Original Article

Efficacy and Safety of the WATCHMAN Left Atrial Appendage System for Stroke Prevention in Chinese Patients with Nonvalvular Atrial Fibrillation: A Single-center, Prospective, Observational Study

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Abstract

Background: In patients with nonvalvular atrial fibrillation (NVAF), embolic stroke is thought to be associated with left atrial appendage (LAA) thrombi. The WATCHMAN LAA Occlusion Device has been shown to be noninferior to conventional oral anticoagulation with warfarin for stroke prevention in patients with NVAF. This study aimed to evaluate the procedural feasibility, safety and 12-month outcomes of the WATCHMAN LAA Occlusion Device in NVAF patients with high risk for stroke in China.

Methods: The clinical data of 106 NVAF patients, who were consecutively underwent LAA closure with the WATCHMAN Device between April 2014 and May 2015, were collected. Patients were followed up at 1, 3, 6, and 12 months after discharge. A transesophageal echocardiograph was performed at 45 days after implantation and repeated in case of an unexpected event during the follow-up period.

Results: This study included 106 NVAF patients with a mean age of 64.2 ± 8.6 years (ranging from 50 to 88 years), and the mean CHA_2DS_2-VASc score of all patients was 3.6 ± 1.6 (ranging from 2 to 9). Among those 106 NVAF patients, 100 (94.3%) patients were implanted with the device successfully. The procedural success rate was 94.3% (100/106), and the occlusion rate was 100.0% (100/100). There were one tamponade, one ischemic stroke, and eight minor pericardial effusions during hospitalization. During 12-month follow-up period, two patients developed a thrombus layer on the device that resolved with additional anticoagulation: one with visible device-thrombus experienced transient ischemic stroke, and one had a hemorrhagic stroke. There were no deaths in this study. The overall survival rate was 100.0%, and nonmajor adverse event rate was 95.0% (95/100). In this study, the expected annual rate of ischemic stroke risk in these patients according to the CHA_2DS_2-VASc score was 4.0%, while the observed ischemic stroke rate was 2.0% per year.

Conclusions: LAA closure with the WATCHMAN Device was feasible, efficient, and safe for NVAF to prevent the accidence of stroke in Chinese patients. During the 12-month follow-up period, the observed ischemic stroke rate (2.0% per year) in our study was lower than the predicted annual stroke risk (4.0%) using the CHA_2DS_2-VASc score.

Key words: Atrial Fibrillation; Left Atrial Appendage Closure; Stroke Prevention

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice,[1] occurring in as many as 0.5–1.3% in the general population. According to conservative estimates, the population of AF patients in China is over 8 million currently.[2] It is associated with substantial mortality and morbidity, particularly due to fatal or severely disabling stroke. The risk of ischemic stroke in patients with nonvalvular AF (NVAF) is 5.0% per year, which is a 5-fold increase over an age-matched population with sinus rhythm.[3] Anticoagulation with warfarin has been the main treatment for prevention of embolic events.[4] Because of the problems associated with long-term warfarin therapy, it is

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often not administered or tolerated in such patients.[5,6] Based on the epidemiological surveys in China, the percentage of AF patients who received oral anticoagulation (OAC) therapy was extremely low, with a 6.6% in hospitalized patients and 1.7% in outpatients.[2] Although new oral anticoagulants have been developed, they cannot be applied widely due to high cost and potential side effects.[7-9] In NVAF patients, more than 90% of atrial thrombus originate from the left atrial appendage (LAA).[10] Percutaneous closure of the LAA has been developed as an alternative to OAC for stroke prevention in NVAF patients, particularly in patients with contraindications to long-term OAC.[11] The PROTECT AF study demonstrated that LAA closure with the WATCHMAN Device was noninferior to warfarin for preventing stroke in NVAF.[12] However, there is still a lack of public data concerning this advanced therapy in China. This study aimed to evaluate the procedural feasibility, safety and 12-month outcome of the WATCHMAN LAA Occlusion Device in NVAF patients with high risk for stroke in China.

Methods

Patients

Between April 2014 and May 2015, 106 patients aged 18 years or older with paroxysmal, persistent, or permanent NVAF and with CHA_2DS_2-VASc score ≥2, who either had contraindication or were unwilling to accept long-term OACs, were eligible for enrollment and enrolled in this study. The exclusion criteria were as following: (1) intracardiac thrombus, including LAA or spontaneous echo-contrast visualized by transesophageal echocardiograph (TEE) within 48 h before WATCHMAN Device implanted; (2) left ventricular ejection fraction <30.0%; and (3) New York Heart Association functional Class III–IV.

All patients provided written informed consent before the procedure. This study was approved by the local Ethics Committee of Wuhan Asia Heart Hospital. All procedures performed in this study involving human participants were in accordance with the principles of the 1975 *Declaration of Helsinki*.

Implantation technique and patient management

All patients received WATCHMAN LAA Occlusion Device. Before the procedure, transthoracic echocardiography and TEE were used to determine eligibility for LAA closure. All procedures were performed by two experienced physicians in cardiac electrophysiology. After a transseptal puncture under TEE and fluoroscopic guidance, one 8-F sheath was positioned within the left atrium; thereafter, a single heparin bolus (100 U/kg of body weight) was given to target an activated clotting time (ACT) between 250 s and 300 s. The transseptal sheath was exchanged with the device delivery sheath (14-F watchman double cure) and continuously flushed with heparinized saline (20 ml/h). LAA dimensions were determined through selective LAA angiograms in standard angulations (right anterior oblique 30/20 caudal and right anterior oblique 30/20 cranial) with a 5-F standard pigtail catheter and TEE measurements (0°, 45°, 90°, and 135°). The appropriate device size was chosen according to the manufacturer recommendations. The final position of the occluder was verified by TEE with the use of color Doppler, a tug-test and by contrast medium injections oriented toward the device surface. All implantations were performed under general anesthesia.

After the procedure, all patients received warfarin (target international normalized ratio [INR]: 2.0–3.0) for 45 days. A TEE was performed at 45 days after implantation and repeated in case of an unexpected event during the follow-up period, to evaluate device stability and positioning, abnormal thrombus apposition, and residual peri-device flow. All patients discontinued warfarin after confirmation of adequate LAA sealing by TEE (defined as residual leak <5 mm around the margins of the device). If residual leak was greater than 5 mm, warfarin was continued. After warfarin treatment was stopped, once-daily low-dose aspirin (100 mg) and clopidogrel (75 mg) were prescribed until completion of 6-month follow-up visit, and then aspirin alone was continued indefinitely. Patients were followed up by assessing their clinical history at scheduled outpatient controls or through telephone contacts after 1, 3, 6, and 12 months. At each contact, the same follow-up questionnaire (information regarding stroke, transient ischemic attack (TIA), bleeding, and other complications) was used. For suspected stroke patients, brain computed tomography would be performed to further confirmation.

Primary and secondary endpoints

Primary endpoints were as following: (1) technical success (defined as successful delivery and release of the occluder into the LAA); (2) occlusion success (defined as residual leak <5 mm assessed by TEE at 45 days after implantation); and (3) procedural success (defined as technical success without any major adverse events [MAEs]). Secondary endpoints were freedom from MAEs within 12 months. MAEs included death, transient myocardial ischemia/TIA/stroke, tamponade, device embolization, air/systemic embolism, myocardial infarction, major bleeding requiring intervention or transfusion, other complication requiring surgery. Minor complications included minor pericardial effusions and vascular complications.

Statistical analysis

Statistical analyses were performed using the SPSS software version 16.0 (IBM Corp., Armonk, NY, USA). Quantitative data were expressed as mean ± standard deviation (SD), and categorical data were expressed as numbers and percentages.

Results

Demographic characteristics

This study included 106 NVAF patients (63 males and 43 females) with a mean age of 64.2 ± 8.6 years (ranging from 50 to 88 years), and the mean CHA_2DS_2-VASc score of all patients was 3.6 ± 1.6 (ranging from 2.0 to 9.0). The 38.7% (41/106) of patients experienced a previous

TIA/ischemic stroke, and the 94.3% (100/106) of patients presented with persistent or permanent AF. The reasons for patients receiving LAA closure were as following: failure to administer or not tolerate with warfarin intake (82 patients), hemorrhage (12 patients), recurrent embolism under anticoagulant therapy (8 patients), and poor compliance or other contraindication for anticoagulant therapy (4 patients). Clinical characteristics of these 106 NVAF patients are listed in Table 1.

Procedure results

Among 106 NVAF patients receiving WATCHMAN LAA Occlusion Device, implantation of the device was successfully performed in 100 patients, with a procedural success rate of 94.3%. For the remaining six patients, five had LAA anatomy abnormality that was unsuitable for device implantation, while one patient underwent urgent surgery due to cardiac tamponade and had recovered well. The occlusion rate was 100.0% (100/100). The mean diameter of the LAA orifice was 21.3 ± 4.2 mm (ranging from 13 to 32 mm). Three common sizes of the device were 27 mm (37.0%), followed by 30 mm (29.0%) and 33 mm (21.0%). The ratio of device compression was 25.2 ± 7.9%. The mean procedure time was 56.1 ± 14.7 min, fluoroscopy time was 6.8 ± 2.5 min, and the contrast amount was 80.5 ± 21.2 ml. The device implantation was successful at the first attempt in 84 patients. A second attempt was needed in 12 patients and a third attempt in 4 patients. The implantation was managed using the first device selected in 97.0% of cases, while the device had to be changed in three cases.

Adverse events

Two hospitalized patients occurred major procedural adverse events. One patient with cauliflower-like LAA had severe cardiac tamponade. In this patient, satisfactory release of the occluder could not be achieved even after repeated adjustment. When doing tug-test, the patient suffered from dramatically decline in blood pressure and weakening in heartbeat. Severe pericardial effusion was detected by TEE and was fixed by an urgent surgery soon. This patient recovered well, and no long-term complications occurred; the other one patient suffered from ischemic stroke 4 days after the procedure, but did not occur negative consequences when discharged. A seated LAA but without thrombus on the device was found in this patient by a TEE. Eight patients experienced minor pericardial effusion but did not need intervention. The 12-month follow-up data could be obtained in 95 patients. During this period, device-associated thrombus formation was verified by TEE in two patients at 45 and 153 days' visits, respectively. Both patients had no residual leak. In former patient, the thrombus was resolved after prolonged anticoagulation for 8 weeks without any clinical consequence; the other one suffered from ischemic stroke, in which the thrombus was resolved within 12 weeks of treatment with warfarin, and all symptoms were gone entirely without the need for lysis or intervention. One patient with INR of 9.5 had intracerebral hemorrhage in hospitalization during the 45-day follow-up period. Despite aggressive treatment, the patient was still in the sequelae of stroke. In our study, 12-month freedom from MAE rate was 95.0% (95/100). The observed rate of ischemic stroke in our patients was 2.0% per year, while the predicted annual stroke rate according to the CHA_2DS_2-VASc score was 4.0%. All procedure/in-hospital and follow-up adverse events are summarized in Table 2.

Transesophageal echocardiograph results

LAA seal was evaluated by TEE during the procedure immediately after device release. The 34 patients presented small residual leak (≤5 mm), and no large residual leak (>5 mm) was observed. In 88 of 100 patients, another TEE was performed 45 days after device implantation. No patients presented a residual leak >5 mm, and occlusion of the LAA was achieved in 100.0% of the investigated cases. Among the above 34 patients, five patients presented complete seal, while 25 patients remained unchanged and four presented slight increase leak. At the same time, 12 patients, who presented no residual leak

Table 1: Clinical characteristics of these 106 NVAF patients

Clinical characteristics	Values
Male, *n* (%)	63 (59.4)
Persistent or permanent atrial fibrillation, *n* (%)	100 (94.3)
Anteroposterior diameter of the left atrium (mm), mean ± SD	49.2 ± 5.5
Age (years), mean ± SD	64.2 ± 8.6
BMI (kg/m^2), mean ± SD	26.5 ± 3.7
CHA_2DS_2-VASc score, mean ± SD	3.6 ± 1.6
LVEF (%), mean ± SD	51.8 ± 5.2
Diabetes, *n* (%)	12 (11.3)
Hypertension, *n* (%)	66 (62.3)
History of TIA/ischemic stroke, *n* (%)	41 (38.7)
Coronary heart disease, *n* (%)	32 (30.2)
Hypertrophic cardiomyopathy, *n* (%)	3 (2.8)
Dilated cardiomyopathy, *n* (%)	4 (3.8)
Congenital heart disease, *n* (%)	5 (4.7)

BMI: Body mass index; LVEF: Left ventricular ejection fraction; TIA: Transient ischemic attack; SD: Standard deviation; NVAF: Nonvalvular atrial fibrillation.

Table 2: Procedure/in-hospital and follow-up adverse events in this study (*n*)

Adverse events	Procedure/ in-hospital	Follow-up	Total
Minor pericardial effusion	8	0	8
Tamponade	1	0	1
Stroke (ischemic/hemorrhagic)	1	2	3
Myocardial infarction	0	0	0
Air embolization	0	0	0
Device embolization	0	2	2
Minor bleeding	0	0	0
Major bleeding	0	1	1
Procedure/device-related death	0	0	0

during the procedure immediately after device release, have been found a new residual leak during follow-up visit.

Discussion

In our single center study, the WATCHMAN Device was implanted successfully in 94.3% of patients (100/106), similar as the successful rate reported in PREVAIL (95.0%) and PROTECT-AF (90.0%) studies.[12,13] Due to complex anatomy, the occluder was not implantable in five patients. It has been recognized that human LAA anatomy may be highly variable.[14,15] Multiple lobes and short LAA diameters may mainly affect the variability of LAA occluder. The rate of device embolization in the current study was 2.0% (2/100). It was possible that the rate of device associated thrombus in our study was underreported since only one TEE examination was performed at 45 days' follow-up visit.

In our study, one patient suffered from cardiac tamponade and was treated by pericardiocentesis and protamine injection at first, but the patient occurred hemodynamic deterioration after the treatment, then the patient received surgery and recovered. In this case, it was speculated that cardiac tamponade were caused by excessive force during the tug test. The rate for insignificant pericardial effusions during hospitalization was 8.0%. Pericardial effusions related to trans-septal puncture or tug techniques mainly occurred at the beginning of the trial, which became less frequent when highly experienced.[12]

The stroke rate in PROTECT AF and PREVAIL studies were reported as 3.2% and 1.9%, respectively.[12,13] In this study, two ischemic strokes and one hemorrhagic stroke were observed during the 12-month follow-up period, the stroke rate was 3.0%. Among two patients with ischemic stroke, one patient's CHA_2DS_2-VASc score was 4 and ischemic stroke occurred 4 days after procedure. The plasma warfarin concentration was in the therapeutic range (INR: 2.0–3.0), and a good monitoring of the activated coagulation time (ACT; >250 s) was obtained during the procedure. In addition, there was no thrombus visible on the device. It was more likely that thromboembolism came from outside the LAA. Theoretically, a LAA occluder cannot prevent stroke from thromboembolism coming from outside the LAA, the larger scale studies as PROTECT-AF and PREVAIL trials have shown that LAA occlusion was not associated with a higher stroke rate when compared to warfarin.[12,13,15,16] However, Holmes *et al*.[12] reported that 5 of 449 patients with WATCHMAN Device implantation suffered from a peri-procedural stroke. The most common cause was air embolism, which was usually short-lived. Hence, we cannot rule out the possibility of air embolism. The etiology of this stroke patient still remained unclear. The other one patient's CHA_2DS_2-VASc score was 6, and ischemic stroke was most likely due to device-related thrombus, which was first diagnosed shortly after the stroke. The endothelialization process may not be finished at 45 days after implantation when warfarin is discontinued,[17,18] OAC may be extended to a longer period to ensure proper device endothelialization especially in patients with no contraindication for anticoagulants. It was reported that complete endothelialization was documented at 9 months in a patient who died of an aortic aneurysm.[19] One patient had hemorrhagic stroke at 45 days follow-up, who had significantly increased INR of 9.5 after irregular warfarin intake. Although the patient was given vitamin K1 antagonist treatment in time, the patient had cerebral hemorrhage at the follow day. Is it beneficial for patients who are not administered or even tolerated in warfarin treatment switch to the new anticoagulants? We are looking forward to large-scale clinical researches to further investigate this question.

In our study, 100.0% (100/100) of the investigated patients had a successful occlusion, and 34.0% (34/100) had small residual leak immediately after release of the procedure. The slight residual leak after WATCHMAN Device implantation is common but not associated with increased thromboembolic events.[20] In the PROTECT-AF trial, patients with a residual leak <5 mm were less likely to have stroke/TIA than patients without a leak.[12] This was confirmed by our study. It is known that peri-device leaks can occur over time despite an initial complete closure of the LAA. Even development of new gaps after the 45th day following the procedure was described,[21] as 12 new gaps in our study. It can be explained by a minor migration of the device caused by the continuous contraction of the LAA myocardium. Nevertheless, the clinical consequence of such leaks remained doubtful as no association between residual peri-device flow and stroke rate has been detected so far.

This was an observational study from a single center with limited cases. Although all patients finished 12-month follow-up visits, prolonged periods of monitoring and follow-up are required to widen our vision about the outcome of LAA closure technique. The frequency and time-point of TEE check-out are also undetermined. In this study, we performed TEE at 45-day follow-up visit that may be associated with lower incidence of device-related thrombus formation. Larger multicenter trials and long-term follow-up are needed.

In conclusion, LAA closure with the WATCHMAN Device was feasible, efficient and safe for NVAF to prevent the accidence of stroke in Chinese patients. During 12-month follow-up, the observed ischemic stroke rate in our study was 2.0% per year, whereas the predicted annual stroke risk using the CHA_2DS_2-VASc score was 4.0%. Device related thrombus formation remains to be concerned. Large multi-center trials and long-term follow-up are needed to evaluate the safety and efficacy of this application.

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Conflicts of interest

There are no conflicts of interest.

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