Risk of device-related thrombosis following short-term oral anticoagulation with low-dose dabigatran versus warfarin after Watchman left atrial appendage occlusion

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Abstract

Background: Percutaneous left atrial appendage occlusion (LAAO) provides an alternative for poor candidates for long-term oral anticoagulation (OAC). To prevent device-related thrombosis (DRT), OAC should be continued for the first 45 days to allow complete endothelialization post-LAAO implantation. Whereas, evidence is limited on the feasibility and safety of direct oral anticoagulants (DOACs) used after LAAO.

Methods: This was a retrospective observational single-center study of AF patients undergoing LAAO with a Watchman device and receiving either low-dose dabigatran (110mg twice daily) or warfarin in the peri- and post-procedural period for 45 days. Transesophageal echocardiography was scheduled to perform at 6 weeks, 6 months, and 12 months after the procedure to assess the stability of the device and to detect DRT. Incidence of thromboembolic and bleeding events were also evaluated during the follow-up period.

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Results: There were a total of 84 patients who successfully underwent Watchman implantation, with 38 patients (45.2%) receiving low-dose dabigatran and 46 patients (54.8%) using warfarin post-LAAO. Peri-procedural complications occurred in 10 patients, with 3 patients in the dabigatran group and 7 patients in the warfarin group (7.9% vs. 15.2%, $p = 0.30$). During the 12-month follow-up, 1 patient experienced major bleeding and 16 patients suffered minor bleeding in the warfarin group, while 5 patients treated with dabigatran had minor bleeding (34.8% vs. 13.2%, $p = 0.02$). Besides, 6 DRT (15.8%) were detected in dabigatran groups, and the incidence was higher than in the warfarin group (15.8% vs. 2.2%, $p = 0.03$). No DRT-related ischemic events were found.

Conclusions: This study suggested that short-term low-dose dabigatran (110 mg twice daily) could significantly decrease the risk of bleeding compared with warfarin at the expense of increased risk of DRT post-LAAO. Therefore, low-dose dabigatran should be used with caution for post-implant anticoagulation of LAAO. Further studies are urgently needed on the feasibility and safety of DOACs post-LAAO.

Keywords
Left atrial appendage occlusion, atrial fibrillation, device-related thrombosis, dabigatran, reduced-dose

Key points
- Short-term use of low-dose dabigatran (110 mg twice daily) could significantly decrease the risk of bleeding compared with warfarin at the expense of increased risk of device-related thrombosis after left atrial appendage occlusion.
- Short-term use of low-dose dabigatran should be used with caution for post-implant anticoagulation of left atrial appendage occlusion.

Introduction
Oral anticoagulation (OAC) is the preferred therapy for stroke prevention in atrial fibrillation (AF) patients. Nevertheless, for poor candidates for long-term OAC, percutaneous left atrial appendage occlusion (LAAO) provides an alternative. LAAO has been compared with warfarin at increased stroke risk for AF patients in 2 randomized controlled trials (RCTs) of the Watchman device: PROTECT-AF$^2$ and PREVAIL$^3$ trials, which supported the non-inferiority of LAAO. Accordingly, Europe and U.S. approved the Watchman device for LAAO to reduce the thromboembolism risk associated with AF. However, there have been some reports of device-related thrombosis (DRT) related to LAAO with the incidence close to 3%-6%.$^4$ Therefore, OAC should be continued for the first 45 days to allow complete endothelialization of the device to prevent DRT.$^{2,3}$ According to European Heart Rhythm Association /European Association of Percutaneous Cardiovascular Interventions expert consensus statement, warfarin with the international normalized ratio (INR) of 2 to 3 should be given for 45 days followed by dual antiplatelet therapy for 6 months after Watchman implantation.$^5$ As the complexity of warfarin use, there has been considerable interest in the direct oral anticoagulants
(DOACs) as an alternative in the peri- and post-procedural period. Whereas, evidence is still limited on the safety and effectiveness of DOACs in this setting.

Dabigatran, as a directly inhibiting thrombin, represents an alternative to warfarin due to the preferable trade-off between embolism and bleeding. In the randomized evaluation of long-term anticoagulation therapy trial, dabigatran administered at a dose of 110 mg twice daily was associated with similar rates of stroke and systemic embolism when compared to warfarin, in reverse with lower rates of major hemorrhage. Given that, dabigatran might be a feasible and safe regimen to prevent DRT, thromboembolic and bleeding events after Watchman LAAO. In this study, we described our initial experience with peri- and post-procedural use of low-dose dabigatran (110 mg) for the Watchman device. We aim to determine the incidence of DRT and clinical consequences according to the short-term use of dabigatran or warfarin anticoagulation therapy after LAAO.

Methods

Study population

This was a retrospective observational single-center study of LAAO with the Watchman device in AF patients. Between October 2018 and September 2019, all patients who successfully underwent Watchman device implantation and received either dabigatran (110 mg twice daily) or warfarin in the peri- and post-procedural period were enrolled consecutively in this study. Indications for LAAO were non-valvular AF with CHA2DS2-VASC (congestive heart failure, hypertension, age 2, diabetes mellitus, stroke 2, vascular disease, age, sex category) score ≥ 2 or HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), Drugs/alcohol) score ≥ 3 and were deemed not eligible for long-term OAC. Exclusion criteria were mechanical heart valve, intracardiac thrombus, and left ventricular ejection fraction < 30%. All physicians who performed the Watchman device implantation have had rigorous training and were certificated to ensure an appropriate level of expertise. The patients receiving dabigatran were those not willing to test the international normalized ratio (INR) regularly, or were considered to have absolute and relative contraindications to warfarin or obvious drug interactions with warfarin. The study was conducted in accordance with the Declaration of Helsinki. The protocol of this study was approved by the Ethics Committee of Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine (#2018-030) and all patients involved signed informed consent for the procedure and data collection.

Procedure, follow-up, and outcomes

A detailed description of the Watchman device implantation procedure could be found elsewhere. The procedure was performed with the patient under general anesthesia and guided with transesophageal echocardiography (TEE). Intravenous heparin was adjusted to achieve a target activated clotting time (ACT) of > 250s. The device was implanted with left atrial appendage (LAA) angiography, and fluoroscopic guidance
via the right femoral vein and transseptal access. The TEE and LAA angiography were used to confirm suitable device size and position. After implantation, the sheath was removed and vascular access hemostasis was achieved with manual compression. Patients were prescribed either a low dose of dabigatran (110mg twice daily) or warfarin with a target INR of 2–3 for at least 45 days after LAAO, followed by aspirin (100 mg daily) and clopidogrel (75 mg daily) for 6 months (Figure 1). Pharmacist-managed anticoagulation services were offered to improve adherence and compliance. After discontinuation of aspirin and clopidogrel, aspirin alone was continued for life. TEE was scheduled to perform at 6 weeks, 6 months, and 12 months follow-up post-LAAO to assess the stability of the device, residual peri-device flow, ostial position, as well as to detect DRT. DRT was defined as a thrombus formation adherent to the luminal (left atrial) side of the device detected with a TEE scan. Incidence of thromboembolic and bleeding events were also evaluated during the follow-up period. Stroke, transient ischemic attack (TIA), and systemic embolism (SE) were considered thromboembolic events. Bleeding events were classified as major bleeding and minor bleeding based on the international society on thrombosis and haemostasis criteria.10

Statistics

Categorical variables are expressed as the number and percentage and compared by Fisher’s exact test or Chi-square test. Continuous variables are expressed as mean with standard deviation and compared by paired student’s t-test or ANOVA test, as appropriate. Statistical analyzes were performed using the SPSS software, version 22.0 (SPSS Inc., Chicago, Illinois, U.S.A).

Results

Study population

There were a total of 84 patients who successfully underwent Watchman implantation. Among them, 38 patients received dabigatran after LAAO, while 46 patients were treated with warfarin. Baseline characteristics of both groups are given in Table 1. The majority (63/84, 75%) of patients receiving LAAO were persistent AF. The mean
CHA<sub>2</sub>D<sub>1</sub>S<sub>2</sub>-VASc score was 3.87 ± 1.48, and mean HAS-BLED score was 2.68 ± 1.01. No significant difference was observed in each characteristic between the two groups (p > 0.05 for each characteristic).

### Table 1. Baseline characteristics of patients with Watchman LAAO.

| Characteristics                        | Overall (n = 84) | Dabigatran (n = 38) | Warfarin (n = 46) | P value |
|----------------------------------------|-----------------|---------------------|-------------------|---------|
| Age, year                              | 68.0 ± 9.8      | 66.1 ± 10.9         | 69.8 ± 8.5        | 0.11    |
| Female                                 | 30 (35.7)       | 11 (28.9)           | 19 (41.3)         | 0.26    |
| BMI, kg/m<sup>2</sup>                  | 24.7 ± 3.2      | 25.2 ± 2.9          | 24.3 ± 3.4        | 0.20    |
| CHA<sub>2</sub>D<sub>1</sub>S<sub>2</sub>-VASc | 3.87 ± 1.48     | 3.8 ± 1.4           | 4.1 ± 1.6         | 0.46    |
| HAS-BLED                               | 2.68 ± 1.01     | 2.7 ± 0.8           | 2.7 ± 1.1         | 0.96    |
| Hypertension                           | 58 (69.0)       | 29 (76.8)           | 29 (63.0)         | 0.24    |
| Diabetes mellitus                      | 14 (16.7)       | 6 (15.8)            | 8 (17.4)          | 1.00    |
| Prior stroke                           | 42 (50.0)       | 21 (55.3)           | 21 (45.7)         | 0.51    |
| Vascular disease                       | 21 (25.0)       | 11 (28.9)           | 10 (21.7)         | 0.52    |
| Persistent AF                          | 63 (75.0)       | 28 (73.6)           | 35 (76.1)         | 0.70    |
| LV ejection fraction, %                | 58.8 ± 9.0      | 55.0 ± 3.0          | 59.1 ± 9.4        | 0.17    |
| Prior ablation                         | 10 (11.9)       | 4 (10.5)            | 6 (13.0)          | 0.93    |
| Prior pacemaker                        | 4 (4.8)         | 1 (2.6)             | 3 (6.5)           | 0.72    |
| Renal insufficiency                    | 3 (3.6)         | 1 (2.6)             | 2 (4.3)           | 1.00    |
| Serum creatinine, mmol/L              | 78.7 ± 20.2     | 80.2 ± 19.8         | 77.6 ± 19.3       | 0.52    |
| LA diameter, mm                        | 47.0 ± 5.1      | 46.0 ± 4.3          | 47.9 ± 5.7        | 0.09    |
| LV end diastolic diameter, mm          | 48.1 ± 5.3      | 47.5 ± 4.0          | 48.4 ± 6.8        | 0.49    |
| LA spontaneous contrast                | 33 (39.3)       | 13 (34.2)           | 20 (43.5)         | 0.50    |
| Device size, mm                        | 27.4 ± 3.6      | 26.9 ± 3.7          | 27.8 ± 3.5        | 0.26    |
| Maximal compression ratio              | 24.7 ± 6.9      | 23.9 ± 7.0          | 25.0 ± 6.7        | 0.45    |
| Release times                          | 1.6 ± 1.1       | 1.6 ± 1.2           | 1.5 ± 0.9         | 0.63    |
| Residue leakage>3mm                    | 13 (15.5)       | 6 (15.7)            | 7 (15.2)          | 0.70    |
| Device shoulder protrusion, mm         | 3.2 ± 2.9       | 2.9 ± 3.0           | 3.1 ± 2.8         | 0.70    |

Values are mean ± SD or n (%). AF, atrial fibrillation; BMI, body mass index; LAAO, left atrial appendage occlusion; LA, left atrial; LV, left ventricular.

CHA<sub>2</sub>D<sub>1</sub>S<sub>2</sub>-VASc score was 3.87 ± 1.48, and mean HAS-BLED score was 2.68 ± 1.01. No significant difference was observed in each characteristic between the two groups (p > 0.05 for each characteristic).

### Adverse events peri-procedurally and during follow-up

All adverse events peri-procedurally and during follow-up are summarized in Table 2. Peri-procedural complications occurred in 10 patients, with 3 patients in the dabigatran group and 7 patients in the warfarin group (7.9% vs. 15.2%, p = 0.30). For patients in the dabigatran group, all 3 peri-procedural complications were thrombus formation on the delivery sheath. For the warfarin group, 1 patient suffered major bleeding with hematoma formation at the puncture site, and 2 patients experienced minor bleeding with airway bleeding and hematoma formation at the esophagus, respectively. The other 4 peri-procedural complications in the warfarin group were 1 femoral arteriovenous fistula, 1 femoral aneurysm, 1 pericardial effusion, and 1 catheter-related urinary tract laceration. No thromboembolic events were observed during the perioperative period.
During the 12-month follow-up, overall complications were observed in 11 patients treated with dabigatran and 19 patients allocated to warfarin (28.9% vs. 41.3%, \( p = 0.15 \)). For bleeding events, 16 patients taking warfarin and 5 patients receiving dabigatran suffered minor bleeding (13.2% vs. 34.8%, \( p = 0.02 \)). 1 patient (2.2%) experienced intracerebral bleeding by accidental mistake of warfarin. For thromboembolic events, 1 stroke and 1 DRT were found in warfarin. It is noteworthy that 6 DRT were detected in dabigatran groups, and the incidence was much higher than in the warfarin group (15.8% vs 2.2%, \( p = 0.03 \)). All 7 DRTs were observed at the first follow-up of 6 weeks after discharge, and complete resolution of thrombosis was

### Table 2. Adverse events peri-procedurally and during follow-up.

| Adverse events               | Dabigatran (n = 38) | Warfarin (n = 46) | P value |
|------------------------------|---------------------|-------------------|---------|
| **Peri-procedure**           |                     |                   |         |
| Overall complications        | 3 (7.9)             | 7 (15.2)          | 0.30    |
| Major bleeding               | 0 (0.0)             | 1 (2.2)           | 1.00    |
| Minor bleeding               | 0 (0.0)             | 2 (4.3)           | 0.56    |
| Stroke, TIA, or SE           | 0 (0.0)             | 0 (0.0)           | 1.00    |
| Other complications          | 3 (7.9)             | 4 (8.7)           | 0.90    |
| **Follow-up**                |                     |                   |         |
| Overall complications        | 11 (28.9)           | 19 (41.3)         | 0.15    |
| Major bleeding               | 0 (0.0)             | 1 (2.2)\(^a\)     | 1.00    |
| Minor bleeding               | 5 (13.2)            | 16 (34.8)         | 0.02    |
| Device-related thrombosis    | 6 (15.8)            | 1 (2.2)\(^b\)     | 0.03    |
| Stroke, TIA, or SE           | 0 (0.0)             | 1 (2.2)\(^b\)     | 1.00    |
| Other complications          | 0 (0.0)             | 0 (0.0)           | 1.00    |

Values are n (%). TIA, transient ischemic attacks; SE, systemic embolism. The bold indicates statistically significant between dabigatran group and warfarin group (\( P < 0.05 \)).

\(^a\)This patient experienced a fatal intracerebral bleeding due to the overdose of warfarin.

\(^b\)This patient experienced an ischemic stroke and resulted in motional dysfunction on the left-side extremities.

During the 12-month follow-up, overall complications were observed in 11 patients treated with dabigatran and 19 patients allocated to warfarin (28.9% vs. 41.3%, \( p = 0.15 \)). For bleeding events, 16 patients taking warfarin and 5 patients receiving dabigatran suffered minor bleeding (13.2% vs. 34.8%, \( p = 0.02 \)). 1 patient (2.2%) experienced intracerebral bleeding by accidental mistake of warfarin. For thromboembolic events, 1 stroke and 1 DRT were found in warfarin. It is noteworthy that 6 DRT were detected in dabigatran groups, and the incidence was much higher than in the warfarin group (15.8% vs 2.2%, \( p = 0.03 \)). All 7 DRTs were observed at the first follow-up of 6 weeks after discharge, and complete resolution of thrombosis was

**Figure 2.** TEE at 45 days showed a typical DRT on Watchman device in a female patient treated with reduced-dose dabigatran after LAAO. (a) After switching to warfarin (INR, 2-3), the DRT disappeared in the 6 months TEE follow-up. (b) LSPV, left superior pulmonary vein.
Table 3. Echocardiographic features in patients with device-related thrombosis.

| Case | Age, sex | Initiation | Thrombus size (D × D × T, mm) | Location       | Thrombus type | Time to thrombus detection (days) | Transition | 6 months follow-up |
|------|----------|------------|-------------------------------|----------------|---------------|----------------------------------|------------|-------------------|
| 1    | 66, Female | Warfarin  | $17 \times 20 \times 10$      | Around the pin | Nonmobile     | 43                               | Warfarin  | Complete resolution |
| 2    | 66, Male  | Dabigatran | $9 \times 6 \times 9$         | Around the pin | Mobile        | 47                               | Warfarin  | Complete resolution |
| 3    | 68, Female | Dabigatran | $20 \times 18 \times 10$      | Around the pin | Mobile        | 45                               | Warfarin  | Partial resolution |
| 4    | 70, Male  | Dabigatran | $16 \times 12 \times 5$       | Edge around LSPV | Nonmobile     | 43                               | Warfarin  | Complete resolution |
| 5    | 66, Male  | Dabigatran | $9 \times 7 \times 10$        | Edge           | Mobile        | 50                               | Warfarin  | Complete resolution |
| 6    | 81, Male  | Dabigatran | $9 \times 10 \times 3$        | Edge around LSPV | Nonmobile     | 41                               | Warfarin  | Complete resolution |
| 7    | 68, Female | Dabigatran | $10 \times 9 \times 3$        | Around the pin | Nonmobile     | 45                               | Warfarin  | Complete resolution |

LSPV, left superior pulmonary vein; D, diameter; T, thickness.

aThis patient failed to attain a well-controlled INR value, and afterward titrated up the warfarin dose within target range of 2.5-3.0.

bEchocardiography detected a partially resolved thrombus on 6 months follow-up, with the thrombus size of $8 \times 6 \times 3$. 
achieved in 6 patients at a subsequent follow-up of 6 months. No DRT-related ischemic events were found. The antithrombotic regimen was changed to warfarin for patients where a thrombus appeared right after the detection. Detailed echocardiographic features and typical TEE imaging in patients with DRT are summarized in Table 3 and Figure 2. One patient experienced an ischemic stroke which resulted in emotional dysfunction on the left-side extremities.

**Discussion**

The present study aims to investigate low-dose dabigatran (110 mg twice daily) for short-term anticoagulation after LAAO with the Watchman device. Dabigatran at a dosage of 110 mg twice daily could significantly decrease the risk of bleeding compared with warfarin during the peri- and post-procedural period. Nevertheless, this benefit was obtained at the expense of increased risk of DRT. Therefore, low-dose dabigatran should be used with caution for post-implant anticoagulation of LAAO.

The DRT is considered the detection method for thrombosis adherent to the luminal side of the device by TEE or CT scan. It is reported that DRT, which is associated with a higher rate of stroke or systemic embolism during the follow-up, is not uncommon after LAAO with the incidence as high as 3%-7%. Both OAC and antiplatelet therapy might decrease the risk of DRT to some degree, implying that a LAAO strategy without antithrombotic is inappropriate. Of note, in both RCTs of PROTECT-AF and PREVAIL trials, warfarin was used for anticoagulation in combination with aspirin in patients receiving LAAO implantation, which was followed by 6 months of dual antiplatelet therapy and lifelong aspirin alone. The DRT rate was reported to be 4.2% (20/478) in PROTECT-AF, and the incidence of stroke attributed to DRT was 0.6%.

Considering that patients indicated for LAAO always had difficulties in OAC use, warfarin now is being fast replaced by DOACs with the quick reach and maintenance of a therapeutic anticoagulation level. Nevertheless, limited information was available upon the exploration of DOACs for DRT prophylaxis post-LAAO. A retrospective multicenter study assessed the feasibility and safety of DOACs in 214 patients undergoing LAAO, and the DRT rate detected in the DOACs group was 0.9% compared with 0.5% in the warfarin group, with no significant difference \((p = 1.0)\). Besides, in the EWOLUTION study, a prospective multicenter observational study, DRT incidence of 1.3% was reported in 109 patients with DOACs treatment after LAAO, compared with the DRT incidence being 0.8% in the warfarin group. Another study evaluated patients in the LAAO Registry of the National Cardiovascular Data Registry who underwent LAAO with the Watchman device and found a lower incidence of DRT in patients receiving DOACs (1.82%) than dual antiplatelet therapy (3.31%) within the 45-day follow-up window. However, in our study, 6 DRT (6/38, 15.8%) were detected in patients receiving low-dose dabigatran, which was much higher than that in the warfarin group (1/46, 2.2%). The results were quite different from the above-mentioned studies, which became a question worthy of consideration. Meanwhile, it is worth noting that dabigatran increased the rate of thromboembolic complications compared with warfarin when used in patients with mechanical heart valves in RE-ALIGN trial, which was in accordance with our results. Whereas, different results were observed in patients using apixaban and...
It was reported that low-dose apixaban (2.5 mg, b.i.d) had a lower rate (8%) of events (including thromboembolic events and bleeding events) compared with antiplatelet therapy (12%). In addition, reduced-dose of rivaroxaban (10 mg or 15 mg, o.d) could be achieved lower thrombin generation measurement and lower incidence of DRT in patients after LAAO. Although different antithrombotic regimens have been explored in patients undergoing LAAO, most studies were retrospective. Therefore, more well-designed prospective studies need to be conducted to find the appropriate antithrombotic therapy. One prospective study evaluated the efficiency and safety of long-term half-dose DOAC compared with standard antithrombotic strategy and found long-term half-dose DOAC could significantly reduce the risk of the composite endpoint of DRT and TE and major bleeding events compared with a standard, antiplatelet-based, antithrombotic therapy. Some prospective randomized clinical trials are ongoing, for example, one randomized clinical trial comparing dual antiplatelet therapy with aspirin and clopidogrel and anticoagulation therapy with apixaban in patients after LAAO, and the results will be obtained in a few years.

The mechanisms of DRT formation on both mechanical heart valves and LAAO might be similar. Contact phase activation might play an important role in DRT formation, in which FXIIa is activated. Meanwhile, activated platelets also seem to be crucial in FXII activation. Therefore, a combination of an antiplatelet agent such as aspirin and DOAC might contribute to better inhibition of the upstream phase of coagulation triggered by device implantation. On the other hand, the low dosage of dabigatran used in this study might not be adequate for DRT prevention. It is reported that dabigatran concentrations of 254 to 488 ng/mL were required to the similar extents as warfarin at an INR of 2.0 to 3.5 to suppress thrombin generation induced by mechanical heart valve. However, the maximum concentrations of dabigatran were detected 116 ng/mL and 175 ng/mL at 110 mg and 150 mg twice daily, respectively. Accordingly, the concentration of reduced-dose dabigatran might be not enough for DRT prevention for the first 45 days post-LAAO, which was a possible reason for increased DRT risk in the dabigatran group in this study.

Moreover, evidence showed that the risk of DRT was not equal for all the patients receiving LAAO. The DRT risk was reported higher in patients with permanent AF, history of stroke or TIA, lower ejection fraction, vascular disease, advanced age, deep implants, and pulmonary ridge coverage and antithrombotic treatment. Although these characteristics are important to consider in DRT risk, there is no threshold level for any of the above predictors to guide clinical practice. In our study, there were a total of 7 patients showing DRT within 6 weeks after LAAO. Among them, 5 were persistent AF, and 2 were paroxysmal AF. The majority of them (5/7, 71.4%) suffered a stroke at least once. Other characteristics of these 7 patients had no significant difference from those of general patients in this study, which suggested that patients involved in this study were not of high risk of DRT. Besides, all the characteristics in patients of both two groups were of no significance (p > 0.05 for each characteristic). Accordingly, it was hypothesized that antithrombotic regimens after LAAO might be a non-negligible factor influencing the occurrence of DRT. Meanwhile, the absence of pulmonary ridge coverage was reported associated with a higher incidence of DRT after LAAO. Nevertheless, this phenomenon was just observed in LAAO with disc and lobe
devices, such as AMPLATZER Amulet and Lambre™, which formed a flat surface after the implantation. In this study, Watchman, an umbrella-shaped lobe-only device, was used, which formed a rounded surface of the lobe. Most cases undergoing LAAO with the Watchman device had pulmonary ridge coverage, and no DRT between the surface of the device and the limbus of pulmonary ridge was observed. As the sample size was small, the influence of pulmonary ridge coverage on the incidence of DRT after LAAO with the Watchman device was not detected. Further studies with a larger sample size might help to confirm the association.

Genetic polymorphism of drug-metabolizing enzymes may be another factor contributing to the formation of DRT. Clopidogrel is generally prescribed together with aspirin after an initial phase of oral anticoagulation to prevent DRT, as the LAA device is not fully endothelialized. However, clopidogrel resistance might influence thrombus formation. It was reported that clopidogrel resistance was more frequently found in Chinese patients than in patients of other ethnic groups. In a recent study, clopidogrel was replaced by either prasugrel or half dose DOAC both in combination with aspirin in patients with clopidogrel resistance, and the results found that the composite endpoint of DRT/TE events was significantly lower among patients receiving a genotype-guided antithrombotic strategy. Moreover, the ABCB1 and CES1 polymorphisms were considered to be associated with dabigatran pharmacokinetics, resulting in lower exposure to active dabigatran metabolite, which could contribute to DRT formation in patients after LAAO. Accordingly, more researches need to be done to explore the effects of genetic polymorphism of drug-metabolizing enzymes on DRT after LAAO.

Except for the high occurrence of DRT, the incidence of overall complications was relatively higher than that in multicenter registries. However, further analysis found that the majority of events were minor bleeding associated with anticoagulants (21/30, 70%). Of these, 16 minor bleeding events (16/21, 76.2%) occurred in the warfarin group. Notably, the need for frequent monitoring, narrow therapeutic range, dietary restrictions, and multiple drug interactions associated with warfarin might contribute to the difficulty of anticoagulation control. Although pharmacist-managed anticoagulation services were offered to improve adherence and compliance in the present study, the mean time in therapeutic range (TTR) level was 48.2%, which was lower than RCTs (> 65%) and may partly explain a higher amount of minor bleeding events in the warfarin group. In addition, differences in the propensity for bleeding between East Asian and white populations also explained the higher rate of minor bleeding. In an analysis of individuals from the USA with atrial fibrillation, Asian patients were at greater risk of warfarin-associated bleeding than white individuals, despite similar international normalized ratios (INR) between the two groups. According to European Society of Cardiology guidelines, the SAMe-TT2R2 (sex, age, medical history, treatment, tobacco use, race) score can be used to predict INR control. Of which, the non-White race has independent risk factors (two points) for predicting poor INR control.

Some limitations remained in this study. First, this is a retrospective observational single-center study of a small sample size. Nevertheless, our study was the first study investigating the feasibility and safety of low-dose dabigatran in the first 45 days after LAAO. Second, adjusted confounding methods, such as propensity-matched comparison, were not conducted because of the small population, which
might introduce certain biases. Third, a small thrombus on the device might not be detected, despite TEE being a gold standard for left atrial thrombosis detection. Further studies focusing on the antithrombotic regimens post-LAAO should be carefully designed and conducted, as different antithrombotic regimens are currently used and no standard is available. Both randomized controlled trials and real-world registries are urgently needed to reveal the feasibility and safety of DOACs for antithrombotic therapy after LAAO.

This study suggested that short-term dabigatran 110 mg twice daily could significantly decrease the risk of bleeding compared with warfarin at the expense of increased risk of DRT during the peri- and post-procedural period of LAAO. Therefore, low-dose dabigatran should be used with caution for post-implant anticoagulation of LAAO. Further studies are urgently needed on the feasibility and safety of DOACs post-LAAO.

Author contributions
Pu is the guarantor of the entire manuscript. Ge and Zhang contributed to the study conception and design, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. Qiao, Hao, Li, Gu, Jiang, and He contributed to the data acquisition, analysis, and interpretation.

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