CE Mark (2015) FDA 510(k) (2006) for surgical use only
Sierra Ligation System	Aegis Medical Innovations (Vancouver, Canada)	Unsuitable anatomies for endocardial devices Universal size No transseptal puncture needed	Epicardial subxiphoid access; appendage grabber and ligator; ECG navigation	One-size	20 F	Clinical evaluation

LAA: Left atrial appendage; LAAC: left atrial appendage closure; RCT: Randomized controlled trial; ACP: Amplatzer Cardiac

2.4.4. Other emerging devices

2.4.4.1. WaveCrest

The WaveCrest device (Biosense Webster, Diamond Bar, California) is a nitinol single-lobe device with an expanded polytetrafluoroethylene (ePTFE) cover on the left atrial side, and a polyurethane foam facing the LAA, with 20 anchoring points (**Table 2.1, Figure 2.1J**).[190] It has the particularity that the occluder and anchoring systems may be manipulated independently, and contrast may be injected proximally through the delivery sheath or distally via the occluder to ensure good sealing. As the device is designed for proximal positioning in the LAA neck, it does not require delivery sheath placement into the LAA, making it particularly attractive for small LAA anatomies. The WaveCrest device obtained CE-mark approval in 2013. A postmarket registry following European approval is currently ongoing (*NCT03204695).*

2.4.4.2. Occlutech LAA Occluder

The Occlutech LAA Occluder (Occlutech International AB, Helsingborg, Sweden) is a conical-shaped self-expanding nitinol wire mesh, that is anchored through closed loops at the distal margin (**Table 2.1, Figure 2.1K**).[191, 192] A polyurethane coverage promotes sealing and endothelization. The Occlutech device received CE mark approval in 2016.

2.4.4.3. LAmbre LAA Closure System

The LAmbre™ LAA Closure System (Lifetech Scientific Co, Ltd, Shenzhen, China) is a nitinol device composed of a left atrial cover and a distal self-expanding umbrella, covered by a double polyethylene terephthalate membrane and connected via a central articulating waist (**Table 2.1, Figure 2.1L**).[193] The device is secured by a double stabilization mechanism with 8 distal hooks and 8 proximal U-shaped anchors. The distal umbrella is deployed first with hooks recessed until deployment, and the proximal cover is then released. There are two types of LAmbre devices, the standard and the special, addressing both single- or double-lobe anatomy respectively, the latter useful for multilobed or small LAAs. The chief advantages of the LAmbre device are its low profile (8-10F) and that is fully recapturable and repositionable. The LAmbre LAA Closure System received CE-mark approval in 2016 and CFDA approval in 2017.

2.4.4.4. Sideris Patch

The Transcatheter Sideris Patch (Custom Medical Devices, Athens, Greece) is a frameless, balloon-deliverable, bioabsorbable device, covered with polyurethane (**Table 2.1, Figure 2.1M**).[194] A single size allows conforming to most LAA sizes. The device is advanced through a 13-F sheath into the LAA. A latex balloon is inflated with diluted contrast (3-10 ml, corresponding to 15-25 mm patch diameter), and an adhesive-activating alkaline solution is injected through the catheter. Forty-five minutes after surgical adhesive activation, the supportive balloon catheter is retrieved. A double nylon retrieval thread is connected to a nylon loop sutured at the tip of the patch. After optimal placement and stability, the retrieval thread is removed and the patch is released. The device is currently under clinical evaluation.

2.4.4.5. Ultraseal

The Ultraseal LAA closure device (Cardia Inc., Eagan, MN) is a self-expandable nitinol device composed of two sections: a soft distal bulb for device anchoring and a 3-leaflet proximal sail for LAA occlusion, connected by a dual articulating joint that allows multidirectional movement and optimal adjustment to different ostium angles and shapes (**Table 2.1, Figure 2.1N**).[195] The device is available in 9 different bulb sizes ranging from 16 to 32 mm, and has 12 stabilizing hooks to avoid device dislodgement; an oversizing of 25-33% is generally recommended. The proximal sail, covered by a polyvinylacetate foam, is 6 mm larger than the distal bulb with diameters varying from 22 to 38 mm. Two delivery sheaths ranging from 10 to 12-F are currently available: single curve (45º) and double curve (45º-45º). The device is currently under evaluation in clinical registries in Canada and Europe.

2.4.4.6. Pfm

The Pfm device (Pfm Medical, Köln, Germany) is a nitinol frame device delivered through a preshaped 10-12 F delivery sheath. It consists of three parts: a primary distal anchor, a middle connector and a proximal disk with secondary anchor (**Table 2.1, Figure 2.1O**).

The adjustable length of the middle connector allows accommodation to variable LAA lengths. The device is secured by a barbless anchor that minimizes the risk of perforation. The Pfm system is currently being evaluated in preclinical studies.

2.4.4.7. LARIAT

The LARIAT device (SentreHEART, Palo Alto, California, USA) is a transcatheter endo-epicardial LAAC device, differing from the above described endocardial techniques (**Table 2.1, Figure 2.1P**).[186, 196] It consists of three components: (1) an endocardial 15-mm compliant occlusion balloon catheter (EndoCATH), (2) a 0.025-inch endocardial and 0.035-inch epicardial magnet-tipped guidewires (FindrWIRZ), each with opposite polarity enabling end-to-end alignment, and (3) an epicardially delivered 12F LARIAT suture delivery device, a pre-tied suture loop made from Teflon-coated, braided polyester (maximum width 40x20x70 mm). Pre-procedural computed tomography screening is required to assess suitability of LAA anatomy for the LARIAT device (favorable in about 60-80% of screened patients). The main contraindications for this approach are: LAA diameter > 40 mm, prior cardiac surgery, pectus excavatum, posteriorly oriented LAA and multi-lobed LAA. The latest generation LARIAT^{+} suture delivery device, with increased snare width from 40 to 45 mm, allows treatment of LAAs >40 mm. The procedure consists of 4 main steps: (1) pericardial and transseptal puncture, (2) advancement of the endocardial magnet-tipped gidewire into the LAA apex (3) connection of the endocardial and epicardial magnet-tipped guidewires, over which the LARIAT snare is advanced; (4) snare positioning and capture of the LAA ostium by TEE-guided placement of the inflated EndoCATH balloon catheter, followed by LAA suture ligation. The LARIAT device received CE-mark approval in 2015. Although 510(k) cleared by the FDA since 2006 for surgical use in soft tissue approximation, the device has not been approved yet for the prevention of stroke in AF patients.

2.4.4.8. Sierra Ligation System

The Sierra Ligation System (Aegis Medical Innovations, Vancouver, Canada) is an epicardial LAAC device, allowing LAAC with a single subxyphoid access, through

electrographic navigation (**Table 2.1, Figure 2.1Q**).[197] In contrast to the LARIAT system, no transseptal puncture is required. The system consists of two components: a LAAC grasper and a ligator (suture). The grasper has articulating jaws with mounted electrodes that identify electrical activity from the LAA, distinguishing it from ventricular tissue or epicardial fat. Once the grasper secures the LAA, a closing hollow suture preloaded with a radio-opaque inner support wire, is advanced over the grasper, around the free margin of the LAA. Hence, the loop is tightened, the wire is removed and the suture is finally fixed with a clip. An early feasibility study is currently ongoing in the US and Canada (*NCT02583178*).

A summary of current available devices for percutaneous LAAC is shown in **Table 2.1** and **Figure 2.1**.

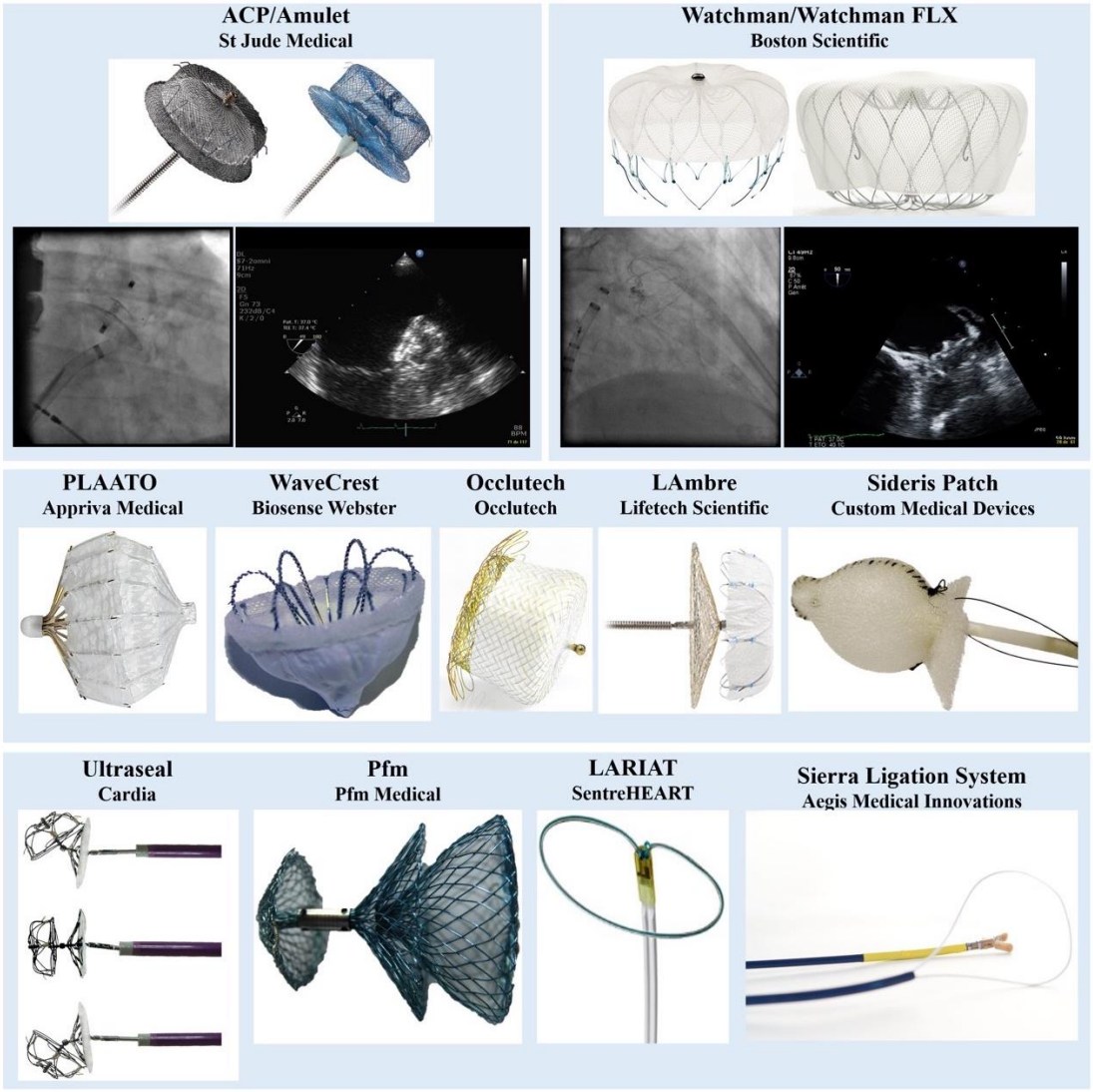

Figure 2.1. Percutaneous left atrial appendage closure devices

(A-B) The WATCHMAN (A) and WATCHMAN FLX (B) devices. Courtesy of Boston Scientific, © 2017 Boston Scientific Corporation or its affiliates, all rights reserved. (C-D) Example of WATCHMAN implantation. Procedural angiographic (C) and echocardiographic (D) views of an implanted WATCHMAN device. (E-F) The AMPLATZER Cardiac Plug (E) and Amulet (F) devices. Reprinted from Swaans *et al.*[186] with permission, Copyright ©2016, Dove Medical Press. (G-H) Example of ACP implantation. Fluoroscopic (G) and transesophageal echocardiography (H) images of a 22-mm ACP deployed. (I) PLAATO. Reprinted from Swaans *et al.*[186] with permission, Copyright ©2016, Dove Medical Press. (J) WaveCrest device, reprinted from De Backer *et al.*[190], with permission, Copyright ©2014, BMJ Publishing Group Ltd. (K) Occlutech image, reprinted from Whisenant and Weiss,[191] with permission, Copyright ©2014, Elsevier. (L) LAmbre™ LAA closure system. Courtesy of Lifetech Scientific. (M) Sideris Transcatheter Patch, reprinted from Toumanides *et al.*[194] with permission, Copyright ©2011, Elsevier. (N) Cardia Ultraseal device. Courtesy of Cardia. (O) Pfm device. Courtesy of Dr. A. Javois (Advocate Hope Children's Hospital, Chicago, IL). (P) LARIAT device. Reprinted from Swaans et al[186], with permission, Copyright ©2016, Dove Medical Press. (Q) Sierra Ligation System. Courtesy of Aegis Medical Innovations.

2.5. PROCEDURAL AND IN-HOSPITAL OUTCOMES

The main procedural outcomes associated with percutaneous LAAC with different devices are summarized in **Table 2.2** and **Figure 2.2**.[102, 130, 131, 137, 138, 140, 146, 151, 189, 198-212] However, direct comparisons between studies are somewhat limited by differing definitions of serious adverse events (SAE), particularly regarding major bleeding and overall major SAEs. Thus, adherence to standardized definitions in forthcoming studies is strongly recommended to facilitate accurate and concordant evaluation of LAAC outcomes.[135]

2.5.1. Watchman device

Safety and early outcomes associated with LAAC with the WATCHMAN device have been extensively evaluated in two randomized controlled trials and several large registries, which have shown continuous improvements in both procedural success and procedure-related complication rates (**Table 2.2, Figure 2.2A**).

The pivotal PROTECT-AF (Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) trial randomized 707 warfarin-eligible patients with nonvalvular AF and $CHADS_2$ score ≥ 1 to warfarin or LAAC with the WATCHMAN device. The main procedural results showed a 9% rate of procedural failure with a high rate (8.7%) of procedure-related complications, mainly secondary to serious pericardial effusion (4.8%), resulting in an increased rate of primary safety events in the WATCHMAN arm vs. the anticoagulation arm (rate ratio [RR] 1.69; 95% confidence interval [CI], 1.01-3.19).[130]

Because of safety concerns, a further confirmatory randomized trial was mandated by the FDA. The subsequent PREVAIL (Prospective Randomized Evaluation of the Watchman LAAC Device in Patients with AF Versus Long-Term Warfarin Therapy) trial, which included 407 OAC-eligible patients, demonstrated a substantial drop in procedural complications, despite including higher-risk patients (mean $CHADS_2$ score: 2.6) and ~40% of "naïve" operators. The results of the trial achieved the pre-specified non-inferiority criterion for safety with a 7-day safety event rate of 2.2% in the device group, and a

significant reduction in the overall rate of serious procedure-related complications compared to the PROTECT-AF trial (4.2% vs 8.7%, p=0.004).[131]

Overall, the 7-day rate of procedure- or device-related SAEs among the two randomized trials and their accompanying registries (CAP and CAP2)[213] declined with increasing operator/center experience from the 9.9% of the first half of the PROTECT AF study to 4.1% and 3.8% in the CAP and CAP2 registries respectively, highlighting a steep "learning curve" effect.

This tendency towards improved procedural outcomes has been confirmed by the two largest real-world experiences with the WATCHMAN device to date. The European EWOLUTION registry and the post-FDA approval US experience, which included 1.021 and 3.822 patients, respectively, showed technical success rates > 95%, and very low rates of SAEs within 7 days post-LAAC (2.8% and 1.4%).[138, 146] In particular, the rates of serious pericardial effusion were 0.3% and 1.0% respectively, with rates of procedure-related stroke, device embolization and procedure-related death < 0.5%. This is particularly reassuring if we consider that half of the implants in the US cohort were performed by inexperienced operators.

2.5.2. Amplatzer Cardiac Plug and Amulet

Several registries support the safety of the ACP and Amulet devices (**Table 2.2**). As with the WATCHMAN device, procedural outcomes have been improving since the very first experiences (Figure 2.2B). In 2011, Park et al[200] reported the early European experience with the ACP device, with procedural success rates of 96%, and overall procedure-related SAE of 7% (3.5% for serious pericardial effusion). Tizkas et al[189] reported the largest multicenter registry with the first-generation ACP device, with 1.047 patients from 22 European centers. In this retrospective experience, the procedural success rate was as high as 97.3%, with a periprocedural SAE rate of 5% (cardiac tamponade and major bleeding: 1.2%, ischemic stroke: 0.9%, device embolization and procedural-related death: 0.8%). The prospective Amulet Observational Study, the largest registry with the second-generation

Amulet device to date with 1.088 patients, showed high technical success rates (99%) and lower procedural or in-hospital complication rates (3.2%) compared to most first-generation ACP registries (pericardial tamponade: 1.2%, procedure-related death: 0.2%, ischemic stroke: 0.2%, device embolization: 0.1%).[140] Whereas the predictors of periprocedural SAEs have not been well established, device repositioning (a maneuver likely related to challenging LAA anatomies) and left ventricular dysfunction were associated with higher SAEs in a large observational registry (n=500).[204]

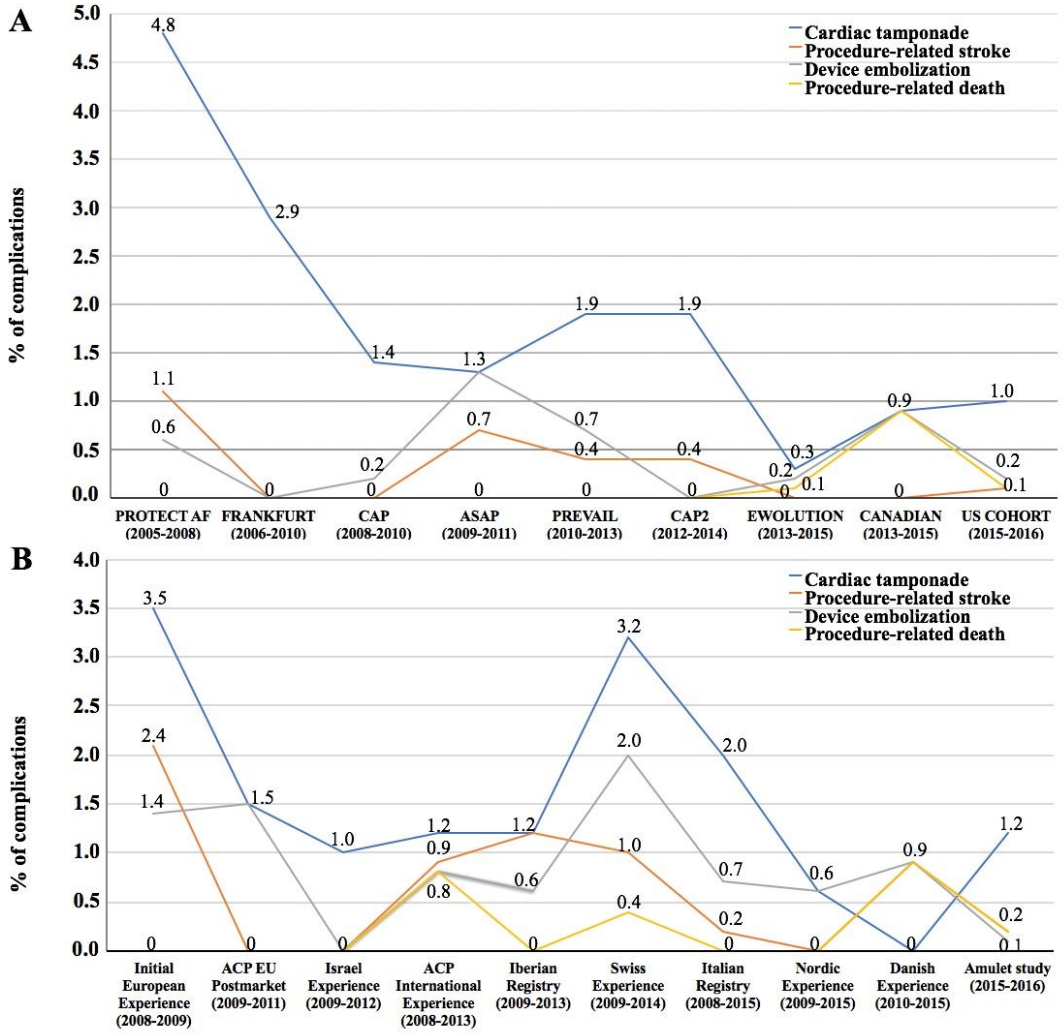

Figure 2.2. Temporal trends in procedural complications following left atrial appendage closure.

(A) Periprocedural complications associated with the WATCHMAN device.[130, 131, 137, 138, 146, 151, 198, 199]

(B) Periprocedural complications associated with the AMPLATZER Cardiac Plug and Amulet devices.[102, 140, 189, 200, 202-206]

2.5.3. Lariat

The LARIAT device has emerged as an alternative for patients with LAA anatomies unsuitable for endocardial LAAC devices, albeit procedural safety remains a concern. Price et al[207] reported the results of a retrospective safety registry with 154 patients from 8 centers. Despite a high technical success rate (94%), major complications occurred in 10% of patients, with a 10% rate of significant pericardial effusions requiring intervention, 9% rate of major bleeding, and emergency surgery required in 2% of patients.

A review comparing SAEs from 5 published LARIAT studies (n=309) with the FDA-MAUDE (Manufacturer and User Facility Device Experience) database, reported a procedural success rate of 90%, 1 in-hospital death and 7 patients requiring emergent open-heart surgery, whereas the FDA-MAUDE database identified 5 in-hospital deaths and 23 additional procedure-related emergent surgeries.[214] As a consequence, an FDA alert for deaths and other SAEs related to the off-label use of the LARIAT device for LAAC was issued in July 2015.

In the largest reported series with the LARIAT device (n=712), a higher success rate (>95%) and lower complication rates (5.3%) were reported compared to prior studies.[208] Procedure-related death was extremely low (0.1%), and cardiac perforations requiring urgent surgery were reduced to 1.4%, while 2.0% did not need surgery. Importantly, the risk of cardiac perforation was significantly decreased with the use of a micropuncture needle for pericardial access. **Table 2.2** outlines the available data with the LARIAT device and the largest experiences combining different LAAC devices.[207-212]

Table 2.2. Technical Success and Procedure-Related Complications Associated with Percutaneous LAAC

	N	Technical success (%)	Serious pericardial effusion* (%)	Device embolization (%)	Ischemic stroke (%)	Major bleeding† (%)	Procedure-related death (%)	Total major safety events (%)
WATCHMAN								
PROTECT-AF[130]	463	90.9	4.8	0.6	1.1	0.6	0	8.7
CAP[131, 137]	566	94.4	1.4	0.2	0	-	0	4.1
ASAP[151]	150	94.7	1.3	1.3	0.7	1.3	0	8.7
PREVAIL[131]	269	95.1	1.9	0.7	0.4	0.4	0	4.2
CAP 2[146]	579	94.8	1.9	0	0.4	-	0	3.8
Frankfurt Experience[198]	102	96.1	2.9	0	0	-	0	8.8
EWOLUTION[138]	1.021	98.5	0.3	0.2	0	0.7	0.1	2.8
Canadian Experience[199]	106	97.2	0.9	0.9	0	1.9	0.9	1.9
US Post-FDA Approval[146]	3.822	95.6	1.0	0.2	0.1	-	0.1	1.4
ACP/Amulet								
Initial European Experience[200]	143	96.4	3.5	1.4	2.1	-	0	7.0
ACP EU Post Market Registry[200]	204	96.6	1.5	1.5	0	-	0	2.9
Bern Experience[201]	120	97.5	1.6	1.6	0.8	-	0.8	6.7
Israel Experience[202]	100	100	1.0	0	0	-	0	1.0
Iberian Registry[203]	167	94.6	1.2	0.6	1.2	-	0	5.4
ACP International Experience[189]	1.047	97.3	1.2	0.8	0.9	1.2	0.8	5.0
Swiss Experience[204]	500	97.8	3.2	2.0	1.0	0.2	0.4	5.8
Nordic Experience[102]	176	97.7	0.6	0.6	0	1.7	0	4.0
Danish Experience[205]	110	100	0	0.9	0.9	2.8	0.9	4.6
Amulet observational	1.088	99.0	1.2	0.1	0.2	2.4‡	0.2	3.2

study[140]								
Italian registry[206]	613	95.4	2.0	0.7	0.2	3.3‡	0	6.2
LARIAT								
US Initial Experience[207]	154	93.5	10.4	-	0	9.1‡	0.6	9.7
US LARIAT Registry[208]	712	95.5	3.4	-	0	2.7	0.1	5.3
Mixed devices								
Leipzig Experience[209]	179	98.9	1.1	1.7	0	-	0	3.3
Korean Registry[210]	96	96.8	2.1	1.0	0	1.0	1.0	4.1
Milan Experience[211]	165	99.4	0.6	0	0	1.8	0	4.8
UK Registry[212]	371	92.5	0.5	0.8	0.5	1.3	0.3	3.5

* Serious pericardial effusion defined as the need for percutaneous or surgical drainage

† Major bleeding defined as requiring surgery or transfusion

‡ Major bleeding defined as Bleeding Academic Research Consortium type 3 or greater, including pericardial bleeding.

Abbreviations: PROTECT-AF: WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation; CAP: Continued Access to PROTECT-AF; ASAP: ASA Plavix Feasibility Study with WATCHMAN Left Atrial Appendage Closure Technology; PREVAIL: Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation vs. Long-Term Warfarin Therapy; CAP2: Continued Access to PREVAIL; EWOLUTION: Registry on Watchman Outcomes in Real-Life Utilization; FDA: Food and Drug Administration; ACP: Amplatzer Cardiac Plug; EU: European Union; US: United States; UK: United Kingdom.

2.6. LATE CLINICAL OUTCOMES

2.6.1. Randomized controlled trials: PROTECT-AF and PREVAIL

Two randomized trials with a non-inferiority design (PROTECT-AF, PREVAIL) have compared LAAC with the WATCHMAN device to anticoagulation (warfarin) for the prevention of stroke, systemic embolism or cardiovascular death (composite primary endpoint) in patients with AF.

The pivotal PROTECT-AF randomized 707 warfarin-eligible patients in a 2:1 fashion to LAAC with the WATCHMAN device or warfarin. Patients treated with the device received warfarin and aspirin for 45 days and, in the absence of peri-device leaks > 5 mm, were switched to aspirin and clopidogrel until 6 months and then lifelong aspirin. At 1065 patient-years (mean follow-up of 18 months), the primary composite endpoint of stroke, systemic embolism or cardiovascular death occurred in 3% in the WATCHMAN arm versus 4.9% (per 100 patient-years) in the control group (RR 0.62, 95% credible interval, 0.35-1.25), meeting the non-inferiority criterion.[130] Furthermore, hemorrhagic strokes were fewer with the WATCHMAN device, and there was a reduction in the composite endpoint of disabling stroke or death in the device arm (RR 0.41, 95% CI, 0.22-0.82). The non-inferiority criterion for the primary efficacy endpoint was sustained at 1588 patient-years (mean 2.3 years, RR 0.71, 95% CI, 0.44-1.30),[184] achieving both non-inferiority and superiority criteria at 2621 patient-years (mean follow-up of 3.8 years), with 8.4%, 2.3% per 100 patient-years in the device arm vs 13.9%, 3.8% per 100 patient-years in the OAC arm (RR 0.60, 95% credible interval, 0.41-1.05) (**Figure 2.3A**).[185] Also, a 60% and 34% reduction in cardiovascular death (RR 0.40, CI 95%, 0.21-0.75) and all-cause mortality (RR 0.66, 95% CI, 0.45-0.98), respectively, and an 85% reduction in hemorrhagic stroke (RR 0.15, 95% CI, 0.03-0.49) were observed in the device group. Finally, the long-term procedural safety events were similar in the two groups (RR 1.17, 95% credible interval, 0.78-1.95), meeting the criterion for non-inferiority for the safety endpoint (**Figure 2.3B**).[185]

In the subsequent PREVAIL trial, 407 OAC-eligible patients were randomized in a 2:1 ratio to LAAC with the WATCHMAN device or warfarin. At a mean follow-up of 12 months, the non-inferiority criterion was not met for the first co-primary efficacy endpoint (composite of stroke, systemic embolism and cardiovascular death) (**Figure 2.3C**).[131] However, the non-inferiority criterion was achieved for the second co-primary endpoint (stroke or systemic embolism >7 days) (0.0253 vs 0.0200, risk difference 0.0053, 95% credible interval -0.0190 to 0.0273) (**Figure 2.3D**).[131]

A meta-analysis of the PROTECT-AF, PREVAIL and their respective registries (CAP, CAP2) showed improved rates of hemorrhagic stroke (hazard ratio 0.22, p=0.004), cardiovascular death (hazard ratio 0.48, p=0.006) and nonprocedural bleeding hazard ratio 0.51, p=0.006) with LAAC compared to warfarin.[215]

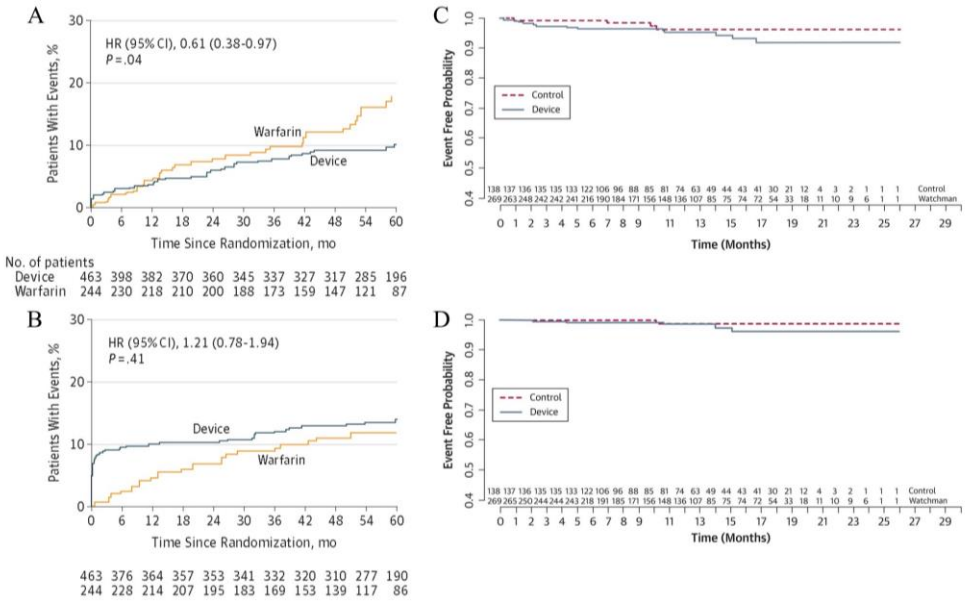

Figure 2.3. Long-term outcomes in randomized trials.

(A-B) *PROTECT AF trial (3.8-year follow-up).* (A) Primary efficacy outcome: stroke, systemic embolism or cardiovascular death. (B) Primary safety outcome: composite of major bleeding events and procedure-related complications. Reprinted from Reddy *et al.*[185], with permission, Copyright © 2014, American Medical Association. (C-D) *PREVAIL trial (18-month follow-up).* (C) Freedom from first co-primary endpoint (composite of stroke, systemic embolism and cardiovascular death). Primary efficacy rates for WATCHMAN (solid line) versus warfarin (dotted line) showed similar event-free rates, but did not met non-inferiority criteria. (D) Freedom from second co-primary endpoint (stroke or systemic embolism > 7 days post-randomization) for WATCHMAN (solid line) versus warfarin (dotted line) achieved non-inferiority for the rate difference endpoint. Reprinted from Holmes *et al.*[131], with permission.

2.6.2. Registries

To date, the vast majority of "real-world" LAAC registries have included patients with contraindications for OAC or at high risk for bleeding events. Despite promising midterm follow-up data of LAAC in this target population with currently available devices (**Table 2.3**[102, 130, 140, 151, 184, 185, 189, 198-201, 203, 205-212, 216-219], some concerns remain regarding device-related thrombosis and residual leaks.

The annualized ischemic stroke rates with current commercialized devices have ranged from 0 to 2.2%. The ACP International and EWOLUTION registries, the largest registries conducted with ≥ 1-year follow-up, showed a 59% and 84% risk reduction in stroke, respectively, compared to the estimated risk according to CHADS2 (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack) and CHA_2DS_2-VAS_C (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category) scores.[189, 219] A meta-analysis including 27 observational studies (>3,000 LAAC patients) revealed lower rates of both thromboembolic events (1.8 events per 100 patient-years vs 2.4% events per 100 patient-years) and major bleeding events (2.2 events per 100 patient-years vs 2.5 events per 100 patient-years) following LAAC compared to DOACs.[220] Notably, the rate of thromboembolic events decreased while extending the follow-up period (2.1, 1.8, 1.0 events per 100 person-years for 1, 1-2 and > 2 years, respectively).

Important reductions in major bleeding rates have been reported in several LAAC registries analyzing patients at high risk for bleeding. Thus, the EWOLUTION registry reported a 48% risk reduction in bleeding events compared to the estimated risk according to the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol) score.[219] In the ACP multicenter experience, a 61% annual reduction in major bleedings was observed (75% risk reduction in patients with prior intracranial bleeding).[189]

The reported incidence of device-related thrombosis (DRT) post-LAAC ranges from 0 to 17%, with wide variations depending on device type, technical issues, post-procedural antithrombotic therapies, and timing and frequency of control TEE post-LAAC. The ASAP, EWOLUTION and Canadian WATCHMAN registries reported lower DRT rates (1-4 %) than the PROTECT-AF trial (5.7%),[216] despite using a more conservative antithrombotic management (OAC within the first weeks post-LAAC: 0-27%, versus 100% in the PROTECT-AF trial).[151, 199, 219] In the largest ACP registry to date, DRT was observed in 4.4% of patients[189] (3.2% after independent adjudication[221]), with no increased risk for thromboembolic events associated with DRT. Despite design improvements with the Amulet device, DRT rates varied from 1.5% in the Amulet Observational Study[140] to 16.7% in a small series of 24 patients,[222] with this complication related to incomplete sealing of the LAA limbus by the Amulet disk. In a recent meta-analysis including > 2000 patients from 30 studies with the three most commercialized used devices, the overall incidence of DRT was 3.9% (3.4% for WATCHMAN, 4.8% for ACP, 2.0% for Amulet), with a median time to diagnosis of 1.5 months, mostly at the time of routine follow-up echocardiography imaging.[223] Importantly, DRT diagnosis was associated with a low rate of neurological complications (4.9% strokes, 2.4% transient ischemic attack) and a high (95%) rate of thrombus resolution after a short-term (median of 6 weeks) anticoagulation treatment with either low-molecular-weight heparin (45%) or OAC (55%). The presence of a high profile proximal pin connector, enlarged left atrium with spontaneous contrast, and high CHA_2DS_2-VAS_C score were associated with an increased risk of DRT.

Albeit somewhat arbitrary, the most commonly accepted definitions for significant residual leaks are > 3 mm for ACP/Amulet and ≥ 5 mm for WATCHMAN and LARIAT devices. The incidence of relevant peri-device leaks under routine TEE surveillance following transcatheter LAAC has varied from 0 to 11.8%. Unlike prior surgical studies,[109] this finding has not been associated with higher rates of stroke or any adverse event.[217, 221] Incomplete sealing with any degree of peridevice leak has been reported in up to 32% of

patients at 12 months post-LAAC with the WATCHMAN device in the PROTECT-AF trial.[217] Of note, single-lobe devices have been associated with higher rates of leaks, compared with lobe-and-disc device designs. Thus, in the TEE sub-study of the ACP multicenter registry, peri-device leaks were observed in 12.5% of patients.[221] In a "real-world" registry including 165 patients treated with the WATCHMAN or ACP systems, peri-device leaks were less common with the ACP device than with the WATCHMAN device (14% vs 34%, p=0.004).[211] A study comparing endocardial (WATCHMAN) versus epicardial (LARIAT) LAAC devices in 478 patients showed a higher incidence of post-procedural leaks with the WATCHMAN device at 12-month follow-up (21% vs 14% with the LARIAT device, p=0.019).[224] Interestingly, the mechanism of leak was different between the two devices, with predominant eccentric peridevice leaks in the endocardial group, compared to central (concentric or gunnysack) in the LARIAT device.

Although frequently identified by routine non-invasive post-procedural surveillance imaging, residual leaks may be missed with TEE imaging post-LAAC. Cardiac computed tomography angiography (CCTA) has recently emerged as a more sensitive tool in the assessment of residual peri-device leaks. The presence of residual leaks as evaluated by CCTA has been reported in about two thirds and one third of patients following LAAC with the ACP/Amulet/WATCHMAN and LARIAT devices, respectively.[225-227] In studies combining both CCTA and TEE imaging at follow-up, CCTA increased the detection of residual shunts by approximately 2-fold (62% vs 36%; 52% vs 35%)[225, 226] to 5-fold (78% vs 17%)[206] compared to TEE. Future studies need to determine the long-term clinical impact of residual peridevice leaks after LAAC.

Table 2.3. Long-Term Clinical Outcomes Following Percutaneous LAAC

	N	$CHADS_2$ (mean ± SD)	Ineligible for OAC* (%)	Follow-up duration** (months)	Ischemic stroke (%)	Device thrombosis (%)	Significant peridevice leak† (%)	Major bleeding (%)	All-cause mortality (%)
WATCHMAN									
PROTECT-AF[130, 184, 185]	463	2.2 ± 1.2	0	18 ± 10 1065 PY	3.2 2.2 per 100 PY	5.7[53]	11.8[54‡]	3.5	4.5 3.0 per 100 PY
				27.6 ± 13.2 1588 PY	4.1 1.9 per 100 PY	-	-	-	7.3 3.2 per 100 PY
				45.6 ± 20.4 2621 PY	5.2 1.4 per 100 PY	-	-	4.8	12.3 3.2 per 100 PY
ASAP[151, 218]	150	2.8 ± 1.2	100	14.4 ± 8.6 176.9 PY	2.0 1.7 per 100 PY	4.0	-	-	6.0 5.0 per 100 PY
				55.4 [1.2-75.6] 651 PY	- 1.8 per 100 PY	-	-	- 1.8 per 100 PY	- 4.6 per 100 PY
PREVAIL[131]	269	2.6 ± 1.0	0	11.8 ± 5.8	1.9	-	-	-	2.6[§]
Frankfurt Experience[198]	102	2.7 ± 1.3	25	36 ± 19.2 276.6 PY	2.1 0.7 per 100 PY	2.1	0	6.3 2.1 per 100 PY	10.4 3.5 per 100 PY
EWOLUTION[219]	1.021	2.8 ± 1.3	73	12	1.1	3.7	1.0	2.6	9.8
Canadian Experience[199]	106	2.8 ± 1.2	99	6.9 ± 6.0	0	1.0	0	4.7	3.8
ACP/Amulet									
ACP EU Post Market Registry[200]	204	2.6 ± 1.3	89	6 101.2 PY	1.0 2.0 per 100 PY	2.4	1.1	-	-
Bern Experience[201‖]	152	3.4 ± 1.7[¶]	70	32 [0.4-120]	1.3	16	-	2.6	9.9
Iberian Registry[203]	167	3 (2-4)	74	22 ± 8.3 290 PY	4.4 2.4 per 100 PY	8.2	0	5.7 3.1 per 100 PY	10.8 5.8 per 100 PY
ACP International Experience[189]	1.047	2.8 ± 1.3	73	13 [6-25] 1349 PY	0.9	4.4	1.9	1.5 2.1 per 100 PY	4.2
Nordic Experience[102]	151	3.9 ± 1.6[¶]	100	6.0 [2.9-12.2] 115 PY	1.3 1.7 per 100 PY	-	-	2.6 3.5 per 100 PY	1.3 1.7 per 100 PY
Danish Experience[205]	107	4.4 ± 1.6[¶]	91	27.6 [19.2-38.4] 265 PY	5.6 2.3 per 100 PY	1.9	-	9.3 3.8 per 100 PY	18.7
Amulet observational study[140]	1.088	4.2 ± 1.6[¶]	83	2.4 ± 0.8	0.1	1.5	1.8	4.0	2.1
Italian Registry[206]	613	4.2 ± 1.5[¶]	85	19.9 ± 17.1 896 PY	2.6 1.6 per 100 PY	1.8	0.5	3.7 2.2 per 100 PY	7.4 4.5 per 100 PY
LARIAT									

US Initial Experience[207]	154	3 (2-4)	62	3.7 [1.6-8.9]	1.5	4.8	6.3	-	2.6
US LARIAT Registry[208]	712	2.7 ± 1.3	79	3	-	2.5	0.2	-	-
Mixed									
Leipzig Experience[209]	179	2.8 ± 1.1	100	6	0	4.2	0.6[#]	0.7	0.7
Korean Registry[210]	96	2.5 ± 1.2	100	21.9	4.2	3.1	0[#]	1.0	5.2
Milan Experience[211]	165	3.9 ± 1.7[¶]	77	14.7 [6-26]	0	0.9	1.8[#]	1.3	3.3
UK Registry[212]	371	2.6 ± 1.2	95	24.7 ± 16.1 706 PY	1.2 0.6 per 100 PY	-	-	0.9 0.4 per 100 PY	3.8 1.8 per 100 PY

[*]Ineligible for OAC defined as prior relevant bleeding or high bleeding risk.
[**]Follow-up expressed as mean ± SD or median [IQR]
[†]Significant residual leak defined as >3 mm for AMPLATZER and ≥5 mm for WATCHMAN and LARIAT
[‡]>3 mm cutoff used in a PROTECT-AF substudy[57]; [§]Cardiovascular death;
[‖]32 non-dedicated Amplatzer devices (PFO, ASD, VSD occluders), 120 dedicated ACP
[¶]CHA_2DS_2-VAS_C; [#]Residual leak ≥5 mm.
Abbreviations as in **Table 2.2**

2.7. REMAINING ISSUES AND FUTURE STUDIES

2.7.1. Optimal post-procedure antithrombotic therapy

Optimal antithrombotic therapy following LAAC remains a controversial issue. In contrast to the unmodified 1-3 months' dual antiplatelet therapy for ACP/Amulet recipients, trends in antithrombotic management with the WATCHMAN device have switched from early aggressive treatments (6 weeks of OAC and aspirin followed by dual antiplatelet therapy until 6 months) to more conservative approaches (OAC rates of 0%, 27% and 20% in the ASAP, EWOLUTION and Canadian registries[138, 151, 199]), mainly because of the inclusion of patients with contraindications for OAC. Indeed, in the EWOLUTION registry, DRT rates were not correlated to differing post-procedural drug regimens. Based on these findings, the latest instructions for use of the WATCHMAN device have shifted towards a lowering postprocedural regimen, allowing at least 3 months of clopidogrel and/or NOAC or OAC in combination with 12-month aspirin.[219] Also, we have recently shown a significant decrease in the markers of coagulation activation at 1-month post-LAAC, suggesting that post-procedural OAC therapy can be limited to 4 weeks instead of the initially recommended 6 weeks.[150] Of keen interest, initial experiences with single antiplatelet therapy following LAAC have shown favorable safety and efficacy outcomes, with relatively low rates of DRT (from 1.9% to 6.8%) and without increasing the risk of stroke.[153, 205, 228] The ongoing ASAP-TOO (Assessment of the WATCHMAN device in patients unsuitable for oral anticoagulation) randomized trial will compare WATCHMAN LAAC (followed by aspirin/clopidogrel) to single or no antiplatelet therapy in nonvalvular AF patients deemed ineligible for OAC (*NCT02928497*, **Table 2.4**).

2.7.2. LAAC vs. DOAC

Randomized controlled trials in OAC-eligible patients have been limited to warfarin, and a direct comparison between LAAC and the current gold standard DOAC for stroke prevention in AF is currently unavailable. Indirect comparisons from a large meta-analysis found lower rates of both thromboembolic and hemorrhagic events with LAAC compared

to DOAC in observational studies, although no superiority of LAAC over DOAC was found in randomized trials.[220] The ongoing PRAGUE-17 (Interventional left atrial appendage closure vs novel anticoagulation agents in high-risk patients with atrial fibrillation) randomized trial will randomize 400 high-risk patients to LAAC or DOAC, and will provide chief information on this matter (*NCT02426944,* **Table 2.4**).

2.7.3. Head-to-head comparison between LAAC devices

Since only a few "real-world" registries have compared clinical outcomes between different currently commercialized LAAC, consistent data from randomized controlled trials is lacking. The ongoing Amulet IDE (Amplatzer Amulet LAA occluder) trial will randomize more than 1500 patients in a 1:1 fashion between the Amulet or WATCHMAN LAAC devices, with up to 5-year follow-up (*NCT02879448,* **Table 2.4**).

2.7.4. Pre- and procedural imaging

TEE remains the standard imaging technique for LAAC pre-procedural planning and procedural guidance. However, 3D computed tomography has emerged as an additional imaging examination that can improve pre-procedural LAAC planning, particularly in complex LAA anatomies.[229, 230] Also, some groups have reported the potential advantages (e.g. no need for general anesthesia) of guiding LAAC procedures with intracardiac echocardiography.[231] Further studies are needed to determine the exact role of this pre-procedural and procedural imaging techniques in the LAAC field.

2.7.5. Combined procedures

Combination of LAAC with other transcatheter heart interventions has shown promising results. Since AF ablation is associated with long term recurrence rates >50%, the association of LAAC with both conventional radiofrequency or cryoballoon AF ablation has emerged as an appealing alternative, allowing concomitant mitigation of AF symptoms and risk reduction for both stroke and bleeding. Several studies combining AF ablation and LAAC have shown high rates (94-100%) of LAAC success, with annual stroke rates of 0-

2.6%, despite recurrence of AF in 22-42% of patients.[232-235] The aMAZE trial (Left atrial appendage ligation with the LARIAT suture delivery system as adjunctive therapy to pulmonary vein isolation for persistent or longstanding persistent atrial fibrillation, NCT02513797) will randomize patients in a 2:1 fashion to epicardial LAAC with the LARIAT device prior to pulmonary vein isolation versus pulmonary vein isolation alone.

Early experience in a small series (n=25) has suggested the feasibility of concomitant MitraClip and LAAC, with no differences in success rates and 30-day outcomes between the combined (LAAC and MitraClip) and the control (MitraClip only) groups, although at the expense of longer procedural and radiation times in the combined procedure group.[236] Combining LAAC with transcatheter aortic valve replacement (TAVR) has also been shown to be both feasible and safe,[237] an attractive alternative since AF is the most common arrhythmia in the TAVR population and is associated with increased morbidity and mortality. In this sense, the TAVR-LAAC (Combined transcatheter aortic valve implantation and percutaneous closure of the left atrial appendage, NCT02678871) and the WATCH-TAVR (Watchman for patients with atrial fibrillation undergoing transcatheter aortic valve replacement, NCT03173534) will add valuable information to this specific target population (**Table 2.4**).

Despite these encouraging preliminary experiences, the combined approach raises some reimbursement issues, since many national payment and reimbursement systems currently cover only one of the two procedures. Whereas cost-effectiveness of percutaneous LAAC in comparison to currently available pharmacologic treatments has already been demonstrated,[238, 239] cost-parity of combined interventions needs further investigation. The potential clinical benefits of a combined approach (single hospitalization, single vascular access and transseptal puncture for concomitant LAAC and AF ablation or MitraClip, prompt OAC interruption) might offset the supplementary upfront costs of this strategy and help to overcome financial disincentives of current reimbursement policies.

Table 2.4. Main Ongoing and Future Studies on Percutaneous LAAC

	Device	Study design	Patients	Intervention	Primary endpoint
ASAP-TOO (NCT02928497)	WATCHMAN	Randomized	888	LAAC vs single or no antiplatelet therapy in patients ineligible for OAC	The primary safety endpoint is the 7-day combined rate of death, ischemic stroke, systemic embolism and complications requiring major cardiovascular or endovascular intervention. The primary efficacy endpoint is the comparison of time to first event of ischemic stroke and systemic embolism.
PRAGUE-17 (NCT02426944)	Amulet or WATCHMAN	Randomized, open-label	400	LAAC vs DOAC	The primary endpoint is the combination of stroke, other systemic cardiovascular event, clinically significant bleeding, cardiovascular death or procedure or device-related complications.
Edoxaban in Patients With nonvalvular AF and LAAC (NCT0308807)	WATCHMAN	Prospective registry	75	Edoxaban after LAAC	The primary outcome is a composite of death, stroke, systemic embolism, or GUSTO moderate/severe bleeding will be collected at 6 weeks post-WATCHMAN LAAC.
Amulet IDE (NCT02879448)	Amulet or WATCHMAN	Randomized	1600	Amulet vs WATCHMAN	Safety: composite of procedure-related complications, or all-cause death, or major bleeding through 12 months. Efficacy: composite of ischemic stroke or systemic embolism through 18 months. Mechanism of action: device closure (defined as residual jet around the device $\leq$ 5 mm) at the 45-day visit documented by transesophageal echocardiogram defined by Doppler flow.
TAVI-LAAC (NCT02678871)	Lotus valve WATCHMAN	Prospective registry	50	Simultaneous TAVR + LAAC	Early safety - composite endpoint of TAVR-related (VARC 2 criteria) and percutaneous LAAC-related events at 30 days: all cause-mortality, all stroke, life threatening bleeding, acute kidney injury, coronary artery obstruction requiring intervention, major vascular complications, valve-related dysfunction requiring repeat procedure, pericardial effusion requiring pericardial drainage, and LAA device embolization requiring surgical intervention.
WATCH-TAVR (NCT03173534)	WATCHMAN TAVR	Randomized	400	TAVR + LAAC (150 staged, 50 combined) vs TAVR alone (n=200)	First occurrence of all-cause mortality, stroke (ischemic or hemorrhagic), or bleeding (life-threatening and major) events through 1 year.

WATCHMAN FLX LAAC device Post Approval study (NCT02654470)	WATCHMAN FLX	Prospective registry	300	LAAC	30-day procedural complications. 2-year incidence of stroke and death.
WaveCrest Post-Market Clinical Follow-up study (NCT03204695***)***	WaveCrest	Prospective registry	65	LAAC	All-cause deaths and device- and/or procedure-related events at 45 days
aMAZE (NCT02513797)	LARIAT	Randomized	600	LARIAT + PVI vs PVI alone	Freedom from episodes of atrial fibrillation > 30 seconds at 12 months post pulmonary vein isolation.
LASSO-AF (NCT02593178)	Aegis Sierra Ligation System	Prospective registry	30	LAAC	Safety: 30-day device or procedure-related major adverse events: all-cause death, stroke, systemic embolism, major bleeding, coronary arteries injury requiring intervention, myocardial infarction, intervention for device or procedure-related complications, complications related to epicardial access.
STROKECLOSE (NCT02830152)	Amulet	Randomized	750	LAAC vs medical treatment in patients with prior intracerebral hemorrhage	Composite endpoint of stroke (ischemic or hemorrhagic), systemic embolism, life-threatening or major bleeding and all-cause mortality.

AF indicates atrial fibrillation; aMAZE, Left Atrial Appendage Ligation With the LARIAT Suture Delivery System as Adjunctive Therapy to Pulmonary Vein Isolation for Persistent or Longstanding Persistent Atrial Fibrillation; Amulet IDE, Amplatzer Amulet LAA Occluder Trial; ASAP-TOO, Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation; DOAC, direct oral anticoagulant; GUSTO, Global Use of Strategies to Open Occluded Arteries; LAAC, left atrial appendage closure; LASSO-AF, Feasibility Study of the Aegis Sierra Ligation System in Left Atrial Appendage Closure in Patients With Atrial Fibrillation; OAC, oral anticoagulation; PRAGUE-17, Interventional Left Atrial Appendage Closure vs Novel Anticoagulation Agents in High-Risk Patients With Atrial Fibrillation; PVI, pulmonary vein isolation; TAVI-LAAC, Combined Transcatheter Aortic Valve Implantation and Percutaneous Closure of the Left Atrial Appendage; TAVR, transcatheter aortic valve replacement; VARC, Valve Academic Research Consortium; and WATCH-TAVR, Watchman for Patients With Atrial Fibrillation Undergoing Transcatheter Aortic Valve Replacement

2.8. CONCLUSIONS

LAAC has emerged as a valid alternative to OAC in AF patients. Whereas randomized clinical data in the field has been limited to the WATCHMAN device in OAC-eligible patients, "real-world" registries have shown a clear shift towards a higher-risk population with contraindications to OAC or deemed at prohibitive bleeding risk, with continuous improvements in procedural safety and long-term efficacy. However, the lack of consistent evidence from randomized trials in this challenging scenario has probably precluded stronger support from international heart societies and a broader expansion of this technique. Ongoing randomized trials focusing on unresolved issues such as LAAC in ineligible-OAC patients, head-to-head comparison with the gold-standard DOAC, emerging devices or safety of combined procedures, will provide definitive data and thus contribute to an inevitable growth in LAAC procedures in the coming years.

2.9. FUNDING SOURCES

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2.10. CONFLICT OF INTEREST DISCLOSURES

None.

CHAPTER 3. Percutaneous Left Atrial Appendage Closure with the Ultraseal Device: Insights from the Initial Multicenter Experience

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3.1. RÉSUMÉ

Étude multicentrique visant à évaluer la faisabilité, la sécurité et l'efficacité du dispositif Ultraseal pour la fermeture de l'auricule gauche (FAG) chez les patients atteints de fibrillation auriculaire à haut risque de saignement dans 15 sites canadiens et européens. Cent vingt-six patients ont été inclus. Le dispositif a été implanté avec succès chez 97% des patients. Un événement indésirable périprocédural majeur est survenu chez 3 (2.4%) patients. L'échocardiographie trans-œsophagienne de suivi était disponible chez 89 patients (73%), sans aucune fuite résiduelle importante (> 5 mm) et 5 (5.6%) cas de thrombose liée au dispositif (tous traités avec anticoagulation avec succès). Lors d'un suivi médian de 6 (IQR: 3-10) mois, les taux d'accident vasculaire cérébral et d'attaque ischémique transitoire étaient de 0.8% et 0.8% respectivement, sans aucune embolie systémique. La FAG avec le dispositif Ultraseal a été associée à un taux de succès élevé et à une faible incidence de complications.

3.2. ABSTRACT

Objectives: This study sought to evaluate the feasibility, safety and efficacy of the Ultraseal device for left atrial appendage closure (LAAC) in patients with nonvalvular atrial fibrillation at high bleeding risk.

Background: The Ultraseal device is a novel bulb-and-sail designed LAAC device, with an articulating joint enabling conformability to heterogeneous angles and shapes of appendage anatomy.

Methods: This was a multicenter study including consecutive patients undergoing LAAC with the Ultraseal device at 15 Canadian and European sites. Periprocedural and follow-up events were systematically collected, and TEE at 45 to 180 days post-procedure was routinely performed in all centers but 3.

Results: A total of 126 patients (mean age: 75±8 years; mean CHA_2DS_2-VAS_C: 5±2; mean HAS-BLED: 4±1) were included. The device was successfully implanted in 97% of patients. A major periprocedural adverse event occurred in 3 (2.4%) patients (clinically relevant pericardial effusion [n=1], stroke [n=1], device embolization [n=1]). Ninety percent of patients were discharged on single or dual antiplatelet therapy. Follow-up TEE was available in 89 (73%) patients, with no cases of large (>5 mm) residual leak and 5 (5.6%) cases of device-related thrombosis (all successfully treated with anticoagulation therapy). At a median follow-up of 6 (IQR: 3-10) months, the rates of stroke and transient ischemic attack were 0.8% and 0.8% respectively, with no systemic emboli. None of the events occurred in patients with device-related thrombosis.

Conclusions: In this initial multicenter experience, LAAC with the Ultraseal device was associated with a high implant success rate and a very low incidence of periprocedural complications. There were no late device-related clinical events and promising efficacy results were observed regarding thromboembolic prevention at midterm follow-up. Larger studies are further warranted to confirm the long-term safety and efficacy of this novel device.

3.3. INTRODUCTION

Anticoagulation with vitamin K antagonists or direct oral anticoagulants remains the mainstay of thromboembolic prevention in patients with non-valvular atrial fibrillation (AF), with robust reductions in the risk of stroke and death.[58, 75] Nevertheless, oral anticoagulation has been associated with increased bleeding risk in a commonly old and comorbid population. Also, more than one third of AF patients at high risk for stroke still fail to receive optimal thromboembolic prophylaxis in contemporary practice.[77] In recent years, left atrial appendage closure (LAAC) has emerged as an alternative treatment to anticoagulation in patients with non-valvular AF and a broad spectrum of LAAC devices have been developed, mainly targeting high-risk patients deemed ineligible for oral anticoagulation.[240]

The Ultraseal LAAC device (Cardia Inc, Eagan, MN) is a new, self-expandable bulb-and-sail occluder, specifically designed for transcatheter LAAC. The first-in-human experience with this device, including a total of 18 patients from 2 centers, showed promising preliminary feasibility data,[195, 241] and the device received Conformité Européenne (CE)-mark approval in March 2016. This first multicenter international experience aimed to evaluate the safety, feasibility and preliminary efficacy of LAAC with the Ultraseal device in a larger patient population.

3.4. METHODS

3.4.1. Study population

This multicenter study included consecutive patients with non-valvular AF who underwent LAAC with the Ultraseal device from 15 centers in Europe and Canada between January 2015 and January 2018. All participating centers but one had previous LAAC experience, with a mean 4.1 ± 2.7-year experience and a median of 79 (interquartile range, 40-118) and 43 (IQR, 12-95) procedures per center and per operator respectively. The procedure was performed by interventional cardiologists, electrophysiologists, or both in 73%, 13% and 13% of the participating centers, respectively. Canadian patients were treated on the basis of a compassionate clinical use program and each procedure was approved by Health Canada. In Europe, all patients were treated following CE mark approval of the device. All patients provided informed consent for the procedures. The device was implanted on an all-comer basis in

unselected patients undergoing LAAC, in the absence of LAA thrombus. Baseline and periprocedural events were collected prospectively in each participating center. Device success was defined as successful device implantation in correct position and technical success as LAA exclusion in the absence of device-related complications (device embolization, device erosion, interference, thrombus, fracture, infection, perforation, allergy) and no leak > 5 mm on color Doppler transesophageal echocardiography (TEE) during the procedure and index hospitalization, in accordance to the Munich consensus statement.[242] Major adverse events (MAE) during the procedure and index hospitalization included death, stroke or transient ischemic attack, systemic embolism, major bleeding (defined as type ≥3 of Bleeding Academic Research Consortium, including cardiac tamponade),[243] myocardial infarction, major vascular complication according to the Valve Academic Research Consortium-2 criteria[244] and device embolization. Cardiovascular events during follow-up included death, stroke or transient ischemic attack, systemic embolization, major bleeding and device-related complications.

3.4.2. Device characteristics and implantation

The Ultraseal LAAC device is a fully retrievable and repositionable self-expandable nitinol device composed of two parts: a soft distal bulb which anchors the device to the LAA through 12 stabilizing hooks, and a 3-leaflet multi-layered sail with a proximal polyvinyl alcohol foam and a distal polyester layer, for LAA occlusion (**Figure 3.1**). Both sections are connected by a dual articulating joint enabling multidirectional movement and optimal adjustment to different ostium angles and shapes. The device is available in 9 different bulb sizes ranging from 16 to 32 mm (fitting landing zone measurements from 11 to 26 mm), with the proximal sail being 6 mm larger than the distal bulb diameter, and requires a minimum LAA depth of 16 mm. A bulb-to-landing zone oversizing of at least 25% is generally recommended. The bulb offers low radial force which allows for permissive oversizing if needed.

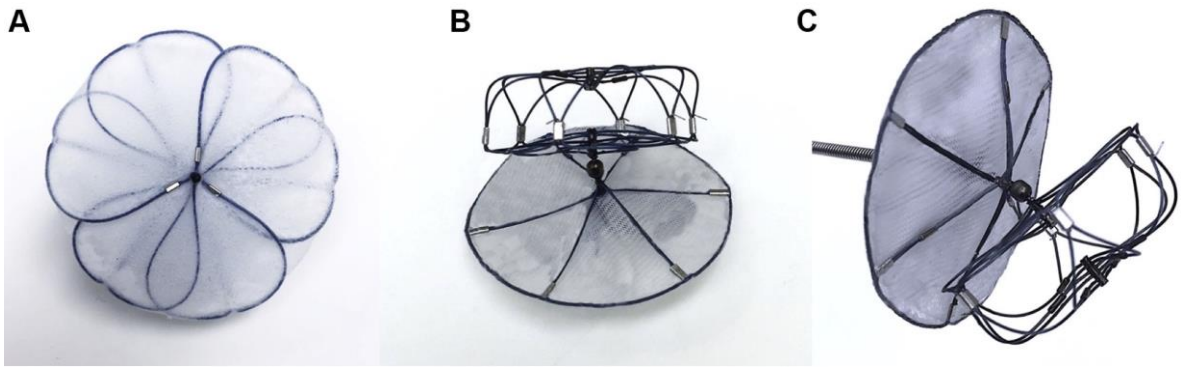

Figure 3.1. The Cardia Ultraseal device.

(A) Left atrial side. The sail is made of three leaflets, and is covered by a proximal polyvinyl alcohol foam and a distal polyester layer. (B) Left atrial appendage side. A distal atraumatic bulb of stranded nitinol anchors the device into the left atrial appendage through 12 stabilizing hooks to prevent device dislodgement. (C) Side view. Both sections are connected by a dual articulating joint allowing multidirectional movement.

The Cardia Delivery System includes three components: the delivery forceps, the introducer and the delivery sheath. The delivery forceps is flexible and has jaws enabling holding and release of the device at a grasping knob located at the center of the proximal sail, while a forceps handle locking mechanism prevents device detachment. A hemostatic introducer allows introduction of the device into the delivery sheath. The Cardia delivery sheath, ranging from 10 to 12 French, is currently available in two different preformed curves: single (45º) and double (45º - 45º) curve.

Procedures were performed under TEE or intracardiac echocardiography and fluoroscopic guidance. After transseptal puncture, heparin was administered to achieve a minimum activated clotting time ≥ 250 sec prior to device insertion. Sizing of the device was performed by using the maximum measured landing zone diameter (at 10 to 12 mm from the LAA orifice) by TEE (45º, 90º, 135º) or intracardiac echocardiography, and angiographic measurements. The delivery sheath was then advanced within the LAA, so that the distal end of its radiopaque marker band was placed at the intended landing zone of the bulb hooks. The distal bulb was deployed into the LAA with a slow unsheathing movement and appropriate compression was assessed by confirming the

fluoroscopic non-symmetric shape of the bulb radiopaque markers and separation between the sail and the lobe (**Figure 3.2**). Subsequently, the sheath was withdrawn by further pullback to expose the proximal sail, allowing LAA ostium sealing. The device could be partially or fully retrieved and redeployed up to five times if implant location or stability were deemed unsatisfactory. After a subtle tug test and upon satisfactory position, the device was released by unscrewing the locking mechanism of the forceps handle.

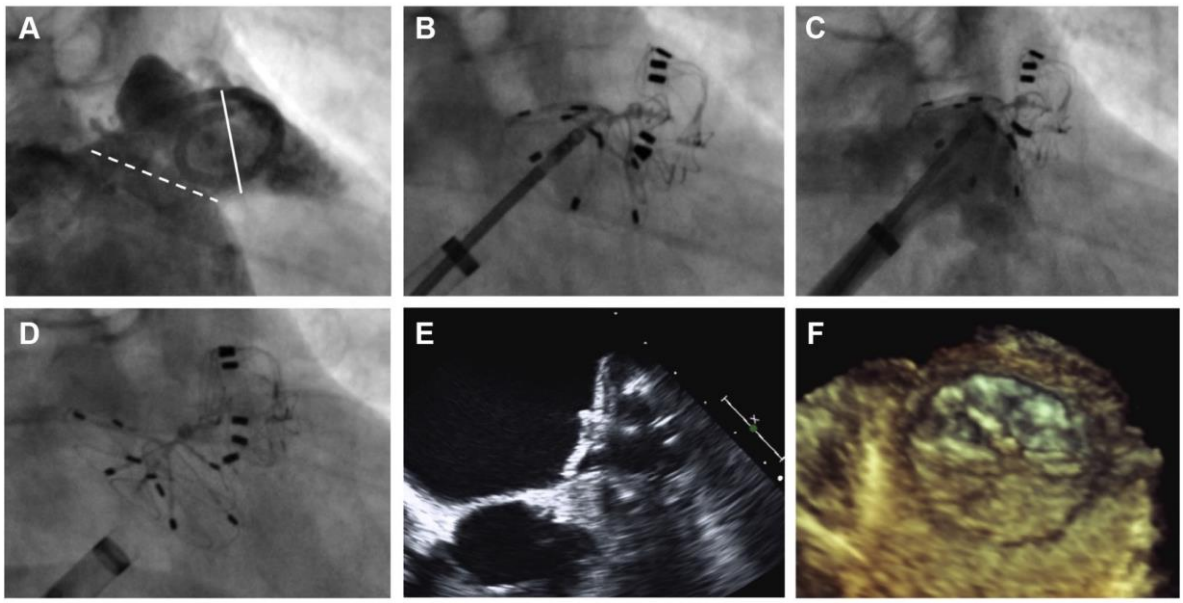

Figure 3.2. Ultraseal device implantation.

(A) Angiographic measurement of the landing zone in right anterior oblique cranial projection (dashed line: ostium; solid line: landing zone). (B) Fluoroscopic view illustrating device articulation during deployment. (C) Angiography showing good sealing after implantation. (D) Device release. 2D- (E) and 3D- (F) transesophageal echocardiography showing appropriately implanted device

A transthoracic echocardiography examination was performed the day after the procedure. Generally, patients were discharged on dual antiplatelet therapy for 3 months followed by lifelong aspirin, or single antiplatelet monotherapy when deemed at too high bleeding risk. Routine TEE was performed at 45 to 180 days post-procedure in all participating centers but 3. Peridevice leaks were categorized according to the width of the color jet as follows: trace (< 1 mm-diameter jet), mild (1-3 mm), moderate (> 3 mm but ≤ 5 mm) and severe (> 5 mm)[221, 242].

3.4.3. Statistical analysis

Categorical variables are reported as counts and percentages and continuous variables as mean ± SD or median (interquartile range). LAAC efficacy on thromboembolic prevention was assessed by comparing the actual annual event rate at follow-up (total number of observed events per 100 patient-years) with the predicted event rate by the CHADS and CHA_2DS_2-VAS_C scores.[245] Risk reduction was calculated as follows: (estimated % event rate – actual % event rate) / estimated % event rate. Analyses were performed using the statistical package STATA version 14.0 (StataCorp LP, College Station, TX).

3.5. RESULTS

A total of 126 consecutive patients from 15 centers were included. Only one patient with a very large LAA was excluded. The main baseline clinical characteristics of the study population are shown in **Table 3.1**. Mean age was 75 ± 8 years and 57% were male. The mean $CHADS_2$ and CHA_2DS_2-VASc score were 3 ± 1 and 5 ± 2, respectively, with an average HAS-BLED score of 4 ± 1. The vast majority of patients had a history of bleeding (78%) and were ineligible for long-term OAC (93%).

3.5.1. Procedural results

Chief procedural details are provided in **Table 3.2**. Most procedures were performed under TEE guidance (87%), whereas 13% were performed with intracardiac echocardiography guidance. Two patients underwent combined procedures with LAAC (percutaneous edge-to-edge mitral valve repair: 1, atrial septal defect closure: 1). Successful device implantation was achieved in 122 (97%) patients and technical success – residual leak < 5 mm in the absence of device-related complications - in 119 (94%) patients. The device could not be implanted in four patients with unsuitable anatomy due to shallow accessory lobes (n=2) or large oval ostia (n=2) yielding to persistent significant gaps. Additional reasons for technical failure were significant pericardial effusion requiring pericardiocentesis (n=1), major residual leak (n=1) and post-procedure device embolization (n=1). The mean device size was 24 ± 4 mm, with an average oversizing of 26 ± 11 %. Successful implantation was achieved with the first device selected in 102/122 (84%) patients, with acute complete LAA seal in 101 (83%) patients and one single case (0.8%) of severe (>5 mm) residual leak.

Table 3.1. Baseline clinical characteristics

	N = 126
Age, years	75 ± 8
Female	54 (42.9)
Hypertension	108 (85.7)
Diabetes mellitus	57 (45.2)
Coronary artery disease	65 (51.6)
Congestive heart failure	36 (28.6)
LVEF, %	49 ± 14
Chronic kidney disease	55/111 (49.5)
Atrial fibrillation type	
Paroxysmal	47 (37.3)
Persistent/Permanent	79 (62.7)
Previous history of TIA/stroke	34 (27.0)
Prior bleeding	98 (77.8)
Contraindication to OAC	117 (92.9)
Absolute	56 (44.5)
Relative	61 (48.4)
Indication for LAAC	
Major bleeding	79 (62.7)
Minor bleeding	19 (15.1)
High bleeding risk	13 (10.3)
Stroke on OAC	2 (1.6)
Labile INR	4 (3.2)
Risk of falls	3 (2.4)
Other	6 (4.8)
$CHADS_2$ score	3 ± 1
CHA_2DS_2-VASc score	5 ± 2
HAS-BLED score	4 ± 1

Values are expressed as n (%) or mean ± SD

LVEF: Left ventricle ejection fraction; TIA: Transient ischemic attack; OAC: Oral anticoagulation; LAAC: Left atrial appendage closure; INR: International normalized ratio; $CHADS_2$: congestive heart failure history, hypertension history, age ≥75 years, diabetes mellitus history, stroke or transient ischemic attack symptoms previously; $CHA_2DS_2VAS_C$: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category; HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol.

Table 3.2. Procedural findings

	N = 126
Device success	122 (96.8)
Technical success	119 (94.4)
Procedural guidance	
TEE	109 (86.5)
ICE	17 (13.5)
LAA ostium, mm	20.5 ± 4.6
LAA landing zone, mm	17.8 ± 3.9
LAA length, mm	25.1 ± 7.4
Device size, mm*	
16	5 (4.1)
18	10 (8.2)
20	19 (15.6)
22	21 (17.2)
24	23 (18.9)
26	17 (13.9)
28	13 (10.7)
30	4 (3.3)
32	10 (8.2)
Oversizing, %	26 ± 11
Number of devices per procedure*	
1	102 (83.6)
2	17 (13.9)
3	3 (2.5)
Number of recaptures*	1.6 ± 1.9
LAA seal*	
Complete	101 (82.8)
Trace leak (< 1 mm)	6 (4.9)
Mild leak (1-3 mm)	11 (9.0)
Moderate leak (>3 but ≤5 mm)	3 (2.5)
Severe leak (> 5 mm)	1 (0.8)
Procedural time, min	73 ± 29

Values are expressed as n (%) or mean ± SD
*Percentage based on 122 successfully implanted patients
TEE: Transesophageal echocardiography; ICE: Intracardiac echocardiography; LAA: Left atrial appendage.

3.5.2. In-hospital outcomes

The main in-hospital outcomes are summarized in **Table 3.3**. The rate of periprocedural MAEs was 2.4%. There was one single case of serious pericardial effusion requiring pericardiocentesis (0.8 %). One ischemic stroke (0.8%) occurred 48 hours after the procedure in a patient undergoing concomitant MitraClip (Abbott Vascular, Santa Clara, California) and LAAC. One device embolization to the left ventricle within the hours following the procedure was reported in the very early experience. The device was retrieved surgically - due to chordae tendineae entanglement -, with postoperative asymptomatic hemoglobin drop requiring transfusion. No episodes of systemic embolism, major vascular complications, myocardial infarction or deaths occurred during the in-hospital period. Most patients (~90%) were discharged on single or dual antiplatelet therapy, whereas only 4% of patients received oral anticoagulation.

Table 3.3. In-hospital outcomes

In-hospital outcomes	**N = 126**
Major adverse events	3 (2.4)
Death	0
Stroke/TIA	1 (0.8)
Systemic embolism	0
Major bleeding (BARC ≥ type 3)	2 (1.6)
Pericardial effusion requiring pericardiocentesis	1 (0.8)
Postoperative Hb drop requiring transfusion*	1 (0.8)
Myocardial infarction	0
Major vascular complications (VARC-2)	0
Device embolization*	1 (0.8)
Other adverse events	
Pericardial effusion not requiring intervention	1 (0.8)
Minor vascular complications	4 (3.2)
Hospitalization length, days	1 (1-2)
Antithrombotic treatment post-LAAC†	
None	1 (0.8)
Single antiplatelet therapy	9 (7.4)
Dual antiplatelet therapy	101 (82.8)
Oral anticoagulation	5 (4.1)
Warfarin	0
Direct OAC	5 (4.1)
Low molecular weight heparin	6 (4.9)

* A single patient had two major adverse events (device embolization and major bleeding)
† Percentage based on 122 successfully implanted patients
BARC: Bleeding Academic Research Consortium; Hb: Hemoglobin; VARC: Valve Academic Research Consortium. Other abbreviations as in Table 3.1.

3.5.3. Follow-up

At a median of 6 (interquartile range: 3-10) months, a total of 7 deaths - five cardiovascular events - were reported, none of them related to the device. There were two cerebrovascular events (one stroke in a patient with prior history of stroke, and one transient ischemic attack) unrelated to DRT or LAA patency. The annualized rates (including both periprocedural and follow-up periods) of ischemic stroke and thromboembolic events (stroke/TIA/systemic embolism) in the study were 2.45% and 3.68%, respectively, translating into a 66% and 60% relative risk reduction for stroke, and 63% and 57% risk reduction for thromboembolic events, according to their $CHADS_2$ and CHA_2DS_2-VASc scores respectively (**Figure 3.3**).[245] Major bleeding events occurred in 4 patients (2 gastrointestinal, 2 anemia without overt bleeding). No episodes of device embolization occurred at follow-up.

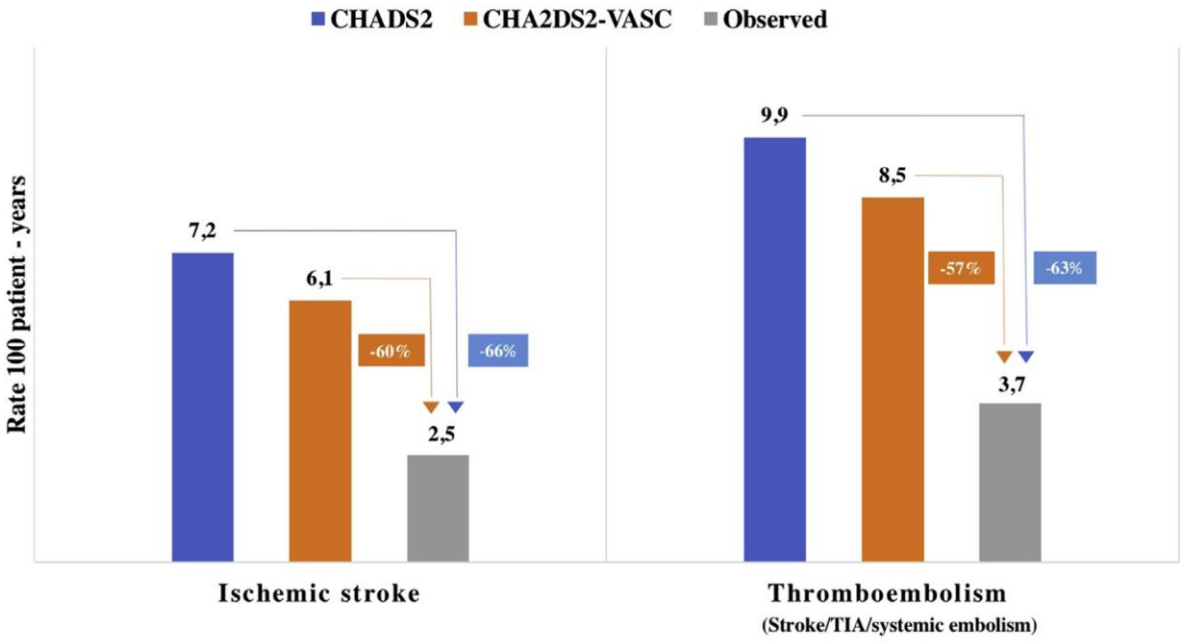

Figure 3.3. Expected versus observed ischemic stroke events.

Effectiveness of LAAC in reduction of ischemic stroke and thromboembolic events (stroke/TIA/peripheral emboli) predicted by $CHADS_2$ and CHA_2DS_2-VASc scores (both periprocedural and follow-up included).[245]
Abbreviations as in Table 3.1.

Eighty-nine out of 122 (73%) patients with successful device implantation underwent TEE within the 6 months after the index procedure (mean: 90 ± 60 days). DRT was observed in five patients (5.6%). Two patients were on aspirin monotherapy at the time of DRT diagnosis, whereas 3 patients were on dual antiplatelet therapy. All 5 patients received oral anticoagulation with complete thrombus resolution and remained asymptomatic with no neurological events during follow-up. Some degree of peridevice leak was found in 19 patients (21%), and it was trace or mild in 16%, and moderate in 5.6%. No patient had severe leak (> 5 mm). Late clinical outcomes and TEE findings are summarized in **Table 3.4**. LAA closure rates immediately after device implantation and within 6-month follow-up are depicted in **Figure 3.4**.

Table 3.4. Follow-Up Clinical and TEE Findings

Adverse events during follow-up	
Median follow-up, months	6 (3-10)
All-cause death	7 (5.7)
Cardiovascular death	5 (4.1)
Cerebrovascular events	2 (1.6)
Stroke	1 (0.8)
Transient ischemic attack	1 (0.8)
Systemic embolism	0
Major bleeding*	4 (3.3)
Device embolization	0
TEE follow-up	**N = 89**
Residual peridevice leak	
None	70 (78.7)
Trace (< 1 mm)	3 (3.4)
Mild (1-3 mm)	11 (12.4)
Moderate (3-5 mm)	5 (5.6)
Severe (> 5 mm)	0
Device-related thrombosis	5 (5.6)

*2 on single and 2 on dual antiplatelet therapy (2 gastrointestinal, 2 anemia without overt bleeding)
TEE: Transesophageal echocardiography

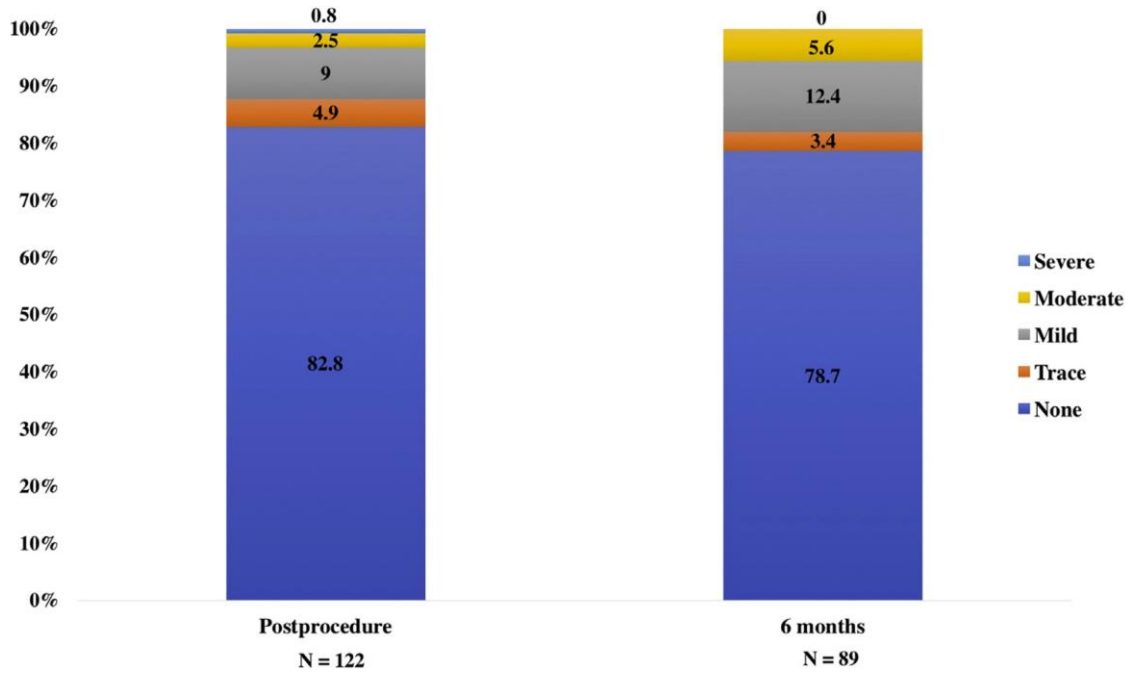

Figure 3.4. Peridevice leak postimplantation and at 6-month follow-up.

The rate of complete LAA seal remained stable during follow-up (~80%), with no evidence of large (> 5 mm) leaks assessed by transesophageal echocardiography within the first 6 months' follow-up.

3.6. DISCUSSION

The present study is the first multicenter evaluation of transcatheter LAAC with the Ultraseal device in patients with non-valvular AF who were deemed poor candidates for long-term oral anticoagulation. The device was successfully implanted in 97% of patients with a low rate of major peri-procedural complications (2.4%) and severe residual leaks (<1%). The rate of DRT within the months following the procedure was 5.6%, and the incidence of cerebrovascular events at midterm follow-up was lower than that expected on the basis of thromboembolic risk scores.

The Amplatzer Amulet (Abbott Vascular, Santa Clara, CA) and the Watchman device (Boston Scientific, Natick, MA) remain the two most widely used endocardial LAAC devices,[139, 140, 219] the latter being the only device studied in randomized clinical trials to

date.[130, 131] However, despite continuous improvements linked to increasing operator experience and device iterations, the wide heterogeneity of LAA morphologies and sizes still limits the suitability of percutaneous LAAC in some of patients.[246] This unmet need and the continuous growth of the LAAC field has fueled the development of novel LAAC technologies.[240]

The Ultraseal LAAC device represents a new-generation self-expandable device with a unique bulb-and-sail design and 3 chief distinguishing features: a fully articulating joint between the distal and proximal sections allowing multidirectional movement and adjustment to different LAA angles and morphologies; a soft distal atraumatic bulb enabling safe deep entry into the LAA and very distal deployment in cases with limited usable length; and the capability of being fully retrieved and redeployed multiple times. The device may accommodate landing zones up to 26 mm – slightly smaller than other devices – although this may be compensated by the soft and flexible characteristics of the bulb, allowing safe deployment of the device distal into the LAA, where the width is frequently smaller. The Ultraseal bulb-and-sail design features the previously called "pacifier principle".[247] The distal bulb anchors the device in the LAA landing zone, whereas the larger proximal sail covers the LAA ostium, akin to a baby pacifier.

The reported rate of successful implantation achieved in this study was as high as 97%, comparable to previous studies with the most commonly used commercialized devices (91-100%).[240] These results are encouraging considering that this series represents the initial experience with a novel device. Overall, LAAC procedures with the Ultraseal device represented 37% (126/345) of the total LAAC cases performed throughout the study period among all participating centers, with a slight decreased share between the first - 46% - and last - 35% - trimester of the inclusion period. All four patients with implant failure presented very challenging anatomies with reduced implantation zone or conical LAAs with oval ostia markedly larger than the LAA landing zone, leading to persistent gaps despite progressive device upsizing. Modifications of the device including wider sails for small bulbs in order to overcome these particularly challenging anatomies, along with increased operator experience, may potentially decrease the rate of implant failure. Further studies addressing anatomical eligibility for Ultraseal are warranted.

Importantly, the results of this study demonstrated the high safety profile of the Ultraseal device, with a low rate of peri-procedural MAEs (2.4%) and a very low rate of significant pericardial effusion (0.8%), similar to the safety outcomes reported in contemporary experiences with other available LAAC devices.[140, 146, 219] Also, these results appear to compare favorably with the initial experiences with other LAAC devices, which exhibited average MAE rates of ~5% (from 3.3 to 8.7%).[130, 200, 248] Acute device embolization is an uncommon complication of LAAC, albeit reported to occur in up to 2% of LAAC procedures.[204] Device embolization in our study occurred only in one patient (0.8%), at the very beginning of the experience. Overall, these safety outcomes are likely explained by the presence of a soft and flexible distal bulb with reduced risk of wall perforation, and a combination of low radial force, 12 stabilizing hooks and meaningful oversizing (~25 %), which minimize device "pop out" during the implantation process and ultimately contribute to the stability of the Ultraseal device.

Incomplete sealing with any degree of peridevice leak under routine TEE surveillance has been reported in up to 41% of patients treated with the Watchman device in the PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) study at 45 days, 34% at six months or 32% at 1 year;[217] 13% in the core lab-adjudicated cohort of the multicenter Amplatzer Cardiac Plug (ACP; Abbott Vascular, Santa Clara, CA) registry, and 16% in the early Canadian experience with ACP at 6 months;[221, 249] up to 12% at 3 months with Amulet[250] or 16% at 1 year in the LAmbre (Lifetech Scientific, Shenzen, China) multicenter study.[248] Leaks may occur at the time of implantation or late after LAAC due to atrial remodeling around the device (edge effect),[224] although unlike prior surgical studies,[109] this finding has not been associated with a higher risk of clinical events.[217, 221] In our experience, complete LAAC sealing was achieved in ~80% of patients at implantation and within 6 months, and most of the observed residual leaks (14/19, 74%) were small (< 3 mm). Definitions of significant residual peridevice leaks have arbitrarily varied from 3 to 5 mm among different LAAC studies, being 5-mm the widest accepted cut-off for peridevice leak severity in most studies conducted to date with either Amplatzer ACP/Amulet[140, 221] or Watchman,[130, 131, 219] as well as in recent consensus documents.[242] Notably, no large residual leaks (> 5 mm) were observed during follow-up, leading to

an adequate occlusion rate of the LAA of 100%, according to current standardized definitions.[242] Albeit lobe-and-disk LAAC devices have typically been associated with lower peridevice leaks as compared to single-lobe devices likely due to the "pacifier effect" of the double-layered barrier, future head-to-head studies with other available lobe-and-disk LAA devices (e.g. Amulet) are needed to assess whether the absence of fabric covering in the distal bulb may associate with an increased risk of residual leaks.

The rate of DRT following LAAC has ranged from 0% to 25%,[154, 240] with wide variations depending on device type, postprocedural antithrombotic treatment and timing of TEE surveillance imaging. In our experience, five patients (5.6%) developed DRT at a mean follow-up of 3 months post-LAAC. Importantly, all five patients experienced complete DRT resolution with oral anticoagulation, and remained asymptomatic. Uncertainty about optimal antithrombotic therapy after LAAC remains a concern in this field. Recent findings have shown a significant activation of the coagulation system very early after LAAC, suggesting a potential benefit of short-term (~4 weeks) anticoagulation following LAAC in the absence of absolute contraindications to anticoagulants.[150] It is noteworthy that patients included in this preliminary clinical experience received more conservative antithrombotic approach (>90% discharged on single or dual antiplatelet therapy and < 5% on oral anticoagulation), than most previous studies with other LAAC devices (100% anticoagulation in PROTECT-AF and PREVAIL [Prospective Randomized Evaluation of the Watchman LAAC Device in Patients With AF Versus Long-Term Warfarin Therapy],[130, 131] 27% anticoagulation EWOLUTION (Registry on Watchman Outcomes in Real-Life Utilization),[219] and 19% anticoagulation in the Amulet Observational Study).[140] Interestingly, complete healing and neointimal coverage was observed at 30-day in a canine model with the Ultraseal device (Cheng Y et al., First in-vivo evaluation of the Ultrasept Left Atrial Appendage Closure Device, 2012 Transcatheter Cardiovascular Therapeutics, Miami, Florida). The low rate of postprocedural oral anticoagulation in the present real-world experience reflects the increasing trend towards less aggressive antithrombotic approaches in this high-risk population currently referred for percutaneous LAAC. Larger studies with longer follow-up are warranted to determine the real incidence of DRT, as well as to elucidate the optimal post-procedural antithrombotic therapy in this population.

Study limitations. There was no independent adjudication event committee and no centralized echo core lab in this study. Because of its all-comer design, the present study did not intend to examine accuracy of preoperative work-up and no data on screen failure was systematically collected. Post-procedural antithrombotic therapy and follow-up TEE imaging were based on each institution's standard practice and some variations were observed among different centers and physicians. However, routine surveillance imaging at intermediate follow-up (1-6 months) was done in most (80%) participating centers, minimizing the risk of patient selection bias regarding the incidence of residual leaks or DRT. Lastly, the limited sample size and follow-up prevent from drawing definite conclusions on the long-term efficacy for thromboembolic prevention.

3.7. CONCLUSIONS

In patients with non-valvular AF at high bleeding risk, LAAC with the Ultraseal device was safe and associated with a high procedural success rate. The low incidence of cerebrovascular events at midterm follow-up provides promising efficacy data on the prevention of thromboembolic events. Larger studies with a longer term follow-up are warranted.

3.8. CLINICAL PERSPECTIVES

WHAT IS KNOWN? Isolated small case series have suggested the feasibility of LAAC with the Ultraseal device.

WHAT IS NEW? This first multicenter global experience showed a high implant success rate and a low incidence of procedure-related complications, along with a low rate of ischemic stroke at midterm follow-up.

WHAT IS NEXT? Larger studies with a longer follow-up are required to adequately define long-term clinical efficacy of this novel device.

3.9. ACKNOWLEDGEMENTS:

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CHAPTER 4. Hemodynamic Impact of Percutaneous Left Atrial Appendage Closure in Patients with Paroxysmal Atrial Fibrillation

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4.1. RÉSUMÉ

Nous avons cherché à évaluer les changements hémodynamiques aigus associés à la fermeture percutanée de l'auricule gauche (FAG) chez les patients atteints de fibrillation auriculaire paroxystique. La population étudiée était composée de 31 patients atteints de fibrillation auriculaire paroxystique qui ont subi une FAG. Tous les patients ont subi une échocardiographie transthoracique de base et le lendemain de la procédure. Un sous-ensemble de 14 patients a subi une tomodensitométrie cardiaque pré-procédurale 3D. Les paramètres de la fonction systolique ventriculaire gauche et les indices volumétriques de l'oreillette gauche sont restés inchangés après la procédure, ainsi que le volume systolique ventriculaire et auriculaire gauche. Le ratio moyen du volume auricule/oreillette gauche par tomodensitométrie 3D était de 10.2±2.3%, sans corrélation entre le ratio auricule/oreillette gauche et les variations du volume systolique post-procédure. En conclusion, la FAG ne s'est pas traduite par des changements significatifs de la fonction auriculaire ou ventriculaire gauche.

4.2. ABSTRACT

Purpose: Percutaneous left atrial appendage (LAA) closure has become a valid alternative to anticoagulation therapy for the prevention of thromboembolic events in patient with atrial fibrillation (AF). However, scarce data exist on the impact of LAA closure on left atrial and ventricular function. We sought to assess the acute hemodynamic changes associated with percutaneous LAA closure in patients with paroxysmal AF.

Methods: The study population consisted of 31 patients (mean age: 73±10 years; 49% of women) with paroxysmal AF who underwent successful percutaneous LAA closure. All patients were in sinus rhythm, and underwent 2D transthoracic echocardiography at baseline and the day after the procedure. A subset of 14 patients underwent pre-procedural cardiac computed tomography (CT) with 3D LA and LAA reconstruction.

Results: Left ventricular systolic function parameters and LA volumetric indexes remained unchanged after the procedure. No significant changes in left ventricular stroke volume (72.4±16.0 mL vs. 73.3±15.7 mL, p=0.55) or LA stroke volume (total: 15.6±4.2 mL vs. 14.6±4.2 mL, p=0.21; passive: 9.0±2.8 vs 8.3±2.6 mL, p=0.31; active: 10.3±5.6 vs 10.0±6.4 mL, p=0.72) occurred following LAA closure. Mean ratio of LAA to LA volume by 3D CT was 10.2±2.3%. No correlation was found between LAA/LA ratio and changes in LA stroke volume (r=0.35, p=0.22) or left ventricle stroke volume (r=0.28, p=0.33).

Conclusions: The LAA accounts for about 10% of the total LA volume, but percutaneous LAA closure did not translate into any significant changes in LA and left ventricular function.

4.3. INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia, and it is predicted to affect >20 million people in the USA and Europe by 2050.[1, 2] Approximately 15-20% of all strokes are attributable to AF,[251] and it is known that close to 90% of atrial thrombi are originated within the left atrial appendage (LAA).[18] Percutaneous LAA closure (LAAC) has emerged as an alternative to anticoagulation therapy for prevention of thromboembolism in patients with non-valvular AF.[240]

The LAA is a remnant of the embryonic left atrium (LA), and it has been suggested to have an important physiological role on cardiac hemodynamics and LA pressure-volume relation regulation, especially in the presence of increased LA pressure or volume overload.[252] Several animal studies have shown significant changes in left ventricular and LA filling and atrial function after LAA removal, suggesting increased compliance of the LAA compared with the left atrium main chamber.[98, 253-255] Data from clinical studies evaluating the impact of surgical LAA exclusion on LA function have noted a decrease in LA reservoir function while preserving LA contractility.[256, 257] A recent study assessing the role of percutaneous LAAC on LA function, showed a mild improvement in LA mechanical function after LAAC.[258] However, whereas the influence of LA systole on effective stroke volume has been widely investigated,[259] scarce data exist in the setting of percutaneous LAAC.[258] Thus, we sought to assess the acute hemodynamic impact of percutaneous LAAC in patients with paroxysmal AF.

4.4. METHODS

4.4.1 Patient selection

A total of 31 consecutive patients with paroxysmal AF who underwent successful percutaneous LAAC were included. All patients underwent a 2D transthoracic echocardiographic examination at baseline - at least one month after last AF episode documented by either physical examination, serial electrocardiogram or continuous monitoring - and the day after LAAC. Since the presence of AF at the time of echocardiography may affect LA contraction function[260] (which contributes by 30% of stroke volume)[261] and LA fibrosis and fatty infiltration – potentially limiting dynamic changes in LA volumes – occur to a greater extent in patients with persistent AF

compared with paroxysmal AF,[262] only patients in sinus rhythm at the time of echocardiography examinations were included.

4.4.2 Echocardiographic examination

All echocardiographic exams were performed in the same laboratory by the same team of sonographers and cardiologists following the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI).[263] Echocardiograms were analyzed off line using the Xcelera Echo Lab Management (Amsterdam, Netherlands). Both LA and left ventricle volumes were obtained via the biplane modified Simpson's method from the apical 4- and 2-chamber views, according to guidelines. Maximal LA volume (LAV max) was obtained at the end of the T wave on electrocardiogram just before mitral valve opening, minimal LA volume (LAV min) at QRS complex just at the closure of the mitral valve, and pre-contraction atrial volume (LAV preA) was obtained from the diastolic frame just before mitral valve reopening at the beginning of the P wave.[261] Total LA stroke volume was calculated as (LAVmax – LAVmin), active LA stroke volume was calculated as (LAVpreA – LAVmin), and passive LA stroke volume was calculated as (LAVmax – LAVpreA). LA phasic functions were derived from the following volumetric measurements: reservoir function or total LA emptying fraction (LAEF): [(LAVmax – LAVmin)/LAVmax]; conduit function or passive LAEF: [(LAVmax - LAVpreA)/LAVmax]; contractile function or active LAEF: [(LAVpreA - LAVmin)/LAVpreA].[261] Left ventricle stroke volume was calculated as: [0.785 x Left ventricular outflow tract (LVOT) diameter^2 x LVOT velocity time integral].[264]

4.4.3. LAA volume assessment by cardiac computed tomography

In a subset of 14 patients, cardiac computed tomography (CT) was also performed prior to procedure using a dual-source 64-slice CT scanner (SOMATOM Definition; Siemens Healthcare; Forchheim; Germany), and 3-dimensional LA and LAA reconstruction was obtained using Aquarius iNtuition version 4.4.12 (TeraRecon, Foster City, California).

4.4.4. Statistical analysis

Continuous variables are shown as mean ± SD unless otherwise specified, and discrete variables as percentages. Normality was evaluated by the Shapiro-Wilk W test. Comparison of means before and following LAAC was performed using paired *t-test*. Correlations between variables were tested by simple linear regression analysis (Pearson's correlation). All analyses were performed using Stata 14.0 (Stata Corp, College Station, TX, USA) with P-values <0.05 considered statistically significant.

4.5. RESULTS

The main baseline and procedural characteristics of the study population are shown in **Table 4.1.** Mean age was 73±10 years, with 49% of women. The CHA_2D_2-VASc and HAS-BLEED scores were 4±2 and 3±2, respectively. The Watchman device (Boston Scientific, Natick, Massachusetts) was implanted in 61% of patients, whereas 23% received the Ultraseal device (Cardia Inc., Eagan, MN), and 16% the Amplatzer Cardiac Plug (Abbott Vascular, Santa Clara, CA).

4.5.1. LA and left ventricular function determined by 2D echocardiography

The heart rate and blood pressure values were comparable at baseline and after LAAC. The average maximal indexed LA volume at baseline was 37.4±8.4 mL/m^2. No changes in LA volumetric indexes occurred post-LAAC (**Table 4.2)**, including the three LA phasic functions (reservoir, conduit and booster function). All LA stroke volumes remained unaltered following LAAC (total 15.6±4.2 mL vs. 14.6±4.2 mL, p=0.21; passive 9.0±2.8 vs 8.3±2.6 mL, p=0.31, active 10.3±5.6 vs 10.0±6.4 mL, p=0.72) (**Fig. 4.1A**).

Left ventricular systolic function variables (**Table 4.3**) remained unchanged compared to baseline measurements, except for a trend towards a decrease in left ventricular end-systolic volume after the procedure (Δ -2.2±6.3 mL, p=0.06). No significant changes in left ventricular stroke volume were observed after LAAC (72.4±16.0 mL vs. 73.3±15.7 mL, p=0.55) (**Fig. 4.1B**). Regarding left ventricular diastolic parameters (**Table 4.4**), the peak late diastolic filling velocity (mitral A) decreased after LAAC (76.9±25.5 vs 68.7±20.3, p=0.04), with no other significant differences in the remaining variables.

Table 4.1. Baseline clinical characteristics

Patient characteristics	**N = 31**
Age, years	73 ± 10
Female	15 (49)
BMI, kg/m2	29 ± 6
BSA, m2	1.9 ± 0.2
Hypertension	27 (87)
Diabetes mellitus	12 (39)
Prior LVEF < 40%	5 (16)
Length history of AF, years	2 (1-5)
Time from last AF episode to TTE, months	9 (3-17)
Prior stroke	8 (26)
Prior bleeding	25 (81)
Contraindication for OAC	28 (91)
$CHADS_2$	3 ± 1
CHA_2DS_2-VASc	4 ± 2
HAS-BLED	3 ± 1
Device	
Watchman	19 (61)
Amplatzer Cardiac Plug	5 (16)
UltraSeal	7 (23)
Residual shunt	
Complete seal	29 (94)
Jet size < 5 mm	2 (6)
Jet size > 5 mm	0

Values are expressed as n (%), mean ± SD or median (IQR)
BMI: Body mass index; BSA: Body surface area; LVEF: Left ventricle ejection fraction; AF: Atrial fibrillation; TTE: Transthoracic echocardiography; OAC: Oral anticoagulation

Table 4.2. Echocardiographic volumetric indexes of left atrial function

	Baseline	Post-LAAC	Delta	P value
LA volume index				
Maximal, mL/m2	37.4±8.4	36.3±10.1	-1.1±6.9	0.39
Pre-A, mL/m2	28.4±8.2	28.0±9.3	-0.4±5.8	0.71
Minimal, mL/m2	21.8±8.1	21.6±8.9	-0.1±5.1	0.87
LA stroke volume				
Total, mL	15.6±4.2	14.6±4.2	-0.9±4.1	0.21
Passive, mL	9.0±2.8	8.3±2.6	-0.7±3.8	0.31
Active, mL	10.3±5.6	10.0±6.4	-0.3±4.9	0.72
LA emptying fraction				
Total (reservoir function), %	42.6±10.5	41.2±10.7	-1.4±8.9	0.40
Passive (conduit function), %	24.6±7.2	23.5±7.3	-1.1±8.9	0.48
Active (pump function), %	24.1±9.9	23.3±10.8	-0.8±9.0	0.63

Values are mean ± SD
LA: Left atrial; Pre-A: preceding atrial contraction volume.

Table 4.3. Hemodynamic and echocardiographic parameters of left ventricular systolic function

	Baseline	Post-LAAC	Delta	P value
Clinical variables				
Heart rate, beats/min	66±12	63±9	-2.8±10.2	0.14
Systolic BP, mmHg	129±17	127±17	-3.0±12.6	0.21
Diastolic BP, mmHg	69±9	67±9	-2.2±9.6	0.23
Echocardiographic variables				
LV end-diastolic volume, mL	97.9±28.1	94.9±28.1	-3.0±13.7	0.23
LV end-systolic volume, mL	48.2±19.3	46.0±19.6	-2.2±6.3	0.06
LV ejection fraction, %	57.8±9.1	59.2±9.8	1.3±5.3	0.17
LV stroke volume, mL	72.4±16.0	73.3±15.7	0.9±8.9	0.55
Cardiac output, L/min	4.7±1.3	4.6±1.2	-0.1±0.8	0.58

Values are mean ± SD
BP: Blood pressure; LV: Left ventricle

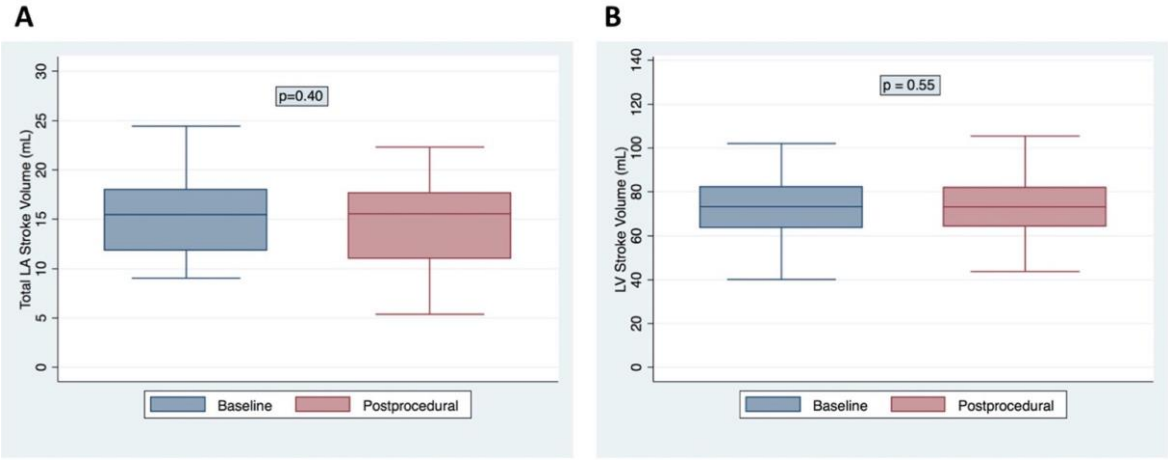

Fig. 4.1. Stroke volume before and after LAA closure.

There were no significant differences in neither total left atrial stroke volume (**A**) nor left ventricle stroke volume (**B**) postprocedure compared to baseline.
LA: Left atrium; LV: Left ventricle.

Table 4.4. Echocardiographic parameters of left ventricular diastolic function.

	Baseline	**Post-LAAC**	**Delta**	**P value**
E, cm/s	86.3±23.8	85.7±21.2	-0.6±14.3	0.84
A, cm/s	76.9±25.5	68.7±20.3	-8.1±20.4	0.04
E', cm/s	6.7±1.7	6.9±1.9	0.2±1.1	0.34
E/A	1.3±0.8	1.4±0.7	0.1±0.4	0.27
E/e'	13.7±5.5	13.5±6.2	-0.2±3.3	0.74
DT, ms	201.3±47.1	207.5±49.3	6.3±35.9	0.36

Values are mean ± SD
E: peak early diastolic filling velocity; A: peak late diastolic filling velocity; E' Tissue Doppler peak early velocity on medial mitral annulus; DT: deceleration time

4.5.2. Cardiac 3D-CT data

A subset of 14 patients underwent cardiac CT with 3-dimensional reconstruction of the LA and LAA. Mean LAA and LA volumes were 9.8±3.6 mL and 94.5±17.0 mL, respectively (**Table 4.5**), with a mean ratio of LAA volume to LA volume of 0.102 (range 0.064 – 0.154). **Fig. 4.2** displays the relationship between LAA/LA ratio by CT and changes (delta) in stroke volume after LAA occlusion based on echocardiographic parameters. There was no correlation between LAA/LA ratio and changes in neither total LA stroke volume (r = 0.352, p=0.217), nor left ventricle stroke volume (r = 0.279, p=0.334). Three-dimensional reconstruction of LA and LAA is shown in **Fig. 4.3.**

Table 4.5. Three-Dimensional computed tomography volumetric measurements

	N = 14
LA volume, mL	94.5±17.0
LAA volume, mL	9.8±3.6
Ratio LAA/LA, %	10.2±2.3

Values are mean ± SD or %; LA: Left atrium; LAA: Left atrial appendage

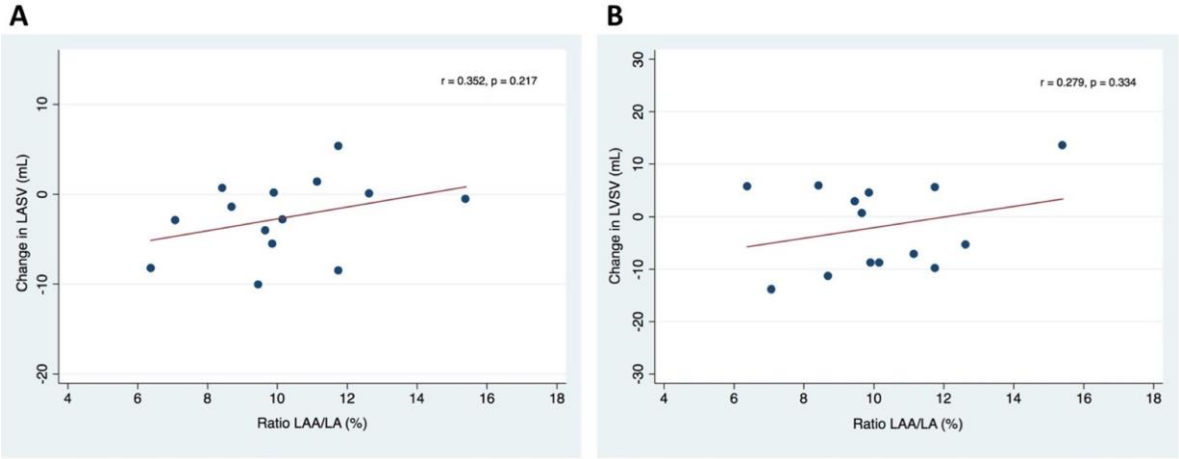

Fig. 4.2. Relationship between LAA/LA ratio and stroke volume.

No correlation was observed between the ratio of left atrial appendage volume to left atrial volume and changes in either total left atrial stroke volume (**A**) or left ventricle stroke volume (**B**).

LASV: Left atrial stroke volume; LVSV: Left ventricle stroke volume; LA: Left atrium; LAA: Left atrial appendage

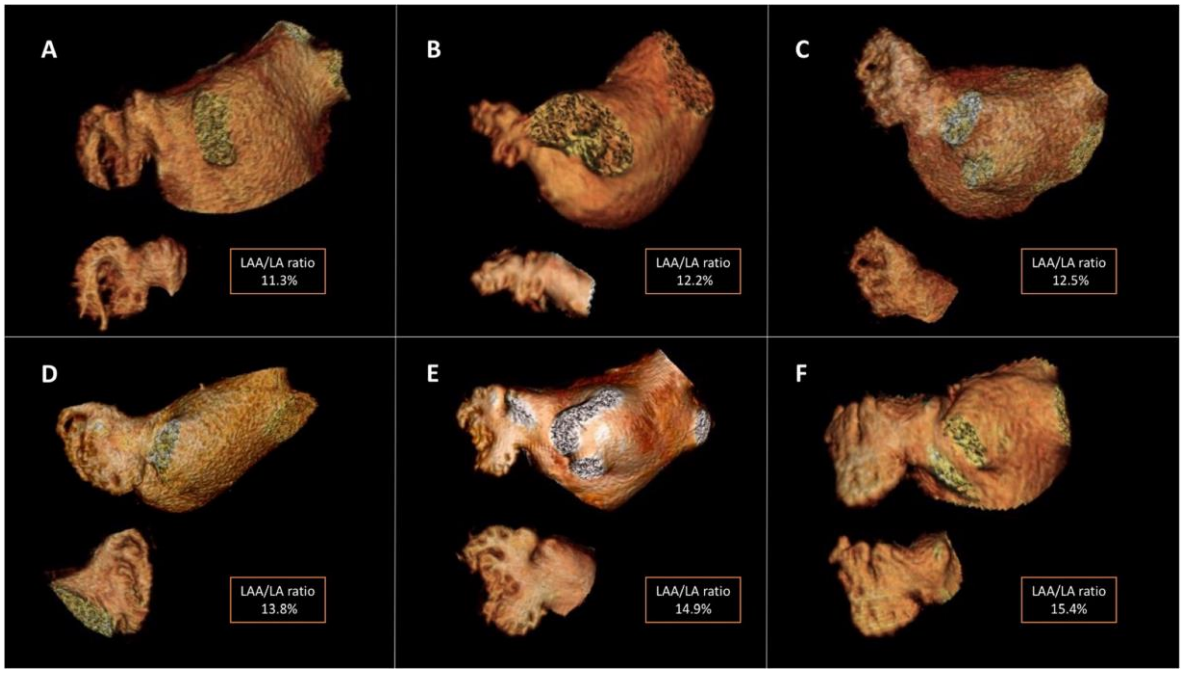

Fig. 4.3. Three-dimensional computed tomography reconstruction of the left atrium and left atrial appendage.

(A-F) Examples of variability in the ratio of left atrial appendage (LAA) to left atrial (LA) volumes.

4.6. DISCUSSION

Our main results can be summarized as follows: (i) the LAA accounts for ~10% of the entire LA volume, (ii) percutaneous LAAC does not impair LA or left ventricular stroke volume, (iii) exclusion of LAA is associated with a tendency towards a decreased late ventricular filling.

Other than an embryologic remnant, several physiologic functions have been attributed to the LAA. First, it acts as a reservoir during left ventricular systole, a conduit for blood transit from the pulmonary veins to the left ventricle during early diastole, and an active pump increasing left ventricular filling in late diastole.[265] Second, it modulates the relationship between pressure and volume in the LA, through its increased distensibility.[98, 253-255] Third, it is an endocrine organ, accounting for nearly 30% of all cardiac natriuretic peptide production. Fourth, it has also been suggested to contribute to stroke volume through its intrinsic contractile function.[266] However, little is known

about these functions after transcatheter LAAC. Recently, Coisne et al.[258] suggested an improvement in all LA reservoir, transport and contractile functions following percutaneous LAAC, through a Frank-Starling effect.

LA actively contracts in late diastole, and contributes between 15 and 30% to the left ventricle stroke volume.[261] However, there are very few reports evaluating LAA contribution to stroke volume and the potential consequences of LAA removal on stroke volume and cardiac output. Massoudy et al.[266] evaluated the hemodynamic effect of LAA ligation in isolated working guinea pig hearts, showing that the cardiac output of hearts with intact LAA was almost 2-fold compared to hearts with ligated LAA. The observed difference was attributed to preservation of intrinsic LAA contractility with subsequent improvement in left ventricular filling. Kamohara et al.[267] assessed the impact of surgical LAA exclusion in nineteen mongrel dogs in sinus rhythm, showing the lack of significant changes in hemodynamics, including ejection fraction, stroke volume and cardiac output. The only study evaluating the physiologic impact of percutaneous LAAC to date included 33 patients (only 13 in sinus rhythm), showing improvement in global LA mechanical function after LAA occlusion, with no differences between preprocedural and discharge echocardiography in left ventricular stroke volume or left ventricle ejection fraction in sinus rhythm patients.[258] Hence, our findings align with contemporary series, confirming the lack of relevant changes in left ventricular stroke volume, while assessing for the first time the impact of transcatheter LAA exclusion on left atrial stroke volume and systemic cardiac output.

Wide variations in LAA shape and size have been described, with reported volumes ranging from 0.8-19.3 cm^3 in post-mortem series.[268] The results of our study are relatively close to previous reports assessing LAA volume by 3D-CT. A mean volume of 12.5±5.8 mL in men and 10.8±3.9 mL in women was found by Boucebci et al.[269] and 9.8±4.2 mL by Budge et al.[270], corresponding to ~9% of the entire LA volume.[270, 271] Although not directly compared due to the small proportion of patients undergoing CT in our cohort and being out of the focus of this study, slight discrepancies between echocardiographic and CT measurements were observed likely due to systematic underestimation of LA volume measurements using transthoracic echocardiography, when compared to CT.[272] In the present study, no correlation was found between

LAA/LA ratio (~10%) and changes in stroke volume. These data provide additional reassurance to patients undergoing percutaneous LAAC, particularly those with reduced left ventricular function, considering that all patients had preserved LAA contraction during sinus rhythm prior to the procedure - suggesting lack of loss of LA contribution to stroke volume and cardiac output despite exclusion of 10% of the entire LA volume.

The role of left atrial contraction in late ventricular diastole has been well-established [14]. In the present study, percutaneous LAAC in patients in sinus rhythm, was associated with a reduction in transmitral spectral Doppler A-wave velocities. Contribution of the left atrial appendage on left ventricular late diastolic filling has also been proved in previous preclinical studies.[273] Removal of the LAA led to a decrease in atrial compliance with altered left ventricular filling in an open-chest study in dogs.[254] Similarly, Hondo et al.[255] showed left ventricular late diastolic filling assistance of the LAA during atrial contraction through the Frank-Starling mechanism. Despite decreased mitral peak A velocity observed in this study, transcatheter LAAC did not result in significant changes in other diastolic parameters or in overall LA mechanical function.

The lack of significant acute hemodynamic effect of percutaneous LAAC in the present study might be explained as follows: (1) LA pressure or volume overload were absent in all but one patient with severe mitral regurgitation. These conditions increase both the reservoir function and modulating role of the LAA in the relationship between pressure and volume.[256] (2) Nearly 90% of the patients had a history of hypertension, a condition resulting in premature impairment of LAA function.[274, 275] (3) Average left ventricle ejection fraction was > 50%; preclinical studies showed little effect of LA and LAA failure on cardiac output in the presence of preserved left ventricle ejection fraction.[276] Potential dynamic adaptive changes in left ventricular and atrial volumes with longer follow-up periods post-LAAC need to be evaluated in future studies.

Limitations. The major limitation of our study was the limited number of patients enrolled. However, the restrictive inclusion of patients in sinus rhythm in this single-centre experience, strengthens our findings and underscore the lack of significant hemodynamic effect of transcatheter LAA exclusion in patients with normal contraction

of the LAA prior to the procedure. The present study did not assess changes in levels of neurohormones such as atrial and brain natriuretic peptides, natriuretic regulating hormones secreted in response to ventricular volume expansion and pressure overload.

4.7. CONCLUSIONS

Our understanding of LAA function is rapidly evolving in response to the wide expansion of surgical and more recently percutaneous LAAC in patients with non-valvular atrial fibrillation at-risk for stroke. In the present study, percutaneous LAAC did not lead to significant acute cardiac hemodynamic effects regarding left atrial/left ventricular stroke volume or cardiac output. These results reinforce the positive outcomes observed in contemporary percutaneous LAAC trials and "real-world" registries, suggesting lack of loss of LA contribution to stroke volume, regardless of the exclusion of ~10% of the entire LA volume. The long-term implications of this finding and its correlation with variations in neurohormonal markers should be evaluated in future studies.

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4.9. CONFLICT OF INTEREST. The authors declare that they have no conflicts of interest.

4.10. ETHICAL APPROVAL. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

CHAPTER 5. Short-Term Oral Anticoagulation Versus Antiplatelet Therapy Following Transcatheter Left Atrial Appendage Closure

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5.1. RÉSUMÉ

Étude visant à comparer les changements dans les marqueurs de coagulation associés à l'anticoagulation orale (ACO) à court terme par rapport à la thérapie antiplaquettaire (TAP) suite à la fermeture d'auricule gauche (FAG) avec le dispositif Watchman chez 78 patients. Le fragment 1+2 de la prothrombine (F1+2) et la thrombine-antithrombine III (TAT) ont été évalués pré-procédure et à 7, 30 et 180 jours post-procédure. Quarante-huit patients ont reçu TAP et 30 patients ACO post-FAG. L'ACO (par rapport à la TAP) a été associée à une atténuation significative de l'activation du système de coagulation dans les 7 jours post-FAG ($p=0.007$ et $p=0.048$ pour F1+2 et TAT, respectivement), les deux groupes revenant progressivement aux valeurs de base à 30 et 180 jours. La présence d'écho-contraste spontané pré-FAG a été associée à une activation accrue du système de coagulation post-FAG, qui à son tour, augmentait le risque de thrombose du dispositif.

5.2. ABSTRACT

Background: The impact of antithrombotic therapy on coagulation system activation after left atrial appendage closure (LAAC) remains unknown. This study sought to compare changes in coagulation markers associated with short-term oral anticoagulation (OAC) versus antiplatelet therapy (APT) following LAAC.

Methods: Prospective study including 78 atrial fibrillation patients undergoing LAAC with the Watchman device. Prothrombin fragment 1+2 (F1+2) and thrombin-antithrombin III (TAT) were assessed immediately before the procedure, and at 7, 30, and 180 days after the procedure.

Results: Forty-eight patients were discharged on APT (dual therapy: 31, single therapy: 17) and 30 on OAC (direct anticoagulants: 26, vitamin K antagonists: 4), with no differences in baseline-procedural characteristics between groups except for a higher rate of spontaneous echo contrast (SEC) in the OAC group. OAC significantly reduced the activation of the coagulation system within 7 days post-LAAC compared to APT (23 [95% CI: 5-41]% vs. 82 [95% CI: 54-111]% increase for F1+2, p=0.007; 52 [95% CI: 15-89]% vs 183 [95% CI: 118-248]% increase for TAT, p=0.048), with all patients in both groups progressively returning to baseline values at 30 and 180 days. SEC pre-LAAC was associated with an enhanced activation of the coagulation system post-LAAC (144 [48-192] vs 52 [24-111] nmol/L, p=0.062 for F1+2; 299 [254-390] vs 78 [19-240] ng/ml, p=0.002 for TAT). Device thrombosis as assessed by TEE at 45 days post-LAAC occurred in 5 patients (6.4%), and all of them were receiving APT at the time of TEE (10.2% vs. 0% if OAC at the time of TEE, p=0.151). Patients with device thrombosis exhibited a greater coagulation activation 7 days post-LAAC (p=0.038 and p=0.108 for F+1 and TAT, respectively).

Conclusions: OAC (vs. APT) was associated with a significant attenuation of coagulation system activation post-LAAC. SEC pre-LAAC associated with enhanced coagulation activation post-LAAC, which in turn increased the risk of device thrombosis. These results highlight the urgent need for randomized trials comparing OAC vs. APT post-LAAC.

5.3. INTRODUCTION

Percutaneous left atrial appendage closure (LAAC) is an alternative stroke prevention therapy in patients with nonvalvular atrial fibrillation (AF).[240] The Watchman device (Boston Scientific, Marlborough, Massachusetts) is one of the most widely used and the only Food and Drug Administration approved device for LAAC. The goal of post-procedural antithrombotic therapy after LAAC is to prevent device-related thrombus (DRT) formation during device endothelization process, which takes from 30 to 90 days according to preclinical studies.[149] The type and duration of antithrombotic therapy following LAAC with the Watchman device has been chosen empirically, lowering from early short-term anticoagulation in the 2 landmark randomized trials,[130, 131] to a minimum of 3 months of dual antiplatelet therapy (APT) in recent real-world registries.[277] However, it is still controversial whether DRT is associated with the type of antithrombotic regimen post-device implantation.[277, 278]

Prothrombin fragment 1+2 (F1+2) and thrombin-antithrombin III (TAT) have been well validated as indicators of coagulation system activation.[279] A significant transient activation of the coagulation system has been shown in patients undergoing LAAC with either the Watchman or Amplatzer Cardiac Plug (Abbott Vascular, Santa Clara, CA) devices, with no detectable effect on activation of the platelet system, suggesting enhanced thrombin generation as the main hemostatic effect associated with LAAC.[150] Nevertheless, there is no biologic basis supporting currently recommended post-LAAC antithrombotic regimens, and no study to date has assessed the impact of different antithrombotic strategies (antiplatelet or anticoagulant therapy) after LAAC from a mechanistic standpoint. Thus, the aim of the present study was to compare the prothrombotic status (as assessed by F1+2 and TAT levels) associated with short-term (45 days) anticoagulation therapy (OAC) vs APT following LAAC with the Watchman device, and to evaluate factors associated with an enhanced thrombogenic status after percutaneous LAAC.

5.4. METHODS

5.4.1. Study Design. The data that support the findings of this study are available from the corresponding author upon reasonable request. This was a prospective, single-center study of patients undergoing endocardial LAAC with the Watchman device. The study

protocol was approved by the institutional review board, and all patients provided signed informed consent to participate in the study. Eligible patients met the following inclusion criteria: 1) ≥18 years-old, 2) paroxysmal, persistent or permanent AF, 3) poor candidate for long-term anticoagulation therapy, 4) at least 1 major or 2 moderate risk factors for ischemic stroke ($CHADS_2$ [congestive heart failure, hypertension, age >75 years, diabetes mellitus, previous stroke or transient ischemic attack] score ≥2). Patients were excluded if they met one of the following exclusion criteria: 1) AF with no additional risk factor for ischemic stroke, 2) contraindication for APT, 3) life expectancy <2 years, valvular heart disease or presence of mechanical prosthetic valves, 4) thrombus in the left atrium or left atrial appendage.

5.4.2. Procedures and follow-up. The procedures were performed under general anesthesia and transesophageal echocardiographic guidance, as described previously.[130, 131] After transseptal puncture, heparin was administered to achieve a minimum activated clotting time ≥250 seconds before device insertion. A transthoracic echocardiography was performed the day after the procedure. Patients were discharged on dual APT for 3 months followed by lifelong aspirin (single APT when deemed at too high bleeding risk) or under OAC for 45 days and then aspirin for life in the absence of absolute contraindications. The final decision was left at the physician's discretion. Routine transesophageal echocardiography was performed at 45 days post-procedure, with additional clinical follow-up at 6 months, 12 months and yearly thereafter.

5.4.3. Blood sample collection. Fasting blood samples were collected according to a standardized method immediately before the procedure, and at 7, 30, and 180 days after the procedure. Blood was collected into 4 Vacutainer tubes prefilled with 0.5mL of 3.2% buffered sodium citrate (Becton Dickinson), kept on ice ≤2 hours before centrifugation at 2000g at 4ºC for 15 minutes. Plasma and serum were pipetted into plastic vials in aliquots and stored at -70ºC until analysis. Enzyme immunoassays were used for the determination of F1+2 and TAT levels (Stago).

5.4.4. Outcomes. The primary outcome was the comparison of the prothrombotic status (as evaluated by F1+2, TAT levels) at 7, 30, and 180 days between patients receiving short-term OAC and APT following LAAC. Secondary outcomes were (i) clinical and

procedural factors associated with enhanced thrombogenic status following LAAC; (ii) incidence of DRT and prothrombotic status in DRT patients (vs. those without DRT); (iii) cardiovascular events (cardiac death, stroke/transient ischemic attack, systemic embolism, bleeding) after LAAC. Clinical event reporting was performed according to the Munich Consensus.[242]

5.4.5. Statistical analysis.

Qualitative variables were reported as counts and percentages and continuous variables as median (interquartile range). Categorical variables were compared using the chi-square or Fisher exact test (if the expected value in any cell was <5). Continuous variables not normally distributed were compared using the Wilcoxon rank sum test. Normality was determined by using the Shapiro-Wilk test. The analysis of the change in the markers of coagulation activation over time between antithrombotic therapy groups (APT or OAC) was conducted using a repeated-measures mixed-model with baseline values as a covariate and treatment, time, and the treatment by time interaction as fixed effects. A p value <0.05 was considered significant for all statistical tests. All data were analyzed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

5.5. RESULTS

A total of 78 patients were included in the study, and the main baseline and procedural characteristics of the study population are summarized in **Table 5.1**. All patients were on single APT or no antithrombotic therapy just before LAAC. The antithrombotic treatment following LAAC consisted of APT in 48 patients (dual-APT in 31, single-APT in 17) and OAC in 30 patients (direct OACs in 26 patients: 22 apixaban, 2 dabigatran, 2 rivaroxaban; vitamin K antagonists in 4 patients) (**Figure 5.1 in the Data Supplement**). The main baseline, procedural and in-hospital characteristics of the study population according to the type of antithrombotic regimen (OAC or APT) post-LAAC are summarized in **Table 5.1**. There were no significant differences in baseline characteristics between the two groups, except for increased blood stasis (41% vs 17%, p=0.022) and lower age (75 [IQR: 67-78] vs 79 [IQR: 69-83], p=0.056) in the OAC group compared to the APT group. Procedural success was achieved in all cases, with complete occlusion in 85% of the patients. Deep implantation (≥10 mm between the device and the pulmonary vein ridge) was present in 61% of patients with no

differences between both groups (63% vs 59%, p=0.702). There were no deaths at 30-day follow-up, and 8 patients died at follow-up.

5.5.1. Changes in the markers of coagulation activation after LAAC. The results of coagulation system activation as assessed by F1+2 and TAT according to the antithrombotic therapy (APT or OAC) at hospital discharge are depicted in **Figure 5.1**. Blood samples were available in all patients at baseline and were missing in 6% (6% and 7% in APT and OAC groups, respectively, p=0.99), 8% (10% and 3% in APT and OAC groups, respectively, p=0.40) and 36% (32% and 43% in APT and OAC groups, respectively, p=0.34) of patients at 7 days, 1- and 6-month follow-up, respectively. Mean baseline levels of F1+2 and TAT were 0.28 nmol/L and 5.35 ng/ml, respectively. At 7 days post-LAAC, levels of F1+2 and TAT were significantly lower in the OAC group than in the APT group (23 [95% CI: 5-41]% vs. 82 [95% CI: 54-111]% increase for F1+2, p=0.007; 52 [95% CI: 15-89]% vs 183 [95% CI: 118-248]% increase for TAT, p=0.048, in the OAC and APT groups respectively), gradually decreasing thereafter, returning to baseline levels at 30 days (p=0.670 and p=0.860 for 30-day vs. baseline F1+2 levels in APT and OAC groups, respectively; 0.988 and p=0.738 for 30-day vs. baseline TAT levels in APT and OAC groups, respectively), and at 180 days (p=0.994 and p=0.912 for 180-day vs. baseline F1+2 levels in APT and OAC groups, respectively; p=0.996 and p=0.988 for 180-day vs. baseline TAT levels in APT and OAC groups, respectively). Activation of the coagulation system was significantly higher regardless of the type of APT regimen, with no significant differences in the changes in coagulation markers between single- and dual-APT (**Figure 5.2**). There was no difference in coagulation activation amongst the 17 patients on single-APT, irrespective of the antiplatelet agent (p=0.973 and p=0.613 between aspirin and clopidogrel, for F1+2 and TAT levels, respectively).

Table 5.1. Baseline, Procedural and In-Hospital Characteristics of the Study population

	Overall population	Antiplatelet therapy	Anticoagulation therapy	p value
	n=78	**n=48**	**n=30**	
Baseline Characteristics				
Age, years	77 [69-81]	79 [69-83]	75 [67-78]	0.056
Male	53 (67.9)	31 (64.6)	22 (73.3)	0.422
Body mass index, kg/m2	28 [26-32]	28 [25-32]	30 [26-33]	0.491
Hypertension	73 (93.6)	44 (91.7)	29 (96.7)	0.380
Diabetes mellitus	28 (3.0)	19 (39.6)	9 (30.0)	0.391
Coronary artery disease	43 (55.1)	24 (50.0)	19 (63.3)	0.250
Creatinine≥100umol/l	41 (52.6)	28 (58.3)	13 (43.3)	0.197
LEVF, %	55 [45-60]	55 [45-60]	53 [45-60]	0.566
Chronic renal failure	33 (42.3)	22 (45.8)	11 (36.7)	0.425
Previous liver disease	3 (3.9)	3 (6.3)	0 (0)	0.163
Atrial fibrillation type				
Paroxysmal	37 (47.4)	26 (54.2)	11 (36.7)	0.132
Chronic	41 (52.6)	22 (45.8)	19 (63.3)	
Spontaneous echo contrast	20 (25.6)	8 (16.7)	12 (40.9)	0.022
Thromboembolic events				
Stroke	29 (37.2)	18 (37.5)	11 (36.7)	0.941
TIA	11 (14.1)	7 (14.6)	4 (13.3)	0.877
Prior bleeding	71 (91.0)	43 (89.6)	28 (93.3)	0.573
Labile INR*	0 (0)	0 (0)	0 (0)	-
$CHADS_2$ score, mean	3 [2-4]	3 [2-4]	3 [2-4]	0.908
CHA_2DS_2-VASc score, mean	5 [3-6]	4 [3-5]	5 [3-6]	0.992
HAS-BLED score, mean	4 [3-5]	4[3-5]	4[3-5]	0.636
Procedural and In-Hospital Characteristics				
Procedural success	78 (100)	48 (100)	30 (100)	-
Device size				
21mm	10 (13.3)	7 (14.6)	3 (10.0)	0.348
24mm	25 (33.3)	18 (37.5)	7 (23.3)	
27mm	29 (37.2)	17 (35.4)	12 (40.0)	
30mm	9 (11.5)	3 (6.3)	6 (20.0)	
33mm	5 (6.7)	3 (6.3)	2 (6.7)	
Residual leak ≥5 mm	11 (14.7)	6 (12.5)	5 (16.7)	0.741
Suboptimal device compression†	29 (38.7)	17 (35.4)	12 (40.0)	0.810

Deep implantation‡	46 (61.3)	29 (63.0)	17 (58.6)	0.702
Protrusion	25 (33.3)	14 (30.4)	11 (37.9)	0.502
Stroke/TIA	0 (0)	0 (0)	0 (0)	-
Life-threatening/Major bleeding	4 (5.1)	4 (8.3)	0 (0)	0.156
Pericardial effusion requiring intervention	2 (2.6)	2 (4.2)	0 (0)	0.521
Prosthesis Embolization	0 (0)	0 (0)	0 (0)	-
Hospital length stay, days	1 [1-1]	1 [1-2]	1 [1-1]	0.456

Values are expressed as n (%) or median (IQR)
*Labile INR was defined as <60% time in therapeutic range (INR 2-3 inclusive)
†Device compression <8% or >20%
‡Implantation depth from left upper pulmonary vein ridge > 1.0 cm
$CHADS_2$: Congestive heart failure, hypertension, age >75 years, diabetes mellitus, previous stroke or transient ischemic attack; CHA_2DS_2-VAS_c: Congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, female sex; HAS-BLED: Hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, age >65 years, drugs or alcohol; LVEF, Left-ventricle ejection fraction; TIA, Transient Ischemic Attack

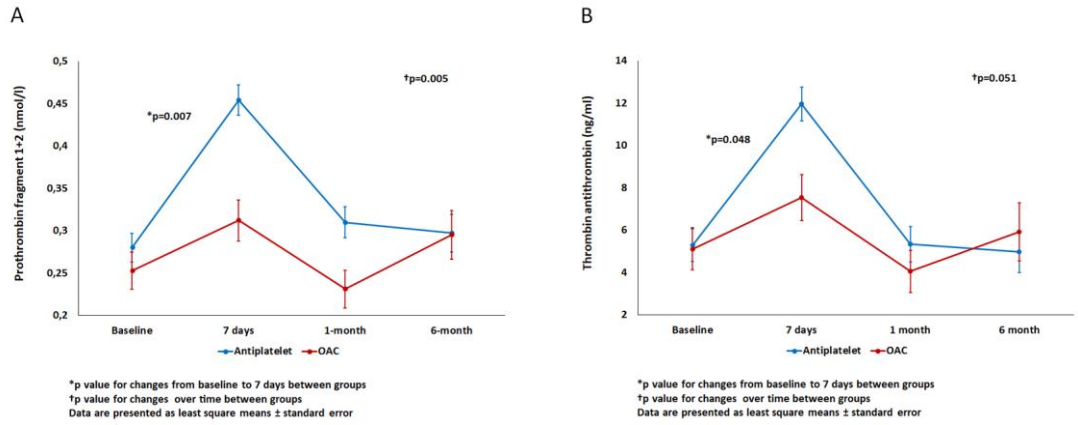

Figure 5.1. Changes in coagulation system activation within the 6 months post-LAAC, according to antithrombotic therapy (antiplatelet versus anticoagulation therapy)

(A) Changes in F 1+2 levels post-LAAC. (B) Changes in TAT levels post-LAAC. APT: Antiplatelet therapy; BL: Baseline; F1+2: Prothrombin fragment 1+2; LAAC: Left atrial appendage closure; OAC: Oral anticoagulation; TAT: thrombin-antithrombin complex

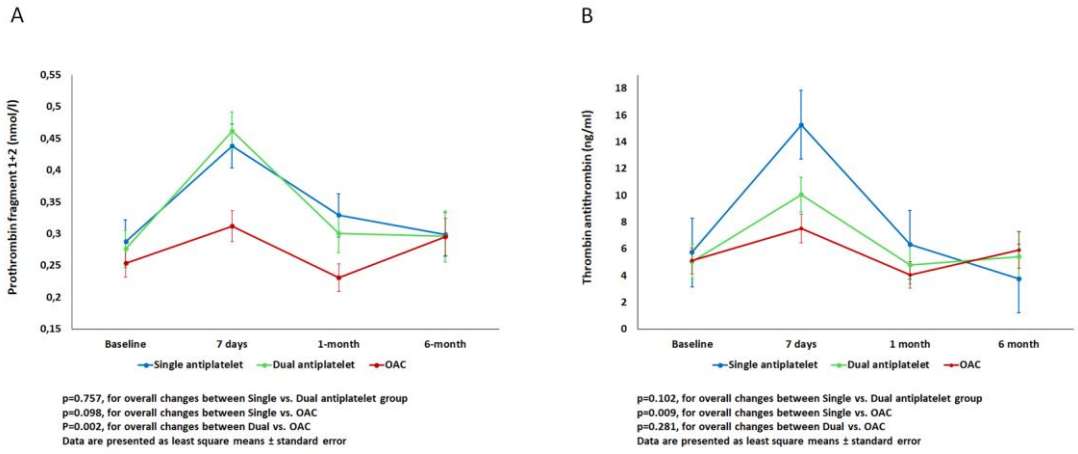

Figure 5.2. Changes in coagulation system activation within the 6 months post-LAAC, according to antithrombotic therapy (SAPT vs DAPT vs OAC therapy)

(A) Changes in F 1+2 levels post-LAAC. (B) Changes in TAT levels post-LAAC. DAPT: dual antiplatelet therapy; SAPT: single antiplatelet therapy. Other abbreviations as in Figure 1.

5.5.2. Factors associated with enhanced prothrombotic status post-LAAC. Table 5.2 outlines the degree of coagulation system activation in patients with APT (group with a higher increase in F1+2 and TAT levels at 7 days after LAAC), according to baseline and procedural characteristics. Preexisting spontaneous echocardiography contrast (SEC) was associated with a higher peak increase in F1+2 (144 [IQR: 48-192] vs 52 [IQR: 24-111] nmol/L, p=0.062) and TAT levels (299 [IQR: 254-390] vs 78 [IQR: 19-240] ng/ml, p=0.002) following transcatheter LAAC. Patients with moderate or severe SEC had enhanced coagulation activation compared with patients with no or mild SEC (178 [47-178] vs 56 [25-111] nmol/L, p=0.184 for F1+2; 355 [254-425] vs 98 [21-245] ng/ml, p=0.014 for TAT). Chronic AF (vs. paroxysmal) was associated with numerically higher levels of F1+2 (85 [IQR: 45-137] vs 48 [IQR: 16-88] nmol/L, p=0.102) and TAT (245 [IQR: 50-294] vs 82 [IQR: 19-240] ng/ml, p=0.181), although the difference did not attain statistical significance. No other clinical or procedural factors (including residual leaks or degree of device protrusion) correlated with a greater activation of the coagulation. No difference in the degree of coagulation activation in relation to baseline characteristics was noted in patients treated with OAC (**Table 5.1 in the Data Supplement).**

5.5.3. DRT following LAAC. TEE post-LAAC was performed in all patients. DRT was detected in 5 patients (6.4%), and all of them were on APT (dual and single APT in 3 and 2 patients, respectively) at the time of TEE (10.2% vs. 0% of patients on OAC at the time of TEE, p=0.151). Baseline characteristics of patients with DRT are shown in **Table 5.2 in the Data Supplement**. DRT occurred in 3/24 (12.5%) patients with device protrusion, 2/44 (4.5%) patients with deep implantation (device >10mm distal to the pulmonary vein ridge), and none of the patients with subostial position (<10mm to the pulmonary ridge). Patients diagnosed of DRT exhibited a greater increase in the levels of F1+2 (p=0.038) and numerically increased levels of TAT (p=0.108) at day 7 post-LAAC diagnosis (**Figure 5.3**), progressively returning to baseline levels at 30-180 days (**Figure 5.2 in the Data Supplement**). A cutoff increase in F1+2 levels of 117% within 7 days post-LAAC identified patients under APT at a higher risk of DRT (sensitivity: 75%, specificity: 80%). Anticoagulation was started in all patients but two (with laminar thrombus and absolute contraindications for OAC), with complete thrombus resolution in all patients.

Table 5.2. Degree of activation of the coagulation markers, according to baseline and procedural variables in patients with antiplatelet therapy (n=48)

Variables	ΔF1+2 (%)	p value	ΔTAT (%)	p value
Age				
≥77 (n=30)	63 [30-113]	0.975	86 [19-253]	0.208
<77 (n=18)	52 [25-125]		196 [66-295]	
Sex				
Male (n=31)	56 [25-115]	0.948	131 [22-253]	0.682
Female (n=17)	56 [32-111]		130 [28-289]	
Diabetes				
Yes (n=19)	65 [29-116]	0.643	135 [14-295]	0.673
No (n=29)	56 [25-113]		128 [51-258]	
Left ventricular ejection fraction				
≥50 (n=35)	66 [32-125]	0.194	158 [28-289]	0.161
<50 (n=13)	36 [25-109]		89 [-6-201]	
Creatinine				
≥100 (n=28)	52 [25-110]	0.503	130 [14-253]	0.232
<100 (n=20)	69 [31-145]		110 [51-484]	
Atrial fibrillation type				
Paroxysmal (n=26)	48 [16-88]	0.102	82 [19-240]	0.181
Chronic (n=22)	85 [45-137]		245 [50-294]	
CHA_2DS_2-VASc score				
≥3 (n=43)	56 [25-113]	0.546	118 [21-254]	0.149
<3 (n=5)	88 [32-178]		240 [234-551]	
Stroke				
Yes (n=18)	63 [32-116]	0.558	147 [22-263]	0.607
No (n=30)	49 [24-113]		110 [40-254]	
Prior bleeding				
Yes (n=43)	52 [29-113]	0.906	135 [28-289]	0.173
No (n=5)	69 [24-88]		54 [16-66]	
Spontaneous echo contrast				
Yes (n=8)	144 [48-192]	0.062	299 [254-390]	0.002
No (n=40)	52 [24-111]		78 [19-240]	
Antiplatelet therapy				
Single (n=17)	49 [29-81]	0.597	135 [52-295]	0.394
Dual (n=31)	61 [24-137]		97 [19-253]	
Device size				
≤24 (n=25)	56 [16-125]	0.522	130 [40-246]	0.806

>24 (n=23)	66 [35-113]		116 [16-295]	
Residual leak ≥5 mm				
Yes (n=6)	47 [25-49]	0.409	45 [21-130]	0.271
No (n=42)	63 [29-116]		157 [28-263]	
Suboptimal device compression*				
Yes (n=17)	56 [30-116]	0.682	86 [22-355]	0.666
No (n=31)	56 [25-113]		133 [28-246]	
Deep implantation†				
Yes (n=29)	66 [30-125]	0.306	120 [21-276]	0.861
No (n=19)	48 [25-74]		135 [50-246]	
Protrusion				
Yes (n=14)	47 [26-74]	0.210	102 [14-245]	0.470
No (n=34)	63 [30-130]		135 [22-289]	

Values are expressed as median (IQR)
*Device compression <8% or >20%
†Implantation depth from left upper pulmonary vein ridge >1.0 cm

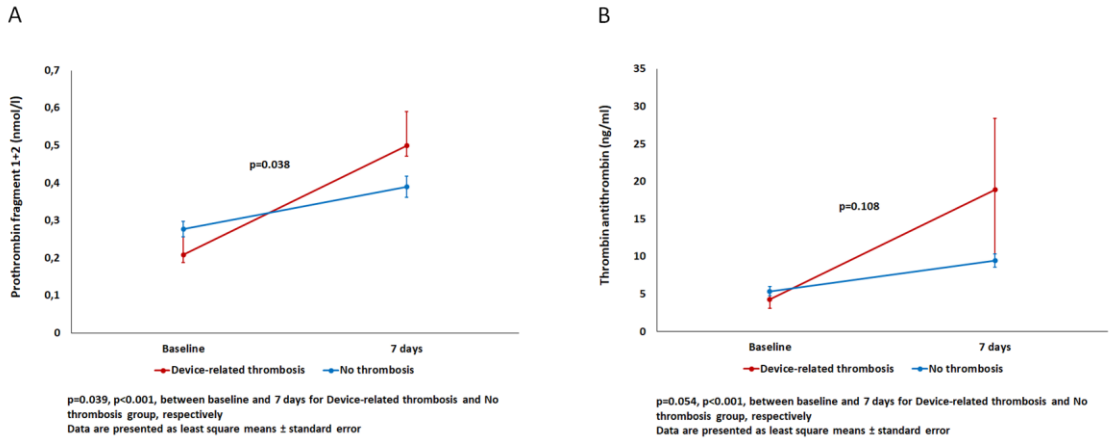

Figure 5.3. Changes in coagulation system activation post-LAAC, according to the occurrence of device-related thrombus

(A) Changes in F 1+2 levels post-LAAC. (B) Changes in TAT levels post-LAAC. Abbreviations as in Figure 1.

5.5.4. Clinical outcomes after LAAC. The clinical outcomes of the study population are shown in **Table 5.3**. After a median follow-up of 13 (IQR: 4-25) months, 3 patients (3.8%) suffered an ischemic stroke, and all of them were in the APT group (6.3% vs 0%, p=0.281). Following hospital discharge, 7 major bleeding events occurred, with no significant differences between the APT and OAC groups (10.4% vs 6.7%, p=0.701). Eight patients died throughout the study period (5 from cardiac cause), all in the APT group (16.7% vs 0%, p=0.021).

Table 5.3. Follow-up outcomes (after hospital discharge)

	Overall population	Antiplatelet therapy	Anticoagulation therapy	p value
	n=78	**n=48**	**n=30**	
Ischemic stroke	3 (3.8)	3 (6.3)	0 (0)	0.281
Systemic embolism	0 (0)	0 (0)	0 (0)	-
Major bleeding	7 (8.9)	5 (10.4)	2 (6.7)	0.701
All-cause death	8 (10.3)	8 (16.7)	0 (0)	0.021
Cardiac death	5 (6.4)	5 (10.4)	0 (0)	0.150

Values are expressed as n (%)
Abbreviations: TIA: transient ischemic attack

5.6. DISCUSSION

The results of this first study assessing the effect of post-procedural antithrombotic regimen (APT vs. OAC) after LAAC on coagulation system activation can be summarized as follows: (i) short-term OAC significantly reduced coagulation activation (F1+2 and TAT levels) following LAAC; (ii) preexisting SEC was associated with a greater activation of the coagulation system following LAAC; (iii) a higher increase in the markers of coagulation activation was observed in DRT patients.

5.6.1. Antithrombotic therapy and hemostatic markers. Short-term anticoagulation with warfarin is the default strategy after LAAC in the United States, albeit current European device labeling allows the use of either OAC or dual APT after Watchman implantation, the latter being the most widely used antithrombotic strategy outside of the United States.[280] Evidence regarding the efficacy of dual APT and direct OAC (used in ~90% of the patients in the OAC group in our study) after Watchman implantation stems mainly from nonrandomized trials, with both strategies having shown low rates of stroke, nonprocedural bleeding and DRT.[151, 152, 277] The increasing tendency to use dual APT after LAAC has been influenced by a widespread perception of apparent better safety of APT in this high bleeding risk population, even though dual APT may carry an increased bleeding risk comparable to that of OAC.[83] Overall, dual APT and direct OAC strategies appear to have similar safety compared with vitamin K antagonist agents following LAAC with Watchman,[277, 278] although APT may associate to slightly higher rates of DRT.[278]

In the present study, short-term OAC, mainly with direct OAC agents, significantly attenuated activation of the coagulation system compared with APT. Of note, we have previously shown a significant activation of the coagulation system, but not platelet activation, within 1 week following LAAC with the Watchman and Amplatzer Cardiac Plug devices.[150] Altogether, these biological-based findings suggest that short-term OAC rather than APT might be the most appropriate antithrombotic regimen after LAAC, in the absence of absolute contraindications for OAC, until the device becomes completely endothelialized. Additionally, these results cast doubt on the benefit of dual-APT over single-APT for patients at prohibitive bleeding risk, given the lack of differences in coagulation activation irrespective of antiplatelet regimen.

5.6.2. Enhanced coagulation activation: associated factors and DRT. SEC was associated with an enhanced activation of the coagulation system following LAAC. The presence of SEC in the left atrium, an indicator of blood stasis, is a well-known risk factor for thrombus formation in the left atrial appendage and an independent predictor for thromboembolism[22, 281] Interestingly, SEC within the atrium has been identified as a potential risk factor for thrombus formation on the device.[157, 222] In our study, permanent AF was associated with higher activation of the coagulation system after LAAC, compared with paroxysmal AF. Previous studies have demonstrated that thrombogenesis in AF occurs in a time-dependent manner, with chronic presentation being associated with higher fibrin D-dimer, TAT III or fibrinogen concentrations, contributing to the increased thromboembolic risk in these patients.[282, 283] Hence, special considerations such as default short-term OAC or tailored monitoring of coagulation activation markers post-LAAC may be given when identifying high-risk features for thrombus formation in LAAC candidates.

DRT remains a major concern and represents the Achilles heel of LAAC, with an estimated incidence of 4% (range 0 to 17%), and a 4- to 5-fold increased risk of ischemic events.[154, 156, 157] The rate of DRT varies widely in the literature due to the lack of standardized definition, differences in antithrombotic regimen and timing of surveillance imaging. Although slightly high, the 6.4% incidence of DRT observed in our study is yet within this range and consistent with one of the largest DRT studies conducted to date.[154] Several patient-specific (female sex, high CHA_2DS_2-$VAS_{c,}$ low ejection fraction, SEC) and procedure-related (deep implantation, poor apposition, incomplete occlusion) factors have been proposed as potential risk factors for DRT formation.[280] In the current study, the presence of a DRT was associated with a higher increase in coagulation activation markers (F1+2 and TAT) within 7 days post-LAAC, with a cutoff increase of 117% in F1+2 best identifying patients at higher risk of DRT. These findings suggest that monitoring of such biological markers after LAAC (in combination with baseline characteristics such as preexisting SEC) may enable early recognition of those patients at higher risk for DRT, in which switching to OAC may be considered. Furthermore, this strategy could be particularly helpful in guiding the management of DRT (type and anticoagulation duration), and a complementary tool to imaging for surveillance of thrombus recurrence after resolution.[284] Indeed, all patients

suffering from DRT in the present study were on APT at the time of the event, suggesting that the biological findings showing the superior effects of short-term OAC post-LAAC may translate into differences in clinically relevant events. However, these results should be interpreted as hypothesis generating and need to be confirmed in a larger cohort of patients undergoing LAAC. Ongoing larger randomized studies comparing direct OAC vs dual-APT post-LAAC (ANDES trial, Short-term Anticoagulation Versus Antiplatelet Therapy for Preventing Device Thrombosis Following Transcatheter Left Atrial Appendage, NCT03568890) will help defining the most appropriate antithrombotic therapy for the prevention of DRT.

5.6.3. Study limitations. First, this was an observational study with limited sample size, which may have contributed to the lack of association between procedural characteristics and coagulation system activation. There was a relatively high percentage of missing data at 6 months, mainly related to logistic reasons (patients living very far from the hospital) in addition to follow-up death. However, the percentage of missing data were similar between groups and the results at 6-month follow-up were rather confirmatory of those observed at 1 month, with the progressive return of coagulation activation to baseline values. Second, APT or OAC therapy at discharge were prescribed at the discretion of the attending physicians, reflecting real-life LAAC practice. However, no significant differences in baseline clinical characteristics were observed between the 2 groups, thus minimizing the risk of patient selection bias. Third, the small number of events precluded a multivariable adjustment to evaluate the relation between antithrombotic therapy and outcome events. Finally, only patients undergoing LAAC with the Watchman device were included in the current study, and may limit generalizability of our findings to other LAAC devices.

5.7. CONCLUSIONS

Short-term direct OAC significantly reduced activation of the coagulation system after LAAC compared to APT. Patients with preexisting SEC as well as those with DRT exhibited greater levels of coagulation activation post-LAAC. These results suggest that short-term OAC may be more appropriate than APT after LAAC. Future randomized trials are warranted to confirm these findings and provide definite evidence on the

optimal antithrombotic strategy for preventing ischemic stroke and DRT while not increasing bleeding complications after LAAC.

5.8. ACKNOWLEDGMENTS

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5.9. DICLOSURES

Dr Rodés-Cabau has received institutional research grants from Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

5.10. SUPPLEMENTAL MATERIAL

Supplementary Table 5.1. Characteristics of patients with device-related thrombus.

Patient	Age	Sex	CHA_2DS_2-VAS_C	HAS-BLED	Type of AF	Device size, mm	Device position	Regimen at discharge	ΔF1+2 nmol/l	ΔTAT ng/ml	Time after LAAC, days	Therapy at time of DRT detection
1	62	M	2	2	Permanent	24	Protrusion	DOAC*	0.034	1.162	46	DAPT
2	80	M	7	4	Permanent	27	Protrusion	DAPT	0.402	12.01	53	DAPT
3	8	F	3	3	Paroxysmal	21	Deep†	SAPT	0.587	48.52	44	SAPT
4	86	M	3	4	Paroxysmal	33	Protrusion	SAPT	0.250	9.11	46	SAPT
5	87	M	3	4	Permanent	27	Deep†	DAPT	0.188	2.28	15	DAPT

AF: Atrial fibrillation; $CHADS_2$: Congestive heart failure, hypertension, age >75 years, diabetes mellitus, previous stroke or transient ischemic attack; CHA_2DS_2-VAS_c: Congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, female sex; DAPT: Dual antiplatelet therapy; DRT: Device-related thrombus; F1+2: Prothrombin fragment 1+2; HAS-BLED: Hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, age >65 years, drugs or alcohol; LAAC: Left atrial appendage closure; SAPT: Single antiplatelet therapy; SEC: Spontaneous echocardiographic contrast; TAT: Thrombin-antithrombin complex

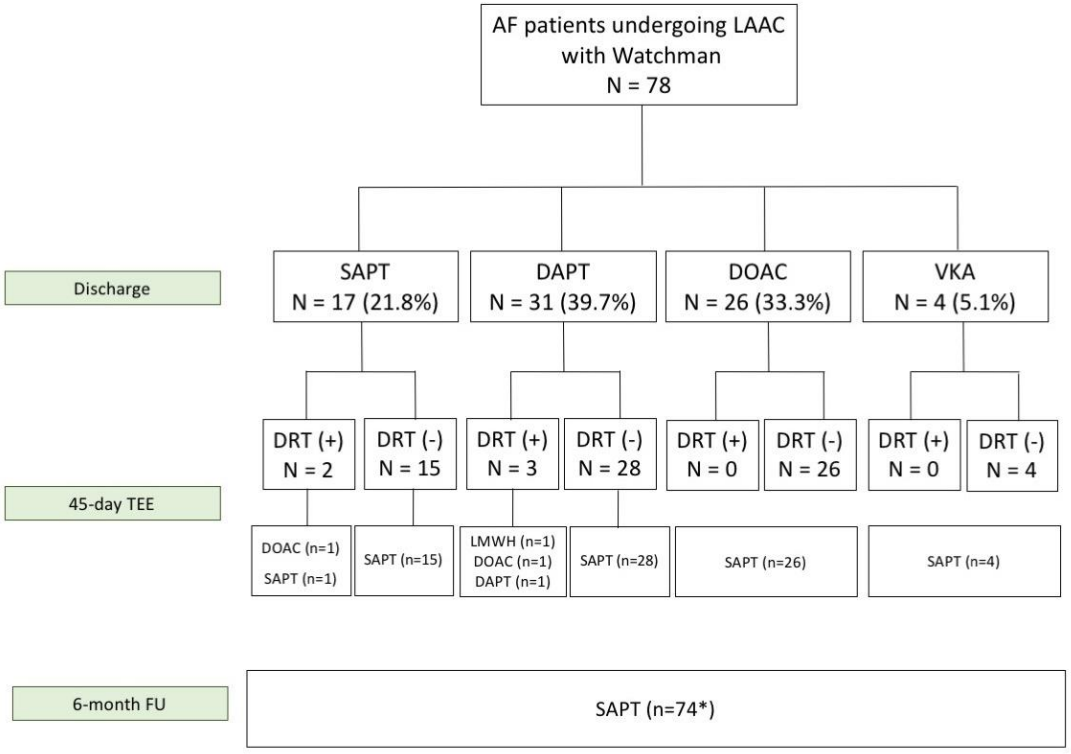
*Rivaroxaban swapped for DAPT at day 18 post-LAAC due to epistaxis
†Implantation depth from left upper pulmonary vein ridge >1.0 cm

Supplementary Table 5.2. Degree of activation of the coagulation markers, according to baseline and procedural variables in patients with oral anticoagulation therapy (n=30)

Variables	ΔF1+2 (%)	p value	ΔTAT (%)	p value
Age				
≥75 (n=16)	27 [-10-169]	0.449	35 [0-135]	0.409
<75 (n=13)	57 [40-94]		57 [40-91]	
Sex				
Male (n=31)	57 [6-96]	0.547	55 [12-92]	0.645
Female (n=17)	29 [-7-109]		47 [14-97]	
Diabetes				
Yes (n=8)	40 [13-419]	0.428	67 [45-148]	0.159
No (n=21)	47 [-1-94]		40 [0-91]	
Left ventricular ejection fraction				
≥50 (n=20)	37 [0.9-109]	0.658	53 [8-81]	0.317
<50 (n=9)	57 [40-94]		74 [12-308]	
Creatinine				
≥100 (n=12)	29 [-4-95]	0.555	54 [7-71]	0.553
<100 (n=17)	48 [6-159]		55 [13-143]	
Atrial fibrillation type				
Paroxysmal (n=10)	29 [-20-95]	0.355	18 [0-67]	0.158
Chronic (n=19)	57 [6-121]		65 [29-126]	
Stroke				
Yes (n=10)	12 [-8-86]	0.187	56 [29-91]	0.749
No (n=19)	57 [7-122]		51 [0-126]	
Prior bleeding				
Yes (n=27)	41 [-1.3-122]	1.00	51 [3.1-92]	0.253
No (n=2)	44 [40-47]		112 [72-153]	
Spontaneous echo contrast				
Yes (n=12)	46 [-7-111]	0.646	48 [6-134]	0.965
No (n=17)	41 [7-96]		55 [13-74]	
Device size				
≤24 (n=21)	40 [2-96]	0.456	55 [13-126]	0.865
>24 (n=8)	74 [30-127]		56 [6-91]	
Incomplete occlusion				
Yes (n=5)	40 [-1-86]	0.932	126 [91-153]	0.158
No (n=24)	44 [4-109]		45 [7-73]	

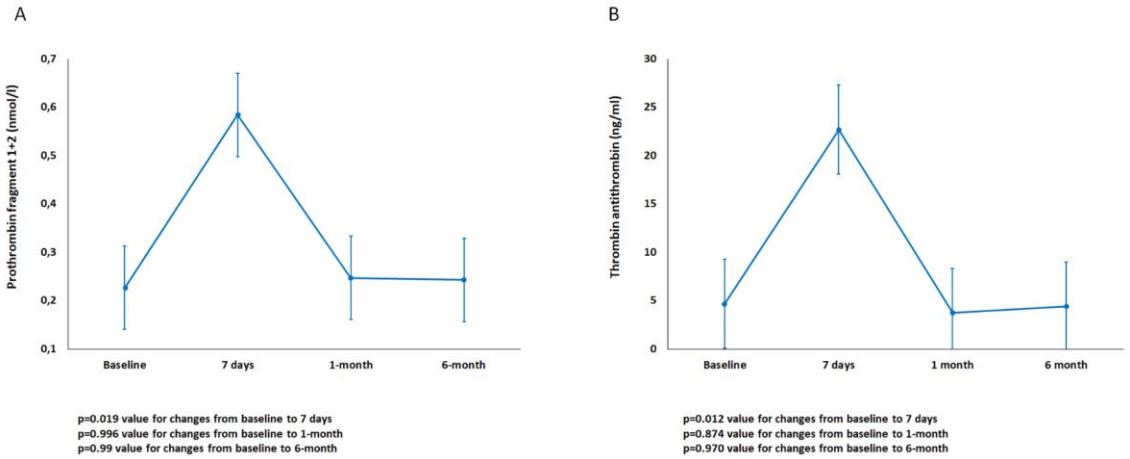
Suboptimal device compression*				
Yes (n=12)	29 [-4-123]	0.615	79 [42-147]	0.136
No (n=17)	48 [7-96]		37 [3-72]	
Deep implantation†				
Yes (n=17)	40 [7-159]	0.487	65 [29-153]	0.154
No (n=11)	48 [-20-94]		39 [0-74]	
Protrusion				
Yes (n=10)	49 [-20-94]	0.464	36 [0-74]	0.108
No (n=18)	44 [7-159]		67 [29-153]	

Values are expressed as median (IQR)
*Device compression <8% or >20%
†Implantation depth from left upper pulmonary vein ridge > 1.0 cm



Supplementary Figure 5.1. Flow chart of the different antithrombotic strategies during the first year following LAAC.

*Four patients died at 6-month follow-up.
AF: Atrial fibrillation; DAPT: Dual antiplatelet therapy; DOAC: Direct oral anticoagulant agents; DRT: Device-related thrombus; FU: follow-up; LAAC: Left atrial appendage closure; LMWH: Low-molecular-weight heparin; SAPT: Single antiplatelet therapy; TEE: Transesophageal echocardiography; VKA: vitamin K antagonists



Supplementary Figure 5.2. Changes in coagulation system activation within the 6 months post-LAAC in patients with device-related thrombus

(A) Changes in prothrombin fragment 1+2 levels post-LAAC. (B) Changes in thrombin-antithrombin levels post-LAAC.

CHAPTER 6. Recurrence of Device-Related Thrombus Following Percutaneous Left Atrial Appendage Closure

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6.1. RÉSUMÉ

Étude multicentrique visant à étudier la récurrence de la thrombose liée au dispositif (TLD) suite à la fermeture percutanée de l'auricule gauche (FAG). Des patients avec une résolution confirmée d'une première TLD post-FAG dans 8 centres du Canada et de l'Europe ont été inclus. L'imagerie de surveillance a été réalisée par échocardiographie transœsophagienne et/ou par tomodensitométrie cardiaque. Parmi 1,344 patients subissant une FAG, 40 TLD ont été observées au cours de la première année de suivi. Les patients avec une imagerie de suivi après résolution d'une première TLD (n=23) ont constitué la base de l'étude. Après un suivi médian de 15 (8-27) mois suite à la résolution du thrombus, la TLD est réapparue chez 8 des 23 patients (34.8%). Après résolution d'une première thrombose, la récidive du thrombus est survenue plus fréquemment chez les patients sous thérapie antiplaquettaire ou sans aucun traitement que chez les patients recevant anticoagulation prolongée (p=0.031).

6.2. ABSTRACT

Background: No data exist on the recurrence of device-related thrombosis (DRT) after left atrial appendage closure (LAAC). This study sought to investigate the incidence and outcomes of recurrent DRT after percutaneous LAAC.

Methods: This multicenter observational study included patients with confirmed resolution of a first DRT following LAAC with any of the approved devices in 8 centers from Canada and Europe, from February 2014 through May 2018. Surveillance imaging was performed by transesophageal echocardiography and/or cardiac computed tomography scan.

Results: Among 1,344 patients undergoing LAAC, 40 DRT were observed within the first year of follow-up. Those patients with follow-up imaging after initial DRT resolution (n=23) formed the basis of the study. After a median follow-up of 15 (8-27) months post-thrombus resolution, DRT recurred in 8 of 23 patients (34.8%), 5 on single antiplatelet therapy and 3 with no antithrombotic medications at the time of recurrence. There were 2 ischemic strokes after initial thrombus resolution, none related to DRT recurrence. Thrombus recurrence occurred more frequently in patients on antiplatelet or no antithrombotic therapy, than in patients on anticoagulation (p=0.031).

Conclusions: DRT recurrence was common (>1/3), particularly among patients not receiving long-term anticoagulation after a first thrombus. Prolonged anticoagulation after resolution of an initial DRT may be considered in patients without absolute contraindications to anticoagulation.

6.3. RESEARCH LETTER

Percutaneous left atrial appendage closure (LAAC) has become a stroke-prevention alternative to oral anticoagulation (OAC).[240] However, there has been increasing concern regarding device-related thrombosis (DRT) post-LAAC, with a reported incidence of ~4% (range: 0 to 17%).[156] Although originally believed to be confined to early (45 days) endothelization, recent reports suggest increased recognition of delayed DRT with extended surveillance imaging.[156, 157] While DRT usually resolves with anticoagulation therapy, no study to date has assessed DRT recurrence. We sought to determine the recurrence rate and clinical outcomes after a first DRT post-LAAC.

This study analyzed patients with resolution of a first DRT following LAAC with any approved device in 8 centers from Europe and Canada, from 2014 through 2018. Only patients with repeat imaging after initial DRT resolution, as assessed by transesophageal echocardiography (TEE) or computed tomography (CT), were included. The study was approved by the institutional review board and all patients gave informed consent. Clinical follow-up and timing of surveillance imaging were performed according to each institution's protocol (TEE in six centers, CT in two). APT/anticoagulant treatment was decided by attending physicians on an individual bleeding risk basis. DRT was defined as a well-circumscribed echo-reflective mass or enhancement defect by TEE or CT, respectively, on the left atrial side of the device.

A total of 1,344 consecutive patients underwent LAAC. DRT was detected on 40 of 1,197 (3.3%) patients undergoing follow-up imaging within the first year post-LAAC. Complete thrombus resolution was documented in 28 of 35 patients (80.0%) with repeat imaging. Patients with surveillance imaging post-resolution of an initial DRT form the basis of the present study (**Figure 6.1**).

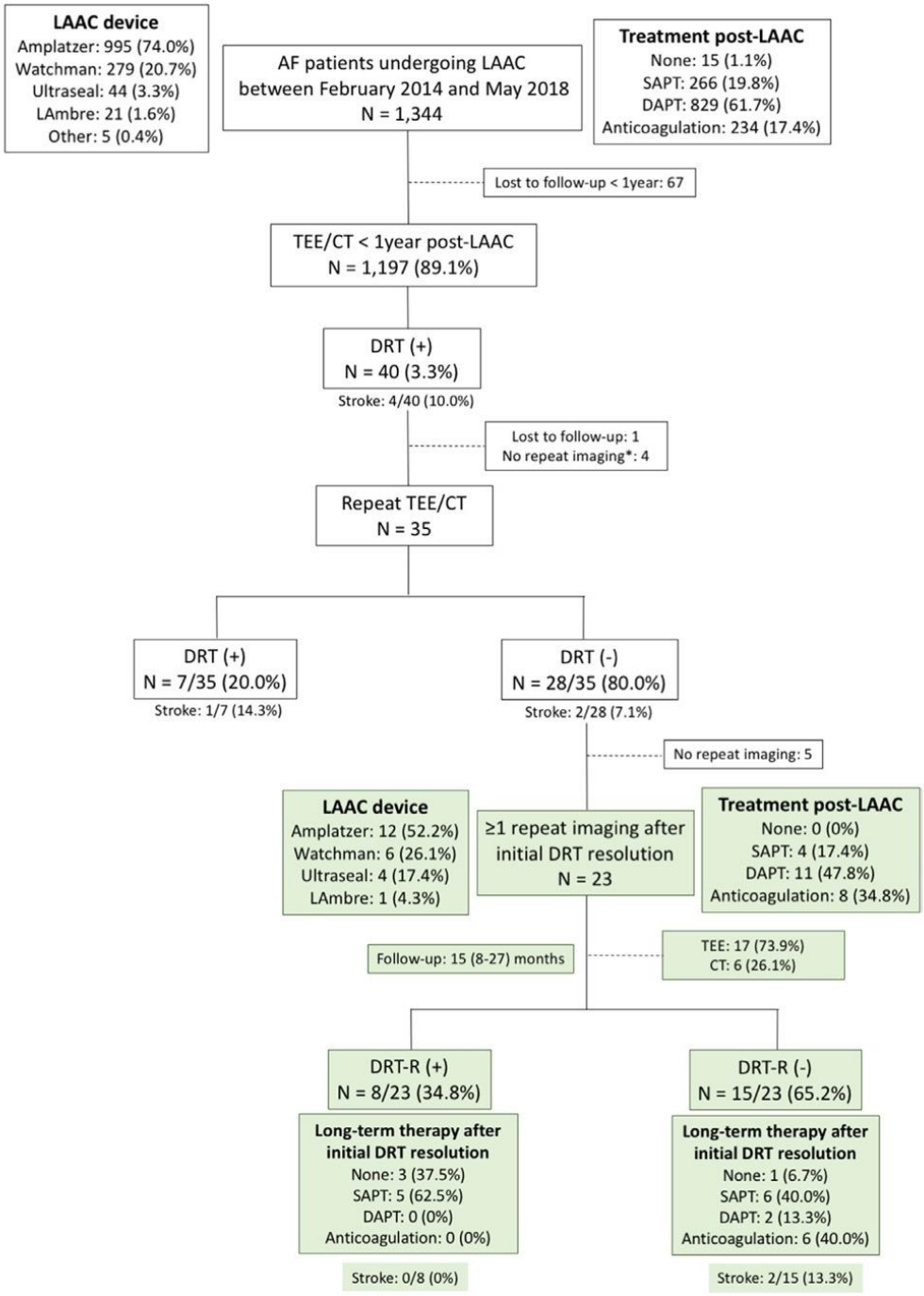

Figure 6.1. Flowchart of Study Population

Among 1,344 patients undergoing LAAC, 40 DRT occurred. Four of these patients suffered a stroke during follow-up (2 patients with initial DRT resolution and no recurrence, 1 with persistent DRT, and 1 with no repeat imaging after initial DRT [*]). Twenty-three patients had follow-up imaging after initial DRT resolution. The recurrence rate of DRT was 34.8% (8 of 23). AF indicates atrial fibrillation; CT, computed tomography; DAPT, dual antiplatelet therapy; DRT, device-related thrombus; DRT-R, device-related thrombus recurrence; LAAC, left atrial appendage closure; SAPT, single antiplatelet therapy; and TEE, transesophageal echocardiography

Twenty-three patients (age: 80±7 years, CHA_2DS_2-VASc score: 4.9±1.4, HAS-BLED score: 3.3±1.1) were included. Most patients (65%) were discharged on single- or dual-antiplatelet therapy (APT) following LAAC. Mean time to first DRT was 3±2 months. Thrombus originated from the central screw/insert in 4 patients (17%) and over the disk or fabric insert in 19 (83%). At the time of thrombus diagnosis, sixteen patients (70%) were receiving single- or dual-APT, four (17%) LMWH and three (13%) no APT/anticoagulant agents. Anticoagulation with therapeutic LMWH (48%) or direct OAC (39%) was initiated or continued in all patients but three (with absolute contraindications for OAC, receiving prophylactic doses of LMWH, dual-APT and none, respectively), with complete thrombus resolution in all patients.

At a median follow-up of 15 (8-27) months post-thrombus resolution, DRT recurred in 8 patients (35%); 5 patients were on single-APT and 3 patients were on no APT/anticoagulation at the time of recurrence. Median time to first imaging study post-resolution was 6 (4-14) months and median time to recurrence was 6 (4-9) months. Surgical excision of a Watchman device was required in one patient. Two ischemic strokes -confirmed by a neurologist- occurred 14 and 9 months after initial DRT resolution, none with evidence of DRT recurrence. One stroke occurred on no APT/anticoagulation therapy, with severe stasis by TEE but no thrombus. A second stroke occurred under aspirin at an outside institution with no imaging at the time of stroke; OAC was initiated, with no evidence of DRT at last follow-up. After initial DRT resolution, patients were stratified according to long-term management: no APT/anticoagulation therapy (n=4), single- or dual-APT (n=13), or vitamin K or non-vitamin K antagonist therapy (n=6). DRT recurrence occurred in 3/4 (75%) of the patients on no APT/anticoagulation, 5/13 (38%) on single- or dual-APT, and none on long-term anticoagulation (p=0.031).

Data on thrombus recurrence has been limited to isolated cases.[285, 286] The present study is the first evaluating DRT recurrence post-LAAC. Thrombus recurrence was common (>1/3), particularly among patients not receiving long-term anticoagulation after a first DRT (~50%). The stroke rate in AF patients with DRT following LAAC in the present

study was similar to that reported in a recent meta-analysis (11.4%).[156] Recurrent DRT appeared to be predominantly clinically silent. Nevertheless, among patients experiencing a stroke after initial DRT resolution, TEE/CT at the time of the event showed dense echo-contrast (n=1) or was not available (n=1), and a relationship between recurrent DRT and stroke cannot be excluded.

Most studies assessing DRT post-LAAC failed to specify the APT/anticoagulation regimen after thrombus resolution, with surveillance imaging being commonly interrupted after DRT resolution. Although the goal of LAAC is to avoid long-term anticoagulation in a high-bleeding risk population, our findings suggest that DRT may carry an increased risk of subsequent thrombosis and that long-term anticoagulation effectively prevents DRT recurrence. Hence, continued anticoagulation should probably be encouraged after a first DRT in the absence of absolute contraindications.

Limitations of our study include lack of core laboratory adjudication and the limited sample size. Imaging follow-up and APT/anticoagulation regimens were not uniform across centers, reflecting real-life LAAC practice. However, these findings raise the importance of close imaging monitoring following thrombus resolution and should stimulate further investigations to address this unmet clinical need.

6.4. DATA SHARING

The data that support the findings of this study are available from the corresponding author and the authors from different participating centers upon reasonable request

6.5. FOUNDING SOURCES

Dr. Asmarats has been supported by a grant from the Fundación Alfonso Martin Escudero. Dr. Rodés-Cabau holds the Canadian Research Chair “Fondation Famille Jacques Larivière” for the Development of Structural Heart Disease Interventions.

6.6. CONFLICT OF INTEREST DISCLOSURES

Dr. Cruz-González is proctor for Boston Scientific, Abbott, Lifetech. Dr. Arzamendi is proctor for Abbott. Dr. Rodés-Cabau has received institutional research grants from Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

DISCUSSION, CLINICAL PERSPECTIVES AND CONCLUSIONS

7.1. DISCUSSION

7.1.1. Role of continuous AF monitoring in high-risk populations

Early recognition of AF plays a major role in preventing embolic stroke. Nevertheless, delays in AF detection are frequent given the often silent and intermittent nature of this cardiac arrhythmia. In recent years, technological innovations in ambulatory electrocardiographic monitoring have permitted longer monitoring periods beyond the traditional 24-48 hours of Holter monitoring, conferring better characterization of AF burden, and more importantly, a greater diagnostic yield for SCAF detection.

In the PARE trial, the first study of this thesis, the authors identified a higher incidence of SCAF than expected (10.1% new-onset atrial tachyarrhythmia, of which 7.6% previously unknown AF), highlighting the high arrhythmic burden encountered among elderly patients currently evaluated for TAVR. Based on the AF prevalence observed in our study through 1-week continuous ECG monitoring, the number needed to screen (NNS) to detect 1 patient with newly diagnosed SCAF was 10-13 people, slightly inferior to that identified by Urena et al.[37] during 24-hour ECG monitoring before TAVR (NNS=16), and much lower than previously reported in other community-based elderly populations using continuous monitoring for up to 2 weeks (NNS 25-40)[32, 287] These findings suggest that given the combination of advanced age, high comorbid burden, and pathophysiological changes linked to aortic stenosis predisposing to rhythm and conduction disturbances, patients currently undergoing TAVR may particularly benefit from this strategy. Of keen interest, prior studies have shown that doubling monitoring duration can translate into up to 80% additional diagnostic yield for SCAF detection.[32] Consequently, the utility of continuous monitoring in TAVR candidates may be even greater by extending heart monitoring beyond 2 to 4 weeks not only before but also after the procedure.

Furthermore, patients undergoing TAVR are at risk of conduction disturbances and need for permanent pacemaker following the procedure. Another major finding of the PARE study was the confirmation that up to one third of rhythm and conduction disorders that occur after TAVR are already present before the procedure, as first suggested by Urena et

al.[37] Although we failed to show a reduction in the need for new-onset permanent pacemaker after TAVR through 1-week monitoring, implementation of extended continuous monitoring in upcoming larger studies may contribute to reduce pacemaker rates and hospital stays post-TAVR. The ongoing RECORD (Assessment of Arrhythmic Burden with Post-Procedural Continuous Electrocardiographic Monitoring in Patients Undergoing Transcatheter Aortic Valve Implantation, NCT04298593) trial, which will include 200 patients undergoing up to 4-week continuous monitoring before and after TAVR will provide helpful information for the management of rhythm and conduction disturbances in this complex group of patients.

7.1.2. Evolution of transcatheter LAAC

Since the early 2000s, several post-marketing registries on percutaneous LAAC have shown dramatic improvements in procedural and late outcomes and decreased complication rates. The second article of this thesis provides an in-depth analysis of the tendencies on patient selection, procedural safety and mid- and long-term clinical outcomes in contemporary LAAC practice.

It is noteworthy that, despite inclusion of higher-risk patients (greater estimated risks of both stroke and bleeding risk by CHA_2DS_2-VAS_c and HAS-BLED scores) and a greater diversity of operators experience in most real-life registries, compared to the PROTECT-AF and PREVAIL trials, the rates of procedural success and procedural-related complications have improved steadily over time. Indeed, the rates of procedural success have increased from 90% in the PROTECT-AF trial to >95% in most contemporary registries, with low complication rates (average pericardial effusion: 1.3% and 1.6%, stroke: 0.2% and 0.6%, device embolization: 0.3% and 0.8%, and peri-procedural death: 0.1% and 0.2%; for Watchman and Amplatzer devices, respectively). Furthermore, there has been a shift in the indications for LAAC over time, from patients eligible for OAC in the early PROTECT-AF and PREVAIL trials, toward patients with contraindications to long-term OAC in ~75% of the patients currently undergoing LAAC with different marketed devices in real-life practice.

Aside from the Watchman and Amulet occluders, several devices are in the clinical investigational pipeline. These novel devices will feature designs and biomaterials that may overcome the shortcomings of current LAAC technologies. In the third article of this thesis, we reported the first-in-human multicenter experience with the Ultraseal device, a novel 2-part occluder with a unique bulb-and-sail design and polyvinyl acetate foam, different from the PET or ePTFE layer used in most other devices. Interestingly, the dual articulating joint connecting the 2 parts may better adapt to sharper LAA anatomies. Of note, there was a 97% success rate and a very low rate of procedural adverse events (2.4%), with less than 1% individual rate of pericardial effusion, device embolization or stroke; consistent with the safety outcomes reported in the latest registries with the Watchman or Amulet devices. No large (>5mm) residual leaks were observed at 6 months. Although the early and mid-term results were certainly encouraging, larger studies need to confirm the long-term safety and efficacy of the Ultraseal and other devices, and contribute to further design improvement of LAAC devices. From a technical standpoint, the common goal of LAAC devices is to provide the easiest and complete anatomical seal with the lowest risk of embolization or thrombus formation. But, first and foremost, the ultimate goal of LAAC must be preventing long-term thromboembolic events while minimizing bleeding risk in AF patients unable to take OAC. In this regard, several studies have shown the long-term (≥2 years) beneficial effect of LAAC, as resumed in **Table 7.1**. Future randomized studies should look into comparative effectiveness between devices and against direct OAC, and evaluate the long-term cost-effectiveness of LAAC.

Table 7.1. Studies on Long-Term Follow-up After Left Atrial Appendage Closure

First author, year	N	Device (%)	CHA_2DS_2-VAS_C	HAS-BLED	Follow-up, months*	Ischemic stroke (%)	Major bleeding (%)	DRT (%)	Death (%)
Nietlispach et al.[201], 2013	152	ND (21) ACP (79)	3.4 ± 1.7	2.4 ± 1.2	32 (1-120)	1.3	2.6	16.0	10.5
López-Mínguez et al.[203], 2015	167	ACP	4 (3-6)	3 (3-4)	22 ± 8	4.4	5.7	8.2	10.8
Wiebe et al.[198], 2015	102	WM	4.3 ± 1.7	2.9 ± 1.2	36 ± 19	2.0	5.9	2.1	9.8
Santoro et al.[288], 2016	134	ACP	4 (3-5)	3 (2-4)	22 ± 12	1.5	2.2	1.4	6.0
Reddy et al.[144], 2017	1,114	WM	3.9 ± 1.5	NA	48 ± 21	6.1**	11.6	NA	14.5
Betts et al.[212], 2017	371	WM (63) ACP (34.7) Lariat (1.7) WC (0.6)	4.2 ± 1.6	3.3 ± 1.2	25 ± 16	1.2	0.9	NA	3.8
Berti et al.[206], 2017	613	ACP/Amulet	4.2 ± 1.5	3.2 ± 1.1	20 ± 17	2.6	3.7	1.8	7.4
Korsholm et al.[205], 2017	107	ACP (67) Amulet (33)	4.4 ± 1.6	4.1 ± 1.1	28 (19-38)	5.6	9.3	1.9	18.7
Regueiro et al.[289], 2018	101	ACP (82) Amulet (3) WM (15)	5 ± 2	4 ± 1	50 ± 16	6.9	19.8	2.5	33.7
López-Mínguez et al.[290], 2018	598 / 176†	ACP (46) Amulet (35) WM (19)	4.4 ± 1.5 / 4.3 ± 1.5†	3.4 ± 1.2 / 3.4 ± 0.9†	23 / 47†	3.0 / 5.7†	7.5 / 9.7†	4.7	13.3 / 17.6†

From Asmarats and Rodés-Cabau,[291] with permission.

ACP: Amplatzer Cardiac Plug, CHA_2DS_2-VAS_c: congestive heart failure, hypertension, age, diabetes, stroke history, vascular disease, sex; DRT: Device-related thrombosis; HAS-BLED: hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly); ND: Non-dedicated devices; WC: WaveCrest; WM: Watchman.
*Follow-up expressed as mean±SD or median (interquartile range); **stroke or systemic embolism; †subgroup with >24 months' follow-up

7.1.3. Impact of transcatheter LAAC on cardiac function

Despite the growing body of evidence supporting the use of LAAC for stroke prevention, concerns remain regarding the potential detrimental effect on cardiac structure and function following the deployment of a foreign body in the LAA with subsequent thrombosis and abolishment of this anatomical structure. To date, several studies have non-invasively evaluated the impact of percutaneous LAAC on left atrial structure and function (**Table 7.2**)

Table 7.2. Changes in cardiac function following percutaneous LAAC

Author, yr	N	Device	LA mechanics	Stroke volume	RAAS	ANS
Hanna et al, 2004[292]	11	PLAATO	=	NA	NA	NA
Jalal et al, 2017[293]	63	ACP Watchman	=	NA	NA	NA
Coisne et al, 2017[258]	33	ACP Watchman	↑	=	NA	NA
Asmarats et al, 2018[294]	31	ACP Watchman Ultraseal	=	=	NA	NA
Madeira et al, 2018	16	ACP	=	NA	NA	NA
Lakkireddy et al, 2018[295]	39	Watchman	NA	NA	=	=
	38	Lariat	NA	NA	↓	↓

ACP: Amplatzer Cardiac Plug; ANS: autonomic nervous system; LA: Left atrium; NA: not assessed; RAAS: renin-angiotensin-aldosterone system

In an early experience with eleven patients undergoing LAAC with the PLAATO device, Hanna et al.[292] showed that endocardial LAAC had little if any impact on the structure and function of the mitral valve and the left upper pulmonary vein. Jalal et al.[293] evaluated the

hemodynamic impact of endocardial LAAC in sixty-three patients, with no evidence of significant left atrial remodeling at 3 months, but a trend toward an increase in left ventricular filling pressure. Interestingly, the LAA HOMEOSTASIS study evaluated the effect of LAAC on systemic homeostasis in 77 patients undergoing LAAC with either endocardial or epicardial devices.[295] The authors observed a significant reduction in the levels of adrenaline, noradrenaline and aldosterone at 24 h and 3 months following epicardial LAAC, with no significant changes in these levels post-endocardial LAAC.

So far, only 2 studies have comprehensively assessed the impact of endocardial LAAC with regard to left atrial phasic functions and left ventricular stroke volume. Coisne et al[258] observed an improvement in both left atrial reservoir and contractile function after LAAC, attributed to modification in left atrial loading conditions (Frank-Starling mechanism), with no significant changes in ventricular function or in left ventricular stroke volume. In the fourth article of this thesis, we confirmed the lack of changes in left ventricular stroke volume, while demonstrating for the first time the lack of relevant changes on left atrial stroke volume and on systemic cardiac output. In addition, we found by using cardiac computed tomography with three-dimensional reconstruction, that even if the LAA accounts for close to 10% of the entire left atrial volume, there is no correlation between the LAA size and the potential hemodynamic effect of excluding it percutaneously. Although we failed to show any improvement in left atrial reservoir or contractile function post-LAAC (likely explained by inclusion of patients in sinus rhythm only, with still preserved atrial compliance and contraction pre-procedure), our findings are in accordance with most prior studies evaluating the possible hemodynamic effect of endocardial LAAC, reporting no significant physiological changes after the procedure (**Table 7.1**). Larger studies combining changes in hemodynamic and neurohormonal modulation with different commercialized endocardial and epicardial devices are warranted.

7.1.4. Antithrombotic therapy and DRT

The choice and duration of post-procedural antithrombotic therapy after LAAC are still unresolved, with DRT remaining the "Achilles Heel" of this stroke prevention therapy. Consequently, numerous trials evaluating different post-procedural antithrombotic strategies are currently underway.

The type and duration of antithrombotic therapy after LAAC have evolved empirically, with dual APT being the most widely used antithrombotic strategy for Amulet implanters, whereas OAC remains the most commonly used regimen among Watchman implanters. So far, very few studies have evaluated the optimal management strategy from a mechanistic view. Rodés-Cabau et al.[150] previously suggested enhanced thrombin generation very early after LAAC in patients discharged on APT, which reached peak levels 7 days after the procedure (but not significant platelet activation), as the most plausible mechanism involved in device thrombosis. In the fifth article of this thesis, which included 78 patients undergoing LAAC with Watchman discharged on either OAC (n=30) or APT (n=48), we observed the same kinetics of coagulation markers, with a peak of prothrombin fragment 1+2 and thrombin-antithrombin III complex at 7 days, progressively returning to baseline levels at 30 days. Furthermore, when we compared kinetics changes according to the immediate post-procedural pharmacotherapy, OAC was associated with a significantly greater attenuation of coagulation system activation (compared with APT), suggesting that short-term OAC may be prioritized over APT after LAAC in patients without contraindications, to protect against DRT formation during endothelialization phase. A 7-day increase in F1+2 levels ≥117% was associated with a higher likelihood of developing DRT after LAAC. All-cause mortality was higher among patients on APT (16.7% vs 0%, p=0.021). In line with our findings, the authors of the ADRIFT (Assessment of Dual Antiplatelet Therapy Versus Rivaroxaban in AF Patients Treated with LAAC, NCT03273322) study, which included 105 patients receiving an Amulet (2/3) or Watchman (1/3) device, reported that low-dose rivaroxaban (compared to dual APT) significantly reduced thrombin generation at 10 days and 3 months. Although 2 DRT occurred in the APT group, no significant difference in net clinical benefit (death, stroke, systemic embolism, infarction or major bleeding) was observed between the 2 groups.[296]

The reported incidence of DRT following LAAC has ranged from 0% to 17%, as shown in the second article of this thesis, reflecting wide differences in the type of LAAC device, type of antithrombotic regimen and timing of surveillance imaging. **Table 7.3**. lists recent studies that addressed the incidence of DRT using different antithrombotic regimens, including three of the articles from our work.

Three major risk factors have been suggested to predispose to DRT: one non-modifiable (patient-specific) and two modifiable (mechanical and pharmacological) factors.[280] Female sex, left ventricular systolic dysfunction (<40%), higher CHA_2DS_2-VAS_c score, spontaneous echo-contrast or pre-existing LAA thrombus have been associated with a higher risk of DRT.[222, 297] Importantly, specific device features such as the proximal connector pin of the Amplatzer ACP device have been linked to an increased thrombus formation.[297] Whether the protruding knob of the Ultraseal device can similarly be associated with increased thrombogenicity, along with the long-term consequences of a different biomaterial (polyvinyl acetate), is an area that deserves further investigation. Insofar, the 5.6% rate of DRT observed in the Ultraseal Multicenter Registry (article 3) remains within the range of previous LAAC studies (5.5% in a recent large French study).[154] Technical issues during device implantation have also been associated with increased risk of DRT, with deep implantation leaving a cul-de-sac between the disk and the left upper pulmonary vein ridge being the only parameter identified in more than one series.[158, 222] In the fifth article of this thesis, baseline spontaneous echo-contrast and permanent AF were associated with an enhanced activation of the coagulation system after LAAC. Although we did not find any association between deep implantation and DRT, thrombosis occurred more frequently in patients with device protrusion, a finding that will require future investigation.

Table 7.3. Recent studies on LAAC using different antithrombotic regimens

	Tzikas, 2016[139]	Boersma, 2019[145]	Hildick-Smith, 2020[298]	Fauchier, 2018[154]	Dukkipati, 2018[157]	Asmarats, 2018[299]	Asmarats, 2019[284]	Asmarats, 2020[300]
Device	ACP	WM	Amulet	ACP, Amulet, WM	WM	Ultraseal	Any	WM
N	1,047	1,020	1,088	469	1,739	126	1,344	78
Registry design	Retrospective	Prospective	Prospective	Retrospective	Prospective	Prospective	Retrospective	Prospective
Drug, %	-	DAPT (60) SAP (7) OAC (27) None (6)	DAPT (58) SAPT (23) OAC (11) LMWH (7)	DAPT (23) SAPT (36) OAC (33) None (8)	OAC (100)	DAPT (83) SAPT (7) OAC (4) LMWH (5) None (1)	DAPT (62) SAPT (20) OAC (17) None (1)	DAPT (40) SAPT (22) OAC (38)
Imaging FU, mo	3-11	1-3	1-3	2.8 ± 2.5	12	1-6	≤12	1-3
Clinical FU, mo	13 (6-25)	24	24	13 ± 13	49	6 (3-10)	15 (8-27)	13 (3-25)
DRT, %	3.9	4.1	1.6	5.5	3.7	5.6	3.3	6.4
DRT recurrence,%	-	-	-	-	-	-	34.8	-
Bleeding, %	5.7	2.7/yr	10.1/y (year 1) 4.0/yr (year 2)	3.8	-	3.3	-	8.9
Stroke, %	2.1	1.3/yr	2.2/yr	4.0	6.28/yr (DRT) 1.65/ yr (nDRT)	0.8	10 (DRT)	3.8

ACP: Amplatzer Cardiac Plug; DAPT: dual antiplatelet therapy; DRT: device-related thrombus; FU: follow-up; LMWH: low-molecular-weight-heparin; nDRT: non-DRT patients; OAC: oral anticoagulation; SAPT: single antiplatelet therapy; WM: Watchman

The potential relationship between post-implantation antithrombotic pharmacotherapy and DRT formation remains a matter of controversy. Two-year data from the EWOLUTION study found no association between the type of antithrombotic regimen and the presence of DRT on the device (p=0.208).[145] In a meta-analysis including more than 12,000 patients from 83 observational studies, Osman et al.[301] reported no differences in the occurrence of DRT, stroke, major bleeding or death in patients treated with short-term OAC or APT following LAAC. Conversely, Fauchier et al.[154] suggested a link between post-implantation regimen and DRT, with dual APT and OAC being associated with a lower risk of DRT (HR: 0.10 and 0.26, for dual APT and OAC, respectively). A recent propensity-matched analysis of the PROTECT-AF and PREVAIL trials, the CAP (Continued Access to PROTECT-AF), CAP2 (Continued Access to PREVAIL), ASAP and EWOLUTION registries, found a higher rate of DRT with APT than with OAC (3.1% vs 1.4%, p=0.014), although both strategies showed similar safety and efficacy in terms of thromboembolic protection and non-procedure-related major bleeding.[278]

The last article of this thesis explores for the first time the recurrence rate of DRT following LAAC. In this multicenter experience, which included more than 1,300 patients undergoing LAAC with any marketed device in 8 centers from Canada and Europe, the incidence of DRT was 3.3%, with thrombus on the device recurring in more than one third (35%) of the patients after complete resolution of an initial DRT. Two patients experienced a stroke after initial DRT resolution, although no difference in freedom from ischemic stroke was observed in patients with or without recurrence, likely due to the relative small number of patients with delayed surveillance imaging after initial thrombus resolution (n=23). Importantly, we found an association between medication regimen and DRT recurrence, occurring more frequently in those patients who stopped any antithrombotic therapy after initial DRT resolution, compared with those who continued OAC (75% vs 0%, p=0.031).

To date, most studies evaluating the incidence of DRT post-LAAC failed to address its recurrence. A recent Chinese single-center experience including 319 patients, noted a DRT incidence of 14/319 (4.5%), with complete thrombus resolution in 6/14 (43%) patients, and subsequent recurrence in 3 patients after OAC discontinuation.[302] In a meta-analysis analyzing 40 DRT patients, the reported recurrence rate was lower (2/40: 5%), although the number of patients with extended imaging follow-up was poorly defined, likely translating an underestimation of the real recurrence rate.[223]

7.2. CLINICAL IMPLICATIONS

The studies presented in this thesis provide novel insights into the conundrum of stroke prevention, that may be incorporated into the daily management of patients with non-valvular AF.

The results of the PARE study suggest that the use of a prolonged continuous ECG monitoring in elderly patients with severe aortic stenosis undergoing TAVR can be useful for detecting previously unknown arrhythmia and implementing specific therapies (therapeutic changes required in up to one-third of the patients) prior to the onset of arrhythmia-related symptoms. This may be particularly relevant with regard to SCAF in patients at high thromboembolic risk, in which early OAC initiation (or LAAC if appropriate) may prevent future cerebrovascular events. Although different SCAF burden thresholds ranging from 5 min to 24 hours have been proposed, most stem from patients with cardiac implantable electronic devices, and the minimum duration of SCAF at which OAC is advisable is still of debate. There is a need for prospective studies clarifying the cut-off values for SCAF that increase thromboembolic risk for both invasive and non-invasive continuous ambulatory cardiac rhythm monitoring devices. The usefulness of prolonged continuous monitoring may extend beyond the scope of TAVR, in other high-risk populations with expected high arrhythmic burden (eg. patients with chronic kidney disease or those undergoing transcatheter mitral valve repair or replacement). Whether this suggested approach to therapy will be cost-effective in reducing arrhythmic-related morbidity and hospitalizations remains to be determined.

The Ultraseal Multicenter Registry adds a novel tool to the therapeutic armamentarium for stroke prevention for patients with AF, with promising data at mid-term follow-up. The device has unique features, such as the articulating hub for managing sharp takeoffs, which enables less stress and potentially a better approximation of the LAA ostium and landing zone. One of the most remarkable points is the security of implantation given the softness of the distal bulb, with safety outcomes that compare favorably to those of other marketed devices, which may be especially useful for less experienced implanters. Importantly, it may better suit in small LAA anatomies (landing zone ≥11 mm), which currently represent the major limitation for most marketed devices, emerging as a potential target for this new technology. Also, the use of different biomaterials may help to mitigate DRT formation, although this hypothesis will need to be evaluated in larger studies. Overall, this initial worldwide experience provides preliminary evidence for the integration of this device into daily clinical practice.

Concerns regarding the potential interaction with cardiac function and hemodynamic impact led to the fourth study of the present thesis. In accordance to previously published data (mainly preclinical or surgical), percutaneous LAAC in patients with paroxysmal AF with either the Amplatzer and Watchman devices did not result into acute hemodynamic changes (stroke volume, cardiac output). Of note, all patients were in sinus rhythm the time of echocardiography and the procedure, and thus, a higher likelihood of hemodynamic changes would have been expected in those patients (preserved LAA contraction, short history of AF with less fibrosis and more compliant atriums). These findings are reassuring, considering the frailty and high comorbidity burden of patients currently referred for LAAC, and may be even more important for those patients with impaired left ventricular function and limited contractile reserve.

The fifth and sixth works of the present studies add valuable data to two of the most debatable issues in the field of LAAC: post-LAAC antithrombotic regimen and DRT. We provide for the first time, insights into the mechanistic effects of OAC vs APT following LAAC, the most frequently used strategies for DRT prevention during device endothelialization in contemporary practice. Importantly, the use of short-term (45-day)

OAC significantly attenuated the activation of the coagulation system within 7 days after LAAC, compared to APT. Hence, the most pragmatic approach would be to prioritize OAC in the absence of contraindications, until confirmation of complete LAAC through transesophageal echocardiography or computed tomography. Patients with preexisting spontaneous echo-contrast at baseline transesophageal echocardiography, as well as those experiencing a DRT during follow-up exhibited a greater activation of the coagulation system activation. According to our findings, the presence of echocardiographic atrial smoke-like swirling pattern along with a peak increase in F1+2 levels by ≥117% within 7 days post-LAAC, may help to promptly identify those patients more likely to develop a DRT and, consequently, those who will benefit the most from OAC therapy following LAAC. In addition, close monitoring of the activation of the coagulation system may help physicians to assess the effectiveness and adapt the duration of anticoagulation therapy for treating DRT on a patient-by-patient basis, as well for surveilling eventual thrombus recurrence, although this will need to be determined in future studies.

Finally, we report for the first time the phenomenon of recurrent DRT, a novel clinically relevant entity, which may occur in more than one third of the patients after complete resolution of an initial thrombus. Interestingly, we found a relation between the long-term antithrombotic management after initial DRT resolution and the risk of thrombus recurrence, occurring in up to one-half of the patients who did not receive long-term OAC therapy after a first DRT. Our findings raise two questions of major importance: the need for extending surveillance imaging after LAAC (particularly in those patients who develop a thrombus on the device, with keen importance of delayed imaging to survey for DRT recurrence), and the effectiveness of long-term anticoagulation in preventing reappearance of thrombus, which should probably be considered in those patients who experience a first DRT and do not have an absolute contraindication to OAC. Rather than a safety warning, and given the retrospective non-randomized nature of the study, our findings should be interpreted with caution and as hypothesis-generating for further investigation to improve our knowledge of this novel entity.

7.3. FUTURE PERSPECTIVES

The present thesis provides important data on the usefulness of latest generation long-term monitoring devices in high-risk elderly patients, and novel evidence on the impact (hemodynamic, biological and ultimately clinical) of transcatheter LAAC with current and emerging devices. However, several questions remain unanswered. First and foremost, identify which patients are likely to have the greatest benefit from LAAC over medical therapy (in OAC ineligible patients) or over the best available direct OAC therapy. For instance, patients in which a potential future bleeding source cannot be fully eliminated (prior intracranial hemorrhage, amyloid angiopathy, or prior gastrointestinal bleeding, the latter with high recurrence rates up to 40% within 1 year),[102, 103] or patients with recurrent stroke despite adequate anticoagulation after excluding other plausible causes.[91, 92] In this respect, the ASAP-TOO (Assessment of the Watchman device in patients unsuitable for OAC, NCT02928497) and the STROKECLOSE (Prevention of stroke by LAAC in AF patients after intracerebral hemorrhage, NCT02830152) trials will randomize AF patients ineligible for OAC or with previous intracranial hemorrhage to LAAC or medical therapy (antiplatelet therapy or nothing). Also, considering the scarcity of randomized data directly comparing LAAC against direct OAC, the ongoing CATALYST (Amulet LAAC vs NOAC, NCT04226547), OPTION (Comparison of anticoagulation with LAAC after AF ablation, NCT03795298), the CHAMPION-AF and the OCCLUSION-AF (LAAC versus novel OAC for stroke prevention in AF, NCT03642509), which are recruiting AF patients to LAAC versus direct OAC, will provide invaluable information. Second, there is a need for randomized trials comparing the broad spectrum of currently available devices, since Watchman remains the only device evaluated in a randomized controlled way to date. This remains an important question of clinical interest, which can support and guide device selection. The results of the AMULET IDE (Amulet LAAC trial, NCT02879448) trial, which compared Amulet to Watchman, are eagerly awaited. Third, prospective examination of the optimal antithrombotic regimen after LAAC, as well as evidence-based guidelines for the prevention and management of DRT post-LAAC are urgently needed. In this regard, the ANDES (Short-Term Anticoagulation Versus Antiplatelet Therapy for Preventing Device Thrombosis Following LAAC, NCT03568890), will provide the first randomized data on the use of short-term OAC vs DAPT for preventing DRT post-LAAC in 350

patients that will be followed for a 2-year period, and will shed light on this controversial issue. Finally, the effect of cardiac rhythm on the risk for development of DRT after LAAC has yet to be defined. Whether the use of continuous long-term monitoring in patients undergoing LAAC may play a role in explaining the pathogenesis of DRT remains a question for future investigation.

7.4. CONCLUSIONS

AF is a growing epidemic, and its prevalence continues to rise worldwide. Stroke prevention remains a major goal and an unmet clinical need in patients with non-valvular AF. Although OAC therapy remains the cornerstone therapy, the compliance in contemporary practice is still limited and many high-risk elderly patients are not eligible to OAC. Over the past 2 decades, we have witnessed a significant growth of percutaneous LAAC, which has become the only possible strategy for thromboembolic prevention for many AF patients at increased bleeding risk who cannot tolerate long-term OAC treatment. The main findings of the present PhD research project can be summarized as follows:

(i) In high-risk elderly populations screened for transcatheter heart valve interventions, prolonged continuous ECG monitoring detected previously unrecognized SCAF in one-tenth of the patients and identified a previously unknown arrhythmia in nearly one-half of them. Likewise, prolonged continuous monitoring pre-TAVR enabled early detection of a third of new-onset arrhythmic events post-TAVR (preexisting, unrelated to the procedure). Newly diagnosed arrhythmic events changed the clinical management in ~30% of the patients.

(ii) Increased operator skills, technological iterations (second-generation Amulet and Watchman FLX) and innovations (Ultraseal, LAmbre, Occlutech), and improvement in patient selection, have significantly decreased peri-procedural complications (<2%) and improved success rates (>95%).

(iii) Although the LAA represents ~10% of the overall left atrium, LAAC does not result in any detrimental acute hemodynamic effect, including either ejection fraction, stroke volume or cardiac output.

(iv) Short-term OAC (compared with APT) significantly reduces coagulation system activation following LAAC with Watchman, and pragmatically, may be the antithrombotic strategy of choice in patients with no contraindications until complete closure has been confirmed by 45-day transesophageal echocardiography or computed tomography. Combination of baseline spontaneous echo-contrast and an increase in F1+2 levels by ≥117% within 7 days post-LAAC may help identify patients at risk for DRT.

(v) Recurrence of DRT after complete resolution of an initial DRT was high (35%), underscoring the importance of delayed surveillance imaging after thrombus resolution. Recurrence of DRT was more frequently documented in patients who discontinued any antithrombotic therapy, suggesting a potential benefit of maintaining long-term OAC after resolution of a first DRT, in the absence of absolute contraindications.

In conclusion, percutaneous LAAC has become safer and a feasible alternative to OAC for stroke prevention in patients with nonvalvular AF. Despite the large body of literature supporting the safety and (mid- and long-term) efficacy of this stroke prevention strategy, there has been a growing recognition of the potential for thrombus formation on the device and the urgent need for a uniform strategy regarding post-implantation antithrombotic regimen. Although our results appear to favor OAC therapy following LAAC (less post-procedural enhanced thrombin generation and lower risk of thrombus recurrence on the surface of the device after a first episode), future randomized studies should elucidate whether discharge antithrombotic medication regimen is related to an increased risk of DRT formation or recurrence, and hopefully, reduce the rate of DRT and improve clinical efficacy in the years to come.

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