

Original Article

Efficacy and safety of dabigatran and dual antiplatelet therapy after left atrial appendage occlusion with the Watchman device

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Abstract: *Objectives:* Antithrombotic therapy for patients undergoing left atrial appendage (LAA) occlusion is controversial. There is no randomized clinical trial to compare the effects of antithrombotic therapy after LAA occlusion. We aimed to explore the efficacy and safety of dabigatran and dual antiplatelet therapy after transcatheter LAA occlusion. *Methods:* Patients with persistent atrial fibrillation were randomly assigned to warfarin, dabigatran and dual antiplatelet groups equally. Transoesophageal echocardiography (TEE) examination was performed at 45-60 days postoperatively to determine whether there was residual shunt, device-related thrombosis and LAA occlusion device displacement. Thromboembolic and hemorrhagic events were evaluated at the time of follow-up. *Results:* All patients underwent successful LAA occlusion with the Watchman device. There was no statistical difference in patient's characteristics among the three groups. The average follow-up period was 18.7 ± 7.4 months. Three patients in the warfarin group, 2 patients in Dabigatran group and 2 patients in dual antiplatelet group developed skin ecchymosis. Occluder-related thrombosis was seen in 1 patient in each group. There were no statistically significant differences between the groups. Of the 3 patients with occluder thrombosis, 1 patient was switched from dual antiplatelet drugs to warfarin, and the other 2 patients had their warfarin and dabigatran therapies respectively extended to 6 months. The thrombus disappeared at 6 months by TEE. No postoperative complications, TIA or ischemic events occurred during the follow-up period. *Conclusions:* Dabigatran and dual antiplatelet therapy proved to be effective and safe for preventing stroke and device-related thrombosis after left atrial appendage occlusion with the Watchman device, without increasing the risk of bleeding.

Keywords: Left atrial appendage, warfarin, dabigatran, thrombosis

Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia, with an overall incidence of 0.4% to 2%. The incidence increases gradually with age; each additional 10 years increase the risk by 1.4 times [1]. AF is one of the leading causes of ischemic stroke. Previous studies have shown that the incidence of stroke is 5 times higher in patients with AF than in those without AF, regardless of whether it is paroxysmal AF, persistent AF, or permanent AF [2]. The mortality rate is about 3 times higher than that in patients without AF. The incidence of stroke in patients with AF who did not receive anticoagulation therapy is as high as 25% [3]. At the same time, compared to that in non-AF patients, the

1-year mortality from cardiac stroke is as high as AF, and might lead to permanent neurological deficits [4].

Many randomized controlled studies have demonstrated that oral anticoagulants are very effective in the prevention of stroke caused by AF. Warfarin is recognized as an anticoagulant that can reduce the risk of AF in patients with stroke [5], but requires frequent monitoring of international normalized ratio (INR). Besides, the patient compliance is poor due to adverse effects like gastro-intestinal symptoms, and risk of bleeding [6]. Clinical studies have demonstrated that New Oral Anticoagulants (NOAC) is better than Warfarin in prevention of stroke with AF patients, and does not require frequent

monitoring of blood coagulation index [7]. However, adverse events like bleeding and renal insufficiency might occur and the price is more expensive [8-11]. Transcatheter occlusion of the left atrial appendage (LAA) has emerged as a new method for the prevention of stroke in patients with non-valvular AF. The benefits and safety of the procedure have been confirmed by several clinical studies [12-18]. The goal of occlusion is to completely close the LAA, isolate the source of thrombus and avoid the long-term use of anticoagulant drugs. However, the procedure involves implanting a metallic foreign body, and there is a risk of thrombus formation on the surface of the occluder before complete endothelialisation of LAA occluder. Therefore, antithrombotic therapy for patients undergoing left atrial appendage occlusion is essential, especially for patients with AF who do not tolerate warfarin.

Nowadays, antithrombotic therapy for patients undergoing LAA occlusion is controversial [19]. There is no randomized clinical trial to compare the effects of antithrombotic therapy after LAA occlusion. In this study, we compared the efficacy and safety of three different types of antithrombotic therapy after LAA occlusion.

Materials and methods

Study population

A total of 99 consecutive patients with AF underwent successful LAA occlusion in our hospital from January 1, 2015 to March 31, 2017. Preoperative evaluation included clinical symptoms, AF lasting time, history of hypertension, coronary heart disease and peripheral vascular disease, diabetes, stroke or transient ischemic attack (TIA). CHA₂DS₂-VASc scores and HAS-BLED scores were calculated for all patients. All patients met the following inclusion and exclusion criteria. Inclusion criteria: 1) patients with non-valvular persistent AF; 2) age more than 18 years; 3) CHA₂DS₂-VASc \geq 2; 4) HAS-BLED \geq 3. Exclusion criteria: 1) patients with valvular heart disease; 2) preoperative transoesophageal echocardiography (TEE) revealing a suspicious or definite thrombosis in the left atrium or LAA; 3) severe heart failure (NYHA IV class); 4) severe liver and renal insufficiency; 5) acute myocardial infarction. All patients provided written informed consent to participate in this study, and the institutional ethics committee approved the study.

Device

The LAA device adopted in this study was the Watchman LAA Occlusion Device and delivery system (Boston Scientific, Natick, MA, USA).

Preoperative examination

Routine examination: All patients underwent blood, urine, stool routine, liver and kidney function, thyroid function, and blood coagulation tests, in addition to twelve lead synchronous electrocardiogram (ECG) and X-ray radiography.

Transthoracic and transoesophageal echocardiography: Transthoracic echocardiography (TTE) was performed to detect the size of cardiac chamber and valve. TEE was performed to investigate whether there was any LAA thrombosis and measure the maximum orifice size and depth of the LAA from different angles (0°, 45°, 90° and 135°) [20].

Patient grouping and medication regimen

The 99 consecutive patients with non-valvular persistent AF were randomly divided into warfarin group, Dabigatran group and dual antiplatelet group equally (n=33). The treatment regimens were as follows: patients in the Warfarin group received warfarin administration after operation, and the INR was maintained between 2.0 and 3.0. After 45 days of treatment, it was replaced by dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg) to 6 months, followed by aspirin (100 mg/day). Patients in the Dabigatran group received dabigatran administration after operation (110 to 150 mg, twice daily; the dosage based on patients' age and renal function status) for 45 days, followed by 45 days to 6 months of dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg) and followed by aspirin (100 mg/day). Patients in the Dual antiplatelet group received dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg) for 6 months after operation, followed by aspirin 100 mg/day.

Left atrial appendage occlusion

Preoperative preparation: All patients provided written informed consent to participate in this study, and the institutional ethics committee approved the study protocol.

Dabigatran and dual antiplatelet therapy after LAA occlusion

Table 1. The basic characteristics of the patients

	Warfarin group	Dabigatran group	Dual antiplatelet group
Sex (male)	15	16	15
Age	70.0±8.6	66.8±9.0	69.0±7.8
AF time	3.2±4.4	3.0±2.8	3.3±2.3
HBP	22 (66.7%)	21 (63.6%)	21 (63.6%)
DM	9 (27.3%)	8 (24.2%)	8 (24.2%)
Stroke or TIA	12 (36.4%)	11 (33.3%)	11 (33.3%)
CHA ₂ DS ₂ VASc	4.5±1.5	4.3±1.4	4.4±1.4
HASBLED	3.3±0.5	3.2±0.4	3.1±0.3

AF, atrial fibrillation; HBP, high blood pressure; DM, diabetes mellitus; TIA, transient ischemic attack.

Table 2. Comparison of LAA occlusion data

	Warfarin group	Dabigatran group	Dual antiplatelet group
LAA Width	20.3±3.1	19.6±2.3 (P=0.15)	20.5±2.7 (P=0.40)
LAA Depth	27.8±3.3	28.2±2.5 (P=0.30)	28.9±2.5 (P=0.08)
Occluder size	27.0±3.0	27.1±3.6 (P=0.46)	26.8±3.2 (P=0.41)
Compression ratio	22.1±6.8	22.0±3.9 (P=0.48)	20.8±7.2 (P=0.27)
Residual shunt	4	3 (P > 0.05)	3 (P > 0.05)

LAA, left atrial appendage.

Left atrial appendage occlusion: The operation was performed under general anaesthesia with TEE monitoring according to our previous study [21]. The catheter was inserted through the right femoral vein and the pulmonary arterial, right ventricular and right atrial pressures were measured. After successful puncture of the atrial septum, the catheter was pushed into left atrium. Then, the specialized Watchman LAA access sheath was replaced into the LAA. LAA angiography was conducted through a pigtail catheter at right anterior oblique (RAO) 30° + cranial angulation 20° and RAO 30° + caudal angulation 20° to measure the maximum orifice size and depth of the LAA, respectively. The occlusion device should be 4-6 mm greater than the maximum orifice size of the LAA in combination with the results of LAA angiography and TEE.

Then, the selected occluder is delivered to the LAA along the delivery sheath and LAA angiography and TEE from multiple angles were performed to locate the position of the LAA occlusion. A traction test was performed to assess the stability and effectiveness of the LAA occlusion device (no residual shunting or

residual shunting below 5 mm). After confirming that the position of the LAA occlusion device is appropriate, the occlusion device was released.

Postoperative treatment

Postoperative medication was administered according to the regimens for warfarin group, Dabigatran group and dual antiplatelet group respectively. All patients were administered low molecular weight heparin on the day of operation and the following morning.

Follow-up

All patients were followed up after 3, 30, 45-60, 90, 180 and 360 days. The symptoms (stroke, TIA, bleeding complications), heart rate, ECG and TTE were recorded during follow up. TEE examination was performed 45-60 days postoperatively to

determine whether there was residual shunt, device-related thrombosis and LAA occlusion device displacement. Warfarin group should be regularly measured INR value.

Statistical analysis

Data was presented as the mean ± standard deviation. Analysis of variance and the X² test were adopted with SPSS software (version 13; SPSS Inc; Chicago, IL). p < 0.05 was considered to be statistical significant.

Results

Basic characteristics of patients

A total of 99 patients with persistent AF were enrolled, including 46 males and 53 females, with a mean age of 68.3±9.0 (51-82) years. The mean AF duration was 3.2±3.3 years. The major co-morbidities included 64 patients of hypertension, 82 patients of coronary heart disease (CHD) or peripheral vascular disease, 25 patients of diabetes mellitus, and 34 patients of stroke or TIA history. The CHA₂DS₂-VASc score was 4.4±1.4, and the HAS-BLED score was 3.2±0.4. **Table 1** shows the basic

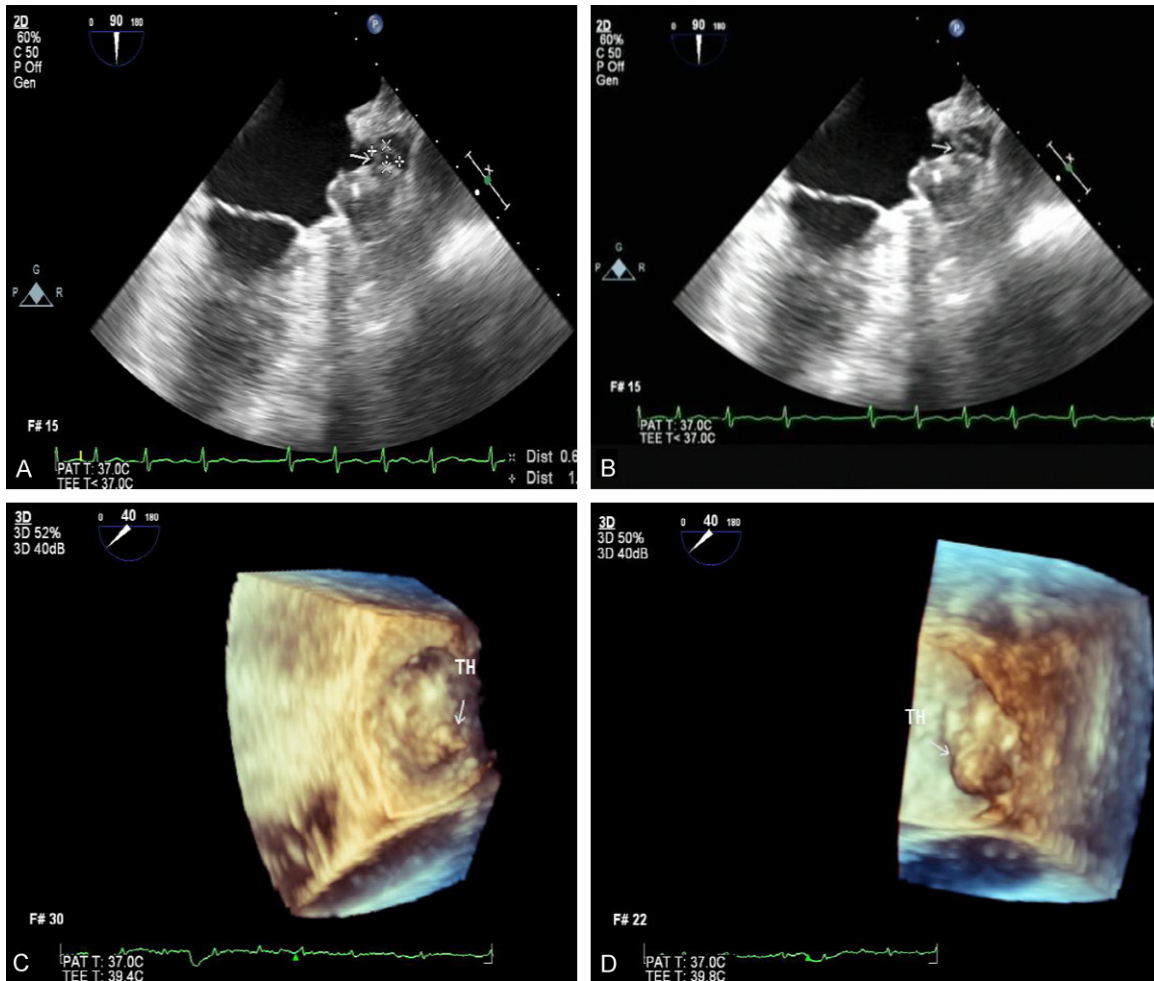


Figure 1. Thrombosis in the left atrial appendage occluder. A, B: Two dimensional ultrasound showed thrombus of the left atrial appendage occluder (arrow). C, D: Three dimensional ultrasound showed thrombosis of the left atrial appendage occluder (arrow).

characteristics of the patients. There was no significant difference in gender, age, AF duration, co-morbidities, CHA₂DS₂-VASc score and HAS-BLED score between the 3 groups ($P > 0.05$).

Comparison of data of left atrial appendage occlusion between the three groups

Table 2 shows the comparative data of the occlusion in all the three groups. There was no significant difference between the three groups with respect to the maximum diameter and depth of the LAA, size of the occluder, compression rate and the residual shunt after occlusion ($P > 0.05$).

Follow-up

All patients were followed-up for more than 6 months, with an average follow-up period of

18.7±7.4 (6-33) months. The INR value of patients in the warfarin group was 2.3±0.2, and all patients in Dabigatran group received an average dose of 290.3±26.5 mg. During the treatment, 3 patients of skin echymosis were seen in the warfarin group, and 2 patients each in the Dabigatran and dual antiplatelet groups; however, there was no significant difference among the three groups ($P > 0.05$). There were 7 patients of residual shunt after operation, of which 4 obliterated within 48-72 h after operation, 2 obliterated in 45-60 days postoperatively, and 1 obliterated after 6 months.

TEE was performed at 45-60 days after transcatheter occlusion, showed that no patient had occluder shift. There were 3 cases of occluder associated thrombosis (**Figure 1**), and 1 patient in each group. There was no statistically significant difference between the groups ($P > 0.05$). Of the 3 patients with occluder associated

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Table 3. The characteristics of the patients with thrombosis on the LAA occluder

	Sex	Age	AF time	CHA ₂ DS ₂ VASc	Maximum thrombus size by TEE	Residual shunt	Morphology of LAA
Dabigatran group	Male	77	3	7	8.8*7.8	0	Cactus
Dual antiplatelet group	Female	67	1	4	10*6.2	2.6	Cauliflower
Warfarin group	Female	68	2	4	13*9	0	Cauliflower

LAA, left atrial appendage; AF, atrial fibrillation; TEE, transesophageal echocardiography.

thrombosis, 1 patient in the dual antiplatelet group was switched to warfarin anticoagulant therapy, while the duration of warfarin and dabigatran therapy was extended to 6 months in another 2 patients. A follow-up TEE after 6 months showed no occluder related thrombosis. No stroke, TIA, or other thromboembolic events occurred during follow-up. The characteristics of the patients with thrombosis on the LAA occluder are shown in **Table 3**.

Discussion

Based on current practice and clinical research, accompanied by advancement in LAA occlusion devices and substantial experience with them, LAA occlusion can be considered as one of the important measures to prevent thromboembolic events in patients with AF. LAA occlusion can be used as an alternative treatment for patients with non-valvular AF who are at high risk for thromboembolic events, such as long-term treatment contraindications, or ineffective treatment, or those at risk of bleeding [22]. The 2016 European Society of Cardiology (ESC) AF guidelines on indications for LAA occlusion placed emphasis on its benefits for the treatment of patients with contraindications to long-term oral anticoagulant therapy [23]. However, after successful implantation of the LAA occluder, it is essential to prevent thrombosis of the occluder, without increasing the risk of bleeding.

There are three stages of antithrombotic therapy after LAA occlusion [24]. The first stage is the period of 45 days after operation. This is the most critical period as rapid endothelialisation of the occluder. Some people advocate anticoagulation therapy with warfarin or NOAC, however, some people advocate dual antiplatelet therapy. The aim is to prevent occluder thrombosis. The second stage is the period of 45 days to 6 month after operation. If no thrombus is detected by TEE, dual antiplatelet therapy

is recommended for 6 months. The third stage is the period after 6 month. Oral enteric-coated aspirin is recommended for long-term treatment. Currently, there is no consensus on the drugs to be administered during first stage therapy. Our study compared three therapeutic regimens with warfarin, Dabigatran and dual antiplatelet therapy after LAA occlusion.

Two randomized clinical studies of PROTECT AF and PREVAIL on Watchman LAA occluder have been published. They compared the efficacy of LAA occlusion and warfarin in the prevention of stroke. Results showed that LAA occlusion was non-inferior to warfarin in preventing stroke, transient cerebral ischemia, systemic embolism and cardiovascular death. In these studies, patients received warfarin and aspirin (75 mg/day) for 45 days, followed by clopidogrel and aspirin (75 mg/day each) dual antiplatelet therapy for 6 months, followed by antiplatelet therapy with aspirin for life. In the PREVAIL study, 99.3% of patients discontinued warfarin. TEE performed 45 days after LAA occlusion revealed thrombosis in 3.4% patients. Additionally, in the first 6 weeks of treatment with warfarin and aspirin, bleeding complications occurred in 6 patients, with an estimated annual haemorrhage rate of 10.5%. During follow-up, 3 (0.6%) patients receiving dual antiplatelet therapy had bleeding complications (an annual rate of about 1.6%). This suggests that anticoagulation therapy after operation is associated with bleeding events, especially during the early stage following LAA occlusion [25]. Our study also observed that the incidence of bleeding after warfarin therapy was 9% higher than that of the dual antiplatelet group and the Dabigatran group, but there was no significant difference between the three groups ($P > 0.05$).

Consistent with the AF guidelines, LAA occlusion was performed in patients with AF who were unable to tolerate oral anticoagulants. Due to the high risk of bleeding in such patients,

reduced use of antithrombotic drugs is necessary. A number of clinical trials have demonstrated the efficacy of dual antiplatelet therapy for 6 months, in patients with intolerance to oral anticoagulants after implantation of the Watchman occluder [26-28]. But there were no randomized clinical trials on such patients currently, only observational studies. Representative studies are PLAATO and ASAP studies. In the PLAATO study, due to the relative contraindication for oral anticoagulants, patients with LAA occlusion were treated with clopidogrel and aspirin dual antiplatelet drugs for 4-6 weeks, and then switched to aspirin for life [29, 30]. After 1 month or 6 months of follow-up, no occlusion thrombosis was detected by TEE. In the ASAP study, a prospective cohort of 150 valvular AF patients with CHADS2 score more than one, and contraindication for warfarin were included. Watchman LAA occlusion devices were placed as per the standard protocol and the success rate was 94% (141/150). The patients were treated with clopidogrel and aspirin for 6 months after operation. The average follow-up duration was 14.2 months, and 93 patients were followed up for more than 1 year. During the follow-up period, 6 patients (4%) developed occlusion thrombosis, of which 1 had a stroke. In the other 5 patients with thrombosis of the occluder, low molecular weight heparin was used for 4-8 weeks after thrombolysis (1 patient had spontaneous dissolution). During the first 6 months of follow-up, bleeding complications occurred in all 5 patients, with an estimated annual bleeding rate of 6.6%. In our study, we also observed that the incidence of bleeding with dual antiplatelet group was 6%. However, there was no significant difference between the three groups ($P > 0.05$). For patients with contraindication for oral anticoagulants, it is important to administer short-term antiplatelet therapy after operation to prevent thrombosis of the occluder.

There were some limitations in our study. First, the number of patients is relatively small. In addition, the follow-up time needs to be further extended.

In our study, there was no statistical difference in thromboembolic and hemorrhagic events for three antithrombotic therapies during 45 days after LAA occlusion. Dabigatran and dual antiplatelet therapies are proved to be effective and safe for preventing stroke and device-related thrombosis after left atrial appendage

occlusion with the Watchman device, without increasing the risk of bleeding.

Disclosure of conflict of interest

None.

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