Practical Guide on Left Atrial Appendage Closure for the Non-implanting Physician. An International Consensus Paper

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Abstract

A significant proportion of patients who suffer from atrial fibrillation and are in need of thromboembolic protection are not treated with oral anticoagulation or discontinue this treatment shortly after its initiation. This undertreatment has not improved sufficiently despite the availability of direct oral anticoagulants which are associated with less major bleeding than vitamin K antagonists. Multiple reasons account for this, including bleeding events or ischaemic strokes whilst on anticoagulation, a serious risk of bleeding events, poor treatment compliance despite best educational attempts or aversion to drug therapy.

An alternative interventional therapy, which is not associated with long-term bleeding and is as effective as vitamin K anticoagulation, was introduced over 20 years ago. Because of significant improvements in procedural safety over the years left atrial appendage closure, predominantly achieved using a catheter-based, device implantation approach, is increasingly favoured for the prevention of thromboembolic events in patients who cannot achieve effective anticoagulation.

This management strategy is well-known to the interventional cardiologist/electrophysiologist but is not more widely appreciated within cardiology or internal medicine. This article introduces the devices and briefly explains the implantation technique. The indications and device follow-up are more comprehensively described.

Almost all physicians who care for adult patients will have many with atrial fibrillation. This practical guide, written within guideline/guidance boundaries, is aimed at those non-implanting physicians who may need to refer patients for consideration of this new therapy, which is becoming increasingly popular.

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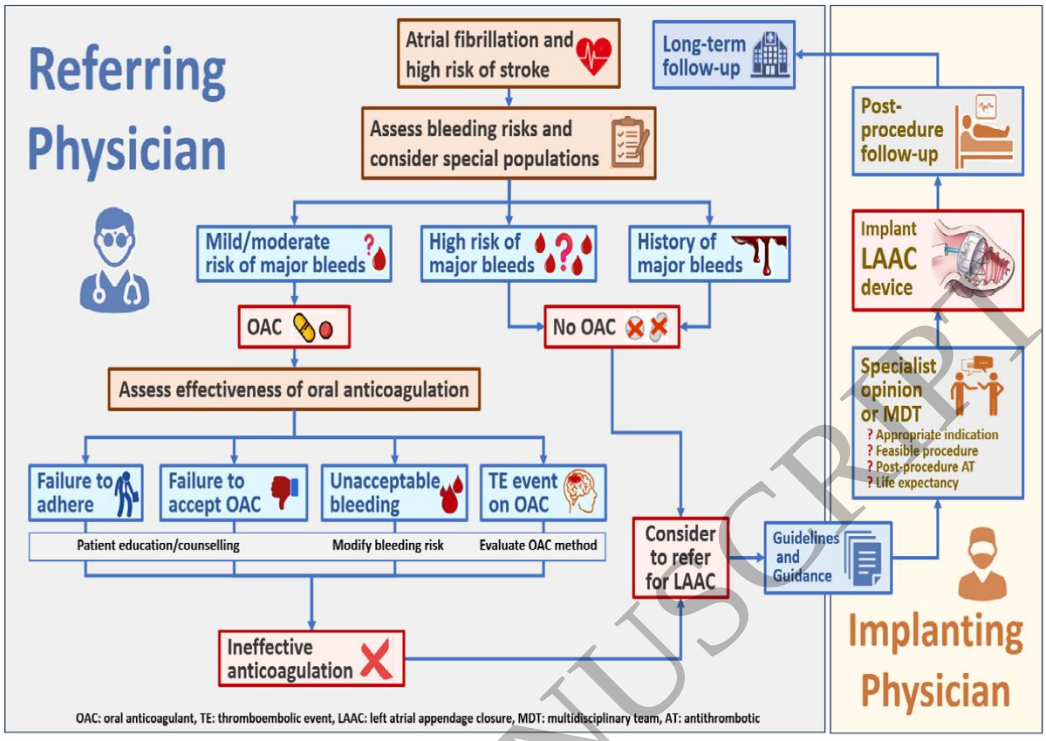

Central Illustration/Graphical Abstract

Acronyms and Abbreviations

ABC: Atrial Fibrillation Better Care
A$_3$ICH: Avoiding Anticoagulation After IntraCerebral Haemorrhage
ACP: Amplatzer Cardiac Plug
ACS: acute coronary syndrome
ACTIVE-A: Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events
ADALA: Apixaban vs Dual Antiplatelet Therapy Study After Left Atrial Appendage Occlusion
AFFIRMO: An integrated patient-centred holistic care pathway for the management of older patients with multimorbidity to enhance cooperation among different health disciplines and promote a shared decision-making process
aMAZE: LAA Ligation Adjunctive to PVI for Persistent or Longstanding Persistent Atrial Fibrillation
AMULET IDE: Amulet Investigational Device Exemption
ANDES: Short-Term Anticoagulation Versus Antiplatelet Therapy for Preventing Device Thrombosis Following Left Atrial Appendage Closure
APACHE-AF: Apixaban After Anticoagulation-associated Intracerebral Haemorrhage in patients with Atrial Fibrillation
APTT: Activated partial thrombin clotting time

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ARMYDA-AMULET: Head-to-head Comparison of Single Versus Dual Antiplatelet Treatment Strategy After Percutaneous Left Atrial Appendage Closure: a Multicenter, Randomized Study
AS: aortic stenosis
ASA: acetyl salicylic acid
ASAP-TOO: ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology
ASD: atrial septal defect
ASPIRE: Anticoagulation in ICH Survivors for Stroke Prevention and Recovery
AVERROES: A Phase III Study of Apixaban in Patients With Atrial Fibrillation
AXADIA-AFNET: Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease
AZALEA-TIMI 71: Safety and Tolerability of Abelacimab (MAA868) vs. Rivaroxaban in Patients With Atrial Fibrillation
BAFTA: Birmingham Atrial Fibrillation Treatment of the Aged Study
BELIEF-RCT: Effect of empirical left atrial appendage isolation on long-term procedure outcome in patients with persistent or longstanding persistent atrial fibrillation undergoing catheter ablation
CABG: coronary artery bypass grafting
CAP 2: Continued Access to PREVAIL
CAP 1: Continued Access to PROTECT
CATALYST: Amplatzer Amulet LAAO vs. NOAC
CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female)
CHAMPION-AF: Watchman FLX versus NOAC for embolic protection in the management of patients with non-valvular AF
CLEARANCE: Comparison of left atrial appendage closure versus oral anticoagulation in patients with non-valvular AF and status post intracranial bleeding
CLOSURE-AF: Left atrial appendage closure in patients with AF compared to medical therapy
COMBINE-AF: A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation
COMPARE-LAAO: COMPARing Effectiveness and safety of Left Atrial Appendage Occlusion to standard of care for atrial fibrillation patients at high stroke risk and ineligible to use oral anticoagulation therapy
CKD: chronic kidney disease
Cryo: cryotherapy
CT: computed tomography
CV: cardiovascular
CVA: cerebrovascular accident
DCCV: direct current cardioversion
DIC: disseminated intravascular coagulation
DOAC: direct oral anticoagulant
DRT: device-related thrombosis
ECG: electrocardiogram
eGFR: estimated Glomerular Filtration Rate
ELAPSE: Early Closure of Left Atrial Appendage for Patients With Atrial Fibrillation and Ischemic Stroke Despite Anticoagulation Therapy
ENRICH-AF: EdoxabaN foR IntraCranial Hemorrhage Survivors With Atrial Fibrillation
ESC: European Society of Cardiology
ESKD: end stage kidney disease
EWOLUTION: Registry on WATCHMAN Outcomes in Real-Life Utilization
FDA: Food and Drug Administration
GIB: gastro-intestinal bleeding
HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly
HD: haemodialysis

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ICB: intracranial bleeding
ICE: intracardiac echocardiology
ICH: intracerebral haemorrhage
INR: international normalised ratio
INTERCEPT: Carotid Implants for PreveNtion of STrokE ReCurrEnce From Large Vessel Occlusion in Atrial Fibrillation Patients Treated With Oral Anticoagulation
ISTH: International Society on Thrombosis and Haemostasis
LAA: left atrial appendage
LAAC: left atrial appendage closure
LAA-KIDNEY: Left Atrial Appendage Closure in Patients With Non-valvular Atrial Fibrillation and End-stage Chronic KIDNEY Disease
LAAO: left atrial appendage occlusion
LAAOS III/LAAOS-4: third/fourth left atrial appendage occlusion study
LAARGE: German left atrial appendage occlusion registry
LIBREXIA-AF: A Study of Milvexian Versus Apixaban in Participants With Atrial Fibrillation
LILAC-TIMI 76: Study to evaLuate the effIcacy and Safety of abeLacimab in High-risk Patients With Atrial Fibrillation Who Have Been Deemed Unsuitable for Oral antiCoagulation
LMWH: low molecular weight heparin
LPV: left pulmonary vein
LVEF: left ventricular ejection fraction
mAFA: mobile health (mHealth) technology for Improved screening and optimized Integrated care in atrial fibrillation
MDT: multidisciplinary team
MIRACLE-AF: A New Model of Integrated Care of Older Patients With Atrial Fibrillation in Rural China: a Cluster Randomization Trial
NASPAF-ICH: Non-VKA Anticoagulants for Stroke Prevention in Patients with AF and Previous IntraCerebral Hemorrhage
NCDR: National Cardiovascular Data Registry
NOAC: non-vitamin K oral anticoagulant
OAC: oral anticoagulant
OCEANIC-AF: A Study to Learn How Well the Study Treatment Asundexian Works and How Safe it is Compared to Apixaban to Prevent Stroke or Systemic Embolism in People With Irregular and Often Rapid Heartbeat (Atrial Fibrillation), and at Risk for Stroke
OCEANIC-AFINA: Oral faCtor Eleven A iNhibitor asundexIan as novel antithrombotiC - Atrial FIbrillation uNtreAted patients study
OCCLUSION-AF: Left atrial appendage occlusion versus novel oral anticoagulation for stroke prevention in **AF:** atrial fibrillation
OCEAN: Optimal Anticoagulation for Higher Risk Patients Post-Catheter Ablation for Atrial Fibrillation Trial
OCEANIC-AF: A Study to Learn How Well the Study Treatment Asundexian Works and How Safe it is Compared to Apixaban to Prevent Stroke or Systemic Embolism in People With Irregular and Often Rapid Heartbeat (Atrial Fibrillation), and at Risk for Stroke
OPTION: Comparison of anticoagulation with left atrial appendage closure after AF ablation
PCI: percutaneous coronary intervention
PDL: peri device leak
PFO: patent foramen ovale
PINNACLE-FLX: Protection against embolism for non-valvular AF subjects: Investigational device evaluation of the Watchman FLX LAA closure technology
PINNACLE: Protection against embolism for non-valvular AF subjects
PRAGUE-17: left atrial appendage closure versus novel anticoagulation agents in AF
PRESTIGE-AF: PREvention of STroke in Intracerebral haemorrhaGE survivors with Atrial Fibrillation
PREVAIL: Evaluation of the Watchman left atrial appendage closure device in

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patients with AF versus long term warfarin therapy
PROTECT-AF: Watchman left atrial appendage system for embolic protection in patients with AF
PT: prothrombin time
PVI: pulmonary vein isolation
RCT: randomised controlled trial
RENAL-AF: (RENal hemodialysis patients Allocated apixaban versus warfarin in Atrial Fibrillation
RENO-EXTEND: Recurrent Ischemic Stroke and Bleeding in Patients With Atrial Fibrillation Who Suffered an Acute Stroke While on Treatment With Nonvitamin K Antagonist Oral Anticoagulants
RESTART: Restart or Stop Antithrombotics Randomized Trial
RF: radiofrequency
SAFE LAAC CKD: Optimal antiplatelet therapy following left atrial appendage closure in dialyzed patients
SE: systemic embolism
SoSTART: Start or STop Anticoagulants Randomised Trial
STABLED: STroke Secondary Prevention With Catheter ABLation and EDoxaban for Patients With Non-valvular Atrial Fibrillation
STATICH: Study of Antithrombotic Treatment After IntraCerebral Haemorrhage
STR-OAC: Stroke despite oral anticoagulation
PRESTIGE-AF: PREvention of STroke in Intracerebral haemorrhaGE survivors with Atrial Fibrillation
STOP-HARM: Strategy to Prevent Hemorrhage Associated With Anticoagulation in Renal Disease Management
STR-OAC: Stroke despite OAC
STROKE-CLOSE: Prevention of stroke by left atrial appendage closure in AF patients after intracerebral haemorrhage
SURPASS: Surveillance Post-Approval Analysis
SWISS-APERO: Comparison of Amulet Versus Watchman/FLX Device in Patients Undergoing Left Atrial Appendage Closure
TAVI: transcatheter aortic valve replacement
TEER: transcatheter mitral valve edge-to-edge repair
TIA: transient ischaemic attack
TOE: trans oesophageal echocardiogram
TTR: time in the therapeutic range
UFH: unfractionated heparin
USRDS: United States Renal Data System
VKA: vitamin K antagonist
VWD: von Willebrand disease
VWF: von Willebrand factor
WASP: WATCHMAN Asia Pacific (registry)
WATCH-AF: WATCH bleeding episodes after left atrial appendage occlusion versus usual care in patients with Atrial Fibrillation and severe to end-stage Chronic Kidney Disease
WATCH-HD: Left Atrial Appendage Occlusion With WATCHMAN® Device in Patients With Non-valvular Atrial Fibrillation and End-stage Chronic Kidney Disease on Hemodialysis
WM/WM-FLX: WATCHMAN / WATCHMAN-FLX

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults and is associated with increased morbidity and mortality, mainly caused by embolic strokes and the development of heart failure [1]. Due to longer life expectancy and better treatment of conditions associated with high AF risk, such as heart failure, the prevalence and incidence of AF have been continuously rising [2].

There are multiple anticoagulant drugs, predominantly from two classes: vitamin K antagonists (VKAs), which reduce the synthesis of functional coagulation factors and direct oral anticoagulants (DOACs), which inhibit the action of certain coagulation factors. Since these agents increase the risk of bleeding, doctors, patients and caregivers are sometimes reluctant to use them.

Oral anticoagulation (OAC) is highly effective in preventing cardioembolic strokes in AF patients. In the trials comparing VKAs with placebo, OAC reduced the risk of stroke by 64% and all-cause mortality by 26%[3]. However, in Europe and North America, VKAs have been almost entirely replaced by DOACs in the management of non-valvular AF patients. These drugs are comparable to VKAs in preventing ischaemic stroke, but superior in terms of bleeding risk. In a meta-analysis of trials comparing VKA with DOACs, with more than 70,000 patients with AF, treatment with DOACs was associated with a significant reduction in all strokes by 19%, which was mainly driven by a significant reduction in haemorrhagic stroke (HR 0.49, 95% CI 0.38-0.64)[4]. However, there remains a residual risk of stroke 0.8 per hundred patient-years[5].

Notwithstanding the impressive reduction in the risk of intracerebral bleeding with DOACs, the risk of major bleeding in the gastrointestinal tract is not much reduced in comparison to VKAs, and may actually be increased as compared to VKAs with some DOACs 4. However, DOACs do not inhibit coagulation factor VII which is fundamentally important for haemostasis but not so relevant for thrombosis [6]. Although the balance between stroke prevention and major bleeding is improved with DOACs, the bleeding problem is not eliminated [7]. The major bleeding rate remains between 1 and 3 per 100 patient-years, but

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over a 3-year period it was 11% in the LAAC/OAC meta-analysis and in the DOAC vs VKA pre-approval trials it was 5.9% with DOACs over 32 months [8]. In AF patients with a GI bleed whilst taking anticoagulant there is a very high risk of a recurrent bleed (27 per 100 patient-years) [9].

In patients who have suffered serious bleeding and/or are at high risk of bleeding or in whom VKA/DOAC treatment has failed to prevent AF-related stroke an interventional technique may be considered. The use of non-pharmacological thromboprophylaxis would also significantly reduce the long-term anticoagulant drug burden. Amongst these techniques, closure or occlusion of the left atrial (LA) appendage [10], the intra-cardiac site at which most thrombi form in patients with AF, can be achieved by a reasonably safe catheter-based procedure known as LA appendage closure (LAAC) or LA appendage occlusion (LAAO).

This procedure is being increasingly offered in developed countries as a robust alternative to OAC)for those in need, but the knowledge of LAAC is often modest outside the interventional cardiology and electrophysiology communities. On the other hand, the patients who might benefit from this therapeutic approach are often under the care of a general cardiologist, general or primary care physician, gerontologist, nephrologist, gastroenterologist, neurologist or stroke physician, etc. An understanding and appreciation of the value and applicability of LAAC are needed by all of those who care for patients with AF at risk of stroke but with a medical history, comorbidity or lifestyle that prevents adequate anticoagulation.

This Practical Guide, written by an international multidisciplinary group consisting of members of the European Society of Cardiology Stroke Council and cardiologists and physicians from other interested specialties, aims to provide an overview of the principles, patient selection, follow-up and limitations of LAAC. The scope is to provide practical information about LAAC to the general medical community dealing with such AF patients, and not a manual for those who implant the device.

Evidence base for LAAC

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The efficacy and safety of LAAC were first shown in the randomised PROTECT-AF (data collection from 2005) and PREVAIL (data collection from 2010) clinical trials in which AF patients without obvious contraindications to warfarin were randomized to either LAAC with Watchman (with warfarin and aspirin for at least 45 days after the procedure) or warfarin aiming at an INR of 2-3 (n=1114). After a 5-year follow-up, LAAC provided stroke prevention comparable to VKA with a significant reduction in major bleeding, haemorrhagic stroke, disabling/fatal stroke, cardiovascular death and all-cause death [11].

The PRAGUE-17 randomized trial (data collection from 2015) compared LAAC (Amulet or Watchman) with DOAC, mainly Apixaban, (n=402) showing non-inferiority for LAAC in the prevention of stroke/TIA, cardiovascular death, clinically-relevant bleeding and superiority in preventing non-procedural bleeding over 4 years [12].

Figure 1 shows clinical outcomes from the three RCTs comparing LAAC vs. VKA/DOAC [13]. It can be seen that the point estimate for the ischaemic stroke rate is 5.6% with LAAC compared with 3.6% with OAC. This adverse trend is not significant but is a concern that detracts from a more fulsome acceptance of LAAC therapy as a legitimate alternative to OAC prophylaxis. However, a propensity-matched analysis has suggested that strokes in patients with LAAC are less disabling than those seen in patients receiving DOAC therapy [14].

Figure 1:

There are multiple observational studies and registries of AF patients undergoing LAAC with various devices (ACP, Amulet, Watchman, Watchman FLX) mostly showing a 60-80% reduction in the rate of ischaemic stroke and major bleeding compared with predicted rates based on the CHA_2DS_2-VASc and HAS-BLED score values (e.g. ACP registry [15], Amulet Observational Study [16], EWOLUTION [17], NCDR-LAAO registry [18, 19], PINNACLE FLX [20]).

A recent meta-analysis of studies comparing LAAC to DOAC (n=4411) showed the risk of stroke/TIA to be similar with LAAC and DOAC, whereas LAAC was superior in reducing cardiovascular mortality, major and non-major bleeding [21]. In the randomized LAAOS-III study (n=4770), surgical LAAC in addition to DOAC (continued in about 70% of all study

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patients) was associated with a 33% reduction in the risk of stroke/TIA after 3 years [22]. Factor XI inhibitors are currently being investigated for thromboprophylaxis in AF patients with a high risk of thromboembolic events. Ongoing trials include OCEANIC-AF and OCEANIC-AFINA with asundexian[23], AZALEA-TIMI 71 [24], LILAC-TIMI 76 with abelacimab [25], and LIBREXIA-AF with milvexian and compare Factor XI inhibitors against DOACs or placebo [26]. If these new drugs can prevent thromboembolism without a substantial bleeding risk a comparison with LAAC will be needed. However, OCEANIC-AF has been terminated prematurely for lack of asundexian efficacy when compared with apixaban. On the other hand, the AZALEA trial was also terminated prematurely but because there was substantially less bleeding with abelacimab than with rivaroxaban. Even if Factor XI inhibitors are not as effective as DOACs but more effective than placebo with a substantial reduction in bleeding when compared with conventional anticoagulation there might still be an important role for these agents in patients who cannot use standard agents.

Currently, there is no RCT-based data on LAAC in patients who are intolerant of or contraindicated for OAC. Data on such patients is very much needed because this is actually the subgroup of AF patients that is treated with LAAC in clinical practice today and the subgroup that would likely have the greatest benefit from LAAC (Table 1). However, patient recruitment has been slow into these trials, e.g., ASAP-TOO [27], CLOSURE-AF [28], STROKECLOSE [29], CLEARANCE [30], COMPARE-LAAO [31, 32], and LAA-KIDNEY [33] among others. The ASAP-TOO trial was terminated prematurely due to slow enrolment but patient follow-up is still active.

Table 1

Based on the currently available evidence and clinical experience, LAAC is now being investigated in broad populations of AF patients in large-scale trials. In the OPTION trial [34, 35], AF patients undergoing catheter ablation for AF were randomized to LAAC or DOAC after ablation. In the CHAMPION-AF trial [36] and CATALYST trial [37], AF patients with no contraindications to DOACs and CHA_2DS_2-VASc of ≥ 2 for men and CHA_2DS_2-VASc of ≥ 3 for women are randomized to LAAC or DOAC (Table 2). In the OCCLUSION-AF trial [38] AF patients with a recent ischaemic stroke are randomized to either LAAC or DOAC [39].

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Table 2

There are also several observational studies on special AF patient subpopulations undergoing LAAC (i.e., patients with prior ICH, prior ischaemic stroke, renal failure, stroke despite anticoagulation) suggesting a net benefit of LAAC in the prevention of stroke and bleeding. Some of those studies are propensity score matched comparing LAAC in AF patients with a prior ICH to standard therapy [40] or LAAC to DOAC [41].

Indications for LAAC

Stroke reduction in patients with AF requires more than thromboprophylaxis, hence the move towards a holistic or integrated care approach to AF management. This is recommended in guidelines as the Atrial fibrillation Better Care (ABC) pathway[42]. Adherence with this evidence-based strategy is associated with a 31% reduction in stroke, as well as lower mortality and bleeding, and is supported by various retrospective and prospective cohort studies from different parts of the world [43], post-hoc analysis from adjudicated outcomes from clinical trials [44, 45].

Transcatheter LAAC has been increasingly used as an antithrombotic approach in patients with AF, especially in the United States of America [18, 46]. While contemporary European AF registry-based studies reported a <1% use of LAAC in clinical practice [47, 48], a trend towards increasing use of LAAC in Europe has been recently observed, including the changing profile of AF patients undergoing the procedure (i.e., less frail and generally less comorbid patients)[49].

Guideline recommendations and consensus statements considering the use of transcatheter LAAC for the prevention of stroke and systemic thromboembolism in patients with AF are summarized in Tables 3 and 4 and Figure 2.

Figure 2

Formal guideline documents have consistently recommended percutaneous LAAC for AF patients with contraindications to long-term OAC, using a low class of recommendation and low level of evidence, although the 2023 ACC/AHA/ACCP/HRS guidelines have recently

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upgraded this to a level IIa recommendation and have added a IIb recommendation for LAAO as an alternative to oral anticoagulation (Table 3) [50-57]. Consensus documents explain the recommendations in more detail and extend the implications (Table 4) [58, 59], thus also including AF patients who:

- suffer major bleeding events during anticoagulant therapy
- have a high risk of non-modifiable anticoagulant bleeding
- had a thromboembolic event or LAA thrombosis while on optimal OAC [60]
- refuse or are non-compliant to long-term OAC
- undergo catheter ablation with electrical isolation of the LAA
- have a procedure involving transseptal puncture and need long-term thromboembolic protection

Both guideline and consensus documents/position papers aim to inform clinical practice. Methodological differences (rigid interpretation of the evidence base, particularly clinical trials for guidelines, and a less formal process also utilising observational data for consensus documents) result in official professional society recommendations in guidelines and broader non-official advice, in consensus documents [61].

The most recent consensus documents addressing the use of transcatheter LAAC for the prevention of stroke and systemic embolism in patients with AF emphasize that LAAC should not be routinely offered to patients unwilling to take OAC therapy or who are simply non-compliant with their anticoagulation medication, before providing them with detailed counselling. Careful individual risk-benefit assessment and shared decision-making should be undertaken in each patient [62].

Table 3

Table 4

Practical Box 1

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Referral considerations

Responsibility of the referring physician

All patients with AF who are being considered for any cardiac intervention must be assessed by taking a cardiac history relating to the presence of AF, major structural or functional heart disease, potentially reversible causes of bleeding, or alternative causes of stroke besides AF. Routine investigations including 12-lead surface electrocardiogram (ECG) and basic laboratory tests will have been performed before a patient is considered for LAAC therapy.

The need for thromboembolic protection in patients with AF must be firmly established utilising risk scores such as CHA_2DS_2-VASc. Their bleeding risk should also be assessed using a validated structured bleeding risk assessment that addresses modifiable and non-modifiable bleeding risks, such as the HAS-BLED score. Any additional factor leading to an increased thromboembolic or bleeding risk should also be documented.

Responsibility of the implanting physician

The first responsibility of the interventional specialist is to confirm the indication for LAAC. There is a practical value of holding a MDT meeting to assess patients who have been or are to be referred for LAAC. As the indication is often for non-cardiac problems (neurological, gastrointestinal, haematological, renal, etc.) such an MDT can assess patient data at an early stage and achieve consensus on the management plan.

In some healthcare systems (e.g., National Institute for Health and Care Excellence [NICE]) an "MDT" is mandatory for selecting patients for LAAC since it helps reduce selection bias, streamlines referrals and facilitates optimal patient management. [63]

Pre-procedural diagnostic workup usually includes trans-oesophageal echocardiography (TOE) or cardiac computed tomography (CT) to delineate LAA anatomy and suitability for closure, and to rule out LAA thrombosis. LAA thrombosis can also be excluded using TOE or intracardiac echocardiography (ICE) at the beginning of the procedure [64]. In general, the presence of LAA thrombus is considered as a contraindication to LAAC. Nonetheless, several

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case series of LAAC have been reported in patients with a thrombus present only in the distal part of the LAA [65] – see below.

The selection of a specific LAA closure device and its size will depend on the operator's experience and the LAA anatomy as assessed by pre-procedural CT or TOE and by peri-procedural TOE or ICE and selective LAA angiography. Cardiac CT offers a better understanding of LAA anatomy and the most accurate measurements [66, 67]. There are several dedicated software packages for planning a LAAC procedure based on cardiac CT.

If the patient is on a DOAC, the treatment may be stopped one day before the procedure (i.e., last dose of rivaroxaban or edoxaban in the morning, or apixaban and dabigatran in the evening before the procedure) without bridging.

Practical Box 2

Current methods of percutaneous LAA closure

Procedural steps

LAAC is a standardized procedure, that requires specific training of the implanter and interventional team. It is most often undertaken under general anaesthesia and is guided by TOE, but ICE or micro/mini TOE is increasingly used making it possible to perform the procedure with local analgesia and light sedation.

Femoral venous puncture

Femoral venous access is usually obtained under ultrasound guidance to reduce the risks of vascular complications [68-72].

Transseptal access

Transseptal puncture is a crucial step to safely access the left atrium and successfully deploy a LAAC device (Video: https://clipchamp.com/watch/4SaJbCrWTed). This technique requires specific training and has a learning curve.

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Deployment of the occluder inside the LAA

Procedural imaging is of crucial importance for a successful LAAC. The procedure is guided by TOE or ICE, depending on the operator's experience. Device deployment is additionally controlled by fluoroscopy and fusion of preprocedural CT images with fluoroscopy is occasionally used (Figure 3). TOE/ICE is also crucial to confirm the optimal placement of the device and complete sealing of the LAA.

Infective Endocarditis prophylaxis

Periprocedural antibiotic prophylaxis and surgical standard aseptic measures in the catheter laboratory environment are recommended during the LAA implant procedure (ESC guidelines). Elimination of potential sources of sepsis (including of dental origin) should be considered two or more weeks before implantation [73].

LAAC devices

A range of devices has been developed in order to provide safe and efficient LAAC (Table 5) [74-79]. Of these the Watchman FLX, Amulet and LAmbre devices have been extensively studied (Figure 4, Panels A, B and C). Another form of LA occlusion may be achieved using a noose inserted epicardially around the os of the LAAC – the LARIAT device (Table 3 and Figure 5).

Table 5

Since the LAAC technique is becoming increasingly popular many other devices are under development.

Figure 3

Figure 4 Panel A

Figure 4 Panel B

Figure 4 Panel C

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Figure 5

Management of acute and early post-implantation complications

LAAC has become a relatively low-risk procedure (Table 6)[80-83]. Some complications may occur over the longer term, such as late pericardial effusions or device-related thrombosis (DRT) and all physicians following patients post-procedure must be aware of these. Complications occur more commonly in patients with a higher CHA_2DS_2-VASc score [84].

Table 6

Pericardial tamponade

Pericardial effusion or tamponade represents a serious complication. Its incidence has decreased from the initially reported rate of 4.3% in the PROTECT AF trial [85], to 0.3% in the SURPASS study that included 16,048 Watchman FLX implants [81].

Most tamponades/effusions occur during the procedure or within 24 hours. To minimise their occurrence, imaging guidance with TOE/ICE is essential for all procedural phases, from a transseptal puncture to device placement and release.

LAA perforation can sometimes be managed just by finalizing the LAA device implantation. For significant active pericardial bleeding, autotransfusion is possible to minimise blood loss and the need for transfusion. Reversal of anticoagulation should be considered only in cases with severe haemodynamic deterioration. Surgical intervention is rarely needed. (Table 7)

Table 7

Although most pericardial effusions occur within 24 hours of LAAC, late pericardial effusions can rarely occur. If a pericardial effusion is suspected, the patient should be immediately referred to the implanting centre or the nearest cardiology site for echocardiography and possible pericardiocentesis.

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While acute pericardial effusion/tamponade is related to trauma to the left atrium, pulmonary veins, or the LAA that may occur during the procedure, it is often difficult to identify the mechanism of late effusions and other common causes of pericardial effusion should also be considered.

Device embolisation

Device embolisation has become a rare complication with the most recent LAAC devices (0.01% with WATCHMAN-FLX in SURPASS). The risk of embolisation is increased with device under-sizing, very proximal implantation, misalignment of the device to the axis of the LAA, and sinus rhythm (Table 8). Device embolization can to a large extent be prevented by adequate preprocedural and intra-procedural imaging. Smaller LAAC devices that embolise will most often travel through the left heart and aortic valve to the descending aorta, whereas larger devices will remain in the LA or LV. Device embolisation is rarely associated with haemodynamic deterioration. Percutaneous retrieval is usually successful with a snare catheter or retrieval forceps. (Figure 6) If the device becomes entangled in the mitral valve apparatus, percutaneous snaring can potentially damage the valve and acute surgery might be required.

Figure 6

Table 8

Device-related thrombosis

The incidence of DRT varies from 2-4%, although recent data with newer devices have reported a lower incidence of 1-2% per year (Figure 7) [86-95]. DRT is most frequently detected by routine imaging at scheduled follow-up visits after the procedure. It can be diagnosed with TOE or cardiac CT and it is associated with a 4-5 times higher risk of stroke/TIA [96]. Besides patient-related risk factors, the risk of DRT can be increased by device implantation that is too deep resulting in incomplete LAA sealing.[97] Hypercoagulability disorders, iatrogenic pericardial effusion, renal failure and permanent AF are other risk factors for DRT [96]. However, as new devices coated with thromboresistant fluorinated polymers are

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introduced DRT should become rare and post-implant antithrombotic therapy may be simplified or eliminated [98].

Figure 7

Management of DRT usually implies escalation of antithrombotic therapy (low molecular weight heparin [LMWH] or DOACs), but this may be challenging or even harmful in patients who are at high bleeding risk. The common practice is to minimize time on anticoagulants until thrombus resolution is verified by imaging (Figure 9).

Figure 8

Figure 9

Procedure-related stroke

During early experience, periprocedural stroke occurred occasionally and mainly due to air embolism. However, nowadays periprocedural stroke is a very rare event. In the SURPASS registry, the rate of all-cause stroke was 0.09% in hospital and 0.38% at 45 days [81]. Procedural stroke/TIA may be related to the presence of thrombus/smoke in the LAA or LA, air embolisation during the procedure, or development of thrombi on the delivery system or implanted device.

Peri-device leak (PDL)

The anatomy of the LAA is highly variable and can be very complex, including the landing zone for the LAA device, which is most often non-circular. Consequently, there is a risk of peri-device leak after implantation or in some cases, a smaller lobe of the appendage may not have been occluded by the device [99]. PDL can be diagnosed by TOE or even better with CT. With current procedural techniques and devices, small PDLs are rather frequent, whereas moderate leaks (3-5 mm) are less common and severe leaks (>5 mm) very rare. Medical therapy is usually needed and is chosen according to bleeding risk. For PDL >5 mm interventional leak closure with plugs, occluders, coils, or radiofrequency ablation may be considered but medical therapy may also be sufficient (Figure 11) [100].

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Figure 10

Figure 11

Practical Box 3

Special populations

There is a large range of medical circumstances in which LAAC therapy may offer an advantage over OAC (Figure 12). Many of these conditions may be associated with severe bleeding complications, ineffectiveness of anticoagulants against thromboembolism or patient adherence difficulties. Even minor bleeding may have severe effects, as for example, patients suffering from cerebral amyloid angiopathy.

Some 'high risk' cardiovascular diseases may require the long-term use of antiplatelet therapy in addition to using an anticoagulant, to prevent new cardiovascular events such as re-infarction or stent-thrombosis, but this comes at the expense of bleeding complications. If the use of OAC could be substituted by LAAC, the bleeding risk is mitigated while stroke prevention is retained. Nonetheless, robust long-term data on this population group are lacking.

There are also patients that suffer a stroke or systemic thrombo-embolic event, or exhibit thrombus formation in the LAA despite using optimal anticoagulation therapy with an adequate INR or good drug compliance.

Figure 12

Life-threatening or major gastrointestinal bleeding

Patients with AF and a high risk of stroke and embolism (CHA_2DS_2-VASc ≥2) who have a major bleeding event represent a highly challenging scenario, since effective chronic anticoagulation can be associated with a high or very high risk of recurrent bleeding. Hence, transcatheter LAAC was initially developed as an alternative mode for stroke prevention [101]. One recent study suggested that only about 50% of patients with AF, admitted after a major

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or life-threatening bleeding are discharged with a plan for stroke prevention strategy, with only 10% being considered for LAAC [102].

Nonetheless, a systematic review and metanalysis found that restarting OAC therapy after a major bleeding event in AF was mostly associated with a positive clinical benefit when compared to not restarting OAC, with a significant reduction in any thromboembolism and all-cause mortality when resuming therapy no more than two weeks after gastrointestinal bleeding (GIB) [103]. For example, one study found that restarting OAC at discharge after GIB was associated with fewer thromboembolic events without a significantly increased risk of recurrent GIB at 90 days [104]. Similar observations for reduced mortality and thromboembolism were seen in the Danish registries, although bleeding was higher in the long term [105]. Nonetheless, the latter study was in the warfarin era, and contemporary studies with some DOACs suggest better GIB safety compared to warfarin [106]. Hence, for many patients, the benefits of continuing anticoagulation (especially with DOAC) may outweigh the risks of recurrent GIB. Also, proton pump inhibitors may be protective in such patients [107]. However, when GIB is associated with angiodysplasia continuation of anticoagulation therapy may be such a high risk as to warrant consideration of other therapies such as LAAC [108].

Clinical registry studies have reported promising results in patients with AF and a high bleeding risk after LAAC [16, 109]. In the case of GIB, largely single-centre reports of LAAC have suggested its use as an alternative to OAC in patients presenting with major, recurrent or potentially unresolvable GIB (Figure 13) [108, 110]. The multicentre ACP registry reported their subgroup of patients with AF and previous major GIB, where LAAC was associated with a low annual rate of stroke/transient ischemic attack, although periprocedural major bleeding events were more frequent [111]. Again, many of these studies were in the warfarin era, rather than with DOACs.

An important consideration in patients undergoing LAAC following a major or life-threatening bleed (especially from GIB) is the antithrombotic treatment regimen after LAA device implantation [112]. This requires individualized decision-making, taking into account the patient's subsequent bleeding risk and the risk of device-associated thrombi, a recognised complication after LAA. In some clinical situations, particularly in patients with

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diffuse angiodysplasia, even a single antiplatelet drug may be enough to trigger recurrences of major haemorrhage. Given the greater biocompatibility of recent LAAC devices, earlier de-escalation of antithrombotic therapy is frequently performed in patients after major or life-threatening bleeding to avoid recurrent bleeding events.

Figure 13

Cirrhosis and hepatic failure

Anticoagulants were contraindicated in patients with cirrhosis owing to concerns about bleeding risks, but recent studies have shown that patients with cirrhosis are not naturally anticoagulated and are at increased risk of prothrombotic events. Anticoagulant therapy may reduce the progression of hepatic fibrosis and be independently associated with increased survival and decreased decompensation [113].

A higher incidence of AF has been observed in patients with cirrhosis, regardless of the underlying cause[114]. There has been a 10% increase in the prescription of anticoagulants, primarily DOACs, for AF in patients with cirrhosis. The use of DOACs was associated with a lower risk of bleeding compared to warfarin [115]. However, most available data are based on retrospective analyses and most studies included only a minimal number of patients with decompensated cirrhosis.

In cirrhotics with portal vein thrombosis, anticoagulation is associated with 9% bleeding complications in men [116], mostly not severe. However, the presence of severe thrombocytopenia < 50.000 u/L (which is present in about 7% of patients) has been associated with increased bleeding complications with warfarin. Decompensated liver disease could be associated with more bleeding complications with OAC outside the indication for the treatment of PVT [117].

Patients with severe portal hypertension can be more at risk of GI bleeding complications independently from variceal bleeding and often in this clinical setting, decompression of the portal system by intrahepatic portosystemic shunting is contraindicated by impaired cardiac function.

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In cirrhosis, LAAC implantation has been associated with an increased cardiac tamponade and readmission rate compared to non-cirrhotic patients and GI bleeding seems to be responsible for this difference [118, 119]Readmissions after the LAAC procedure are partially due to the prescription of antiplatelet therapy associated with concomitant chronic renal failure in about one-third of patients. Liver cirrhosis is a complex pathology, increasing both bleeding and thromboembolic risk. Careful patient selection and shared decision-making are critical for LAAO in cirrhotics due to increased complications and mortality. Pre-procedural optimisation of haemostasis is necessary due to the increased bleeding risk.

Intracranial haemorrhage

Stopping OAC and antagonizing the anticoagulant effect in patients with acute ICH)is needed to reduce ICH-associated morbidity and mortality regardless of the presence of AF and the associated thromboembolic risk. In addition, surgical or catheter-based intervention may be needed in selected ICH patients. The residual risk of ischaemic stroke in non-anticoagulated AF patients is up to 15% per year, and about 80% of all ICH patients with AF are at high risk of ischaemic stroke. This underscores the need to manage thromboembolic stroke prevention after ICH.

Current evidence for the re-starting of OAC after intracranial bleeding (ICB) is mainly based on prospective cohort studies and three RCTs, APACHE-AF [120], SoSTART [121], NASPAF-ICH [122], including no more than 340 patients in total [123]. Taking these three RCTs together, re-starting OAC was associated with reduced risk of ischaemic stroke on the one hand but increased risk (of borderline significance) for recurrent ICH [124]. The threat of ICH recurrence is daunting but many physicians will consider restarting anti thrombotic therapy at least 30 days after the ICH [125]. The results of ongoing RCTs focussing on OAC vs. no anticoagulation (without considering LAAC) in ICB patients with AF (such as ENRICH-AF [126], PRESTIGE-AF [127], A_3ICH [128], STATICH [129], and ASPIRE are awaited [130].

Despite the fact that there is no proven benefit of LAAC in ICH patients according to a RCT so far, LAAC is recommended by AF guidelines [53, 131] and consensus papers worldwide [132]. Publications based on propensity-score matched analyses in AF patients with ICH undergoing LAAC vs. medical treatment conclude a benefit of LAAC regarding the composite

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of ischaemic stroke, major bleeding and all-cause mortality [40, 41]. At present, moderate sized RCTs comparing LAAC to OAC/best medical treatment exclusively including ICH patients such as CLEARANCE [30], and STROKECLOSE [29], or patients at very high risk of bleeding including ICH patients, such as CLOSURE-AF [28] are ongoing. Special attention has to be paid to ICH patients with (suspected) cerebral amyloid angiopathy, refractory hypertension or concomitant chronic renal failure (including those on dialysis), who might benefit most from LAAC and such studies are underway (SAFE LAAC CKD [133], LAA-Kidney [33]).

In clinical practice, LAAC after ICH has "an acceptable peri-procedural and post-procedure risk" according to expert consensus [134]. Of note, restarting of antiplatelet therapy (as needed after LAAC) is safe after ICH as demonstrated in the RESTART study, randomizing patients on antithrombotic therapy for the prevention of occlusive vascular disease at the time of ICB to restarting or avoiding antiplatelet therapy [134]. However, it remains to be established in RCTs such as CLOSURE-AF whether stopping antiplatelet(s) several months after LAAC is safe or associated with increased risk of thrombus formation and (subsequent) stroke in AF patients and prior ICH.

Ischaemic stroke in atrial fibrillation patients while on an oral anticoagulant

There is a surprising shortage of evidence of evidence regarding efficacy and safety of LAAC compared to OAC in secondary stroke prevention. The RCTs focusing on LAAC vs. medical therapy (such as PROTECT-AF, PREVAIL and PRAGUE-17) and even large prospective LAAC-registries (such as LAARGE, Ewolution, AMULET observational registry) did not focus on AF patients after ischaemic stroke. However, residual stroke risk in anticoagulated AF patients is about 1-2% per year in RCTs and may be even higher in clinical practice and in secondary stroke prevention. In the prospective Berlin AF Registry, about 60% of all registry patients with known AF were on OAC at the time of the index-stroke or TIA [135, 136]. Of note, under-dosing of DOAC/VKA or a competing stroke aetiology (besides AF) is a frequent finding in AF patients with acute ischaemic stroke or TIA [136, 137]. However, a pooled observational cohort study underlines that about half of all AF patients with ischaemic stroke while taking an OAC are neither under-dosed nor have a competing stroke mechanism [137].

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As demonstrated by the COMBINE-AF investigators [138], and by multi-centre observational RENO-EXTEND study [139], there is a relevant recurrent stroke risk and a rather high mortality rate after ischaemic stroke while on OAC. Interestingly, a pooled analysis of observational cohort studies did not demonstrate a benefit of changing the type of OAC [140] or changing DOAC treatment in secondary stroke prevention or adding an antiplatelet on top of OAC [137].

Therefore, AF patients suffering an ischaemic stroke while on DOAC therapy (properly dosed and taken adherently) are a call to A-C-T-I-O-N, (Figure 14) referring to A - *Aetiology of stroke revisited?*, C - *Compliance to oral anticoagulation optimised?*, T - *Therapeutic options in secondary stroke prevention personalized?, I - Intake and interactions of present medication checked?*, O - *Other risk factors for stroke or death treated?* and N - *Novel stroke prevention strategies available?* [141].

Figure 14

Because of a significant residual risk of stroke under anticoagulation (that may be estimated to be 7% at 1 year and 10% at 2 years) novel stroke prevention strategies may include LAAC.[138] In an international collaboration of LAAO registries (STR-OAC) a propensity score-matched comparison between those treated with LAAC compared to those managed by the standard of care, the LAAC cohort was associated with fewer subsequent ischaemic strokes [142]. LAAC on top of OAC therapy may also be worth considering in light of the results of the randomized LAAOS III trial demonstrating risk reduction of stroke and systemic embolism after surgical LAAC in AF patients undergoing heart surgery and continuing OAC afterwards [22]. Prospective RCTs using catheter-based LAAC on top of OAC vs. OAC are underway and will hopefully start enrolment soon (LAAOS-4;[143]; ELAPSE [144]).

Further novel prevention strategies may include early rhythm-control therapy in addition to OAC [145], left atrial catheter ablation on top of DOAC treatment (as in the ongoing randomized STABLED trial [146], bilateral permanent percutaneous carotid artery filter [147] on top of DOAC treatment (as in the planned randomized INTERCEPT trial [148] or, if and when approved, a factor XIa inhibitor form of OAC.

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LAA thrombus despite optimal OAC

Despite optimal OAC treatment, thrombus formation may be detected in the LAA in patients with AF. The current recommendations suggest that LAAC should not be performed, because of the high risk of promoting dislodgement of the thrombus and, thus potential cerebral and systemic embolism. Therefore, the therapeutic options in this category of patients are limited. On the other hand, the presence of thrombus in the LAA *per se* is considered at high risk of favouring ischaemic stroke and TIA [149-151]. In a recent meta-analysis, the prevalence of left atrial thrombus in patients with AF or atrial flutter during optimal anticoagulation was 2.7%, regardless of whether patients were treated with a VKA or DOAC [152].

The management of these patients is usually challenging, ranging from reaching a higher INR in patients treated with a VKA, switching one DOAC drug to another, to adding antiplatelet medication to VKA or DOAC treatment. Alternatively, also using LMWH or unfractionated heparin (UFH) in combination with aspirin or clopidogrel was reported [53, 151-153]. Notably, these approaches result in the dissolution of thrombus only in 42.6% of cases [154]. This indicates the need to devise alternative modalities of treatment for patients with resistant LAA thrombus [155], particularly after LAAC electrical isolation [156].

The use of LAAC in case of thrombus formation in the LAA is anecdotal [157, 158] and even if formally contraindicated by the current guidelines, there is neither any formal agreement nor technical indication. One of the main aspects is the differentiation between fresh and old thrombus, the latter being more manageable. The anatomic location is also important since an old thrombus deep in the LAA might be more organized and considered less prone to be dislodged and provoke an ischaemic event during LAAC. If LAAC is considered in a patient with LA thrombus, the first crucial step is to ensure cerebral protection during the procedure, e.g. using Sentinel (Boston Scientific, Marlborough, Massachusetts, USA), to minimize the risk of intraprocedural ischaemic events (Figure 15).

Figure 15

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Coagulation disorders

Disorders of haemostasis have a double-sided relation with LAAC: as an increased risk for bleeding, they may represent an indication for LAAC -- at the same time they also represent a bleeding risk during implantation and during subsequent antithrombotic treatment. Haemorrhagic disturbances occur due to:

- Impaired number or function of platelets
- Deficiencies of coagulation factors
- Vasculopathy such as angiodysplasias or increased capillary fragility

All of these may be either congenital or acquired. Some of those patients may develop a thromboembolic risk in spite of their coagulation disorder, particularly with increasing age, which then may necessitate stroke prevention if AF develops (see below).

If a relevant bleeding disorder is identified, a treatment plan for LAAC and the subsequent antithrombotic treatment should be provided by a coagulation expert working with a LAAC implant specialist. Most mild bleeding disorders respond to desmopressin and/or antifibrinolytic drugs, regardless of aetiology. Platelet function disorders also require specialist management [159].

Important practical issues:

Von Willebrand's disease (VWD) is the most common congenital haemorrhagic disorder. Acquired VWD can be due to consumption/destruction of von Willebrand factor (VWF) in patients with valvular stenosis or artificial valves, also in patients with myeloproliferative neoplasia. VWD cannot be excluded by an APTT and PT test. Thromboembolic complications may occur in VWD, particularly in mild VWD and/or because VWF generally increases with age. The indication for anticoagulation should be discussed within an MDT appreciating the overall risks, including bleeding history, relevant bleeding scores, laboratory findings and CHA_2DS_2-VASc score.

Indication for LAAC implantation in haemostatic disorders

VWF typically increases with age in type 1 VWD, so that these patients may require thromboembolic protection in case of AF. Anticoagulation could be considered, if VWF has

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returned to the normal range and the bleeding history has been negative for at least the last decade. In other types of VWD, or low VWF or a positive bleeding history, LAAC can be considered. This may also apply to myeloproliferative disorders, which can lead to acquired VWD and/or impaired platelet function. The same considerations apply to patients with a reduction of single coagulation factors, in which the therapeutic decisions between anticoagulation and LAAC should also be made by an MDT with cardiology and haemostaseology expertise.

Patients with vasculopathies such as Rendu-Osler-Weber hereditary telangiectasia suffer from repetitive bleeding, most prominently from the nasopharyngeal tract, and although this may sometimes be acutely solvable by cauterization, it is often recurring and exacerbated using platelet-inhibitors and anticoagulants. More severe arterio-venous malformations may exist in the lungs, intestine, bladder, and brain, which may also lead to major bleeding events and may not be solved so easily without an arterial coil or endoscopic cauterization operation that carries substantial risk. Although the bleeding impact may not always be severe, its repetitive nature bringing discomfort to the patient is justification enough to not make it worse by using long-term anticoagulation, if indicated otherwise.

Severely reduced glomerular filtration rate and kidney failure

The prevalence of AF is high in patients with an estimated glomerular filtration rate (eGFR) between 15-29 ml/min (stage chronic kidney disease, CKD, G4) and <15 ml/min not on dialysis (stage CKD G5) or undergoing dialysis (stage CKD G5D). The United States Renal Data System (USRDS) reports that about one out of four CKD G4-5 and G5D have AF [160]. The finding is probably underestimated, particularly in the haemodialysis (HD) population, because of the high rate of intra-dialytic AF episodes that often remain undiagnosed [161]. An HD session can also trigger arrhythmia because of the often large and abrupt intra-dialytic volume and electrolyte changes [162].

Thromboembolic and haemorrhagic risks are elevated in patients with very low eGFR. Both pro-thrombotic factors (the presence of endothelial dysfunction and hypercoagulability (Figure 16 Panel A) and factors promoting bleeding (abnormal platelet adhesion and

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aggregation and abnormal platelet release reaction (Figure 16, Panel B) are simultaneously present [163].

Figure 16

AF is associated with a worse prognosis in terms of all-cause and cardiovascular death in patients with reduced eGFR and kidney failure, as in the general population [164, 165]. USRDS reports adjusted 2-year survival probabilities of 55.1% in HD patients with AF and of 72.1% in those without AF [160].

There are several uncertainties and difficulties in treating these patients. RCTs demonstrating the efficacy of VKA for thromboembolic prevention are lacking and observational studies in HD patients have yielded uncertain results on VKA efficacy and negative results on safety [166]. As eGFR worsens, the INR time in the therapeutic range (TTR) decreases, leading to an increased risk of bleeding [167, 168]. VKAs are also known to increase the risk of vascular calcifications [169], which is an important issue in uraemic patients, already particularly prone to this cardiovascular complication. The presence of eGFR < 25-30 ml/min was an exclusion criterion for recruitment in DOAC versus VKA phase III RCTs [170-173]. Two recent meta-analyses of studies performed in severely reduced eGFR and kidney failure populations were unable to demonstrate that OAC therapy (both VKAs and DOACs) was associated with a reduced risk of thromboembolism [174, 175].

Neither cardiology nor nephrology guidelines have been able to provide clear guidance on what is the best treatment for a patient with AF and eGFR < 15 ml/min [132, 176]. Therefore, nephrologists often decide not to prescribe OAC therapy to their patients or discontinue the drug after major bleeding [177].

LAAC may be a valuable alternative for treating these patients. Limited data, derived largely from retrospective registry studies, are available in CKD G4-5 and G5D patients undergoing the procedure. Overall, these studies show an increased in-hospital and long-term mortality risk in patients with severely reduced eGFR and kidney failure compared with those with preserved renal function who underwent the procedure. However, no significant differences

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were reported between the two populations in terms of thromboembolic and bleeding events incidence [178-183]. WATCH-HD which employed both retrospective a d prospective registry data demonstrated that LAAC was a safe and effective therapy for carefully selected haemodialysis patients.[184].

Data comparing the efficacy and safety of LACC versus OAC therapy are very few in patients with stage CKD G4-G5D.Two RCTs evaluating the safety of LAAC *vs.* OAC therapy in patients with eGFR <30 ml/min WATCH AFIB [185], and STOP-HARM [186], were terminated prematurely due to failure to recruit patients [187]. However, another RCT, LAA-KIDNEY [33], recently started and recruitment is ongoing. The only prospective study that included a fair-sized sample of dialysis patients showed a reduction in thromboembolic events in patients undergoing LAAC with respect to the events observed in both a cohort of dialysis patients with AF not taking OAC therapy and a cohort of patients taking warfarin. The risk of bleeding in the LAAC cohort was lower compared to the Warfarin cohort, while there were no significant differences between the LAAC and the cohort not taking any therapy. Nearly half of the bleedings occurred in the first three months after the procedure, when most patients were taking dual antiplatelet therapy[188]. Post-LAAC antithrombotic therapy is also currently being investigated in the SAFE LAAC CKD trial [133].

Whilst awaiting the results of further studies in CKD G4 and G5D patients with a high risk of AF-related stroke it is reasonable to evaluate the use of anti-thrombotic therapies in the context of the individual's stroke and bleeding risk. Certainly, for those patients who have a high bleeding risk, especially if they have already sustained a major or life-threatening bleed, or are incapable of taking OAC, LAAC therapy is a possible therapy (Figure 17). Similarly, for those who have a low bleeding risk and can take OAC without difficulty, OAC is the therapy of choice and LAAC is inappropriate. In other situations, the choice between LAAC and OAC is less clear and highly patient-dependent.

Figure 17

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Prolonged dual antiplatelet therapy

A previous history of cardiovascular disease and myocardial infarction is prevalent in about 10% of patients with AF[189, 190]. Incident myocardial infarction increases the risk of mortality[191]. In order to prevent arterial thrombotic events, patients with complex coronary artery disease, e.g. acute coronary syndrome (ACS) and PCI require antiplatelet therapy. In the acute phase, intensified inhibition of platelet function, commonly as dual antiplatelet therapy including aspirin and a P2Y12 inhibitor is most effective. In combination with OAC in AF patients bleeding risk remains very high even with DOAC therapy [192-195]. With a single antiplatelet therapy in combination with DOAC, the risk of stent thrombosis is mildly elevated [196, 197]. Therefore, patients with high ischaemic risk, e.g. recurrent coronary events, multivessel or complex stenting, prior stent thrombosis may require prolonged dual antiplatelet therapy.

The relevance of dual antiplatelet therapy has been shown in a sub-analysis of the AUGUSTUS trial: maintaining aspirin in the antithrombotic regimen as triple therapy for one month after PCI or ACS is beneficial to reduce ischaemic events at a high risk of bleeding (7.45%) [198]. In addition, timely de-escalation in the ambulatory setting is often not performed [199]. Previous ESC/EACTS guidelines stated that percutaneous LAAC may be considered in patients at high stroke risk and contraindication for long-term combined antiplatelet and OAC therapy (class IIb, level of evidence B)[200].

The choice of LAAC rather than OAC in high bleeding risk patients needing prolonged therapy with antiplatelet therapy may offer the opportunity to reduce or stop OAC. First, small studies have examined LAAC in combination with PCI [201, 202]. Performing the procedures in 24 ACS patients with AF in the same session may be feasible [201]. In a Korean cohort study that compared 41 AF patients undergoing drug-eluting stent implantation with LAAC and dual antiplatelet therapy with 434 patients on dual pathway inhibition could show better net clinical outcomes for cerebrovascular and major bleeding events in the occluder group. Two ongoing studies are investigating the role of LAAC in patients with complex coronary artery disease and PCI in comparison with DOAC-based antithrombotic regimens [203, 204].

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LAA closure during/after other cardiac interventions

Since LAAC is a preventive intervention, it may be considered when another procedure is performed in the left atrium, thereby offsetting procedural complications of a seperate intervention. In addition, workflow and cost-effectiveness optimisation may be improved in this context. The argument for combining interventions is analogous to the rationale studied in the LAAOS III trial where patients undergoing cardiac surgery (and thus exposed to the risks of surgery anyway) experienced a clear stroke risk reduction without an increase in undesirable outcomes if surgical LAAC was performed during the procedure [22]. On the other hand, both procedures must be independently indicated, and LAAC is not indicated simply because another procedure is taking place.

The very favourable evolution of contemporary LAAC complication risks, as outlined elsewhere in this document, makes this argument viable in the setting of several other routine cardiac interventions. Specific considerations may exist for specific procedure types as outlined below.

Left atrial ablation

A high rate of OAC discontinuation after AF ablation is seen in several studies, despite an increased stroke risk associated with discontinuation after 3 months in patients with CHA_2DS_2-VASc ≥ 2 [205]. Current guidelines, therefore, recommend continuing OAC indefinitely in these high-risk groups. A strategy combining AF ablation and LAAC for the purpose of allowing OAC cessation appears attractive and has been shown to be safe and efficient without interference when a repeat ablation is needed [206, 207]. A small proof-of-concept RCT comparing LAAC to warfarin post-ablation showed no events in either group [208]. Whether there is a net clinical benefit of such a strategy as compared to contemporary DOAC continuation as per current guidelines is the subject of the OPTION randomised controlled trial [35].

Conversely, arguments can be made for a staged approach to ablation and LAAC (typically in that order although not necessarily so). First and foremost, an apparently successful AF ablation may reduce stroke risk although existing evidence for this is sparse. Formal testing of OAC versus aspirin alone is being conducted in the OCEAN trial [209]. In addition, concerns exist regarding the location of the transseptal puncture site, which may be suboptimal for

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LAAC in the typical PVI positions. The presence of ablation-induced oedema at the LAA-LPV ridge immediately after ablation may occasionally lead to sizing errors and to suboptimal occlusion during follow-up [210].

Left atrial appendage electrical isolation

There is conflicting evidence for electrical isolation of the LAA to improve catheter ablation outcomes. The aMAZE randomized trial failed to show a rhythm control benefit of LAA exclusion and isolation over PVI alone [211]. However, the BELIEF RCT and several observational studies showed improved rhythm control [212]. For the latter, strategies of LAA isolation without LAA exclusion (i.e. not using surgery or the LARIAT device), there is an additional concern regarding increased stroke risk after LAA isolation (intentional or not) even for patients on OAC, due to loss of LAA mechanical function [213]. Firm recommendations on the usefulness of LAA isolation are not available at this point, although there does appear to be growing consensus to recommend LAAC in case of electrical isolation [214].

Transcatheter aortic valve replacement and LAAC

Transcatheter aortic valve implantation (TAVI) has emerged as the standard treatment modality for patients with severe aortic stenosis across the full risk spectrum. AF occurs in more than 10% of octogenarians and is the most common arrhythmia in the TAVI population, being present in about 30-40%. Typically, TAVI patients are older than 75 years with multiple comorbidities. In patients with AF undergoing TAVI, bleeding complications were reported to be as high as 50%, and in those who experience bleeding complications during the first year, 1-year mortality is doubled [215, 216]. LAA closure-obviating the need for OAC may therefore be an attractive treatment for the AF TAVI population.

Current evidence remains limited to only a handful of observational and prospective studies [217, 218]. Limited data indicate that a combined TAVI-LAA closure intervention is a feasible and potentially effective approach for stroke prevention in patients with symptomatic, severe AS and AF with a high bleeding risk. Larger randomized trials with longer follow-up are needed to confirm safety and to further show the efficacy of combining these two increasingly common interventions.

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Transcatheter mitral valve edge-to-edge repair and LAAC

Patients undergoing Transcatheter Mitral Valve Edge-to-Edge Repair (TEER) are frequently affected by AF and are at high risk for major bleeding due to comorbidities or concomitant indications for antithrombotic therapy. From a procedural aspect, there are similarities. TEER and LAAC are performed via the femoral venous route and both require a similar transseptal crossing, hence it seems reasonable to combine them. Currently, available evidence on simultaneous or successive TEER and LAAC is very limited, derived from case reports and very small case series [219-224], with short follow-up, showing high immediate technical success and an acceptable rate of major complications as well as in the long-term comparable efficacy (stroke, death) and safety (major bleeding). With TEER becoming more and more mainstream therapy, there is a need for larger prospective studies to address the potential of these therapies to be performed simultaneously or successively.

LAA Closure and Other Concomitant Cardiac Interventions (PCI, ASD, PFO closures)

There is very limited reporting of LAAC performed as a simultaneous procedure with PCI and also with atrial septal defect closures [201, 225]. Similar procedural outcomes were reported for isolated LAA closure procedures and the combined procedure [226]. At the current state of knowledge, such interventions should only be carried out on an individual basis with prior careful assessment by the structural heart team. To be applied more widely, validation in larger studies is needed.

Patient refusal/non-adherence/non-compliance

Physicians may decide not to prescribe OAC to patients who fall or are frail or instead they may offer treatment with OAC at doses less than those that are effective [227]. Patients may refuse OAC because of relatively mild bleeding or because they hear from their friends and neighbours that the therapy is dangerous. Others may be completely averse to taking regular medication especially when it is preventive rather than directed at symptoms which are troubling the patients. Even when patients receive and accept appropriate prescriptions, evidence suggests that a high proportion of patients no longer persist with their medication or frequently lapse from their therapy, leaving them at risk for stroke [228]. A recent meta-analysis on adherence showed that adherence/persistence to DOAC was particularly poor: one third of AF patients starting DOAC stopped the drug by 1 year, and

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another third of patients were taking the DOAC less than 80% of the time [229]. Elderly patients, especially those with physical disabilities or mental illness, may need to rely on others to ensure optimal adherence and such a supportive social framework is often not readily available. In these patients LAAC may provide an alternative treatment that is not limited by such compliance issues.

For patients treated with VKA, regular assessment of the INR easily reveals those whose therapy is inadequate but for those taking DOACs prescription monitoring, pill counting, and the recollections of patients or their carers is usually all there is to assess how well the oral anticoagulation regimen is being followed. A counselling programme might be started to help the patient understand the value of the treatment and how important it is to follow the prescription. When patients cannot be relied on to take their medications regularly, a LAAC device may be preferable (Figure 18).

Also, if the patient is rigidly drug therapy averse, LAAC therapy can be considered, provided that the patient is willing to use antithrombotic medication for a limited period after implantation of the device. It is also relevant to be sure that the patient has no other life-threatening comorbidities that require continuous drug therapy which might be refused.

Patients may learn about LAAC therapy and simply prefer this option to taking regular anticoagulant drugs. This is often the case when the patient has been referred for consideration of LAAC implantation and has been informed about some of the advantages of this therapy. It may then be very difficult to re-align the patient towards anticoagulant therapy. However, this should be attempted because there is still only limited evidence that LAAC is as beneficial as DOAC therapy. The 2023 ACC/AHA/ACCP/HRS guidelines do accept that patient preferences may be considered (a level IIb recommendation – see above)[57].

Figure: 18

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Anticoagulant/antiplatelet therapy regimens after left atrial appendage closure

Antithrombotic therapy is required after LAAC in order to prevent device-related thrombus and this is of special importance in the initial phase, before device endothelization (Figure 19) [62, 230, 231].

Figure 19

Published data on antithrombotic regimens were derived from studies performed on patients who were eligible for anticoagulation (who received VKA or DOAC), as well as from studies performed on patients with intolerance or relative contraindications to anticoagulation, mainly related to prior major bleeding complications (who received antiplatelet therapy) [230].

Clinical RCT data on patients without LAAC have shown that dual antiplatelet therapy with aspirin-clopidogrel had similar major bleeding and ICH rates to warfarin (ACTIVE-W) [232]. When aspirin was compared to apixaban in AF patients who refused or were deemed ineligible for warfarin, there was clear superiority of apixaban for the reduction of stroke/SE but the rates of major bleeding and ICH were similar (AVERROES) [233]. In the BAFTA trial of elderly (age ≥75 years) AF patients managed in primary care, aspirin monotherapy had similar rates of major bleeding or ICH as warfarin [234]. In elderly AF patients with high-risk features for bleeding, low dose edoxaban 15mg was superior for stroke risk reduction, with a nonsignificant difference in major bleeding or ICH to placebo, although major GI bleeding was increased with edoxaban (ELDERCARE-AF) [235].

In practice, after LAAC there is a need to tailor the antithrombosis regimen according to the patient. The best antithrombotic therapy after LAAC needs to provide a balance between the prevention of DRT and the occurrence of major bleeding. The rationale for choosing between the available options (Table 9 and Figure 20) should be based on physician assessment of individual patient characteristics, such as bleeding risk and stroke risk, an overall clinical evaluation of the patient's condition, comorbidities and preference, as well

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as an evaluation of the reasons for LAAC [61, 62, 236]. As reported in Table 9, discontinuations of OAC or antiplatelet therapy after LAAC is subject to the absence of other clinical indications for that medication and an assessment, including proper imaging (TOE or CT), demonstrating that there are no significant peri-device leaks (>5mm), thrombus on the device or recent history of clinical events. Currently accepted antithrombotic regimens are illustrated in Figure 20.

Table 9: List of main antithrombotic schemes used after LAAC. DOAC: direct oral anticoagulation; INR: International normalized ratio; LAAC: left atrial appendage closure; VKA: vitamin K antagonist. *OAC schemes are not recommended with the Amulet device unless residual flow around the device is >5 mm.

In a pooled analysis of data on patients from the PROTECT-AF, PREVAIL, CAP, CAP2, ASAP and EWOLUTION studies patients receiving either oral anticoagulants or antiplatelets post-LAAC implant were matched and compared with regard to the occurrence of non-procedural bleeding and stroke/systemic thromboembolism over 6 months following implantation Although DRT was more frequently observed with antiplatelet therapy, the occurrence of major bleeding and of stroke/systemic thromboembolism was similar between regimens based on antiplatelets or OAC [237]. Figure 20 shows various manufacturer recommendations and less "official" strategies for thrombotic therapy post implant [238-251].

Figure 20

Upper panel: Manufacturer-recommended antithrombotic regimens after LAAC (adapted and updated [238, 239]). LAAC: left atrial appendage closure; OAC: oral anticoagulant.
Lower panel: Emerging strategies for antithrombotic regimens after LAAC (limited evidence and some ongoing studies): initial anticoagulant without concomitant aspirin ([240-242]) followed by a DAPT or SAPT period; single antiplatelet ([243-246]); low-dose DOAC ([247-251]). LAAC: left atrial appendage closure; (D)OAC: (direct) oral anticoagulant.
Hatching indicates variable adoption depending on benefit-risk.

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Observational data from the years 2016-2018 in the United States highlighted how the antithrombotic regimen approved by the FDA for use of the Watchman device was rarely applied [240]. In particular, discharge after implantation on VKA or DOAC without concomitant aspirin was common and associated with lower risk of adverse outcomes. Updated data were presented at the HRS conference in 2023, confirming this finding [241]. In a recent meta-analysis comparing initial antithrombotic therapy following LAAO, monotherapy with DOAC had the highest likelihood of lower thromboembolic events and major bleeding.[242]

A simplified regimen with a short period (2-4 weeks) of a single antiplatelet (ASA or clopidogrel) has also been applied to very selected patients with an extremely high bleeding risk on the basis of expert consensus [62], and reported in observational studies [243-245]. Additional data on this approach may become available from the CLOSURE-AF [28] and the ARMYDA-Amulet [246] ongoing studies.

Limited but promising observational data are available on post LAAC treatment with low dose DOACs, showing reduction of DRT, thromboembolism and major bleeding events compared with a standard, antiplatelet-based, antithrombotic therapy [247, 248], however further controlled data are required to assess the value of this strategy. The small randomized ADALA trial [249] aimed to compare long-term low dose DOAC therapy (apixaban 2.5 mg BID) to a standard dual antiplatelet therapy scheme. The study was terminated after a planned interim analysis showed a significant reduction of bleedings and DRT at 3 months post-implant in the low dose DOAC arm [250]. The larger ongoing randomized ANDES trial [251] may confirm these preliminary findings.

Future randomized studies should better define which antiplatelet and antithrombotic regimens are indicated after LAAC implant, in terms of safety and net outcomes, specifically focusing on patients who have contraindications to long-term therapy with OAC

Post discharge LAAC patient follow-up

In clinical studies, assessment of the patient's clinical status as well as of the antithrombotic medication was performed 6 months after the implant. In clinical routine, this is less

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common. Depending on the antithrombotic treatment regimen, however, it may be appropriate to schedule a counselling appointment.

One year after LAAC, the large majority of patients reduce the antithrombotic regimen to a single agent or stop this therapy. In controlled clinical studies TOE imaging was mandatory at the 12-month follow-up visit, although this is rarely done in clinical practice. It was noted, that depending on the device type and the medication used, not uncommonly DRT may occur late after implantation [252]. This may be associated with an increased risk for stroke during long-term follow-up [253].

Similarly, the presence of PDL at the 12-month imaging contributes to an increased rate of stroke [254, 255]. Both scenarios, DRT as well as PDL, have an impact on the future medical management of the patient. Therefore, it may be advisable to incorporate routine imaging at the 12-month follow-up visit into clinical routine but it is not a common practice in many centres.

In clinical studies with long-term follow-up, patient management beyond one year was usually limited to routine clinical assessment. Depending on co-morbidities, it seems appropriate to tailor the individual follow-up schedule to the individual risk profile depending on co-existing medical conditions (e.g. every 6-12 months). Specific device-related imaging is not recommended.

In case of adverse clinical events such as stroke, unscheduled visits including imaging for DRT or PDL should be considered.

Practical Box 4

Other cardiac procedures after left atrial appendage closure

Direct current cardioversion

Direct current cardioversion (DCCV) is frequently used in AF patients as part of a rhythm control strategy. According to current guidelines, patients should be treated by anticoagulation at least 3 weeks before DCCV (AF duration >48 hours) and 4 weeks after to

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prevent thromboembolic complications. However, patients after LAAC are often at high bleeding risk and therefore unsuitable for anticoagulation before and after DCCV. In two prospectively enrolled patient cohorts with a total of 242 LAAC patients, DCCV was used effectively without thromboembolic events despite the majority of patients being without anticoagulation before and after DCCV [256, 257]. In those studies, the majority of patients underwent TOE before DCCV to rule out device-related thrombus (DRT), large peri-device leaks, device malposition and other cardiac thrombi.

Currently, the recommendations below can be used as a guide for DCCV in this patient group. There are no specific precautions for pharmacological cardioversion in LAAC patients.

- DCCV Should be avoided the first 3 weeks after LAAC unless there is an acute indication, e.g. acute cardiac decompensation considered to be related to AF.
- TOE should always be performed before to rule out DRT, large PDL, device malposition, other cardiac thrombi. CT can be used as an alternative to TOE.
- DCCV can be performed without anticoagulation before and after.
- Anticoagulation can be considered before and after in patients with a predicted very high risk of thromboembolic events (severe left atrial dilatation, pronounced spontaneous contrast or sludge in the left atrium, LVEF<25%, high CHA_2DS_2-VASc score etc.) depending on an individual assessment of bleeding risk. Recent ACC/AHA/ACCP/HRS Guidelines recommend (CoR: IIb, LOE: N-BR) pre-cardioversion imaging for LAAO patients who are not anticoagulated, and anticoagulation peri-cardioversion if there is a device-related thrombus or peri device leak [57].

Atrial fibrillation catheter ablation

AF catheter ablation and all other types of transcatheter cardiac ablation using various energy delivery sources (RF, cryo or pulsed-field) can be performed in patients after LAAC. TOE should be performed before AF ablation to rule out DRT and elective ablation should not be performed before the first follow-up imaging after LAAC which is typically done after 45 days or later. Anticoagulation post-ablation is recommended but adjusted according to the predicted bleeding risk for the individual patient.

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Transcatheter mitral interventions, TAVI and PCI

Transcatheter mitral interventions, TAVI and PCI can all be performed in LAAC patients. Elective mitral intervention or TAVI should be planned not earlier than 45 days after LAAC or later, if possible. TOE should be performed before mitral intervention to rule out DRT or malposition of the device. For PCI, there are no specific LAAC-related precautions.

Summary

The summary points for this practical guide are displayed in an unusual format. Those physicians who are considering referring a patient for an LAAC will often be asked by the patient a series of questions about the procedure, the necessary preparation and follow-up. The basis for answering these common questions has formed the content of this practical guide and the rationale and evidence base for the answers have been fully described in the guide for the benefit of the physician. The document is now summarised by proposing brief and accurate responses, in lay language, to these important questions.

What is the left atrial appendage (LAA) and why do we need to close it?

The LAA is a 2–6 cm-long, blind-ended, finger-like, extension of the left atrium of the heart. It is a remnant of the development of the heart and does not have a significant role in the body. It is the place where most clots form in patients with atrial fibrillation (AF), and if they detach these clots can cause a stroke.

Am I a candidate for left atrial appendage closure (LAAC)?

LAAC is offered to patients who have AF, are at high risk for stroke and cannot take oral anticoagulants (OACs – also known as blood thinners) for a prolonged period. The main reason for recommending the LAAC is because of serious bleeding complications of OACs. Also, LAAC may be offered to patients who had a stroke while they were optimally treated with OAC.

How is LAAC done?

The LAAC device is introduced into the heart using a catheter (long and thin tube) inserted through the veins in the groin. The collapsed device is expanded when it

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emerges from the tube when in the correct place within the heart to block the entrance to the left atrial appendage.

Does it work?

According to the current information, for those patients able to take blood thinners (anticoagulants), LAAC may be equally effective to OAC drug therapy for stroke prevention, but does not cause long-term bleeding complications.

Is it safe?

Yes. There is a small immediate risk related to the procedure. However, in experienced hands, this is considered a safe procedure, similar to other routine catheterization procedures.

How about the long-term safety?

Late complications are very rare. The most common is device-related thrombosis, (clotting on the LAAC device) which is typically treated with a short period of OAC therapy.

Is LAAC a lifelong solution?

Yes. A device will achieve lifelong closure of the LAA. Over months, the surface of the device will be covered by the patient's own tissue forming a smooth layer in continuation with the inner surface of the heart. This greatly reduces the likelihood of blood clotting on the device.

Is there enough scientific evidence?

A few randomized clinical trials and many large registries have shown positive results. Larger clinical trials comparing the device to other medicines in a wider variety of patients are currently underway.

Do I need to have any pre-procedural exams?

Often, a transoesophageal echocardiogram (TOE) or a cardiac computed tomography (CT X-ray) is required before the procedure.

Is AF going to stop after LAAC?

No. LAAC is a stroke prevention therapy and does not cure AF.

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Do I need to be hospitalized for the procedure?

In most centres, the patient needs to stay overnight but same-day discharge is sometimes offered.

Do I have to undergo general anaesthesia?

General anaesthesia is commonly used but some centres perform the procedure under light sedation or local anaesthesia.

Is the procedure painful?

The procedure is not painful. It is performed through catheters, with a 4-5 mm incision of the skin in the groin. Pain after the procedure is unlikely, but a few days of avoiding vigorous activities is recommended to allow this small incision to heal.

Will I stop taking blood thinners?

Yes. A few weeks after LAAC, the majority of patients may stop blood thinners. However, a short period of low-dose aspirin and/or clopidogrel therapy is required for some weeks, until the closure device is covered with the patient's own body tissue and healed. If you also have a reason other than AF for taking the OAC or antiplatelet therapy, you may have to continue the treatment.

Do I need to have any exams after the procedure?

Yes. A TOE or CT is required, usually 6 weeks to 4 months after the procedure to check that everything is satisfactory.

Can I feel the device in my chest?

There have been no reports of discomfort due to the device, nor any need for device removal for this reason.

Can I have a magnetic resonance exam (MRI) if needed in the future? How about airport security?

Yes. LAAC devices are compatible with up to 3 Tesla (strength of scanner) MRI scanners. Also, there are no special requirements for metal detectors at airport security checks.

Do I need antibiotic treatment to prevent device infection?

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During the implantation, a single dose of antibiotics is administered. After the procedure antibiotic prophylaxis (for more invasive dental procedures, etc.) is recommended for a period of 6 months. After that antibiotics are not needed.

Can I continue to play tennis, golf and other sports after insertion of the device

Yes. You should avoid vigorous exercise for a few days after the procedure, but after that there is no reason to avoid sports or other vigorous activities. In fact, stopping OAC therapy reduces the risk of serious bleeding in case of any injury related to such activities.

Is it possible for the device to dislodge?

This complication is very rare and it is manageable. A dislodgement after the healing phase is highly unlikely.

Can the device be removed from the LAA?

The device becomes firmly attached to the tissue after it is inserted. The only way to remove it is by (minimally invasive) heart surgery, although this is rarely needed.

Please note that these Q&A's are written in order to help a referral physician to aid discussion with the patient being referred for placement of an LAAC device. Detailed explanations, such as those that might be given by the implanting physician are not provided. The answers are not written primarily for the patient although some words and phrases are chosen when they are more easily understood by the patient.

Conclusions

The advice provided is fully in line with current guidelines and guidance documents provided by professional societies such as the European Society of Cardiology.

Research investigating the value of LAAC in comparison to approved alternatives is being rapidly conducted. For patients with high AF-related stroke risk who cannot be treated with anticoagulants to prevent stroke and other systemic emboli, LAAC is the only option and is often considered in such circumstances. These patients include those with anticoagulant-

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related major or life-threatening bleeding, a substantial threat of such bleeding in the presence of anticoagulants, failure of anticoagulants to prevent an embolic ischaemic stroke, or inability to comply sufficiently with anticoagulation treatment regimens, etc.

LAAC has been shown to be almost as effective and safer than VKA therapy but data comparing DOACs and LAAC are still insufficient to justify considering LAAC as a valid alternative to DOAC for treatment unless anticoagulation is contra-indicated. For the time being LAAC is a second-line therapy. However, many patients may qualify for LAAC treatment. These patients are spread throughout the full range of clinical specialties and care settings. For that reason this Practical Guide for the referral of patients for consideration for LAAC therapy is necessary.

References

[1] Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation* 2019; **139**: e56-e528.

[2] Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013; **34**: 2746-2751.

[3] Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; **146**: 857-867.

[4] Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014; **383**: 955-962.

[5] Ray WA, Chung CP, Stein CM, Smalley W, Zimmerman E, Dupont WD, et al. Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation. *JAMA* 2021; **326**: 2395-2404.

[6] Hedner U. Mechanism of action of factor VIIa in the treatment of coagulopathies. *Semin Thromb Hemost* 2006; **32 Suppl 1**: 77-85.

[7] Marijon E, Le Heuzey JY, Connolly S, Yang S, Pogue J, Brueckmann M, et al. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. *Circulation* 2013; **128**: 2192-2201.

[8] Carnicelli AP, Hong H, Connolly SJ, Eikelboom J, Giugliano RP, Morrow DA, et al. Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation: Patient-Level Network Meta-Analyses of Randomized Clinical Trials With Interaction Testing by Age and Sex. *Circulation* 2022; **145**: 242-255.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/europace/advance-article/doi/10.1093/europace/euae035/7593802 by St George's, University of London user on 07 February 2024

[9] Little D, Chai-Adisaksopha C, Hillis C, Witt DM, Monreal M, Crowther MA, Siegal DM. Resumption of anticoagulant therapy after anticoagulant-related gastrointestinal bleeding: A systematic review and meta-analysis. *Thromb Res* 2019; **175**: 102-109.
[10] Karim N, Ho SY, Nicol E, Li W, Zemrak F, Markides V, et al. The left atrial appendage in humans: structure, physiology, and pathogenesis. *Europace* 2020; **22**: 5-18.
[11] Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, et al. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. *J Am Coll Cardiol* 2017; **70**: 2964-2975.
[12] Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, et al. 4-Year Outcomes After Left Atrial Appendage Closure Versus Nonwarfarin Oral Anticoagulation for Atrial Fibrillation. *J Am Coll Cardiol* 2022; **79**: 1-14.
[13] Turagam MK, Osmancik P, Neuzil P, Dukkipati SR, Reddy VY. Left Atrial Appendage Closure Versus Oral Anticoagulants in Atrial Fibrillation: A Meta-Analysis of Randomized Trials. *J Am Coll Cardiol* 2020; **76**: 2795-2797.
[14] Turagam MK, Kawamura I, Neuzil P, Nair D, Doshi S, Valderrabano M, et al. Severity of Ischemic Stroke After Left Atrial Appendage Closure vs Nonwarfarin Oral Anticoagulants. *JACC Clin Electrophysiol* 2023.
[15] Tzikas A, Shakir S, Gafoor S, Omran H, Berti S, Santoro G, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. *EuroIntervention* 2016; **11**: 1170-1179.
[16] Hildick-Smith D, Landmesser U, Camm AJ, Diener HC, Paul V, Schmidt B, et al. Left atrial appendage occlusion with the Amplatzer Amulet device: full results of the prospective global observational study. *Eur Heart J* 2020; **41**: 2894-2901.
[17] Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial. *Heart Rhythm* 2017; **14**: 1302-1308.
[18] Freeman JV, Varosy P, Price MJ, Slotwiner D, Kusumoto FM, Rammohan C, et al. The NCDR Left Atrial Appendage Occlusion Registry. *J Am Coll Cardiol* 2020; **75**: 1503-1518.
[19] Price MJ, Slotwiner D, Du C, Freeman JV, Turi Z, Rammohan C, et al. Clinical Outcomes at 1 Year Following Transcatheter Left Atrial Appendage Occlusion in the United States. *JACC Cardiovasc Interv* 2022; **15**: 741-750.
[20] Doshi SK, Kar S, Sadhu A, Horton R, Osorio J, Ellis C, et al. Two-Year Outcomes With a Next-Generation Left Atrial Appendage Device: Final Results of the PINNACLE FLX Trial. *J Am Heart Assoc* 2023; **12**: e026295.
[21] Waranugraha Y, Lin LY, Tsai CT. Head-to-head comparison between left atrial appendage occlusion and non-vitamin K oral anticoagulants in non-valvular atrial fibrillation patients: A systematic review and meta-analysis study(). *Trends Cardiovasc Med* 2023.
[22] Whitlock RP, Belley-Cote EP, Paparella D, Healey JS, Brady K, Sharma M, et al. Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke. *N Engl J Med* 2021; **384**: 2081-2091.
[23] Bayer. A Study to Learn How Well the Study Treatment Asundexian Works and How Safe it is Compared to Apixaban to Prevent Stroke or Systemic Embolism in People With Irregular and Often Rapid Heartbeat (Atrial Fibrillation), and at Risk for Stroke: https://classic.clinicaltrials.gov/show/NCT05643573 2022.

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[24] Anthos Therapeutics Inc., The TIMI Study Group, Laboratory Corporation of America. Safety and Tolerability of Abelacimab (MAA868) vs. Rivaroxaban in Patients With Atrial Fibrillation: https://classic.clinicaltrials.gov/show/NCT04755283 2021.
[25] Anthos Therapeutics Inc. Study to evaLuate the effIcacy and Safety of abeLacimab in High-risk Patients With Atrial Fibrillation Who Have Been Deemed Unsuitable for Oral antiCoagulation (LILAC-TIMI 76): https://classic.clinicaltrials.gov/show/NCT05712200 2022.
[26] Janssen Research Development LLC, Bristol-Myers Squibb. A Study of Milvexian Versus Apixaban in Participants With Atrial Fibrillation: https://classic.clinicaltrials.gov/show/NCT05757869 2023.
[27] Boston Scientific Corporation. Assessment of the WATCHMAN™ Device in Patients Unsuitable for Oral Anticoagulation: https://classic.clinicaltrials.gov/show/NCT02928497 2017.
[28] Charite University Berlin Germany, Deutsches Zentrum für Herz-Kreislauf-Forschung, Atrial Fibrillation Network, Stiftung Institut fuer Herzinfarktforschung. Left Atrial Appendage CLOSURE in Patients With Atrial Fibrillation Compared to Medical Therapy: https://classic.clinicaltrials.gov/show/NCT03463317 2018.
[29] Karolinska Institutet, Abbott Medical Devices. Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Hemorrhage: https://classic.clinicaltrials.gov/show/NCT02830152 2017.
[30] Jena University Hospital. Comparison of LAA-Closure vs Oral Anticoagulation in Patients With NVAF and Status Post Intracranial Bleeding: https://classic.clinicaltrials.gov/show/NCT04298723 2020.
[31] Huijboom M, Maarse M, Aarnink E, van Dijk V, Swaans M, van der Heijden J, et al. COMPARE LAAO: Rationale and design of the randomized controlled trial "COMPARing Effectiveness and safety of Left Atrial Appendage Occlusion to standard of care for atrial fibrillation patients at high stroke risk and ineligible to use oral anticoagulation therapy". *Am Heart J* 2022; **250**: 45-56.
[32] R&D Cardiologie, Research ZTNOfH, Development. Left Atrial Appendage Occlusion for AF Patients Unable to Use Oral Anticoagulation Therapy: https://classic.clinicaltrials.gov/show/NCT04676880 2021.
[33] Eitel I. Left Atrial Appendage Closure in Patients With Non-valvular Atrial Fibrillation and End-stage Chronic KIDNEY Disease: https://classic.clinicaltrials.gov/show/NCT05204212 2022.
[34] Wazni OM, Boersma L, Healey JS, Mansour M, Tondo C, Phillips K, et al. Comparison of anticoagulation with left atrial appendage closure after atrial fibrillation ablation: Rationale and design of the OPTION randomized trial. *Am Heart J* 2022; **251**: 35-42.
[35] Boston Scientific Corporation. Comparison of Anticoagulation With Left Atrial Appendage Closure After AF Ablation: https://classic.clinicaltrials.gov/show/NCT03795298 2019.
[36] Kar S, Doshi SK, Alkhouli M, Camm AJ, Coylewright M, Gibson MC, et al. Rationale and design of a randomized study comparing the Watchman FLX device to DOACs in patients with atrial fibrillation. *Am Heart J* 2023; **264**: 123-132.
[37] Abbott Medical Devices. Amplatzer Amulet LAAO vs. NOAC: https://classic.clinicaltrials.gov/show/NCT04226547 2020.
[38] University of Aarhus, Aarhus University Hospital, Aalborg University Hospital, Odense University Hospital, Sahlgrenska University Hospital Sweden, Karolinska University Hospital,

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et al. Left Atrial Appendage Occlusion Versus Novel Oral Anticoagulation for Stroke Prevention in Atrial Fibrillation: https://classic.clinicaltrials.gov/show/NCT03642509 2019.
[39] Korsholm K, Damgaard D, Valentin JB, Packer EJS, Odenstedt J, Sinisalo J, et al. Left atrial appendage occlusion vs novel oral anticoagulation for stroke prevention in atrial fibrillation: rationale and design of the multicenter randomized occlusion-AF trial. *Am Heart J* 2022; **243**: 28-38.
[40] Nielsen-Kudsk JE, Johnsen SP, Wester P, Damgaard D, Airaksinen J, Lund J, et al. Left atrial appendage occlusion versus standard medical care in patients with atrial fibrillation and intracerebral haemorrhage: a propensity score-matched follow-up study. *EuroIntervention* 2017; **13**: 371-378.
[41] Nielsen-Kudsk JE, Korsholm K, Damgaard D, Valentin JB, Diener HC, Camm AJ, Johnsen SP. Clinical Outcomes Associated With Left Atrial Appendage Occlusion Versus Direct Oral Anticoagulation in Atrial Fibrillation. *JACC Cardiovasc Interv* 2021; **14**: 69-78.
[42] Lip GYH, Proietti M, Potpara T, Mansour M, Savelieva I, Tse HF, et al. Atrial fibrillation and stroke prevention: 25 years of research at EP Europace journal. *Europace* 2023; **25**.
[43] Romiti GF, Pastori D, Rivera-Caravaca JM, Ding WY, Gue YX, Menichelli D, et al. Adherence to the 'Atrial Fibrillation Better Care' Pathway in Patients with Atrial Fibrillation: Impact on Clinical Outcomes-A Systematic Review and Meta-Analysis of 285,000 Patients. *Thromb Haemost* 2022; **122**: 406-414.
[44] Patel SM, Palazzolo MG, Murphy SA, Antman EM, Braunwald E, Lanz HJ, et al. Evaluation of the atrial fibrillation better care pathway in the ENGAGE AF-TIMI 48 trial. *Europace* 2022; **24**: 1730-1738.
[45] Proietti M, Romiti GF, Olshansky B, Lane DA, Lip GYH. Comprehensive Management With the ABC (Atrial Fibrillation Better Care) Pathway in Clinically Complex Patients With Atrial Fibrillation: A Post Hoc Ancillary Analysis From the AFFIRM Trial. *J Am Heart Assoc* 2020; **9**: e014932.
[46] Shrestha B, Poudel B, Poudel D, Diaz Fraga J. National Yearly Trend of Utilization and Procedural Complication of the Watchman Device in the United States. *Cureus* 2022; **14**: e25567.
[47] Boriani G, Proietti M, Laroche C, Fauchier L, Marin F, Nabauer M, et al. Association between antithrombotic treatment and outcomes at 1-year follow-up in patients with atrial fibrillation: the EORP-AF General Long-Term Registry. *Europace* 2019; **21**: 1013-1022.
[48] Potpara TS, Dan GA, Trendafilova E, Goda A, Kusljugic Z, Manola S, et al. Stroke prevention in atrial fibrillation and 'real world' adherence to guidelines in the Balkan Region: The BALKAN-AF Survey. *Sci Rep* 2016; **6**: 20432.
[49] Juhl Madsen O, Lamberts MK, Fosboel EL, Gislason G, Olesen JB, Strange JE. Trends in percutaneous left atrial appendage occlusion and 1-year mortality: a nationwide cohort study. *European Heart Journal* 2022; **43**.
[50] Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest* 2018; **154**: 1121-1201.
[51] NHFA CSANZ Atrial Fibrillation Guideline Working Group, Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. *Heart Lung Circ* 2018; **27**: 1209-1266.
[52] January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of

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Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019; **74**: 104-132.
[53] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; **42**: 373-498.
[54] Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol* 2020; **36**: 1847-1948.
[55] Chao TF, Joung B, Takahashi Y, Lim TW, Choi EK, Chan YH, et al. 2021 Focused Update Consensus Guidelines of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation: Executive Summary. *Thromb Haemost* 2022; **122**: 20-47.
[56] Saw J, Holmes DR, Cavalcante JL, Freeman JV, Goldsweig AM, Kavinsky CJ, et al. SCAI/HRS Expert Consensus Statement on Transcatheter Left Atrial Appendage Closure. *JACC Cardiovasc Interv* 2023; **16**: 1384-1400.
[57] Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2023.
[58] Glikson M, Wolff R, Hindricks G, Mandrola J, Camm AJ, Lip GYH, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update. *EuroIntervention* 2020; **15**: 1133-1180.
[59] Tzikas A, Holmes DR, Jr., Gafoor S, Ruiz CE, Blomstrom-Lundqvist C, Diener HC, et al. Percutaneous left atrial appendage occlusion: the Munich consensus document on definitions, endpoints, and data collection requirements for clinical studies. *Europace* 2017; **19**: 4-15.
[60] Anic A, Bakovic D, Jurisic Z, Farkowski M, Lisica L, Breskovic T, et al. Diagnostic and therapeutic pathways for the malignant left atrial appendage: European Heart Rhythm Association physician survey. *Europace* 2023; **25**.
[61] Camm AJ. Leap or lag: left atrial appendage closure and guidelines. *Europace* 2023; **25**.
[62] Glikson M, Wolff R, Hindricks G, Mandrola J, Camm AJ, Lip GYH, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update. *Europace* 2020; **22**: 184.
[63] National Institute for Health and Clinical Excellence. Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism2010.
[64] Di Biase L, Briceno DF, Trivedi C, Mohanty S, Gianni C, Burkhardt JD, et al. Is transesophageal echocardiogram mandatory in patients undergoing ablation of atrial fibrillation with uninterrupted novel oral anticoagulants? Results from a prospective multicenter registry. *Heart Rhythm* 2016; **13**: 1197-1202.
[65] Lee OH, Kim JS, Pak HN, Hong GR, Shim CY, Uhm JS, et al. Feasibility of Left Atrial Appendage Occlusion for Left Atrial Appendage Thrombus in Patients With Persistent Atrial Fibrillation. *Am J Cardiol* 2018; **121**: 1534-1539.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/europace/advance-article/doi/10.1093/europace/euae035/7593802 by St George's, University of London user on 07 February 2024

[66] Korsholm K, Berti S, Iriart X, Saw J, Wang DD, Cochet H, et al. Expert Recommendations on Cardiac Computed Tomography for Planning Transcatheter Left Atrial Appendage Occlusion. *JACC Cardiovasc Interv* 2020; **13**: 277-292.
[67] Osmancik P, Herman D, Linkova H, Hozman M, Labos M. A Comparison of Cardiac Computed Tomography, Transesophageal and Intracardiac Echocardiography, and Fluoroscopy for Planning Left Atrial Appendage Closure. *J Atr Fibrillation* 2021; **13**: 20200449.
[68] Sharma PS, Padala SK, Gunda S, Koneru JN, Ellenbogen KA. Vascular Complications During Catheter Ablation of Cardiac Arrhythmias: A Comparison Between Vascular Ultrasound Guided Access and Conventional Vascular Access. *J Cardiovasc Electrophysiol* 2016; **27**: 1160-1166.
[69] Yamagata K, Wichterle D, Roubicek T, Jarkovsky P, Sato Y, Kogure T, et al. Ultrasound-guided versus conventional femoral venipuncture for catheter ablation of atrial fibrillation: a multicentre randomized efficacy and safety trial (ULTRA-FAST trial). *Europace* 2018; **20**: 1107-1114.
[70] Sobolev M, Shiloh AL, Di Biase L, Slovut DP. Ultrasound-guided cannulation of the femoral vein in electrophysiological procedures: a systematic review and meta-analysis. *Europace* 2017; **19**: 850-855.
[71] Brass P, Hellmich M, Kolodziej L, Schick G, Smith AF. Ultrasound guidance versus anatomical landmarks for subclavian or femoral vein catheterization. *Cochrane Database Syst Rev* 2015; **1**: CD011447.
[72] Kupo P, Pap R, Saghy L, Tenyi D, Balint A, Debreceni D, et al. Ultrasound guidance for femoral venous access in electrophysiology procedures-systematic review and meta-analysis. *J Interv Card Electrophysiol* 2020; **59**: 407-414.
[73] Delgado V, Ajmone Marsan N, de Waha S, Bonaros N, Brida M, Burri H, et al. 2023 ESC Guidelines for the management of endocarditis. *Eur Heart J* 2023.
[74] Vizzari G, Grasso C, Sardone A, Mazzone P, Laterra G, Frazzetto M, et al. Real-world experience with the new Watchman FLX device: Data from two high-volume Sicilian centers. The FLX-iEST registry. *Catheter Cardiovasc Interv* 2022; **100**: 154-160.
[75] Price MJ, Friedman DJ, Du C, Wang Y, Lin Z, Curtis JP, Freeman JV. Comparative Safety of Transcatheter LAAO With the First-Generation Watchman and Next-Generation Watchman FLX Devices. *JACC Cardiovasc Interv* 2022; **15**: 2115-2123.
[76] Paitazoglou C, Meincke F, Bergmann MW, Eitel I, Fink T, Vireca E, et al. The ALSTER-FLX Registry: 3-Month outcomes after left atrial appendage occlusion using a next-generation device, a matched-pair analysis to EWOLUTION. *Heart Rhythm* 2022; **19**: 917-926.
[77] Lakkireddy D, Thaler D, Ellis CR, Swarup V, Sondergaard L, Carroll J, et al. Outcomes of the roll-in cohort of the Amulet IDE trial of left atrial appendage occlusion. *Heart Rhythm O2* 2022; **3**: 493-500.
[78] Chen S, Chun KRJ, Bordignon S, Weise FK, Nagase T, Perrotta L, et al. Left atrial appendage occlusion using LAmbre Amulet and Watchman in atrial fibrillation. *J Cardiol* 2019; **73**: 299-306.
[79] Tilz RR, Fink T, Bartus K, Wong T, Vogler J, Nentwich K, et al. A collective European experience with left atrial appendage suture ligation using the LARIAT+ device. *Europace* 2020; **22**: 924-931.

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Downloaded from https://academic.oup.com/europace/advance-article/doi/10.1093/europace/euae035/7593802 by St George's, University of London user on 07 February 2024

[80] Betts TR, Grygier M, Nielsen Kudsk JE, Schmitz T, Sandri M, Casu G, et al. Real-world clinical outcomes with a next-generation left atrial appendage closure device: the FLXibility Post-Approval Study. *Europace* 2023; **25**: 914-921.
[81] Bhogal S, Aladin AI, Wermers JP, Morrison N, Gray N, Waksman R. Review of Late-Breaking Trials From CRT 2022. *Cardiovasc Revasc Med* 2022; **40S**: 3-7.
[82] Merdler I, Reddy PK, Bhogal S, Wermers JP, Salimes BG, Gray N, et al. Review of late-breaking trials from CRT 2023. *Cardiovasc Revasc Med* 2023.
[83] Lakkireddy D, Thaler D, Ellis CR, Swarup V, Sondergaard L, Carroll J, et al. Amplatzer Amulet Left Atrial Appendage Occluder Versus Watchman Device for Stroke Prophylaxis (Amulet IDE): A Randomized, Controlled Trial. *Circulation* 2021; **144**: 1543-1552.
[84] Messele LF, Khan MZ, Darden D, Agarwal S, Krishan S, Pasupula DK, et al. Outcomes of percutaneous left atrial appendage occlusion device implantation in atrial fibrillation patients based on underlying stroke risk. *Europace* 2023; **25**: 1415-1422.
[85] Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009; **374**: 534-542.
[86] Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation* 2013; **127**: 720-729.
[87] Bergmann MW, Betts TR, Sievert H, Schmidt B, Pokushalov E, Kische S, et al. Safety and efficacy of early anticoagulation drug regimens after WATCHMAN left atrial appendage closure: three-month data from the EWOLUTION prospective, multicentre, monitored international WATCHMAN LAA closure registry. *EuroIntervention* 2017; **13**: 877-884.
[88] Berti S, Pastormerlo LE, Rezzaghi M, Trianni G, Paradossi U, Cerone E, et al. Left atrial appendage occlusion in high-risk patients with non-valvular atrial fibrillation. *Heart* 2016; **102**: 1969-1973.
[89] Korsholm K, Nielsen KM, Jensen JM, Jensen HK, Andersen G, Nielsen-Kudsk JE. Transcatheter left atrial appendage occlusion in patients with atrial fibrillation and a high bleeding risk using aspirin alone for post-implant antithrombotic therapy. *EuroIntervention* 2017; **12**: 2075-2082.
[90] Landmesser U, Schmidt B, Nielsen-Kudsk JE, Lam SCC, Park JW, Tarantini G, et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: periprocedural and early clinical/echocardiographic data from a global prospective observational study. *EuroIntervention* 2017; **13**: 867-876.
[91] Saw J, Tzikas A, Shakir S, Gafoor S, Omran H, Nielsen-Kudsk JE, et al. Incidence and Clinical Impact of Device-Associated Thrombus and Peri-Device Leak Following Left Atrial Appendage Closure With the Amplatzer Cardiac Plug. *JACC Cardiovasc Interv* 2017; **10**: 391-399.
[92] Kar S, Doshi SK, Sadhu A, Horton R, Osorio J, Ellis C, et al. Primary Outcome Evaluation of a Next-Generation Left Atrial Appendage Closure Device: Results From the PINNACLE FLX Trial. *Circulation* 2021; **143**: 1754-1762.
[93] Ellis CR, Jackson GG, Kanagasundram AN, Mansour M, Sutton B, Houle VM, et al. Left atrial appendage closure in patients with prohibitive anatomy: Insights from PINNACLE FLX. *Heart Rhythm* 2021; **18**: 1153-1161.

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[94] Korsholm K, Samaras A, Andersen A, Jensen JM, Nielsen-Kudsk JE. The Watchman FLX Device: First European Experience and Feasibility of Intracardiac Echocardiography to Guide Implantation. *JACC Clin Electrophysiol* 2020; **6**: 1633-1642.
[95] Paitazoglou C, Bergmann MW, Ince H, Kische S, Romanov A, Schmitz T, et al. True Efficacy of LAA Closure: Patient Outcomes on Long-term Single-Antiplatelet or No Therapy: Insights From the EWOLUTION Registry. *J Invasive Cardiol* 2022; **34**: E348-E355.
[96] Simard T, Jung RG, Lehenbauer K, Piayda K, Pracon R, Jackson GG, et al. Predictors of Device-Related Thrombus Following Percutaneous Left Atrial Appendage Occlusion. *J Am Coll Cardiol* 2021; **78**: 297-313.
[97] Cepas-Guillen P, Flores-Umanzor E, Leduc N, Bajoras V, Perrin N, Farjat-Pasos J, et al. Impact of Device Implant Depth After Left Atrial Appendage Occlusion. *JACC Cardiovasc Interv* 2023; **16**: 2139-2149.
[98] Saliba WI, Kawai K, Sato Y, Kopesky E, Cheng Q, Ghosh SKB, et al. Enhanced Thromboresistance and Endothelialization of a Novel Fluoropolymer-Coated Left Atrial Appendage Closure Device. *JACC Clin Electrophysiol* 2023; **9**: 1555-1567.
[99] Lakkireddy D, Nielsen-Kudsk JE, Windecker S, Thaler D, Price MJ, Gambhir A, et al. Mechanisms, predictors, and evolution of severe peri-device leaks with two different left atrial appendage occluders. *Europace* 2023; **25**.
[100] Della Rocca DG, Murtaza G, Di Biase L, Akella K, Krishnan SC, Magnocavallo M, et al. Radiofrequency Energy Applications Targeting Significant Residual Leaks After Watchman Implantation: A Prospective, Multicenter Experience. *JACC Clin Electrophysiol* 2021; **7**: 1573-1584.
[101] Sievert H, Lesh MD, Trepels T, Omran H, Bartorelli A, Della Bella P, et al. Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. *Circulation* 2002; **105**: 1887-1889.
[102] Gorgis S, Dabbagh MF, Mishra K, Ahluwalia G, Hana A, Fram G, et al. Unprotected discharge: absence of stroke prevention strategies in patients with atrial fibrillation admitted for bleeding. *J Interv Card Electrophysiol* 2021; **62**: 337-346.
[103] Proietti M, Romiti GF, Romanazzi I, Farcomeni A, Staerk L, Nielsen PB, Lip GYH. Restarting oral anticoagulant therapy after major bleeding in atrial fibrillation: A systematic review and meta-analysis. *Int J Cardiol* 2018; **261**: 84-91.
[104] Sengupta N, Feuerstein JD, Patwardhan VR, Tapper EB, Ketwaroo GA, Thaker AM, Leffler DA. The risks of thromboembolism vs. recurrent gastrointestinal bleeding after interruption of systemic anticoagulation in hospitalized inpatients with gastrointestinal bleeding: a prospective study. *Am J Gastroenterol* 2015; **110**: 328-335.
[105] Staerk L, Lip GY, Olesen JB, Fosbol EL, Pallisgaard JL, Bonde AN, et al. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2015; **351**: h5876.
[106] Deitelzweig S, Keshishian A, Kang A, Dhamane AD, Luo X, Balachander N, et al. Burden of major gastrointestinal bleeding among oral anticoagulant-treated non-valvular atrial fibrillation patients. *Therap Adv Gastroenterol* 2021; **14**: 1756284821997352.
[107] Ahn HJ, Lee SR, Choi EK, Rhee TM, Kwon S, Oh S, Lip GYH. Protective effect of proton-pump inhibitor against gastrointestinal bleeding in patients receiving oral anticoagulants: A systematic review and meta-analysis. *Br J Clin Pharmacol* 2022; **88**: 4676-4687.
[108] Sanz Segura P, Jimeno Sanchez J, Arbones-Mainar JM, Sanchez-Rubio Lezcano J, Galache Osuna G, Bernal Monterde V. Percutaneous left atrial appendage closure in patients

ACCEPTED MANUSCRIPT

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with gastrointestinal bleeding associated with oral anticoagulants. *Scand J Gastroenterol* 2023: 1-8.
[109] Boersma LV, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J* 2016; **37**: 2465-2474.
[110] Qureshi W, Mittal C, Patsias I, Garikapati K, Kuchipudi A, Cheema G, et al. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. *Am J Cardiol* 2014; **113**: 662-668.
[111] Lempereur M, Aminian A, Freixa X, Gafoor S, Shakir S, Omran H, et al. Left Atrial Appendage Occlusion in Patients With Atrial Fibrillation and Previous Major Gastrointestinal Bleeding (from the Amplatzer Cardiac Plug Multicenter Registry). *Am J Cardiol* 2017; **120**: 414-420.
[112] Gallo F, Ronco F, D'Amico G, Della Rocca DG, Mazzone P, Bordignon S, et al. Clinical outcomes of left atrial appendage occlusion in patients with previous intracranial or gastrointestinal bleeding: Insights from the LOGIC (Left atrial appendage Occlusion in patients with Gastrointestinal or IntraCranial bleeding) International Multicenter Registry. *Catheter Cardiovasc Interv* 2023; **101**: 1144-1153.
[113] Senzolo M, Garcia-Pagan JC. A major research gap: The use of anticoagulants in cirrhosis. *J Hepatol* 2023.
[114] Chokesuwattanaskul R, Thongprayoon C, Bathini T, O'Corragain OA, Sharma K, Preechawat S, et al. Epidemiology of atrial fibrillation in patients with cirrhosis and clinical significance: a meta-analysis. *Eur J Gastroenterol Hepatol* 2019; **31**: 514-519.
[115] Simon TG, Schneeweiss S, Singer DE, Sreedhara SK, Lin KJ. Prescribing Trends of Oral Anticoagulants in US Patients With Cirrhosis and Nonvalvular Atrial Fibrillation. *J Am Heart Assoc* 2023; **12**: e026863.
[116] Senzolo M, Garcia-Tsao G, Garcia-Pagan JC. Current knowledge and management of portal vein thrombosis in cirrhosis. *J Hepatol* 2021; **75**: 442-453.
[117] Lee SR, Lee HJ, Choi EK, Han KD, Jung JH, Cha MJ, et al. Direct Oral Anticoagulants in Patients With Atrial Fibrillation and Liver Disease. *J Am Coll Cardiol* 2019; **73**: 3295-3308.
[118] Mir T, Rawasia WF, Uddin M, Sheikh M, Munir MB, Balla S. Left atrial appendage closure device outcomes among cirrhosis patients with atrial fibrillation: a United States National Cohort Study. *Europace* 2023; **25**: 1408-1414.
[119] Calvert P, Gupta D. Left atrial appendage occlusion in patients with cirrhotic liver disease: the importance of patient selection. *Europace* 2023; **25**: 1315-1317.
[120] Schreuder F, van Nieuwenhuizen KM, Hofmeijer J, Vermeer SE, Kerkhoff H, Zock E, et al. Apixaban versus no anticoagulation after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation in the Netherlands (APACHE-AF): a randomised, open-label, phase 2 trial. *Lancet Neurol* 2021; **20**: 907-916.
[121] SoSTART Collaboration. Effects of oral anticoagulation for atrial fibrillation after spontaneous intracranial haemorrhage in the UK: a randomised, open-label, assessor-masked, pilot-phase, non-inferiority trial. *Lancet Neurol* 2021; **20**: 842-853.
[122] Population Health Research Institute. NOACs for Stroke Prevention in Patients With Atrial Fibrillation and Previous ICH: https://classic.clinicaltrials.gov/show/NCT02998905 2017.
[123] Liu X, Guo S, Xu Z. Meta-Analysis of Oral Anticoagulants and Adverse Outcomes in Atrial Fibrillation Patients After Intracranial Hemorrhage. *Front Cardiovasc Med* 2022; **9**: 961000.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/europace/advance-article/doi/10.1093/europace/euae035/7593802 by St George's, University of London user on 07 February 2024

[124] Cochrane A, Chen C, Stephen J, Ronning OM, Anderson CS, Hankey GJ, Al-Shahi Salman R. Antithrombotic treatment after stroke due to intracerebral haemorrhage. *Cochrane Database Syst Rev* 2023; **1**: CD012144.
[125] Ivany E, Lane DA, Dan GA, Doehner W, Farkowski MM, Iliodromitis K, et al. Antithrombotic therapy for stroke prevention in patients with atrial fibrillation who survive an intracerebral haemorrhage: results of an EHRA survey. *Europace* 2021; **23**: 806-814.
[126] Population Health Research Institute. EdoxabaN foR IntraCranial Hemorrhage Survivors With Atrial Fibrillation (ENRICH-AF): https://classic.clinicaltrials.gov/show/NCT03950076 2019.
[127] Imperial College London, Wuerzburg University Hospital, Julius-Maximilians University, Medical University of Graz, University of Liverpool, King's College London, et al. PREvention of STroke in Intracerebral haemorrhaGE Survivors With Atrial Fibrillation: https://classic.clinicaltrials.gov/show/NCT03996772 2019.
[128] University Hospital Lille, Ministry of Health France, Institut National de la Santé Et de la Recherche Médicale France. Avoiding Anticoagulation After IntraCerebral Haemorrhage: https://classic.clinicaltrials.gov/show/NCT03243175 2019.
[129] Oslo University Hospital. Study of Antithrombotic Treatment After IntraCerebral Haemorrhage: https://classic.clinicaltrials.gov/show/NCT03186729 2018.
[130] Yale University, National Institute of Neurological Disorders and Stroke. Anticoagulation in ICH Survivors for Stroke Prevention and Recovery: https://classic.clinicaltrials.gov/show/NCT03907046 2020.
[131] January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation* 2019; **140**: e125-e151.
[132] Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. *Europace* 2021; **23**: 1612-1676.
[133] National Institute of Cardiology Warsaw Poland, Medical Research Agency Poland. Optimal Antiplatelet Therapy Following Left Atrial Appendage Closure in Dialyzed Patients: https://classic.clinicaltrials.gov/show/NCT05660811 2022.
[134] Garg J, Shah S, Shah K, Bhardwaj R, Contractor T, Mandapati R, et al. Left atrial appendage closure in patients with intracranial hemorrhage. *J Interv Card Electrophysiol* 2022; **64**: 551-556.
[135] Haeusler KG, Tutuncu S, Kunze C, Schurig J, Malsch C, Harder J, et al. Oral anticoagulation in patients with atrial fibrillation and acute ischaemic stroke: design and baseline data of the prospective multicentre Berlin Atrial Fibrillation Registry. *Europace* 2019; **21**: 1621-1632.
[136] Tutuncu S, Olma M, Kunze C, Dietzel J, Schurig J, Fiessler C, et al. Off-label-dosing of non-vitamin K-dependent oral antagonists in AF patients before and after stroke: results of the prospective multicenter Berlin Atrial Fibrillation Registry. *J Neurol* 2022; **269**: 470-480.
[137] Polymeris AA, Meinel TR, Oehler H, Holscher K, Zietz A, Scheitz JF, et al. Aetiology, secondary prevention strategies and outcomes of ischaemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. *J Neurol Neurosurg Psychiatry* 2022; **93**: 588-598.

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[138] Benz AP, Hohnloser SH, Eikelboom JW, Carnicelli AP, Giugliano RP, Granger CB, et al. Outcomes of patients with atrial fibrillation and ischemic stroke while on oral anticoagulation. *Eur Heart J* 2023; **44**: 1807-1814.
[139] Paciaroni M, Caso V, Agnelli G, Mosconi MG, Giustozzi M, Seiffge DJ, et al. Recurrent Ischemic Stroke and Bleeding in Patients With Atrial Fibrillation Who Suffered an Acute Stroke While on Treatment With Nonvitamin K Antagonist Oral Anticoagulants: The RENO-EXTEND Study. *Stroke* 2022; **53**: 2620-2627.
[140] Seiffge DJ, De Marchis GM, Koga M, Paciaroni M, Wilson D, Cappellari M, et al. Ischemic Stroke despite Oral Anticoagulant Therapy in Patients with Atrial Fibrillation. *Ann Neurol* 2020; **87**: 677-687.
[141] Karl Georg H. Ischaemic stroke in atrial fibrillation patients while on oral anticoagulation-a call for A-C-T-I-O-N. *Eur Heart J* 2023; **44**: 1815-1817.
[142] Maarse M, Seiffge D, Fierro N, Tondo C, Pracon R, De Backer O, et al. Left atrial appendage occlusion versus standard of care in patients with atrial fibrillation and a prior thrombo-embolic event despite oral anticoagulant therapy: a propensity score matched comparison. *European Heart Journal* 2022; **43**.
[143] Hamilton Health Sciences Corporation, McMaster University, Population Health Research Institute, Boston Scientific Corporation. The Fourth Left Atrial Appendage Occlusion Study: https://classic.clinicaltrials.gov/show/NCT05963698 2023.
[144] Insel Gruppe AG University Hospital Bern. Early Closure of Left Atrial Appendage for Patients With Atrial Fibrillation and Ischemic Stroke Despite Anticoagulation Therapy: https://classic.clinicaltrials.gov/show/NCT05976685 2024.
[145] Jensen M, Suling A, Metzner A, Schnabel RB, Borof K, Goette A, et al. Early rhythm-control therapy for atrial fibrillation in patients with a history of stroke: a subgroup analysis of the EAST-AFNET 4 trial. *Lancet Neurol* 2023; **22**: 45-54.
[146] Nippon Medical School, Daiichi Sankyo Co. Ltd. STroke Secondary Prevention With Catheter ABLation and EDoxaban for Patients With Non-valvular Atrial Fibrillation: STABLED Study: https://classic.clinicaltrials.gov/show/NCT03777631 2018.
[147] De Potter T, Yodfat O, Shinar G, Neta A, Reddy VY, Neuzil P, et al. Permanent Bilateral Carotid Filters for Stroke Prevention in Atrial Fibrillation. *Curr Cardiol Rep* 2020; **22**: 144.
[148] Javelin Medical, Population Health Research Institute. Carotid Implants for PreveNtion of STrokE ReCurrEnce From Large Vessel Occlusion in Atrial Fibrillation Patients Treated With Oral Anticoagulation: https://classic.clinicaltrials.gov/show/NCT05723926 2023.
[149] Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996; **61**: 755-759.
[150] Stoddard MF, Singh P, Dawn B, Longaker RA. Left atrial thrombus predicts transient ischemic attack in patients with atrial fibrillation. *Am Heart J* 2003; **145**: 676-682.
[151] Zhan Y, Joza J, Al Rawahi M, Barbosa RS, Samuel M, Bernier M, et al. Assessment and Management of the Left Atrial Appendage Thrombus in Patients With Nonvalvular Atrial Fibrillation. *Can J Cardiol* 2018; **34**: 252-261.
[152] Lurie A, Wang J, Hinnegan KJ, McIntyre WF, Belley-Cote EP, Amit G, et al. Prevalence of Left Atrial Thrombus in Anticoagulated Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2021; **77**: 2875-2886.

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Downloaded from https://academic.oup.com/europace/advance-article/doi/10.1093/europace/euae035/7593802 by St George's, University of London user on 07 February 2024

[153] Steffel J, Heidbuchel H. 2021 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: comment-Authors' reply. *Europace* 2021; **23**: 1685-1686.
[154] Kolakowski K, Farkowski MM, Pytkowski M, Gardziejczyk P, Kowalik I, Dabrowski R, et al. The Comparative Effectiveness and Safety of Different Anticoagulation Strategies for Treatment of Left Atrial Appendage Thrombus in the Setting of Chronic Anticoagulation for Atrial Fibrillation or Flutter. *Cardiovasc Drugs Ther* 2023; **37**: 159-168.
[155] Boccuzzi GG, Montabone A, D'Ascenzo F, Colombo F, Ugo F, Muraglia S, et al. Cerebral protection in left atrial appendage closure in the presence of appendage thrombosis. *Catheter Cardiovasc Interv* 2021; **97**: 511-515.
[156] Fink T, Ouyang F, Heeger CH, Sciacca V, Reissmann B, Keelani A, et al. Management of thrombus formation after electrical isolation of the left atrial appendage in patients with atrial fibrillation. *Europace* 2020; **22**: 1358-1366.
[157] Popescu SS, Heeger CH, Keelani A, Tilz RR. Percutaneous Left Atrial Appendage Closure with the LAmbre Device Protected by a Cerebral Protection System in a 76-Year-Old Man with Persistent Left Atrial Appendage Thrombus. *Am J Case Rep* 2022; **23**: e937063.
[158] Mohandes M, Moreno C, Guillen M, Anmad Shihadeh L, Zambrano D. Percutaneous left atrial appendage closure containing thrombus. *Cardiol J* 2022; **29**: 884-885.
[159] Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. *Eur J Anaesthesiol* 2017; **34**: 332-395.
[160] Saran R, Robinson B, Abbott KC, Agodoa LYC, Bragg-Gresham J, Balkrishnan R, et al. US Renal Data System 2018 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis* 2019; **73**: A7-A8.
[161] Buiten MS, de Bie MK, Rotmans JI, Gabreels BA, van Dorp W, Wolterbeek R, et al. The dialysis procedure as a trigger for atrial fibrillation: new insights in the development of atrial fibrillation in dialysis patients. *Heart* 2014; **100**: 685-690.
[162] Vincenti A, Passini E, Fabbrini P, Luise MC, Severi S, Genovesi S. Recurrent intradialytic paroxysmal atrial fibrillation: hypotheses on onset mechanisms based on clinical data and computational analysis. *Europace* 2014; **16**: 396-404.
[163] Ng KP, Edwards NC, Lip GY, Townend JN, Ferro CJ. Atrial fibrillation in CKD: balancing the risks and benefits of anticoagulation. *Am J Kidney Dis* 2013; **62**: 615-632.
[164] Carrero JJ, Trevisan M, Sood MM, Barany P, Xu H, Evans M, et al. Incident Atrial Fibrillation and the Risk of Stroke in Adults with Chronic Kidney Disease: The Stockholm CREAtinine Measurements (SCREAM) Project. *Clin J Am Soc Nephrol* 2018; **13**: 1314-1320.
[165] Genovesi S, Vincenti A, Rossi E, Pogliani D, Acquistapace I, Stella A, Valsecchi MG. Atrial fibrillation and morbidity and mortality in a cohort of long-term hemodialysis patients. *Am J Kidney Dis* 2008; **51**: 255-262.
[166] Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, Major Bleeding, and Mortality Outcomes in Warfarin Users With Atrial Fibrillation and Chronic Kidney Disease: A Meta-Analysis of Observational Studies. *Chest* 2016; **149**: 951-959.
[167] Szummer K, Gasparini A, Eliasson S, Arnlov J, Qureshi AR, Barany P, et al. Time in Therapeutic Range and Outcomes After Warfarin Initiation in Newly Diagnosed Atrial Fibrillation Patients With Renal Dysfunction. *J Am Heart Assoc* 2017; **6**.
[168] Rebora P, Moia M, Carpenedo M, Valsecchi MG, Genovesi S. Best quality indicator of vitamin K antagonist therapy to predict mortality and bleeding in haemodialysis patients with atrial fibrillation. *Blood Transfus* 2021; **19**: 487-494.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/europace/advance-article/doi/10.1093/europace/euae035/7593802 by St George's, University of London user on 07 February 2024

[169] Weijs B, Blaauw Y, Rennenberg RJ, Schurgers LJ, Timmermans CC, Pison L, et al. Patients using vitamin K antagonists show increased levels of coronary calcification: an observational study in low-risk atrial fibrillation patients. *Eur Heart J* 2011; **32**: 2555-2562.
[170] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139-1151.
[171] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**: 883-891.
[172] Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365**: 981-992.
[173] Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369**: 2093-2104.
[174] Kuno T, Takagi H, Ando T, Sugiyama T, Miyashita S, Valentin N, et al. Oral Anticoagulation for Patients With Atrial Fibrillation on Long-Term Hemodialysis. *J Am Coll Cardiol* 2020; **75**: 273-285.
[175] Su X, Yan B, Wang L, Lv J, Cheng H, Chen Y. Oral Anticoagulant Agents in Patients With Atrial Fibrillation and CKD: A Systematic Review and Pairwise Network Meta-analysis. *Am J Kidney Dis* 2021; **78**: 678-689 e671.
[176] Turakhia MP, Blankestijn PJ, Carrero JJ, Clase CM, Deo R, Herzog CA, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Eur Heart J* 2018; **39**: 2314-2325.
[177] Genovesi S, Rebora P, Gallieni M, Stella A, Badiali F, Conte F, et al. Effect of oral anticoagulant therapy on mortality in end-stage renal disease patients with atrial fibrillation: a prospective study. *J Nephrol* 2017; **30**: 573-581.
[178] Kefer J, Tzikas A, Freixa X, Shakir S, Gafoor S, Nielsen-Kudsk JE, et al. Impact of chronic kidney disease on left atrial appendage occlusion for stroke prevention in patients with atrial fibrillation. *Int J Cardiol* 2016; **207**: 335-340.
[179] Fink T, Paitazoglou C, Bergmann MW, Sano M, Keelani A, Sciacca V, et al. Left atrial appendage closure in end-stage renal disease and hemodialysis: Data from a German multicenter registry. *Catheter Cardiovasc Interv* 2023; **101**: 610-619.
[180] Munir MB, Khan MZ, Darden D, Nishimura M, Vanam S, Pasupula DK, et al. Association of chronic kidney disease and end-stage renal disease with procedural complications and in-hospital outcomes from left atrial appendage occlusion device implantation in patients with atrial fibrillation: Insights from the national inpatient sample of 36,065 procedures. *Heart Rhythm O2* 2021; **2**: 472-479.
[181] Fastner C, Brachmann J, Lewalter T, Zeymer U, Sievert H, Borggrefe M, et al. Left atrial appendage closure in patients with chronic kidney disease: results from the German multicentre LAARGE registry. *Clin Res Cardiol* 2021; **110**: 12-20.
[182] Luani B, Genz C, Herold J, Mitrasch A, Mitusch J, Wiemer M, et al. Cerebrovascular events, bleeding complications and device related thrombi in atrial fibrillation patients with chronic kidney disease and left atrial appendage closure with the WATCHMAN device. *BMC Cardiovasc Disord* 2019; **19**: 112.
[183] Al Ali R, Vukadinovic D, Maziak W, Katmeh L, Schwarz V, Mahfoud F, et al. Cardiovascular effects of waterpipe smoking: a systematic review and meta-analysis. *Rev Cardiovasc Med* 2020; **21**: 453-468.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/europace/advance-article/doi/10.1093/europace/euae035/7593802 by St George's, University of London user on 07 February 2024

[184] Fundación EPIC. Left Atrial Appendage Occlusion With WATCHMAN® Device in Patients With Non-valvular Atrial Fibrillation and End-stage Chronic Kidney Disease on Hemodialysis: https://classic.clinicaltrials.gov/show/NCT03446794 2018.
[185] University of Magdeburg. Left Atrial Appendage Occlusion vs. Usual Care in Patients With Atrial Fibrillation and Severe Chronic Kidney Disease: https://classic.clinicaltrials.gov/show/NCT02039167 2014.
[186] Population Health Research Institute. The Strategy to Prevent Hemorrhage Associated With Anticoagulation in Renal Disease Management (STOP HARM) Trial: https://classic.clinicaltrials.gov/show/NCT02885545 2016.
[187] Vallurupalli S, Sharma T, Al'Aref S, Devabhaktuni SR, Dhar G. Left Atrial Appendage Closure: An Alternative to Anticoagulation for Stroke Prevention in Patients with Kidney Disease. *Kidney360* 2022; **3**: 396-402.
[188] Genovesi S, Porcu L, Rebora P, Slaviero G, Casu G, Bertoli S, et al. Long term safety and efficacy of left atrial appendage occlusion in dialysis patients with atrial fibrillation: a multi-center, prospective, open label, observational study. *Clinical Kidney Journal* 2023.
[189] de Groot JR, Weiss TW, Kelly P, Monteiro P, Deharo JC, de Asmundis C, et al. Edoxaban for stroke prevention in atrial fibrillation in routine clinical care: 1-year follow-up of the prospective observational ETNA-AF-Europe study. *Eur Heart J Cardiovasc Pharmacother* 2021; **7**: f30-f39.
[190] Kornej J, Henger S, Seewoster T, Teren A, Burkhardt R, Thiele H, et al. Prevalence of atrial fibrillation dependent on coronary artery status: Insights from the LIFE-Heart Study. *Clin Cardiol* 2020; **43**: 1616-1623.
[191] Camen S, Csengeri D, Geelhoed B, Niiranen T, Gianfagna F, Vishram-Nielsen JK, et al. Risk Factors, Subsequent Disease Onset, and Prognostic Impact of Myocardial Infarction and Atrial Fibrillation. *J Am Heart Assoc* 2022; **11**: e024299.
[192] Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *N Engl J Med* 2017; **377**: 1513-1524.
[193] Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. *N Engl J Med* 2019; **380**: 1509-1524.
[194] Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet* 2019; **394**: 1335-1343.
[195] Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N Engl J Med* 2016; **375**: 2423-2434.
[196] Gargiulo G, Goette A, Tijssen J, Eckardt L, Lewalter T, Vranckx P, Valgimigli M. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J* 2019; **40**: 3757-3767.
[197] Potpara TS, Mujovic N, Proietti M, Dagres N, Hindricks G, Collet JP, et al. Revisiting the effects of omitting aspirin in combined antithrombotic therapies for atrial fibrillation and acute coronary syndromes or percutaneous coronary interventions: meta-analysis of

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pooled data from the PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS trials. *Europace* 2020; **22**: 33-46.
[198] Alexander JH, Wojdyla D, Vora AN, Thomas L, Granger CB, Goodman SG, et al. Risk/Benefit Tradeoff of Antithrombotic Therapy in Patients With Atrial Fibrillation Early and Late After an Acute Coronary Syndrome or Percutaneous Coronary Intervention: Insights From AUGUSTUS. *Circulation* 2020; **141**: 1618-1627.
[199] Ancedy Y, Lecoq C, Saint Etienne C, Ivanes F, Angoulvant D, Babuty D, et al. Antithrombotic management in patients with atrial fibrillation undergoing coronary stent implantation: What is the impact of guideline adherence? *Int J Cardiol* 2016; **203**: 987-994.
[200] Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014; **35**: 2541-2619.
[201] Wang Y, Wu D, Ma J, Liu X, Zhang H, So CY, et al. The feasibility and safety of "one-stop" left atrial appendage closure and percutaneous coronary intervention in atrial fibrillation patients with significant coronary artery disease (PCI-LAAC study). *Am J Cardiovasc Dis* 2021; **11**: 679-687.
[202] Losik D, Romanov A, Grazhdankin I, Shabanov V, Ponomarev D, Mikheenko I, et al. Feasibility of concomitant left atrial appendage closure and percutaneous coronary intervention in patients with acute coronary syndrome and atrial fibrillation: a randomized pilot study. *Heart Vessels* 2023; **38**: 881-888.
[203] Meshalkin Research Institute of Pathology of Circulation, Boston Scientific Corporation. Left Atrial Appendage Closure Compared to Standard Antiplatelet Therapy in Patients With AF Who Underwent PCI: https://classic.clinicaltrials.gov/show/NCT02492230 2015.
[204] Yonsei University. Safety and Efficacy of Left Atrial Appendage Closure Versus Antithrombotic Therapy in Patients With Atrial Fibrillation Undergoing Drug-Eluting Stent Implantation Due to Complex Coronary Artery Disease: https://classic.clinicaltrials.gov/show/NCT02606552 2016.
[205] Noseworthy PA, Yao X, Deshmukh AJ, Van Houten H, Sangaralingham LR, Siontis KC, et al. Patterns of Anticoagulation Use and Cardioembolic Risk After Catheter Ablation for Atrial Fibrillation. *J Am Heart Assoc* 2015; **4**.
[206] Wintgens L, Romanov A, Phillips K, Ballesteros G, Swaans M, Folkeringa R, et al. Combined atrial fibrillation ablation and left atrial appendage closure: long-term follow-up from a large multicentre registry. *Europace* 2018; **20**: 1783-1789.
[207] Pasupula DK, Siddappa Malleshappa SK, Munir MB, Bhat AG, Anandaraj A, Jakkoju A, et al. Combined atrial fibrillation ablation and left atrial appendage occlusion procedure in the United States: a propensity score matched analysis from 2016-2019 national readmission database. *Europace* 2023; **25**: 390-399.
[208] Romanov A, Pokushalov E, Artemenko S, Yakubov A, Stenin I, Kretov E, et al. Does left atrial appendage closure improve the success of pulmonary vein isolation? Results of a randomized clinical trial. *J Interv Card Electrophysiol* 2015; **44**: 9-16.
[209] Ottawa Heart Institute Research Corporation, Canadian Institutes of Health Research, Bayer, Biotronik Canada Inc. Optimal Anticoagulation for Higher Risk Patients

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/europace/advance-article/doi/10.1093/europace/euae035/7593802 by St George's, University of London user on 07 February 2024

Post-Catheter Ablation for Atrial Fibrillation Trial: https://classic.clinicaltrials.gov/show/NCT02168829 2016.
[210] Phillips KP, Walker DT, Humphries JA. Combined catheter ablation for atrial fibrillation and Watchman(R) left atrial appendage occlusion procedures: Five-year experience. *J Arrhythm* 2016; **32**: 119-126.
[211] Wilber DJL, D.J. aMAZE: Outcomes of Adjunctive LAA Utilizing LARIAT Compared to Pulmonary Vein Atrial Isolation Alone*American Heart Association*. 2021.
[212] Nishimura M, Lupercio-Lopez F, Hsu JC. Left Atrial Appendage Electrical Isolation as a Target in Atrial Fibrillation. *JACC Clin Electrophysiol* 2019; **5**: 407-416.
[213] Rillig A, Tilz RR, Lin T, Fink T, Heeger CH, Arya A, et al. Unexpectedly High Incidence of Stroke and Left Atrial Appendage Thrombus Formation After Electrical Isolation of the Left Atrial Appendage for the Treatment of Atrial Tachyarrhythmias. *Circ Arrhythm Electrophysiol* 2016; **9**: e003461.
[214] Panikker S, Jarman JW, Virmani R, Kutys R, Haldar S, Lim E, et al. Left Atrial Appendage Electrical Isolation and Concomitant Device Occlusion to Treat Persistent Atrial Fibrillation: A First-in-Human Safety, Feasibility, and Efficacy Study. *Circ Arrhythm Electrophysiol* 2016; **9**.
[215] Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011; **364**: 2187-2198.
[216] Adams DH, Popma JJ, Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014; **371**: 967-968.
[217] Attinger-Toller A, Maisano F, Senn O, Taramasso M, Shakir S, Possner M, et al. "One-Stop Shop": Safety of Combining Transcatheter Aortic Valve Replacement and Left Atrial Appendage Occlusion. *JACC Cardiovasc Interv* 2016; **9**: 1487-1495.
[218] Drosos I, De Rosa R, Cremer S, Seppelt PC, Hemmann K, Oppermann J, et al. Percutaneous left atrial appendage occlusion in a frail, high-risk, octogenarian patient population, after having undergone transcatheter aortic valve implantation. *BMC Cardiovasc Disord* 2022; **22**: 349.
[219] D'Amico G, Estevez-Loureiro R, Rofastes XF, Ronco F, Nombela-Franco L, Melica B, et al. Combined Procedure of Percutaneous Mitral Valve Repair and Left Atrial Appendage Occlusion: A Multicenter Study. *JACC Cardiovasc Interv* 2021; **14**: 590-592.
[220] Kleinecke C, Buffle E, Link J, Haner J, Sedaghat A, Galea R, et al. Amplatzer left atrial appendage closure: Single versus combined procedures. *Catheter Cardiovasc Interv* 2021; **97**: E973-E981.
[221] Kuwata S, Taramasso M, Zuber M, Suetsch G, Attinger-Toller A, Wicki D, et al. Feasibility of concomitant MitraClip and left atrial appendage occlusion. *EuroIntervention* 2017; **12**: 1940-1945.
[222] Lane CE, Eleid MF, Holmes DR, Jr. An under-recognized high-risk atrial fibrillation population: Analyzing transcatheter mitral valve repair patients for left atrial appendage closure device application. *Catheter Cardiovasc Interv* 2019; **94**: 274-279.
[223] Arellano-Serrano C, Monivas V, Estevez-Loureiro R. Combined Percutaneous Treatment of Severe Triscuspid Regurgitation and Left Atrial Appendage Closure. *J Invasive Cardiol* 2019; **31**: E4-E5.
[224] Belli M, Zanin F, Macrini M, Barone L, Marchei M, Muscoli S, et al. Combined MitraClip and Left Atrial Appendage Occlusion: Is It Still a Utopia? *Front Cardiovasc Med* 2022; **9**: 940560.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/europace/advance-article/doi/10.1093/europace/euae035/7593802 by St George's, University of London user on 07 February 2024

[225] Kuwata S, Vierecke J, Gloekler S, Maisano F, Meier B, Nietlispach F. Left atrial appendage closure for "primary primary" prevention during percutaneous closure of septal defects in patients with large atria but no atrial fibrillation. *Cardiol J* 2018; **25**: 179-187.
[226] Song Y, Xing H, Koch PD, Li X, Zhang Y. The feasibility and safety of combining atrial septal defect/patent foramen ovale and left atrial appendage closure: A systematic review and meta-analysis. *Front Cardiovasc Med* 2022; **9**: 1080257.
[227] Tzikas A, Samaras A, Kartas A, Vasdeki D, Fotos G, Dividis G, et al. Motivational Interviewing to Support Oral AntiCoagulation adherence in patients with non-valvular Atrial Fibrillation (MISOAC-AF): a randomized clinical trial. *Eur Heart J Cardiovasc Pharmacother* 2021; **7**: f63-f71.
[228] Martinez C, Katholing A, Wallenhorst C, Freedman SB. Therapy persistence in newly diagnosed non-valvular atrial fibrillation treated with warfarin or NOAC. A cohort study. *Thromb Haemost* 2016; **115**: 31-39.
[229] Ozaki AF, Choi AS, Le QT, Ko DT, Han JK, Park SS, Jackevicius CA. Real-World Adherence and Persistence to Direct Oral Anticoagulants in Patients With Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Circ Cardiovasc Qual Outcomes* 2020; **13**: e005969.
[230] Chen S, Weise FK, Chun KRJ, Schmidt B. Antithrombotic strategies after interventional left atrial appendage closure: an update. *Expert Rev Cardiovasc Ther* 2018; **16**: 675-678.
[231] Branca L, Tomasoni D, Cimino G, Cersosimo A, Lombardi CM, Chizzola G, et al. Impact and predictors of device-related thrombus after percutaneous left atrial appendage closure. *J Cardiovasc Med (Hagerstown)* 2023; **24**: 12-19.
[232] Active Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006; **367**: 1903-1912.
[233] Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; **364**: 806-817.
[234] Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007; **370**: 493-503.
[235] Okumura K, Akao M, Yoshida T, Kawata M, Okazaki O, Akashi S, et al. Low-Dose Edoxaban in Very Elderly Patients with Atrial Fibrillation. *N Engl J Med* 2020; **383**: 1735-1745.
[236] Riegler L, Palermi S, Scarafile R, Gioia R, Pastore F, Lombardi A, et al. Clinical and multi-modality imaging approach in the selection of patients for left atrial appendage closure. *Rev Cardiovasc Med* 2021; **22**: 1197-1204.
[237] Sondergaard L, Wong YH, Reddy VY, Boersma LVA, Bergmann MW, Doshi S, et al. Propensity-Matched Comparison of Oral Anticoagulation Versus Antiplatelet Therapy After Left Atrial Appendage Closure With WATCHMAN. *JACC Cardiovasc Interv* 2019; **12**: 1055-1063.
[238] Cruz-Gonzalez I, Trejo-Velasco B. Percutaneous left atrial appendage occlusion in the current practice. *Kardiol Pol* 2021; **79**: 255-268.
[239] Ledwoch J, Sievert K, Boersma LVA, Bergmann MW, Ince H, Kische S, et al. Initial and long-term antithrombotic therapy after left atrial appendage closure with the WATCHMAN. *Europace* 2020; **22**: 1036-1043.

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Downloaded from https://academic.oup.com/europace/advance-article/doi/10.1093/europace/euae035/7593802 by St George's, University of London user on 07 February 2024

[240] Freeman JV, Higgins AY, Wang Y, Du C, Friedman DJ, Daimee UA, et al. Antithrombotic Therapy After Left Atrial Appendage Occlusion in Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2022; **79**: 1785-1798.
[241] Freeman J, Hsu JC, Kapadia S, Yeh R, Price M, Nair DG, et al. Ce-452771-4 Outcomes with Different Postprocedural Antithrombotic Therapy Regimens Following Left Atrial Appendage Occlusion. *Heart Rhythm* 2023; **20**: S36-S37.
[242] Carvalho PEP, Gewehr DM, Miyawaki IA, Nogueira A, Felix N, Garot P, et al. Comparison of Initial Antithrombotic Regimens after Left Atrial Appendage Occlusion: A Systematic Review and Network Meta-analysis. *J Am Coll Cardiol* 2023.
[243] Mhanna M, Beran A, Al-Abdouh A, Jabri A, Al-Aaraj A, Sajdeya O, et al. Single Versus Dual Antiplatelet Therapy following Left Atrial Appendage Occlusion in Patients With High Bleeding Risk. *Curr Probl Cardiol* 2022; **47**: 101269.
[244] Vignali L, Gurgoglione FL, Barocelli F, Cattabiani MA, Solinas E, Maini A, et al. Looking for optimal antithrombotic strategy after transcatheter left atrial appendage occlusion: a real-world comparison of different antiplatelet regimens. *Int J Cardiol* 2023; **371**: 92-99.
[245] Rodriguez-Gabella T, Nombela-Franco L, Regueiro A, Jimenez-Quevedo P, Champagne J, O'Hara G, et al. Single Antiplatelet Therapy Following Left Atrial Appendage Closure in Patients With Contraindication to Anticoagulation. *J Am Coll Cardiol* 2016; **68**: 1920-1921.
[246] Azienda Ospedaliero Universitaria Maggiore della Carita, Abbott Medical Devices. Head-to-head Comparison of Single Versus Dual Antiplatelet Treatment Strategy After Percutaneous Left Atrial Appendage Closure: a Multicenter, Randomized Study: https://classic.clinicaltrials.gov/show/NCT05554822 2021.
[247] Cepas-Guillen PL, Flores-Umanzor E, Regueiro A, Brugaletta S, Ibanez C, Sanchis L, et al. Low Dose of Direct Oral Anticoagulants after Left Atrial Appendage Occlusion. *J Cardiovasc Dev Dis* 2021; **8**.
[248] Della Rocca DG, Magnocavallo M, Di Biase L, Mohanty S, Trivedi C, Tarantino N, et al. Half-Dose Direct Oral Anticoagulation Versus Standard Antithrombotic Therapy After Left Atrial Appendage Occlusion. *JACC Cardiovasc Interv* 2021; **14**: 2353-2364.
[249] Freixa X. Apixaban vs Dual Antiplatet Therapy Study After Left Atrial Appendage Occlosure (ADALA): https://classic.clinicaltrials.gov/show/NCT05632445 2019.
[250] Freixa X, Cruz-González I, Cepas-Guillén P, Millan X, Flores-Umanzor E, Asmarats L, et al. Low dose direct oral anticoagulation vs. DAPT after LAAO *EuroPCR*. 2023.
[251] Centre de Recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Quebec, Institut universitaire de cardiologie et de pneumologie de Québec University Laval. Short-Term Anticoagulation Versus Antiplatelet Therapy for Preventing Device Thrombosis Following Left Atrial Appendage Closure: https://classic.clinicaltrials.gov/show/NCT03568890 2018.
[252] Schmidt B, Nielsen-Kudsk JE, Ellis CR, Thaler D, Sabir SA, Gambhir A, et al. Incidence, Predictors, and Clinical Outcomes of Device-Related Thrombus in the Amulet IDE Trial. *JACC Clin Electrophysiol* 2023; **9**: 96-107.
[253] Dukkipati SR, Kar S, Holmes DR, Doshi SK, Swarup V, Gibson DN, et al. Device-Related Thrombus After Left Atrial Appendage Closure: Incidence, Predictors, and Outcomes. *Circulation* 2018; **138**: 874-885.
[254] Dukkipati SR, Holmes DR, Jr., Doshi SK, Kar S, Singh SM, Gibson D, et al. Impact of Peridevice Leak on 5-Year Outcomes After Left Atrial Appendage Closure. *J Am Coll Cardiol* 2022; **80**: 469-483.

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[255] Alkhouli M, Du C, Killu A, Simard T, Noseworthy PA, Friedman PA, et al. Clinical Impact of Residual Leaks Following Left Atrial Appendage Occlusion: Insights From the NCDR LAAO Registry. *JACC Clin Electrophysiol* 2022; **8**: 766-778.
[256] Sharma SP, Turagam MK, Gopinathannair R, Reddy V, Kar S, Mohanty S, et al. Direct Current Cardioversion of Atrial Fibrillation in Patients With Left Atrial Appendage Occlusion Devices. *J Am Coll Cardiol* 2019; **74**: 2267-2274.
[257] Maarse M, Wintgens LIS, Ponomarenko A, Phillips KP, Romanov AB, Ballesteros G, et al. Impact of anticoagulation strategy after left atrial appendage occlusion in patients requiring direct current cardioversion. *J Cardiovasc Electrophysiol* 2021; **32**: 737-744.

Figure legends

Central Illustration or Graphical Abstract: *no legend is needed*

Figure 1: Clinical outcomes from the PROTECT, PREVAIL and PRAGUE-17 randomized clinical trials. Adapted with permission from [13]. LAAC: left atrial appendage closure; OAC: oral anticoagulation; SE: systemic embolism

Figure 2: Possible candidates for LAAC. ASD: atrial septal defect; CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female); LAA: left atrial appendage; LAAC: left atrial appendage closure; OAC: oral anticoagulation.

Figure 3: Fluoroscopy image with a 3-D reconstructed CT-scan image fusion in order to guide LAA occluder positioning and deployment. A: Tracheal landmark used for the fusion between the CT-Scan image (blue and red colours) and the fluoroscopy system; B: Transesophageal echocardiography probe used to guide the LAA occluder positioning; C: Quadripolar catheter placed inside the coronary sinus in order to guide the transseptal puncture (optional); D: Transseptal puncture area; E: Left Atrial Appendage (LAA) in right anterior projection; F: Catheter positioned in front of the LAA entrance before occluder release.

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Figure 4 Panel A: Watchman FLX (Boston Scientific). The Watchman FLX is deployed at the proximal part of the LAA, at the level of the circumflex artery and the ridge. There are two rows of anchors distributed across the distal half of the device. Small arrow: circumflex artery; large arrow Watchman FLX; **: distal part of the LAA; LA: left atria; LV: left ventricle.

Figure 4 Panel B: Amulet (Abbott). The Amulet is deployed at the proximal part of the LAA, at the level of the circumflex artery, and the ridge. Amulet is a dual-seal technology consisting of a lobe to anchor in the neck of the LAA and a disc to close off the opening into the LAA. Small arrow: circumflex artery; large arrow: the lobe of the Amulet; ** : distal part of the LAA; LA: left atrium.

Figure 4 Panel C: LAmbre (Lifetech) offers a design very similar to the Amulet, with a distal anchoring umbrella and a proximal disc.

Figure 5: Lariat Suture Delivery Device (SentreHeart). After proper alignment, the Lariat suture is tightened from the epicardium, providing a ligature of the LAA at its neck.

Figure 6: Embolisation of an ACP device (Abbott) to the LA due to inappropriate sizing (A) Effective device retrieval with a goose neck snare (B).

Figure 7: Incidence per 100 patient-years of DRT in LAAC registries with more than 100 patients.[86-95]

Figure 8: Device-related thrombosis (DRT) after LAA occlusion in a patient implanted with an Amulet device. The 3-month follow-up CT scan shows the Amulet device in a good position (yellow arrow) with a large thrombus on the device disk (red arrow).

Figure 9: Flowchart showing an algorithm for treatment of DRT. DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulant; DRT: device related thrombus; OAC: oral anticoagulant; FU: follow up; LMWH: low molecular weight heparin; CT: computed tomography; TOE: transoesophageal echocardiogram; VKA: vitamin K antagonist.

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Figure 10: Follow-up CT scan (6 months) of a Watchman Flex device that is not positioned correctly (yellow arrow) showing a severe leak (white arrow). A 3D-segmented model demonstrates that the device is rotated by 90° causing the leak at the inferior site of the device. CT: computed tomogram; TOE: transoesophageal echocardiogram

Figure 11: Flowchart showing a therapeutic approach when a peri device leak is detected during follow-up. DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulants; TOE: transoesophageal echocardiogram.

Figure 12: Clinical populations where LAAC may be considered for patients with AF at-risk of stroke but refractory to or contraindicated for anticoagulation and when no otherwise satisfactory management is available.

Figure 13: Management of (recurrent) major gastrointestinal bleeds. DOAC: direct oral anticoagulant; GI: gastrointestinal; INR: International Normalised Ratio; LAAC: left atrial appendage closure; PPI: proton pump inhibitor; TTR: time in therapeutic range; VKA: vitamin K antagonist.

Figure 14: A-C-T-I-O-N items that should be considered in atrial fibrillation (AF) patients suffering an ischaemic stroke whilst on an anticoagulant [141]. A-C-T-I-O-N items that should be considered in atrial fibrillation (AF) patients suffering an ischaemic stroke.

Figure 15: Diagram illustrating positioning of the Sentinel™ Cerebral Protection Filter System (CPS) (Boston Scientific, Marlborough, Massachusetts, USA). The System is designed to protect the cerebral vasculature from embolic events and remove debris/thrombus during interventional procedures, such as TAVI, but it has been used for LAAC in patients with thrombus formation in LAA. The device comprises dual-filter embolic protection and is percutaneously placed in the aortic arch. The two self-expandable filters directed into the carotid arteries can adapt to a wide variety of anatomies and have the ability to block even debris of less than 0.5 mm in size.

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Figure 16: Diagrams illustrating the prothrombotic (Panel A) and pro-haemorrhagic (Panel B) tendences seen in severe chronic kidney disease. CKD: chronic kidney disease; G4-G5D: grade of severity of CKD (Modified from [163])

Figure 17: Proposed algorithm for treatment choice in patients with severely reduced glomerular filtration rate and kidney failure. OAC: oral anticoagulant therapy; DOAC: Direct oral anticoagulant, GFR: Glomerular filtration rate; LAAC: Left atrial appendage closure TTR: Time in therapeutic range, VKA: Vitamin K antagonist.

Figure: 18: Management of refusal/non-compliance/non-persistence with OAC therapy and use of LAAC. The patient may be averse to oral anticoagulant therapy, non-compliant or simply prefer LAAC therapy. In these cases, the physician and other health care professionals are expected to educate the patient, the family and/or carers and friends. The patient may resume or improve compliance in which case anticoagulant therapy should continue, but if best efforts fail a LAAC device may be the best solution. OAC: oral anticoagulant, LAAC: left atrial appendage closure device.

Figure 19: 3-D echocardiogram, demonstrating endothelium growing over the device which was implanted 7 weeks previously

Figure 20

Upper panel: Manufacturer-recommended antithrombotic regimens after LAAC (adapted and updated [238, 239]). LAAC: left atrial appendage closure; OAC: oral anticoagulant.
Lower panel: Emerging strategies for antithrombotic regimens after LAAC (limited evidence and some ongoing studies): initial anticoagulant without concomitant aspirin ([240-242]) followed by a DAPT or SAPT period; single antiplatelet ([243-246]); low-dose DOAC ([247-251]). LAAC: left atrial appendage closure; (D)OAC: (direct) oral anticoagulant.
Hatching indicates variable adoption depending on benefit-risk.

Table Legends

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Table 1: Ongoing randomized trials comparing LAAC vs. best medical care in AF patients with contraindications for long-term anticoagulation. APT: antiplatelet therapy; CV: cardiovascular; CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female); ICH: intracerebral bleeding; LAAC: left atrial appendage closure; SE: systemic embolism; TIA: transient ischaemic attack.

Table 2: Ongoing large-scale randomized trials comparing LAAC vs. DOAC. CV: cardiovascular; CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female); DOAC: Direct oral anticoagulant; WM FLX: Watchman FLX; SE: systemic embolus.

Table 3: Recommendations for the use of LAA closure in the international guideline documents. LAA: left atrial appendage; ACCP: American College of Chest Physicians; OAC, oral anticoagulant; ICH: intracerebral haemorrhage; CSANZ: Cardiac Society of Australia and New Zealand; ACC/AHA/HRS: American College of Cardiology/American Heart Association/Heart Rhythm Society; ESC: European Society of Cardiology; CCS: Canadian Cardiovascular Society; APHRS: Asia Pacific Heart Rhythm Society; INR: International Normalized Ratio; B-NR: level of evidence B according to non-randomised data; B-R: level of evidence B according to randomised data).

Table 4: Recommendations for the use of LAA closure in consensus statements. CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female); EAPCI: European Association of Percutaneous Coronary Intervention; EHRA: European Heart Rhythm Association; ICH: intracranial haemorrhage; INR: International Normalized Ratio); LAA: left atrial appendage; LAAC: left atrial appendage closure; OAC: oral anticoagulant.

Table 5: Different types of occluders currently in use and their characteristics. LAA: left arial appendage; OAC: oral anticoagulant.

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Table 6: Incidence of periprocedural LAAC complications. Data were derived from the SURPASS registry of 66.894 Watchman FLX implants performed in the US from August 2020 to March 2022 and from 915 Amulet implants in the randomized Amulet IDE trial 2016-2020. [81; 82, 83]

Table 7: Mechanisms of pericardial effusion and tamponade and their prevention and treatment. The table lists the most frequent mechanisms of pericardial effusion and actions to prevent and to manage them. ICE: intracardiac echocardiography; TOE: transoesophageal echocardiogram; CT: computed tomography.

Table 8: Mechanisms of device embolisation and its treatment.

Table 9: List of main antithrombotic schemes used after LAAC. DOAC: direct oral anticoagulation; INR: International normalized ratio; LAAC: left atrial appendage closure; VKA: vitamin K antagonist. *OAC schemes are not recommended with the Amulet device unless residual flow around the device is >5 mm.

Tables

Table 1:

	CLOSURE-AF [28]	**STROKE-CLOSE** [29]	**CLEARANCE** [30]	**LAA-KIDNEY** [33]	**COMPARE LAAO** [31, 32]
Patient population	AF and high bleeding risk (HAS-BLED ≥3; prior major bleeding; CRF)	AF and ICH within 12 months	AF and ICH or intracerebral amyloid vasculopathy	AF and end-stage kidney disease	NVAF pts with CHA_2DS_2-VASc ≥ 2 and absolute contra-indication to (D)OAC
Number of	1000	600	530	430	609

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patients					
Random-isation	LAAC vs. best medical care	Amulet vs. best medical care (2:1)	Watchman FLX vs. best medical care	Amulet vs. best medical care	Amulet or Watchman FLX vs. nothing +/- APT (2:1)
Primary endpoint	Stroke, SE, major bleeding or CV death at 2 years	Stroke, SE, major bleeding or all-cause mortality at 2 years	Stroke, SE, major bleeding or CV death at 3 years	Time to first stroke, SE, CV death or major bleeding	1. Any stroke. 2. composite of stroke, TIA and SE

Table 2:

	OPTION [35]	CHAMPION-AF [36]	CATALYST [37]
Patient population	CHA_2DS_2-VASc≥2 (men) CHA_2DS_2-VASc≥3 (women)	CHA_2DS_2-VASc≥2 (men) CHA_2DS_2-VASc≥3 (women)	CHA_2DS_2-VASc≥3 initially , now updated to CHA_2DS_2-VASc≥2 (men) CHA_2DS_2-VASc≥3 (women)
Number of patients	1600	3000	2650
Randomization	WM FLX vs OAC	WM FLX vs DOAC	Amulet vs DOAC
Primary endpoint	Stroke, SE or death at 3 years (non-inferiority) Major or clinically relevant bleeding at 3 years (superiority)	Stroke, SE or CV death at 3 years (non-inferiority) Major or clinically relevant bleeding at 3 years (superiority)	Stroke, SE or CV at 2 years (non-inferiority) Major or clinically relevant bleeding at 2 years (superiority)
Enrolment status	Completed	Completed	Enrolling

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2 **Table 3:**

Guideline recommendations for transcatheter LAAC for stroke prevention in patients with AF at increased (moderate to high) risk of stroke				
Society	Wording of recommend-ation	AF patient group(s) for which LAA closure is recommended	Class / Strength	Level of evidence
ACCP 2018 [50]	We suggest We suggest	With absolute contraindications for OAC In ICH survivors at high risk of recurrent ICH (e.g., those with probable cerebral amyloid angiopathy)	Weak Ungraded	Low
CSANZ 2018 [51]	May be considered	With contraindications to OAC	Strong	Low
ESC 2020 [53]	May be considered	With contraindications for long-term OAC (e.g., ICH without a reversible cause)	IIb	B
CCS 2020 [54]	We suggest	With absolute contraindications to OAC	Weak	Low
APHRS 2021 [55]	May be considered	With clear contraindications for long-term OAC (e.g., ICH without a reversible cause)	NA	NA
SCAI/HRS [56]	May be considered	With contraindications for long-term anticoagulant treatment (e.g., those with a previous life-threatening bleed without reversible cause).	IIb	B
ACC/HRS/ ACCP/HRS [57]	Is reasonable	With a moderate to high risk of stroke (CHA2DS2-VASc score ≥2), and a contra-indication to long-term oral anticoagulation due to a non-reversible cause	IIa	B-NR
	May be reasonable	With AF and a moderate to high risk of stroke and a high risk of major bleeding on oral anticoagulation, LAAO may	IIb	B-R

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		be a reasonable alternative to oral anticoagulation based on patient preference, with careful consideration of procedural risk and with the understanding that the evidence for oral anticoagulation is more extensive		

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2 **Table 4:**

Consensus statements for percutaneous LAAC for stroke prevention in patients with AF at increased (or moderate to high) risk of stroke		
Group	Wording of the statement	Consensus statement
EHRA/EAPCI 2020 [58]	May receive / be considered for	PATIENTS ELIGIBLE FOR LONG-TERM OAC Patients who are eligible for long-term OAC may receive an LAAC instead of long-term OAC only if they refuse OAC despite explanation.
	May receive / be considered for	PATIENTS AT HIGH RISK OF BLEEDING WITH LONG-TERM OAC In patients with an elevated bleeding risk during long-term OAC, LAAC may be considered.
	May receive / be considered for	PATIENTS NON-COMPLIANT TO OAC In patients with documented noncompliance, LAAC can be discussed as a therapeutic alternative after attempts to resolve the reasons for noncompliance.
	Should	AF patients with CHA_2DS_2-VASc score ≥ 2 (3 in females) who have absolute contraindications for long-term OAC may be considered for LAAC if a minimum period (2-4 weeks) of a single antiaggregant can be given. In patients with an elevated bleeding risk during long-term OAC (e.g., post-ICH) an individual risk-benefit assessment needs to be carried out between OAC and LAAC. Any AF patients with an increased risk for stroke and embolism and no contraindication for OAC should receive personal and detailed advice that according to current evidence long-term OAC treatment is the preferred prophylactic strategy.

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	Should not	In patients who are opposed to chronic drug intake, LAAC is currently not offered as an equally effective treatment alternative.
The Munich consensus document 2017 [59]	Potential indications	Patient not eligible for long-term OAC therapy (absolute or relative contraindications to OAC), including: I. High risk of bleeding (ICH or gastrointestinal bleeding), II. History of major or minor bleeding with or without OAC (symptomatic bleeding in critical organ, i.e. ocular, pericardial, spinal cord, or recurrent epistaxis needing medical attention), III. Increased risk of bleeding due to a physical condition and/or comorbidities (i.e., recurrent falls with head trauma and significant musculoskeletal injury, need for additional dual antiplatelet therapy for coronary artery disease/stenting, diffuse intracranial amyloid angiopathy, bowel angiodysplasia, severe renal insufficiency/haemodialysis, blood cell dyscrasia), or IV. Inability to take OAC for reasons other than high risk of bleeding (intolerance, documented poor adherence, documented variability in the INR on VKA, high-risk occupation with increased injury potential, patient's choice). Thromboembolic event or documented presence of thrombus in the LAA despite adequate OAC therapy.

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Table 5:

	Company	Structure	Features	Limitations
Watchman FLX (Figure 5A) [74-76]	Boston Scientific, Marlborough, Massachusetts, USA	Endocardial Single component	High degree of conformability, sealing and safety	Shallow LAAs with proximal bifurcation
AMPLATZER Amulet-ACP (Figure 5B) [77]	Abbott, St Paul, Minnesota, USA	Endocardial Dual component	Possible to seal complex LAA anatomies	More complex to manoeuvre
LAmbre (Figure 5C) [78]	Lifetech Scientific, Shenzhen, China	Endocardial Dual component	Possible to seal complex LAA anatomies	More complex to manoeuvre
LARIAT (Figure 5D)[79]	SentreHeart, Redwood City, California, USA	Epicardial suture	Adjustable size No need for post-procedural OAC	Both epicardial and endocardial access Postprocedural pericardial pain Not suitable when prior cardiac surgery or thoracic radiation

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Table 6:

Complication	SURPASS registry	Amulet IDE
Pericardial tamponade/effusion	0.32%	2.4%
Device embolisation	0.01%	0.7%
Stroke	0.09 %	0%
Death	0.07%	0%
Device-related thrombosis at 45 days	0.23%	2.2%
Peri-device leaks at 45 days	12.9% (<3 mm) 3.7% (3-5 mm) 0.4% (>5 mm)	27% (<3 mm) 9% (3-5 mm) 1% (>5 mm)

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Table 7:

Most frequent mechanisms of pericardial effusion/tamponade
Transseptal puncture
Manipulation of a stiff guidewire
Recurrent repositioning of the device
Deep positioning of the device
How to prevent effusion/tamponade
CT scan/TOE pre-procedure
TOE/ICE intra-procedure
Angio intra-procedure
Pericardial effusion/tamponade – what to do?
Percutaneous drainage in the catheter laboratory
Blood transfusion
Intensive care unit
Surgical drainage as backup

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Table 8:

Most frequent mechanism of device embolisation
Device under-sizing
Too proximal implantation of the device
Inadequate coaxial placement of the device within LAA
Sinus rhythm
Device embolisation – what to do?
Catheter-based retrieval of devices
Surgical removal of the device (rarely needed)

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Table 9:

Antithrombotic regimen	Supporting studies	Main scheme
VKA*	PROTECT-AF, PREVAIL, Amulet IDE	1. Aspirin + VKA (INR 2.0-3.0) for at least 45 days post-implant 2. Aspirin + clopidogrel from 45 days until 3 months post-implant 3. Then aspirin alone until 12 months post implant
DOAC*	PINNACLE-FLX, EWOLUTION;	1. Aspirin + DOAC for at least 45 days post-implant 2. Aspirin + clopidogrel from 45 days until 3 months post-implant 3. Then aspirin alone until 12 months post implant
Dual antiplatelet	ASAP, EWOLUTION, AMULET Registry, Amulet IDE	1. Aspirin + clopidogrel until 3 months (WATCHMAN FLX) or 6 months (Amulet) post-implant 2. Then aspirin alone until 12 months post implant

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Practical Boxes

Practical Box 1:

When to consider referral for LAAC:
AF and significant risk of stroke CHA_2DS_2VASc ≥2 (men) CHA_2DS_2VASc ≥3 (women) and:
• History of recurrent or irremediable major bleeding
• Recurrent non-major bleeding
• Predicted high risk of bleeding (HAS-BLED ≥3)
• Bleeding disorder (coagulopathy or angiodysplasia)
• Indication for long-term antiplatelet therapy
• Cerebral microbleeds/amyloid cerebral vasculopathy
• Advanced renal failure including dialysis
• Hepatic failure
• Stroke despite appropriate OAC
• Non-adherence to OAC despite attempts to educate the patient
• Electrically isolated LAA after ablation

Practical Box 2:

Before LAAC at implanting center:
Clinical examination and biochemistry: rule out infection; assess renal function
TTE: LV function, valves, pericardium
Cardiac CT or TEE: LAA anatomy; device selection and size; rule out LAA thrombus
Stop OAC; loading dose of anti-platelets
Intravenous prophylactic antibiotics

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Practical Box 3:

LAAC: benefits, procedure and periprocedural risk
Stroke prevention similar to OAC
No need for long-term OAC; reduced risk of bleeding
Procedure carried out in local analgesia/light sedation guided by ICE or micro/mini-TEE
Procedure carried out in sedation/general anaesthesia guided by TEE
Duration of procedure: 30-60 min
Procedural risks:
Pericardial tamponade/effusion: 0.32-2.4%
Device embolisation: 0.01-0.7%
Stroke: 0.09%
Death: 0.07%

Practical Box 4:

After LAAC: postprocedural risk, medication and follow-up
Same-day procedure or short hospitalisation stay
TTE before discharge: Device position and screening for pericardial effusion
Cardiac CT or TEE: 45 days to 3 months; screening for DRT and PDL
Device-related thrombosis (DRT): 0.23-2.2%
Peri-device leak (PDL): <3 mm: 12.9-27%; 3-5 mm: 3.7-9%; >5 mm: 0.4-1%
Post-procedural medication to reduce risk of DRT: DAPT or OAC 1-3 months, SAPT 6-12 months, reduced-dose DOAC 3-12 months (depending on risk for DRT and bleeding)
Endocarditis prophylaxis 6 months

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Figures

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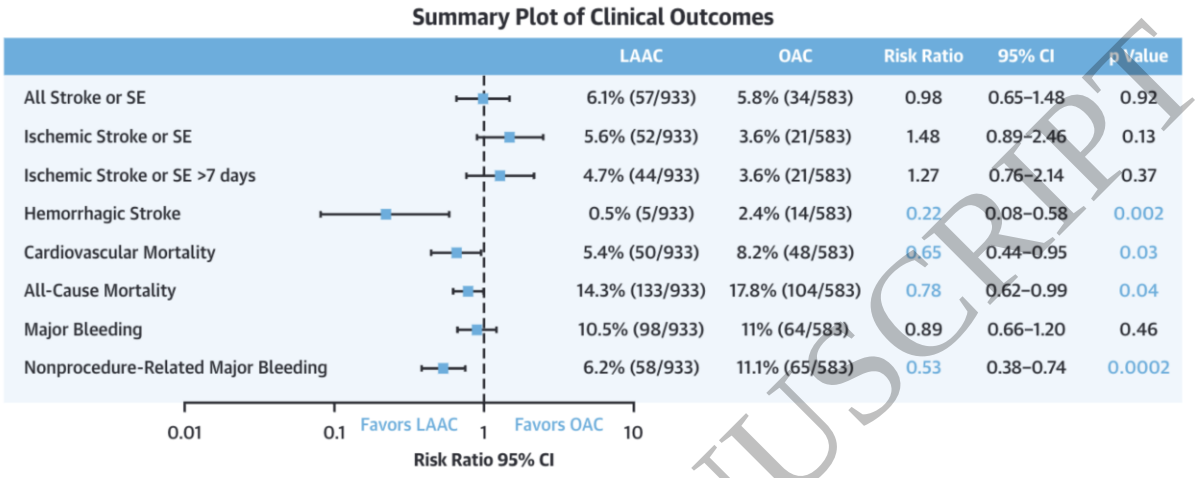

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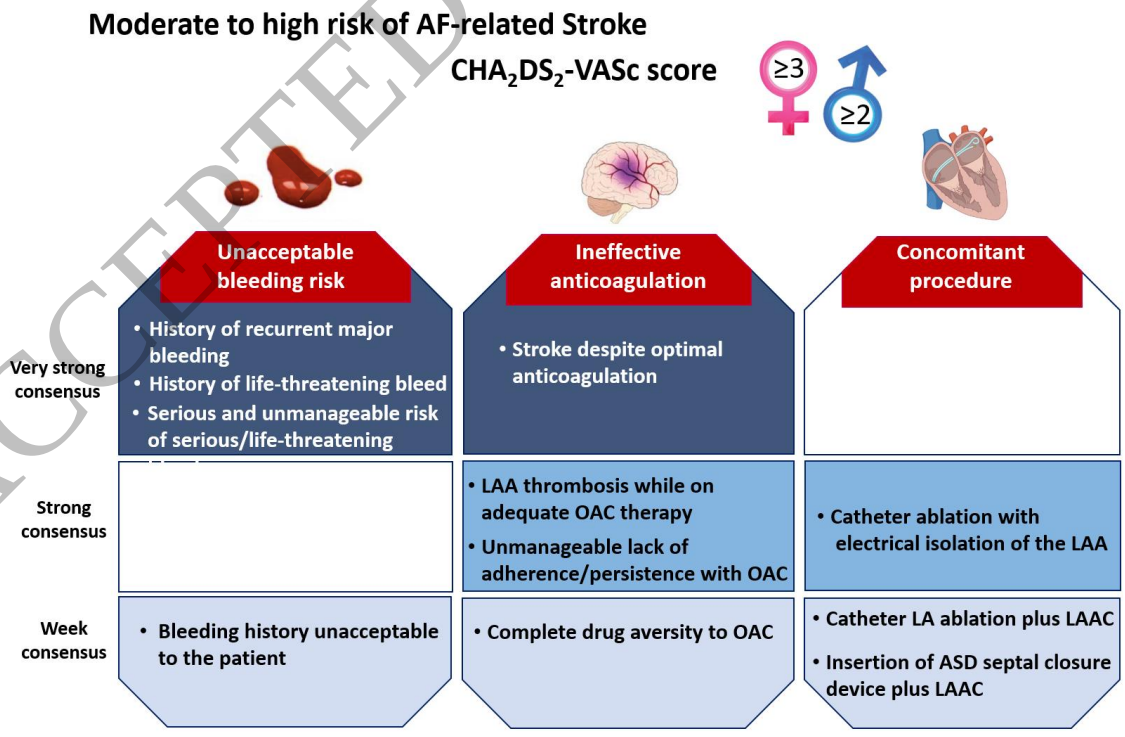

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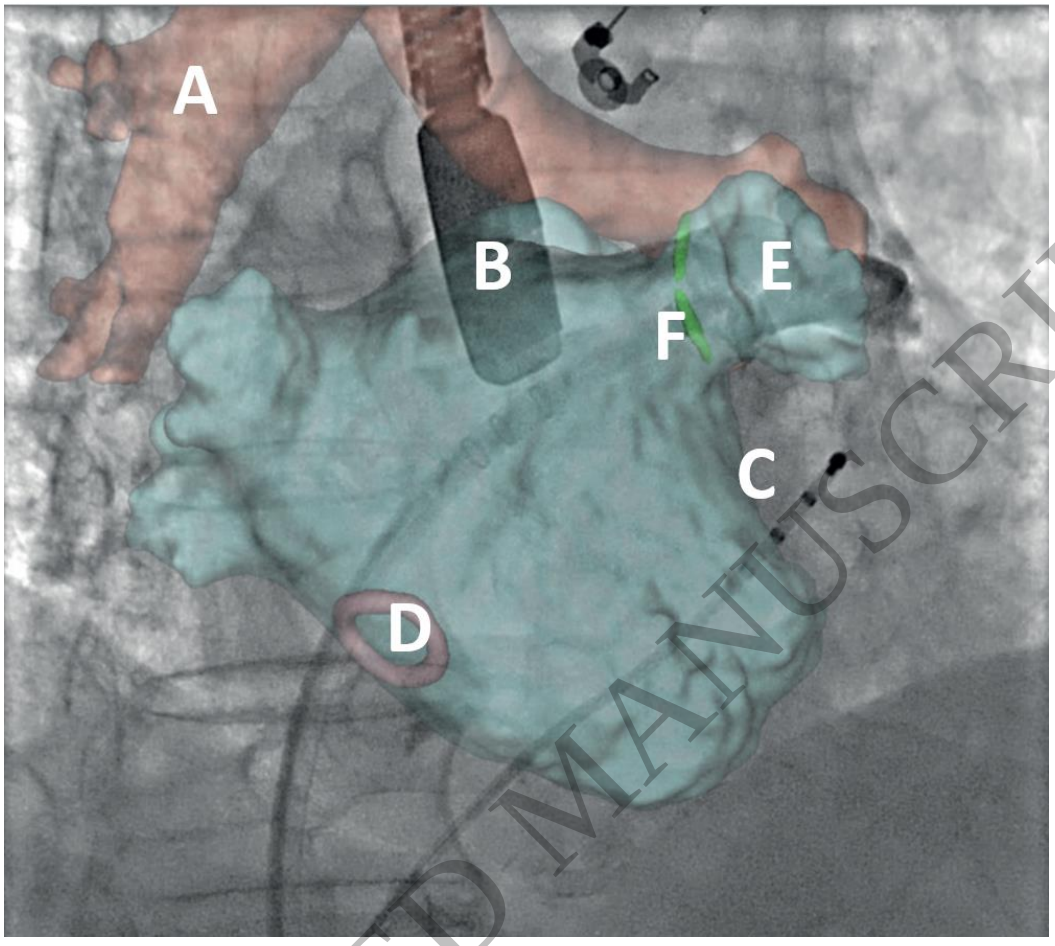

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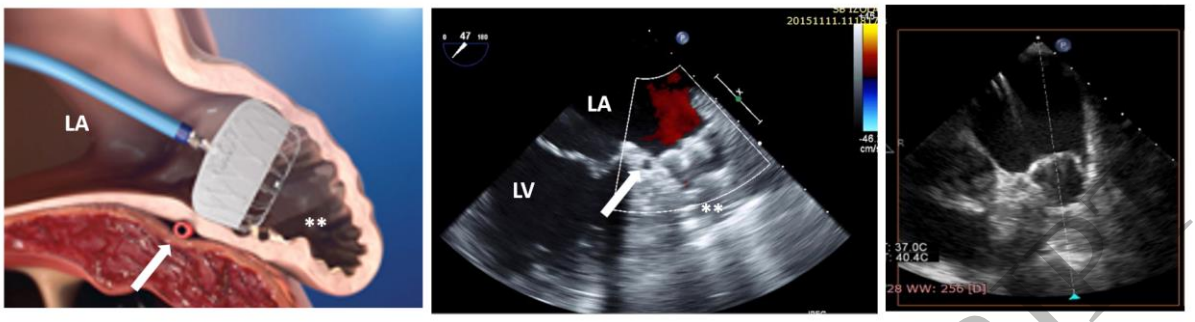

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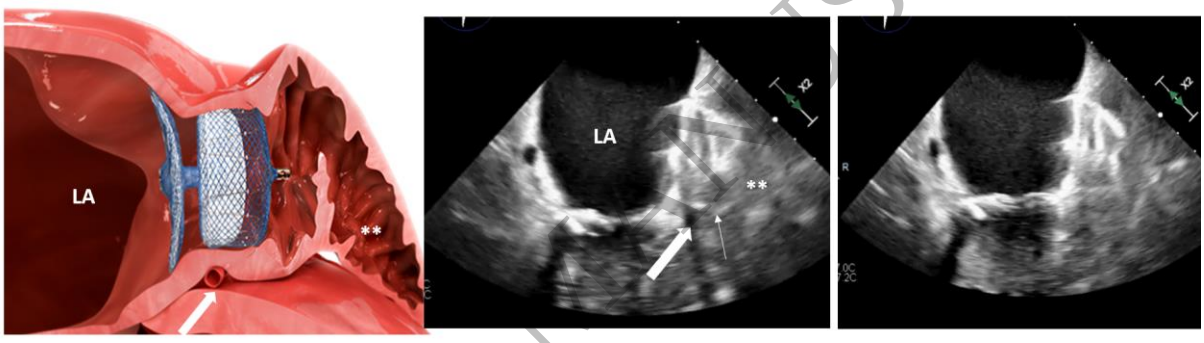

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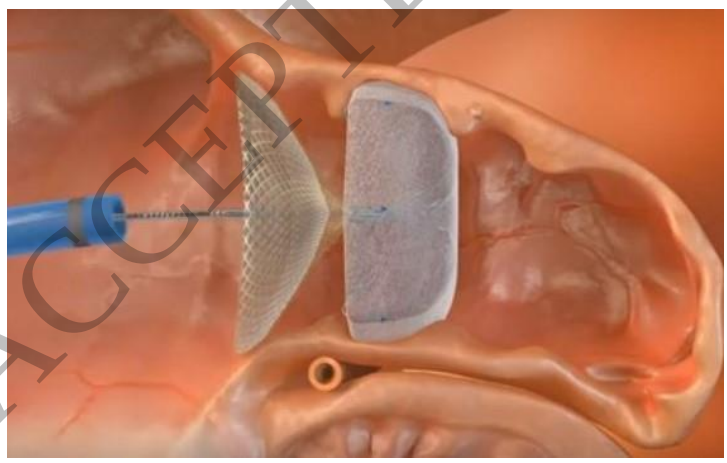

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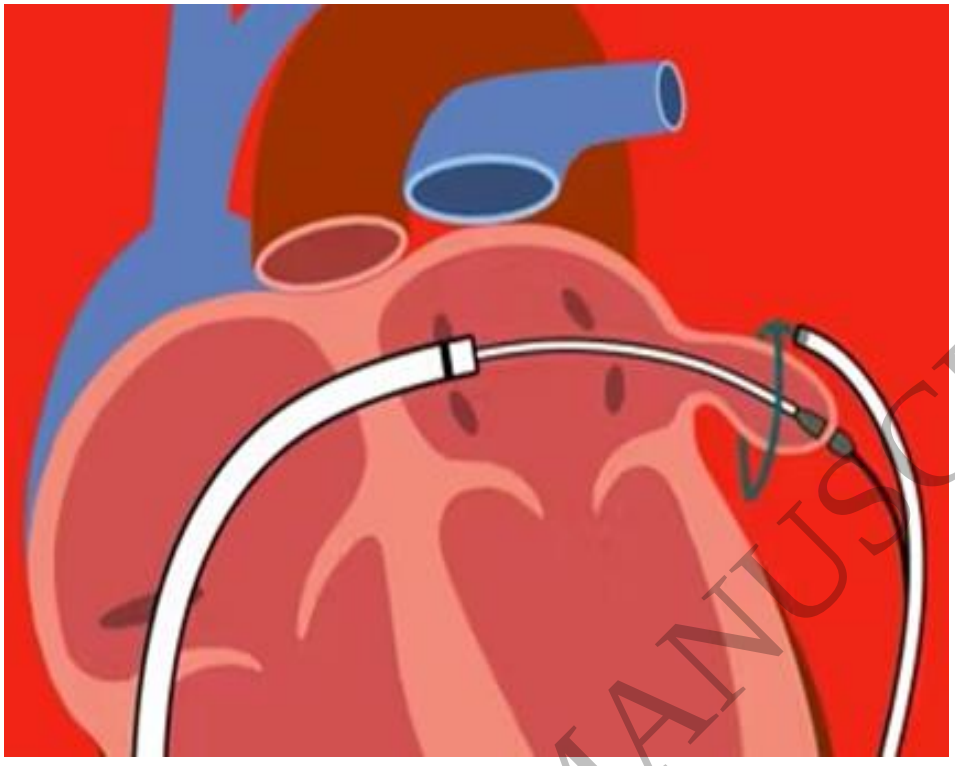
Figure 5



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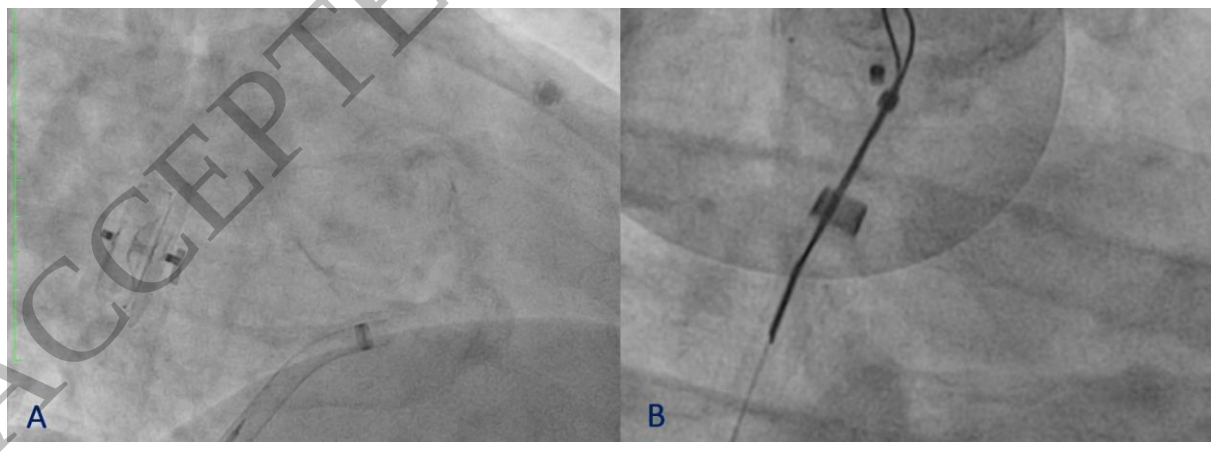

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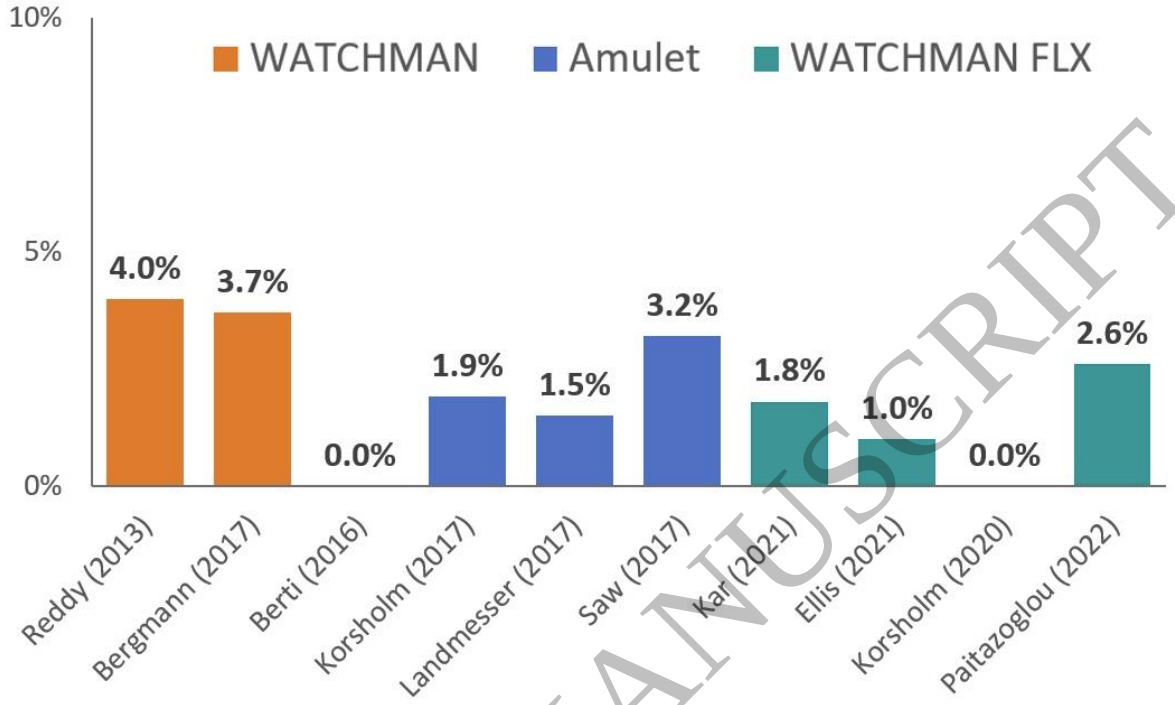

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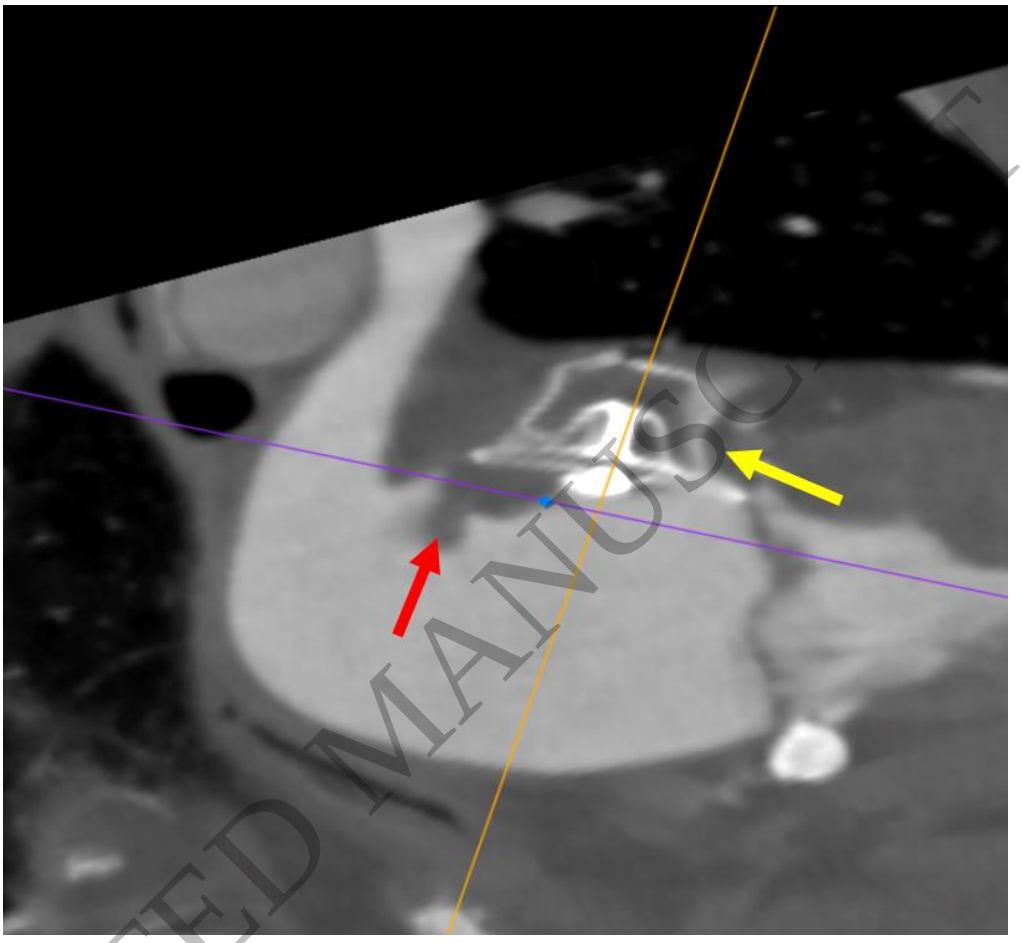

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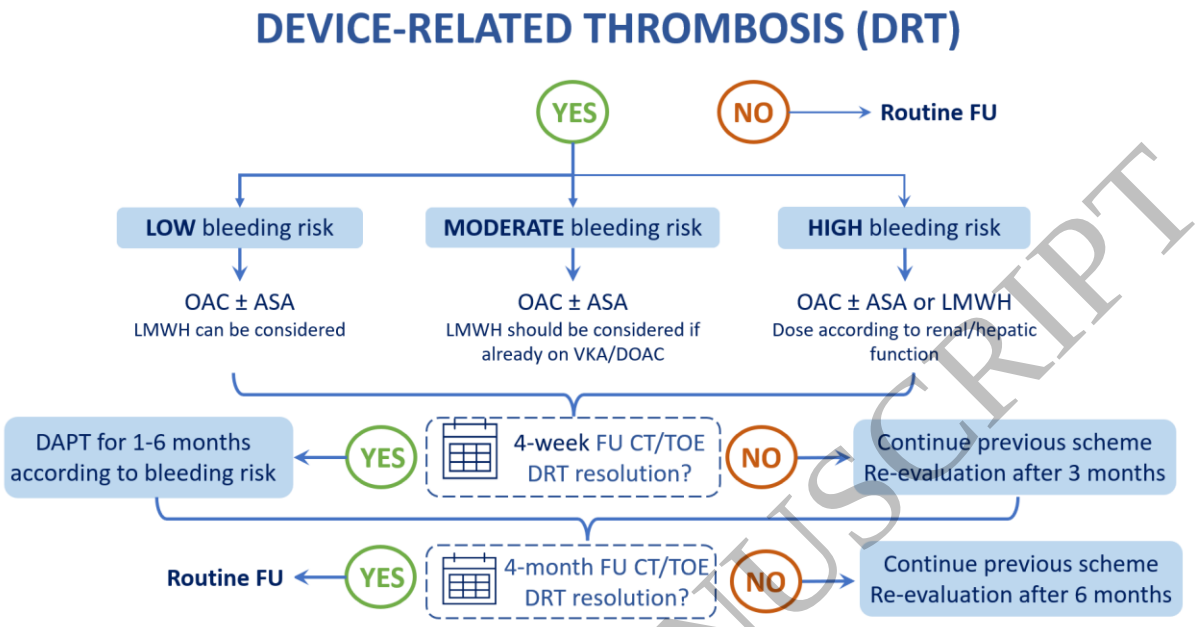

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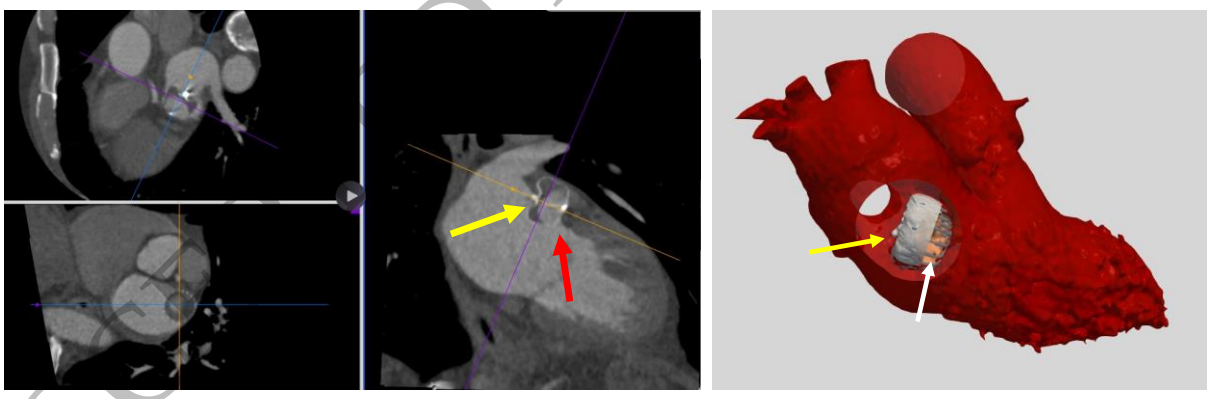

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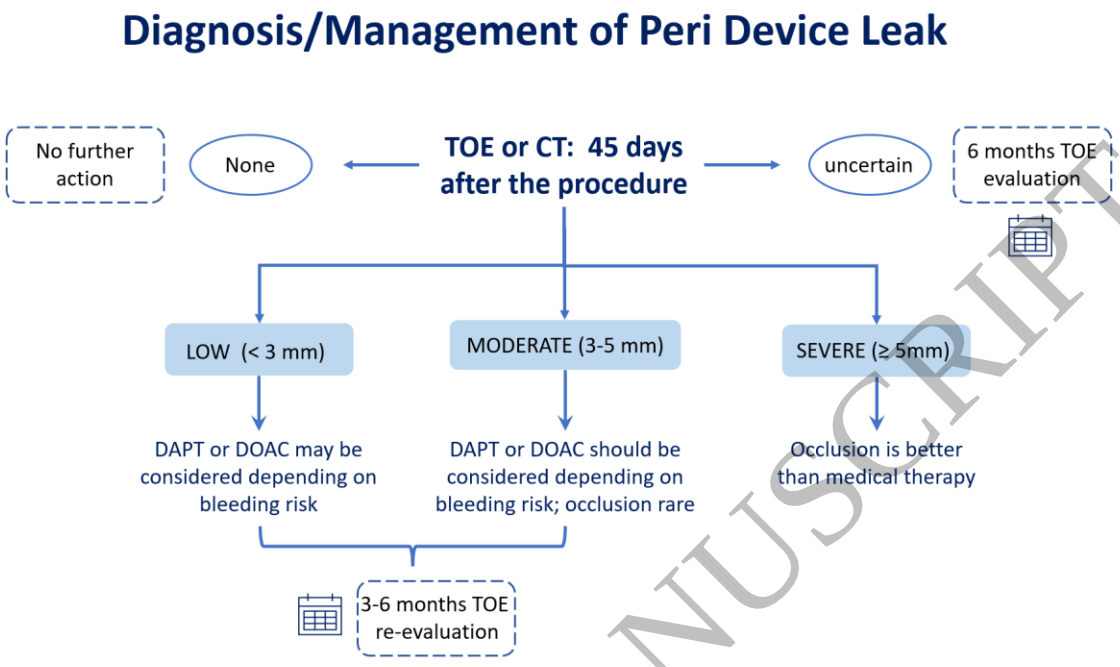

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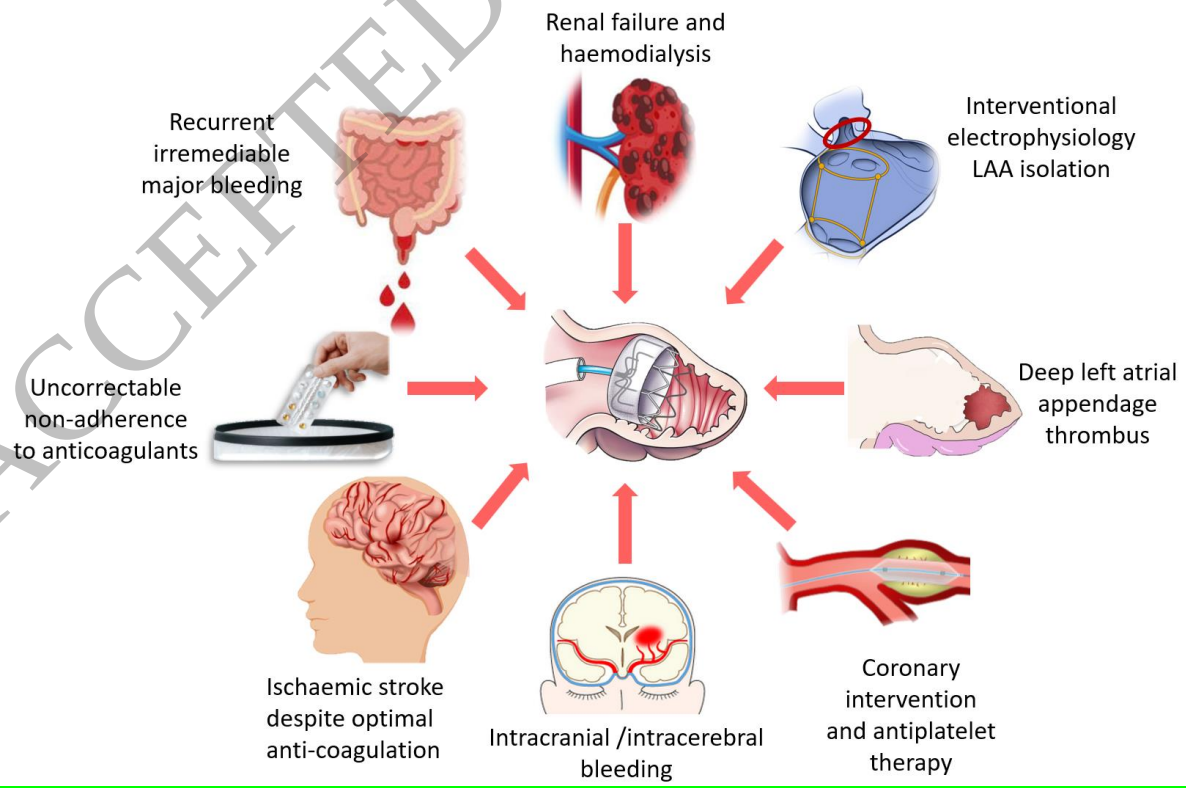

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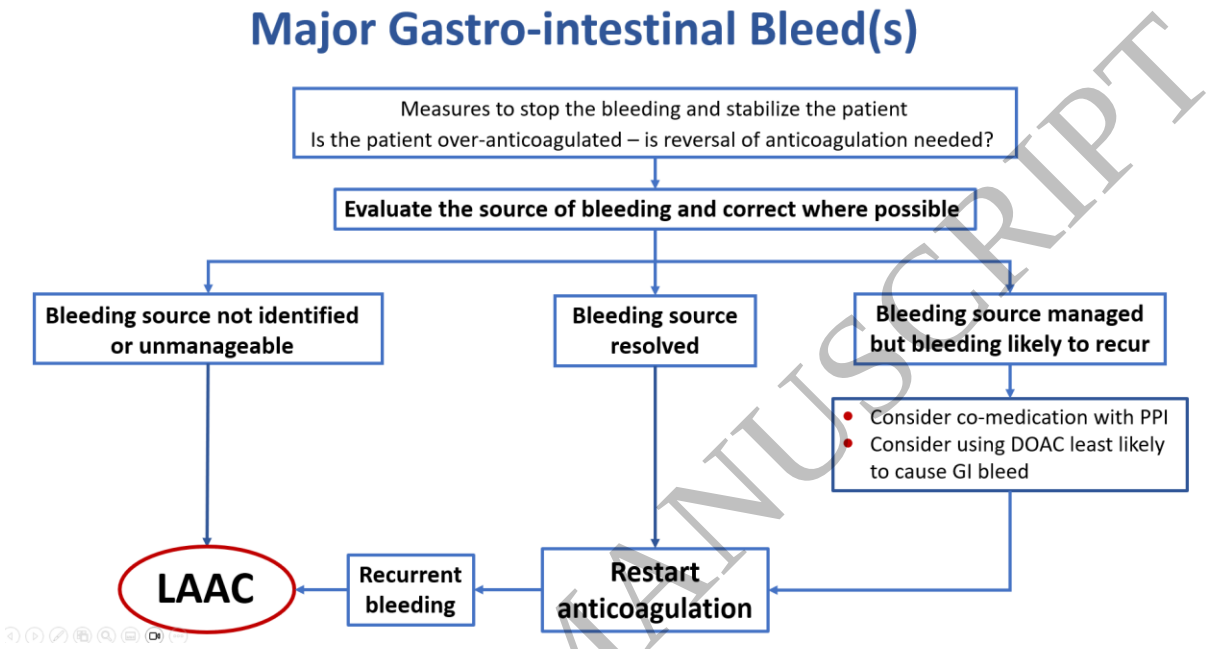

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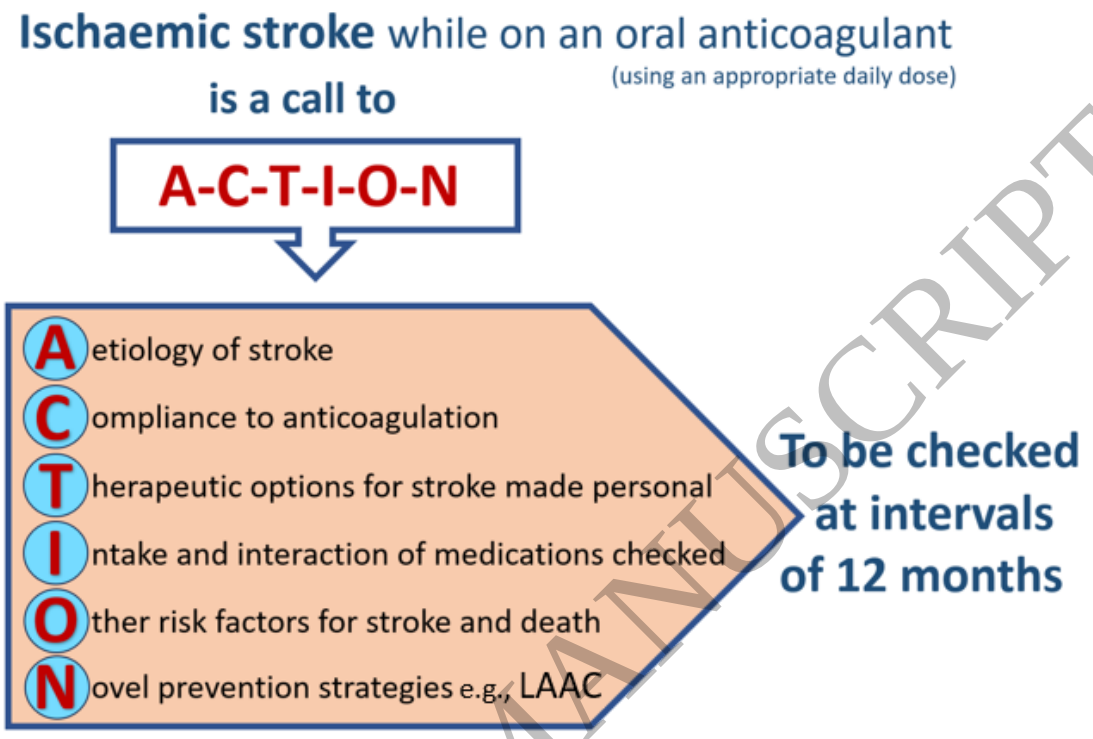
1 **Figure 14:**



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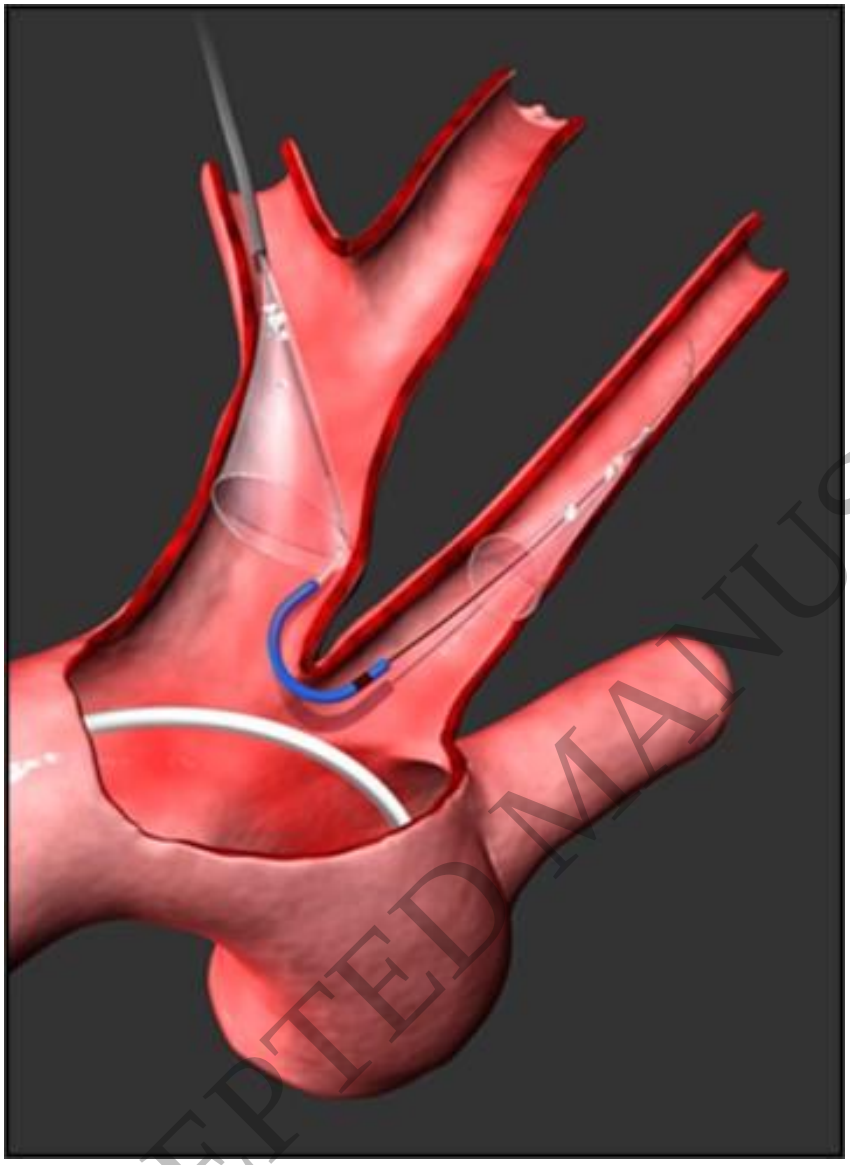

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Figure 16:

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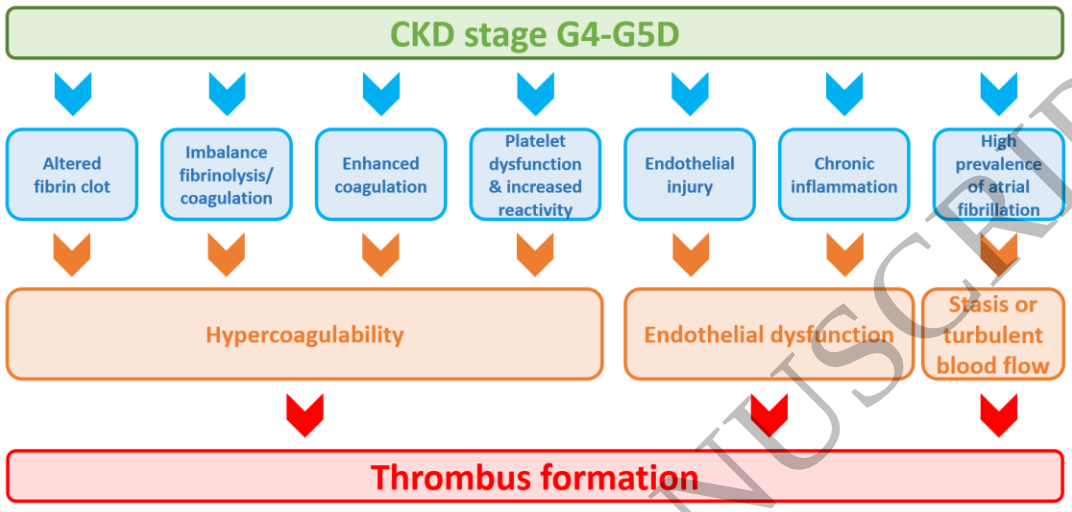

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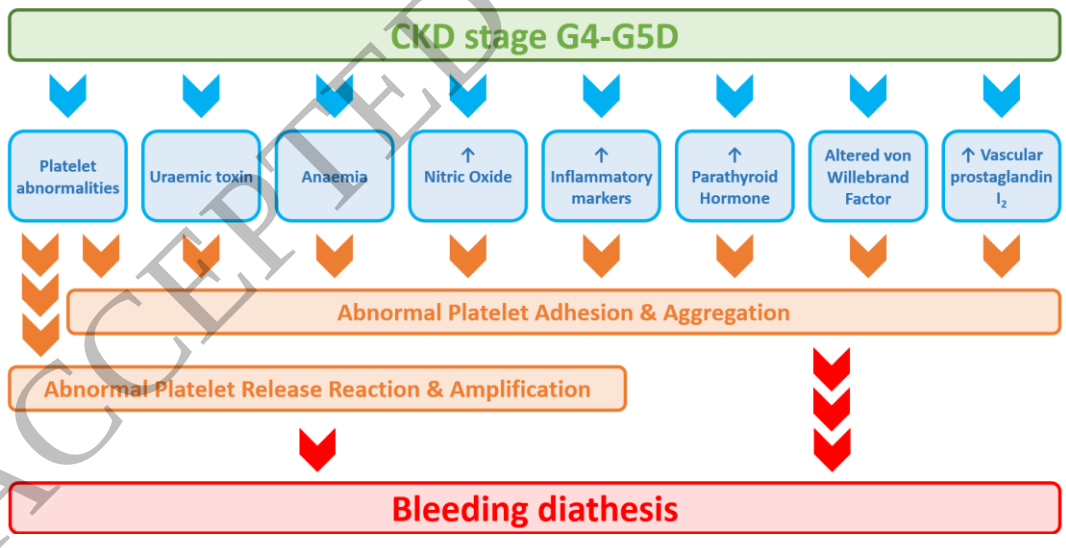

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Figure 17:

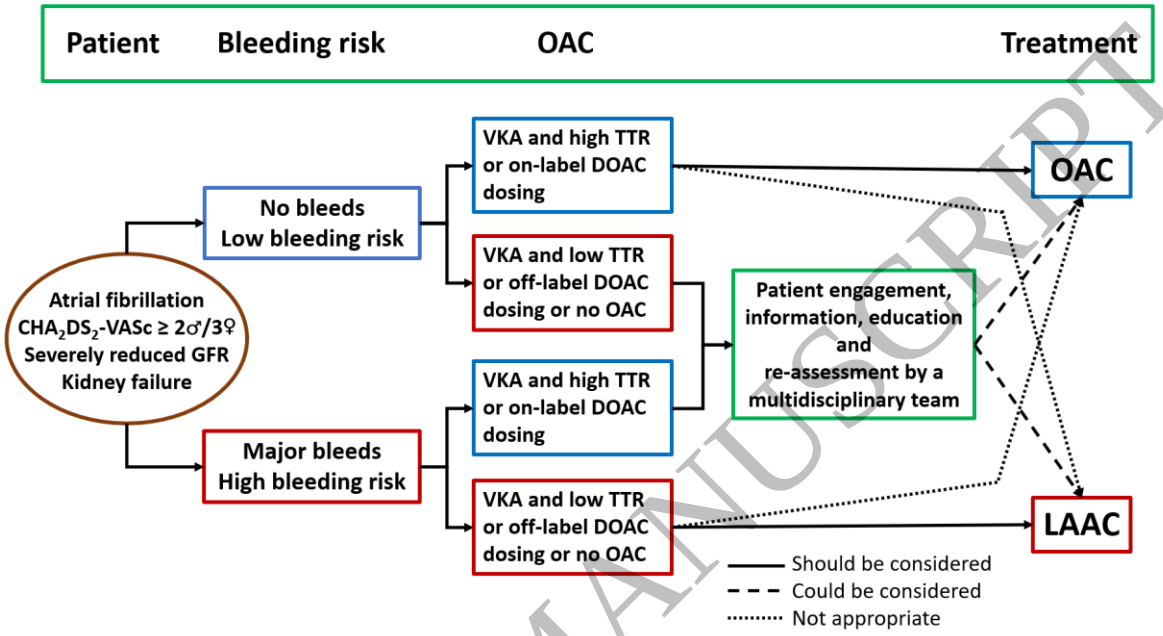

Figure 18:

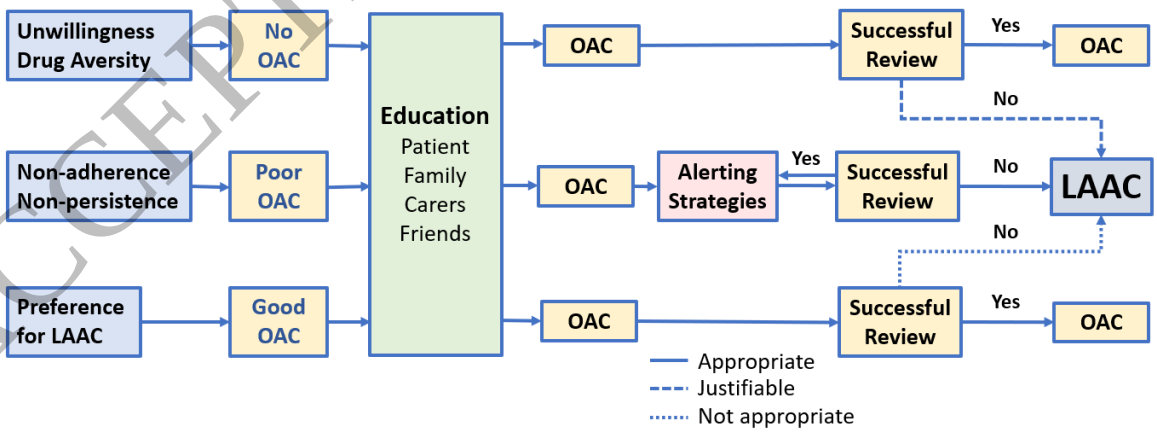

Figure 19:

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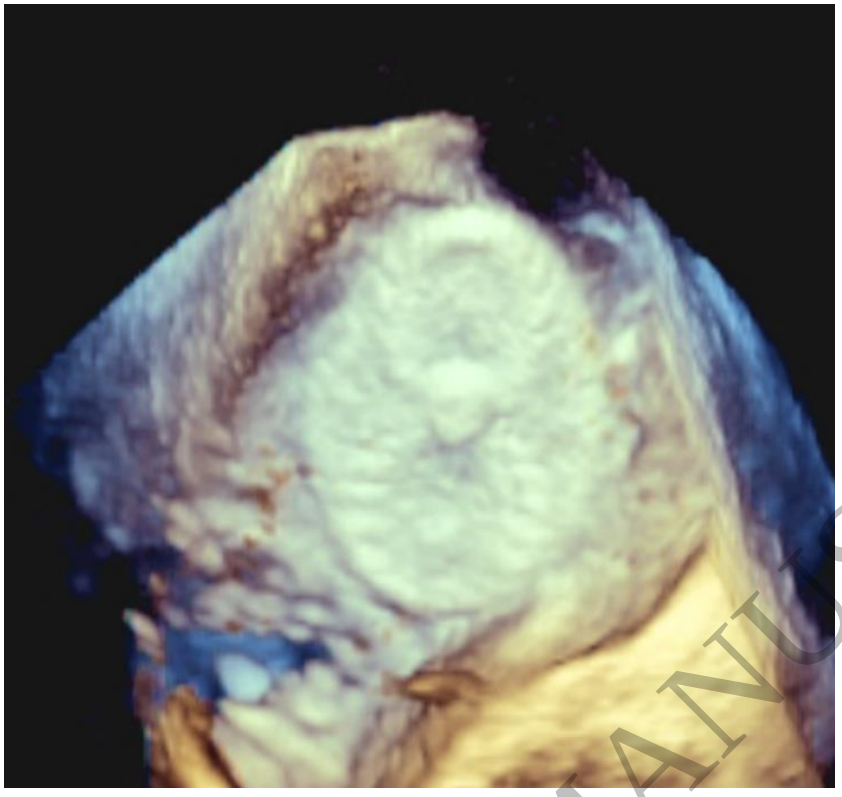

1

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Figure 20 Upper Panel:

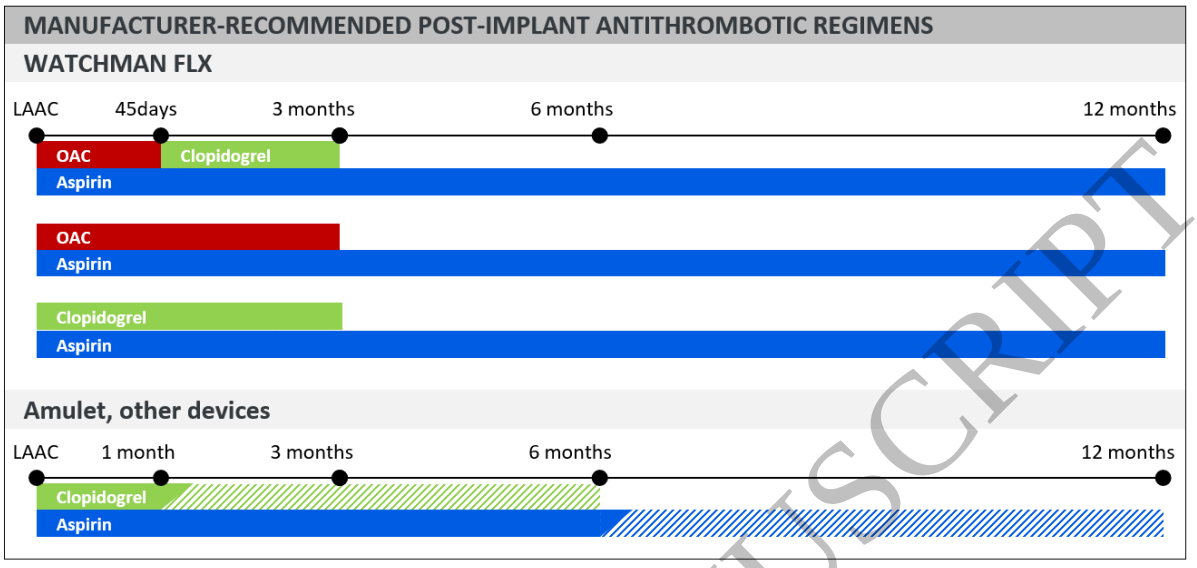
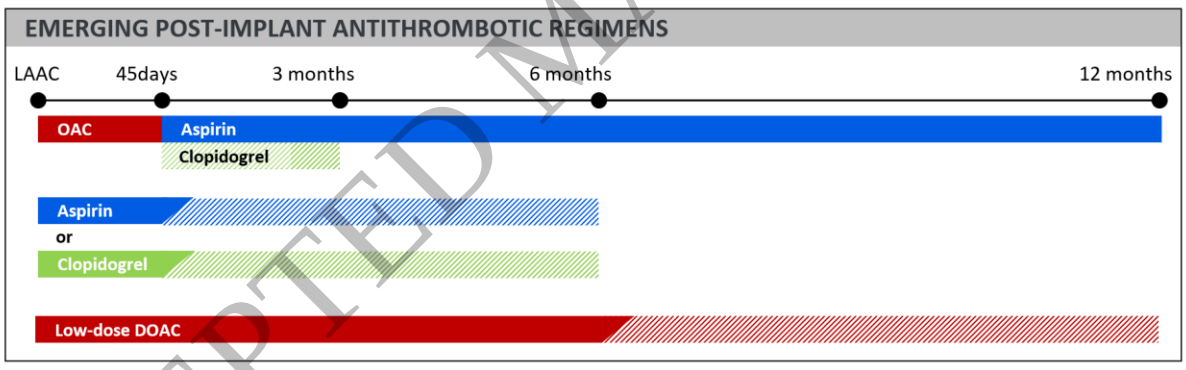


Figure 20 Lower Panel:



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