Percutaneous left atrial appendage closure for stroke prevention in patients with atrial fibrillation: Current status and future perspective

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Abstract  Atrial fibrillation (AF) is one of the most prevalent arrhythmias worldwide and associated with an increased risk of stroke and systemic thromboembolism. Stroke prevention with direct oral anticoagulation (DOAC) is recommended in patients with non-valvular AF (NVAF) at high risk of stroke. WATCHMAN™ percutaneous left atrial appendage closure (LAAC) device is currently introduced as an alternative to DOAC for patients with NVAF ineligible for long-term administration of DOAC due to high risk of bleeding. This review article may contribute to recognize the paradigm shift in which stroke prevention should be carried out topically but not systemically, because left atrial appendage (LAA) is the main source of thrombus formation in AF patients. In addition, this review article introduces the current knowledge and future perspective of LAAC strategy and technology.

Keywords  left atrial appendage closure, WATCHMAN™, non-valvular atrial fibrillation, cardiogenic thromboembolism, anticoagulation, bleeding events

1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias worldwide, and the prevalence of AF increases with senescence. The incidence of AF is gradually increasing according to the aging society, and the number of the AF patients in 2050 was predicted as 1.03 million (1.1% of Japanese population) [1]. The risk of stroke increased in five times in AF patients, and stroke is the biggest cause of bedridden status and the secondary biggest cause of dementia [2]. Among the three major subtypes of cerebral infarction (lacunar, atherothrombotic, and cardioembolic infarction), the incidence of lacunar and atherothrombotic infarction in Japan tended to decline in the recent 4 decades, whereas the incidence of cardioembolic stroke was not declined [3]. Moreover, the prognosis of the cardioembolic infarction is poor because of its larger cerebral damage and higher recurrence rate than the other two subtypes of infarction [4].

Systemic anticoagulation, the most common treatment of stroke prevention, is sometimes problematic for AF patients with high-bleeding risks. To resolve the dilemma, left atrium appendage closure (LAAC) devices were developed. Indeed, emerging LAAC devices shifted the conventional paradigm of systemic anticoagulation for stroke prevention to the new paradigm of local stroke prevention to occlude left atrium appendage (LAA) most responsible for cardiogenic stroke. In this review, we present a summary of knowledge about the LAAC that are currently performed in AF patients with high-bleeding risks.

2. Stroke Prevention in AF

In patients with AF, blood in the left atrium (LA) shows stagnant flow and hypercoagulable state associated with local D-dimer elevation. Shear rate in LA blood flow is low enough to allow the red cell aggregation (Rouleaux formation) and the microthrombus formation. These are reflected by spontaneous echo contrast (SEC) observed by echocardiogram (Figure 1). Especially in the LA structure, LAA has many parallel pectinate muscles in its inner surface area that promotes blood flow stagnation leading to the thrombus formation in the pectinate muscle groove. Indeed, the LAA thrombus were found in more than 90% of 222 non-valvular AF (NVAF) patients [5]. Thrombogenicity is evident in LAA by the complicated inner LAA surface structure, the procoagulant status of local blood, and the stagnant local blood flow with low shear rate. These are well known as Virchow’s triad.

Among the population of AF, those with AF that is not
attributed to the valvular diseases, NVAF, are increasing. The first-line therapy to prevent thromboembolism in patients with NVAF is anticoagulation with vitamin K antagonist (warfarin) or direct oral anticoagulant (DOAC). However, bleeding and poor adherence are the problems of the long-term anticoagulation in patients with NVAF. Indeed, even the international phase III trials of DOACs demonstrated the efficacy and safety of DOACs to prevent thromboembolism in patients with NVAF, the bleeding was reported to be 3 to 4% per year [6–8]. In addition, in a retrospective database cohort study to investigate the discontinuation of the anticoagulation in the 12,129 patients with NVAF with the mean follow-up period 416.6 ± 141.7 days, almost half of the patients discontinued anticoagulation [9]. In this article, patients with prior episode of bleeding and those taking warfarin compared with DOAC were apt to discontinue anticoagulation.

3. Percutaneous Left Atrial Appendage Closure

From February 2019, WATCHMAN™ (Boston Scientific Corp., Natick, MA, United States) was available to use in Japan. This LAAC device was developed for stroke prevention in AF patients mainly with contraindication of oral anticoagulation due to high bleeding risk. This device is made of a self-expanding nitinol frame and a permeable polyethylene terephthalate (PET) cap (Figure 2a). Device diameter ranges for the PET cap were 20 to 35 mm for appropriate device size selection. PET membrane prevents formation of thromboembolism originated from LAA and promotes endothelial coating on the membrane surface and thrombus formation in the occluded LAA space. Anticoagulation is discontinued 45 days after the deployment of WATCHMAN™ in the standardized regimen validated by PROTECT AF trial (Watchman left atrial appendage system for embolic protection in patients with atrial fibrillation) [10].
4. Clinical Evidence

The WATCHMAN™ and its successor, the WATCHMAN FLX™ (Boston Scientific) are the standard devices for LAAC, which are associated with largest scale of deployment and abundant clinical evidence. PROTECT AF study [11] and the PREVAIL trial (Prospective randomized evaluation of the watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy) [12] the landmark trials of randomized study designed to investigate the efficacy and the safety of LAAC in comparison with long-term treatment with warfarin, a classic vitamin K antagonist. In the meta-analyses of these multicenter trials of LAAC, indicated non-inferiority to the oral anticoagulation in the composite primary efficacy end point (stroke, systemic embolism, and cardiovascular/unexplained death) and the composite primary safety end point (major bleeding and procedure-related complications) [11–13]. In addition, compared to the oral anticoagulation, five years clinical outcomes of LAAC demonstrated that the LAAC was associated with lower incidence of cardiovascular/unexplained death (hazard risk (HR) 0.59, p = 0.027), post-procedure bleeding (HR 0.48, p = 0.0003) and hemorrhagic stroke (HR 0.2, p = 0.0022) [13]. The similar results were obtained from the Japanese trial of LAAC [14]. Furthermore, in the PRAGUE-17 trial (Left atrial appendage closure vs. novel anticoagulation agents in atrial fibrillation) to compare the anticoagulation and LAAC in NVAF patients who had a history of bleeding requiring intervention or hospitalization, a history of a cardioembolic event while taking a DOAC, and/or a high bleeding risk, LAAC was concluded to be non-inferior to the administration of DOAC for prevention of AF-related cardiovascular, neurologic and hemorrhagic events [15].

5. Therapeutic Indication

CHADS2 score is a hallmark of the stroke prediction and the indication of anticoagulation therapy in AF patients. Scoring performed as congestive heart failure (1 point), hypertension (1 point), aging (75 years old or older, 1 point), diabetes (1 point), and episode of prior stroke (2 point). Total score of 1 point or more indicates the necessity of anticoagulation using DOAC rather than warfarin [16]. Likely, HAS-BLED score is also a well-validated clinical prediction tool to estimate the major bleeding risk in anticoagulated AF patients. Scoring of the HAS-BLED score perform as hypertension, abnormal renal/liver function, stroke, bleeding history, labile international normalized ratio of prothrombin time under warfarin administration, elderly (age of 65 years old or older), drugs/alcohol consumption counted as 1 point in each [17]. Total HAS-BLED score of 3 point or more means high risk of the major bleeding requiring transfusion. Importantly, some components (hypertension, stroke and aging) in CHADS2 score were overlapped with those in HAS-BLED score, indicated that thrombosis and bleeding are vascular accidents based commonly on the senescent pathological vasculature.

Physicians had a dilemma to use oral anticoagulation for the NVAF patients with high-bleeding risks. However, the strategy was sifting nowadays to use the LAAC to avoid using the systemic anticoagulation because the clinical outcomes of LAAC was noninferior to systemic anticoagulation for stroke prevention in NVAF patients [15].

In the guidelines of LACC, LAAC was recommended as class IIb for stroke prevention in NVAF patients with contraindication of long-term anticoagulation [18, 19]. In the proper use guidelines of LAAC in Japan, LAAC was highly indicated in NVAF patients with high CHADS2 score (2 point or more), high HAS-BLED score (3 point or more),
long-term (one year or longer) dual antiplatelet therapy, and encephalopathy with diffuse amyloid angiopathy. The guidelines also described about the contraindication of LAAC in patients with 1) intracardiac (intra-atrial) thrombus, 2) previous repair of atrial septal defect/patent foramen ovale, 3) anatomical LAA structure inappropriate for LAAC, 4) procedural contraindications of implant-related catheterization or transesophageal echocardiography (TEE), 5) contraindications of oral anticoagulation and antiplatelets (aspirin and thienopyridine derivatives such as clopidogrel, prasugrel and ticagrelor) [20].

6. Implantation Procedure

Because the implantation procedures are different in each LAAC device, we limited to describe here about the WATCHMAN™ implantation. WATCHMAN™ implantation is performed under the systemic sedation and the guidance of fluoroscopy and 3-dimensional TEE that is indispensable for appropriate device sizing. The device is deployed from femoral vein using a 14-F access sheath into LA after trans-septal puncture and confirming the LA pressure ≥ 10 mmHg. Pig-tail catheter is introduced into LA to escort access sheath into the LAA entrance. After conforming LAA morphology by local injection of contrast media into LAA (Figure 3a), WATCHMAN™ advance into the tip of access sheath and unfolded within LAA by keeping the device position at the LAA entrance while retracting access sheath. Partial or total collection of positioning by refolding device is possible in the case of unsuccessful deployment. During the procedure, TEE sonographers estimate the position of the device, size of LAA, and device leak after the device deployment (Figure 3b).

Warfarin and aspirin should be administered to the patients until 45 days after the device implantation, and TEE should be performed 45 days after the procedure to confirm the fixation of LAAC device without any device-related thrombi formation. Warfarin should be withdrawn, and dual antiplatelet therapy should be started for the next six months. Thereafter, single antiplatelet therapy (aspirin) should be continued.

7. Device-Related Thrombosis

One of the biggest adverse events of the LAAC is the thrombus formation on the device when the surface is not fully endothelialized. The incidence of device-related thrombus (DRT), which is easily detected by TEE and computed tomography (Figure 4), was 3–4%, and found frequently during the day 45 and 12 months after the device implantation [21]. Compared to the patients without DRT, the risk of ischemic stroke and transient ischemic attack are 4 times higher in the patients with DRT. Even though, many cases of DRT were successfully treated by anticoagulation [22]. The independent risk factor for DRT includes hypercoagulability, pericardial effusion, renal insufficiency, deep implantation of LAAC device, and persistent or permanent AF [23]. Prevention of DRT by DOAC is reported to be equivalent to that by using warfarin [24]. In addition, DRT prevention performed by double antiplatelet therapy for patients with high-bleeding risks indicated the incidence of DRT was 4.0% [25, 26]. Because the risks of bleeding and thrombolysis are different in each patient and in the peri- and post-procedural period, physicians should select the appropriate antithrombotic or antiplatelet therapy.

8. Future Perspective

WATCHMAN FLX™ is the next-generation of WATCH-
MAN™ was approved in Japan in February 2020 (Figure 2b). Although LAAC device implantation has been shown to be feasible with clinical evidence of reducing stroke and bleeding complications, the risk of periprocedural complications such as cardiac tamponade, DRT, and subsequent thromboembolism were resided for the WATCHMAN™ implantation. However, according to an improvement of procedural technique and device design, procedural complications are gradually decreasing. Indeed, WATCHMAN FLX™, the next-generation of WATCHMAN™, achieved an improvement of procedural performance and met the primary safety endpoint (free from death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring surgery/intervention) with 0.5% (PROTECT AF: 8.7%, PREVAIL: 4.2%) and the primary effectiveness endpoint with 98.8% (PROTECT AF: 90.9%, PREVAIL: 95.1%) [10, 12, 27]. Because of the clinical superiority of the WATCHMAN FLX™, CHAMPION-AF trial (WATCHMAN FLX™ vs NOAC for embolic protection in the management of patients with non-valvular atrial fibrillation) was conducted in the US to compare the safety and the efficacy of LAAC, which was limited to WATCHMAN FLX™, with those of long-term DOAC administration. Target population of this trial was patients who were able to tolerate long-term anticoagulant therapy. The results of CHAMPION-AF trial will publish nearly in the future.

LAAC device technology has advanced further and developed AMPLATZER AMULET™ (Abbott Laboratories, Figure 4 Transesophageal echocardiographic (TEE) image (A) and schematic illustration (B) of device-related thrombus (DRT) visualized by TEE. DRT was located on the surface of the left atrial appendage (LAA) closing (LAAC) device. LAA is occupied by thrombus after the implantation of LAAC device.
Chicago, IL, USA), that is approved in the US in 2021 August. This new device is a self-expanding nitinol mesh that consists of distal and proximal parts, i.e., distal lobe anchors the device to the inner wall of LAA and proximal disc seals the LAA orifice (Figure 2c). The advantage of AMPLATZER AMULET™ is a wide applicability to the NVAF patients with complicated LAA structure. This new device may appear in Japan in near future, and head-to-head comparison of this new device to the conventional LAAC device will be expected.

9. Conclusions

LAAC for NVAF patients with high-bleeding risks is aiming to stop the long-term anticoagulation. In Japan, WATCHMAN FLX™ is using as a standard LAAC device and AMPLATZER AMULET™ may appear in near future. To prevent DRT after LAAC, because the risks of bleeding and thrombolysis are different, appropriate antithrombotic or antiplatelet therapy should be needed in each patient.

In the NVAF patients with high-bleeding risks, emerging LAAC devices shifted the conventional paradigm of systemic anticoagulation for stroke prevention to the new paradigm of local stroke prevention to occlude LAA most responsible for cardiogenic stroke. Moreover, the improvement of the LAAC outcomes and reduction of the LAAC complications because of the development of the science and technologies, the indications of LAAC are expanding. Further improvement of procedural techniques of LAAC and development of LAAC device may have a chance to expand the indications of LAAC as the first-line therapy of stroke prevention in all of the AF patients in the future.

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