Left Atrial Appendage Thrombus Prior to Atrial Fibrillation Ablation in the Era of Direct Oral Anticoagulants

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Background: In atrial fibrillation (AF) patients, the effect of direct oral anticoagulant (DOACs) therapy on the incidence of left atrial appendage thrombus (LAT) remains poorly investigated. This study examined the prevalence and risk factors of LAT in AF patients on DOACs undergoing catheter ablation, and sought an anticoagulation strategy for LAT.

Methods and Results: In 407 AF patients on DOACs, transesophageal echocardiography (TEE) was performed 1 day before ablation. If patients had LAT, initial DOACs were switched to dabigatran (300 mg) or warfarin based on their renal function; TEE was repeated after treatment for ≥4 weeks. LAT was detected in 18 patients (4.4%). The prevalence of persistent AF and low-dose treatment/inappropriate dose reduction of DOACs, CHADS2/CHA2DS2-VASc scores, serum N-terminal pro-brain natriuretic peptide levels, and LA dimension/LA volume index significantly increased in patients with LAT vs. those without LAT. AF rhythm on TEE and spontaneous echo contrast also increased in patients with LAT; LA appendage flow velocity decreased. In the multivariate analysis, persistent AF and inappropriately reduced DOAC dose were risk factors for LAT. On repeat TEE, LAT had disappeared in 13 of 16 patients treated with dabigatran and in 2 of 2 patients treated with warfarin.

Conclusions: DOACs still carry a finite risk of LAT in AF patients. Inappropriately reduced DOAC dose should be avoided to minimize the thromboembolic risk. Regular-dose dabigatran may have therapeutic efficacy against LAT.

Key Words: Anticoagulation; Atrial fibrillation; Catheter ablation; Thrombus; Transesophageal echocardiography
Methods

Study Population
From November 2014 to December 2017, 446 AF patients undergoing catheter ablation at Fujita Health University were enrolled. Written informed consent was given by all patients. We excluded 39 patients because they were on warfarin therapy, resulting in 407 AF patients on DOACs being included in this study.

Baseline demographics and clinical information were obtained, and transthoracic echocardiography (TTE) and laboratory examinations were performed before catheter ablation. CHADS2 and CHA2DS2-VASc scores were calculated.12 13

OAC Therapy
All patients had continuous OAC therapy with a DOAC at regular or low doses for ≥24 weeks before the procedure (dabigatran 150mg/110mg b.i.d., rivaroxaban 15mg/10mg q.i.d., apixaban 5mg/2.5mg b.i.d., edoxaban 60mg/30mg q.i.d.). Of note, 15mg and 10mg q.i.d. of rivaroxaban were officially approved as regular and low doses, respectively, for Japanese because of their small bodies and different pharmacokinetics.14 Approved dose criteria were specific to each DOAC, according to the patient’s renal function, weight, age, and concomitant medications, as indicated in the approved package inserts (PIs).15 16 Inappropriate dose reduction was defined as low-dose treatment by physician decision/preference that did not follow the PI for each drug. Regarding dabigatran, when 110mg b.i.d. was prescribed for patients aged <70 years with normal renal function, a CrCl ≥50 mL/min, it was defined as an inappropriately low dose. In all patients, the initial choice and dose of DOACs were decided by the physician or general practitioner who first diagnosed AF and were continued before ablation without change, interruption or heparin bridging. Although expected to show insufficient anticoagulation effect, inappropriate low-dose treatment based on physicians’ clinical decisions/preferences was allowed because the optimal periprocedural anticoagulation strategy for DOACs had not been established at the beginning of this study.

Echocardiography
TTE was performed with a cardiovascular ultrasound system (iE33, Philips Healthcare, Andover, MA, USA) to assess LA diameter (LAD), LA volume index (LAVI), left ventricular systolic/diastolic dimensions, and left ventricular ejection fraction (EF). Parasternal long-axis/short-axis views and apical 4-/2-chamber/long-axis views were obtained. The M-mode-derived anteroposterior LAD was measured in the parasternal long-axis view.

The first TEE was performed 1 day before catheter ablation, using an ultrasound system equipped with a TEE transducer (X7-2t, Philips Healthcare). Multiple planes of the LAA, including a continuous sweep from 0 to 180 degrees with long-axis views of the LAA, were obtained at the mid-esophagus. LAT was defined as a circumscribed intracavitary echo-dense mass showing acoustic characteristics distinct from the surrounding endocardium and pectinate muscles observed in multiple planes.6 Spontaneous echo contrast (SEC) was defined as dynamic “smoke-like” echoes with characteristic chaotic swirling during the cardiac cycle. Investigators noted the presence of SEC. The peak diastolic emptying velocity in the LAA was measured; diastolic LAA emptying waves were obtained from 5 continuous beats, and the flow velocities were measured and averaged.17 Two observers (a cardiologist and an echocardiography technician) examined and confirmed the findings. In the case of a split decision, another observer (a cardiologist) examined the TEE findings in a blinded manner; LAT was diagnosed based on majority decision.

Ablation Procedure
In paroxysmal AF patients, pulmonary vein isolation (PVI) was performed using either cryoballoon ablation (CBA) or radiofrequency catheter ablation (RFCA) based on the LA/PV anatomy evaluated by cardiac CT imaging before the procedure; in patients with common PV or large PV ostium (>28mm), PVI was performed with RFCA. In persistent AF patients, only RFCA was used for PVI. The CBA procedure was achieved using electroanatomical mapping (EnSite NavX, St Jude Medical Inc., St. Paul, MN, USA) and fluoroscopic guidance to position the cryoballoon catheter. In the RFCA procedure, PVI was achieved using a focal “point-by-point” catheter approach, delivering RF energy to the cardiac tissue. RFCA lesion sets encircled the PV antra using electroanatomical mapping (CARTO3, Biosense Webster, Diamond Bar, CA, USA or EnSite NavX, St Jude Medical Inc.) and fluoroscopy guidance. In all patients, only the PVI strategy was used for the first AF ablation.

A bolus of 5,000–10,000 international units of unfractionated heparin (100–150 U/kg) was administered before trans-septal puncture to achieve activated clotting time (ACT) ≥300 s. ACT was measured every 20 min after the first heparin shot and additional heparin boluses were given to maintain the ACT ≥300 s.

Anticoagulation for LAT
If the first TEE detected LAT, the catheter ablation was canceled. Initial anticoagulants were then switched to dabigatran 150mg b.i.d. or warfarin q.i.d. In patients who had CrCl ≥50 mL/min, the initial anticoagulant was switched to dabigatran 150mg b.i.d., while in patients who had CrCl <50 mL/min or had already been treated with dabigatran 150mg b.i.d., the initial agent was switched to warfarin. Warfarin dose was adjusted to achieve optimal PT-INR control (2.0–3.0). Although the Japanese guideline recommends lower intensity of warfarin therapy (PT-INR 1.6–2.6) for elderly patients (≥70) with nonvalvular AF, the target PT-INR range was set to 2.0–3.0 irrespective of age for AF patients with LAT.18 After dabigatran treatment or optimal warfarin therapy for ≥24 weeks, TEE was repeated to determine if the LAT had dissolved.

Follow-up
Follow-up complication data were assessed within 30 days of the procedure. Transient ischemic attack (TIA), cerebrovascular accidents, and systemic embolic events were identified as thromboembolic events.

Statistical Analysis
Continuous variables, represented as mean±standard deviation (or median and interquartile range for skewed distributions), were compared using unpaired t-test or Wilcoxon analysis. Categorical data were expressed as frequencies and percentages and compared using χ² test. To identify the predictors of LAT, multivariable logistic regres-
DOACs and LA Thrombus in AF

were used at inappropriately reduced doses (n=9 for dabigatran 110 mg b.i.d., n=10 for rivaroxaban 10 mg q.i.d., n=7 for apixaban 2.5 mg q.i.d., n=9 for edoxaban 30 mg q.i.d.).

Prevalence of LAT on TEE
On the first TEE 18 patients (4.4%) had a LAT (n=2 for dabigatran, n=5 for rivaroxaban, n=9 for apixaban, n=2 for edoxaban). Table 1 compares the demographics of patients with LAT (LAT[+]) and without LAT (LAT[−]). LAT[+] showed a higher prevalence of persistent AF than LAT[−]. The CHADS2/CHA2DS2-VASc scores were higher in the LAT[+] than in the LAT[−] group; the prevalence of congestive heart failure (CHF) and of hypertension was increased in LAT[+]. The serum N-terminal pro-brain natriuretic peptide (NT-ProBNP) levels were higher in LAT[+] than in LAT[−]. The LAT[+] group had larger LAD and greater LAVI than the LAT[−]. The average

Results

Patients’ Characteristics

The 407 AF patients were treated with DOACs for ≥4 weeks before catheter ablation (n=45/14 for dabigatran 150 mg/110 mg b.i.d., n=117/11 for rivaroxaban 15 mg/10 mg q.i.d., n=83/9 for apixaban 5 mg/2.5 mg b.i.d, n=66/62 for edoxaban 60 mg/30 mg q.i.d.). Baseline patient characteristics are shown in Table 1. In total, 311 patients (77%) were treated with DOACs at regular doses; 96 patients (23%) were treated with low doses. In 35 patients, DOACs

were used at inappropriately reduced doses (n=9 for dabigatran 110 mg b.i.d., n=10 for rivaroxaban 10 mg q.i.d., n=7 for apixaban 2.5 mg q.i.d., n=9 for edoxaban 30 mg q.i.d.).
duration of anticoagulation before ablation did not differ between the 2 groups (Table 1). In the first TEE findings, the prevalence of AF rhythm at the time of examination and the prevalence of SEC were higher in LAT[+] than in LAT[−]; LAA flow velocity was slower in LAT[+]. The patients on DOACs at low doses (n=96) had increased prevalence of LAT (n=8, 8.3%; n=2 for dabigatran, n=1 for rivaroxaban, n=3 for apixaban, n=2 for edoxaban) compared with those on regular doses (n=10, 3.2%; odds ratio=2.74, P=0.033). In patients treated with DOACs at an appropriate dose (n=372, regular or appropriately reduced doses), the prevalence of LAT was 3.2% (n=12). In those who had DOACs at an inappropriately reduced dose (n=35), the prevalence of LAT significantly increased (n=6, 17.1%; n=2 for dabigatran, n=1 for rivaroxaban, n=3 for apixaban, odds ratio=6.41, P<0.001).

The clinical characteristics of each patient with LAT are shown in Table 2. Patients who had both a CHADS2 score of 0 and a CHA2DS2-VASc score of 0 did not develop LAT; 4 LAT patients with a CHADS2 score of 1 and with a CHA2DS2-VASc score of 1 or 2 had persistent AF and/or inappropriate dose reduction (nos. 2, 9, 10, and 12, Table 2).

### Risk Factors for LAT
Significant univariate factors were persistent form of AF, CHADS2 score (≥2 points), CHA2DS2-VASc score (≥3 points), low-dose treatment and inappropriate dose reduction of DOAC, serum NT-ProBNP level, LAD, and LAVI, all of which were directed to the multivariate analysis. LAD and LAVI were considered as categorical data with clinical cutoff values of 40 mm and 40 mL/m², respectively. After adjusting for age and sex, multivariate logistic analysis demonstrated that persistent AF and inappropriate dose reduction of DOAC were significant risk factors for LAT (Table 3).

### Anticoagulation for LAT
In the LAT[+] group, 16 patients were assigned to dabigatran (150 mg b.i.d.), and 2 patients were assigned to warfarin (Table 2). In all these patients, TEE was repeated after

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**Table 2. Clinical Characteristics of Patients With LAT**

<table>
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<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Type of AF</th>
<th>CHADS2 score (points)</th>
<th>CHA2DS2-VASc score (points)</th>
<th>NT-proBNP (pg/mL)</th>
<th>LAD (mm)</th>
<th>LAVI (mL/m²)</th>
<th>Duration of OAC before 1st TEE (days)</th>
<th>OACs</th>
<th>IDR</th>
<th>TR</th>
<th>Duration of OAC after 1st TEE (days)</th>
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<td>149</td>
<td>37</td>
<td>40.3</td>
<td>55</td>
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<td>+</td>
<td>28</td>
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<td>2</td>
<td>3</td>
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<td>66</td>
<td>Edo LD → Dab RD</td>
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NA, not available; OAC, oral anticoagulant/oral anticoagulation; PAF, paroxysmal AF; RD, regular dose; TR, thrombus resolution. Other abbreviations as in Table 1.
treatment for ≥4 weeks. LAT had disappeared in 15 patients (n=13 for dabigatran, n=2 for warfarin); representative TEE images before and after dabigatran treatment in an AF patient with LAT are shown in Figure. In the 2 patients with warfarin, PT-INR levels at the time of the second TEE were 2.48 (no. 5) and 2.86 (no. 8). Catheter ablation was successful in 15 patients after LAT had disappeared. However, LAT remained in 3 patients despite dabigatran treatment for ≥4 weeks (nos. 11, 12, and 14).

<table>
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<th>Risk factor</th>
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<td>0.64–6.99</td>
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CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

Figure. Transesophageal echocardiography (TEE) findings in an atrial fibrillation (AF) patient with left atrial appendage thrombus (LAT). (A) LAT was detected by the first TEE prior to catheter ablation. (B) Color Doppler imaging on the first TEE. (C) LAT has disappeared on the second TEE after 1-month treatment with dabigatran. (D) Color Doppler imaging on the second TEE.
Thromboembolic Events at 30-Day Follow-up
Among the patients who underwent catheter ablation (n=404), including those in whom LAT dissolved, none had TIA/stroke or systemic embolic events within 30 days of their ablation procedure.

Discussion
LAT was detected by TEE in 4.4% of AF patients on DOACs undergoing catheter ablation, albeit with ≥4 weeks of continuous anticoagulation therapy before the procedure. Persistent AF and inappropriate dose reduction of DOACs were risk factors for LAT. LAT disappeared in 13 of 16 patients (81%) treated with regular-dose dabigatran.

Prevalence of LAT in AF Patients on DOACs
Despite continuous warfarin therapy, LAT was detected by TEE in AF patients before catheter ablation and electrical cardioversion. Prior studies have shown a wide variation in the diagnostic yield of LAT, ranging from 0.6% to 6.4%.6–8 The difference in the rate of LAT occurrence is likely associated with variations in the clinical milieu and anticoagulation strategies on warfarin.

Although DOACs are preferred in clinical practice, information is limited on the effect of DOACs on LAT. Several recent studies have reported the percentage of LAT on TEE ranging from 2.1% to 4.4% in AF patients on DOACs before catheter ablation.19–23 There was no difference in the prevalence of LAT between patients with DOACs and those with warfarin.19–20 Mitamura et al22 identified 4% LAT in persistent AF patients on dabigatran undergoing electrical cardioversion. Of note, 7 of 8 patients with LAT were treated at a low dose (110mg b.i.d.). Kawabata et al23 reported that the prevalence of LAT was 2.6% in Japanese AF patients on DOACs, similar to that in those on warfarin (2.8%). In the present study, the rate of LAT was 4.4% in AF patients on DOACs, almost similar to or even higher than the rate in the prior reports.19–23 In the previous studies, DOACs were not evenly distributed, likely stemming from the later introduction of apixaban and edoxaban for clinical use compared with dabigatran and rivaroxaban during the study period. However, in the present study, the 4 DOACs were evenly distributed, and the number of patients on apixaban treatment with LAT was relatively higher. Dabigatran may be preferable for administration to younger patients with relatively lower thromboembolic risk and was prescribed more in the previous study19,23 than in the present study. TEE examination is inherently subjective, which may have resulted in different interpretations of whether LAT was present or not. The present study excluded TEE findings, such as LAA flow velocity, in the multivariate analysis to predict LAT before TEE. Medication adherence was not evaluated in this study, and it was unclear whether patients were adequately anticoagulated. These factors may have contributed to the inconsistencies in the results between studies.

Risk Factors for LAT
In AF patients on warfarin, higher CHADS2 score, LA enlargement, decreased EF, CHF, increased serum B-type natriuretic peptide (BNP) level, being elderly, cardiomyopathy, and persistent AF are reported as predictors for LAT and SEC on TEE.3,6 As for DOACs, Frenkel et al reported that CHF and persistent AF were predictors for LAT.19 Kawabata et al reported that elevated serum BNP level was the risk factor for LAT.23 However, those studies included AF patients treated not only with DOACs but also with warfarin, so these findings may not be specific for DOACs. We included patients only on DOACs; persistent AF and inappropriate dose reduction of DOACs were the risk factors for LAT. DOACs were irregularly reduced in 8.6% (35/407) of patients in this study, and inappropriately reduced DOACs were continued before ablation. The inappropriate low-dose treatment was expected to cause inadequate anticoagulation but was considered to have the advantage of preventing bleeding events. We do not know how the irregular dose of DOACs would affect the periprocedural anticoagulation and ablation procedure; no optimal anticoagulation strategy for DOACs before ablation had been established at the beginning of this study. One worldwide survey found that approximately 10% of patients were treated with irregular doses of DOAC; the bleeding event rate did not decrease but the mortality rate did increase in patients treated with an irregular dose compared with those treated with a recommended dose.18 Although physicians may prefer to use low-dose DOACs in patients with a marginal risk of bleeding, inappropriate dose reduction should be avoided.

TEE Screening for LAT
Stratifying patients who should or should not require TEE screening seems beneficial. As for warfarin treatment, preprocedural TEE might not be recommended for patients without risk factors of LAT, such as LA enlargement, structural heart disease, persistent AF, low EF, and high CHADS2/CHA2DS2-VASc scores.24–26 In the era of DOACs, Frenkel et al demonstrated that no patients with a CHA2DS2-VASc score of 0 and normal EF (≥55%) had LAT.19 Kawabata et al also reported that LAT was not found in patients with a CHA2DS2-VASc score of 0, or in paroxysmal AF patients without a prior stroke/TIA history.23 In this study, no patients with CHADS2/CHA2DS2-VASc score of 0 had LAT. Patients with both a CHADS2 score of 1 and a CHA2DS2-VASc score of 1 or 2 also did not develop LAT if they have neither persistent AF nor inappropriate dose reduction. These findings highlight a low-risk subset of patients for whom TEE may not be required before AF ablation.

Anticoagulation Strategy for LAT
Dabigatran (150mg b.i.d.) has shown superiority to warfarin in terms of the prevention of ischemic stroke, suggesting its potential antithrombotic efficacy.11 In an experimental study, dabigatran promoted fibrinolysis at clinically relevant concentrations by reducing the activation of the thrombin-activatable fibrinolysis inhibitor, an antifibrinolytic molecule.25 However, in clinical studies, the efficacy of DOACs on LAT is limited to isolated case reports or small case series.26,27 European guidelines recommend warfarin therapy for 3 weeks when LAT is detected in AF patients.28 However, bridging to warfarin is difficult in patients initially treated with DOACs because of the different pharmacokinetics and half-lives. Switching to dabigatran may be an option for LAT patients already on DOACs. Nevertheless, the number of patients was small and the protocol was not randomized so we could not identify a causal relationship in this study. Additional prospective and multicenter studies are required.
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Study Limitations
The number of patients in this study was small. Treatment adherence with DOACs was not carefully evaluated and poor adherence in some patients could have caused inadequate anticoagulation. Regular-dose rivaroxaban in Japan is different from that in Europe/North America; TEE cannot detect a small preexisting LA thrombus or sludge. Baseline myocardial structures such as the pectinate muscles of the LAA may be misdiagnosed as LAT. Although our study included a 30-day follow-up on thromboembolic events, we did not examine the clinical implication of LAT with respect to thromboembolic events during long-term follow-up.

Conclusions
DOACs still carry a finite risk of LAT and TEE-based screening is considered especially necessary in patients with thromboembolic risk. Inappropriately reduced DOAC dose increased the risk of LAT and therefore should be avoided. Regular-dose dabigatran has potential therapeutic efficacy against LAT and may be an option for an alternative anticoagulation strategy in AF patients with LAT and already on DOACs.

Disclosures
M.H. has received speaker honoraria from Boehringer Ingelheim; F.W. from Daiichi-Sankyo, Biontronik Japan, and Bristol-Myers. M.K., Y.M., T.I., K.S., and Y.O. have nothing to disclose.

References