Comparison of Amplatzer Amulet vs Watchman device in patients undergoing left atrial appendage closure: the SWISS-APERO randomized clinical trial

Clinical Study Protocol

Study Type:	Clinical trial of medical device
Study Categorisation:	Risk category A
Study Registration:	*www.clinicaltrials.gov NCT03399851*
Sponsor, Sponsor-Investigator:	InselgruppeAG -Bern University Hospital, 3010 Bern, Switzerland Prof. Dr. med. Lorenz Räber, Lorenz.Raeber@insel.ch
Coordinating-Investigator	Prof. Marco Valgimigli MD PhD Cardiocentro Ticino Via Tesserete 48 ,CH-6900 Lugano marco.valgimigli@cardiocentro.org
InvestigationalProducts:	Amplatzer Amulet St. Jude-Abbott; Watchman/FLX Boston Scientific.
Protocol Version and Date:	Version 5 /29.05.2020

Signature Page(s)

Project number	www.clinicaltrials.gov NCT03399851
Project Title	Comparison of Amplatzer Amulet vs Watchman device in patients undergoing left atrial appendage closure: the SWISS-APERO randomized clinical trial

The Sponsor-Investigator and trial statistician have approved the protocol Version 5 /29.05.2020, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki[1], ICH-GCP guidelines[2,3] or ISO 14155[4] norm if applicable and the local legally applicable requirements.

Sponsor-Investigator:

Prof.Dr.med. Räber, Lorenz, Department of Cardiology, Bern University Hospital, Bern, Switzerland

Place/Date _____ Signature _____

The Coordinating-Investigator has approved this trial protocol and agrees to coordinate and conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Coordinating-Investigator:

Prof. Marco Valgimigli, MD PhD, Cardiocentro Ticino Via Tesserete 48 ,CH-6900 Lugano; Switzerland

Place/Date _____ Signature _____

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site

Principal investigator

Place/Date	Signature

**Note:* In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

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STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Inselgruppe AG - Inselspital - Bern University Hospital, 3010 Bern, Switzerland / Prof. Dr. med. Lorenz Räber, Cardiology, Bern University Hospital, Bern, Switzerland
Coordinating Investigator	Prof. Marco Valgimigli, MD PhD, Cardiocentro Ticino Via Tesserete 48 ,CH-6900 Lugano; Switzerland
Study Title:	Comparison of Amplatzer Amulet vs Watchman device in patients undergoing left atrial appendage closure: a randomized clinical trial
Short Title:	SWISS-APEROrandomized clinical trial
Protocol Version and Date:	Version 5 /29.05.2020
Trial registration:	www.clinicaltrials.gov NCT03399851
Study category and Rationale	Clinical trial of device products, risk category A: all products are authorized in Switzerland and their use is according to the instructions for use.
Clinical Phase:	Phase 4
Background and Rationale:	Non-valvular Atrial fibrillation (NVAF) is the most common cardiac arrhythmia and a major cause of morbidity and mortality because of cardioembolic stroke. Cardiac embolism due to AF causes up to 25% of all ischemic strokes, which makes it socioeconomically highly relevant. Oral anticoagulation (OAC) with vitamin K antagonists (VKA) or Non-vitamin K antagonist anticoagulant (NOAC) is the most effective prophylaxis for stroke in AF. Yet, (N)OAC therapy is associated with a significant bleeding liability and long-term (N)OAC therapy in patients with NVAF and concomitant high bleeding risk poses safety issues in a sizable and growing population in clinical practice. Post-mortem and echocardiographic studies have shown that the vast majority of all cardiac thrombi in patients with NVAF form in the left atrial appendage (LAA). Thus, a new and emerging therapeutic option in this high-risk patient population is the exclusion of the LAA cavity from the circulation via percutaneous intervention. Currently, the Amplatzer ACP/Amulet ™ (St. Jude Medical-Abbott), and the Watchman ™ (Boston Scientific, Natick, MA, USA) are the devices with most clinical experience reported to date for percutaneous closure of LAA. The Watchman was tested in the setting of two randomized control trials, which demonstrated the safety of the procedure and the non-inferiority in terms of stroke reduction compared to OAC. A second-generation device, the Watchman FLX was developed and released for simplified implantation to fit a wider range of patients and to enhance sealing within the left atrial appendage. It gained the CE mark at the begin of 2019. Until a few years ago in Europe the device most frequently utilized for LAA closure was the Amplatzer Cardiac Plug™ (ACP, St. Jude Medical-Abbott), which gained CE approval in late 2008. There is no RCT comparing ACP with OAC, but many prospective and retrospective studies had shown the same safety profile and the non-inferiority with the OAC. A second-generation device, the Amulet™, was developed and released in 2013 for easier delivery, better coverage, and reduction of complications. A critical step for each LAA closure procedure is the appraisal of LAA residual or new patency/leaks after device implantation. In the setting of available randomized trials (currently only limited to the Watchman device), successful closure was defined by the presence of a peridevice flow ≤ 5 mm assessed with TEE 45 days after the procedure. In these trials, as well as according to the current instruction for use of Watchman, the appraisal of residual leaks 45 days after LAAC was/is considered mandatory for a correct postprocedural management of pharmacotherapy (in terms of continuation or reinstitution of OAC therapy). Furthermore, there is a growing attention to the natural history of peridevice leaks given their unpredictable evolution. Currently the gold standard for the assessment of LAA patency after closure is the TEE. However it is an invasive and operator dependent examination, and replacing it with an alternative non-invasive exam is also desirable for patient's comfort In the last years, several groups (including ours) assessed the value of CCTA as non-invasive post-procedural surveillance imaging modality after endovascular LAA closure to evaluate residual leak and reported higher sensitivity for CCTA as compared to TEE in the identification of LAA residual patency. There are currently no randomized controlled trials assessing the degree of LAA closure between Amulet and Watchman/FLX.
Primary Objective:	To assess whether Amplatzer Amulet is superior to Watchman/FLX in terms of degree of LAA occlusion as evaluated by CCTA 45 days after implantation.

Outcome(s):	The primary outcome is the composite of LAA patency at 45 day CCTA or the crossover from one device to the other device based on morphological/anatomical considerations during device implantation. Secondary outcome include: • LAA patency (arterial and/or venous phase) at 45 day CCTA and 13-month CCTA in the per protocol and as treated populations • All cause of death, stroke, systemic or pulmonary embolism and spontaneous MI • Cardiovascular death • Ischemic stroke • Hemorrhagic stroke • Bleeding events according to the BARC classification at each follow-up. • Procedure-related complications • Rate of patients on (N)OAC at 45 days and 6 months • Device related thrombosis (DRT) at 45 day TEE/CCTA and 13-month CCTA in the per protocol and as treated populations • Feasibility outcome (number of device implantation attempts, total time procedure, x-ray dose and total contrast dose used in the procedure) • LAA patency at 45 day TEE in the per protocol and as treated populations
Study design:	Randomized open-label multicentre trial.
Inclusion / Exclusion criteria:	Inclusion criteria • Written informed consent • Male or female subject aged 18 years or more with no upper age limit and willing to comply with the protocol • Indication to a LAA closure as indicated in study population (HAS BLEED ≥3 or High bleeding risk as defined by Munich consensus document and CHA_2DS_2-VASc≥2). Exclusion criteria: • New York Heart Association class IV congestive heart failure • ASD or atrial septal repair or closure device • Single occurrence of AF • Cardioversion or ablation procedure planned within 30 days • Implanted mechanical valve prosthesis • Heart transplantation • Enrolled in another IDE or IND investigation of a cardiovascular device or an investigational drug • Female of childbearing potential (age < 50 years and last menstruation within the last 12 months), who did not undergo tubal ligation, ovariectomy or hysterectomy • Active infection of any kind • Severe chronic kidney insufficiency (CrCl< 30 ml/min) • Terminal illness with life expectancy < 1 yr • Echocardiographic exclusion criteria • LVEF < 20% • Intra-cardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days before implant • Significant mitral valve stenosis (ie, MV <1.5 cm2) • Complex aortic atheroma with mobile plaque of the descending aorta and/or aortic arch • Cardiac tumor.

Measurements and procedures:	Patients with indication to LAA closure will be randomly assigned in a 1:1 ratio to Amulet or Watchman/FLX device implantation. In the event that the patient is randomized to the Watchman/FLX arm, the operator will be able to choose, on the basis of clinical reasons, if implant Watchman or the new generation Watchman FLX (if available in the center).Study procedures will be as follows: • A CCTA will be performed before the procedure as per standard of care in order to obtain the morphological features of LAA (useful for the procedure planning) and to exclude the presence of LAA thrombus. • Implantation will be performed according to device specific instruction for use and latest consensus document[5], based on preprocedural CCTA images, TEE guidance and angiography. • After the procedure, patients will receive acetylsalicylic acid (ASA) and clopidogrelor (N)OAC at discretion of the treating physician(according to the bleeding risk, the stroke risk and intra-procedural TEE evaluation) for 45 days and then will undergo TEE as well as CCTA) assessment. o If a residual peridevice leak flow > 5 mm or a an intra-cardiacthrombus is detected, treatment with ASA and (N)OAC should be considered up a sequential TEE evaluation at 6 months. Final decision to implement an OAC regimen with or without ASA will eventually be left to the discretion of the treating physician taking the ischemic ad bleeding risk into account; o If residual peridevice leak flow ≤ 5 mm, patients will receive ASA and clopidogrel or (N)OAC (at discretion of the treating physician according to the bleeding and stroke risks)up until 3 months after procedure. Thereafter, monotherapy with ASA will be continued until 12 months after procedure. Further follow-ups will take place at 13months and yearly until 5 years.
Study Product / Intervention:	The WATCHMAN (Atritech, Boston Scientific, Natick, MA, USA) LAAC technology consists of the Access System (Access Sheath and Dilator) and Delivery System (Delivery Catheter and WATCHMAN Device). The Access System and Delivery System permit Device placement in the left atrial appendage (LAA) via femoral venous access and inter-atrial septum crossing into the left atrium. WATCHMAN device is a self-expanding nitinol structure with a porous covering on the proximal face. The device is constrained within the Delivery System until deployment in the LAA. The Device is available in 5 sizes from 21 to 33 mm. The new generation Watchman FLX has a shorter device length and a less taper angle to simplify implantation and to fit a wider range of patients, Furthermore, the frame of the new device is designed to enhance sealing within the left atrial appendage. The AMPLATZER Amulet (St. Jude Medical-Abbott) is a self-expanding device made of nitinol that has a distal lobe and a proximal disc, connected by an articulated waist. The device lobe has six to 10 pairs of stabilising wires and is meant to be implanted in the proximal 10-15 mm of the left atrial appendage (LAA), whereas the device disc is intended to cover the ostium at the left atrial side. The proximal female screw is recessed to minimise thrombus formation on the disc and potentially facilitate re-attachment of the device to the pusher screw. The lobe sizes range from 16 to 34 mm.
Number of Participants with Rationale:	Total number of patients with primary endpoint assessment: 200 100 patients in the Watchman/FLX group 100 patients in the Amplatzer Amulet group Sample size is calculated to state superiority of Amplatzer Amulet compared with Watchman/FLX
Study Duration:	8 years
Study Schedule:	February 2018 February 2026

Statistical Considerations:	Assuming an incidence of the primary composite end-point in the range of 50% in the Watchman/FLX group, which is a conservative estimate based on previous reports, 200 patients will provide greater than 80% power to prove superiority of Amulet as compared to Watchman/FLX assuming a 40% risk reduction (i.e. corresponding to an event rate in the range of 30%) and a significance level of 5% (alpha). Primary and secondary end points will be analysed on an intention-to-treat basis. Additional analyses of the primary endpoint will be also carried out in the per-protocol and as-treated populations. Similarly, LAA patency and DRT at 45-day and 13-month CCTA and at 45-day TEE as well as clinical outcomes will also be analyzed in the per-protocol and as-treated population.Categorical outcome measures will compared using a $\chi 2$ test or Fisher exact test as required. Continuous variables will be compared using a 2-sided unpaired t test or a Mann-Whitney test, as appropriate. Estimation of the cumulative incidence of safety and efficacy endpoints will be performed using the Kaplan-Meier method, and event rates will be compared by the log rank test The estimated relative risk (RR) is the ratio of the risk probabilities, and a confidence interval will constructed based on a logarithmic transformation. Correlations between variables will analysed with a Cox regression.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

ABBREVIATIONS

AF	Atrial fibrillation
ACP	Amplazer Cardiac Plug
ACT	Activated clotting time
AE	Adverse Event
AESI	Adverse Event of Special Interest
ASA	Acetylsalicylic acid
BARC	Bleeding Academic research Consortium
CA	Competent Authority (e.g. Swiss medic)
CCTA	Cardiac computed tomography angiography
CEC	Clinical Events Committee
CTU	Clinical Trials Unit
CV	Cardiovascular
DAPT	Dual antiplatelet therapy
DRT	Device related Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	EuropeanMedicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H1	Alternative hypothesis
HBR	High bleeding risk
Ho	Null hypothesis
ICE	Intracardiac echocardiography
ISO	International Organisation for Standardisation
LAA	Left atrial appendage
LAAC	Left atrial appendage closure
LUPV	Left upper pulmonary vein

NOAC	New oral anti-coagulation
NVAF	Non-valvular atrial fibrillation
OAC	Oral anti-coagulation
PDL	Perideviceleak
PI	Principal Investigator
PREVAIL	Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy
PROTECT AF	Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial
RCT	Randomized clinical trial
SAE	Serious Adverse Event
TEE	Transesophageal echocardiography
TIA	Transient Ischemic Attack
VKA	Vitamin K antagonist

STUDY SCHEDULE

Study Periods	Enrolment	Procedure	Post procedural Hospital discharge	45- day follow up	6- month follow up	13-month follow up	2- year follow up	3- year follow up	4-year follow up	5-year follow up
Time point	1	2	3	4	5	6	7	8	9	10
Time	-90 / 0 d	0 d	up to 48 h	45±7 d	180±7 d	395 ±30 d	730±30 d	1095 ±30 d	1460 ±30 d	1825 ±30 d
Type of follow up[1]				Medical contact	Medical contact orphone[2]	Medical contact or phone[2]	Medical contact or phone[2]	Medical contact or phone[2]	Medical contact or phone[2]	Medical contact or phone[2]
Patient Information and Informed Consent	x									
Demographics	x									
Medical History	x			x		x	x	x	x	x
In- /Exclusion Criteria	x									
Physical Examination	x		x	x		(x)	(x)	(x)	(x)	(x)
Vital Signs	x		x	x		x	x	x	x	x
Laboratory test[2]	x		x							
Randomization	X[5]									
12 lead ECG	x	x	x	x		(x)	(x)	(x)	(x)	(x)
TEE	x[3]	x[4]		x[4]	x[3]	(x)[3]				
CCTA	x[4]			X[5]		(x)[5]				
Concomitant therapy, Intervention	x		x	x	x	x	x	x	x	x
LAAC		x								
AESI[6] and SAE collection		x	x	x	x	x	x	x	x	x

[1]All types of follow up will be described in Section 9.1.

[2]In case of impossibility of a follow up by medical contact a telephone contact should be performed. It will consist of reporting vital status, adverse events of special interest (as defined in 11.1) and pharmacotherapy.

[3]Performed if clinically indicated

[4]:As per standard of care

[5]:Study specific intervention

[6]As defined in 11.1

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor

This is an Investigator Initiated Trial, the Sponsor is Inselgruppe AG - Bern University Hospital, 3010 Bern, Switzerland.

1.2 Principal Investigator(s)

Sponsor Investigator/CoordinatingInvestigator:

Prof. Dr med, Lorenz Räber, InselspitalUniversitätsspital, Freiburgstrasse 8, 3010 Bern (CH). Phone: +41 31 632 2111

A Local Principal Investigators will be appointed at every center involved in the trial.

1.3 Statistician

Clinical Trials Unit – University of Bern - Finkenhubelweg 11, 3012 Bern, Phone +41 31 631 35 56

1.4 Any other relevant Committee, Person, Organisation, Institution

Clinical Event Committee for Adjudication of clinical events endpoints will be defined prior to the first patient enrolment.

2. ETHICAL AND REGULATORY ASPECTS

The decision of the competent Ethics Committee (EC) concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

www.clinicaltrials.gov NCT03399851

www.kofam.ch

2.2 Categorisation of study

Category A

This is a clinical trial of medical devices. The devices used for the study (Amplatzer Amulet and Watchman/FLX) are authorised in Switzerland and used in accordance with the Instructions for Use (Appendix 2). The risk category is A.

Premature study end or interruption of the study will be reported to the EC within 15 days. The regular end of the study will be reported within 90 days, the final study report shall be submitted within one year after study end.

2.3 Ethical Conduct of the Study and declaration of interests

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the European Directive on medical devices 93/42/EEC and the ISO Norm 14155, the Swiss Law and Swiss regulatory authority's requirements. The EC will receive annual safety reports and be informed about study stop/end in agreement with local requirements.

The study will be conducted with intellectual, financial and property independence. The financial support from St. Jude Medical-Abbott (see section 15) will be disclosed.

2.4 Patient Information and Informed Consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study

and providing sufficient information for participant to make an informed decision about their participation in the study.

The patient information sheet and the consent form will be submitted to the EC to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant on the procedure's day (or on the day before) should read and consider the statement before signing and dating the informed consent form, and will be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.5 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files and eCRF.

For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.6 Early termination of the study

The Sponsor-Investigator (and any competent authority) may terminate the study prematurely according to certain circumstances, for example:

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk, respectively,
- Alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- Early evidence of benefit or harm of the experimental intervention.

2.7 Protocol amendments

Substantial amendments are only implemented after approval of the EC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible.

All non-substantial amendments are communicated to the EC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Atrial fibrillation (AF) is the most common cardiac arrhythmia and a major cause of morbidity and mortality because of cardioembolic stroke. The prevalence of AF increases with age up to 15% in high octogenarians and continues to grow rapidly because the proportion of the aging population is increasing just as the prevalence of predisposing conditions for AF such as diabetes, heart failure, hypertension, and coronary heart disease[6]. Cardiac embolism because of AF causes up to 25% of all ischemic strokes, which makes it socioeconomically highly relevant[7]. Oral anticoagulation (OAC) with vitamin K antagonists (VKA) or Non-vitamin K antagonist anticoagulant (NOAC) is the most effective prophylaxis for stroke in AF. Yet, (N)OAC therapy is associated with a significant bleeding liability and long-term (N)OAC therapy in patients with NVAF and concomitant high bleeding risk poses safety issues in a sizable and growing population in clinical practice. Postmortem and echocardiographic studies have shown that the vast majority of all cardiac thrombi in patients with AF form in the left atrial appendage (LAA)[8]. Thus, a reasonable alternative is the exclusion of the LAA cavity from the circulation.[9]

Currently, the Amplatzer ACP/Amulet ™ (St. Jude Medical-Abbott), and the Watchman ™ (Boston Scientific, Natick, MA, USA) are the devices with most clinical experience reported to date for percutaneous closure of LAA. The Watchman was tested in the setting of two randomized control trials. The PROTECT AF[10] (Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial) trial was a multicentre, randomized controlled trial in NVAF patients comparing the Watchman device to warfarin for a composite primary endpoint of stroke, systemic embolism, and cardiovascular (CV) death. Noninferiority to warfarin was documented early and long term (2,621 patient-years [PY]), LAA closure (LAAC) demonstrated a significant (40%) relative risk reduction to warfarin for the primary efficacy endpoint, an 85% relative risk reduction in hemorrhagic stroke, a 60% relative reduction in CV mortality

(absolute annual risk reduction of 1.4%), and a 34% relative reduction in all-cause mortality (absolute annual risk reduction of 1.6%).
The PREVAIL trial[11] (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) was a confirmatory randomized trial comparing LAAC with the Watchman™ device to warfarin, which mandated inclusion of new operators, slight modifications in inclusion criteria, and elimination of 7-day clopidogrel therapy before implantation. Bayesian statistical methodology was agreed upon using informative prior data from the PROTECT AF trial. At the pre-defined evaluation time point, the PREVAIL trial demonstrated improved safety compared to the PROTECT AF trial, and non-inferiority of 1 of the 2 co-primary efficacy endpoints; an 18-month rate ratio (RR) for primary efficacy, and an 18-month rate ratio difference for post-procedure ischemic stroke and systemic embolism. A second-generation device, the Watchman FLX was developed and released for simplified implantation to fit a wider range of patients and to enhance sealing within the left atrial appendage. It gained the CE mark at the begin of 2019.

Until a few years ago, in Europe the device most frequently utilized for LAA closure was the Amplatzer Cardiac Plug™ (ACP, St. Jude Medical-Abbott), which gained CE approval in late 2008. The ACP study was recently published, including data from 1,047 consecutive patients treated in 22 centers[12] It showed a favourable outcome for the prevention of AF-related thromboembolism with an annual reduction of 59% as compared to the rate predicted by the CHA2DS2-VASc score, and a 61% annual reduction in major bleeding events as compared to the rate predicted by the HAS- BLED score. A second-generation device, the Amulet™, was developed and released in 2013 for easier delivery, better coverage, and reduction of complications. Similar to the first generation ACP device, Amulet is engineered with a distal hook-crowned lobe for anchoring in the lumen of the LAA and a proximal disc for excluding the ostium of the LAA according to the pacifier principle. This plug and disc concept is different from the plug only design of Watchman/FLX device.

A critical step for each LAA closure procedure is the appraisal of LAA residual or new patency/leaks after device implantation. Kanderian et al [13] showed a trend towards a decreased risk of post procedural cerebral embolism in patients with successful LAA surgical closure as compared to patients with a perideviceleak >1cm assessed with trans-esophageal echocardiography (TEE) at 8 months after intervention. In the setting of available randomized trials (currently only limited to the Watchman device), successful closure was defined by the presence of a peridevice flow ≤ 5 mm assessed with TEE 45 days after the procedure. In these trials, as well as according to the current instruction for use of Watchman, the appraisal of residual leaks 45 days after LAAC was/is considered mandatory for a correct postprocedural management of pharmacotherapy (in terms of continuation or reinstitution of OAC therapy). Whether a similar practice should be implemented after Amulet or other devices is still unclear given the lack of controlled randomized data comparing this specific device with current standard of care consisting of oral anticoagulation. It is relevant to emphasize here that while across pooled Watchman trials there is no clear evidence that the presence or the size of peridevice leaks are associated to higher risk of stroke or systemic embolism, the protocols have mandated the continuation or re-institution of OAC therapy in all cases where a leaks of 5 mm or greater was observed at the end of the procedure or at follow-up. Therefore, it remains highly probable that the risk associated to the presence of peridevice leaks has been mitigated by the concomitant use of this imaging-based pharmacological intervention.

Furthermore there is a growing attention to the natural history of peridevice leaks. Freixa et al [14] showed that among twenty-five patients treated with LAAC, the two patients with major leaks after device deployment did not show significant leaks at follow-up (8 months after procedure) whereas the two patients with major leak at follow-up did not show significant leaks after device deployment. Given the unpredictable evolution of peridevice leaks, it is becoming clear the need for a long term imaging follow-up (both short and long-term after LAAC).

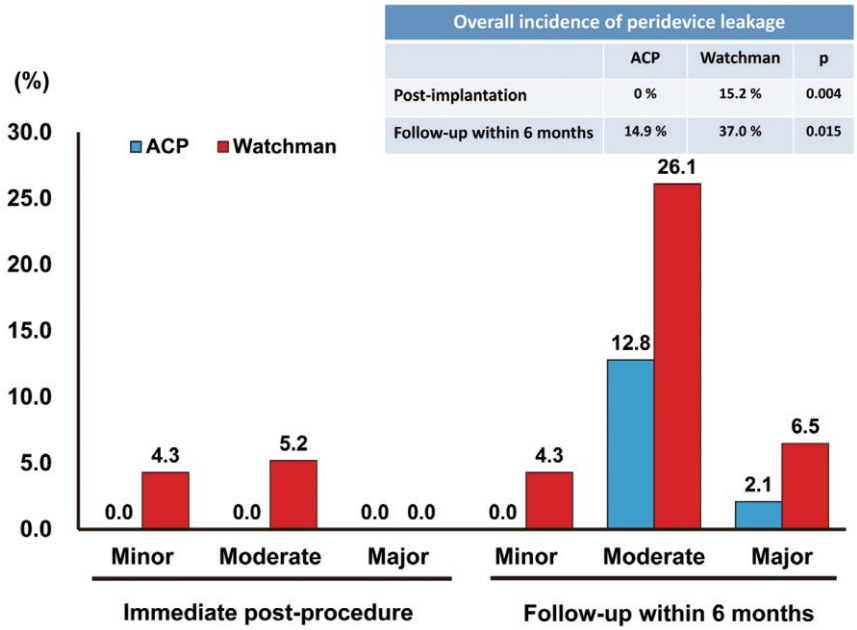
Currently the gold standard for the assessment of LAA patency after closure is the TEE. However it is an invasive and operator dependent examination, and replacing it with an alternative non-invasive exam is also desirable for patient's comfort. Saw et al [15] reported a case series of 45 patients treated both with ACP than with Watchman, with a CCTA and TEE performed at follow-up. This study reported higher sensitivity for CCTA as compared to TEE in the identification of LAA residual patency. At TEE evaluation, only half of the patients where LAA patency was documented at CCTA were confirmed to have a leak as assessed by standard criteria. In particular, authors described a series of 23 patients treated with LAAC in whom both TEE and cardiac CT were available at follow up. Authors observed that cardiac CT identified as many as 52% of LAA patent after intervention as compared with only 34% at TEE. In patients in whom LAA was patent at CT patent LAA, only 58% were also recognized by TEE suggesting that CT would be able to identify patency that would be not recognized at TEE. Also, by measuring the HU in the LAA distal to the device and comparing the contrast density with surrounding cardiac chambers, they also noted that all patients with occluded LAA at TEE had a value <100 HU, suggesting this as threshold for cardiac CT evaluation. In addition, Jaguszewski et al [16] reported a series of 19 patients in whom both cardiac CT and TEE were performed after LAAC. The rates of patency were 62% and 36% identified by CT and TEE respectively. These two pivotal investigations have suggested a two-fold higher sensitivity for CT as compared to TEE in identifying the presence of device leaks both immediately after as well as during follow-up in LAAC patients. Importantly, the lower than expected sensitivity towards LAA leaks after closure may contribute to explain the apparently lack of association between presence/size of LAA leaks and increased stroke risk, in addition to the fact that (as alluded to above) those patients with greater LAA leaks (i.e. those also indetified at TEE) were freqneutjly concomitantly treated with OAC.

Recently our group has retrospectively analyzed 56 patients who underwent LAACof whom 40 who received TEE as well as a clinically indicated CCTA after intervention.[17] ACP Amplatzer was used in 38 (67.9%) patients, while Amulet in 12 (21.4%) and Watchman in 6 (10.7%) patients. TEE guidance was used in 3 cases only, all receiving the Watchman device. Device success was achieved in 100% of cases, while technical and procedural success

was obtained in 53 cases (94.6%). The median time from LAAC to CT was 217 [86-401] days, whereas median time from LAAC to TTE was 90 [74-131] days. Based on 100 HU cut-off value, 24/56 (43%) patients had patent LAA after intervention (i.e. >100 HU measured in the LAA). The mean HU of LAA was significantly higher in patent LAA as compared with occluded LAA (209.0±67.3 vs. 63.8±21.8; p<0.001), whereas HU, as measured in LA, did not differ between the two groups. LAA/LA HU ratio was also significantly higher in patients with patent LAA (0.65±0.2 vs. 0.25±0.1; p<0.001). Using CT patency as gold standard, we calculated that a cutoff of 0.43 for the LAA/LA HU ratio provided a 92% of sensitivity and 94% specificity, with an AUC of 0.94. When the echocardiographic criteria recommended by the ACP/Amulet device manufacturer were applied to CT images, at least 2 mm separation between the lobe and the pacifier disk was identified in 46/50 (92%) of cases; the disc was concave at visual estimation in 47/50 (94%) of cases; the lobe was implanted at least 2/3 deeper than the circumflex artery crossing axis in 30/50 (60%) cases; the lobe and the disk were aligned in 36/50 (72.0%) of cases; finally > 10 % lobe compression was present in 24/50(48%) of patients. None of the above reported criteria, either separately or in combination, differ between patients with or without patent LAA at CT images. Multiplanar reconstruction of CT images identified lack of proximity between the disk and LAA ostium as obvious reasons for LAA patency in 22/24 cases (91.7%), of whom 15 (68%) were in the posterior quadrants. Therefore, these three retrospective series of patients who underwent LAAC do consistently suggest that only CCTA can reliably indentify all patients with LAAC who present shortly after or at later time point peridevice leaks.

There are currently no randomized controlled trials assessing the degree of LAA closure between Amulet and Watchman/FLX.

Kim et al [18] reported in a retrospective series of 96 patients treated with both devices a similar rate of procedure success and complications, similar clinical outcome for two devices, but peridevice leakage was more frequent with the Watchman than the ACP (37% vs 14.9% p=0.015).



An additional role of pre- and post-procedural CCTA is its capability to reliable detect the presence of LAA/LAA device thrombus as well as allowing a proper device sizing in the planning phase of the procedure.[19]

Indeed, it is well recognized that a preprocedural CCTA improves proper sizing of the LAAC device and is useful to detect LAA thrombus before LAAC. Nowadays many centres across the world including ours, recommend CCTA before and frequently after the planned intervention.

3.2 Medical Devices and Indication

The WATCHMAN (Atritech, Boston Scientific, Natick, MA, USA) LAAC technology consists of the Access System (Access Sheath and Dilator) and Delivery System (Delivery Catheter and WATCHMAN Device). The Access System and Delivery System permit Device placement in the left atrial appendage (LAA) via femoral venous access and inter-atrial septum crossing into the left atriumWATCHMAN device is a self-expanding nitinol structure with a porous covering on the proximal face. The device is constrained within the Delivery System until deployment in the LAA. The Device is available in 5 sizes from 21 to 33 mm.The new generation Watchman FLX has a shorter device length and a less taper angle to simplify implantation and to fit a wider range of patients, Furthermore, the frame of the new device is designed to enhance sealing within the left atrial appendage.

The AMPLATZER Amulet (St. Jude Medical-Abbott) is a self-expanding device made of nitinol that has a distal lobe and a proximal disc, connected by an articulated waist. The device lobe has six to 10 pairs of stabilising wires and is meant to be implanted in the proximal 10-15 mm of the left atrial appendage (LAA), whereas the device disc is intended to cover the ostium at the left atrial side. The proximal female screw is recessed to minimise thrombus formation on the disc and potentially facilitate re-attachment of the device to the pusher screw. The lobe sizes range from 16 to 34 mm.

3.3 Preclinical Evidence

Not applicable, all the devices used in this study have been previously approved for use in humans in the context of LAAC.

3.4 Clinical Evidence to Date

Addition to the two randomized clinical trials previous reported, there are many prospective and retrospective study reported both for the Watchman that for the Amulet the safety and efficacy of the LAAC procedure. In a recent meta-analysis, Xu et al.[20] reported the data of 2779 patients underwent to LAAC with the two devices. They reported a rate of stroke about 1.2/100 person-year, with a rate of major bleeding (that is the most important procedure adverse event) of 2.6%.

3.5 Explanation for choice of comparator

The two devices selected for this study are the two most used in Europe. No previous randomized studies are reported about the comparison between the two devices in terms of safety and efficacy and between the two evaluation techniques (CCTA and TEE).

3.6 Risks / Benefits

Patients will not be exposed to any adjunctive procedural hazard by participating into the present study because LAAC is a clinically-indicated procedure in this specific patient population. As previously described, AF patients are at risk of cardioembolic stroke. So it is mandatory to prescribe an anticoagulant therapy if AF is detected. The most important risk of this therapy is related to bleeding events. On the other side, the interventional procedure itself exposes the patient to the risk of possible complications, sometimes also severe such as migration/embolization of the device or major bleeding (pericardial effusion or pericardial tamponade) requiring an intervention. However, as reported in literature, these events are rare and their incidence is lower than the incidence of stroke in AF patients or as compared to the risk of bleeding complications inpatients taking (N)OAC.

Patients are to receive, as per current standard of care, CCTA before LAAC and TEE both during the procedure and at follow-up. As multiple reports [21] exist indicating that CCTA improves proper sizing of the LAAC device and is useful to detect LAA thrombus before LAAC, nowadays many centres across the world including ours, recommend CCTA before (and frequently after) the planned intervention.

The only added risk in this study for the participating patients is represented by the routine performance of two CCTAs undertaken after the procedure, since these diagnostic assessments are, at least partially, study-specific procedures. As previously described, we will use the CCTA performed 45 days after procedure as primary endpoint measure since it is more sensitive in detecting LAA leaks after LAAC as compared to TEE[15], and CCTA at 13 months after procedure as secondary endpoint measure to better charachterize the natural history of peridevic leak(s). Replacing TEE with CCTA is also desirable for patients as it is non-invasive and less time consuming.

Unlike TEE however, CCTA is associated to ionizing radiation to patients and contrast exposure. With the most recent technology and new acquisition protocols, the radiation dose for each exam is lower than 5 mSv. In a recent publication,[19] the median radiation dose (range) for the dual-phase protocol of patients submitted to a CCTA for LAA evaluation prior LAAC was ***3.5 mSv*** (2.1–5.2 mSv), with a dose-length product (DLP) of 251 mGy cm (150–374). However taking all CCTAs performed before the index procedure, after 45 days and after 13±1 months into account, the total dose per year is projected to exceed the limit of 5mSv yearly limit and so, as required by Ordinance on Clinical Trials in Human Research of 20 September 2013 (Status as of 1 January 2018- Sect.2 Art. 28), an additional submission to the FOPH will be accomplished.

Since patients with reduced kidney function (i.e. CrCl< 30 ml/h/kg) are excluded, we believe additional contrast exposure will not result in additional kidney injury in our patient population.

3.7 Justification of choice of study population

High bleeding risk (HBR) patients are the ones that most benefit from the LAAC, as it suppresses the need for chronic anticoagulation therapy.

4. STUDY OBJECTIVES

4.1 Overall Objective

The purpose of this study is to compare the efficacy and safety of the two devices for the LAAC.

4.2 Primary Objective

The main objective is to evaluate the feasibility and the efficacy of the devices in terms of LAA complete occlusion with a non-invasive imaging technique such as CCTA.

4.3 Secondary Objectives

Other secondary objectives will include the incidence of adverse clinical events in the two groups, a comparison between the two devices in terms of procedure feasibility, LAA patency and device thrombus over time as assessed with both 45-day and 13-month CCTA and with 45 day TEE. Furthermore, a secondary objective of the study will bethe comparison between TEE and CCTA with respect to LAA patency and device thrombus.

4.4 Safety Objectives

Safety objective is to show that there is no significant difference in terms of procedure complications up to 48 hours from randomization across the two groups.

5. STUDY OUTCOMES

5.1 Primary Outcome

The study primary endpoint is the composite of LAA patency at 45 day evaluated with CCTA or the crossover from one device to the other device based on morphological/anatomical considerations during device implantation.

Post-intervention LAA patency will also assessed via TEE based on the more conservative criterion of residual flow ≥ 3 mm.

5.2 Secondary Outcomes

Secondary end-points include[1]:

- LAA patency (arterial and/or venous phase) at 45-day and 13-month CCTA in the per protocol and as treated populations
- All cause of death, stroke, systemic or pulmonary embolism and spontaneous MI
- Cardiovascular death
- Ischemic stroke
- Haemorrhagic stroke
- Bleeding events according to the BARC classificationat each follow up.
- Procedure-related complications[2]
- Rate of patients on (N)OAC at 45 days and 6 months
- Device related thrombosis (DRT) at 45 day TEE/CCTA and 13-month CCTA in the per protocol and as treated populations
- Feasibility outcome (number of device implantation attempts, total time procedure, x-ray dose and total contrast dose used in the procedure)
- LAA patency at 45 day TEE in the per protocol and as treated populations

Adverse clinical events will be assessed at up to 48 hours or discharge whichever comes first, at 45 days, and yearly.

[1] For the definitions of endpoint and adverse clinical events see the Appendix 1.
[2]As defined in 5.3.

5.3 Procedure-related complications[1]

Procedure related complications are defined as adverse clinical events occurring during the procedure or within 7 days after. In particular, the following complicationswill be adjudicated by the Clinical Events Committee (CEC) : death, TIA/stroke, systemic and pulmonary thromboembolic event, pericardial effusion, cardiac tamponade, air embolism, bleedings vascular access-related complications, epicardial or minimal invasive surgical access-related complications, device complications and acute renal injury. Any events potentially related to the above complications (“adverse events of special interests” [AESI], see the definition in the section 11) should be reported into the ecrf.
[1]For the definitions of endpoint and adverse clinical events see the Appendix 1.

5.4 Other Outcomes of Interest

A comparison between CCTA and TEE at 45 days and then at 13 months will be performed in order to obtain a validation of CCTA to reveal the LAA patency.

5.5 Safety Outcomes

Main safety outcomes are:

- Bleeding Academic Research Consortium (BARC) bleeding grade 2, 3 and 5 at up to 48 hours or discharge whichever comes first and 45 days
- Net adverse clinical events (NACE) defined as the composite of death, fatal and non-fatal stroke, peripheral embolizationand BARC 2, 3, or 5 at up to 48 hours or discharge whichever comes first and 45 days
- Device related thrombosis at 45 day TEE/CCTA and 13-month CCTA in the per protocol and as treated populations

5.6 Feasibility Outcomes

A composite of following outcomes will be analysed in order to assess the feasibility of two devices:

- Number of attempts of LAA closure with a single device.
- Number of same type device used in a procedure.
- Total time procedure, x-ray dose and total contrast dose used in the procedure.

6. STUDY DESIGN

6.1 General study design and justification of design

This will be a multicentre, open-label, prospective, randomized study in patients with AF and an indication for anticoagulant therapy with high bleeding risk, that agree to the LAAC procedure. Patients will be submitted to a screening protocol in a period not greater than 90 days before procedure, including medical and drug history, physical examination, 12-lead ECG, CCTA(as per standard of care) and TEE if clinically indicated.

Once the patient is judged eligible and the informed consent has been signed, the patient will be randomly assigned in a 1:1 to receive a LAAC with Amplatzer Amulet or Watchman/FLX device. In the event that the patient is randomized to the Watchman/FLX arm, the operator will be able to choose, on the basis of clinical reasons, if to implant Watchman or the new generation Watchman FLX (if available in the center).

Sizing device and implantation will be performed according to common practice guidelines[5] (and so based on both preprocedural CCTA and intraprocedural TEE-angiography images). Furthermore, as recommended by the recent consensus document,[5] the first operator will be able to choose if use intracardiac echocardiography (ICE) instead of TEE to guide the procedure, on condition that a TEE evaluation is performed within 2 days before the procedure (in order to exclude LAA thrombus, to confirm the LAA suitability for both devices and to make the device sizing). Angiography at the end of the procedure is recommended to assess PDL. In case of concomitant procedure during LAAC, it will be reported separately in term of duration time, contrast dose and x-ray dose.
At the end of procedure, a measure of PDL must be provided.

A transthoracic echocardiogramis encouraged (but not mandatory) before the hospital discharge in order to detect pericardial effusion.

All patients randomly allocated to the Watchman/FLX or Amulet arm will receive acetylsalicylic acid (ASA) and clopidogrel or (N)OAC (at discretion of the treating physicianand according to the bleeding risk,stroke risk as well as based on post-procedural TEE evaluation) for 45 days and then will undergo TEE assessment(as well as CCTA):

- If a residual peri-device leak flow at 45 days> 5 mm or a intra-cardiac thrombus is detected, a therapy with ASA and (N)OACcould be consideredup a sequential TEE evaluation at 6 months.
- If a residual peri-device leak flow at 45 days≤ 5 mm is detected, patients will continue to receive ASA and clopidogrelor(N)OAC (at discretion of the treating physician according to the bleeding and stroke risk)up until 3 months after procedure. Thereafter, monotherapy with ASA will be continued until 12 months after procedure.

These drug regimensare strongly recommended according the actually evidence and the instruction for use of the two devices (Appendix 2). Nevertheless, if a clinical condition lead to prescribe other drugs regimen, it will be permitted given an exhaustive explanation by physician.

Further procedures, such as physical examination or blood sampling will be done according the study schedule and Section 9, in particular visits or phone calls will take place after 6 and 13 month as well as 2/ 3/ 4/ 5 years.

6.2 Randomization

Balanced (1:1) randomization will be performed via a web-based interactive randomization system (ICE-Advice Pharma), based on a computer-generated random sequence with a random block size stratified according to site and a allocation to either Amulet Amplatzer device or Watchman/FLX. In the event that the patient is randomized to the Watchman/FLX arm, the operator will be able to choose, on the basis of clinical reasons, if to implant Watchman or the new generation Watchman FLX (if available in the center). Randomization will occur as close as possible to but always before the procedure and once the patient is judged eligible and the informed consent has been signed.

6.3 Other methods of minimising bias

Not applicable.

7. STUDY POPULATION

7.1 Eligibility criteria

Participants fulfilling all the following **inclusion criteria** are eligible for the study:

- Written informed consent
- Male or female subject aged 18 years or more with no upper age limit and willing to comply with the protocol
- Indication to a LAA closure as indicated in study population (HAS BLEED ≥3 or High bleeding risk as defined by Munich consensus document and CHA2DS2-VASc≥2).

[1] For the definitions of high bleeding risk (HBR) see Appendix 1.

The presence of anyone of the following **exclusion criteria** will lead to exclusion of the participant:

- New York Heart Association class IV congestive heart failure
- ASD or atrial septal repair or closure device
- Single occurrence of AF
- Cardioversion or ablation procedure planned within 30 days
- Implanted mechanical valve prosthesis
- Heart transplantation
- Enrolled in another IDE or IND investigation of a cardiovascular device or an investigational drug
- Female of childbearing potential (age < 50 years and last menstruation within the last 12 months), who did not undergo tubal ligation, ovariectomy or hysterectomy.
- Active infection of any kind
- Severe chronic kidney insufficiency (CrCl< 30 ml/min)
- Terminal illness with life expectancy < 1 year
- Echocardiographic exclusion criteria
- LVEF < 20%
- Intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days before implant
- Significant mitral valve stenosis (ie, MV <1.5 cm2)
- Complex aortic atheroma with mobile plaque of the descending aorta and/or aortic arch
- Cardiac tumor.

7.2 Recruitment and screening

Patients will be screened previous the admission index. After complete screening pre-evaluation resulting in eligibility for LAAC, patients will be adequate informed and those accepting to participate will sign the informed consent form and will be enrolled in the study by dedicated staff previously identified at each center. See 9.1.1 for additional details.

Study participants will not receive any payment or compensation for participation in the study.

7.3 Assignment to study groups

Once the patient is judged eligible and the informed consent has been signed, patients will be randomly assigned 1:1 to one of the study groups. Randomization is described in 6.2.

7.4 Criteria for withdrawal / discontinuation of participants

Patients can be withdrawn from the study at every time from the enrolment if any of the following criteria occurs:

withdrawal of informed consent, non-compliance, safety issue (i.e. unexpected risk related to study procedure), premature interruption of the study, presence of any exclusion criteria that was not known at the time of enrolment.

8. STUDY INTERVENTION

8.1 Identity of Investigational Medicinal Devices

The WATCHMAN (Atritech, Boston Scientific, Natick, MA, USA) LAAC technology consists of the Access System (Access Sheath and Dilator) and Delivery System (Delivery Catheter and WATCHMAN Device). The Access System and Delivery System permit Device placement in the left atrial appendage (LAA) via femoral venous access and inter-atrial septum crossing into the left atrium.WATCHMAN device is a self-expanding nitinol structure with a porous covering on the proximal face. The device is constrained within the Delivery System until deployment in the LAA. The Device is available in 5 sizes from 21 to 33 mm. The new generation Watchman FLX has a shorter device length and a less taper angle to simplify implantation and to fit a wider range of patients, Furthermore, the frame of the new device is designed to enhance sealing within the left atrial appendage.
The AMPLATZER Amulet (St. Jude Medical-Abbott) is a self-expanding device made of nitinol that has a distal lobe and a proximal disc, connected by an articulated waist. The device lobe has six to 10 pairs of stabilising wires and is meant to be implanted in the proximal 10-15 mm of the left atrial appendage (LAA), whereas the device disc is intended to cover the ostium at the left atrial side. The proximal female screw is recessed to minimise thrombus formation on the disc and potentially facilitate re-attachment of the device to the pusher screw. The lobe sizes range from 16 to 34 mm.

8.2 Procedural intervention

Generally, general anaesthesia or at least conscious sedation is used for the procedure, due to the discomfort caused by the use of intra-procedural TEE for guidance. At the beginning, TEE is performed to exclude thrombus, to detect any pericardial effusion prior to the procedure and to evaluate the function of the mitral valve and the patency of the left upper pulmonary vein (LUPV). Since cardiac tamponade is a potential complication, it may be of benefit to establish an invasive (femoral or radial) arterial pressure monitoring with heart rate sound in order to detect and remedy haemodynamic instability rapidly.

Depending on the clinical condition of the patient (left ventricular function, mitral regurgitation, and pulmonary pressures), it may be advisable to administer 500-1,000 cc of saline prior to TEE measurements in order to increase mean left atrial pressure to >12 mmHg, reducing the likelihood of inadequate LAA filling and minimizing the risk of device undersizing and subsequent embolization. Then, the TEE operator obtains the baseline LAA measurements (or confirms the measurements obtained during patient screening). The LAA is scanned from 0° to 135° (0° - 45° - 90° - 135°) and the maximum and minimum diameters of the ostium and the landing zone are recorded. The TEE operator should be familiar with the implantation technique and device characteristics. However, as recommended by the recent consensus document,[5] the first operator will be able to choose if use ICE instead of TEE to guide the procedure, on condition that a TEE evaluation is performed within 2 days before the procedure (in order to exclude LAA thrombus, to confirm the LAA suitability for both devices and to make the device sizing).

Currently, real-time 3D TEE is used more frequently for assessing the LAA during the implantation procedure. Real-time 3D TEE allows better spatial visualization of the LAA and more comprehensive evaluation of the device during the procedure. Furthermore, with 3D TEE the device may be visualized more completely during the tug test and after deployment

For the implantation of the LAAC device, femoral venous access is obtained in the right femoral vein. A 3-4 mm skin incision and perhaps subcutaneous separation of the access site are done to ease advancement of the transseptaland delivery sheath. Some operators prefer to use a short 12-16 Fr introducer for the groin. Transseptal puncture (TSP) is performed under fluoroscopic and preferably TEE guidance in the infero-posterior portion of the fossa ovalis using, e.g., a BRK-1™ needle (St. Jude Medical-Abbott) which usually provides adequate support and proper angulation for accurate puncture. Other systems are available and used with excellent success. TSP at the optimal puncture site is important to facilitate proper orientation of the delivery sheath in relation to the LAA. In this respect TEE guidance of TSP is instrumental. The TEE operator initially provides a bicaval view, to show the superior and inferior portion of the fossa. This view allows the operator to place the transseptal needle at the inferior axis of the fossa. Once tenting of the atrial septum has been observed, the TEE operator switches the view to a short-axis aortic view to show the anterior and posterior axis of the fossa. In this view the position of the transseptal sheath may be corrected to ensure a posterior puncture. A 3D TEE probe may allow the use of biplanar views showing the inferior and posterior axes of the atrial septum at the same time (x-plane). A PFO may be used for LAAO. However, it may result in more challenging delivery sheath orientation due to the superior entrance into the left atrium. The majority of operators prefer a directed infero-posteriortransseptal approach. If the interatrial septum

is thick and difficult to puncture, the needle stylet or diathermy may help. Radiofrequency puncture needles are also available.

Administration of unfractionated heparin is required, targeting an activated clotting time (ACT) of 250-300 seconds. The initial dose is 100 IU/kg. The timing of heparinisation varies. Some operators administer the complete dosage before, others only half of the dosage before and the remaining half after successful TSP. Some give the full dosage only after TSP. The half dose approach is a good compromise as it provides some antithrombotic protection in case of a difficult or prolonged TSP. Once access to the LA has been attained, it is of paramount importance to ensure adequate anticoagulation to avoid thrombus formation on wires and on or in catheters within the thrombogenic environment of the fibrillating LA. Adequate and regular flushing of the catheters serves the same purpose.

8.3 Device sizing

Optimal device sizing is critical for the procedure in order to avoid device embolisation, incomplete LAA closure, or multiple recaptures and repositioning of the device, prolonging the procedure. Device sizing is customarily based on multimodality imaging (TEE, CCTA und LAA angiography).[5] Baseline CT angiography of adequate quality is an emerging accurate method due to its high spatial resolution and 3D capabilities. It needs to be carried out under adequate volume loading of the patient. TEE, 3D TEE, and ICE have lower spatial resolution but have the advantage of real-time evaluation during the implantation procedure. Angiography in at least two of threesuggested views (RAO 30° CRA 20°; RAO 30° CAU 20°; LAO 90°) is mandatory. Calibration has to be accurate and will be based on preprocedural CCTA, intraprocedural TEE guidance and angiography. Noteworthy, auto-calibration or calibration based on catheter diameters may be imprecise, leading to miss sizing. French sizes (1 Fr=0.33 mm) of sheaths refer to the inner lumen, whereas those of catheters refer to the outer diameter. Finally, it is important to choose the frame depicting the maximum LAA distention.

ACP Amulet sizing depends on the widest landing zone on fluoroscopy or TEE. A standard recommendation is to upsize the device by 3 to 6 mm for the Amulet device from the widest measured landing zone measured by 2D TEE. This degree of oversizing improves stability of the device and proper anchoring of the lobe. However, caution should be exercised if the landing zone is very elliptical to avoid dramatic oversizing (> 5 mm) in the narrowest dimension.

The delivery sheath size depends on the device size and is chosen based on a relevant chart, either 12 or 14 Fr. Oversizing of the sheath was not recommended for the ACP but is allowed for the Amulet, allowing an approach using a default 14 Fr in all cases. To accommodate this, a loading catheter adapter is included with the 12 Fr compatible devices. The AMPLATZER™ TorqVue™ 45-45° sheath (St. Jude Medical-Abbott) is the default sheath for Amulet devices.

WATCHMAN/FLX sizing is based on the maximum LAA ostium diameter, which should be 17 to 31 mm to accommodate available devices. Oversizing is recommended by 8-10% to 20-30% based on the widest measurement.

8.4 Crossover

In case of impossibility during the procedure to implant the randomized device, operator can be choose to implant another device or stop the procedure. In any case the patient will continue to be considered enrolled in the trial. The crossover endpoint will be centrally adjudicated by the Clinical Events Committee (CEC) as justified if there will be evidence that the randomly allocated device has been positioned at least once in the LAA but LAA ostium sealing remained suboptimal (peri-device leak ≥ 3 mm) or concerns were present over the device stability and consequent risk of device embolization.

8.5 Compliance with study procedures

Expert operators must perform all procedures, with at least 20 successful cases of implant for each device. In case of operators with less than 20 procedures performed, a proctoring supervisor is requested during the implantation.

8.6 Data Collection and Follow-up for withdrawn participants

Data of withdrawn participants will be collected and evaluated up to the time of withdrawn. However, withdrawn participants will be asked the permission to continue collecting and evaluate data about them from routine data or other sources (general practitioners, Health System Softwares available) in order to respect the patient choice without affecting the scientific quality of the study

8.7 .Concomitant medicaments

As anticoagulant therapy with unfractionated heparin (UFH) during procedure will be administer according operator preference in order to maintain the ACT time more than 250 during all procedure time. No particular restriction are

established for previous medicament, so it is allow both DAPT then (N)OAC.

After the procedure, patients will receive ASA and clopidogrel or (N)OAC at discretion of the treating physician (according to the bleeding risk, the stroke risk and intra-procedural TEE evaluation) for 45 days and then will undergo TEE assessment.

- If a residual peridevice leak flow > 5 mm or a an intracardiac thrombus is detected, treatment with ASA and (N)OAC should be considered up a sequential TEE evaluation at 6 months. Final decision to implement an OAC regimen with or without ASA will eventually be left to the discretion of the treating physician taking the ischemic ad bleeding risk into account;
- If residual peridevice leak flow ≤ 5 mm, patients will receive ASA and clopidogrel or (N)OAC (at discretion of the treating physician according to the bleeding and stroke risk) up until 3 months after procedure. Thereafter, monotherapy with ASA will be continued until 12 months after procedure.

These drugs regimens are recommended according the current evidence and the instructions for use of the two devices(Appendix 2).

8.8 Study Device Accountability

Watchman and Amulet used for the study are already in use at the enrolling hospitals, local standard procedures of products management will be applied.

8.9 Return or Destruction of Study device

Local standard procedures of products management will be applied.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

The Study Procedures are summarized in table study schedule.

9.1.1 Screening and enrolment

Screening will be performed up to 90 days prior LAAC. Potential patients will be informed about the study and asked for participation. Subjects are considered provisionally enrolled with the signature on the written informed consent form (screening phase). Formal inclusion into the study will occur after baseline eligibility is confirmed and only once randomization takes place as close as possible to but always before LAAC. A copy of the informed consent form with the patient's information document will be given to the patient.

The following evaluations will be performed at baseline/enrolment:

- Demographics;
- Relevant medical history that includes: general medical, cardiovascular, neurologic and renal history; cardiovascular risk factors (e.g. dyslipidaemia, hypertension, diabetes mellitus, tobacco use); history of peripheral vascular disease, stroke, transient ischemic attack;documentation of current cardiovascular and diabetic medications;Stroke and bleeding risk evaluation with $CHADS_2$, CHA_2DS_2VASc, HAS-BLEED and ABC score;
- Evaluation of In-/Exclusion criteria;
- 12-lead ECG;
- Routine laboratory tests within 48 hours prior to the index procedure as defined in 9.1.7;
- CCTA according to current standard of care (useful to exclude LAA thrombus and to plan the procedure);[5]
- TEE if clinically indicated or if no intraprocedural TEE is performed to guide the procedure.

9.1.2 Randomization and Procedure

Patients who have signed the informed consent form and meeting all inclusion and exclusion criteria will be included in the study and randomized before LAAC procedure.

After randomization, patients will receive the LAAC with the randomized device. In the event that the patient is randomized to the Watchman/FLX group, the operator will be able to choose, on the basis of clinical reasons, if to implant Watchman or the new generation Watchman FLX (if available in the center).

In case of impossibility to implant the randomized device, the operator can change the device or stop the procedure

and the patient will be considered for crossover adjudication (see section 8.4).
Fluoroscopy images will be digitalized and encoded for adjudication.

The following evaluations will be performed before, during and after the procedure:

- 12 lead ECG
- TEE or ICE to guide intervention according to the current standard of care
- Procedure-related data collection including duration, fluoroscopic time and overall contrast medium dose as well as any procedure-related complications (described in 5.3)
- Collection of of any Serious Adverse Event (SAE) and adverse events of special interest ([AESI] as defined in 111 and Appendix 1) up to 48 hours or discharge whichever comes first.

9.1.3 Post procedure management and hospital discharge

After the procedure, patients will receive ASA and clopidogrel or (N)OAC at discretion of the treating physician (according to the bleeding risk, the stroke risk and intra-procedural TEE evaluation) for 45 days and then will undergo TEE assessment (as per standard of care):

- If a residual peridevice leak flow > 5 mm or a an intracardiac thrombus is detected, treatment with ASA and (N)OAC should be considered up a sequential TEE evaluation at 6 months. Final decision to implement an OAC regimen with or without ASA will eventually be left to the discretion of the treating physician taking the ischemic ad bleeding risk into account;
- If residual peridevice leak flow ≤ 5 mm is detected, patients will receive ASA and clopidogrel or (N)OAC (at discretion of the treating physician according to the bleeding and stroke risk) up until 3 months after procedure. Thereafter, monotherapy with ASA will be continued until 12 months after procedure.

These drug regimens are recommended according the current evidence and the instructions for use of the two devices (Appendix 2).

The following evaluations will be performed at up to 48 h after the procedure or at hospital discharge whichever comes first:

- Physical examination as defined in 9.1.6
- Measurementof vital signs as defined in 9.1.5
- Collection of concomitant therapy and assessment of any additional intervention, if any, which occurred after LAAC
- Assessment of SAE and AESI as defined in 11.1 and Appendix 1
- 12 lead ECG
- Routine laboratory tests within 48 hours prior to the index procedure as defined in 9.1.7
- A transthoracic echocardiogram is encouraged (but not mandated) before the discharge in order to detect pericardial effusion and for the assessment of the post-procedure positioning of the LAA device.

9.1.4 45 days, 6month, 13 month, 2/ 3/ 4/ 5 year follow up

Patients will be followed-up with hospital visits at after 45 days(primary endpoint assessment) and thereafter at 6 and 13 months as well as after 2, 3, 4 and 5 years the index procedure. In case of impossibility to have an in hospital visit, a phone call to the patient and/or to the general practitioner will be performed (except for the 45 days visit).

The following evaluations will be performed at follow up visits:

- Collection of medical history
- Physical examination as defined in 9.1.6
- Measurement of vital signs as defined in 9.1.5
- Collection of concomitant therapy
- Assessment of SAE and AESI as defined in 11.1 and Appendix 1
-
- 12 lead ECG
- TEE will be performed at 45 days. TEE could be repeated at 6 and 13 months after procedure if clinically indicated (in case of an intra-cardiac thrombus or/and a PDL >5 mm are revealed at 45 days) according to current standard of care
- CCTA at 45 days and at 13 months after procedure will be performed as study specific interventions.

In the event of pandemic or any other condition for which the participation to follow-up visits would put at risk the health of the patients and/or of the medical staff, the hospital visits will be replaced by phone call. Furthermore, the performance of imaging follow-up outside of protocol temporal window will be allowed.

If a phone call is performed instead of an hospital visit,the following data will be collected:

- Vital status
- Assessment and reporting of adverse clinical events as defined in 9.1.8 and Appendix 1
- Assessment and reporting of SAEs and AESI
- Assessmentand reporting of pharmacotherapy, and additional interventions received since last contact.

9.1.5 Definition of measurement of vital signs

The vital signs collected will be: heart rate and arterial blood pressure.

The 12 lead ECG will be recorded first of procedure, at the discharge and at the follow up visits.

9.1.6 Definition of physical examination

The physical examination will consist of measurement of weight, height, arterial blood pressure,heart rate and a standard physical exam.

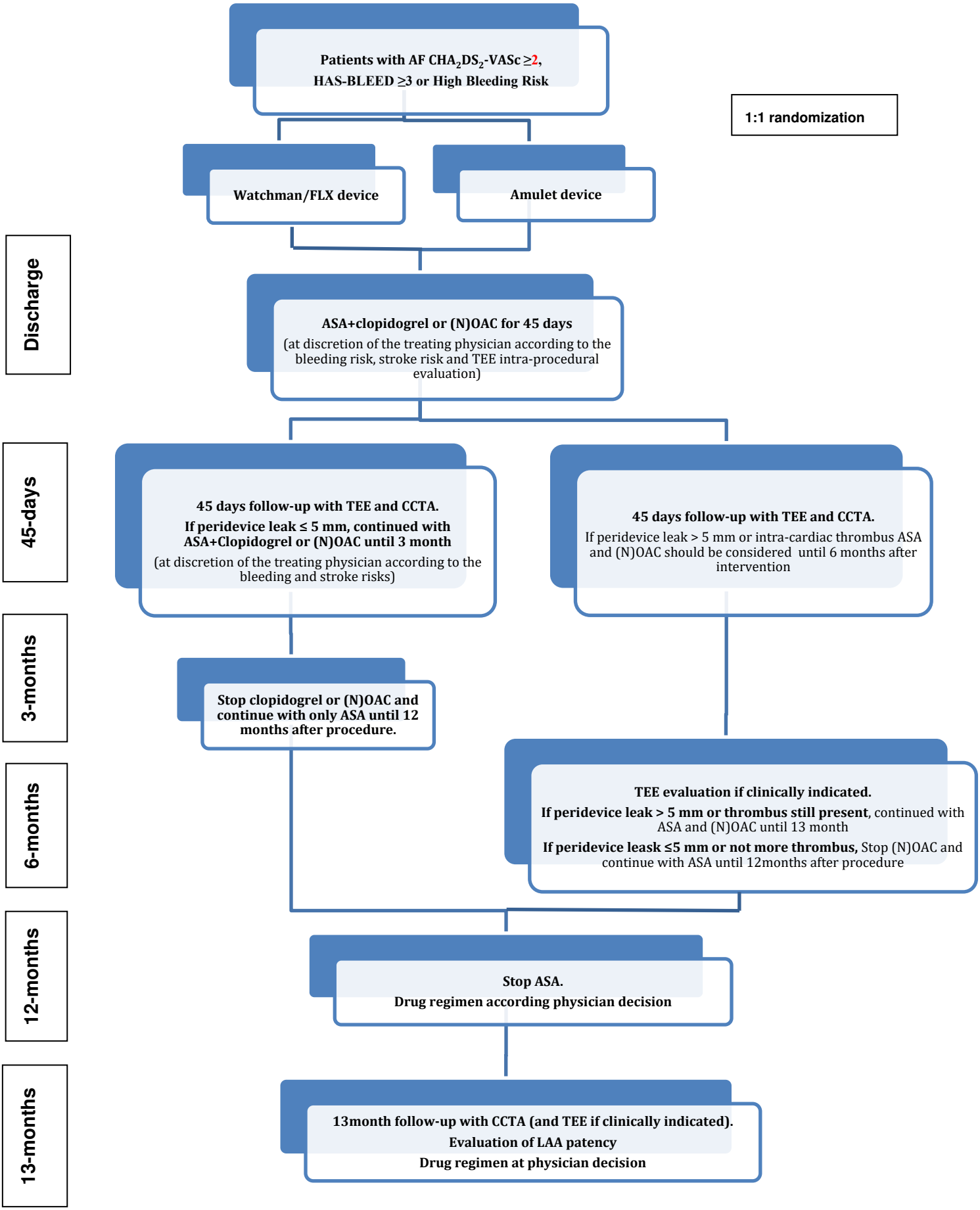
9.1.7 Definition of laboratory parameters assessed at enrolment andat up to 48 h post procedure

Laboratory test consist of complete blood count, creatinine, troponin T hs and NT-proBNP. These will be assessed at enrolment and at up to 48 h post procedure or discharge whichever comes first.

9.1.8 Definition of adverse clinical events:

The Adverse clinical events are overall and CV death, ischemic and haemorrhagic stroke, systemic or pulmonary embolization, spontaneous MI, periprocedure related complications (defined in the section 5.3)and BARC bleeding grade 2, 3, or 5 (see the definitions in Appendix 1). CEC will adjudicate these adverse clinical events.

Figure 1.


Patients with AF CHA2DS2-VASc ≥2,
HAS-BLEED ≥3 or High Bleeding Risk
1:1 randomization
Watchman/FLX device
Amulet device
Discharge
ASA+clopidogrel or (N)OAC for 45 days
(at discretion of the treating physician according to the bleeding risk, stroke risk and TEE intra-procedural evaluation)
45-days
45 days follow-up with TEE and CCTA.
If peridevice leak ≤ 5 mm, continued with ASA+Clopidogrel or (N)OAC until 3 month
(at discretion of the treating physician according to the bleeding and stroke risks)
45 days follow-up with TEE and CCTA.
If peridevice leak > 5 mm or intra-cardiac thrombus ASA and (N)OAC should be considered until 6 months after intervention
3-months
Stop clopidogrel or (N)OAC and continue with only ASA until 12 months after procedure.
6-months
TEE evaluation if clinically indicated.
If peridevice leak > 5 mm or thrombus still present, continued with ASA and (N)OAC until 13 month
If peridevice leask ≤5 mm or not more thrombus, Stop (N)OAC and continue with ASA until 12months after procedure
12-months
Stop ASA.
Drug regimen according physician decision
13-months
13month follow-up with CCTA (and TEE if clinically indicated).
Evaluation of LAA patency
Drug regimen at physician decision

9.2 Assessments of outcomes

Assessment of primary outcome

The primary outcome is the composite of LAA patency at 45 day evaluated with CCTA or the crossover from one device to the other device based on morphological/anatomical considerations during device implantation.

Patency LAA will be estimated at CCTA by measurement of the linear attenuation coefficient (Hounsfield unit, HU) in the LAA distal to the device and comparison of contrast density to atrial chamber. LAA patency was defined with HU≥100 or HU ≥ 25% of the atrium, as reported in a previous publication.[15] The occurrence of LAA patency will be centrally evaluated and adjudicated by an Imaging Core Lab (ICL) composed of three imaging experts who will independently score each of the studies as positive or negative for LAA patency. In the event of inconsistent primary end point adjudication between the three readers, a consensus between all of them will be required. Adjunctive CCTA criteria of complete occlusion (as described in section 10.2) will be collected in order to validate them. A TEE evaluation of PDL presence will be performed at 45-days in order to compare the two imaging technique. The crossover is defined as the switch from the randomized device to the other device based on morphological/anatomical considerations during device implantation. It will be centrally adjudicated by CEC as justified if there will be evidence that the randomly allocated device has been positioned at least once in the LAA but LAA ostium sealing remained suboptimal (peri-device leak ≥ 3 mm) or concerns were present over the device stability and consequent risk of device embolization.

Assessment of secondary outcomes

Secondary outcomes will be collected at 45 days,6 months, 13 months, 2 years, 3 years, 4 years and 5 years follow up. Data about adverse clinical events (listed in the section 9.1.8) will be collected by means of electronic forms and related documents (medical reports, CT and other imaging report). LAA patency on arterial phase has been already defined in the previous section ("Assessment of primary outcome"). LAA patency on venous phase is defined, as reported in a previous publication,[22] as a LAA density ≥ 100 HU or ≥ 150% of that measured at the same site on arterial phase. Leak at TEE is defined as any communication jet between LA and LAA detectable by means of color-Doppler (high velocity 50-60 cm/sec). The size is measured taking the narrowest flow region of the jet that occurs at, or just close to, the device). Of note, rate of LAA patency at 45 day CCTA will be compared with rate of leak at 45 day TEE.

Assessment of safety outcomes

Safety outcomes will be assessed 45 days,6 months, 13 months, 2 years, 3 years, 4 years and 5 years follow up. Data about adverse clinical events (listed in the section 9.1.8) will be collected by means of electronic forms (ICE-Advice Pharma) and related documents (medical reports, CT and other imaging report).

Assessments in participants who prematurely stop the study

Data of withdrawn participants will be collected up to the time of withdrawn. However, withdrawn participants will be asked the permission to continue collecting and evaluate data about them from routine data or other sources (general practitioners, Health System Softwares available) in order to respect the patient choice without affecting the scientific quality of the study.

10. CARDIAC COMPUTER TOMOGRAPHY ANGIOGRAPHY

10.1 CCTA PROTOCOL [19]

The CCTAs will be carried out according an identical protocol, by using a 64- to 320-detector scanner, with a multiphasic acquisition. Iodinated contrast medium (70–90 mL) will be administered through an antecubital vein (flow rate: 5 mL/s), followed by 50 mL of saline chaser bolus (sodium chloride 0.9%), administered at the same flow rate. Patients will receive nitroglycerin, if no contraindicated (known sensitivity to nitrate medications, administration of PDE5 inhibitor medications within the past 24 hours, systolic blood pressure <90mmHg, history of increased intracranial pressure, severe anemia), and betablockers (aimed at achieving a heart rate of <65 beat/min) prior to the CCTA acquisition. A prospective high-pitch flash mode or broad coverage single shot/step and shoot ECG-gated CT acquisition technique typically at 70 % of R–R interval or a retrospectively ECG gated CT-acquisition at 30–70 % of R–R interval will be used. The dose modulation will be used when possibleExposure parameters will be adjusted according to patient size. Images will be reconstructed using iterative reconstruction or filtered back-projectionat 0.75 mm slice width,0.5 mm slice increment. The standard scan will be performed using a a bolus tracking technique for optimal scan acquisition timing. The delayed scan will be performed 60 s following the beginning of the standard scan to allow contrast equilibration within the blood pool. The delayed scan will be planned at the level of the carina and extended 4–8 cm caudally to include the LAA but not the whole heart, to minimize unnecessary radiation exposure.

10.2 Adjunctive CCTA analyses

Adjunctive analyses not included among study endpoints, will be performed.

10.2.1 Further LAA patency analyses

In the event of LAA patency, two elements will be assessed: presence of PDL, presence of intradevice leak.
PDL, defined as a visible continuity of contrast between LA and LAA along the side of the device, will be looked for on the lobe margins (and on the disk margins in Amulet patients as well) by using reconstructed plane parallel to LAA orifice.
Intradevice leak, defined as a visible continuity of contrast through the entire length of the device, will be looked for by using reconstructed plane parallel to device long axis. In the event that an intradevice leak is incomplete, passing only through a portion of the device and then continuing at its margin (or vice versa), the leak will be defined as "mixed".
The device covering will be semiquantitatively evaluated on venous phase and scored by the ICL as one of the following: device completely uncovered, device covered less than 50%, device covered more than 50%, device completely covered.

10.2.2 Adjunctive CCTA criteria for LAA closure

In order to evaluate the complete LAA occlusion with the CCTA, we proposed following criteria

Amulet-CT criteria for LAA occlusion	**Watchman**/FLX **-CT criteria for LAA occlusion**
Lobe compression >10%	Position: plane of maximum diameter of the device is at or just distal (<2 mm) to the orifice of the LAA, and that it spans the entire LAA ostium. Position of the lobe in relation to left lateral ridge
Disc-lobe separation (>2 mm)	Size: measure the plane of the maximum diameter of the device, ensuring the threaded insert is visible. The device should be 80-92% of the original size
Device axis consistent with landing zone and landing zone and angle between disc and lobe	Seal: no contrast in the distal lobes
Concave disc	Consistency between device axis and ostium
Width of the lobe is ≥2/3 within the circumflex artery and position of the disc in relation to left lateral ridge	Lobe's shape
Lobe's shape	

Lobe compression (%) was calculated as: [(manufacturer device diameter - measured diameter)/manufacturer device diameter] × 100%

10.2.3 Amulet subgroup

Due to the double system of closure in Amulet device, some additional data will be collected in this subgroup.
The HU will be measured, if possible, also in the small region between the disc and the lobe by the same method used to assess LAA patency.
Furthermore, in addition to PDLs assessment, that in Amulet subgroup refer to the leak passing along the side of the lobe, leaks passing marginally to the disc (peridisc leaks) will be assessed as well (with the same method used for PDLs). Finally, in Amulet subgroup the percentage of disc covering will be assessed as well.

10.2.4 Coronary artery assessment subgroup

Circumflex artery has a close anatomical relationship with LAA and both Watchman/FLX and Amulet devices are implanted in a region adjacent to that vessel. Our group has recently observed some cases of subocclusive stenosis of proximal circumflex artery occurred few years after LAAC. In both cases, despite of the close proximity between the LAAC device and the stenosis, no signs of external compression have been detected. Therefore, we speculated that LAAC could have accelerated the local inflammatory process and the progression of coronary plaque burden in the circumflex artery compared to other coronary arteries. In order to test this hypothesis (with the aim to detect some trend), we will use the serial CCTAs, to assess the difference between the circumflex artery and the remaining coronary arteries in terms of coronary plaque burden progression after 1 year. The coronary plaque burden progression is defined as the absolute annual increase in total, calcified, and noncalcified plaque volume; therefore

it consists of the difference between of total plaque volume (in particular the non calcified component) measured by 13 month CCTA and that measured by the preprocedural or 45 day CCTA.

In this subgroup analysis will be included all the patients with at least one of the first two CCTAs and the third CCTA with a sufficient images quality (as evaluated by the ICL) to assess coronary plaque burden. The use of nitrates and betablocker is aimed at obtaining CCTA images suitable not only for LAA patency but also for coronary artery disease assessment.[23] Images reconstruction will be optimized using the most suitable cardiac cycle phase (i.e. diastole at 70-80% of the R-R interval).

11. SAFETYREPORTING

During the entire duration of the study, all serious adverse events (SAEs) and Adverse Events of special interest (AESI) are collected, fully investigated and documented in source documents and electronic case report forms (eCRF). The software platform selected for this study is ICE-Advice Pharma. Study duration encompassed the time from when the participant s is randomized until the last protocol-specific procedure has been completed, including a safety follow-up period.

11.1 Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical/device product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a device (investigational) product, whether or not related to the device (investigational) product. [ICH E6 1.2]

The AESI are the clinical endpoints of the study (see the list and/or any AEs potentially related to them: overall and CV death, cerebrovascular events (including possible events like fall, syncope, headaches, blurred vision, etc.), cardiovascular events (including possible events like hypotension, myocardial infarction, chest pain, unstable angina), bleeding events (including anemization without overt bleeding); procedure-related complications (any AE occurred within 7 days after LAAC and potentially related to the procedure). All the AESI will be evaluated by the CEC and adjudicated as clinical endpoints of the study according the definitions mentioned in Appendix 1.

A **Serious Adverse Event (SAE)** is classified as any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires in-patient hospitalization or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

11.2 Reporting of serious adverse events (SAE) and other safety related events

Adverse events (SAE and AESI) reporting will start once the patient is considered fully enrolled for the study (after randomization).

All SAEs must be reported immediately and within a maximum of 24 hours of awareness to the Sponsor of the study. SAEs should be reported to the Sponsor using the eCRF. All SAE will be reported to the EC by the Sponsor in the Annual Safety Report. AESI should be reported to the Sponsor using the eCRF within a maximum of 10 days of awareness.

If safety measures are required, these have to be reported to the EC by the Investigator as well as by the Sponsor within 2 days.

11.3 Follow up of (Serious) Adverse Events

SAEs will be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilisation of the disease after termination.

12. STATISTICAL METHODS

Statistical considerations

12.1 Hypothesis

Null hypothesis A (H_{0A}): ACP Amulet is superior in terms of complete LAA occlusion to WATCHMAN/FLX device and is more feasibility.

Null hypothesis B (H_{0B}): there is no difference between ACP Amulet and WATCHMAN/FLX in terms safety, feasibility and LAA patency.

12.2 Determination of Sample Size

Considering an incidence of the primary composite end-point in the range of 50% in the Watchman/FLX group, which is a conservative estimate based on previous reports, we estimate that 200 patients will provide greater than 80% power to prove superiority of Amulet as compared to Watchman/FLX assuming a 40% risk reduction (i.e. corresponding to an event rate in the range of 30%) and a significance level of 5% (alpha).

12.3 Statistical criteria of termination of trial

No statistical interim analyses are planned.

12.4 Planned Analyses

Datasets to be analysed, analysis populations

The main analysis of the primary endpoint will be conducted on all randomized patients who have completed the 45-day follow-up according to the intention to treat principle, in keeping with the superiority prespecified study hypothesis. Additional analyses of the primary endpoint will be also carried out in the per-protocol and as-treated populations. Similarly, LAA patency and DRT at 45-day and 13-month CCTA and at 45-day TEE **as well as clinical outcomes** will also be analyzed in the per-protocol and as-treated population.

Primary and secondary Analysis

Primary and secondary end points will be analysed on an intention-to-treat basis; as above mentioned some of them will be analysed also in the per-protocol and as-treated populations. Categorical outcome measures will compared using a $\chi 2$ test or Fisher exact test as required. Continuous variables will compared using a 2-sided unpaired t test or a Mann-Whitney test, as appropriate. Estimation of the cumulative incidence of safety and efficacy endpoints will be performed using the Kaplan-Meier method, and event rates will be compared by the log rank test The estimated relative risk (RR) is the ratio of the risk probabilities, and a confidence interval will constructed based on a logarithmic transformation. Correlations between variables will analyzed with a Cox regression.

Interim analyses

No statistical interim analyses planned.

Safety analysis

No statistical interim analyses planned.

Deviation(s) from the original statistical plan

Any deviation from the planned analyses will be reported in the final trial report.

12.5 Handling of missing data and drop-outs

Patients with missing data for the primary end-point will be excluded from the primary analysis.

13. QUALITY ASSURANCE AND CONTROL

13.1 Data handling and record keeping / archiving

The Local Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual enrolled in the study.

An electronic data capture (EDC) system will be developed for the study. The software platform selected for this study is ICE-Advice Pharma, a webbased system has an integrated audit trail fulfils the legal requirements for an EDC system. It will include electronic case report forms (eCRFs) designed to capture study information. The forms

will be completed by trained site staff. eCRFs documenting SAEs should be submitted via the EDC system within 24 hours after the investigator becomes aware of the event. All other eCRFs should be completed in a timely manner, preferably within 5-10 days of the subject's enrolment or follow-up visit.

The subject's anonymity will be maintained and the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with applicable legal requirements.Patients data will be encoded:

- Subjects will be identified only by their assigned study number and year of birth on all CRFs
- The investigator will keep a Patient Identification List with complete identification information (name, address, contact number) on each subject.
- The investigator will maintain all study documents in strict confidence.
- CRF entries will be performed by authorized persons only, who will validate the data with an electronic signature after entering it into the eCRF. Copy of procedural angiogram, cardiac CCTA, TEE and ECG will be stored at the main site in Bern.

All data will be cleared of any sensible personal information, patients will be identified by their assigned study number. For end-point adjudication data will be examined without any form of identification (blinded).

13.2 Specification of source documents

Source data must be available at the site to document the existence of the study participants. Source data must include the original documents or certified copies relating to the study, as well as the medical treatment and medical history of the participant. Source documents include demographic data, visit dates, participation in study and Informed Consent Forms, randomization number, SAEs, AESI and concomitant medication, and results of relevant examinations. The investigator assures that source documents are appropriately stored and completed. The patient's file will reveal that this patient is a study participant by entering the following details: study name, protocol number, date of enrolment, informed consent obtained prior to any study specific procedure. Each follow up visit will be reported in the source data and should at least contain the information required according the protocol. The investigator assures that medical files and Case Record Forms are accessible for inspection by authorities and monitoring visits.

All study data must be archived for a minimum of 15 years after study termination or premature termination of the clinical trial.

13.3 Data management

Clinical Trial Unit (CTU) – Bern University, will be in charge for data management and analysis.

Every investigator has access to data of patients enrolled in the own site. CTU in Bern has access to all patient data and can lock patient's data at the end of the trial. Once locked, data can no longer be modified by site investigator.

13.4 Monitoring

Monitoring, which will be carried out by experienced personel employed by CTU (Dr Enrico Frigoli, MD) and Advice Pharma as well as by cardiologists in training working at our institution as research or clinical/research fellows independent from the SWISS Apero study team, will verify that the rights and well-being of the patients are protected, the trial is conducted according to Good Clinical Practices (GCP) and ISO14155, and that the protocol is followed. The dates of the visits will be recorded by the monitor in a log kept at the site. The source data/documents should be accessible to monitors and questions should be answered during monitoring. The Local Investigator and their relevant personnel should be available during monitoring visit and possible audits and sufficient time should be devoted to the process. The progress of the study will be monitored by:

- Informed Consent Forms for each study participant
- Ensuring completed eCRFs match source documents, and resolution of any discrepancies. Direct access to complete source documents must be made available during monitoring visits for verification of eCRF data
- Periodic on-site visits and, if necessary, remote monitoring of data.

13.5 Audits and Inspections

The study site may be subject to audits and inspections to verify that the rights and well-being of the patients are protected, the trial is conducted according to Good Clinical Practices (GCP) and ISO14155, and that the protocol is followed. The study documentation and the source data/documents should be accessible to auditors/inspectors (also EC) and questions should be answered during inspections. All involved parties must keep the participant data strictly confidential.

13.6 Confidentiality, Data Protection

Direct access to source documents will be permitted for monitoring, audits and inspections.Clinical Trial Unit – Bern

has full access to protocol, dataset and statistical codes, during and after the study.

14. PUBLICATION AND DISSEMINATION POLICY

After the database has been closed, findings will be shared and discussed with all of the investigators for the study. An estimated timeline for creation of an abstract will be defined at that time. An abstract of the completed study, after input from all the authors, will be submitted to the most important and representative international meetings. A manuscript of the study, having received input from all of the authors, is tentatively scheduled for submission in a renowned international medical journal. Authorship will be selected according to the requirements of the New England Journal of Medicine (http://www.icmje.org/). These indicate that every author provided such contribution to the clinical trial and the subsequent publication that he can take public responsibility for the integrity of the entire work. Therefore the credit for authorship requires substantial contributions to:

1. The conception and design or analysis and interpretation of the data.

2. The drafting of the article or critical revision for important intellectual content.

3. Final approval of the version to be published.

Authors must have fundamentally taken part in all of the 3 aspects.

For the main publication each of the 4 main centres will obtain at least 1 authorship, if the above-mentioned requirements 1-3 are met. Prior to sub-publication consultation and agreement of the coordinating investigator and the steering committee are mandatory.

15. FUNDING AND SUPPORT

This study is an Investigator Initiated Trial supported by a grant from St. Jude Medical-Abbott.

16. INSURANCE

Subjects who participate in this study will be insured against study related injury according to local regulatory requirements. A copy of the certificate is filed in each investigator site file and in the trial master file.

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APPENDIX 1: ENDPOINT AND ADVERSE CLINICAL EVENT DEFINITIONS [24]

17.1 INDICATIONS FOR LAAC THERAPY

Potential indications	Example
A.Patient not eligible for long-termOACtherapy (absolute or relative contraindications to OAC)	
1. High bleeding risk (HBR)	
• History of major or minor bleeding (with or without OAC therapy)	• Intracranial bleeding • GI bleeding • Symptomatic bleeding in critical organ (i.e. ocular, pericardial, spinal cord) • Recurrent epistaxis needing medical attention
• Increased risk for bleeding due to physical condition and/orco-morbidities	• Recurrent falls with head trauma and significant musculoskeletal injury • Need for additional dual antiplatelet therapy for CAD and stenting. • Diffuse intracranial amyloid angiopathy • Bowel angiodysplasia • Severe renal insufficiency/haemodialysis • Blood cell dyscrasia
2. Inability to take OACs for reasons other than high risk for bleeding	• Intolerance • Documented poor adherence to medication • Documented variability in international normalized ratio on warfarin • Higher-risk occupation with increased injury potential • Patient's choice
B. Thromboembolic event or documented presence ofthrombus in the LAA despite adequate OAC therapy	• Embolic stroke or other systemic thromboembolism on adequate OACtherapy with evidence for thrombus origin from the LAA ('malignant LAA') • Documented thrombus formation in the LAA on adequate OAC therapy

17.2 MORTALITY DEFINITIONS

All deaths will be categorized as cardiovascular (CV) or non-cardiovascular based on the definitions below.

Cardiovascular Death

CV Death is defined as death resulting from a proximate cardiac cause (e.g. myocardial infarction, worsening heart failure, etc.), vascular cerebral nervous system (CNS) causes, sudden cardiac death, from CV procedures, from other cardiovascular causes, and death of unknown cause.

Death due to proximate cardiac causes

Death related to proximate cardiac causes include those resulting from one or more of the following conditions: acute myocardial infarction (AMI), worsening heart failure, endocarditis.

Acute Myocardial Infarction- Death by any mechanism (arrhythmia, heart failure, low output) within 30 days after an AMI and related to its immediate consequences, such as progressive congestive heart failure (CHF), inadequate cardiac output, or refractory arrhythmia. If these events occur after a "break"

(e.g., a CHF and arrhythmia free period of at least a week), they should be designated by the immediate cause, even though the AMI may have increased the risk of that event. AMI should be verified to the extent possible by the diagnostic criteria outlined for AMI or by autopsy findings showing recent myocardial infarction or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Death resulting from a procedure to treat a myocardial infarction percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction, should also be considered death due to AMI. Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a myocardial infarction that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure. Worsening Heart Failure- Death due to worsening heart failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure not following an AMI. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, endocarditis, hypertension, valvular disease.

Death due to vascular cerebral nervous system causes

Death that occurs after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

Sudden Cardiac Death

Death that occurs unexpectedly, not following an AMI, and including the following deaths:
death witnessed and occurring without new or worsening symptoms; death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless documented (i.e. by ECG or other objective) to be due to acute myocardial infarction; death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review); death after unsuccessful resuscitation from cardiac arrest; death after successful resuscitation from cardiac arrest and without identification of a noncardiac etiology; unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available).
General Considerations- A subject seen alive and clinically stable 24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death." Typical scenarios include: Subject well the previous day but found dead in bed the next day;
Subject found dead at home on the couch with the television on. Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes".

Death due to Cardiovascular procedures

Death related to CV procedures refers to death caused by the immediate complications of a CV procedure and excludes death resulting from procedures to treat an AMI or the complications resulting from an AMI.

Death due to Other Cardiovascular Causes

CV deaths not included in the above categories will be considered "due to other CV causes". This category includes deaths resulting from one of the following conditions: pulmonary embolism, peripheral arterial disease, non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

Death of unknown cause

Death of unknown cause refers to a death not attributable to CV or non CV death due to absence of any information (e.g., the only available information is "patient died"). The use of this category of death is discouraged and should apply to a minimal number of cases when no information at all on the circumstances of death are available (i.e. found on obituary of local newspaper). In all circumstances

the reviewer will use all available information to attribute to one of the categories based on best clinical judgment.

Non Cardiovascular Death

Non Cardiovascular Death is defined as death of a primary cause that is clearly related to another condition (e.g. trauma, cancer, suicide).

17.3 DIAGNOSTIC CRITERIA FOR STROKE AND TIA

Stroke is defined as brain, spinal cord, or retinal cell death attributable to ischemia or hemorrhage, based on at least one of the following conditions:

-clinical evidence of focal ischemic injury with symptoms persisting ≥24 hours or until death and without any possible etiologies, OR

-objective evidence of focal ischemic injury in a defined vascular distribution.[25]

Based on this definition, stroke endpoint will be adjudicated taking into account three elements: the neurological dysfunction, absence of a nonvascular mechanism, and imaging evidence of ischemic injury. The neurologic dysfunction consists of an acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, one-sided numbness or sensory loss, dysphasia or aphasia, hemianopia, amaurosis fugax, any other neurological signs or symptoms consistent with stroke. Furthermore, duration of neurological dysfunction longer than 24h helps to exclude transient ischemic attack (TIA). Other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumour, trauma, infection, hypoglycaemia, peripheral lesion, pharmacologic influences) will be excluded based on clinical/imaging assessment. The objective evidence of focal ischemic injury will be performed by means of neuroimaging procedure (computed tomography (CT) scan or brain magnetic resonance imaging (MRI)) findings. Again, imaging-documented new haemorrhage or infarction will be useful to exclude TIA in the event that duration of neurological dysfunction is shorter than 24 h.

Classification:

Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by CNS infarction. Evidence of infarction is defined as pathological, imaging, or other objective evidence of acute cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution. In absence of the above (i.e. imaging or autopsy unavailable), clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury is based on symptoms persisting ≥24 hours or until death, after excluding other etiologies.

Note, hemorrhagic infarction, defined as a parenchymal hemorrhage after CNS infarction, is considered an ischemic stroke.

Haemorrhagic Stroke

Haemorrhagic Stroke is defined as a rapidly developing clinical signs of neurological dysfunction (focal or global) attributable to a focal collection of blood within the brain parenchyma, ventricular system or subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), that is not caused by trauma. Hemorrhages in the CNS are classified as stroke if they are nontraumatic, caused by a vascular event, and result in injury to the CNS. In contrast,

traumatic hemorrhages and subdural hematoma will not be characterized as stroke. The diagnoses included in this section are intracerebral hemorrhage (intraparenchymal and intraventricular) and subarachnoid hemorrhage (both aneurysmal and nonaneurysmal).

Undetermined Stroke
Undetermined Stroke is defined as an acute episode of focal or global neurological dysfunction persisting ≥24 hours (or until death) caused by presumed brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction but with insufficient information to allow categorization as an ischaemic or haemorrhagic stroke.

Stroke severity
Disabling strokes will be adjudicated based on residual neurological dysfunction.
Stroke is defined as "disabling" if at 90 days after the index event, a modified Rankin Scale (mRS) score of ≥ 3 and a mRS score increases of at least 1 compared with pre-stroke baseline.
Non-disabling stroke are defined as any stroke not satisfying the criteria for disabling stroke (i.e. an mRS score of 2 at 90 days or an increase in mRS score of 1 compared with pre-stroke baseline).
Furthermore mortality stroke related will be assessed. Death will be considered stroke related (CV death) even if it results from other causes but occurs ≤ 30 days after onset of stroke.

17.4 DEFINITION OF SYSTEMIC EMBOLISM

- Systemic embolism is defined as an acute vascular insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (e.g. trauma, atherosclerosis, or instrumentation). When there is presence of prior peripheral artery disease, angiographic or surgical or autopsy evidence is required to show abrupt arterial occlusion.

17.5 PULMONARY EMBOLISM

- Pulmonary embolism (PE) is defined as an acute vascular insufficiency or occlusion in one of the pulmonary arteries or one of their branches. Clinical signs and symptoms suggesting PE should be confirmed by a recommended imaging diagnostic test as CT (or perfusion/ventilation pulmonary scintigraphy if CT is not available). Clinical features such as cyanosis, dyspnoea, tachycardia and hypotension should be documented to enable assessment of severity but are not sufficient for diagnosis because of lack of specificity and low sensitivity. Similarly changes in electro-cardiographs, pulse oximetry and chest x-ray cannot be relied upon for diagnosis but may be used as auxiliary tests.

17.6 DEFINITIONS FOR SEVERITY AND TIME OF OCCURRENCE OF PERICARDIAL EFFUSION

Clinically non-relevant	• Requiring no intervention • Treated pharmacologically
Clinically relevant	• Treated with therapeutic pericardiocentesis • Treated with surgical intervention • Requiring blood transfusion • Resulting in shock and/or death

17.7 BLEEDING DEFINITIONS

All potential bleeding events will be adjudicated according to Bleeding Academic Research Consortium (BARC) classification (see the table below) as well as

according to TIMI and GUSTO classifications.

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional. May include episodes leading to self-discontinuation of medical therapy by the patient, without consulting a health care professional.
Type 2	Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5 but does meet at least one of the following criteria: -Requiring non-surgical, medical intervention by a health care professional -Leading to hospitalization of increased level of care -Prompting evaluation
Type 3a	Overt bleeding plus hemoglobin drop of 3 to <5* g/dL (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding
Type 3b	Overt bleeding plus hemoglobin drop ≥5* g/dL (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental / nasal / skin / hemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal) Subcategories: confirmed by autopsy or imaging or lumbar puncture Intra-ocular bleed compromising vision
Type 4	CABG-related bleeding Perioperative intracranial bleeding within 48 hours Reoperation following closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥ 5 units of whole blood or packed red blood cells within 48 hour period† Chest tube output ≥ 2 L within a 24 hour period
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious
Type 5b	Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood_1g/dL hemoglobin). † Cell saver products will not be counted

17.8 DEFINITION OF VASCULAR ACCESS-RELATED COMPLICATIONS

Any of the following events:

- Haematoma at access site >6 cm
- Retroperitoneal haematoma,
- Arteriovenous fistula
- Arterial complications (thrombosis and/or stenosis and/or distal embolization with clinical ischaemia, perforation, dissection, aneurysm,
- pseudoaneurysm)
- Venous complications (venous dissection, laceration, perforation)
- Symptomatic peripheral ischaemia/nerve injury with clinical symptoms lasting >24 h
- Vascular surgical repair at catheter access sites
- Pulmonary embolism
- Ipsilateral deep vein thrombosis
- Access site-related infection requiring intravenous antibiotics or extended hospitalizationand at the follow up visits.

17.9 DEFINITION OF EPICARDIAL OR MINIMAL INVASIVE SURGICAL ACCESS-RELATED COMPLICATIONS

Any of the following events:

- Perforation of cardiac vessel or cardiac wall requiring blood transfusion or surgical or percutaneous intervention,
- Puncture of pulmonary tissue requiring blood transfusion, chest tube, or surgical or percutaneous intervention,
- Puncture of abdominal organs requiring blood transfusion or surgical intervention,
- Perforation or laceration of superficial epigastric artery or LIMA requiring surgical or percutaneous intervention.

17.10 DEVICE-RELATED COMPLICATIONS

- Device embolization
    - Major: Device embolization that requires repeated catheterization or surgery or results in damage to surrounding cardiovascular structures.
    - Minor: Device embolization resolved by percutaneous retrieval during the procedure without surgical intervention or damage to surrounding cardiovascular structures.
- Device erosion
- Clinically significant device interference with surrounding structure (circumflex coronary artery, mitral valve, pulmonary artery, pulmonary vein)
- Device thrombus
- Device fracture
- Device infection/endocarditis/pericarditis
- Device perforation/laceration
- Device allergy.

17.11 DEVICE RELATED THROMBOSIS

DRT is a clot that forms on the atrial surface of the device during or after its implantation. However, there is currently no uniform definition or classification of DRT for LAA closure devices. The shape could be pedunculated or laminar. It can develop on many different parts of the device's surface, mostly on the central part of the lobe/disc (at the level of the pin) or in the recess adjacent to the Coumadin ridge.

This endpoint will be separately adjudicated by means of two imaging methods: TEE and CCTA.

TEE – DRT is defined at TEE evaluation as a homogenous mass with an echogenicity comparable to the myocardium on the atrial surface of the device, inconsistent with normal healing/device incorporation process and not explained by imaging artefact. DRT can have a pedunculated shape with an independent motion or be sessile without any motion and is visible in multiple planes. The occurrence of DRT will be locally ascertained at the very time of the TEE by an expert echocardiographer with extensive previous and ongoing work imaging on LAAC devices.

CCTA – DRT is defined at CCTA evaluation as homogenous hypoattenuated thickening (HAT) on the atrial surface of the device. Currently there is no uniform definition of DRT and differentiating it from prominent endothelialization by CCTA is not always easy. The occurrence of DRT will be centrally evaluated and adjudicated by the ICL, composed of three imaging experts who will independently score each of the studies as positive, possible or negative for DRT. In the event of inconsistent adjudication between the three readers, a consensus between all of them will be required. As previously suggested, assessment and scoring of HAT will be based on the following parameters: shape, maximum tickening, continuation onto the LA wall, HU HAT/HU LA ratio, cross sectional area at the base.

17.12 SUCCESS DEFINITIONS

Device success	• Device deployed and implanted in correct position

Technical success	• Exclusion of the LAA • No device-related complications • No leak ≥ 3 mm on colour Doppler TEE
Procedural success	• Technical success • No procedure-related complications, except for uncomplicated (minor) device embolization.

17.13 LAA PATENCY ASSESSED BY TEE

At 45 days after LAAC, patients will undergo a TEE assessment (and a CCTA as well). Device deployment will be assessed from 0° to 135° (0° - 45° - 90° - 135°) with and without color Doppler (using a scale 50-60 cm/sec). Presence of leak will be locally ascertained by expert echocardiographers with extensive previous and ongoing work imaging on LAAC devices. Leak on TEE is defined as any jet between LAA and LA or conversely detectable by means of color-Doppler (high velocity 50-60 cm/sec). The size is measured taking the narrowest flow region of the jet that occurs at, or just close to, the device.

Of note, rate of LAA patency at 45 day CCTA will be compared with rate of leak at 45 day TEE.

17.14 FEASIBILITY OUTCOMES

During the index procedure, data related to number of device implantation attempts, total time procedure, x-ray dose and total contrast dose used in the procedure will be recorded (secondary endpoints).

Number of device implantation attempts

Device implantation attempt is defined as any delivery sheath retracting (or any advancement of device outside of delivery sheath in the event of “advancement technique” with Watchman FLX) aimed at exposing and implanting the device lobe. The number of partial and complete device recaptures will be recorder. Partial recapture is defined as the partial re-entry of the device into the delivery sheath keeping the hooks/anchors outside. Complete recapture is defined as the complete re-entry of the device into the delivery sheath (including the hooks/anchors).

Total time procedure

It refers to the time between the venous access puncture and its closure. In the event of a concomitant procedure performed right after LAAC, the ending time will be considered the time of device release.

X-ray dose procedure and total contrast dose procedure

Data related to X-ray and medium contrast doses used during LAAC will be recorded. In the event of a concomitant procedure, a careful differentiation between LAAC data and concomitant procedure data will be performed.

17.15 STAGING SYSTEM FOR ACUTE RENAL INJURY

Acute kidney injury (AKI) refers to an abrupt decrease in kidney function, resulting in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes. AKI will be adjudicated, according the latest Guidelines for AKI management,8 if one of the following criteria is met:

- Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L) within 48 hours;
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have

occurred within the prior seven days;

- Urine volume <0.5 mL/kg/hour for six hours.

AKI will be subsequently staged for severity according to the criteria mentioned below.

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine to 150–200% (1.5–1.99× increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 mmol/L)	Less than 0.5 mL/kg/h for more than 6 but<12 h
2	Increase in serum creatinine to 200–300% (2.0–2.99× increase compared with baseline)	Less than 0.5 ml/kg/h for more than 12 but <24 h
3	Increase in renal creatinine to ≥300% (.3× increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L)	Less than 0.3 mL/kg/h for 24 h OR anuria for 12 h

18. APPENDIX 2: ISTRUCTIONS FOR USE

See Instructions for Use - AMPLATZER™ AMULET™Left Atrial Appendage Occluder, 2017-02St Jude Medical

See Instructions for Use - WATCHMAN™Left Atrial Appendage Closure Device withDelivery System 2017-08Boston Scientific Corporation

See Instructions for Use – WATCHMAN FLX™Left Atrial Appendage Closure Device withDelivery System 2017-08Boston Scientific Corporation

UNIVERSITÄT BERN

Faculty of Medicine

CTU Bern

Statistical Analysis Plan (SAP)

SWISS-APERO

Comparison of Amplatzer Amulet vs Watchman device in patients undergoing left atrial appendage closure: the SWISS-APERO randomized clinical trial

Administrative Information

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Contributors

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Contents

1. Introduction

1.1 Background and rationale

Non-valvular Atrial fibrillation (NVAF) is the most common cardiac arrhythmia and a major cause of morbidity and mortality because of cardioembolic stroke. Cardiac embolism due to AF causes up to 25% of all ischemic strokes, which makes it socioeconomically highly relevant. Oral anticoagulation (OAC) with vitamin K antagonists (VKA) or Non-vitamin K antagonist anticoagulant (NOAC) is the most effective prophylaxis for stroke in AF. Yet, (N)OAC therapy is associated with a significant bleeding liability and long-term (N)OAC therapy in patients with NVAF and concomitant high bleeding risk poses safety issues in a sizable and growing population in clinical practice. Post-mortem and echocardiographic studies have shown that the vast majority of all cardiac thrombi in patients with NVAF form in the left atrial appendage (LAA). Thus, a new and emerging therapeutic option in this high-risk patient population is the exclusion of the LAA cavity from the circulation via percutaneous intervention.

Currently, the Amplatzer ACP/Amulet ™ (St. Jude Medical-Abbott), and the Watchman™ (Boston Scientific, Natick, MA, USA) are the devices with most clinical experience reported to date for percutaneous closure of LAA. The Watchman was tested in the setting of two randomized control trials, which demonstrated the safety of the procedure and the non-inferiority in terms of stroke reduction compared to OAC. A second-generation device, the Watchman FLX was developed and released for simplified implantation to fit a wider range of patients and to enhance sealing within the left atrial appendage. It gained the CE mark in the beginning of 2019.

Until a few years ago in Europe the device most frequently utilized for LAA closure was the Amplatzer Cardiac Plug™ (ACP, St. Jude Medical-Abbott), which gained CE approval in late 2008. There is no RCT comparing ACP with OAC, but many prospective and retrospective studies had shown the same safety profile and the non-inferiority with the OAC. A second-generation device, the Amulet™, was developed and released in 2013 for easier delivery, better coverage, and reduction of complications.

A critical step for each LAA closure procedure is the appraisal of LAA residual or new patency/leaks after device implantation. In the setting of available randomized trials (currently only limited to the Watchman device), successful closure was defined by the presence of a peridevice flow ≤ 5 mm assessed with TEE 45 days after the procedure. In these trials, as well as according to the current instruction for use of Watchman, the appraisal of residual leaks 45 days after LAAC was/is considered mandatory for a correct post procedural management of pharmacotherapy (in terms of continuation or reinstitution of OAC therapy). Furthermore, there is a growing attention to the natural history of peridevice leaks given their unpredictable evolution.

Currently the gold standard for the assessment of LAA patency after closure is the TEE. However it is an invasive and operator dependent examination, and replacing it with an alternative non-invasive exam is also desirable for patient's comfort

In the last years, several groups (including ours) assessed the value of CCTA as non-invasive post-procedural surveillance imaging modality after endovascular LAA closure to evaluate residual leak and reported higher sensitivity for CCTA as compared to TEE in the identification of LAA residual patency.

There are currently no randomized controlled trials assessing the degree of LAA closure between Amulet and Watchman/FLX.

1.2 Objectives

The purpose of this study is to compare the efficacy and safety of the two devices for the LAAC, to assess whether Amplatzer Amulet is superior to Watchman/FLX in terms of degree of LAA occlusion as evaluated by CCTA 45 days after implantation.

The primary outcome is the composite of LAA patency at 45 day CCTA and the adjudicated crossover from one device to the other device based on morphological/anatomical considerations during device implantation, including failed implantation adjudicated cross-overs. Post-intervention LAA patency will also assessed via TEE based on the more conservative criterion of residual flow ≥3mm.

2. Study methods

2.1 Trial design

This will be a multicentre, open-label, prospective, randomized study in patients with AF and an indication for anticoagulant therapy with high bleeding risk, that agree to the LAAC procedure. Patients will be submitted to a screening protocol in a period not greater than 90 days before procedure, including medical and drug history, physical examination, 12-lead ECG, CCTA(as per standard of care) and TEE if clinically indicated.

Once the patient is judged eligible and the informed consent has been signed, the patient will be randomly assigned in a 1:1 to receive a LAAC with Amplatzer Amulet or Watchman/FLX device. In the event that the patient is randomized to the Watchman/FLX arm, the operator will be able to choose, on the basis of clinical reasons, if to implant Watchman or the new generation Watchman FLX (if available in the center).

Implantation will be performed according to common practice guidelines (and so with TEE/ICE guidance of procedure). Angiography at the end of the procedure is recommended to assess PDL. In case of concomitant procedure during LAAC, it will be reported separately in term of duration time, contrast dose and x-ray dose.

At the end of procedure, a measure of PDL must be provided.

A transthoracic echocardiogramis encouraged (but not mandatory) before the hospital discharge in order to detect pericardial effusion.

All patients randomly allocated to the Watchman/FLX or Amulet arm will receive ASA and clopidogrel or (N)OAC (at discretion of the treating physician and according to the bleeding risk, stroke risk as well as based on post-procedural TEE evaluation) for 45 days and then will undergo TEE assessment(as well as CCTA):

- *If a residual peri-device leak flow at 45 days > 5 mm or a intra-cardiac thrombus is detected, a therapy with ASA and (N)OAC could be considered up a sequential TEE evaluation at 6 months.*
- *If a residual peri-device leak flow at 45 days ≤ 5 mm is detected, patients will continue to receive ASA and clopidogrelor (N)OAC (at discretion of the treating physician according to the bleeding and stroke risk) up until 3 months after procedure. Thereafter, monotherapy with ASA will be continued until 12 months after procedure.*

These drug regimens are strongly recommended according the actually evidence and the instruction for use of the two devices. Nevertheless, if a clinical condition lead to prescribe other drugs regimen, it will be permitted given an exhaustive explanation by physician.

Further procedures, such as physical examination or blood sampling will be done according the study schedule, in particular visits or phone calls will take place after 6 and 13 month as well as 2/ 3/ 4/ 5 years.

2.2 Randomization

Balanced (1:1) randomization will be performed via a web-based interactive randomization system (ICE-Advice Pharma), based on a computer-generated random sequence with a random block size stratified according to site and an allocation to either Amulet Amplatzer device or Watchman/FLX. In the event that the patient is randomized to the Watchman/FLX arm, the operator will be able to choose, on the basis of clinical reasons, if to implant Watchman or the new generation Watchman FLX (if available in the center). Randomization will occur as close as possible to but always before the procedure and once the patient is judged eligible and the informed consent has been signed.

2.3 Sample size

Considering an incidence of the primary composite end-point in the range of 50% in the Watchman/FLX group, which is a conservative estimate based on previous reports, we estimate that 200 patients will provide greater than 80% power to prove superiority of Amulet as compared to Watchman/FLX assuming a 40% risk reduction (i.e. corresponding to an event rate in the range of 30%) and a significance level of 5% (alpha).

2.4 Framework

We formulate the following hypotheses:

- *Null hypothesis A (H0A): Amulet is superior to WATCHMAN/FLX device in terms of complete LAA occlusion degree and feasibility.*
- *Null hypothesis B (H0B): there is no difference between Amulet and WATCHMAN/FLX in terms of LAA occlusion degree and feasibility.*

2.5 Statistical interim analyses and stopping guidance

No statistical interim analyses are planned.

2.6 Timing of final analysis

The primary endpoint analyses will be performed after all 45 days follow-up visits are conducted and completely entered into the data capture system; and after all data are cleaned and events have been adjudicated. Longer follow-up analyses at e.g. 13 months, 2 years, 3 years, 4 years and 5 years will be conducted as requested, after all data have completely entered into the data capture system; and after all data are cleaned and events have been adjudicated.

2.7 Timing of outcome assessments

Assessment of primary outcome

The primary outcome is the composite of LAA patency at 45 day evaluated with CCTA; or the crossover from one device to the other device based on morphological/anatomical considerations during device implantation, including failed implantation attempts.

Patency LAA will be estimated at CCTA by measurement of the linear attenuation coefficient (Hounsfield unit, HU) in the LAA distal to the device and comparison of contrast density to atrial chamber. LAA patency was defined with LAA HU ≥ 100 or LAA HU ≥ 25% of LA HU, as reported in a previous publication Saw et al. 2015. Adjunctive CCTA criteria of complete occlusion will be collected in order to validate them.

A TEE evaluation of PDL presence will be performed at 45-days in order to compare the two imaging technique.

Assessment of secondary outcomes

Secondary outcomes will be collected at 45 days, 6 months, 13 months, 2 years, 3 years, 4 years and 5 years follow up. Data about event will be collected both in electronic form that with related document (medical reports, CT and other imaging report). LAA patency on arterial phase has been already defined in the previous section

("Assessment of primary outcome"). LAA patency on venous phase is defined, as reported in a previous publication22, as a LAA density ≥ 100 HU or ≥ 150% of that measured at the same site on arterial phase.

Assessment of safety outcomes

Safety outcomes will be assessed 45 days, 6 months, 13 months, 2 years, 3 years, 4 years and 5 years follow up. Data about adverse clinical events will be collected both in electronic form (ICE-Advice Pharma) that with related document (medical reports, CT and other imaging report).

Assessments in participants who prematurely stop the study

Data of withdrawn participants will be collected up to the time of withdrawn. However, withdrawn participants will be asked the permission to continue collecting and evaluate data about them from routine data or other sources (general practitioners, Health System Softwares available) in order to respect the patient choice without affecting the scientific quality of the study.

Study Periods	Enrol ment	Proce dure	Post procedural Hospital discharge	45- day follow up	6- month follow up	13- month follow up	2- year follow up	3- year follow up	4-year follow up	5-year follow up
Time point	1	2	3	4	5	6	7	8	9	10
Time	-90 / 0 d	0 d	up to 48 h	45±7 d	180±7 d	395 ±30 d	730±30 d	1095 ±30 d	1460 ±30 d	1825 ±30 d
Type of follow up[1]				Medica l contact	Medical contact orphone[2]	Medical contact or phone[2]	Medica l contact or phone[2]	Medica l contact or phone[2]	Medica l contact or phone[2]	Medica l contact or phone[2]
Patient Information and Informed Consent	x									
Demographics	x									
Medical History	x			x		x	x	x	x	x
In- /Exclusion Criteria	x									
Physical Examination	x		x	x		(x)	(x)	(x)	(x)	(x)
Vital Signs	x		x	x		x	x	x	x	x
Laboratory test[2]	x		x							
Randomizatio n	X[5]									
12 lead ECG	x	x	x	x		(x)	(x)	(x)	(x)	(x)
TEE	x[3]	x[4]		x[4]	x[3]	(x)[3]				
CCTA	x[4]			X[5]		(x)[5]				
Concomitant therapy, Intervention	x		x	x	x	x	x	x	x	x
LAAC		x								
AE[6] and SAE collection		x	x	x	x	x	x	x	x	x

[1]All types of follow up will be described in Section 9.1.

[2]In case of impossibility of a follow up by medical contact a telephone contact should be performed. It will consist of reporting vital status, adverse clinical events (as defined in 9.1.8 and Appendix 1) and pharmacotherapy.

[3]Performed if clinically indicated

[4]:As per standard of care

[5]:Study specific intervention

[6]As defined in 9.1.8 and Appendix 1

2.8 Blinding

Allocation to the two randomized devices Amulet vs Watchman/FLX is concealed. After the randomization result is available, the study personnel, monitors, the trial statistician receiving the raw data download are not blinded to the randomized device.

However, independent blinded analyses will be conducted by a second statistician who does not know the allocation result of the randomization (e.g. coded X vs Y). Moreover, also the clinical event adjudication committee adjudicating the events is blinded to the randomized device.

The Sponsor will be provided with blinded tables of the primary outcome analyses (e.g. coded X vs Y with no denominators), which the Sponsor can use for final plausibility checks and queries for e.g. outliers to be send to the centres. If this final cleaning process is performed, the Sponsor will receive the unblinded results.

3. Data management

3.1 Data export

Data are stored in the web-based electronic data capturing portal of ICE-Advice Pharma. Data are exported from the ICE-Advice Pharma data capture portal in comma delimited text files with a codebook also in comma delimited text files, by the statisticians.

3.2 Data validation

Before locking, the data will be checked for completeness using e.g. missing tables functions. The plausibility of the primary and secondary outcomes will be checked using outlier analyses and histograms, and will be queried if they are outside the expected range, including dates of events. Only events occurring after the implantation (attempt) of the LAAC device will be analysed, in case no LAAC procedure was started the randomization date will be used instead.

3.3 Data preparation

LAA patency is derived from the average Linear attenuation coefficient within the LAA distal to the device's lobe (artphase_mean2) ≥100 HU OR average Linear attenuation coefficient within the LAA distal to the device's lobe ≥25% of the average Linear attenuation coefficient within the LAA (artphase_mean2/artphase_mean1≥0.25), as recorded inside the follow-up 45 days visit of the Consensus estimate (this is the consensus of the three Core laboratory assessments by three different assessors). LAA patency is a marker of leaks in/out of the LA and therefore a marker of potential thrombus material migration from the LAA to blood circulation system.

Cross-overs are captured in the procedure eCRF and Adjudicated by the clinical event adjudication committee, both successful and failed attempts to cross-over.

The primary endpoint is defined as LA patent or adjudicated cross-overs including failed cross-overs.

Table 1: Derivation of LA patency used in the primary outcome.

Outcome	eCRF sheet	Variable	Variable type	Remarks
LAA patency				
patent = 1	CCTA	`fu_reader = 6 = Consensus`	Categorical	Consensus assessment of three assessors
		`AND (artphase_mean2≥100 OR artphase_mean2/artphase_mean1≥0.25`	Continuous	LAA HU mean distal from device's lobe in arterial phase = artphase_mean2 LA HU mean in arterial phase = artphase_mean1
not patent = 0				artphase_mean2 not missing and not patent as reverse of the above

Clinical events are also adjudicated and these adjudicated events up to 45 days after the LAAC procedure (or randomization date if no procedure was initiated) will be analysed, excluding events occurring before the LAAC procedure (or randomization date if no procedure was initiated) and excluding events occurring on day 46 and later. Adjudicated events beyond 45 days are used for the longer-term follow-up analyses and censored accordingly (e.g. at 1 year, at 5 years).

3.4 Data sharing (if applicable)

Data sharing will be prepared using the CTU Bern Anonymization SOP. Data will be shared on the portal BORIS of the University Bern or equivalent portal. Data can be shared after formal requests with a study proposal are evaluated by the Sponsor.

4. Statistical principles

4.1 Confidence intervals and *P* values

Primary and secondary end points will be analysed on an intention-to-treat basis. Additional analyses will be also carried out in the per-protocol and as-treated populations. Categorical outcome measures will compared using a $\chi 2$ test or Fisher exact test as required. Continuous variables will compared using a 2-sided unpaired t test or a Mann-Whitney test, as appropriate. Estimation of the cumulative incidence of safety and efficacy end-points will be performed using the Kaplan-Meier method in case of time-to-event endpoints, and event rates will be compared by the log rank test. The estimated relative risk (RR) is the ratio of the risk probabilities, and a confidence interval will constructed based on a logarithmic transformation.

The primary endpoint LAA patency or adjudicated cross-over including failed cross-over to other device at 45 days will be analyzed using risk ratios and risk differences.

All statistical tests will be performed using a 5% significance level.

4.2 Analysis populations

The primary endpoint analysis will be performed using the intention to treat principle on the intention-to-treat, full-analysis set population. Sensitivity analyses will be performed on the per-protocol population. Crossover patients will be considered as a primary end-point event in all analyses.

4.2.1 Full analysis set (FAS)

The full analysis set (FAS) will include all randomized subjects. Following the intent-to-treat principle, subjects will be analyzed according to the treatment they are assigned to at randomization.

4.2.2 Per-protocol (PP)

Per-protocol population PP consists of all subjects in the FAS who do not have any major protocol violation. The following items will be considered such a major protocol deviations, which will exclude the patient from the PP (Table 2):

Table 2: Derivation of major protocol violations used for PP definition.

Protocol deviation	eCRF sheet	Variable	Variable type	Derivation of violation
Violation of inclusion or exclusion criteria				
Age ≥18 years (ic1)	Baseline	`age`	Continuous	**age<18**
Written informed consent (ic2)	Baseline	`ic2`	Binary: yes/no	**no**
CHADS2VASC score ≥2 (ic5)	Baseline	`{score based on baseline variables, add points into score}`	Add points	hf=yes (1 point), hypertension=yes (1 point), age≥75 (2 points) OR age 65-74 years (1 point), diabetes=yes (1 point), prior_cerebr=yes OR arterial_embolism=yes OR conc_th=yes (2 points), vasculopathy=yes OR prior_mi=yes OR aortic_plaque=yes (1 point), gender=female (1 point). **Violation if score<2**
HASBLED ≥3 **or** High bleeding risk HBR as defined by Munich consensus document (ic6)	Baseline	`{score based on baseline variables, add points into score}`	Add points	**HASBLED**: uncontroll=yes (1 point), kidney_disease=yes (1 point), liverdisease=yes (1 point), type_cerebr=stroke (1 point), priorbleeding=yes OR anemia=yes OR ind_primary={any of: history of major or minor bleeding, wish to avoid triple therapy, risk of fall, concomitant disease improving bleeding risk ,HASBLED≥3} (1 point) OR hb≤130g/L in male/hb<120g/L in female, inab_oac_variability=3 (1 point), age>65 (1 point), bl_drugs _{oac, noac, aspirin, thienopyridine,fans }=any yes (1 point), alcohol=yes (1 point) **HBR**: priorbleeding=yes OR anemia=yes OR hb≤130g/L in male/hb<120g/L in female **Violation if score≤2 AND HBR=no**
Exclusion criteria not met	Randomization	`exclusion_criteria_exclusion_crit`	Binary: yes/no	**no**
First LAAC device used not according to randomization	Procedure	`first_device, first_imp_att`	Categorical, Number	`Equal to randomized but implantation attempts = 0` **OR**
	Procedure	`first_device`	Categorical	`Unequal to randomized`

CHADS2VASC: see https://www.mdcalc.com/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk

HASBLED: see https://www.mdcalc.com/has-bled-score-major-bleeding-risk

4.2.3 Safety population

The safety population is the population with at least one LAAC device implanted, and is analysed according to the LAAC device actually implanted.

4.3 Estimands

The primary outcome which is the composite of LAA patency at 45 day evaluated with CCTA; or the crossover from one device to the other device based on morphological/anatomical considerations during device implantation, will be reported as the number of occurrences and the proportion of these occurrences given the number of patients.

5. Trial Population

5.1 Screening data

Screening will be performed up to 90 days prior LAAC. Potential patients will be informed about the study and asked for participation. Subjects are considered provisionally enrolled with the signature on the written informed consent form (screening phase). Formal inclusion into the study will occur after baseline eligibility is confirmed and only once randomization takes place as close as possible to but always before LAAC. A copy of the informed consent form with the patient's information document will be given to the patient.

The following evaluations will be performed at baseline/enrolment:

- *Demographics;*
- *Relevant medical history that includes: general medical, cardiovascular, neurologic and renal history; cardiovascular risk factors (e.g. dyslipidaemia, hypertension, diabetes mellitus, tobacco use); history of peripheral vascular disease, stroke, transient ischemic attack;documentation of current cardiovascular and diabetic medications;Stroke and bleeding risk evaluation with CHADS2, CHA2DS2VASc, HAS-BLEED and ABC score;*
- *Evaluation of In-/Exclusion criteria;*
- *12-lead ECG;*
- *Routine laboratory tests within 48 hours prior to the index procedure as defined in 9.1.7;*
- *CCTA according to current standard of care;*
- *TEE if clinically indicated.*

5.2 Eligibility

Participants fulfilling all the following inclusion criteria are eligible for the study:

- *Written informed consent*
- *Male or female subject aged 18 years or more with no upper age limit and willing to comply with the protocol*
- *Indication to a LAA closure as indicated in study population (HAS BLEED ≥3 or High bleeding risk as defined by Munich consensus document and CHA2DS2-VASc≥2).*

The presence of anyone of the following exclusion criteria will lead to exclusion of the participant:

- *New York Heart Association class IV congestive heart failure*
- *ASD or atrial septal repair or closure device*
- *Single occurrence of AF*

- *Cardioversion or ablation procedure planned within 30 days*
- *Implanted mechanical valve prosthesis*
- *Heart transplantation*
- *Enrolled in another IDE or IND investigation of a cardiovascular device or an investigational drug*
- *Female of childbearing potential (age < 50 years and last menstruation within the last 12 months), who did not undergo tubal ligation, ovariectomy or hysterectomy.*
- *Active infection of any kind*
- *Severe chronic kidney insufficiency (CrCl< 30 ml/min)*
- *Terminal illness with life expectancy < 1 year*
- *Echocardiographic exclusion criteria*
- *LVEF < 20%*
- *Intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days before implant*
- *Significant mitral valve stenosis (ie, MV <1.5 cm2)*
- *Complex aortic atheroma with mobile plaque of the descending aorta and/or aortic arch*
- *Cardiac tumor.*

5.3 Recruitment

Patients will be screened previous the admission index. After complete screening pre-evaluation resulting in eligibility for LAAC, patients will be adequate informed and those accepting to participate will sign the informed consent form and will be enrolled in the study by dedicated staff previously identified at each center.

Study participants will not receive any payment or compensation for participation in the study.

5.4 Baseline patient characteristics

A Table of baseline clinical and risk factors will be produced, no comparison randomized to Amulet vs randomized to Watchman will be made.

Table 1. Baseline Clinical Characteristics

	Watchman/FLX N = xx	Amulet N = xx
Demographics		
Age — years mean(SD)	mean +- sd	mean +- sd
Male gender — no. (%)	count (%)	count (%)
Body mass index — kg/m² mean(SD)	mean +- sd	mean +- sd
Behavioural risk factors		
Smoker — no. (%)	count (%)	count (%)
Alcohol abuse — no. (%)	count (%)	count (%)
Medical history		
Arterial hypertension — no. (%)	count (%)	count (%)
Dyslipidemia — no. (%)	count (%)	count (%)
Family history of CAD — no. (%)	count (%)	count (%)
Diabetes mellitus — no. (%)	count (%)	count (%)
Chronic renal failure — no. (%)	count (%)	count (%)
Uncontrolled hypertension — no. (%)	count (%)	count (%)
Abnormal liver function — no. (%)	count (%)	count (%)
Coronary artery disease — no. (%)	count (%)	count (%)
Documented anaemia — no. (%)	count (%)	count (%)
Long-term oral NSAIDs use — no. (%)	count (%)	count (%)
Long-term steroids use — no. (%)	count (%)	count (%)
Active malignancy — no. (%)	count (%)	count (%)
Prior Cerebrovascular event — no. (%)	count (%)	count (%)
Known carotid artery disease — no. (%)	count (%)	count (%)
History of extracranial systemic embolic events — no. (%)	count (%)	count (%)
History of clinically-overt pulmonary embolism — no. (%)	count (%)	count (%)
Primary reason for an alternative to OAC		
History of Major bleedings	count (%)	count (%)
Wish to avoid triple therapy	count (%)	count (%)
Risk of fall or prior falls	count (%)	count (%)
Concomitant disease increasing bleeding risk	count (%)	count (%)
HASBLED score >=3	count (%)	count (%)
Rejection of OAC	count (%)	count (%)
Embolic event under OAC	count (%)	count (%)
Others	count (%)	count (%)
Prior myocardial infarction — no. (%)	count (%)	count (%)

Valvular heart disease — no. (%)	count (%)	count (%)
History of heart failure — no. (%)	count (%)	count (%)
Decompensated heart failure at randomisation — no. (%)	count (%)	count (%)
EHRA III — no. (%)	count (%)	count (%)
Ejection fraction — mean (SD)	mean +- sd	mean +- sd
Pacemaker or ICD — no. (%)	count (%)	count (%)
CHA2DS2VASC Score — mean(SD)	mean +- sd	mean +- sd
— no. (%)		
0	count (%)	count (%)
1	count (%)	count (%)
2	count (%)	count (%)
3	count (%)	count (%)
4	count (%)	count (%)
5	count (%)	count (%)
6	count (%)	count (%)
7	count (%)	count (%)
8	count (%)	count (%)
HASBLED Score — mean(SD)	mean +- sd	mean +- sd
— no. (%)		
0	count (%)	count (%)
1	count (%)	count (%)
2	count (%)	count (%)
3	count (%)	count (%)
4	count (%)	count (%)
5	count (%)	count (%)
6	count (%)	count (%)
Atrial fibrillation or flutter — no. (%)		
paroxysmal — no. (%)	count (%)	count (%)
persistent or chronic — no. (%)	count (%)	count (%)
undetermined — no. (%)	count (%)	count (%)
atrial flutter — no. (%)	count (%)	count (%)
History of relevant bleeding — no. (%)	count (%)	count (%)
Intracranial bleeding — no. (%)	count (%)	count (%)
Gastrointestinal bleeding — no. (%)	count (%)	count (%)
Urinary — no. (%)	count (%)	count (%)
Epistaxis — no. (%)	count (%)	count (%)
Other bleeding — no. (%)	count (%)	count (%)
unknown — no. (%)	count (%)	count (%)

Data expressed as n (%) or means±standard deviations.

MI: myocardial infarction; LAA: left-atrial appendage; EHRA: European Heart Rhythm score.

5.5 LAAC procedural characteristics

A Table of LAAC details will be produced comparing randomized to Amulet vs randomized to Watchman. In case none or very few second, third or fourth devices are used or implanted, this table will be simplified accordingly.

Table 2. LAAC Procedural Characteristics

	Watchman/FLX N = xx	Amulet N = xx	p-value
Starting cardiac rhythm— no. (%)			x.xxx
Sinus	count (%)	count (%)	x.xxx
Atrial fibrillation or flutter	count (%)	count (%)	x.xxx
Other (e.g.pacemaker)	count (%)	count (%)	x.xxx
General anaesthesia — no. (%)	count (%)	count (%)	x.xxx
Left atrium reached by — no. (%)			x.xxx
atrial septum	count (%)	count (%)	x.xxx
fossa ovalis	count (%)	count (%)	x.xxx
PFO or ASD	count (%)	count (%)	x.xxx
Nr of transeptal punctures — no. (%)			x.xxx
zero	count (%)	count (%)	x.xxx
one	count (%)	count (%)	x.xxx
two or more	count (%)	count (%)	x.xxx
Distance between puncture and mitral plane — mm (SD)	mean +- sd	mean +- sd	x.xxx
Mean left atrial pressure before implantation — mmHg	mean +- sd	mean +- sd	x.xxx
Intracardiac echocardiography — no. (%)	count (%)	count (%)	x.xxx
Procedure time — minutes	mean +- sd	mean +- sd	x.xxx
Fluoroscopy time — minutes	mean +- sd	mean +- sd	x.xxx
Contrast medium — ml med(IQR)	mean +- sd	mean +- sd	x.xxx
Contrast medium/body mass — ml/kg	mean +- sd	mean +- sd	x.xxx
X-ray dose — cGy.cm2 med(IQR)	median (IQR)	median (IQR)	x.xxx
Concomitant procedure* — no. (%)	count (%)	count (%)	x.xxx
Final device			
LAAC device — no. (%)			x.xxx
Amulet	count (%)	count (%)	x.xxx
Watchman	count (%)	count (%)	x.xxx
Watchman FLX	count (%)	count (%)	x.xxx
Implanted device size — mm (SD)	mean +- sd	mean +- sd	x.xxx
Procedure aborted	count (%)	count (%)	x.xxx
All LAAC devices			
Total Nr of implantation attempts — no. (%)			x.xxx
1	count (%)	count (%)	x.xxx
2	count (%)	count (%)	x.xxx

3	count (%)	count (%)	x.xxx
4 or more	count (%)	count (%)	x.xxx
Total Nr of partial recaptures — no. (%)			x.xxx
0	count (%)	count (%)	x.xxx
1	count (%)	count (%)	x.xxx
2	count (%)	count (%)	x.xxx
3	count (%)	count (%)	x.xxx
4 or more	count (%)	count (%)	x.xxx
Total Nr of complete recaptures — no. (%)			x.xxx
0	count (%)	count (%)	x.xxx
1	count (%)	count (%)	x.xxx
2	count (%)	count (%)	x.xxx
3	count (%)	count (%)	x.xxx
4 or more	count (%)	count (%)	x.xxx
Total nr of LAAC devices implanted			x.xxx
none	count (%)	count (%)	x.xxx
one	count (%)	count (%)	x.xxx
two	count (%)	count (%)	x.xxx
Total nr of LAAC devices used			x.xxx
1	count (%)	count (%)	x.xxx
2	count (%)	count (%)	x.xxx
3	count (%)	count (%)	x.xxx
End of procedure cardiac rhyth no. (%)			x.xxx
Sinus	count (%)	count (%)	x.xxx
Atrial fibrillation or flutter	count (%)	count (%)	x.xxx
Pacemaker (incl.temporary pacer)	count (%)	count (%)	x.xxx
Post-procedure peri-LAAC device leaks PDL — no. (%)			
Any PDL detected by TEE or Angiography?	count (%)	count (%)	x.xxx
detected by TEE only	count (%)	count (%)	x.xxx
detected by Angiography only	count (%)	count (%)	x.xxx
detected by TEE and Angiography	count (%)	count (%)	x.xxx
Periprocedural complications — no . (%)			
Death	count (%)	count (%)	x.xxx
Stroke or TIA	count (%)	count (%)	x.xxx
Bleeding	count (%)	count (%)	x.xxx
BARC 1	count (%)	count (%)	x.xxx
BARC 2	count (%)	count (%)	x.xxx
BARC 3abc	count (%)	count (%)	x.xxx
BARC 4	count (%)	count (%)	x.xxx
BARC 5ab	count (%)	count (%)	x.xxx
BARC 3-5	count (%)	count (%)	x.xxx
Peripheral or pulmonary embolization	count (%)	count (%)	x.xxx
Pericardial effusion (new onset)	count (%)	count (%)	x.xxx
Pericardial effusion clinically relevant	count (%)	count (%)	x.xxx

Vascular access site complication	count (%)	count (%)	x.xxx
Device embolization	count (%)	count (%)	x.xxx
Acute kidney injury	count (%)	count (%)	x.xxx
Electrical or mechanical resuscitation	count (%)	count (%)	x.xxx

Data expressed as n (%, p-value from Fisher's tests) or means±standard deviations (p-value from unpaired t-tests) or median[IQR] (p-value from Mann-Whitney U-test).

LAAC: left-atrial appendage closure; PFO: patent foramen ovale; ASD: atrial septal defect; ICU: intensive care unit; TIA: transient ischemic attack; TEE: transoesophagal echocardiography.

* Coronary angiography included

5.6 Medication

A Table of medications at each visit will be produced, comparing randomized to Amulet vs randomized to Watchman.

Table 3. Medication use

	Watchman/FLX N = xx	Amulet N = xx	p-value
within 7 days before LAAC — no. (%)			
Aspirin	count (%)	count (%)	
Clopidogrel	count (%)	count (%)	
Prasugrel	count (%)	count (%)	
Ticagrelor	count (%)	count (%)	
Vitamin K-antagonist	count (%)	count (%)	
NOAC	count (%)	count (%)	
Dabigatran	count (%)	count (%)	
Rivaroxaban	count (%)	count (%)	
Apixaban	count (%)	count (%)	
Edoxaban	count (%)	count (%)	
Others	count (%)	count (%)	
Low-molecular weight heparin	count (%)	count (%)	
Therapy			
None	count (%)	count (%)	
SAPT *	count (%)	count (%)	
DAPT **	count (%)	count (%)	
OAC ***	count (%)	count (%)	
SAPT+OAC	count (%)	count (%)	
Triple therapy ***	count (%)	count (%)	
During/after LAAC procedure § — no. (%)			
Aspirin			x.xxx
maintenance dose	count (%)	count (%)	x.xxx
loading dose	count (%)	count (%)	x.xxx
No	count (%)	count (%)	x.xxx
Clopidogrel			x.xxx
maintenance dose	count (%)	count (%)	x.xxx
loading dose 300mg	count (%)	count (%)	x.xxx
loading dose 600mg	count (%)	count (%)	x.xxx
No	count (%)	count (%)	x.xxx
Prasugrel			x.xxx

maintenance dose	count (%)	count (%)	x.xxx
loading dose 60mg	count (%)	count (%)	x.xxx
No	count (%)	count (%)	x.xxx
Ticagrelor			x.xxx
maintenance dose	count (%)	count (%)	x.xxx
loading dose 180mg	count (%)	count (%)	x.xxx
No	count (%)	count (%)	x.xxx
Vitamin K-antagonist	count (%)	count (%)	x.xxx
NOAC	count (%)	count (%)	x.xxx
NOAC Type			x.xxx
Dabigatran	count (%)	count (%)	x.xxx
Rivaroxaban	count (%)	count (%)	x.xxx
Apixaban	count (%)	count (%)	x.xxx
Edoxaban	count (%)	count (%)	x.xxx
Others	count (%)	count (%)	x.xxx
Low-molecular weight heparin	count (%)	count (%)	x.xxx
Discharge — no. (%) ¥	**n=xx**	**n=xx**	
Aspirin	count (%)	count (%)	x.xxx
Clopidogrel	count (%)	count (%)	x.xxx
Prasugrel	count (%)	count (%)	x.xxx
Ticagrelor	count (%)	count (%)	x.xxx
Vitamin K-antagonist	count (%)	count (%)	x.xxx
NOAC	count (%)	count (%)	x.xxx
NOAC Type			x.xxx
Dabigatran	count (%)	count (%)	x.xxx
Rivaroxaban	count (%)	count (%)	x.xxx
Apixaban	count (%)	count (%)	x.xxx
Edoxaban	count (%)	count (%)	x.xxx
Others	count (%)	count (%)	x.xxx
Low-molecular weight heparin	count (%)	count (%)	x.xxx
Therapy			x.xxx
None	count (%)	count (%)	x.xxx
SAPT *	count (%)	count (%)	x.xxx
DAPT **	count (%)	count (%)	x.xxx
OAC ***	count (%)	count (%)	x.xxx
SAPT+OAC	count (%)	count (%)	x.xxx
Triple therapy ***	count (%)	count (%)	x.xxx
Follow-up 45 days — no. (%) ¶	**n=xx**	**n=xx**	
Aspirin	count (%)	count (%)	x.xxx

Clopidogrel	count (%)	count (%)	x.xxx
Prasugrel	count (%)	count (%)	x.xxx
Ticagrelor	count (%)	count (%)	x.xxx
Vitamin K-antagonist	count (%)	count (%)	x.xxx
NOAC	count (%)	count (%)	x.xxx
NOAC Type	count (%)	count (%)	x.xxx
Dabigatran	count (%)	count (%)	x.xxx
Rivaroxaban	count (%)	count (%)	x.xxx
Apixaban	count (%)	count (%)	x.xxx
Edoxaban	count (%)	count (%)	x.xxx
Others	count (%)	count (%)	x.xxx
Low-molecular weight heparin	count (%)	count (%)	x.xxx
Therapy	count (%)	count (%)	x.xxx
None	count (%)	count (%)	x.xxx
SAPT *	count (%)	count (%)	x.xxx
DAPT **	count (%)	count (%)	x.xxx
OAC ***	count (%)	count (%)	x.xxx
SAPT+OAC	count (%)	count (%)	x.xxx
Triple therapy ***	count (%)	count (%)	x.xxx

Data expressed as n (%) and p-values are from Fisher's tests.
* SAPT (Only Aspirin, Only Clopidogrel, Only Prasugrel, Only Ticagrelor)
** DAPT (Aspirin+Clopidogrel, Aspirin+Prasugrel, Aspirin+Ticagrelor)
*** OAC (NOAC, Vitamin K-Antagonist, Low molecular weight heparin)
**** Triple therapy (any combination between DAPT groups AND OAC groups)
§ within 6 hours of the device implantation
¥ xx patients died before discharge
¶ xx patients did not perform 45 day followup

5.7 Primary and secondary outcomes at 45 days of Follow-up

A Table of the primary and secondary outcomes at 45-day visit will be produced, randomized to Amulet vs randomized to Watchman

Table 4. Primary and secondary outcomes at 45 days

	Watchman/FLX N = xx	Amulet N = xx	Amulet vs Watchman Mean difference (95% CI)	p-value
Patent Appendage or justified cross-over to non-randomized device	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Patent Appendage*	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Justified cross-over to non-randomized device¶	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Death	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Cardiovascular death	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Cerebrovascular event	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Stroke	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
ischaemic stroke	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
haemorrhagic stroke	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
TIA	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Systemic or pulmonary embolism	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Systemic embolism	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Pulmonary embolism	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Myocardial infarction	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Device embolization	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Bleeding	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
BARC 2	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
BARC 3abc	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
BARC 4	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
BARC 5ab	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
BARC 3-5	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
TIMI major or minor	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
TIMI major	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
TIMI minor	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
TIMI minimal	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
GUSTO moderate or severe	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
GUSTO severe	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
GUSTO moderate	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
GUSTO mild	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Patient on (N)OAC at 45 days visit	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx

Data expressed as n (%, p-value from Fisher's tests)

¶ Justified crossover is defined as the switch from the randomized device to the other device based on morphological/anatomical considerations during device implantation as centrally assessed by an independent and multidisciplinary clinical event committee (CEC). This parameter was included in the composite primary outcome together with *LAA Patency.

CCTA: cardiac computer tomography angiography. TTE: Transthoracic Echocardiography.

5.8 LAA assessments at 45 days of Follow-up

A Table of the LAA assessments (CCTA by the Core laboratory, TEE by the local teams) at 45-day visit will be produced, randomized to Amulet vs randomized to Watchman.

Table 5. Imaging assessment at 45 days visit

	Watchman/FLX N = xx	Amulet N = xx	Amulet vs Watchman Mean difference (95%	p-value
CCTA assessment				
45day CCTA performed	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Linear attenuation HU— mean (SD) ¶	n = xx, mean +- sd	n = xx, mean +- sd	n = xx, mean +- sd	x.xxx
Patent LAA — no. (%) ¶	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
LAA HU ≥100 arterial phase — no. (%) ¶	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
LAA HU ≥25% arterial phase — no. (%) ¶	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Peridevice leak (PDL) — no. (%) ¶	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Mixed leak (MIL) — no. (%) ¶	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Intradevice leak (IDL) — no. (%) ¶	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Patent LAA with no visible leak — no. (%) ¶	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Linear attenuation HU — mean venous phase (SD) ¥	n = xx, mean +- sd	n = xx, mean +- sd	n = xx, mean +- sd	x.xxx
LAA patency venous phase — no. (%) ¥	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
LAA HU ≥100 venous phase — no. (%) ¥	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
LAA HU on venous phase ≥150% of LAA HU on arterial phase images — no. (%) ¥	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Potential thrombus — no. (%)	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Device related thrombus — no. (%)	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
TEE assessment				
45day TEE performed	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Peridevice leak PDL — no. (%)	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
first PDL — no. (%)	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
PDL leak width — mm mean(SD)	n = xx, mean +- sd	n = xx, mean +- sd	n = xx, mean +- sd	x.xxx
second PDL — no. (%)	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
PDL leak width — mm mean(SD)	n = xx, mean +- sd	n = xx, mean +- sd	n = xx, mean +- sd	x.xxx
Any PDL width ≥3mm — no. (%)	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx
Device related thrombus — no. (%)	n = xx, xx (%)	n = xx, xx (%)	x.x% (x.x%; x.x%)	x.xxx

Data expressed as n (%, p-value from Fisher's tests) or means±standard deviations (p-value from unpaired t-tests) or median[IQR] (p-value from Mann-Whitney U-test).

CCTA: cardiac computer tomography angiography assessed by Core Laboratory. TEE: Transoesophagus Echocardiography assessed by local team.

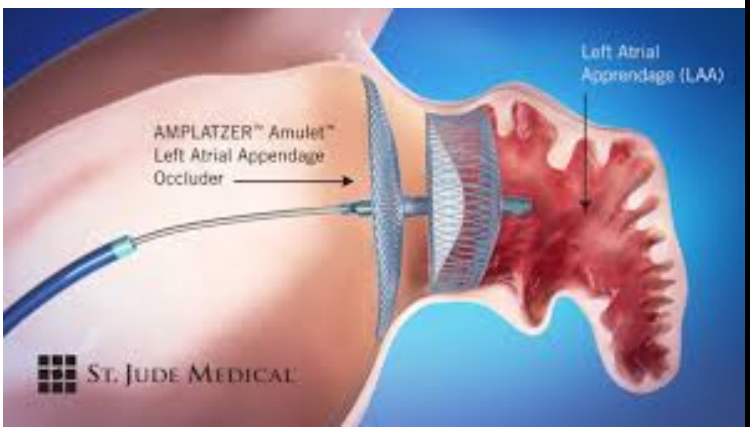
Mixed PDL: PDL transferring into intradevice leak, or intradevice leak transferring into

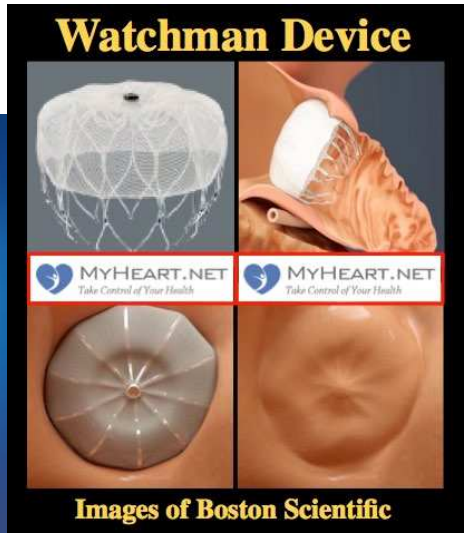
¶: In x of xx CCTAs performed, LAA patency was not assessable (n=xx)

¥: in x of xx CCTAs the venous phase scan was not performed (n=xx)

5.9 Evaluation of Amulet and Watchman implantations

A Table of the Amulet implantation assessment post-procedure and at 45 days will be produced (according to actual device implanted). Similarly, a separate Table with the Watchman implantation assessment post-procedure and at 45 days will be produced (according to actual device implanted). Note that these assessments are not directly comparable across the devices, as these assessments depend on the shape and the structure of the device, e.g. Amulet has lobes with a separate disk, whereas the Watchman only has lobes.





Supplemental Table 1. Evaluation of Amulet / ACP implantation post-procedure and at 45 days visit

	Amulet ACP implanted (N=xx)
Post-procedural TEE assessment	
Is the disc over the left lateral ridge LLR? — no. (%)	x (x.x%)
Distance disc from LLR — mm (SD)	n = xx, xx.x ± x.x
Complete occlusion of the ostium by the disc	x (x.x%)
Concavity of the disc — no. (%)	n = xx, xx.x ± x.x
Separation lobe from the disc >2mm — no. (%)	x (x.x%)
Lobe's shape	
tire — no. (%)	x (x.x%)
strawberry/bell — no. (%)	x (x.x%)
square — no. (%)	x (x.x%)
Angle between lobe-axis and disc-axis of the device — degrees angulation (SD)	n = xx, xx° ± x°
Minimum device diameter — mm (SD)	n = xx, xx.x ± x.x
Partial prolapse of the lobe into left appendage* — no. (%)	x (x.x%)
Peridisk leak PDiL¶ — no. (%)	x (x.x%)
one PDiL — no. (%)	x (x.x%)
two PDiL— no. (%)	x (x.x%)
45 days visit CCTA assessment	
Is the disc over the left lateral ridge LLR? — no. (%)	x (x.x%)
Distance disc from LLR — mm (SD)	n = xx, xx.x ± x.x
Concavity of the disc — mm (SD)	n = xx, xx.x ± x.x
Lobe's shape	
tire — no. (%)	x (x.x%)
strawberry/bell — no. (%)	x (x.x%)
square — no. (%)	x (x.x%)
Separation lobe-disc maximum — mm (SD)	n = xx, xx.x ± x.x
Separation lobe-disc minimum — mm (SD)	n = xx, xx.x ± x.x
Angle between lobe-axis and disc-axis of the device — degrees angulation (SD)	n = xx, xx° ± x°
Lobe diameter minimum — mm (SD)	n = xx, xx.x ± x.x
Lobe diameter maximum — mm (SD)	n = xx, xx.x ± x.x
Partial prolapse of the lobe into left appendage* — no. (%)	x (x.x%)
Peridisk leak PDiL¶ — no. (%)	x (x.x%)
one PDiL — no. (%)	x (x.x%)
two PDiL— no. (%)	x (x.x%)

Only successfully implanted LAAC devices evaluated.

*width of the lobe is $<^2/_3$ within the circumflex artery.

¶leak visible between the disc and the lobe, but only measured if distance between disc and lobe large enough to allow assessment of hue.

CCTA: cardiac computer tomography angiography assessed by Core Laboratory. TEE: Transoesophagus Echocardiography assessed by local team.

includes n=x patient randomized to Watchman / FLX, but were implanted a cross-over Amulet device instead.

Supplemental Table 2. Evaluation of Watchman / FLX implantation post-procedure and at 45 days visit

	Watchman / FLX implanted (N=xx)
Post-procedural TEE assessment	
Maximum device diameter TEE — mm (SD)	n = xx, xx.x ± x.x
Maximum device compression* — % (SD)	n = xx, xx.x ± x.x
Minimum device diameter TEE — mm (SD)	n = xx, xx.x ± x.x
Minimum device compression¶ — % (SD)	n = xx, xx.x ± x.x
Lobe's shape	
inverted— no. (%)	x (x.x%)
marshmallow — no. (%)	x (x.x%)
bell — no. (%)	x (x.x%)
hotdog — no. (%)	x (x.x%)
Position of device from LAA ostium	
at the same level — no. (%)	x (x.x%)
distally — no. (%)	x (x.x%)
proximally — no. (%)	x (x.x%)
Position of the device in respect to the left lateral ridge LLR?	
at the same level — no. (%)	x (x.x%)
distally — no. (%)	x (x.x%)
proximally — no. (%)	x (x.x%)
How far is the Watchman device off-axis to the LAA axis — degrees angulation (SD)	n = xx, xx° ± x°
45 days visit CCTA assessment	
Minimum device diameter — mm (SD)	n = xx, xx.x ± x.x
Minimum device compression¶ — % (SD)	n = xx, xx.x ± x.x
Maximum device diameter — mm (SD)	n = xx, xx.x ± x.x
Maximum device compression* — % (SD)	n = xx, xx.x ± x.x
Lobe's shape	
inverted— no. (%)	x (x.x%)
marshmallow — no. (%)	x (x.x%)
bell — no. (%)	x (x.x%)
hotdog— no. (%)	x (x.x%)
Position of device from LAA ostium	
at the same level — no. (%)	x (x.x%)

distally — no. (%)	x (x.x%)
proximally — no. (%)	x (x.x%)
Position of the device in respect to the left lateral ridge LLR?	
at the same level — no. (%)	x (x.x%)
distally — no. (%)	x (x.x%)
proximally — no. (%)	x (x.x%)
How far is the device from the left lateral ridge LLR? — mm (SD)	n = xx, xx.x ± x.x
How far is the Watchman device off-axis to the LAA axis — degrees angulation (SD)	n = xx, xx° ± x°

Only successfully implanted LAAC devices evaluated.

*(Manufacturer device diameter - maximum implanted device diameter)*100%

¶(Manufacturer device diameter - minimum implanted device diameter)*100%

CCTA: cardiac computer tomography angiography assessed by Core Laboratory. TEE: Transoesophagus Echocardiography assessed by local team.

includes n=x patient randomized to Amulet / ACP, but were implanted a cross-over Watchman device instead.

5.10 Withdrawal/follow-up

Withdrawal, lost-to-follow-up and missed assessments of the primary outcome will be reported in the flowchart, separately for randomized to Amulet and randomized to Watchman.

6. Analysis

6.1 Outcome definitions

Outcomes will be compared randomized to Amulet vs randomized to Watchman.

6.1.1 Primary outcome

The primary outcome is the composite of LAA patency at 45 day CCTA or the crossover from one device to the other device based on morphological/anatomical considerations during device implantation.

6.1.2 Secondary outcome

Secondary outcomes are:

- *LAA patency (arterial and/or venous phase) at 45 day CCTA and 13-month CCTA in the per protocol and as treated populations*
- *All cause of death, stroke, systemic or pulmonary embolism and spontaneous MI*
- *Cardiovascular death*
- *Ischemic stroke*
- *Hemorrhagic stroke*
- *Bleeding events according to the BARC classification at each follow-up.*
- *Procedure-related complications*
- *Rate of patients on (N)OAC at 45 days and 6 months*
- *Device related thrombosis at 45 day TEE/CCTA and 13-month CCTA in the per protocol and as treated populations*
- *Feasibility outcome (number of device implantation attempts, total time procedure, x-ray dose and total contrast dose used in the procedure)*
- *LAA patency at 45 day TEE in the per protocol and as treated populations*

6.1.3 Safety outcome

The main safety outcomes are:

- *Bleeding Academic Research Consortium (BARC) bleeding grade 2, 3 and 5 up to 48 hours or discharge whichever comes first and 45 days*

- *Net adverse clinical events (NACE) defined as the composite of death, fatal and non-fatal stroke, peripheral embolization and BARC 2, 3, or 5 up to 48 hours or discharge whichever comes first and 45 days*
- *Device related thrombosis at 45 day TEE/CCTA and 13-month CCTA in the per protocol and as treated populations*

6.1.4 Feasibility outcome

A composite of following outcomes will be analysed in order to assess the feasibility of two devices:

- *Number of attempts of LAA closure with a single device.*
- *Number of same type device used in a procedure.*
- *Total time procedure, x-ray dose and total contrast dose used in the procedure.*

6.2 Analysis methods

6.2.1 Primary analysis

The primary outcome analysis will be conducted by measuring the LAA patency at 45 days using the CCTA, combined with adjudicated cross-over including failed cross-over to another non-randomized LAAC device during the index LAAC procedure.

6.2.2 Secondary analyses

Secondary analyses of events at longer follow-ups (e.g. 1 to 5 years of follow-up) will be conducted using Cox's regressions comparing the randomized arms (hazard ratios with 95% confidence intervals) and reporting event rates (from Kaplan-Meier estimates accounting for lost-to-follow-up and withdrawal of consent). In most cases only the first event of each event (sub)type will be reported, except if requested otherwise and the statistical analyses will be adapted to a multi-event analyses design.

6.2.3 Sensitivity analyses

The primary and secondary outcomes will be analyses in multiple imputed data-sets using chained equations and combining estimates and p-values using Rubin's rule, if requested. It will also be explored whether delayed 45 days visit CCTA assessments (scheduled was 45 days ± 7 days, but e.g. delays can be due to e.g. the SARS-CoV-2 pandemic forcing postponement of some clinical visits) impacted the primary outcome comparison Amplatzer vs Watchman, by adding the delay in days of the follow-up CCTA as a covariate in the analyses.

6.2.4 Additional analyses

The following subgroups are defined for additional analyses (e.g. primary endpoint):

- Age > vs.<= 75 years old
- Gender male vs female
- Left ventricular ejection fraction >40% vs.<= 40% (EF)
- Diabetes yes vs no
- Prior bleeding yes vs no
- Prior cerebrovascular event yes vs no
- Device (Watchman 2.5 vs. Amulet), Watchman FLX vs Amulet
- Pre-procedural therapy with all combinations (none vs. SAPT vs DAPT vs. OAC vs. OAC+APT)

6.2.5 Assessment of statistical assumptions

Time-to-event curves will be compared and checked for the proportional hazards assumption using Schoenfeld's residuals.

6.3 Interim analyses

No statistical interim analyses are planned.

6.4 Missing data

The primary and secondary outcomes will be analyses in multiple imputed data-sets using chained equations and combining estimates and p-values using Rubin's rule, if requested.

6.5 Safety evaluation

The safety outcomes, AE and SAEs will be summarized in tables at all study periods, namely:

- Enrolment
- Procedure
- Post procedural hospital discharge
- 7 days
- 45-day follow-up
- 6-month follow-up
- 13-month follow-up
- 2-year follow-up
- 3-year follow-up
- 4-year follow-up
- 5-year follow-up

6.6 Statistical software

Stata version 16.1 or higher and R version 4.03 or higher will be used.

6.7 Quality control

The primary and secondary outcomes will be double-programmed.

7. References

Saw J, Fahmy P, DeJong P, et al. Cardiac CT angiography for device surveillance after endovascular left atrial appendage closure. Eur Heart J Cardiovasc Imaging. 2015;16(11):1198-1206