Early Experience Using a Left Atrial Appendage Occlusion Device in Patients with Atrial Fibrillation

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Purpose: Atrial fibrillation (AF) is one of the major risk factors for ischemic stroke, and 90% of thromboembolisms in these patients arise from the left atrial appendage (LAA). Recently, it has been documented that an LAA occlusion device (OD) is not inferior to warfarin therapy, and that it reduces mortality and risk of stroke in patients with AF. **Materials and Methods:** We implanted LAA-ODs in 5 Korean patients (all male, 59.8±7.3 years old) with long-standing persistent AF or permanent AF via a percutaneous trans-septal approach. **Results:** 1) The major reasons for LAA-OD implantation were high risk of recurrent stroke (80%), labile international neutralizing ratio with hemorrhage (60%), and 3/5 (60%) patients had a past history of failed cardioversion for rhythm control. 2) The mean LA size was 51.3±5.0 mm and LAA size was 25.1×30.1 mm. We implanted the LAA-OD (28.8±3.4 mm device) successfully in all 5 patients with no complications. 3) After eight weeks of anticoagulation, all patients switched from warfarin to anti-platelet agent after confirmation of successful LAA occlusion by transesophageal echocardiography. **Conclusion:** We report on our early experience with LAA-OD deployment in patients with 1) persistent or permanent AF who cannot tolerate anticoagulation despite significant risk of ischemic stroke, or 2) recurrent stroke in patients who are unable to maintain sinus rhythm.

Key Words: Atrial fibrillation, left atrial appendage, occlusion device, thromboembolism

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia disease; its prevalence has been known to be 1-2% in the general population[1] and is expected to rise.[2] Due to inefficient atrial contractions and tissue factors, patients with AF have an annual 6-10% risk of ischemic stroke, and the condition is responsible for 20% of ischemic strokes.[3,4] In patients with non-valvular AF, the vast majority of intra-cardiac thrombus are generated in the left atrial appendage (LAA), according to post-mor-

tem and echocardiographic studies.[5-7] Therefore, it has been established that appropriate anticoagulation is the best treatment for stroke prevention with mortality benefits in patients with AF.[8,9] However, anticoagulation with warfarin has many limitations, such as clinical under-utility,[10,11] difficulties in achieving optimal international neutralizing ratio (INR) values (64% in Rely, 63.8% in ACTIVE W),[12,13] pharmacokinetic interactions with other drugs, food, and a lifestyle that requires regular blood test monitoring.[14] Warfarin has an annual 3-5% risk of major bleeding and still has a 1.4-1.6% risk of stroke during anticoagulation in patients with AF.[12,13] The rate of intracerebral hemorrhage has been found to be between 0.1% and 0.6% during warfarin monotherapy in contemporary reports, but the major bleeding risk increases dramatically to 7.4-10.3% when warfarin is combined with aspirin and clopidogrel.[15] In contrast to the warfarin strategy, surgeons have been reducing the risk of stroke by excising the LAA during mitral valve surgery or coronary artery bypass surgery.[16,17] Recently, a PROTECT-AF investigation revealed the percutaneous mechanical occlusion of LAA not to be inferior to that of warfarin therapy.[18] Therefore, percutaneous closure of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with AF, especially to those who cannot tolerate warfarin or who have high risk of major bleed-

ing. Here, we report our very early experiences with LAA occlusion devices in Korean patients with AF.

MATERIALS AND METHODS

Study population

This study included patients with persistent or permanent AF who had a significant risk of stroke or could not tolerate warfarin therapy. Proper informed consent was obtained from all patients. The inclusion criteria were as follows: 1) permanent AF refractory to the electrical cardioversion, 2) persistent AF with failed maintenance of sinus rhythm with anti-arrhythmic drugs, 3) persistent AF and recurrent ischemic stroke despite proper anticoagulation, and 4) inability to tolerate warfarin due to adverse effects, labile INR, or recurrent hemorrhagic complications. We excluded patients with AF who were optimal candidates for rhythm control strategy, anticoagulation, or who were at low risk for ischemic stroke.

Structure of the LAA occlusion device

We used a WATCHMAN LAA occlusion device (Atritech, Plymouth, MN, USA) for LAA closure. The WATCHMAN device is composed of three parts as displayed in Fig. 1: 1) a delivery catheter (Fig. 1A, B and C), 2) a trans-septal
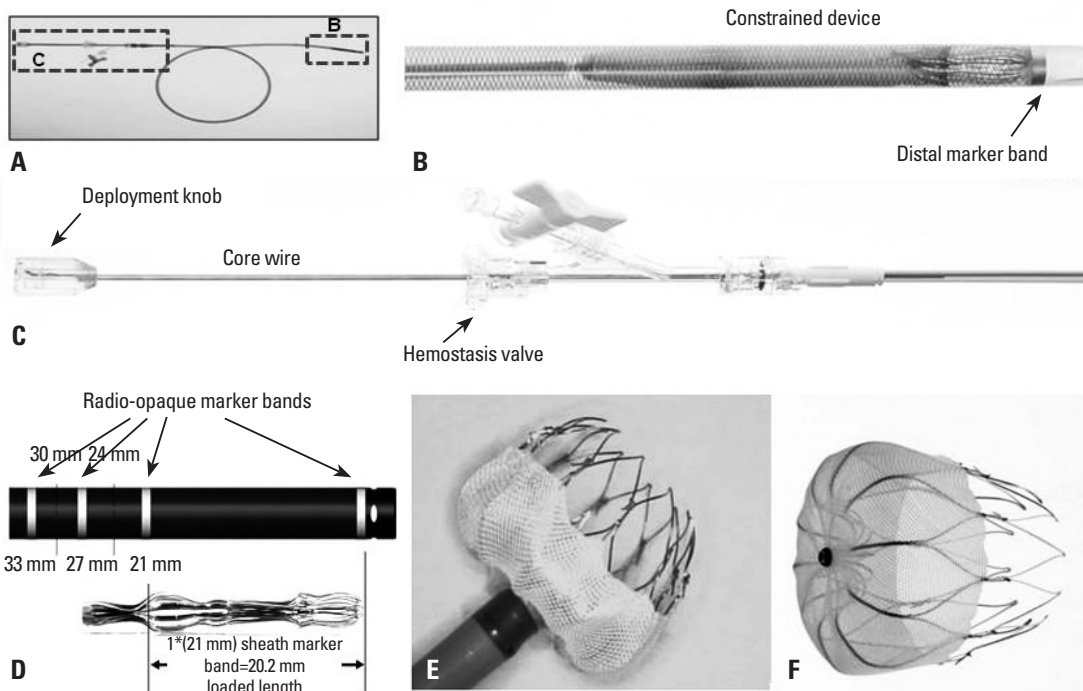

Fig. 1. LAA occlusion device. (A, B and C) Delivery catheter (A) including folded WATCHMAN device inside the catheter lumen (B) connected to the deployment knob (C) and detachable by being unscrewed. (D) Trans-septal sheath has multiple radio-opaque marker bands that indicate the locations of delivery catheter and LAA ostium. (E and F) WATCHMAN device is unfolded by elastic recoil outside of delivery sheath (E) and remains in LAA after being detached from the delivery catheter (F). LAA, left atrial appendage.

sheath (Fig. 1D), and 3) the WATCHMAN device (Fig. 1E and F). The trans-septal sheath guides the delivery catheter safely to the target site, and its depth in the LAA can be estimated under fluoroscopy by radio-opaque marker bands (Fig. 1D). The WATCHMAN device is folded inside the delivery catheter (Fig. 1B) and is designed to open like an umbrella in the LAA via plastic recoil (Fig. 1E) when the operator pulls back the delivery catheter, maintaining a fixed position of the deployment knob (Fig. 1C). The WATCHMAN device can be detached from the delivery sheath by screwing out the deployment knob, and it remains in the LAA. The WATCHMAN device is a self-expandable nitinol frame covered with a polyethyl terephthalate fabric cap. The fabric cap works as a filter with 160 μm-sized micro-pores. Five different diameters of WATCHMAN devices are currently available, depending on the size of the LAA (21, 24, 27, 30, and 33 mm).

Implantation procedure of the LAA occlusion device

Before the procedure, LAA size and shape were evaluated by trans-esophageal echocardiography (TEE; iE33, Philips Medical System, Andover, MA, USA). Anticoagulation therapy was maintained on the date of procedure and continued at least for 8 weeks after successful implantation of the LAA occlusion device. The procedure was performed under general anesthesia and using intra-procedural TEE guidance. The ostial size and depth of LAA were measured

by intra-procedural TEE at the angles of 0°, 45°, 90°, and 135° (Fig. 2A, B and C), and decided the optimal WATCHMAN device diameter, which was 8-20% larger in size than the maximal LAA ostial size. We performed a trans-septal puncture with an 8 Fr Schwartz Left 1 sheath (St. Jude Medical Inc., Minnetonka, MN, USA) via the right femoral vein approach, and exchanged it with an 11 Fr trans-septal sheath (WATCHMAN Access system, Atritech, Plymouth, MN, USA) for the delivery catheter. Immediately after the trans-septal puncture, 150 U/kg of unfractionated heparin was administered intravenously, and activated clotting time (ACT) maintained at 300-350 sec. An LAA angiogram was taken at the right anterior oblique 45° with a pig-tail catheter (6Fr, A&A Medical Device Inc., Gyeong-gi-do, Korea) inside the trans-septal sheath. The delivery catheter replaced a pig-tail catheter and was introduced into the trans-septal sheath in LAA. We lined up a distal radio-opaque marker band on the trans-septal sheath with the delivery catheter marker band, and a proximal marker band on the trans-septal sheath with ostium of LAA. After confirming the correct position via injection of contrast media, we deployed the WATCHMAN device by withdrawing the whole system (trans-septal sheath and delivery catheter together) slowly at the fixed position of the deployment knob. The WATCHMAN device is a self-expanding nickel titanium (nitinol) frame structure with fixation barbs and a permeable polyester fabric cover. After confirming secure cap-
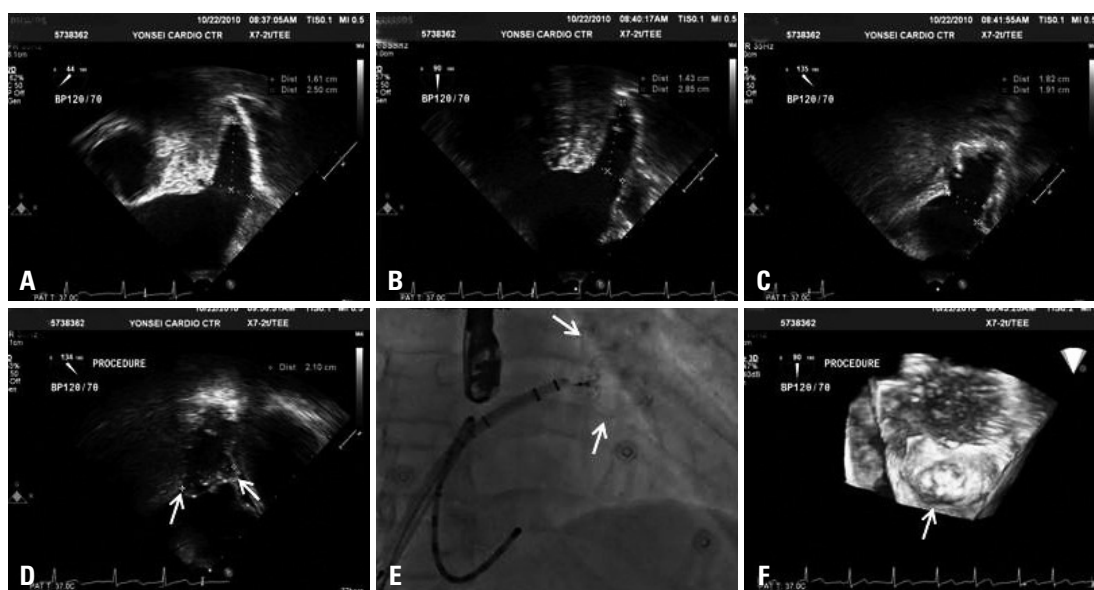

Fig. 2. Intra-procedural TEE images before (A, B and C) and after (D) deployment of LAA occlusion device. Diameter of LAA ostium and depth of LAA were measured from 4 different angles of TEE images to determine the appropriate size of WATCHMAN device. (D) Successful deployment of device should be confirmed using a tug test and color Doppler. (E) RAO 45° fluoroscopic view after deployment of WATCHMAN device. (F) Eight week follow-up 3-D TEE showed complete sealing off of LAA by WATCHMAN device. TEE, trans-esophageal echocardiography; LAA, left atrial appendage; RAO, right anterior oblique.

Table 1. Patient Characteristics

Patient number	Sex	Age	Reason for LAA occlusion	Type of AF	CHADS$_2$ score	LAAP diameter (mm)	Previous history of rhythm control trial	Type of LAA	Size of LAA (mm)	Device size (mm)	Procedure time (min)	Complication	8 weeks TEE follow up	Current antithrombotic strategy
1	M	53	Stroke, labile INR, recurrent bleeding	PtAF	3	50.0	Yes	Single lobe	21.5×29.0	27	57	None	No leakage	Antiplatelet
2	M	67	Recurrent stroke, warfarin-induced cerebral hemorrhage	PtAF	5	47.6	No	Multiple lobe	27.7×30.7	30	72	None	No leakage	Antiplatelet
3	M	60	Recurrent stroke	PeAF	4	49.4	Yes	Single lobe	19.5×28.5	24	75	None	No leakage	Antiplatelet
4	M	52	MCA infarction, left	PtAF	3	49.4	Yes	Broccoli shape	28.2×29.3	30	85	None	No leakage	Antiplatelet
5	M	67	Labile INR	PtAF	1	60.0	No	Single Lobe	28.4×33.2	33	75	None	No leakage	Antiplatelet

PtAF, permanent AF; PeAF, persistent AF; AF, atrial fibrillation; TEE, trans-esophageal echocardiography; LAA, left atrial appendage; INR, international normalized ratio clopidogrel; MCA, middle cerebral artery; LA AP, left atrial anterior-posterior.

ture of the device inside LAA via tug test and contrast injection, the device was disconnected from the deployment knob by being screwed out (Fig. 2C-F).

Post-procedural follow-up

After deployment of the WATCHMAN device, we stopped heparin and removed the sheath when ACT <250 sec. The patients were discharged the next day and maintained aspirin 100 mg and an optimal dose of warfarin (INR 2.0-3.0) for 8 weeks. TEE was repeated 8 weeks after the procedure, and we stopped warfarin and added clopidogrel 75 mg after confirming that there was no flow leakage between the WATCHMAN device and LAA.

Data analysis

We reviewed the reasons for deploying the LAA occlusion device, degrees of LA remodeling, CHADS$_2$ score, shape and size of LAA, procedure time, adverse effects, and clinical outcome.

RESULTS

We implanted LAA occlusion devices in 5 patients with AF, and the characteristics of these patients are summarized in Table 1. The mean age of the patients was 59.8±7.3 years old, and all of them were male. The major reasons for LAA occlusion device implantation were high risk of recurrent stroke (80%) and labile INR with hemorrhage (60%); 3/5 (60%) patients had a history of failed cardioversion for rhythm control. The mean LA anterior posterior diameter was 51.3±5.0 mm and LAA size was 25.1×30.1 mm. We implanted LAA occlusion devices (28.8±3.4 mm device) successfully in all 5 patients without complications. The mean procedure time was 72.8±10.1 min. After 8 weeks of anticoagulation, all patients switched from warfarin to antiplatelet agent after confirmation of successful LAA occlusion by trans-esophageal echocardiography.

Case 1

A 53-year-old male taxi driver came to the emergency room after suddenly developing right-side motor weakness. His electrocardiography showed low voltage QRS with AF, and brain computed tomography revealed an embolic cerebral infarction in the region of the left side middle cerebral artery. He had a history of persistent AF lasting longer than 4 years and initially presented with symptomatic pericardial

effusion. At that time, we could not find any pathology for pericardial effusion except for mediastinal lymphadenopathy and high adenosine deaminase level in the pericardial fluid. The mediastinal lymph node biopsy results indicated reactive hyperplasia. Anti-tuberculous medication was prescribed for one year under the impression that the patient had tuberculous pericarditis. However, he still had a mild degree of pericardial effusion, despite medication. His LA anterior posterior diameter measured by trans-thoracic echocardiography was 50.0 mm and his left ventricular ejection fraction was within the normal limits. To prevent ischemic stroke, anti-coagulation was maintained, but it was very hard to keep INR at the optimal level, despite strict drug and diet control. INR levels fluctuated remarkably, and the patient came to the emergency room several times due to severe bruising (Fig. 3). Because of labile INR with warfarin, we attempted rhythm control using cardioversion, but AF recurred very soon after cardioversion. We stopped warfarin and switched to clopidogrel; his CHADS$_2$ score was 1 at that time. Unfortunately, this patient had an embolic stroke 9 months after switching to an anti-platelet agent. Fig. 3 displays the warfarin dosage and INR values. When he started anti-tuberculous medication, his INR level was sub-optimal despite a high warfarin dosage, but it rose after stopping rifampin and increased rather drastically, even with 0.5 mg of warfarin. After an ischemic stroke, the neurologist prescribed low-dosage warfarin, but the INR value increased to higher than 8.0. Therefore, we decided to implant an LAA closing device, and the procedure was successful, with no complications (Fig. 2D and F). Because the device was well-fitted within the LAA (Fig. 2E) and there was no flow leakage between the LAA and the WATCHMAN device, we stopped warfarin and switched to clopidogrel.

Case 2

The second case was a 67-year-old male patient with hypertension and diabetes who had experienced an embolic stroke 3 years prior. Unfortunately, cerebral hemorrhage and optic nerve damage had occurred related to an adverse event of anticoagulation 2 years prior. Therefore, we switched from warfarin to aspirin and clopidogrel. However, the patient had another ischemic stroke again 7 months after starting the antiplatelet agent in place of warfarin. We decided to deploy the LAA occlusion device due to his recurrent strokes and high risk of bleeding with anticoagulation. The WATCHMAN device implantation was successful and we maintained warfarin for 8 weeks with very careful INR monitoring, and finally stopped anticoagulation after confirmation of no leakage with TEE.

Cases 3 and 4

Cases 3 and 4 had recurrent ischemic strokes and a large middle cerebral artery infarction, respectively (Table 1). The patients did not want continuous warfarin therapy because they had frequent minor bleeding despite optimal INR. Rhythm control with electrical cardioversion was attempted in both patients, but AF recurred within a week despite anti-arrhythmic drugs. Therefore, we successfully deployed a
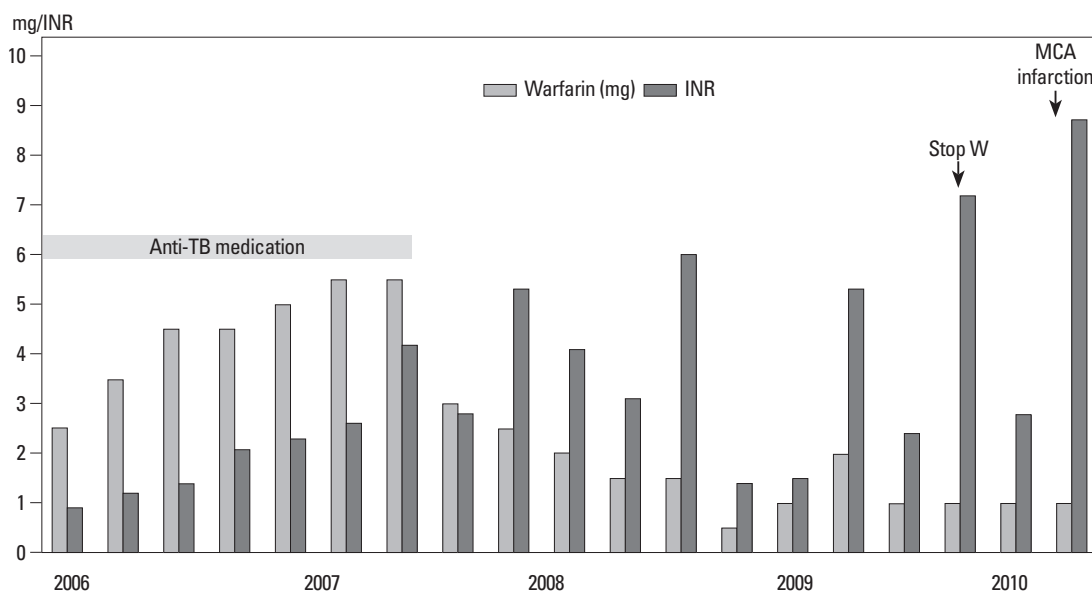

Fig. 3. Warfarin dosage and INR values of case 1. INR values were extremely labile, and ischemic stroke occurred 9 months after switching to clopidogrel. INR, international neutralizing ratio; MCA, middle cerebral artery.

WATCHMAN device in each patient. The shape of the LAA in patient #4 was of the multi-lobulated Broccoli type, with a broad base and short length. In this type of LAA, the device was easily shifted or tilted to the dominant lobe of the LAA. Therefore, we repeated deployment and recapture of the device several times, and finally implanted a 30.0 mm sized device at the optimal site without complication. The eight week follow-up TEE showed successful implantation of the device in both patients, and so warfarin was switched to anti-platelet agent.

Case 5

Case #5 was a 67-year-old patient with permanent AF. Although his CHADS$_2$ score was 1, his LA diameter was 60.0 mm and TEE showed severe spontaneous echo contrast. His INR value was very unstable and he experienced frequent purpura on his skin. Therefore, we successfully deployed the LAA occlusion device, and switched from warfarin to clopidogrel 8 weeks after implantation.

DISCUSSION

We report five cases of persistent or permanent AF that were successfully treated with LAA occlusion devices. None of the patients had been able to tolerate anticoagulation, despite significant risk of stroke because of labile INR or adverse hemorrhagic events. Three of them failed to maintain rhythm control after electrical cardioversion, and cardioversion was not attempted in two of them due to a huge atrium or to a high risk of bleeding with anticoagulation. Therefore, an LAA occlusion device might be considered for patients with persistent or permanent AF who cannot tolerate anticoagulation and cannot maintain sinus rhythm.

Efficacy of LAA closure and ideal indications
in patients with AF

It is well established that more than 90% of atrial thrombi originate from the LAA,[19] and the surgical MAZE procedure typically includes occlusion of the LAA. Current evidence regarding embolic risk reduction with percutaneous LAA occlusion is encouraging. There have been several trials evaluating less invasive LAA closure devices, such as thoracoscopic extracardiac obliteratin of LAA (LAPTO-NI)[20] or percutaneous LAA transcatheter occlusion (PLAA-TO device)[21] in order to prevent stroke in patients with AF, but the clinical outcomes were only partial successful. The

percutaneous epicardial LAA suture ligation approach was also tested for pre-clinical feasibility.[22] Recently, the PROTECT-AF trial, the largest-scale study to date, with 707 patients, showed that hemorrhagic stroke occurred less often with the WATCHMAN device than with warfarin treatment; stroke and all-cause mortality outcomes were non-inferior.[18] The inclusion criteria were: patients aged >18 years old with paroxysmal, persistent, or permanent non-valvular AF and CHADS$_2$ score ≥1. In the WATCHMAN group, the procedure success rate was 88%; 85% of them had stopped warfarin after 45 days and 92% after six months, if TEE showed residual peri-device flow jet <5 mm in width. Therefore, the WATCHMAN device is ideally indicated for patients with persistent or permanent AF who cannot tolerate anticoagulation despite a significant risk of ischemic or recurrent stroke, and who are unable to maintain sinus rhythm. If anticoagulation is contraindicated, the patient is not candidate for the WATCHMAN device, as the procedure requires that patients undergo anticoagulation for several weeks after deployment. It is not clear whether an LAA occlusion device can replace warfarin or rhythm control strategy in patients with AF; further study with a longer follow-up period is warranted.

Potential complications of LAA occlusion device

Although the PROTECT-AF trial showed the non-inferiority of the LAA occlusion device compared to warfarin (>99.9% with regard to any kind of stroke, cardiovascular or unexplained death, or systemic embolism within up to 3 years), procedure-related adverse events should be accounted for, such as cardiac tamponade (4.8%), device embolization or dislodgement (0.4%), procedure-related stroke (mostly air embolism 1.1%), or sepsis.[18] However, Reddy, et al.[23] recently reported that such adverse events were dependent on the level of experience of the operator. The subsequent registry after the PROTECT AF trial showed a significantly improved success rate of implantation (91.3% to 95.0%), and reduced procedure time as well as the occurrence of procedure-related adverse events (6.5% to 3.7%). The procedure-related stroke rate was reduced to 0%.

Unsolved issue

Long-term safety data for the WATCHMAN device are still unavailable and need to be taken into account for clinical consensus. Complex aortic plaque on the descending aorta is an independent risk factor for stroke in AF[24] and the degree of electroanatomical remodeling of LA may affect the

risk and event of stroke in patients with AF. The current guidelines recommend switching from warfarin to dural antiplatelet therapy 6-8 weeks after successful deployment of the LAA occlusion device.[18] However, the risk of bleeding with dual anti-platelet therapy should be considered even after deployment of the LAA occlusion device. Theoretically, complete rhythm control might be better than an LAA occlusion device in terms of etiology of ischemic stroke and hemodynamics. Therefore, LAA occlusion devices should be compared with catheter ablation of AF or newly developed effective anti-arrhythmic drugs.[25-27] Comparisons with direct thrombin or coagulation factor Xa inhibitors will be required.[28] The clinical efficacy of newly designed LAA closure devices, such as the Amplatzer cardiac plug, need to be evaluated in a large randomized trial.[29]

In conclusion, here we report our early experience with LAA-OD deployment in patients with 1) persistent or permanent AF who cannot tolerate anticoagulation despite significant risk of ischemic stroke or 2) recurrent stroke and inability to maintain sinus rhythm.

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