We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Interventional Left Atrial Appendage Closure: Focus on Practical Implications

Christian Fastner, Michael Behnes, Uzair Ansari,
Ibrahim El-Battrawy and Martin Borggrefe

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/67773>

Abstract

Catheter-based left atrial appendage closure is an evolving therapy for the prophylaxis of thromboembolic complications in nonvalvular atrial fibrillation patients, which are ineligible for long-term oral anticoagulation. For this indication, it is recommended by the current European guidelines. This review of the existing literature should facilitate the understanding of the therapy's practical implications. It presents a clinical approach toward a correct patient selection, gives an overview of the different devices and the procedural aspects, reflects differences and benefits between several postprocedural regimens for device surveillance as well as antithrombotic medication and rounds off with a summary of the relevant studies concerning efficacy and safety outcome measures.

Keywords: atrial fibrillation, left atrial appendage closure, thromboembolism, stroke, oral anticoagulation

1. Atrial fibrillation, thromboembolic risk, and prevention

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a significant burden of disease. The prevalence is age-dependent and increases with the age [1, 2]. While it is uncommon in patients younger than 40, about 10% of the 80-year olds are affected [1, 2]. AF nowadays is prevalent in about 3% of the western population, but it is estimated that the incidence will rise over the next decades linked to the increased life expectancy [1, 2]. As in the case of

other cardiovascular diseases, males are more frequently affected than females [1, 2]. Though AF rather rarely causes acute fatal complications at the time of onset, medium-term prognostic complications such as left ventricular dysfunction, cognitive decline, and utmost important cerebral ischemic stroke change AF toward a harmful cardiac disease [3]. AF accounts for 20–30% of all strokes and many patients are diagnosed with AF for the first time after they have been affected by a stroke (so-called “silent” AF) [3]. Therefore, the prognosis of AF patients is substantially determined by the risk for thromboembolic events.

1.1. Thrombogenesis during atrial fibrillation

Due to the electrical storm occurring on the atrial myocardium and the irregular ventricular excitation during AF episodes, the atrial mechanical function is impaired. Consecutively, the atrial cavities are distended, the intraatrial pressure is increased and the blood flow is reduced. These mechanisms connected to the Virchow’s triad are only part of a multifactorial network leading to thrombogenesis also including the expression of prothrombotic factors [4–6]. The changes are especially prominent in the blind-ended left atrial appendage (LAA) located in front of the anterior wall of the left atrium (LA) with its ostium between the left upper pulmonary vein and the mitral valve annulus [6, 7]. The walls of the LAA are highly trabeculated which renders them thrombogenic [7]. Four general LAA shapes are described in the literature, i.e., the chicken wing, cactus, windsock, and cauliflower shaped LAA (**Figure 1A**), whereby the data of the proportional distribution substantially vary within the literature [8]. Certain LAA morphologies were identified as an independent risk factor for thromboembolic events [9, 10]. Altogether, in patients with nonrheumatic AF more than 90% of all atrial thrombi occur in the left atrial appendage (**Figure 1B**) [11].

Figure 1. (A) The four different left atrial appendage morphologies with (a) the chicken wing, (b) the cactus, (c) the windsock and (d) the cauliflower type. (B) Echocardiographic visualization of a left atrial appendage thrombus (*).

1.2. Pros and cons of an oral anticoagulation therapy for thromboembolic prophylaxis

Because of these interrelationships, the risk stratification for thromboembolic events and a risk-based indication for thromboembolic prophylaxis are important pillars in the AF patient's therapy. For this purpose, the CHA₂DS₂-VASc score is recommended (IA) [3]. It incorporates all the relevant risk factors for stroke in AF patients: congestive heart failure (+1), hypertension (+1), age (65–74 +1 and ≥ 75 years +2, respectively), diabetes mellitus (+1), prior stroke, transient ischemic attack (TIA) or thromboembolism (+2), vascular disease (+1), and female gender (+1). According to the current European guideline recommendations, a thromboembolic prophylaxis by oral anticoagulants is recommended for all males with a CHA₂DS₂-VASc score ≥ 2 and for all females with a CHA₂DS₂-VASc score ≥ 3 (IA). Furthermore, this prophylaxis should be considered in males with a CHA₂DS₂-VASc score = 1 and in females with a CHA₂DS₂-VASc score = 2 according to the individual characteristics and the patient's preferences (IIaB) [3]. The evaluation of biomarkers, e.g., high-sensitive troponins and natriuretic peptides, can be helpful in this context (IIbB) [3]. For several decades, vitamin K antagonists have served as the gold standard for thromboembolic prophylaxis in AF patients [12], but their clinical use is limited by an increased and substantial bleeding risk which especially harms vulnerable patients [13, 14]. The vulnerability to bleedings can be assessed by the HAS-BLED score including arterial hypertension (+1), abnormal renal (+1) or liver (+1) function, prior stroke (+1), bleeding history or predisposition (+1), labile international normalized ratio (INR) (+1), age > 65 (+1) and drugs (+1) or alcohol (+1) concomitantly [15]. While dual antiplatelet agents failed to be an effective and safe alternative to vitamin K antagonists [16], recently, non-vitamin K antagonist oral anticoagulants (NOACs), i.e., dabigatran, rivaroxaban, apixaban, and edoxaban, were gaining ground [17–20]. In the current European guidelines, these substances are preferentially recommended for all eligible nonvalvular AF patients (IA) [3]. However, stoked by a higher incidence of gastrointestinal bleedings in comparison to vitamin K antagonists and other side effects [21], patients' adherence to NOAC therapy was also shown to be limited [22].

1.3. Alternatives to an oral anticoagulation therapy

By the implication of the LAA as a primary source of thrombi for thromboembolic events in nonvalvular AF, locoregional techniques to avoid thromboembolism out of the LAA were developed. Besides the surgical resection of the LAA during open heart surgery and the epicardial LARIAT® Suture Delivery Device (SentreHEART, Redwood City, CA, USA) with limited evidence for efficacy and safety [23, 24], six CE-marked devices for transvenous catheter-based LAA closure are currently available: the WATCHMAN™ left atrial appendage closure device (Boston Scientific, Natick, MA, USA), the AMPLATZER™ Cardiac Plug (ACP) and its next generation the AMPLATZER™ Amulet™ left atrial appendage occluder (both St. Jude Medical, Minneapolis, MN, USA), the WaveCrest™ LAA Occlusion System (Coherex Medical, Salt Lake City, UT, USA), the Occlutech® LAA occluder (Occlutech, Jena, Germany) and the LAmbré™ LAA Closure System (Lifetech Science, Shenzhen, China), respectively. However, only the WATCHMAN™ device was compared to oral anticoagulation (OAC), i.e., warfarin, in a prospective randomized controlled trial (RCT) in patients eligible for OAC

[25]. Long-term data revealed a noninferiority and superiority compared to OAC for preventing the combined outcome of stroke, systemic embolism, and cardiovascular death as well as superiority for cardiovascular and all-cause mortality [26]. Moreover, the PREVAIL trial stated adequate safety of the WATCHMAN™ procedure [27]. The efficacy and safety of other devices were exclusively evaluated by observational studies.

2. The interventional left atrial appendage closure

2.1. Indications and decision-making

Worthy of note, the patients with the strongest indication for a thromboembolic prophylaxis often also have a relevantly increased bleeding risk, represented by a major intersection of the risk factors included in the CHA₂DS₂-VASc and the HAS-BLED score. Based on the different approval procedures the necessary indications for the interventional closure of the LAA vary geographically and will subsequently be presented in the European context. The current European guidelines recommend the interventional LAA closure (LAAC) as an alternative to OAC for nonvalvular AF patients with an indication for OAC but on the other hand contraindications for a long-term treatment with this substances (IIbB) [3]. They note that, for example, patients with a prior life-threatening bleeding without a reversible cause may have a contraindication for long-term OAC [3]. However, further examples for the practical implementation are not given. Furthermore, the indication is impeded by the fact that numerous patients that formerly have been considered unsuitable for long-term OAC nowadays can take an oral prophylactic medication due to an adequate management [3, 28].

As the two currently available RCTs in the field of interventional LAAC only included, by their nature, patients which were eligible for long-term OAC [25, 27], they do not appear suitable for the identification of guideline-conform reasons for an interventional approach. The best practical help may be provided by the EHRA/EAPCI expert consensus statement [29] from which the presented decision-making algorithm is derived (**Figure 2**). If possible contraindications for a long-term anticoagulation arise and the individual CHA₂DS₂-VASc score is low, i.e., 1 in males and 2 in females, the necessity for OAC should be strictly checked in a risk-tailored approach with the aid of biomarkers (cf. 1.2 and [3]). Only patients with a persisting indication should be further evaluated.

In a *first step*, patients, which are presented for the LAAC evaluation, should be divided into those who are per se eligible for OAC and those who are not. All eligible patients should be well informed about the guideline recommendation for a prophylaxis by OAC, preferentially by a NOAC whenever possible. Some patients, however, will still refuse to take one of these substances due to various reasons, e.g., subjective anxiety, increased professional bleeding risk, OAC intolerance due to other side-effects than bleedings or noncompliance with OAC. If so, patients' refusal may be considered as an adequate contraindication for long-term OAC.

Figure 2. Decision-making algorithm derived from Ref. [29]; # = 1 in males or 2 in females; † = HAS-BLED score ≥ 3, bleeding risk not reflected by the HAS-BLED score, prolonged triple therapy or recurrent minor bleedings under (N)OAC, e.g., gastrointestinal bleedings.

Two prospective, observational studies demonstrated safety and efficacy of LAAC in patients who were ineligible for any OAC [30, 31]. This indication is depicted most clearly by the formulation in the European guidelines [3]. It covers, in particular, prior life-threatening bleedings according to Bleeding Academic Research Consortium (BARC) type 3 [32] without a reversible or controllable cause. This includes bleedings due to angiodysplasia, amyloid

angiopathy, malignoma, chronic inflammatory bowel disease, thrombocytopenia, platelet dysfunctions, or other coagulation disorders as well as recurrent falling in the course of epilepsy or frailty [30, 31, 33, 34]. As well as for the patients refusing OAC, it must be stated, that a postinterventional temporary intake of at least two antiplatelet agents regularly followed by a lifelong single antiplatelet therapy is mandatory in most centers and cases of relevant postinterventional bleedings under dual antiplatelet therapy (DAPT) can be found in literature [35, 36]. There is growing evidence for the efficacy of a single antiplatelet therapy following LAAC but a strategy of discontinuation of any antiplatelet therapy is still based on single-center experience [37–40]. In this context, at least the bleeding risk under acetylsalicylic acid (ASA) should be included in the considerations [29, 41].

In other patients, the risk for a severe bleeding under long-term OAC might be estimated unacceptably high even without the existence of a prior life-threatening bleeding event. These patients with an increased HAS-BLED score (≥ 3 according to [29]) or recurrent minor bleedings (according to BARC type 1 and 2 [32]) require a thorough individual risk-benefit profile evaluation by taking into account the lowered bleeding event rates under NOAC therapy. But, thereby, especially patients with recurrent minor gastrointestinal (GI) bleedings as well as those with a risk for GI bleedings perform very poor [21]. Due to the practical necessity of a postinterventional lifelong ASA intake, again, the risk for bleedings under ASA should be determined [29, 41]. In addition to the above-mentioned causes for bleedings and the ones depicted by the HAS-BLED score, a prolonged triple therapy due to a complex coronary artery disease may be a particularly relevant indication in this group of patients. AF patients with a highly impaired renal function, i.e., glomerular filtration rate <15 ml/min, or those with chronic renal replacement therapy reflect special cases. In these patients, both a high bleeding risk and a high stroke risk are associated with an increased mortality [42, 43]. These patients cannot be treated by NOACs and the benefit of a treatment with vitamin K antagonists is controversially discussed [44–46]. The value of an interventional closure of the LAA in these patients cannot be stated at this point. However, promising data concerning safety and efficacy exist in patients with chronic kidney disease compared to the estimated TIA, stroke and bleedings rates of the collective even in patients with an end-stage renal disease [47].

Special cases where a LAAC may be indicated without a contraindication for long-term OAC are patients with thromboembolic events despite a well monitored treatment with OAC even after switching to another substance or to higher INR values. In these patients, and especially if it is likely that the thrombus originated from the LAA, LAAC can be an alternative or an additional treatment to OAC [29].

In a European multicenter observational trial consecutively including slightly more than 1000 patients with a LAAC procedure, 47% had suffered a major hemorrhage, 35% were defined as being prone to a high bleeding risk, 22% had an indication for a triple therapy, 16% suffered a stroke under OAC, and 8% had an elevated risk of falling [33]. By reflecting the above-presented indications in a real-life cohort, it was emphasized that in some patients the combination of several reasons resulted in the indication.

In a *second step*, after establishing the indication, the patients' medical documents should be screened for contraindications for catheter-based LAAC. These are valvular or rheumatic AF

as, in these patients, thrombi do not originate from the LAA in up to 60% of cases [11, 48], contraindications for catheterization and transseptal puncture such as active infection, left atrial thrombus or tumor as well as the presence of a closure device on the atrial septal puncture site and indications for lifelong OAC besides AF such as mechanical heart valves, recurrent pulmonary embolism and deep vein thrombosis.

In a *third step*, if these contraindications can be excluded, anatomical feasibility should be checked by thorough two- and three-dimensional transesophageal (TEE) measurements prior to the intervention [49–51]. Not only the absence of a thrombus in the LA and LAA must be confirmed but also LAA dimensions must fulfill certain device-specific requirements. Ultrasound contrast agent use may facilitate the detection of a thrombus [52]. Therefore, the LAA is visualized and measured in multiple views (0, 45, 90 and 135°) at the end of the atrial diastole when the LAA volume is largest to avoid undersizing. First of all, the maximal ostial width is measured from a point right next to the left circumflex coronary artery or the mitral valve annulus to a point 1–2 cm from the tip of the left superior pulmonary vein limbus (**Figure 3**). While the orifice usually is oval shaped, the largest diameter is of procedural interest for the WATCHMAN™ device implantation. For the Amplatzer™ devices a so-called landing zone 10–12 mm from the orifice into the LAA is important. Furthermore, the LAA depth is measured perpendicular to the ostial plane. The WATCHMAN™ device is unsuitable if the depth-width ratio is < 1 , the Amplatzer™ Amulet™ is limited to a depth of ≥ 7.5 mm. An orifice of 30 mm for the WATCHMAN™ device and a landing zone of 31 mm for the Amplatzer™

Figure 3. Echocardiographic measurements prior to the left atrial appendage closure; solid line = orifice diameter, dashed line = depth, dotted line = landing zone.

Amulet™, respectively, are the upper limitations concerning the LAA width. Large secondary lobes should be assessed accurately as they might impede the complete sealing of the LAA orifice, especially when a second large lobe branches off close to the ostium.

In cases where the LAA evaluation by TEE is difficult, especially if multiple lobes are present, further imaging methods, e.g., computed tomography (CT) angiography, may help to ensure correct measurements [53–57]. In case of an existing LAA thrombus, several attempts with different substances can become necessary to resolve it [58], but this effort will not be possible in patients with absolute contraindications to even short-term (N)OAC treatment.

2.2. Device types and procedural aspects

The five CE-marked devices for catheter-based LAAC can be divided into two groups, the ball and the disk type, respectively. The WATCHMAN™ device, the WaveCrest™ system and the Occlutech® occluder form the ball-type group while the Amplatzer™ devices and the Lambre™ system form the disk-type group. All devices consist of a self-expanding nitinol mesh with wires to anchor in the LAA walls and they are covered by different patches. The disk-type group is characterized by a so-called waist connecting a proximal disk with a distal lobe. Newer LAAC devices are optimized for intraprocedural repositioning by retractable anchors, for instance, to facilitate the procedure in complex anatomies. The WaveCrest™ system has a foam coat to minimize residual leaks after implantation. Operators evaluated the ACP's "pacifier principle" was particularly user-friendly, which might be reflected by high success rates in the early trials [29]. Furthermore, it might have advantages in anatomies with two large main lobes originating from one ostium. But these assertions are mainly based on expert opinions and ongoing studies will have to further evaluate the individual advantages of the latest developments on the device market and the value of a certain device type for different morphologies.

The catheter-based LAAC procedure (**Figure 4**) is usually performed under deep conscious sedation or general anesthesia. Antibiotic prophylaxis is recommended prior to the intervention. The procedure is guided by fluoroscopy, angiography, and TEE. Some centers use additional intracardiac echocardiography (ICE) [59]. The correct device type and size (10–30% larger than the measured diameter to allow device stabilization by compression forces) is chosen by the above mentioned preinterventional TEE or CT measurements. In Seldinger technique, vascular access is taken via the right femoral vein and the transseptal puncture is performed in a standard fashion in the posterior and inferior atrial septum. This allows to easily access the LAA ostium. If a patent foramen ovale is present, this "natural" way can also be used for transseptal crossing provided it is suitable for the LAA access [33]. Again, the freedom from thrombus is confirmed by angiography via an intraatrial pigtail catheter (right anterior oblique 30°/cranial 30°) and by TEE or ICE. Prior to the transseptal puncture, unfractionated heparin is administered to achieve an activated clotting time >250 s. Via the transseptal wire the device delivery sheath (8–14 French) is inserted. It is particularly important to avoid air embolism by flushing the sheath and the device with isotonic saline prior to the insertion. All devices are preinstalled on the catheters. The device is deployed by retracting the delivery sheath over the device which then self-expands. The deployment is conducted by fluoroscopy and echocardiography. In case of incorrect positioning, all current devices can be repositioned by retraction into the delivery

Figure 4. Fluoroscopic and angiographic images of the left atrial appendage closure procedure. (A) Angiographic illustration of the cauliflower shaped left atrial appendage (*); # = delivery sheath. (B) The WATCHMAN™ device (+) is pushed forward through the delivery sheath. (C) The device (+) is implanted in the left atrial appendage. (D) Stable anchoring is confirmed by pulling the device (+) in the direction of the white arrow (“tug test”). (E) The correct sealing of the left atrial appendage by the device (+) is illustrated by angiography. (F) The released left atrial appendage occluder (+).

sheath prior to device releasement. When the correct landing position is achieved, the stable device anchoring is confirmed by a so-called “tug test” and correct sealing of the LAA ostium is illustrated by angiography and color Doppler imaging. After complete device deployment and before TEE retraction, a pericardial effusion should be ruled out. It is naturally clear that the procedural steps might slightly vary between the different devices. In relation to procedural success, an operator-related learning curve could be demonstrated [33, 60, 61]. Procedures combined with other cardiac interventions, e.g., percutaneous coronary intervention, closure of a persistent foramen ovale or an atrial septum defect, atrial fibrillation ablation, or even transcatheter aortic valve implantation, are not untypical in clinical practice [33]. The value of combined procedures especially of those which both require a transseptal puncture is currently not completely elucidated. Moreover, despite the knowledge of the chicken wing morphology being a highly challenging LAA anatomy [62], procedural characteristics and outcomes related to different LAA morphologies still remain to be evaluated.

2.3. Postprocedural measures and antithrombotic regimens

It is a frequent practice to perform a chest X-ray as well as a transthoracic echocardiography 24 hours after the procedure to reconfirm the device position and the absence of a pericardial

effusion prior to the patients' discharge from hospital. The average length of stay is around 2–5 days [63, 64]. Endocarditis prophylaxis is usually considered prior to at-risk procedures for 6 months after the implantation.

The follow-up visits as well as the imaging modalities for device surveillance are closely linked to the initiated postinterventional antithrombotic regimen. Subsequently, different regimens for the most common devices, the WATCHMAN™ and the Amplatzer™ devices, respectively, are presented. For the other devices, regimens must be adopted by having regard to the instructions for use.

If the patient is eligible for short-term OAC after the WATCHMAN™ device implantation, it is usually conducted for 45 days reflected by the two RCTs [25, 27], two observational studies with NOACs [65, 66] and the instructions for use. TEE is performed after this period to rule out device thrombus prior to switching to DAPT and again after 6 months when switching from DAPT to ASA therapy is intended. In the PROTECT-AF trial, 86% of all implanted patients could be discontinued with warfarin after 45 days and 92% after 6 months as the TEE criterion (peridevice leak <5 mm) was met. In the more recent PREVAIL trial, 92 and 98% of all implanted patients were able to discontinue warfarin after 45 days and 6 months, respectively. While there is no evidence for increased thromboembolic event rates associated to peridevice leaks <5 mm independent of OAC discontinuation based on a limited source of evidence [67], peridevice leaks ≥ 5 mm remain an indication for continuation or reinitiation of OAC whenever possible or for a second occlusion attempt [29, 68].

As many patients are ineligible to even short-term OAC, postinterventional regimens without OAC prescription had been urgently needed. Therefore, two smaller prospective observational studies evaluated a DAPT after LAAC and revealed adequate efficacy and safety for such regimen with the WATCHMAN™ device and the ACP [30, 31]. This regimen is also adopted in the instructions for use for the Amplatzer™ devices. DAPT was prescribed 1–6 months after the procedure and then switched to an indefinite single antiplatelet therapy. As above-stated, the efficacy of a single antiplatelet therapy following LAAC for specific high-risk patients appears adequate but the complete discontinuation of antithrombotic treatment at some point is based on limited experience [37–40]. While the optimal timing for postinterventional device surveillance cannot be completely justified by the existing literature, a follow-up between a minimum of 1.5 and a maximum of 6 months as a compromise between the fast switch to minimal antithrombotic therapy after ensuring adequate LAA occlusion and the secure identification of device-related thrombi appears reasonable [69]. Platelet count, CHA₂DS₂-VASc score and reduced ejection fraction were identified as risk factors for device-related thrombi under DAPT [70]. Although the thrombus-associated stroke rate appears low [61], it is recommended to resolve it by a new initiated or continued anticoagulation whenever possible [29]. Additional clinical visits or imaging procedures may not be mandatory apart from study protocols, but by bearing in mind late device embolizations [71] (cf. 2.4) and the underlying cardiovascular disease of the intervened patients, it appears reasonable to follow them up regularly.

TEE currently remains the gold standard for postimplant device surveillance. Magnetic resonance tomography imaging is hindered by artefacts from the device and especially in light of radiation exposure and the need for contrast agent use [72], the value of CT angiography compared to TEE for postimplant imaging has not been finally clarified [73, 74].

2.4. Procedure-related complications and short-term outcome

Procedure-related complications are mainly associated with bleedings such as pericardial effusion and tamponade and access site complications, i.e., hematoma, overt bleeding, AV fistula, and pseudoaneurysm. Moreover, periinterventional TIA and stroke as well as early device embolization and air embolism have also been reported. Additional late device embolizations have been observed and there are several surgical and interventional techniques to retrieve an embolized device in relation to its location [71, 75]. **Table 1** summarizes the reported complications from the most representative studies for the most common devices. The presented

Study	Patients in the treatment arm [n]	Successful implantation [%]	Relevant pericardial effusion [%]	Access site complication and other major bleeding [%]	TIA or stroke; hemorrhagic stroke [%]	Early device embolization [%]
WATCHMAN™ device						
Holmes et al. [25]	463	88	4.8	3.5	1.1; 0.2	0.6
Reddy et al. [61]	460	95	2.2	0.7	0.0	0.0
Reddy et al. [31]	150	95	1.3	2.0	0.7	1.3
Holmes et al. [27]	269	95	0.4	0.7	0.7	0.7
Boersma et al. [34]	1019	99	0.1	1.1	0.0 (0.3 between days 8 and 30)	0.2
Amplatzer™ devices						
Park et al. (ACP) [84]	143	96	3.5	n/a	2.1	1.4
Lam et al. (ACP) [78]	20	95	0.0	0.0	n/a	0.0
Urena et al. (ACP) [30]	52	98	0.0	3.8	1.9	1.9
Gloekler et al. (ACP and Amulet™) [76]	100	96	6.0	0.0	0.0	5.0
Tzikas et al. (ACP) [33]	1047	97	1.2	1.2	0.9	0.8
Abualsaud et al. (ACP and Amulet™) [77]	59	98	0.0	n/a	0.0	0.0
Berti et al. (ACP and Amulet™) [64]	110	96	2.7	0.9	0.9	0.0

Table 1. Implantation success and procedural safety; n/a = not applicable; TIA = transitory ischemic attack.

data usually refer to events within the first 7 days following the procedure. No procedure-related death occurring during the first week and only one procedure-related death (0.1%) within 30 days after the WATCHMAN™ device implantation was recently reported from the large multicenter observational EWOLUTION registry [34], a low rate, which also could be recently observed in a multicenter observational registry for the ACP [33]. The implantation success ($\geq 95\%$) was highly satisfactory most recently. Comparing the periprocedural safety, the first and second generation Amplatzer™ devices appear equal [76, 77]. Not only for the procedural success but also for the reduction of overall complications, a learning curve over time was obvious [33, 60, 61].

2.5. Medium- and long-term outcome

As mentioned in the beginning, the WATCHMAN™ device was shown to be superior (posterior probability 96.0%) for the combined outcome of stroke, systemic embolism and cardiovascular death compared to a warfarin treatment in a long-term follow-up to the PROTECT-AF trial with a 2:1 randomization for the device implantation [26]. After a mean follow-up of 3.8 years (2621 patient-years) the primary annual event rate was 2.3% in the device versus 3.8% in the warfarin group (rate ratio 0.60; 95% credible interval 0.41–1.05) [26]. In the initial PROTECT-AF trial with a follow-up of 1065 patient-years, only the noninferiority could be demonstrated (posterior probability $>99.9\%$) [25]. The primary annual event rate in the device group was 3.0 versus 4.9% in the warfarin group (rate ratio 0.62; 95% credible interval 0.35–1.25). The study is limited by a high dropout rate in the control groups as well as by collecting a per se OAC eligible collective with a low stroke risk (CHADS₂ score 2.2 ± 1.2).

Under the conditions of an equal study protocol but of a higher CHADS₂ score of 2.6 ± 1.0 the PREVIAL trial failed to reach noninferiority for the primary efficacy outcome within 18 months [27]. Only for the stroke and systemic embolization rate >7 days after randomization noninferiority could be stated. But the key message of this trial was the lower rate of safety events compared to PROTECT-AF despite a high proportion of untrained operators (25%) and a more inclusive definition of safety events compared to PROTECT-AF event rates were still lower (annual rates of 4.2 versus 8.7%, respectively; $p = 0.004$).

With a total of 5931 patient-years, a meta-analysis of the PROTECT-AF trial, the PREVAIL trial and the subsequent registries confirmed noninferiority for the predefined combined primary efficacy endpoint compared to warfarin treatment [79]. Annual event rates were 2.7 and 3.5%, respectively (hazard ratio 0.79; 95% credible interval 0.53–1.20 ; $p=0.22$). Worthy of note, only after subtracting the procedure-related strokes from the total number of strokes, the event rates in the device and the warfarin group were no longer significantly different (hazard ratio 1.56; 95% credible interval 0.78–3.09; $p = 0.21$). Reflecting a bleeding benefit, hemorrhagic stroke was significantly less frequent in the device group (0.15%; 95% credible interval 0.07–0.40) compared to the warfarin group (0.61%; 95% credible interval 0.55–1.70) (hazard ratio 0.22; 95% credible interval 0.08–0.61; $p = 0.004$).

The largest data set for the ACP was published by Tzikas et al. (prospective collection of the data and retrospective analyzation). He reports, after 1349 patient-years of follow-up, an annual systemic thromboembolism rate of 2.3% [33]. In terms of safety, an annual rate of major bleeding of 2.1% was registered. Based on a mean CHA₂DS₂-VASc score of $4.5 \pm$

1.6 and a mean HAS-BLED score 3.1 ± 1.2 , this meant a risk reduction of 59% for systemic thromboembolism and 61% for major bleeding respectively, compared to the rates predicted by the scores.

Postinterventional DAPT was mainly proven effective and safe by the prospective observational studies of Reddy et al. (WATCHMAN™) [31] and Urena et al. (ACP) [30]. Annual event rates for all-cause stroke and systemic thromboembolism were 2.3 and 3.4%, respectively. Reddy et al. found an annual rate for hemorrhagic stroke of 0.6%. Urena et al. observed an annual major bleedings rate of 3.4%. Thus, these outcome measures were completely comparable to the event rates in the RCTs including OAC eligible patients. The mean/median CHA₂DS₂-VASc scores of 4.4 ± 1.7 and 5 (4–6), respectively, thereby correspond to a high-risk collective.

Concerning alternatives to vitamin K antagonists and DAPT following LAAC, two recently published studies reported data for the strategy of a single antiplatelet therapy after LAAC. After a total of 265 patient-years an annual stroke rate of 2.3% was observed by Korsholm et al. under a single ASA therapy [40]. The mean CHA₂DS₂-VASc score was 4.4 ± 1.6 and the mean HAS-BLED score was 4.1 ± 1.1 . Jalal et al. [39] reported an annual stroke/TIA rate of 4.0% and an annual major bleeding rate of 1.3% after 75 patient-years of follow-up under ASA or clopidogrel monotherapy. The mean CHA₂DS₂-VASc score was 4.4 ± 1.3 and the mean HAS-BLED score 3.4 ± 0.9 . Here again, the rates are in good accordance with the ones reported in the earlier mentioned RCTs. Initial retrospective data comparing NOAC to warfarin for 6 weeks following LAAC showed comparable rates for device-related thrombus, composite of thromboembolism or device-related thrombosis and postprocedural bleeding events [65].

In summary, LAAC with different devices was proven to be effective and safe or, in the long run, even superior to long-term warfarin treatment in respect to all-cause and cardiovascular mortality when it is combined with a 45-day warfarin intake following procedure. Moreover, LAAC could be shown to be more effective and less costly relative to warfarin and NOACs in recent analyses [80, 81]. LAAC was dominant over NOACs by year 5 and warfarin by year 10 [80].

2.6. Perspectives

On this basis, meanwhile, the LAAC procedure has found its status in clinical practice. Due to the inherent character of complications regarding any interventional cardiac procedure, it is unlikely that complication rates will further strongly decrease and, therefore, an individualized and risk-tailored approach in patient selection is a crucial step prior to the patient's transfer to the catheterization laboratory. It is hoped that further studies will focus on the identification of patients who will derive the most benefit from an interventional approach and will help to better characterize the term "contraindication for long-term OAC" [82].

As more and more patients will be implanted which are even ineligible for a short-term OAC treatment, the alternatives, i.e., DAPT and single antiplatelet agents following LAAC, have to be further evaluated. In this context, the knowledge of the optimal duration of DAPT and about the possibility of discontinuing any antithrombotic medication will help to treat certain very high-risk patients based on reliable data.

Unsolved questions derived from the postprocedural practice are the relevance of paradevice leaks especially ≥ 5 mm revealed during follow-up imaging procedures and the related need for action. Moreover, the value of CT angiography for device surveillance is not conclusively clarified yet.

But the most important would be to thoroughly compare LAAC to different NOACs as these substances currently are clearly recommended in AF patients without contraindications by the European guidelines [3]. Initial data show that the interventional approach does not need to be hidden away [83].

Author details

Christian Fastner*, Michael Behnes, Uzair Ansari, Ibrahim El-Battrawy and Martin Borggrefe

*Address all correspondence to: christian.fastner@umm.de

First Department of Medicine, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

References

- [1] Go, A.S., et al., *Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study*. JAMA, 2001. **285**(18): pp. 2370-2375.
- [2] Haim, M., et al., *Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation*. J Am Heart Assoc, 2015. **4**(1): p. e001486.
- [3] Kirchhof, P., et al., *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS*. Eur Heart J, 2016. **37**(38): pp. 2893-2962.
- [4] Calenda, B.W., et al., *Stroke risk assessment in atrial fibrillation: risk factors and markers of atrial myopathy*. Nat Rev Cardiol, 2016. **13**(9): pp. 549-559.
- [5] Lim, H.S., et al., *Effect of atrial fibrillation on atrial thrombogenesis in humans: impact of rate and rhythm*. J Am Coll Cardiol, 2013. **61**(8): p. 852-860.
- [6] Watson, T., E. Shantsila, and G.Y. Lip, *Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited*. Lancet, 2009. **373**(9658): pp. 155-166.
- [7] Al-Saady, N.M., O.A. Obel, and A.J. Camm, *Left atrial appendage: structure, function, and role in thromboembolism*. Heart, 1999. **82**(5): pp. 547-554.
- [8] Lupercio, F., et al., *Left atrial appendage morphology assessment for risk stratification of embolic stroke in patients with atrial fibrillation: A meta-analysis*. Heart Rhythm, 2016. **13**(7): pp. 1402-1409.

- [9] Kimura, T., et al., *Anatomical characteristics of the left atrial appendage in cardiogenic stroke with low CHADS2 scores*. Heart Rhythm, 2013. **10**(6): pp. 921-925.
- [10] Di Biase, L., et al., *Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study*. J Am Coll Cardiol, 2012. **60**(6): pp. 531-538.
- [11] Blackshear, J.L. and J.A. Odell, *Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation*. Ann Thorac Surg, 1996. **61**(2): pp. 755-759.
- [12] Hart, R.G., et al., *Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis*. Ann Intern Med, 1999. **131**(7): pp. 492-501.
- [13] Kakkar, A.K., et al., *Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry*. PLoS One, 2013. **8**(5): p. e63479.
- [14] Waldo, A.L., et al., *Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation*. J Am Coll Cardiol, 2005. **46**(9): pp. 1729-1736.
- [15] Pisters, R., et al., *A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey*. Chest, 2010. **138**(5): pp. 1093-1100.
- [16] Investigators, A.W.G.o.t.A., 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**(9526): pp. 1903-1912.
- [17] Connolly, S.J., et al., *Dabigatran versus warfarin in patients with atrial fibrillation*. N Engl J Med, 2009. **361**(12): pp. 1139-1151.
- [18] Patel, M.R., et al., *Rivaroxaban versus warfarin in nonvalvular atrial fibrillation*. N Engl J Med, 2011. **365**(10): pp. 883-191.
- [19] Granger, C.B., et al., *Apixaban versus warfarin in patients with atrial fibrillation*. N Engl J Med, 2011. **365**(11): pp. 981-992.
- [20] Giugliano, R.P., et al., *Edoxaban versus warfarin in patients with atrial fibrillation*. N Engl J Med, 2013. **369**(22): pp. 2093-2104.
- [21] Ruff, C.T., 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**(9921): pp. 955-962.
- [22] Alamneh, E.A., L. Chalmers, and L.R. Bereznicki, *Suboptimal use of oral anticoagulants in atrial fibrillation: has the introduction of direct oral anticoagulants improved prescribing practices?* Am J Cardiovasc Drugs, 2016. **16**(3): pp. 183-200.
- [23] Tsai, Y.C., et al., *Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: a meta-analysis*. Eur J Cardiothorac Surg, 2015. **47**(5): pp. 847-854.

- [24] Chatterjee, S., et al., *Safety and procedural success of left atrial appendage exclusion with the lariat device: a systematic review of published reports and analytic review of the FDA MAUDE database*. JAMA Intern Med, 2015. **175**(7): pp. 1104-1109.
- [25] Holmes, D.R., 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**(9689): pp. 534-542.
- [26] Reddy, V.Y., et al., *Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial*. JAMA, 2014. **312**(19): pp. 1988-1998.
- [27] Holmes, D.R., Jr., et al., *Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial*. J Am Coll Cardiol, 2014. **64**(1): pp. 1-12.
- [28] Kuramatsu, J.B., et al., *Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage*. JAMA, 2015. **313**(8): pp. 824-836.
- [29] Meier, B., et al., *EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion*. Europace, 2014. **16**(10): pp. 1397-1416.
- [30] Urena, M., et al., *Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy*. J Am Coll Cardiol, 2013. **62**(2): pp. 96-102.
- [31] Reddy, V.Y., et al., *Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology)*. J Am Coll Cardiol, 2013. **61**(25): pp. 2551-2556.
- [32] Mehran, R., et al., *Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium*. Circulation, 2011. **123**(23): pp. 2736-2747.
- [33] Tzikas, A., et al., *Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug*. EuroIntervention, 2016. **11**(10): pp. 1170-1179.
- [34] Boersma, L.V., 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**(31): pp. 2465-2474.
- [35] Ruiz-Garcia, J. and R. Moreno, *Percutaneous closure of left atrial appendage: device-indicated antiplatelet therapy may also lead to fatal bleeding. A call for evidence-based antiplatelet regimen*. J Thromb Thrombolysis, 2014. **37**(3): pp. 359-361.
- [36] Llull, L., et al., *Intracranial hemorrhage during dual antiplatelet therapy after percutaneous left atrial appendage closure*. Cerebrovasc Dis, 2014. **38**(1): pp. 73-74.

- [37] Rodriguez-Gabella, T., et al., *Single antiplatelet therapy following left atrial appendage closure in patients with contraindication to anticoagulation*. J Am Coll Cardiol, 2016. **68**(17): pp. 1920-1921.
- [38] Renou, P., et al., *Left atrial appendage closure in patients with atrial fibrillation and previous intracerebral hemorrhage*. J Stroke Cerebrovasc Dis, 2016 **26**(3): pp. 545-551.
- [39] Jalal, Z., et al., *Percutaneous left atrial appendage closure followed by single antiplatelet therapy: short- and mid-term outcomes*. Arch Cardiovasc Dis, 2017. [Epub ahead of print].
- [40] Korsholm, K., et al., *Transcatheter left atrial appendage occlusion in patients with atrial fibrillation and a high bleeding risk using aspirin alone for post-implant antithrombotic therapy*. EuroIntervention, 2016. [Epub ahead of print].
- [41] Connolly, S.J., et al., *Apixaban in patients with atrial fibrillation*. N Engl J Med, 2011. **364**(9): pp. 806-817.
- [42] Zimmerman, D., et al., *Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis*. Nephrol Dial Transplant, 2012. **27**(10): pp. 3816-3822.
- [43] Olesen, J.B., et al., *Stroke and bleeding in atrial fibrillation with chronic kidney disease*. N Engl J Med, 2012. **367**(7): pp. 625-635.
- [44] Chan, K.E., et al., *Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis*. Circulation, 2015. **131**(11): pp. 972-979.
- [45] Bonde, A.N., et al., *Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study*. J Am Coll Cardiol, 2014. **64**(23): pp. 2471-2482.
- [46] Shah, M., et al., *Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis*. Circulation, 2014. **129**(11): pp. 1196-1203.
- [47] Kefer, J., 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**: pp. 335-340.
- [48] Mahajan, R., et al., *Importance of the underlying substrate in determining thrombus location in atrial fibrillation: implications for left atrial appendage closure*. Heart, 2012. **98**(15): pp. 1120-1126.
- [49] Yosefy, C., et al., *A new method for direct three-dimensional measurement of left atrial appendage dimensions during transesophageal echocardiography*. Echocardiography, 2016. **33**(1): pp. 69-76.
- [50] Nucifora, G., et al., *Evaluation of the left atrial appendage with real-time 3-dimensional transesophageal echocardiography: implications for catheter-based left atrial appendage closure*. Circ Cardiovasc Imaging, 2011. **4**(5): pp. 514-523.
- [51] Donal, E., et al., *The left atrial appendage, a small, blind-ended structure: a review of its echocardiographic evaluation and its clinical role*. Chest, 2005. **128**(3): pp. 1853-1862.

- [52] Jung, P.H., et al., *Contrast enhanced transesophageal echocardiography in patients with atrial fibrillation referred to electrical cardioversion improves atrial thrombus detection and may reduce associated thromboembolic events*. Cardiovasc Ultrasound, 2013. **11**(1): p. 1.
- [53] Saw, J., et al., *Comparing measurements of CT Angiography, TEE, and fluoroscopy of the left atrial appendage for percutaneous closure*. J Cardiovasc Electrophysiol, 2016. **27**(4): pp. 414-422.
- [54] Krishnaswamy, A., et al., *Planning left atrial appendage occlusion using cardiac multidetector computed tomography*. Int J Cardiol, 2012. **158**(2): pp. 313-317.
- [55] Romero, J., et al., *Detection of left atrial appendage thrombus by cardiac computed tomography in patients with atrial fibrillation: a meta-analysis*. Circ Cardiovasc Imaging, 2013. **6**(2): pp. 185-194.
- [56] Bai, W., et al., *Assessment of the left atrial appendage structure and morphology: comparison of real-time three-dimensional transesophageal echocardiography and computed tomography*. Int J Cardiovasc Imaging, 2016 [Epub ahead of print].
- [57] Rajwani, A., et al., *CT sizing for left atrial appendage closure is associated with favourable outcomes for procedural safety*. Eur Heart J Cardiovasc Imaging, 2016 [Epub ahead of print].
- [58] Miwa, Y., et al., *Resolution of a warfarin and dabigatran-resistant left atrial appendage thrombus with apixaban*. J Arrhythm, 2016. **32**(3): pp. 233-235.
- [59] Masson, J.B., et al., *Transcatheter left atrial appendage closure using intracardiac echocardiographic guidance from the left atrium*. Can J Cardiol, 2015. **31**(12): pp. 1497 e7-1497 e14.
- [60] Ledwoch, J., et al., *Learning curve assessment for percutaneous left atrial appendage closure with the WATCHMAN occluder*. J Interv Cardiol, 2016. **29**(4): pp. 393-399.
- [61] Reddy, V.Y., et al., *Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry*. Circulation, 2011. **123**(4): pp. 417-424.
- [62] Freixa, X., et al., *The chicken-wing morphology: an anatomical challenge for left atrial appendage occlusion*. J Interv Cardiol, 2013. **26**(5): pp. 509-514.
- [63] Badheka, A.O., et al., *Utilization and adverse outcomes of percutaneous left atrial appendage closure for stroke prevention in atrial fibrillation in the United States: influence of hospital volume*. Circ Arrhythm Electrophysiol, 2015. **8**(1): pp. 42-48.
- [64] Berti, S., et al., *Left atrial appendage occlusion in high-risk patients with non-valvular atrial fibrillation*. Heart, 2016. **102**(24): pp. 1969-1973.
- [65] Enomoto, Y., et al., *Use of non-warfarin oral anticoagulants instead of warfarin during left atrial appendage closure with the Watchman device*. Heart Rhythm, 2017. **14**(1): pp. 19-24.
- [66] Bosche, L.I., et al., *Initial experience with novel oral anticoagulants during the first 45 Days after left atrial appendage closure with the Watchman device*. Clin Cardiol, 2015. **38**(12): pp. 720-724.

- [67] Viles-Gonzalez, J.F., et al., *The clinical impact of incomplete left atrial appendage closure with the Watchman Device in patients with atrial fibrillation: a PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) substudy*. J Am Coll Cardiol, 2012. **59**(10): pp. 923-929.
- [68] Hornung, M., et al., *Catheter-based closure of residual leaks after percutaneous occlusion of the left atrial appendage*. Catheter Cardiovasc Interv, 2016. **87**(7): pp. 1324-1330.
- [69] Main, M.L., et al., *Assessment of device-related thrombus and associated clinical outcomes with the WATCHMAN left atrial appendage closure device for embolic protection in patients with atrial fibrillation (from the PROTECT-AF Trial)*. Am J Cardiol, 2016. **117**(7): pp. 1127-1134.
- [70] Plicht, B., et al., *Risk factors for thrombus formation on the Amplatzer Cardiac Plug after left atrial appendage occlusion*. JACC Cardiovasc Interv, 2013. **6**(6): pp. 606-613.
- [71] Aminian, A., et al., *Embolization of left atrial appendage closure devices: a systematic review of cases reported with the watchman device and the amplatzer cardiac plug*. Catheter Cardiovasc Interv, 2015. **86**(1): pp. 128-135.
- [72] Behnes, M., et al., *--LAA Occluder View for post-implantation Evaluation (LOVE)--standardized imaging proposal evaluating implanted left atrial appendage occlusion devices by cardiac computed tomography*. BMC Med Imaging, 2016. **16**: p. 25.
- [73] Saw, J., et al., *Cardiac CT angiography for device surveillance after endovascular left atrial appendage closure*. Eur Heart J Cardiovasc Imaging, 2015. **16**(11): pp. 1198-1206.
- [74] Jaguszewski, M., et al., *Cardiac CT and echocardiographic evaluation of peri-device flow after percutaneous left atrial appendage closure using the AMPLATZER cardiac plug device*. Catheter Cardiovasc Interv, 2015. **85**(2): pp. 306-12.
- [75] Fastner, C., et al., *Veno-venous double lasso pull-and-push technique for transseptal retrieval of an embolized Watchman occluder*. Cardiovasc Revasc Med, 2016. **17**(3): pp. 206-208.
- [76] Gloekler, S., et al., *Early results of first versus second generation Amplatzer occluders for left atrial appendage closure in patients with atrial fibrillation*. Clin Res Cardiol, 2015. **104**(8): pp. 656-665.
- [77] Abualsaud, A., et al., *Side-by-Side comparison of LAA occlusion performance with the amplatzer cardiac plug and amplatzer amulet*. J Invasive Cardiol, 2016. **28**(1): pp. 34-38.
- [78] Lam, Y.Y., et al., *Left atrial appendage closure with AMPLATZER cardiac plug for stroke prevention in atrial fibrillation: initial Asia-Pacific experience*. Catheter Cardiovasc Interv, 2012. **79**(5): pp. 794-800.
- [79] Holmes, D.R., Jr., et al., *Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: a patient-level meta-analysis*. J Am Coll Cardiol, 2015. **65**(24): pp. 2614-2623.
- [80] Reddy, V.Y., et al., *Time to cost-effectiveness following stroke reduction strategies in AF: Warfarin Versus NOACs Versus LAA closure*. J Am Coll Cardiol, 2015. **66**(24): pp. 2728-2739.

- [81] Reddy, V., et al., *TCT-617 Cost effectiveness following treatment initiation of stroke reduction strategies in non-valvular atrial fibrillation: Warfarin vs NOACs vs left atrial appendage closure*. J Am Coll Cardiol, 2016. **68**(18S): pp. B251-B252.
- [82] Tzikas, A., et al., *Percutaneous left atrial appendage occlusion: the Munich consensus document on definitions, endpoints and data collection requirements for clinical studies*. EuroIntervention, 2016. **12**(1): pp. 103-111.
- [83] Sahay, S., et al., *Efficacy and safety of left atrial appendage closure versus medical treatment in atrial fibrillation: a network meta-analysis from randomised trials*. Heart, 2017. **103**(2): pp. 139-147.
- [84] Park, J.W., et al., *Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience*. Catheter Cardiovasc Interv, 2011. **77**(5): p. 700-6.