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Review Article

Internal Medicine Section

Percutaneous Left Appendage Closure with the Watchman Device; The Challenges Lie Ahead: A Narrative Mini Review

MOHAMMAD HASAN NAMAZI[1], ISA KHAHESHI[2], ELHAM BARKHORDARI[3], MOHAMMADREZA NADERIAN[4], FARBOD ZAHEDI TAJRISHI[5]

ABSTRACT

Atrial Fibrillation (AF) is the most prevalent arrhythmia occurring especially in the elderly. The extremely dire complication of this condition is cardiac thromboembolism that commonly arises from the Left Atrial Appendage (LAA) and may lead to stroke. Currently, guidelines recommend Oral Anticoagulants (OACs) as the therapy of choice for AF patients who are considered susceptible to develop stroke. Although, OACs have been proven effective for this purpose, they are not always an appropriate choice as they increase the likelihood of major bleeding, which can be specifically problematic to patients who for any reason, already have a moderate to high risk for bleeding. Moreover, the need for frequent PT, PTT and INR assessments and patients' non-compliance can add to the problems of long-term use of OACs. The search for alternative treatment choices has resulted in the evolution of Percutaneous Left Atrial Appendage Closure (LAAC). Multiple devices have been developed to be applied to this method, the most well-studied of which is the Watchman device. At the moment, percutaneous LAAC is being recommended only by European guidelines and just for patients with non-valvular AF (NVAF) who have a high potential for stroke and who are contraindicated to OAC therapy. The method still offers several challenges and requires more evidence to be approved as a definitive treatment option. In this article, we reviewed the concept behind LAAC and its indications, the available evidence on safety and effectiveness of LAAC with Watchman and focused on the challenges underlying this developing therapy.

Keywords: Atrial fibrillation, Device occlusion, Percutaneous left atrial appendage closure, Stroke, Thromboembolism

INTRODUCTION

The importance of AF is not a secret to any health professional nowadays With a global prevalence of approximately 2%, it is certainly one of the most common types of arrhythmia affecting especially the elderly [1]. There is strong evidence suggesting Non-Valvular AF (NVAF) is independently and significantly associated with increased risk of stroke, mainly because of the clots formed predominantly (>90%) in the LAA [2,3].

To prevent stroke in patients with NVAF, two main strategies can be applied. The first one is to reduce the risk of clot formation through oral anticoagulation therapy either with Vitamin K Antagonists (VKA) such as warfarin or Novel Oral Anticoagulants (NOAC). Despite differences in mechanism of action, efficacy and complications, both categories have been proven effective for stroke prevention in patients with NVAF who have a high stroke risk and are currently the standard treatment for this purpose. However, they increase the risk of bleeding as a major complication and are contraindicated in a significant portion of patients, not to mention a fear to the clinician prescribing them. Additionally, there have been reports of patients' non-compliance to these medications following their long-term use [4-8]. These problems have led to the search for alternative options to prevent stroke in NVAF patients, the most important of which is physical exclusion of the LAA which isolates it from the systemic circulation. The use of highly invasive procedures such as surgical removal or ligation of the LAA has been limited due to their complications and undesirable success rates [9,10]. Among the exclusion methods, the more minimally invasive percutaneous LAA closure (LAAC)/occlusion with several types of available devices (epicardial or endocardial- [Table/Fig-1]) has been a prominent point of focus in recent studies. The Watchman (Boston Scientific, Maple Grove, MN) is the only device among them that has gained FDA approval for local (LAA) stroke prophylaxis in NVAF patients who are deemed unsuited for OAC treatment. The device has been tested in 2 major Randomized Controlled Trials (RCTs) and several other registries. The RCTs- The PROTECT-AF (WATCHMAN Left Atrial Appendage Closure Device for Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy) have shown that Watchman has not been inferior to long term OAC therapy in terms of efficacy and safety, although the evidence is not enough to set a guideline protocol [11,12]. This review article aims to discuss the current evidence on the effectiveness of Watchman Percutaneous LAA occlusion therapy with a particular focus on the complications and challenges this method brings about.

Endocardial		Epicardial	
Device	**Manufacturer, headquarters**	**Device**	**Manufacturer, headquarters**
Watchman	Boston Scientific, United States	Lariat	SentreHeart, United States
ACP	St. Jude Medical, United States	AtriClip	AtriCure, United States
Amulet	St. Jude Medical, United States	Aegis	AEGIS Medical Innovations, Canada
WaveCrest	Coherex Medical, United States	Cardioblate Closure System	Medtronic, United States
Occlutech LAA Occluder	Occlutech, Germany		
SIDERIS Transcatheter Patch	Custom Medical Devices, Greece		
LAmbre	Lifetech, China		
Pfm	Pfm Medical, Germany		
Ultrasept	Cardia Inc., United States		

[Table/Fig-1]: Available devices for percutaneous LAA closure.
ACP: Amplatzer cardiac plug

The Rationale Behind LAA Closure

The LAA is an attachment to the left atrium located anterior to the atrioventricular sulcus. Its proximities include the left circumflex artery, the left pulmonary veins and the left phrenic nerve [13]. During AF, the atriums do not contract in a synchronized fashion which will give rise to a higher risk of blood stasis and the subsequent clot formation, particularly in the LAA. These clots may then travel to the brain through the circulation and cause the most feared complication of AF- ischemic strokes [14]. All this evidence has led to the hypothesis suggesting that the isolation of LAA from the circulation will decrease the risk of cardio embolic stroke in patients with NVAF.

Indications for LAA Closure

Several studies have proposed LAAC for AF patients who are unsuitable for treatment with OACs and who are also at increased risk of cardio-embolic strokes. This increased potential is evaluated by some scoring systems, most of which primarily contain clinical criteria. Although, these scoring systems are reported to be poor predictors of central nervous system complications, one of them –the CHADS2 (Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, Stroke/transient ischemic attack) score-has been the most popular model for this purpose. It's worth noting however, that this model has recently been replaced by the CHA2DS2 VASC (Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category: female) score [Table/Fig-2] [15], which is able to better assess the risk of stroke in lower-risk patient groups [16,17].

Among the several models to predict increased potential for medication-related bleeding complications in AF patients undergoing OAC treatment, the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or pre-disposition, a labile International Normalized Ratio (INR), >65 years, drug or alcohol use) score is the most commonly used [18]. While having only a moderate predictive value for any relevant major bleeding as the other bleeding risk assessment models, HAS-BLED is perhaps the best one available with a significant ability to specifically predict intracranial haemorrhage [19].

The latest guideline on the management of AF released by European Society of Cardiology (ESC) in 2012 states that LAA closure is a fine option to be considered in AF patients with a high risk for stroke who for any reason could not be treated with OACs since the benefits provided by LAAC seem to outweigh the risk for probable complications from the procedure (Class IIb, level of evidence B) [4]. A 2015 European survey responded by 33 European hospital centres, showed that most of them (94%) indeed chose to perform LAA occlusion in NVAF patients with a high stroke risk (CHA2DS2-VASc ≥ 2) [Table/Fig-2] who were ineligible for OAC therapy, although they specifically reported a high complications rate along with their results [20]. On the other hand, none of the American cardiology societies (AHA, ACC, HRS) recommend LAAC in their guidelines because of low available evidence [21]. A recent high-quality systematic review by Noelck N et al., confirms this statement by deducing that percutaneous LAA occlusion should not be a definite recommendation for AF patients who are contraindicated for OAC therapy as the evidence on its superiority is insufficient [20].

Overview of Watchman and Other Available Devices

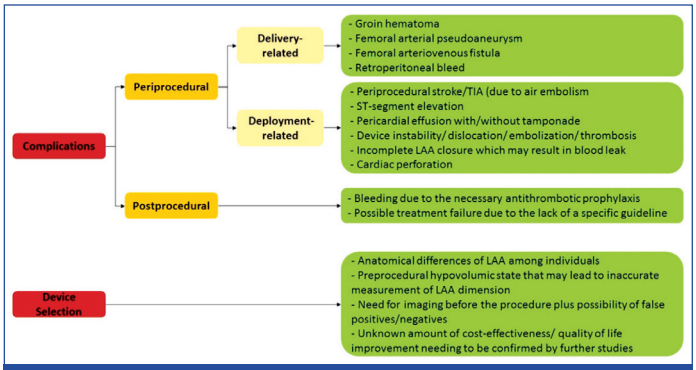
The available devices for LAA exclusion have been precisely reviewed several times during recent years. These devices can be divided into two groups; epicardial and endocardial, with the Watchman being probably the most rigorously studied among them. Being available in five different sizes, the device is an umbrella-shaped implant consisting of a self-expanding nitinol cage, several fixation barbs and a polyester membrane that lies on the left atrium facing the surface of the cage– where it maintains a constant contact with the bloodstream- to prevent clot formation. It is delivered and placed into the desired location by a catheter. The other manufactured devices are briefly reviewed in [Table/Fig-1].

CHA2DS2-VASc			HAS-BLED		
	Risk Factor	Points		Risk Factor	Points
C	Congestive Heart Failure	1	H	Hypertension	1
H	Hypertension	1	A	Abnormal liver/renal	1 or 2
A2	Age ≥ 75 years	2	S	function (1 for each)	1
D	Diabetes mellitus	1	B	Stroke	1
S2	History of Stroke or TIA	2	L	Bleeding	1
V	Vascular disease	1	E	Labile INR	1
A	Age 65-74 years	1	D	Elderly (age > 65 years)	1 or 2
Sc	Sex Category (female)	1		Drugs/alcohol (1 for each)	
Maximum points = 10			Maximum points = 9		

[Table/Fig-2]: CHA2DS2-VASc and HAS-BLED criteria for evaluation of risks for ischemic stroke and bleeding.
TIA: Transient ischemic attack

Complications and Challenges

Percutaneous LAAC can produce a wide range of complications that can be summarized into two main categories: periprocedural and postprocedural [22]. A range of serious adverse events are possible, including device embolization/instability/dislocation, major bleeding, procedure-related stroke, cardiac perforation and pericardial effusion with/without tamponade to name a few. [Table/Fig-3] shows the full list of these complications. Noelck N et al., have reported the incidence of serious adverse events with percutaneous device LAA occlusion to be 1 in every 15 patients undergoing the procedure. Although, one can instinctively assume that most of these complications may strongly be associated with operator's experience, patient selection criteria and the selected device thus, the evidence has not been enough to support such a claim [23].



[Table/Fig-3]: Complications and device selection for patients, candidate for LAA closure.

DISCUSSION

In a 2012, retrospective substudy of the PROTECT-AF, Viles-Gonzalez and colleagues assessed the incidence and clinical significance of incomplete LAAC in patients undergoing Watchman device implantation. They demonstrated that peri-device blood leak into the LAA was common after the procedure, but they claimed the leak to be in no association with increased risk for stroke. Although this report may have been attractive for hypothesis making at the time, they suggested further research to be conducted for a more definitive result, given the low sample size and event rate of the study. Moreover, they acknowledged their study was restricted to the Watchman device only, which would make it even more inappropriate to formulate a generalized hypothesis based on its findings [24].

In a 2015 meta-analysis of randomized controlled trials, Briceno et al., came to the conclusion that LAA occlusion with Watchman device is "non-inferior to warfarin therapy in terms of efficacy"; however, they recommended cautious use of the device as they found a higher rate of complications in the Watchman group [25].

The implanted device needs some time to fit into the endothelium, during which it can paradoxically act as a site for clot formation. A systematic review by Lempereur M et al., indicated that this complication- also known as Device-Associated Thrombosis (DAT) is not common and not significantly associated with cerebrovascular events [26]. They also claimed that thrombus formation due to hypersensitivity to nitinol, a nickel-titanium alloy used in several interventional cardiology devices including the Watchman device, is a rare phenomenon, if not impossible. They suggested that the polyethylene terephthalate membrane covering the nitinol frame in the Watchman device makes thrombus formation even less likely. However, they didn't completely rule out the possibility of allergy to nitinol and proposed hypersensitivity testing for patients with a history of nickel hypersensitivity [27]. Despite the low incidence rate of DAT, all current post-LAAC management strategies recommend prophylactic antithrombotic agents after the procedure because of the potential risk thromboses. In the PROTECT-AF trial that was done on patients who were NOT contraindicated for long-term OAC therapy, individuals were assigned to warfarin therapy for at least 45 days after Watchman device deployment (until closure was confirmed), followed by six months of DPI prophylaxis and then single-drug therapy with ASA [12]. During follow-up, clots were reported in 4.2% of the patients. Since most of the patients who undergo LAAC are contraindicated to OACs, prophylactic Dual Antiplatelet Therapy (DPI) with Aspirin and Clopidogrel has become a popular choice. There is no well-defined and definitive management guideline, however, stating the exact duration for dual therapy after LAAC. Different studies have suggested various durations up to six months. The ASAP trial was one of these studies that was similar to PROTECT-AF in most aspects, but was performed on the patients who were unsuitable for warfarin therapy [28,29]. In this registry, patients were first treated with DPI for six months after the procedure and afterwards with ASA only. This postprocedural therapy (without warfarin) proved to be both safe and effective, reducing the stroke rate by 77%. In a relevant study on 80 patients divided into two groups; watchman or ACP, Chun KR et al., administered a regimen of DPI (76% of patients) or preexisting OAC for six weeks after LAAC, followed by an aspirin-only strategy [30]. They found that regardless of the type of implanted device, in DPI group, the incidence of thrombus was significantly lower than OAC group (1.7% vs 15.8%). However; it was a relatively small study, and its results need to be supported by other larger trials in order to be accepted as strong evidence. The latest trial on this issue is the ASAP-TOO (The Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation), a large prospective randomized trial which is currently being performed. The population of interest and study design are somehow different from ASAP. However, patients who undergo LAAC with Watchman are those who are contraindicated for not only warfain, but also OAC therapy in general. They will be given a regimen solely based on aspirin one day before the procedure and during the whole follow-up period [31]. Considering all this information, the lack of a uniform guideline for postprocedural management seems to remain a concern and adds to the challenges that lie ahead of LAAC method.

In 2015, Price et al., compared the relative risk of major bleeding between LAAC with Watchman device and long-term warfarin stroke prophylaxis. In their pooled, patient-level analysis of 1114 NVAF patients with a 3-year follow-up period, they found no significant difference between the two groups in terms of overall (procedural and nonprocedural) incidence of major bleeding. Nevertheless, LAAC proved to be more effective in reducing the risk after six months following the procedure- when all necessary postprocedural medications except for aspirin were discontinued. With a 72% relative risk reduction for major bleedings, they concluded that while LAAC can have considerable periprocedural bleedings, it can better decrease the risk of major bleeds in the long run compared with warfarin [32].

There's still much more to be meticulously observed and studied with regards to the complications of LAAC. Until then, they will still remain a major concern when choosing this therapy method.

In addition to the mentioned complications, device-based percutaneous LAA closure in general offers several other challenges as well, all of which call for reconsideration when it comes to choosing this method as a first-line treatment. The first challenge is the anatomical differences of the LAA among individuals. There are four main recognized shapes for the LAA (each of which corresponding to a different likelihood for stroke): "cactus", "windsock", "cauliflower" and "chicken wing". It is suggested that AF patients with the first three mentioned LAA morphologies may be at a significantly higher risk for embolic events compared with those who have a chicken wing LAA [33,34]. However, this proposal has remained as a matter of controversy since in a 2013 study of 678 patients, Khurram IM et al., declared that LAA morphology was not associated with a potential stroke. They suggested instead that the extent of trabeculations within the LAA and LAA orifice dimension may be stronger predictors of stroke [35]. Spencer and colleagues highlighted the importance of LAA dimensions and their alterations with the patient's volume status as another challenge to overcome in a 2015 study. Selecting the correct device size relevant to each patient's LAA dimensions is vital since both underestimation and overestimation may result in treatment failure and/or complications. Based on the fact that pre-procedural measurements of LAA dimensions (depth and orifice diameter) by routine methods such as Computed Tomography (CT) or Trans-Esophageal Echocardiography (TEE) are usually performed after several hours of fasting, which leads to a hypovolumic state, they hypothesized the routinely administered Intravenous (IV) fluids during percutaneous LAA closure may change LAA dimensions. They demonstrated that periprocedural volume loading by infusing 500- to 1000-ml IV bolus of normal saline increases the dimensions of the compliant LAA orifice by almost 2mm. This amount is significant considering it can change the optimal device size to a whole size larger than estimated by the preprocedural assessments for many of the available devices, thus making the device selection much more difficult [36]. Although this was a small study with a low sample size (31 patients), it once more indicated the necessity of precision and paying attention to several factors before selecting the suitable device.

Apart from giving an estimate of LAA dimensions and a detailed view of the anatomy of the appendage and its neighboring structures, preprocedural cardiac CT also provides useful insight on whether a patient is suitable and not contraindicated for LAA closure by showing any thrombus already residing in LAA- an absolute contraindication to device implantation. Experts even predict this modality to overshadow TEE and become the first choice as it lends more practical information regarding device selection and evaluation of postprocedural outcomes [37,38]. However, both TEE and CT bare some limitations as pectinate muscles residing within the LAA can resemble thrombus in both modalities, making room for unnecessary patient exclusions from the procedure [39].

Clearly, more complementary studies have to be performed to further investigate the role of LAA characteristics and imaging in predicting embolic events and to establish a valid risk assessment system. Nevertheless, it seems reasonable to suggest that physical characteristics of LAA should be well taken into consideration when choosing the type of the device and its appropriate size for treatment.

Another vague aspect of choosing a device LAAC as prophylaxis for stroke in NVAF patients is the cost-effectiveness of the method through the course of time. In a 2015, well-modeled study, Reddy et al., compared LAAC (mainly with Watchman device) with warfarin and NOACs in terms of cost-effectiveness {cost per QALY (Quality-Adjusted Life-Year)} and dominance (more efficacies and less cost). According to them, LAAC becomes cost-effective relative to warfarin

(by seven years after the initiation of therapy) and NOACs (by five years). It also became dominant at 10 and five years compared with warfarin and NOACs, respectively. Though, these are promising results confirming the cost-effectiveness of LAAC in the long run, their analysis contained major limitations, which stress upon the necessity for further investigations on the true cost-effectiveness of the available treatments in general [28]. Finally, despite all the complications listed above, a recent systematic review has reported that the overall complications rate of device LAA closure has declined since the development of this method [40]. Moreover, another review has even gone further and directly suggested that performing the operation by an experienced interventionist along with the assistance of a professional echocardiographer to guide the procedure with TEE could substantially lower the complications rate [41]. Also, a recent multicenter registry has yielded low rates of both mortality and cardio-embolic events [42]. Both the effectiveness of percutaneous LAA closure and the possibility to reduce its complications, instruct for further studies on the adverse effects of the method and how to minimize them.

CONCLUSION

Device-based percutaneous LAA closure has enlightened a new path to prevent cardio-embolic strokes in NVAF patients, specifically those who are ineligible for OAC therapy. Several devices have been introduced for this purpose, but Watchman is the most well-studied one. Device-dependent trials and registries have been performed to assess the safety and efficacy of the procedure, but they haven't yet provided sufficient proof for a definitive recommendation. Ongoing and future studies can be a great help to broaden our understanding about the subject. Although researchers have suggested that percutaneous LAAC is non-inferior to clot-preventing medications, there are still a lot of challenges to overcome when selecting a device LAAC for stroke prophylaxis in NVAF patients. We strongly encourage the physicians to consider these challenges in their clinical judgments. We also suggest future studies to aim for further evaluation of the mentioned challenges.

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PARTICULARS OF CONTRIBUTORS:
1. Professor, Department of Cardiology, Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Assistant Professor, Department of Cardiology, Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
3. Resident, Department of Cardiology, Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
4 Resident, Department of Cardiology, Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran; and Cardiac Outcome Research and Education (CORE), Universal Scientific Education and Research Network (USERN), Tehran, Iran.
5. Physician, Department of Cardiology, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Farbod Zahedi Tajrishi,
Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran.
E-mail: farbodzt@gmail.com

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