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ANMCO/AIAC/SICI-GISE/SIC/SICCH Consensus Document: percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation patients: indications, patient selection, staff skills, organisation, and training

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Atrial fibrillation (AF) is the most common arrhythmia and its prevalence is increasing due to the progressive aging of the population. About 20% of strokes are attributable to AF and AF patients are at five-fold increased risk of stroke. The mainstay of treatment of AF is the prevention of thromboembolic complications with oral anticoagulation therapy. Drug treatment for many years has been based on the use of vitamin K antagonists, but recently newer and safer molecules have been introduced (dabigatran etexilate, rivaroxaban, apixaban, and edoxaban). Despite these advances, many patients still do not receive adequate anticoagulation therapy because of contraindications (relative and absolute) to this treatment. Over the last decade, percutaneous closure of left atrial appendage, main site of thrombus formation during AF, proved effective in reducing thromboembolic complications, thus offering a valid medical treatment especially in patients at increased bleeding risk. The aim of this consensus document is to review the main aspects of left atrial appendage occlusion (selection and multidisciplinary assessment of patients, currently available methods and devices, requirements for centres and operators, associated therapies and follow-up modalities) having as a ground the significant evolution of techniques and the available relevant clinical data.

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Introduction

Non-valvular atrial fibrillation (AF) is the most common form of cardiac arrhythmia and its incidence and prevalence are constantly increasing[1] due to the ageing of the population and the higher survival rates of patients with conditions such as ischaemic cardiopathy, valve defects, congenital heart defects, and cardiac insufficiency. The estimated prevalence in the general population is about 2% and increases with age.[1] The lifetime risk of onset of AF is 25% in men and women with age $>$ 40 with heart defects, while for those without heart defects the risk is about 15%.[2,3] A diagnosis of AF features in about 3–6% of hospitalizations for acute heart conditions,[3] especially coronary heart diseases and congestive cardiac insufficiency. In the general population, arterial hypertension is the most common condition associated with AF.[3,4] Moreover, AF is a common post-operative complication, especially after cardiothoracic surgery.[3,4] However, there are also isolated forms of AF, diagnosed mainly by exclusion once concomitant cardiac diseases have been ruled out.

Most patients are asymptomatic and AF is an occasional occurrence. In some patients, it may occur with minor symptoms (palpitations) while in others the first onset may be a complication of AF such as ischaemic stroke. The presence of AF is an independent risk factor for increased mortality and morbidity, and is a cause of stroke and/or thromboembolism, congestive cardiac insufficiency, and seriously reduced quality of life, with a consequent increase in health-care costs.[3,4] The risk of stroke in patients with non-valvular AF is ~5% per year and at least 15-20% of all ischaemic strokes are associated with AF.[5] AF is also an independent risk factor for the recurrence of stroke[6] and is associated with higher mortality and morbidity than stroke not correlated to AF, underlining the need for more effective stroke prevention in these patients.[5,6]

AF, subdivided into 'valvular' (patients with mechanical valve prostheses or mitral stenosis) and 'non valvular', is classified in four different categories depending on the mode of presentation and duration of the arrhythmia:

(1) paroxystic AF (ends spontaneously or after therapy within 7 days after onset),
(2) persistent AF (lasts more than 7 days),
(3) persistent or long-standing AF (continues for more than 1 year), and
(4) permanent AF (continual, and the patient and physician have decided together against attempts at cardioversion and maintenance of the sinus rhythm).

The risk of stroke is basically the same for all four types of AF.[4]

Stroke and thromboembolic risk layering: risk of haemorrhage associated to oral anticoagulant treatment

The presence of AF is an independent risk factor for ischaemic stroke and thromboembolic events, significantly increases mortality and morbidity and can cause serious disabilities, as well as longer hospitalization.

The treatment of choice for the prevention of ischaemic stroke is oral anticoagulant therapy (OAT) with warfarin or, in the case of non-valvular AF, with the new oral anticoagulants (NOACs). In the case of non-valvular AF, warfarin has been shown to reduce the risk of stroke by about 62%, but it increases the risk of haemorrhage in percentages which vary from 1.2% to 3.4% per year.[7] NOACs have proved equally effective with a lower risk of cerebral haemorrhage.[4]

In about 90% of non-valvular AF patients, the thrombi form in the left atrial appendage (LAA);[8] however, it is fundamental to bear in mind that, even in AF patients, ischaemic stroke can be correlated to other factors, such as hypercoagulability or atherosclerosis of the ascending aorta and carotids.

Basically, the management of AF can be summed up in two main steps:

(1) identification and treatment of predisposing factors and concomitant pathologies and
(2) assessment of the thromboembolic risk and haemorrhagic risk for choice of the best therapeutic strategy.

In AF patients, risk layering is crucial. In fact, in spite of the plentiful, universally accepted evidence of the benefits of OAT in reducing the risk of ischaemic stroke, many studies have revealed that this therapy is underused, especially in high-risk patients.[8,9] A large number of stroke risk layering methods have been produced on the basis of risk factors identified in the control arms of clinical studies on warfarin, cohort studies and consent documents. These methods vary in complexity and the number of risk factors assessed, but they have almost all divided AF patients, by convention, into low, moderate and high risk.[4,10]

CHA_2DS_2-VASc[10] is the thromboembolic risk assessment score recommended by the European Society of Cardiology (ESC), the American Heart Association (AHA) and the American College of Cardiology (ACC), which considers gender, vascular diseases, cardiac insufficiency, hypertension, age (divided into two classes), diabetes and ischaemic stroke as risk factors.

The HAS-BLED score is the most widely used for the layering of haemorrhage risk.[11] HAS-BLED has been compared with the $HEMORR_2HAGES$ method and with ATRIA and, although, like the others, it has shown only a moderate ability to predict the risk of bleeding, it has proved the most effective in significantly predicting the risk of intracranial haemorrhage, and is also the simplest.[12] A HAS-BLED score ≥ 3 identifies patients with high risk of haemorrhage but is not a criterion for exclusion from OAT.

Tables 1 and 2 summarize the risk factors assessed in CHA_2DS_2-VASc and HAS-BLED with the relative scores.

The final decision on the type of antithrombotic treatment in AF patients must therefore balance the degree of reduction of the risk of thromboembolism against the minimization of serious haemorrhagic complications (in other words intracranial haemorrhage) associated with these therapies.

Current antithrombotic treatment recommendations

An analysis of the net clinical benefit (balancing the reduction of ischaemic and haemorrhagic events) of vitamin K antagonists was conducted on a large population of AF patients in the real world ($n = 130\ 000$) using the CHA_2DS_2-VASc and HAS-BLED scores. This study revealed a net benefit for anticoagulant therapy in patients with CHA_2DS_2-VASc ≥ 2. The effect was neutral in patients with CHA_2DS_2-VASc $= 1$, while there was no net benefit in patients with CHA_2DS_2-VASc $= 0$. Moreover, this study further confirmed the absence of benefits from aspirin alone in any risk layer.[13,14]

The most recent guidelines (2014) on the treatment of AF are those of the AHA/ACC,[15] which suggest, in AF patients with CHA_2DS_2-VASc ≥ 2, the use of warfarin with class I and level of evidence A and of NOACs with class I and level of evidence B, while the 2012 ESC guidelines[16] recommend class I with level of evidence A for both warfarin and NOACs in the same patients. In patients with CHA_2DS_2-VASc $= 1$,

Table 1 CHA_2DS_2-VASc score and incidence of stroke

Risk factors for stroke and thromboembolism in non-valvular AF	
'Major' risk factors	'Significant' risk factors
Previous stroke, TIA or systemic embolism	Cardiac insufficiency or moderate or severe systolic dysfunction (EF < 40%)
Age > 75 years	Arterial hypertension, diabetes mellitus, female gender, age 65–74 years, peripheral vascular disease
Risk factors included in the CHA_2DS_2-VASc score	
Risk factors	Score
Cardiac insufficiency/ systolic dysfunction	1
Arterial hypertension	1
Age 65–74 years.	1
Age > 75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Peripheral vascular disease	1
Female gender	1

EF, ejection fraction; TIA, transient ischaemic attack.

Table 2 HAS-BLED score

Letter	Clinical characteristics	Score
H	Hypertension	1
A	Impaired kidney or liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Old age (>65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2

INR, international normalized ratio.

the US guidelines basically advise against antithrombotic therapy (IIb, C), while the European ones are more in favour (IIa, A). All guidelines advise against any anticoagulant therapy in patients with CHA_2DS_2-VASc = 0.

Warfarin or NOACs are definitely the most widely used therapy with the highest level of evidence in the prevention of AF-related thromboembolism. NOACs, in particular, have been shown to be as effective as warfarin [in patients with international normalized ratio (INR) on target], and are associated with a lower risk of haemorrhagic events.[17]

Although OAT with warfarin has been shown to significantly reduce the incidence of AF-related stroke, a high percentage of patients with AF (~40%) do not receive appropriate prophylactic therapy.[18,19] Moreover, about 20% of patients have contraindications for OAT and a further 30–40% of patients receiving OAT are unable to maintain a TTR of ≥65%, meaning that the risk of inefficacy of the therapy is high. Furthermore, a considerable proportion of patients suspend anticoagulant treatment within 1 year.[20] In addition, although NOACs are more manageable and apparently safer than warfarin, they are still associated with a risk of haemorrhagic events (1.6–3.6% haemorrhagic events/year). Moreover, in the trials which tested these new drugs, between 20% and 35% of patients were forced to suspend administration due to the onset of side effects, and a high risk of bleeding was one of the exclusion criteria in all trials.

Specific clinical situations associated to high risk of haemorrhage

The decision with regards to any antithrombotic treatment must necessarily involve an assessment of the risk of stroke as against the risk of major bleeding, especially cerebral haemorrhage, which is the most dangerous complication, associated with a high rate of mortality and disability.[21] However, the risk of cerebral haemorrhage in AF patients receiving OAT with vitamin K antagonists is currently quite low, between 0.1% and 0.6%. The percentage of intracranial haemorrhages increases for INR values around 3.5–4.0, while there is no difference in haemorrhage risk in patients with INR between 2.0 and 3.0 compared to those with lower INR.[21]

In the general population of AF patients, there are some categories with particularly high risk of haemorrhage, specifically:

(1) elderly patients: it is known that the prevalence of AF is dramatically higher in patients with age > 75 years and that in these patients the risk of thromboembolism and haemorrhage is often much higher than in younger patients;
(2) patients with a history of major bleeding episodes, especially intracranial;
(3) patients with gastrointestinal diseases (liver diseases, angiodysplasias) or with peptic ulcer, a condition which is a significant problem for the use of NOACs, which are associated with a higher number of gastrointestinal haemorrhages than warfarin[16–18];
(4) patients with chronic renal failure, who account for about 3% of AF patients; in 90% of cases, this population of patients with kidney disease has a CHA_2DS_2-VASc >2 and has a HAS-BLED ≥ 3 in 40% of cases.[16–18] Moreover, there is no concrete proof on the efficacy-safety ratio of anticoagulants in patients undergoing dialysis or with glomerular filtration rate <30 mL/min.[22] In dialysis patients, the risk of ischaemic stroke is higher than that of the general population, even in the absence of AF,[23] as is the risk of haemorrhage.[24] Moreover, in haemodialysis patients an association has been suggested between the use of warfarin and an increase in vascular calcification[25–27];
(5) patients with coagulation disorders;
(6) patients with acute coronary diseases who have received stent implants and require prolonged dual

antiplatelet therapy (DAPT). AF may, for example, occur in 5–10% of patients with acute coronary syndrome and is associated with a significant increase in mortality.[20] In view of the fact that the vast majority of patients with acute coronary syndrome undergo coronary angioplasty with stent implant, the population of patients requiring DAPT + anticoagulant therapy (triple therapy) is presumably very large. It is known and also logical that the combination of antiplatelet agents with anticoagulants increases the risk of bleeding in the case of both warfarin and NOACs. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, the risk of major bleeding increased by 2.8% to 4.8% per year when antiplatelet agents were added to warfarin and from 2.6% to 4.4%/year with dabigatran 150 mg[18]; and

(7) patients with mental disabilities or at risk of frequent falls.

All these categories represent a large segment of patients for whom randomized trials fail to provide clear evidence with regard to the best therapeutic strategy.

Anatomy of the left atrial appendage

The LAA is an embryonic remnant of the primordial left atrium, a small offshoot opening off the side wall of the atrium, with variable, elongated, trabecular, often multilobed shape. The appendage's orifice on the atrial cavity is oval in form and is located between the left upper pulmonary vein, from which it is separated by the fibrous ligament of Marshall, and the mitral valve. On the outside the LAA extends antero-laterally parallel with the left atrioventricular sulcus, just above the proximal part of the circumflex artery. On the inside, the distal part is trabecular, with the distinctive uneven surface of the endocardium, while the proximal end has a smooth surface. It varies in length (16–51 mm), volume (0.7–19.2 mL) and orifice diameter (5–40 mm).[28]

The LAA consists of a main body onto which one or more lobes may be attached and its variable in both shape and size. The study performed by Di Biase *et al.*,[29] using computed tomography and magnetic resonance, gathered information about the morphology of the LAA and also correlated the various forms with risk of ischaemic stroke/transient ischaemic attack (TIA). Four main forms emerged: Cactus (30%), Chicken Wing (48%), Windsock (19%), and Cauliflower (3%). The correlation with thromboembolic events revealed a diverse, significant ($P < 0.001$) distribution, of 12, 4, 10, and 18%, respectively, in patients with Cactus, Chicken Wing, Windsock, and Cauliflower morphology. The Chicken Wing morphology showed a significantly lower prevalence of events compared with the other morphologies; in particular, patients with Cactus morphology showed a risk of cerebral ischaemic events 4 times higher, those with Windsock morphology 4.5 times higher and those with Cauliflower morphology 8 times higher than patients with Chicken Wing morphology.

Surgical closure (occlusion) of the left atrial appendage

Surgical closure of the LAA has been proposed since the '40s as prophylaxis for thromboembolism in patients with mitral valve disease.[30-32] Even then, the observation that in this condition about 50% of thrombi were located in the LAA pointed to its occlusion as prophylaxis for the risk of stroke.[33] During the same period, Belcher and Somerville[32] noted that after mitral surgery LAA thrombosis occurred in 64% of patients who experienced embolic events. In the '80s, further to the findings of a review of the mitral commissurotomy procedure, Halseth *et al.*[34] suggested that surgical occlusion was only indicated in cases of large-sized LAA.

In modern times, LAA amputation has been reintroduced as an integral part of the surgical procedure for AF ablation, initially proposed by Cox[35] in the '90s and still performed with various technologies.

The history of the surgical treatment of the LAA originated in 1949, when Madden[31] performed a complete amputation of the LAA on 2 patients with rheumatic mitral disease. An analysis of the literature only reveals 7 studies with detailed assessments (*Table 3*).[36-43] These 7 studies recruited a total of 3653 patients with an LAA occlusion group (LAAO) (1716 patients) compared to a non LAAO group (1937 patients). In three works,[37,39,42] the main operation was mitral valve surgery, in one[39] it was coronary surgery and in the other three[40,41,43] there was a mix of aortocoronary bypass and valve procedures. Four studies used surgical sutures for the LAAO[37,38,41,42] while in two the LAA was amputated with a Stapler.[38,43]

Results

The incidence of stroke was significantly reduced in patients who underwent LAAO. Mortality was significantly lower in the LAAO group. No significant differences were identified between the two groups with regards to periprocedural bleeding requiring reoperation.

The Left Atrial Appendage Occlusion Study (LAAOS)[38] is the first randomized trial to assess the feasibility, safety, and efficacy of LAAO during elective coronary surgery using surgical sutures or automatic staplers. The study, conducted in Germany during 2001–2002, considers 52 patients who underwent LAAO vs. 25 non-LAAO patients. Occlusion was found to be effective in 66% of patients and it was even more so when the surgeon performed a complete amputation of the LAA rather than simply suturing it; the studies analysed reveal the uncertainty concerning the efficacy of surgical suturing in LAAO.

Echocardiogram assessment

Imaging plays a fundamental role in both the pre- and the intraprocedural phase, and in the follow-up.[44] The LAA can occasionally be viewed by transthoracic echocardiography, but the transoesophageal method (TEE), sometimes with three-dimensional assessment, is always necessary.

TEE plays a fundamental role in the pre-procedural assessment, to confirm that the LAA is free from thrombi; any thrombi must be carefully considered to ensure that

Table 3 Studies in the literature which assessed surgical treatment of the left atrial appendage

Author	Period	Type of study	Number of LAA	Number of non-LAA	LAA occlusion method
Lee *et al.*[39]	1999–2011	Propensity-score matched	119	119	LAA amputation during crio-Maze
Whitlock *et al.*[43]	2009–2010	Miscellaneous	26	25	Amputation and stapler
Kim *et al.*[40]	2001–2010	Propensity-score matched	631	631	Amputation or closure of LAA
Zapolanski *et al.*[41]	2005–2012	Observational	808	969	Double ligature with suture
Nagpal *et al.*[37]	2007	RCT	22	21	Amputation, suture
Healey *et al.*[38]	2001–2002	RCT	52	25	Suture or stapler
Garcia-Fernandez *et al.*[42]	1996–2001	Observational	58	147	Ligature of LAA with endocardial suture

LAA, left atrial appendage; RCT, randomized controlled trial.

the procedure is safe and free from complications. It also allows the acquisition of additional information concerning the size, shape and position of the LAA. At the end of the surgical procedure, TEE is fundamental for defining the positioning of the device and the achievement of LAAO, by checking for any leaks. During follow-up, TEE is the most accurate assessment method for the description of any leaks or thrombosis.

TEE is the gold standard for confirming the failure of LAAO; in this case the patient continues to be exposed to the risk of thromboembolism, with an increased risk of stroke.[45,46] In fact, incomplete occlusion of the LAA has been reported in up to over 50% of cases, with thrombi recorded in up to more than 25% of these patients.[46] Furthermore, thromboembolic events have been reported in up to 22% of these cases.[47]

A variety of surgical techniques are currently used in LAAO: surgical removal, surgical suture, and more recently the application of specific devices (Tiger Paw and Atriclip).

Surgical removal of the LAA generally involves tangential clamping as close as possible to the orifice. It is then removed and the orifice is sealed with a double surgical suture. Since the LAA is an extremely fragile structure, this technique may lead to tearing at its orifice, with bleeding and difficulties in achieving haemostasis. This technique is therefore not widely used, although in the literature no increase in morbidity arising from the surgical operation is described.[38]

Occlusion of the LAA by means of surgical suture is currently the most commonly used technique. Especially during mitral valve surgery, it is a simple, quick procedure with no complications. The surgical suture can be created with a tobacco-pouch shape around the orifice, or by means of two seams at its point of origin. During the last few years, the data in the literature indicate that the use of dedicated devices has been introduced. The devices currently available remain epicardial and therefore are not fitted into the cavity, and they potentially have a low incidence of thrombosis, infections and embolization.[43]

The Tiger Paw System II (Maquet Cardiovascular, Mahwah, NJ, USA) is currently not available on the market because of a suspicion that it may apply traction to the atrial tissues. The Atriclip LAA Occlusion System device (Atricure, Inc, West Chester, OH, USA) allows easy, safe LAAO. It has been approved by the Food and Drug Administration since 2009 and consists of a convenient handle with the device at one end; the latter comprises a self-clamping clip consisting of two parallel crossbars in titanium with etinol, with a polyester cladding; during the operation the system can be positioned several times prior to deployment, and it comes in different sizes for selection in relation to the dimensions of the orifice of the LAA. It is a simple, safe procedure with minimal complications and allows complete occlusion of the LAA. It is an epicardial and therefore not an intracavitary device, usable for all the various shapes and sizes of LAA, and it allows anatomical and electric LAAO with short procedural times. This device is currently used in a large number of patients who undergo mini-invasive surgery or mini-invasive surgical treatment for AF.

Indications for surgical occlusion of the left atrial appendage

The ESC guidelines maintain that there is no conclusive evidence concerning the efficacy of LAAO or the best techniques for its performance and provide a recommendation of IIB, evidence level C, only for patients who are to undergo cardiac surgery.[17] Nor have the recent AHA/ACC guidelines[16] on the management of AF arrived at a clear consensus on this procedure, and they confirm this recommendation with the same level of evidence.

The panel agrees with these recommendations and maintains that every candidate must be discussed by the Heart Team. Potential candidates may be:

(1) patients with high thromboembolic risk with permanent, persistent or paroxystic AF undergoing concomitant cardiac surgery, possibly in association with surgical ablation of the AF and
(2) patients with high-thromboembolic risk undergoing mini-invasive surgery (mini-thoracotomy) or a sternotomy surgical procedure for AF.

Requirements for staff and centres

In-depth knowledge of cardiac anatomy, especially of the left atrium, the LAA, and the surrounding structures, is essential for staff performing LAAO. Staff must have in-depth knowledge of the anatomical variables of the LAA in terms of size, angles and mobility. The procedure's success and safety depend to a large extent on the knowledge and

experience of every member of the team, including the echocardiographer.

Specific, properly organized training is necessary for every staff member, including the echocardiographer. The training must include basic principles and study of the characteristics of the device and the procedure. It must comprise a short course on anatomy, clinical procedures and device implantation techniques and the analysis of critical factors such as patient and device selection and the possible complications and their prevention and management, as well as a practical part and the use of simulators on virtual cases. The nurses and technicians on the team must also receive training. During the first few procedures, a surgeon with documented experience in use of the device must be present.[44]

Percutaneous occlusion of the left atrial appendage

Left atrial appendage occlusion devices currently available

There are currently four endocardial devices with CE marking available for percutaneous occlusion of the LAA: the Watchman (Boston Scientific, Maple Grove, MN, USA), the Amplatzer Cardiac Plug and Amulet (St. Jude Medical, Minneapolis, MN, USA), the WaveCrest (Coherex Medical, Salt Lake City, UT, USA) and the Lariat (SentreHEART, Inc., Palo Alto, CA, USA), which has a combined endocardial/epicardial percutaneous access.

The Watchman is a self-expandable device with a basket-like structure in nitinol clad with a polyethylene membrane covering the exposed surface in the left atrium; it has hooks around its external perimeter which anchor it to the walls of the LAA. The device is available in various sizes (21, 24, 27, 30, and 33 mm) and is deployed with the aid of a delivery catheter of 14 Fr which may have one or two bends at its distal end for easier approach to the LAA. The device's length is equal to its diameter (*Figure 1*).

As of today, clinical studies conducted with the Watchman medical device have included more than 2400 patients with more than 6000 patient years of follow-up. The most important clinical studies supporting the efficacy and safety of this device are the Watchman Left Atrial System for Embolic Protection in Patients With Atrial Fibrillation (PROTECT AF)[48–50] and Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL)[51] randomized studies. In the PROTECT AF randomized study, Holmes *et al.*[48] compared implantation of the Watchman with conventional pharmacological treatment with warfarin in 707 patients with non-valvular AF and $CHADS_2$ score ≥ 1. The device was successfully implanted in 90.9% of the patients who underwent the procedure and the administration of warfarin was stopped in 87% of them 45 days later. The primary endpoint for efficacy was defined as the composite of stroke, cardiovascular or unexplained death, and systemic embolism. The rate of events recorded for effectiveness was 3.0 per 100 patient years in the Watchman group compared to 4.9 per 100 patient years in the warfarin group; this 38% reduction is

Figure 1 Watchman Device (Boston Scientific).

equivalent to a non-inferiority of the Watchman in relation to warfarin. However, ischaemic stroke was more frequent in the group treated with the Watchman than in the control group due to five pre-procedural events linked to gaseous embolism. Excluding these events, the incidence of ischaemic stroke was not substantially different between the two groups (1.3%/year in the successfully implanted group compared to 1.6%/year in the control group). The primary endpoint for safety, on the other hand, was defined as a composite of major bleeding and complications correlated to the procedure. The rate of these adverse events was 7.4 per 100 patient years in the Watchman group compared to 4.4 per 100 patient years in the warfarin group. The complications which occurred in the patients treated with the Watchman were: cardiac tamponade (5%), major haemorrhages (3.5%), pericardial effusions (1.7%), periprocedural stroke (1%) mainly arising from gaseous embolism, embolization of the device (0.6%), which in most cases (67%) made surgical removal necessary, and the induction of arrhythmias (0.2%). In total, 2.2% of attempts to implant the device led to cardiac surgery to deal with complications correlated to it. Most of these events occurred in the periprocedural period (55% of adverse events relate to the day of implantation) and pericardial effusion was the most common event (7.1% of the first 3 patients at each centre and 4.4% of subsequent patients); none of these events caused permanent disability or death. In fact, it should be emphasized that the adverse events correlated to the procedure decreased as the staff's experience grew. In particular, pericardial effusions, which accounted for about 50% of adverse events recorded in the PROTECT AF study, decreased significantly in the subsequent CAP registry as the operators' experience increased (5 vs. 2.2%, $P = 0.019$), as did periprocedural strokes (0.9 vs. 0%; $P = 0.039$).[48,49]

The PREVAIL study enrolled 407 patients with the aim of comparing the Watchman device with warfarin patients with AF at high risk of thromboembolism (average $CHADS_2$ score of 2.6) and eligible for long-term therapy with warfarin. The implantation success rate was 95.1%, a higher value than reported in the previous PROTECT AF randomized study (90.9%). In this study, LAAO with the Watchman proved to be not inferior to warfarin in the prevention of ischaemic stroke or peripheral embolism 1 week after the procedure. Although statistical non-inferiority

was not achieved for the total efficacy of the procedure, including periprocedural events, it should be kept in mind that the incidence of these events was low and similar in the two arms of the study.

With regards to adverse events correlated to the procedure (within 7 days), an event was reported in 2.2% of implanted patients. Major complications correlated to the device or the procedure within 7 days of implantation occurred in 4.4% of patients compared to the 8.7% of the PROTECT AF study, meaning a 49% reduction. Pericardial effusion occurred in 1.9% of patients compared to 4.0% in PROTECT AF, and thus with a reduction of 52%. It is important to underline that the results of the PREVAIL study revealed very low-complication rates amongst both clinicians who were performing their first implantations and more skilled clinicians. The data relating to the use of this device in patients with contraindications for OAT are rather limited. Specifically, in the ASAP study[52] LAAO was performed in 150 patients: the rate of cerebral ischaemic events observed was 2.3%/year, meaning a risk reduction calculated as 77% in a population of patients with an expected rate of events per year of 7.3%.

A meta-study including 2406 patients recruited to PROTECT AF, PREVAIL, and the respective registries has recently been published.[53] Compared to warfarin therapy, percutaneous occlusion of the LAA was associated with a significant reduction of haemorrhagic stroke [0.15 vs. 0.96 events/100 patient years, hazard ratio (HR) 0.22, $P = 0.004$], cardiovascular or undefined mortality (1.1 vs. 2.3 events/patient year, HR 0.48, $P = 0.006$) and non-procedural bleeding (6 vs. 11.3 events/100 patient years, HR 0.51, $P = 0.006$).[53]

The Amplatzer Cardiac Plug (ACP) is a self-expanding nitinol device, clad completely in polyester, in three parts: a nitinol cylinder, called the lobe, at the tip, used to anchor the device inside the LAA, a larger disc below it which covers and blocks the orifice of the LAA, and a very short wire in the middle connecting the lobe and disc (*Figure 2*).

There are anchor hooks around the edge of the lobe. The lobe sizes available are 16, 18, 20, 22, 24, 26, 28, and 30 mm, while the disc is 4 mm larger for the sizes from 16 to 22 m and 6 mm larger for the 24 to 30 mm sizes. The lobe's length is much less than its diameter, making it preferable for particularly shallow LAAs. The only data available for the ACP are provided by feasibility reports covering only small patient populations. A retrospective registry study on a population of 137 patients in which an attempt at occluding the LAA with ACP was performed[54] show that the procedure was successful in 96% of cases; major intraprocedural complications were observed in 7% of cases (3 ictus, 2 device embolizations, and 5 cardiac tamponades). The percentage rose if minor complications, including four negligible pericardial effusions and transient myocardial ischaemia caused by gaseous embolism, were also considered. In another study conducted on 20 patients, the ACP was successfully implanted in 95% of cases with 2 periprocedural complications (one transient myocardial ischaemia caused by gaseous embolism and one oesophageal lesion due to the TEE). In this study, no adverse events such as stroke or death were observed during a follow-up of 12.7 ± 3.1 months, compared to a theoretical risk of ischaemic events of 5.3%.[55]

Figure 2 Amplatzer Cardiac Plug (St. Jude Medical).

The first Italian registry study, including a population of 134 patients with high-cardioembolic risk (average CHA_2DS_2-VASc 4.3 ± 1.3) with contraindication to the administration of anticoagulant therapy) was published in 2014. The authors report a high-procedural success rate (95.5%) and a low rate of major complications (2.2%). In the follow-up, a reduction in cerebral ischaemic events of 85.5% compared to the risk predicted by the scores was described.[56] Recently, Tzikas *et al.*[57] published the data of a multicentric registry study which describes, on a total of 1047 patients, a procedural success rate of 97.3%, and an incidence of procedural complications of 5%, with a 59% reduction in embolic events and a 60% decrease in haemorrhagic events calculated in relation to the CHA_2DS_2-VASc and HAS-BLED scores.

Another registry study, performed on the Iberian Peninsula, collected the data of 167 patients with contraindication for OAT and indicated a procedural success rate of 94.6% with an incidence of procedure-related complications of 5.38%. The incidence of embolic events was lower than that predicted by the CHA_2DS_2-VASc score (2.4 vs. 8.3%), and the incidence of haemorrhagic events was also below the prediction provided by the HAS-BLED score (3.1 vs. 6.6%).[58]

The latest version of this device is the Amulet, which has the same three-part structure as the ACP but a wider range of sizes (16, 18, 20, 22, 25, 28, 31, and 34 mm), allowing the treatment of a wider spectrum of anatomies, a longer lobe with more anchor hooks, a longer central wire and a screw fitting for the disc, which has been retracted to create a uniform surface (*Figure 3*).

The WaveCrest, not currently available on the market, is a self-expanding device in nitinol with a polytetrafluoroethylene coating on the surface which remains exposed in the left atrium; it has anchor hooks around its circumference, which engage with the walls of the left atrium appendage. This device is designed to be positioned close to the orifice of the left atrium appendage, with no need to penetrate deep down with the deployment system (*Figure 4*).

At present, data from feasibility and safety trials[59] are available, but there are no major clinical studies.

Figure 3 Amulet Device (St. Jude Medical).

Figure 4 WaveCrest Device (Coherex Medical).

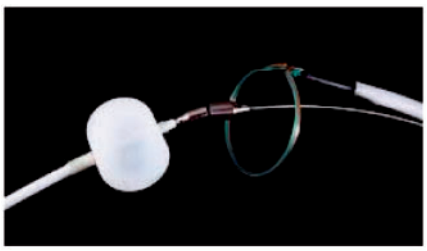

Figure 5 Lariat (SentreHEART) system with its three components.

The Lariat, not currently available in Italy, is an occlusion system with a combined approach consisting of three components: a balloon, a guide wire with magnetic tip and a loop suture wire which will be closed on the orifice of the LAA (*Figure 5*).

The system requires the collimation of two magnets at the tips of the first two components (used with percutaneous and epicardial approach), which form a single body that serves as guide for the third component, the lariat, positioned with epicardial approach to occlude the orifice of the LAA. The benefit of this procedure is that once it has been performed nothing prosthetic is left inside the left atrium, and therefore no anticoagulant or antiplatelet therapy is required. However, the only studies performed on this device so far are feasibility studies on small populations of patients.

Figure 6 Watchman FLX Device (Boston Scientific).

Figure 7 Lariat (SentreHEART) system with its three components.

The results of a study on LAAO on 89 patients using this device revealed that the LAA was completely occluded in 91% of cases with 3 acute complications (2 during pericardial access and 1 during transseptal catheterization). After the procedure 2 cases of pericarditis, 1 delayed pericardial effusion, 2 sudden deaths from undetermined causes, and 2 strokes considered not to be of cardioembolic origin were observed.[60]

Devices currently under development

The Watchman FLX device, (Boston Scientific) a development on the Watchman device already described, will apparently soon be available. It differs from the previous version in shorter length, the presence of a fluoroscopic marker on the distal tip, the possibility of recapture and redeployment, a larger range of sizes (20, 24, 27, 31, and 35 mm) allowing treatment of a wider range of anatomies, a larger number of perimeter anchors arranged in two rows and retraction of the device's screw connection, to create a flat surface on the atrial side (*Figure 6*).

The Transcatheter Patch (Custom Medical Devices, Athens, Greece) is a device consisting of a polyurethane patch with an adhesive band at the distal end which is carried into the LAA by a balloon; the proximal side of the patch is tightened with a loop, and is then released once the balloon has been deflated and the insertion catheter has been withdrawn (*Figure 7*).

This device is currently undergoing clinical assessment.

Lifetech (Lambre™, Lifetech Scientific Corp., Shenzhen, China) is a self-expanding nitinol device

consisting of three parts: a disc and an umbrella, connected by a very short central component. This device is undergoing preclinical assessment.

Cost-effectiveness studies

A number of cost-effectiveness studies have been performed in different social and health-care contexts. An analysis of the German health system, which compared costs and outcomes in terms of mortality of the LAAO procedure compared to warfarin and dabigatran, reveals long-term medical and financial benefits in favour of LAAO. In fact, after 8 years LAAO is less expensive than dabigatran (€15,061 vs. €16,184) and at 10 years it only costs 10% more than warfarin (€16,736 vs. €15,168). The assumption is therefore that LAAO may be financially beneficial for the health system over the long term.[61]

Another study, based on costs and the years of quality-adjusted life (QALY) gained by percutaneous occlusion of the LAA compared to warfarin and dabigatran therapy, reveals that the cost per QALY of medical therapy is $46 560, while for this device this value is $41 565 over a lifetime period.[62]

From the point of view of the Italian National Health Service, the comparison between LAAO and treatment with a single antiplatelet drug or no drug in patients with contraindications for OAT is in favour of occlusion of the LAA with a benefit which comes into effect at 3 years, due to the increase in the cost of stroke-related disability in patients treated with antiplatelet medication.[63]

A comparison between the costs of treatment with the Watchman and with the NOAC drugs by the United Kingdom Department of Health also found in favour of LAAO in patients with high risk of embolism with contraindications for OAT: an investigation of the cost of 10 patients reveals that the cost of the device (€49 300) is recouped within 3 years, considering that the cost per annum of the untreated patients would amount to €14 600 (1 stroke prevented per year for every 10 patients).[64]

The cost-effectiveness studies therefore reveal the potential benefit of LAAO compared to anticoagulant therapy in the long term. This benefit apparently also occurs in the short-medium term for populations with high risk of embolism and haemorrhage.

Indications for left atrial appendage occlusion

According to the current indications for percutaneous LAAO, which reflect the ESC guidelines,[17] the procedure is indicated (recommendation class IIb, level of evidence B) in patients with non-valvular AF with high-thromboembolic risk (CHA_2DS_2-VASc score ≥ 2) with long-term contraindication for OAT (e.g. history of intracranial bleeding, life-threatening bleeding, coagulation diseases).

The recent EHRA/EAPCI[44] consensus suggests that the spectrum of patients who could benefit from this technique should be extended (*Table 4*). Moreover, this therapy could also be considered in the following clinical situations:

Table 4 Left atrial appendage occlusion: possible clinical situations

As an alternative to OAT in patients intolerant of OAT
Patients with high risk of stroke and high risk of haemorrhage
Patients with thromboembolic events during OAT in the therapeutic range or during treatment with NOACs (when no other origin of the bleeding can be identified)
Patients who can be treated with oral anticoagulants but may have indication for left atrial appendage occlusion

NOACs, new oral anticoagulants; OAT, oral anticoagulant therapy.

- patients with non-valvular AF with high-thromboembolic risk and high-haemorrhagic risk (HAS-BLED ≥ 3);
- patients requiring triple antithrombotic therapy indefinitely;
- patients with tumours with increased risk of haemorrhage, underestimated by the HAS-BLED score;
- patients in whom OAT is ineffective in providing protection against cerebral ischaemic events probably correlated to thromboembolisms originating from the LAA;
- patients with kidney failure or undergoing dialysis, bearing in mind that all NOACs are contraindicated with creatinine clearance < 15 mL/min and that in these patients warfarin could increase tissue calcification and the degree of atherosclerosis;
- patients with major bleeding of the urogenital or gastrointestinal system, or any other districts, such as the ocular area;
- frail patients (the very old, dementia, neurodegenerative diseases, malnutrition, etc.);
- patients with difficulty in managing oral therapies (e.g. mental illnesses, vision impairment); and
- patients who, after being suitably informed about the OAT/NOACs therapy, refuse it and demand a 'definitive' therapy. In this context, it should be underlined that the Watchman has had approval by the US regulatory authority as a valid alternative to warfarin in patients who refuse or prefer not to take OAT.

The decision must therefore be made in the context of the doctor–patient relationship, after appropriate information about all the benefits and drawbacks related to the percutaneous LAAO procedure or the alternative OAT/NOACs therapies (*Figure 8*). It should however be underlined that at present there is no evidence on this question and additional clinical studies are required to assess the usefulness of LAAO in these clinical situations before the indications for this type of treatment are extended to the aforesaid groups of patients.

Screening of patients who are possible candidates for left atrial appendage occlusion

Screening must be carried out in the context of discussion and choice of a strategy in agreement with the patient, giving due consideration to personal preferences and health

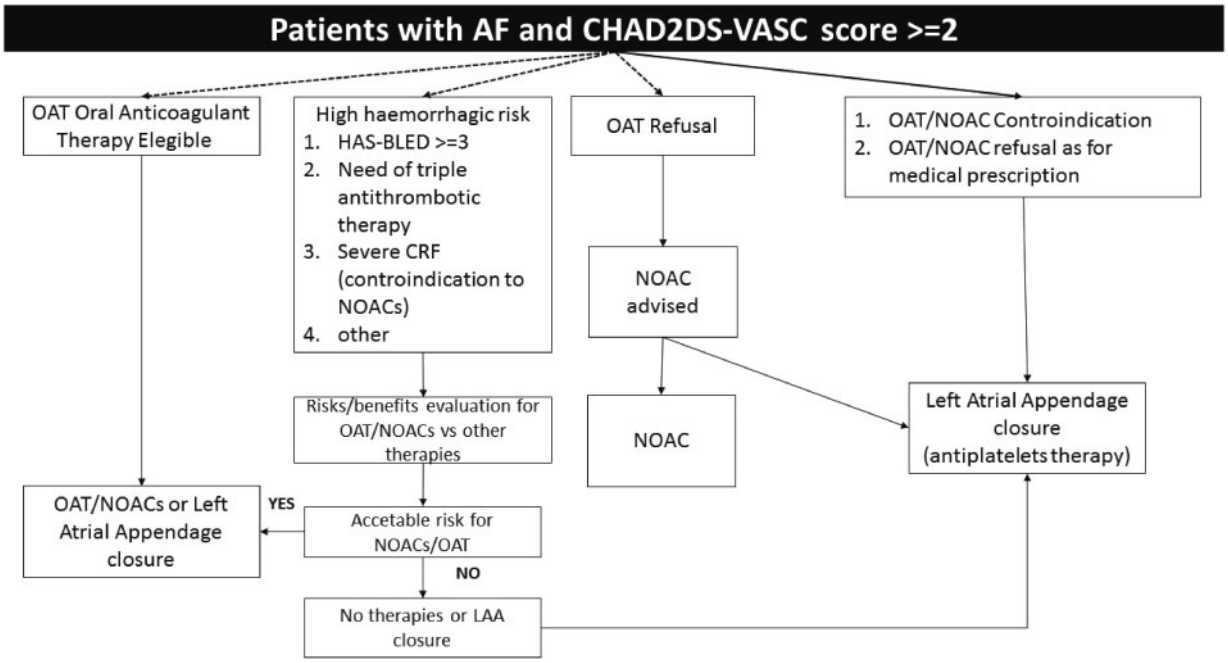

Figure 8 Algorithm for stroke prevention in patients with atrial fibrillation. CRF, chronic renal failure; NOACs, new oral anticoagulants, OAT, oral anticoagulant therapy. Adapted from Meier *et al.*[44]

expectations[65] and avoiding superfluous tests or investigations.

Screening must aim to establish the individual risk/benefit profile and in particular the ratio between embolic and haemorrhagic risk and its progression over time, and include the anatomical characteristics of the LAA in order to allow planning of the most important procedural aspects.

As has been shown to be the case in cardiac surgery, with large benefits for outcomes,[66] screening must be disciplinary and preferably use local protocols which clearly identify the role of each player within the team, and ensure strong interaction between its members and the patient.[67] Assessment of the patient's preferences and health and quality of life factors must include clear, appropriate methods for their formal expression.[68]

Table 5 summarizes the main factors to be considered in this phase of the diagnostic and therapeutic process. From the anatomical point of view, in-depth echocardiogram examination is required. An anatomical assessment of the LAA with computed tomography or magnetic resonance can be useful if echocardiography is not definitive.

Echocardiogram assessment and echocardiogram anatomy of the left atrial appendage

TEE is the method of choice for the anatomical and functional assessment of the LAA. Three-dimensional echocardiography may be useful although not essential for a correct assessment.

When assessing thrombotic risk, it is important to consider both anatomical and functional aspects in order to assign a specific LAA-related risk within the overall cardiac and systemic thrombotic risk. As already described, the LAA often has several lobes and its contractility is the main determinant of its blood outflow.[69] In the context of AF, it has been shown that a LAA outflow rate $>$ 40 cm/s is correlated, after cardioversion of the arrhythmia, with a reduction in spontaneous echo contrast.[70] A high level of spontaneous echo contrast correlates with endo-LAA flow rates $<$ 40 cm/s and the formation of sludge in the LAA (a pre-thrombotic condition).

The main data on the linear average measurements relating to this anatomical structure are derived from autopsy investigations, which have also revealed a correlation with age and gender. More recently, a study of LAA volumes has been conducted using multilayer computer tomography, reaching the conclusion that there are no gender-related differences although there are differences linked to age-band (larger at 60–70 years than at 40–59 years).[71,72] TEE allows calculation of the main planimetric parameters (transverse and longitudinal dimensions and area) which allow correct planning of the occlusion procedure (*Table 6*).

'Step by step' procedure

There are now a large number of publications which offer a detailed description of the LAAO procedure.[45] Below, we list some suggestions to be considered useful for standardising the procedure as far as possible, in order to render outcomes reproducible and reduce complications.

Choice of anaesthesia

Although the procedure can be performed both under general anaesthesia and in analgosedation, the former option appears to be advisable. On the one hand, the need for transoesophageal monitoring requires prolonged collaboration from patients, who often have difficulty in tolerating the presence of the oesophageal probe. On the other hand,

Table 5 Screening factors

Thromboembolic risk score
Haemorrhage risk score
Age
Patient's preference and health expectations
Diagnosis of diabetes mellitus
Arterial pressure assessment
Kidney function assessment
Cardiac function assessment, NYHA class
Carotid and/or aortic vascular assessment
Liver and gastrointestinal diseases (angiodysplasia, peptic ulcer)
Assessment of coagulative factor and haemorrhagic diathesis
Assessment of contraindications for coagulants
Assessment of multi-drug interaction
Assessment of therapeutic compliance and frailty
Assessment of psychiatric diseases (dementia, alcoholism)
Colour-Doppler transthoracic echocardiogram
Colour-Doppler transoesophageal echocardiogram
Cardiac angio-CT or angio-MR

CT, computed tomography; MR, magnetic resonance; NYHA, New York Heart Association.

Table 6 Main echocardiographic parameters to be obtained

Dimensions of LAA and atrium
Shape of LAA
Flow rates within LAA
Relations with mitral isthmus and annulus
Presence/absence of structural defects of the atrium (patent foramen ovale, interatrial septum aneurysm, atrial or LAA thrombosis, spontaneous echo contrast)
Left ventricle functions and dimensions
Mitral valve function
Presence/absence of pericardial effusion

LAA, left atrial appendage.

general anaesthesia allows the patient's complete immobility to be guaranteed, preventing small, involuntary movements which may increase the risk of mechanical complications, especially during the transseptal puncture or during manipulation of the deployment system inside the LAA. Although the possibility of performing the procedure under local anaesthetic with intracardiac echocardiographic guidance is intriguing, sufficient data are not available for this approach to be recommended. In fact, although transseptal puncture under intracardiac echocardiography is feasible, it currently appears difficult to establish the size of the device and assess its positioning without the use of TEE.

Choice of vascular access

The access of choice is the right femoral vein, which simplifies the manipulation of the materials and gives more safer transseptal puncture; the literature describes performance of the procedure through a puncture in the left femoral vein,[73] but this access should only be used in patients where the right access is impracticable (severely twisted vessel, previous vascular access, large arteriovenous fistula, etc.). Here again, in-depth knowledge of the materials and specific experience in the management of the possible vascular complications are important.

Transseptal puncture

This is one of the most delicate phases of the procedure. Although for a skilled electrophysiologist or haemodynamics specialist performance of the transseptal puncture with fluoroscopic monitoring only (with or without aids such as a coronary catheter) is not a specific problem, the use of echocardiographic guidance for the puncture is strongly recommended in order to obtain a better angle of approach to the LAA. A puncture low down to the rear exposes the LAA with the ideal angle for existing deployment systems (*Figure 9*). Passage of the interatrial septum through the patency of the foramen ovale offers an angle which is less than ideal, which may render the subsequent procedure more problematical and less safe.

Intraprocedural antithrombotic therapy

Although the literature describes cases of LAAO performed during therapy with warfarin in the therapeutic range, in order to minimize the risks all anticoagulant therapy should have been suspended at least 48 h prior to the procedure, and the INR value should be <2. Once the transseptal puncture has been performed, antithrombotic therapy must be administered: non fractionated heparin (dosage 70–100 U/kg to obtain an activated coagulation time of 250–300 s) is the first choice. In our opinion, the dwell time in the left atrium should be minimized in order to reduce the risk of embolism. In the event that the TEE reveals thrombosis on the deployment system, we advise manual aspiration of the thrombus through the catheter, associated with the administration of heparin; if this strategy fails, the procedure should be interrupted.

Insertion of the deployment system into the left atrium

There are two possible approaches:

a. the deployment system delivery catheter is exchanged over a stiff guidewire which is placed in the left upper pulmonary vein and then manoeuvred, containing a pigtail catheter through which the angiography of the LAA will also be performed. If this approach is chosen when using the ACP-Amulet system, a longer pigtail catheter (125 cm) will be needed. It should be emphasized that with this procedure the system can be manoeuvred with greater safety and the risk of iatrogenic damage when the delivery catheter is moved into the LAA is reduced and
b. the alternative method is to use the pigtail for the angiography and then exchange it for the deployment system delivery catheter on a rigid guide positioned in the LAA (this 'saves' one exchange but increases the risks of tearing of the wall of the LAA).

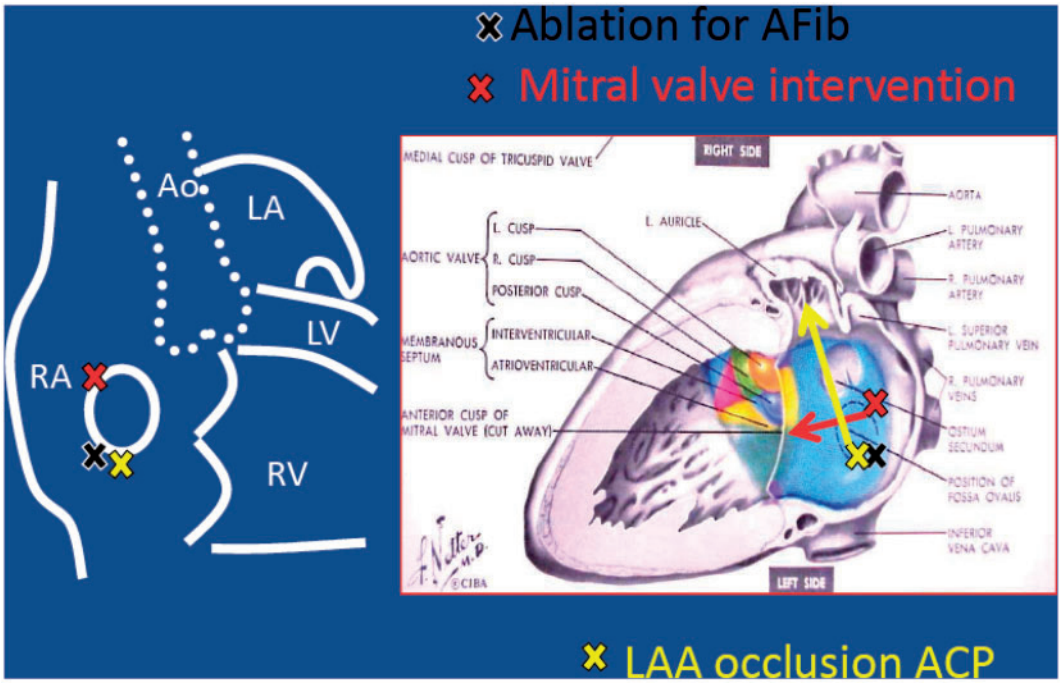

Figure 9 View of the fossa ovalis and the preferred points for the puncture for LAA occlusion. ACP, Amplatzer Cardiac Plug; AF, atrial fibrillation; Ao, aorta; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; RA, right atrium; RV, right ventricle.

Choice of device

A number of devices have been developed and placed on the market. However, in clinical practice the devices currently available are the Watchman (Boston Scientific) and the New Amulet (St. Jude). The Lariat device is used for combined endocardial-epicardial ligature of the LAA and will not be discussed here. The scientific findings supporting the use of the devices were discussed in the previous section; here, we will simply detail the devices' specific technical features. It should be underlined that both the devices available on the market are completely repositionable and recapturable in the event of imperfect deployment or if the chosen size is not suitable.

The Watchman device is inserted by means of a preformed deployment system (single or double bend) of 14 Fr. For optimal sealing, it is recommended that the device chosen should be oversized by 10–20% (it is available in sizes from 21 to 33 mm). A higher device oversizing percentage appears to offer better leak reduction but could be more risky. The new generation of the device, which will probably be on the market from 2016, will provide better sealing even without oversizing, thanks to an increase in the number of anchor hooks and a shallower profile. For the current generation of the device, the depth of the LAA must be similar to the diameter to allow safe deployment. In the Panel's experience this characteristic, which is apparently the device's biggest drawback, has never prevented safe implantation, probably because several studies[74] have shown that as AF persists, LAA increase in size, generally with the same rate of expansion in their diameter and depth. However, if in doubt it is important to use the radiopaque markers provided on the deployment system which easily reveal the minimum device deployment depth.

The New Amulet occlusion device (the evolution of the Amplatzer ACP system, now more or less replaced on the market by the New Amulet) has an unusual structure which enables it to adapt to virtually any LAA morphology. This device is able to occlude all LAAs between 11 and 31 mm and is inserted in a deployment system with 9–14 Fr delivery catheters (depending on the size of the device). It should be remembered that while the delivery catheters of the ACP were available in diameters 9, 10, and 13 Fr, those of the Amulet are in sizes 12 or 14 Fr.

Preparation of the system and device

After the device and size have been chosen, the implantation system and device must be prepared. Experience has shown that through flushing of the catheter and device is essential to minimize the risk of air embolization during implantation.

Implantation of the device

Once the deployment system is in an appropriate positon, it is withdrawn, enabling the device to open. In this phase, small movements are sometimes required to adjust the device's positon, turning, pushing, or pulling to correct the angle of access to the LAA, which is not always optimal in spite of careful planning of the transseptal puncture. Once the device is open, a combined check is performed by angiography (the electrical projections are the right cranial and right caudal arteries) and echocardiography, to check stability (shape and compression) and efficacy (presence of leaks). This is followed by a tug test on the deployment wire.

Deployment of the device

Once the result is considered satisfactory, the device can be deployed by turning the deployment wire anticlockwise. At the end of the procedure, an additional echocardiographic check is required to ensure that the device is correctly positioned and that there are no pericardial effusions (which may occur at any phase of the implantation process). The system is then removed and local haemostasis is performed (manual compression or figure-of-8 suture). The decision as to whether to administer protamine sulphate will depend on the assessment of its clinical utility as appropriate to the individual patient.

Management of antithrombotic therapy after the procedure

After the procedure, antithrombotic therapy is recommended to prevent the formation of thrombi on the device until its complete endothelialization. The current management protocol is the outcome of the PROTECT AF,[48] PREVAIL,[51] and ASAP[52] studies based on the Watchman device and experience gained from use of the Amplatzer PFO Occluder device.

For the Watchman device, the antithrombotic protocol of the PROTECT AF trial involved the suspension of warfarin 45 days after the procedure and its replacement with dual antiplatelet therapy if the TEE revealed the absence of thrombi or a residual leak $<$ 5 mm; the second antiplatelet medication was suspended after 6 months if the follow-up TEE did not show significant periprosthetic leaks around the device. The PREVAIL trial and the ASAP study revealed the feasibility of DAPT as an alternative to therapy with warfarin after implantation of the Watchman device.

Observational studies assessed DAPT for 1 month after implantation of the ACP device and single antiplatelet therapy for the next 3–6 months, in accordance with the antithrombotic therapy protocol acquired from experience with the Amplatzer PFO Occluder.[75]

In all these various therapeutic approaches, single antiplatelet therapy is indicated *quoad vitam*.

DAPT with aspirin and clopidogrel can be suggested with the execution of TEE at 3 months or even earlier in the event of significant post-procedural leaks ($\geq$5 mm). If there are no complications of any kind, the second antiplatelet therapy could be suspended after this period and an echocardiogram (by the transoesophageal approach) repeated after about 1 year. However, widely varying protocols are found in the records of the largest centres for patients with high and very high risk of haemorrhage, with the use of low molecular weight heparin therapy for a period ranging from a few days to some weeks, the use of a single antiplatelet therapy or, in specific cases, no antithrombotic therapy.

The incomplete occlusion of the LAA is another topic open to discussion. In theory, this could create pockets, which would be a potential source of cardioembolism. However, small residual leaks ($<$5 mm) are considered irrelevant and may close spontaneously; their presence has not been shown to imply an increased risk of thromboembolism compared to patients with complete LAAO[76] although their clinical significance requires assessment in large randomized prospective studies with longer term follow-up.

Recommended organisational and operating standards

The expansion of the LAAO procedure within interventionist cardiology has led both national[77] and international[48,67] scientific societies to put forward recommendations and propose operating standards for the centres intending to adopt it. Some requirements should be considered essential; those listed below are the requirements to be considered fundamental for centres and staff.

General requirements

Within the hospital, the LAAO procedure should include joint decision-making within the Heart Team, including the interventionist cardiologist (haemodynamic specialist or electrophysiologist), the clinical cardiologist, the echocardiographer, the anaesthetist, and the cardiac surgeon, to ensure optimal coordination of the procedure. Since patient selection is the first fundamental step, other specialists (neurologists, nephrologists, internists, geriatrists, and haematologists) may be involved in indicating LAAO as the most appropriate antithrombotic strategy for a given patient. Therefore, the formation of a multidisciplinary team should be a prerequisite for the choice of the ideal candidate, the success of the procedure and post-procedural management. The presence/availability of a cardiac surgery unit on site is considered as a requirement in the North American Heart Society document[67] and is also recommended by the recent EHRA/EAPCI guidelines[44] which consider access to a cardiac surgery theatre within 60 min. adequate. The joint document issued by the Società Italiana di Cardiologia Interventistica/Associazione Italiana di Aritmologia e Cardiostimolazione (GISE/AIAC) requires the presence of a cardiac surgery unit on-site.[77]

Staff training and preparation

Interventionist cardiologists or electrophysiologists intending to perform the LAAO procedure must have in-depth knowledge of the anatomy of the heart, and of the morphological characteristics of the atrium and the LAA in particular. All scientific societies underline the need for the professional performing the procedure to have specific expertise in transseptal puncture and how to perform it in relation to implementation of LAAO devices. With regards to the transseptal puncture, the position of the national and international electrophysiology societies [AIAC/Heart Rhythm Society (HRS)] is that the professional should have performed at least 50 transseptal punctures and be skilled in manoeuvring catheters/inserters in the left atrium. The professional must be familiar not only with the anatomical position of the LAA and how to reach it but also the relationships between this structure and the surrounding anatomical formations. He or she must also have sufficient experience in the interpretation of radiological images (from angiography, tomography and magnetic resonance) and echocardiogram images of the LAA to obtain all the information needed for the correct choice of device. In particular, the

scientific societies emphasize the need for consultation between the professional performing the procedure and the echocardiographer, a key factor for success.

Professional performing the procedure must also have experience in pericardial puncture (or at least an interventionist cardiologist with this technical skill must be present) in order to deal with the eventuality of pericardial tamponade during manoeuvres in the left atrium or positioning of the device in the LAA.

Training of the first professional in the skills needed to perform the procedure is the fundamental first step in becoming autonomous. Training is provided by a proctor who is able to supply the trainee with explanations of all the phases of the procedure for successful LAAO. In detail, the recommendations of all the various scientific societies agree that every professional must attend theoretical lessons together with technical support through familiarization with the procedure and the instruments required, involving virtual sessions using simulators and/or practical sessions, in animal laboratories where possible.

It is advisable for those who are learning the procedure to attend implantation operations in order to learn the various steps with precision. The proctor must be present at the first implantation performed in every centre. Although there is no minimum number required to allow a professional to acquire complete independence, it is reasonable to assume that at least 15 implants must be performed in each centre before a satisfactory degree of autonomy and independence is gained.

One key factor for the achievement of procedural success, strongly recommended in the documents of the various scientific societies, is the creation of a well-organized operating team including the echocardiographer, the anaesthetist, and the nursing staff, who must also be familiar with the characteristics of the various devices and have proven experience in interventionist cardiology/electrophysiology procedures.

Requirements for the centre and operating room

Since most procedures are performed under general anaesthetic, the operating room must have the instrumentation required for anaesthesiology and have sufficient physical space not only for the anaesthetist but also for the echocardiographer, who plays a fundamental role in the procedure. The international scientific societies require the operating room staff, including nursing and technical staff, to have experience in interventionist procedures and be able to understand every step of the procedure, such as, for example, how to respond quickly to emergencies.

Staff's familiarity with the materials used is an additional factor in facilitating all steps of the procedure. Although not specifically recommended by the various scientific societies, it would be preferable for the nursing members of the team also to be involved in the technical training, attending LAAO sessions performed by the proctor and getting to know the materials by means of virtual sessions.

All operating room staff involved in the procedure must have a clearly defined role to play, in order to prevent overlaps during the procedure and delays in responding to emergencies.

Procedural recommendations and minimum skill levels

In view of the large number of procedures already performed and the potential additional increase in the near future, it appears appropriate for the national and scientific societies to draw up a position which can act as a consensus guideline. Therefore, on the one hand, the existing literature has been combined to extract indications for the selection and preparation of patients for the procedure. On the other hand, considering the opinions of staff skilled in the procedure, it appears useful to analyse the most purely technical aspects of percutaneous LAAO in order to standardize the various steps of the method, increasing its success in acute cases and reducing complications.

Requirements for the facility and staff

As already stated, percutaneous LAAO is a procedure which requires a multidisciplinary approach and can be performed either by an electrophysiologist or by a haemodynamic specialist: professionals from both these disciplines can combine their specific skills. However, the general opinion is that this procedure is technically complex and is a considerable challenge within interventionist-structural cardiology, due to the large number of skills required (transseptal puncture, navigation in left atrium and LAA, use of contrast medium, catheters and specific materials) (*Figure 10*).

Therefore, this working group believes that a facility wishing to start a percutaneous LAAO programme must have a multidisciplinary team allowing optimal assessment of the patient for the procedure. Particular attention will be focused on cardiac imaging techniques, in order to assess feasibility and plan the procedure most effectively: the presence of a specialist echocardiographer, both to monitor the positioning of the device and to recognize acute complications, is fundamental (*Table 7*).

Although it is not a *sine qua non*, radiological imaging plays a major role: high definition multidetector computed tomography and cardiac magnetic resonance are able to identify any thrombotic formations and study the anatomy of the LAA most effectively.[78] However, it must be underlined that these techniques are not the ideal support during the procedure, although they are useful, especially during the initial phases.

It thus appears advisable to perform the entire procedure under the guidance of echocardiography and fluoroscopy, as already emphasized in the PROTECT AF study. In all cases, according to the data in the literature and the experience of many professionals, it does not seem to be more risky than other interventionist procedures such as transcatheter ablation of AF, with which it shares the risk of mechanical complications (cardiac tamponade and damage to the structures adjoining the left atrium). It is important to point out that the incidence of what is to all effects the most serious complication, cardiac tamponade, has fallen over the years as operators' experience has increased and the technical characteristics of devices have improved: the rate has decreased from the about 5% of PROTECT AF[48] to a minimum of 0.8–1.3% in the latest 'real world' registry studies.[51,58] Analysing the data available to

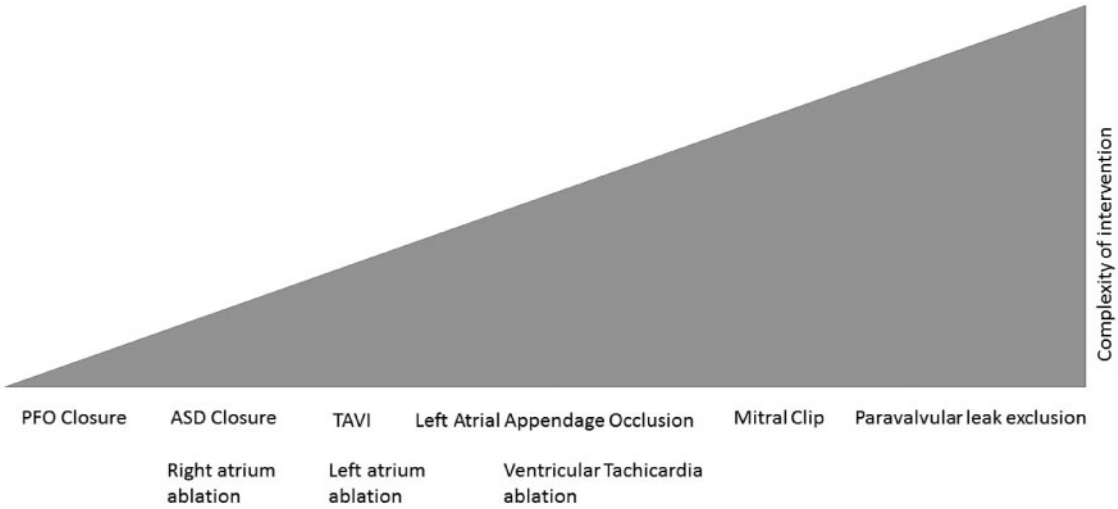

Figure 10 Complexity ratio between the procedures used in interventionist cardiology. ASD, atrial septal defect; PFO, patent foramen ovale; TAVI, transcatheter aortic valve implantation.

Table 7. Intraprocedural complications which can be identified by echocardiography.

1. Pericardial effusion
2. Cardiac tamponade
3. Embolization of the device
4. Thrombosis on the catheter
5. Tearing of the left atrial appendage
6. Damage to nearby structures:
7. During transseptal puncture
8. During manipulation or deployment of the device
9. Interference with the mitral valve, the circumflex artery or the left upper pulmonary vein

us from the PROTECT AF[48] and PREVAIL[51] studies, which together total 1271 patients, we find 40 (3.1%) pericardial effusions; the two studies report that 10 (0.8%) of these were surgically drained within 7 days after deployment of the device. If we compare the data of the two studies, PROTECT AF and PREVAIL, there is a significant reduction in surgically drained pericardial effusions ($P = 0.027$), with a fall from 1.6% to 0.4%.

Considering the complexity of the procedure and the potential complications, with current knowledge and the data now available, the need for a cardiac surgery team on-site has been the subject of debate, as reflected by the different positons taken in the international documents. Although the majority of the Panel believed that the presence of a cardiac surgery team on-site was not an indispensable requirement and that access to a cardiac surgery room within 60 min. was sufficient a unanimous position on this point was not achieved, even after lengthy discussion. One essential prerequisite (relevant for both interventionist cardiologists and electrophysiologists) is skill in pericardiocentesis.[79]

Management of complications

Pericardial effusion and cardiac tamponade

Pericardial effusion, in all its clinical forms (from asymptomatic effusion to cardiac tamponade) is one of the most serious complications of the percutaneous LAAO procedure. The risk factors include the transseptal puncture, the manipulation of rigid structures like the delivery catheters and the devices themselves inside the left atrium, and the intrinsic fragility of the atrial wall.[80]

In the PROTECT AF study, conducted on the Watchman device, the incidence of pericardial effusion within 7 days of implantation was 4.4%, with pericardiocentesis required in 3.3% of patients.[48]

It should be underlined that this complication was observed more frequently at the start of the learning curve. In the registry of the PAC system, which contains the results achieved by skilled staff, the rate of pericardial effusion fell to 2.2%[74] and the same values were also reported in the subsequent PREVAIL trial.[51] The recent study performed by Tzikas *et al.*[57] on the results achieved with the ACP device in more than 20 European and Canadian centres revealed a rate of pericardial effusion requiring drainage of 1.2%. In a multicentric study analysing the data on the use of the Lariat device, Price *et al.*[81] report an incidence of pericardial effusion requiring drainage of 10.4%.

The procedural strategies to reduce the incidence of pericardial effusion include:

- performance of the device implantation procedure under TEE guidance and pressure monitoring to ensure safe transseptal puncture in the correct position;
- use of a pigtail catheter inside the access sheath or a loop wire in the LAA to facilitate safe, trauma-free movement inside it;
- the use of slow, careful movements during manipulation of the catheter and occlusion device inside the left atrium; and

- performance of the tug test after implantation of the device under echocardiographic and fluoroscopic guidance, with injection of small amounts of contrast medium.

With regards to the therapeutic management of pericardial effusion, in the case of cardiac tamponade with hypotension a swift, aggressive approach is required, with pericardiocentesis and suspension of anticoagulation therapy. Early diagnosis of a pericardial effusion by means of TEE/intracardiac echography can often prevent the onset of cardiac tamponade, leading to serious deterioration of the haemodynamic condition.

Pericardiocentesis can be performed by means of a subxiphoid or subcostal transcutaneous puncture with echocardiographic guidance, or through a small cutaneous incision of about 3–5 cm underneath the xiphoid appendix (subxiphoid window), which allows the pericardial cavity to be accessed directly through its incision, followed by insertion of a pericardial drain.

In the event of recurrent tamponade or perforation of the left atrial wall, conventional surgery is required to review the pericardial cavity, suturing the breach in the atrial wall in an off-pump, beating heart procedure (if possible). If the lesion requires luxation of the heart for better surgical exposure, and tolerance of this procedure is poor, extracorporeal circulation may be necessary.

In selected cases, a thoracoscopic approach may initially be indicated, with fitting of an epicardial device (e.g. AtriClip) to close the breach in the LAA, if the lesion does not involve its orifice. This technique has not yet been described in the literature, and where it is not indicated the thoracoscopic approach can be transformed into mini-thoracotomy, which allows easier control of the anatomical structures and control of the haemostasis.

Although most cases of pericardial effusion occur early, subacute forms and delayed effusions are still described in the literature after the implantation of percutaneous LAAO devices. Therefore, monitoring of heart rate and arterial pressure are recommended for at least 48 h after implantation of the device, with performance of a transthoracic echocardiogram before discharge to ensure that no pericardial effusion has occurred and that the device is correctly positioned. Subacute effusions may be due to rubbing or irritation caused by the device's anchors against the wall of the atrium, in which lesions may eventually occur in view of its thinness. In these cases, if the pericardial effusion is of significant extent or produces instrumental signs of haemodynamic impairment, pericardiocentesis, or in some cases conventional surgical exploration, must be performed.

Delayed, haemodynamically insignificant effusions can probably be ascribed to post-procedural inflammation. They are normally treated with non-steroid anti-inflammatories such as aspirin, ibuprofen and diclofenac, or more rarely with steroid therapy.

Gaseous embolism

Gaseous embolism is often a clinically silent event, although in rare cases it may cause TIA, acute coronary ischaemia, hypotension and/or cardiac arrest.[48] Gaseous embolisms may reach the left atrium due to an accidental injection of air or may be the consequence of gas bubbles generated by a gradient between atmospheric and intracardiac pressure due to a deep intake of breath.[82]

Most of the management of gaseous embolisms consists of support. Hyperbaric oxygen has shown clinical benefits in 80% of cases of cerebral gaseous embolism, although no controlled studies have yet been performed. Gaseous embolism in the coronary circulation most often becomes evident in the right coronary due to the anatomical position of its orifice, and is often resolved within a few minutes. However, it may generate an ST depression, hypotension and ventricular arrhythmias, through to cardiogenic shock. Aspiration of the air with a specific device or the injection of contrast medium into the coronary artery may be useful in these cases.

Embolization of the device

The implantation procedure may be complicated by immediate or delayed formation of embolisms around the perimeter of the device itself. The careful selection of patients with favourable LAA morphology and use of the appropriate size of device are crucial for preventing this complication. Conversely, negative predictors are:

- large LAA orifice size,
- use of undersized devices,
- short LAA, and
- unusual anatomical variants.

Embolized devices in the left atrium or left ventricle can be captured and then driven forwards towards the mitral and aortic valves by means of endocatheters, allowing them to be recovered in the descending aorta. The recovery of devices from inside the heart itself is difficult and dangerous, while recovery in the aorta with a loop or bioptome catheter is a safer, more reproducible method. In the rare cases of the embolization of larger-sized devices in the direction of the iliac-femoral axis, recovery through open surgery is necessary.

Conclusions

OAT is the strategy of first choice for the prevention of thromboembolic events in AF patients with medium/high risk (CHA_2DS_2-VASc $\geq$1). However, many of these patients are difficult to treat, especially due to bleeding, a dangerous adverse event related to the therapy, which limits or contraindicates its use. The observation that most thrombi are generated by the LAA has led to the consideration of its surgical or percutaneous occlusion as an alternative; during the last few years, the Watchman percutaneous occlusion device has proved to be not inferior to anticoagulant therapy for the prevention of thromboembolic events, with the added benefit of a lower rate of haemorrhagic events; other, new devices have recently been introduced or are under development.

The procedure for the percutaneous occlusion of the LAA requires considerable technical skill and theoretical knowledge, as well as suitable training under the supervision of expert colleagues. Anyone wishing to perform it will

require the cooperation of skilled echocardiographers, familiar with the transoesophageal technique, to obtain the support of suitable imaging; he or she must also be capable of managing any complications, meaning, in particular, experience in the execution of pericardiocentesis, since cardiac tamponade is the most common and most dangerous complication.

The presence of a cardiac surgery unit on-site does not appear to be indispensable although it is reasonable to ensure access to a cardiac surgery room within 60 min. if necessary.

At present, the main indication for LAAO is the relative or absolute contraindication of anticoagulant therapy in patients with AF. These indications derive from observational or registry studies made comparing devices with the use of warfarin. Fur the future, the indication for LAAO in association with the AF ablation procedure AF[83-85] and MitraClip implantation, and the data obtained from comparison with the NOACs, remain to be assessed.

Large populations of very high-risk patients have still not been studied, including those who are unable to take any type of anticoagulant or antiplatelet therapy, in order to establish the impact of these factors on the prevention of complications and mortality.

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Annex

Consensus Document Approval Faculty

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