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Valvular Heart Disease

Percutaneous Left Atrial Appendage Closure Confirmed by Intra-Procedural Transesophageal Echocardiography under Local Anesthesia: Safety and Clinical Efficacy

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Background: Percutaneous left atrial appendage closure (LAAC) is usually performed under general anesthesia (GA) guided by transesophageal echocardiography (TEE), or under local anesthesia (LA) guided by intracardiac echocardiography (ICE). GA is known to carry some disadvantages. It is sometimes technically challenging to obtain adequate imaging of the left atrial appendage (LAA) with LAAC guided by ICE. This study aimed to assess the safety and clinical efficacy of LAAC guided by TEE under LA in patients with non-valvular atrial fibrillation (AF).

Methods: A total of 159 patients (70.5 ± 8.2 years; 66% male) with AF who had a high risk of stroke and bleeding or who had contraindications for oral anticoagulation underwent LAAC under LA. TEE or computed tomography (CT) follow-up was scheduled approximately 6 weeks after the procedure. Patients were followed to assess ischemic stroke and major bleeding events.

Results: The LAA was successfully occluded in 152 patients (95.6%). There were 2 (1.3%) periprocedural major adverse events. A total of 142 patients (93.4%) finished TEE or CT follow-up. Thrombus formation as seen on the device was documented in 2 patients. All of the LAAs were completely sealed with the absence of flow or with minimal flow. The median follow-up period was 522 days, resulting in a total of 216 patient-years. Ischemic stroke occurred in 4 patients. The annual ischemic stroke rate was 1.9/100 person-years. Major bleeding occurred in 2 patients. The annual major bleeding rate was 1.9/100 person-years.

Conclusions: In this study, percutaneous LAAC using TEE under LA was safe and showed encouraging results for stroke prevention and major bleeding reduction.

Key Words: Atrial fibrillation • Local anesthesia • Major bleeding • Percutaneous left atrial appendage closure • Stroke prevention

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia. Approximately 20% to 30% of strokes are attributable to AF.[1] Oral anticoagulation (OAC) therapy using vitamin K antagonists or novel oral anticoagulants has been shown to significantly reduce the rate of stroke in patients with AF.[2-4] Percutaneous left atrial appendage closure (LAAC) has been proven to be an alternative option for patients with non-valvular AF and with contraindications for long-term OAC therapy.[5]

When LAAC was initially performed, the procedure was carried out under general anesthesia (GA) with endotracheal intubation or conscious sedation and was

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guided by transesophageal echocardiography (TEE).[5-7] GA is known to carry some disadvantages, such as the cardiac depressant effect of general anesthetics that may trigger cardiovascular instability upon induction of GA and during the procedure. In particular, hypotension and bradycardia may present upon induction, consequently resulting in the need for vasoconstrictors.[8] Recently, increasing operator experience has led to the use of local anesthesia (LA) in some high-volume centers.[9,10]

Although guidance with intracardiac echocardiography (ICE) can be performed under LA,[11-13] it is sometimes technically challenging to obtain adequate imaging of the left atrial appendage (LAA) in order to guide device implantation and evaluate device stability and peri-device leakage using ICE. Additionally, ICE is not always available in many hospitals. Recently, So et al. performed LAAC using the LAmbre device under LA without sedation and with fluoroscopic guidance alone, which appeared to be feasible and safe.[9] However, the position and residual flow of the device were difficult to confirm without echocardiography monitoring.

In this study, we aimed to assess the safety and clinical efficacy of percutaneous LAAC guided by TEE under LA for stroke prevention in patients with non-valvular AF.

METHODS

Study population

Between January 2016 and June 2018, consecutive patients with non-valvular AF who were scheduled for percutaneous LAAC were prospectively included in the study. All of the patients underwent LAAC in the Arrhythmia Center of Ningbo First Hospital (Ningbo, Zhejiang, China). All clinical, echocardiographic, and periprocedural baseline data were prospectively collected. The CHA_2DS_2-VASc score and HAS-BLED score were calculated by two investigators for each patient based on comorbidities. Informed consent was obtained from all studied patients, and the study was approved by the Ethics Committee of Ningbo First Hospital. The inclusion criteria were as follows: age > 18 years; non-valvular AF; CHA_2DS_2-VASc score $\geq$ 2; HAS-BLED score $\geq$ 3; or contraindications for long-term OAC therapy (e.g., patients with bleeding events or thromboembolic events under OAC or intolerance or refusal to take OAC). The exclusion criteria were thrombus formation in the left atrium; left ventricular ejection fraction < 30%; acute myocardial infarction or unstable angina; prior stroke or transient attack within 30 days; acute infective endocarditis; hemorrhagic disease; pregnancy; mechanical valve prosthesis; and the presence of an atrial septal repair or a closure history.

Device implantation

TEE was performed 1 day before the procedure to rule out LAA thrombus formation and to determine the LAA size with measurements of the orifice and the depth from different angles (0°, 45°, 90°, and 135°). LAAC devices, including Watchman (Boston Scientific, Natick, Massachusetts), Amplatzer Cardiac Plug (ACP, St. Jude Medical, Saint Paul, Minnesota), and LAmbre (Lifetech Scientific, Shenzhen, China), were selected by the operator according to the pre-procedure TEE measurements and LAA angiogram results. The methods used for device implantation have been published previously.[6,14,15] Briefly, all procedures were performed under LA by experienced operators in our center. After transseptal puncture, the transseptal sheath was exchanged with a delivery sheath, and intravenous heparin was administered to achieve an activated clotting time of more than 250 s. After selective LAA angiography, the size of the device was chosen based on the angiographic and pre-procedure TEE measurements. The device was advanced into the LAA through the delivery sheath and deployed via sheath retraction. Lidocaine hydrochloride mucilage was used to anaesthetize the oropharynx, and the TEE probe was then placed to assess the position of the device. A successful device position was defined as no or minimal contrast leakage ($\leq$ 3 mm) into the LAA according to angiography as well as TEE. A gentle tug test was performed to ensure device stability. If the device location or stability was unsatisfactory, the device was retrieved and redeployed unless proper device position was achieved. The device was released after confirmation of an adequate position and a tug test. Transthoracic echocardiography was performed on day 1 post-procedure to exclude device embolization and pericardial effusion. Thromboembolic events included ischemic stroke, transient ischemic attack (TIA) and systemic embolism. Bleeding events were classified as major (intra-

cranial, retroperitoneal, intraspinal, intraocular or pericardial hemorrhage; drop in hemoglobin > 2 g/dL; transfusion of ≥ 2 units of packed red blood cells) and minor (remaining bleeding events).[16] The major peri-procedure adverse events included death, stroke, TIA, device embolization and major bleeding events. The minor complications included minor bleeding or vascular complications (e.g., arteriovenous fistula, femoral hematoma, and pseudoaneurysm) without the need for further intervention.

Follow-up

All of the patients were followed until September 30, 2018. For the first 6 weeks after the procedure, most patients were treated with anticoagulants [warfarin with an international normalized ratio (INR) of 2-3, 15-20 mg rivaroxaban once daily, or 110-150 mg dabigatran twice daily], followed by dual antiplatelet therapy (DAPT, 100 mg aspirin and 75 mg clopidogrel once daily) between 6 weeks and 6 months, and aspirin or clopidogrel only after 6 months. Patients with contraindications for OAC and those who refused to take OAC were treated with DAPT for the first 6 months, followed by single antiplatelet therapy (SAPT, 100 mg aspirin or 75 mg clopidogrel once daily). Clinical follow-up was arranged at 6 weeks, 3 months, 6 months, and 12 months post-procedure. TEE follow-up was scheduled approximately 6 weeks after the procedure to evaluate the device position, LAA residual flow, and device-related thrombus. Computed tomography (CT) was the alternative choice if the patient refused to undergo TEE.

Clinical outcomes

Clinical outcomes included death, ischemic stroke, TIA, systemic embolism, and major bleeding. Device efficacy for preventing thromboembolic events (defined as stroke, TIA, and systemic embolism) and reducing major bleeding events was tested by comparing the actual event rate during follow-up with the predicted event rate by the CHA_2DS_2-VASc score[17] and HAS-BLED score.[18] The individual patient annual risk was recorded, and the average annual risk was calculated. The total number of thromboembolic events during both the periprocedural and follow-up periods was divided by the total patient-years of follow-up and multiplied by 100 to obtain the actual annual rate. Thromboembolism and bleeding reduction were calculated as follows: (estimated – actual event rate) / estimated event rate.

Statistical analysis

Continuous data were presented as mean ± standard deviation (SD) for normally distributed data, and median and interquartile range (IQR) for variables with skewed distribution. Categorical variables were expressed as frequencies and percentages. The statistical analyses were performed using SPSS 19.0 (IBM, Armonk, NY, USA).

RESULTS

Patient characteristics

A total of 159 (66.0% male) patients were included in this study. The baseline characteristics are summarized in Table 1. The mean age was 70.5 ± 8.2 years. Fifty

Table 1. Baseline characteristics (n = 159)

Variable	
Age, years	70.5 ± 8.2
Male	105 (66.0)
AF patterns	
Paroxysmal AF	25 (15.7)
Persistent AF	95 (59.7)
Long-standing persistent AF	39 (24.5)
Congestive heart failure	20 (12.6)
Hypertension	97 (61.0)
Age 65-74 years	79 (49.7)
Age ≥ 75 years	50 (31.4)
Diabetes mellitus	19 (11.9)
Previous history of TIA or stroke	111 (69.8)
Vascular disease	142 (89.3)
Previous history of bleeding	56 (35.2)
Liver/renal disfunction	11 (6.9)
Labile INR	49 (30.8)
Alcohol taken	27 (17.0)
Drugs predisposing to bleed	40 (25.2)
CHA_2DS_2-VASc score	4.6 ± 1.4
HAS-BLED score	3.3 ± 0.9
Transthoracic echocardiography parameters	
Left atrial diameter, mm	46.9 ± 7.3
Left ventricular end diastolic dimension, mm	49.1 ± 5.1
Left ventricular ejection fraction, %	61.0 ± 6.5

Values are mean ± SD or n (%).
AF, atrial fibrillation; INR, international normalized ratio; TIA, transient ischemic attack.

patients were older than 75 years of age. All patients had non-valvular AF (25 paroxysmal, 95 persistent, and 39 long-standing persistent AF). The distributions of the CHA_2DS_2-VASc score and HAS-BLED score are displayed in Figure 1. The mean CHA_2DS_2-VASc score was 4.6 ± 1.4. Based on the CHA_2DS_2-VASc score, the expected annual risk for ischemic stroke was 7.6% (if untreated) or 6.5% (if treated with aspirin). The mean HAS-BLED score was 3.3 ± 0.9. A score of ≥ 3 was demonstrated in 139 patients (87.4%). The expected annual risk of major bleeding based on the HAS-BLED score was 6.7%. A total of 117 (69.8%) patients had a previous history of TIA or stroke, 56 (35.2%) patients had a previous history of bleeding, 11 (6.9%) patients had liver/renal dysfunction, and 49 (30.8%) patients had labile INR. Transthoracic echocardiography showed that the mean left atrial diameter was 46.9 ± 7.3 mm, the mean left ventricular end diastolic dimension was 49.1 ± 5.1 mm, and the mean left ventricular ejection fraction was 61.0 ± 6.5%. The indications for LAAC in the study population are listed in Figure 2.

Procedural characteristics

During the procedure, all of the patients were under LA. As shown in Table 2, the device was successfully implanted in 152 (95.6%) patients (87 Watchman, 47 ACP, and 18 LAmbre devices). Seven patients experienced procedure failure due to a very challenging LAA morphology or a very large LAA orifice. The mean LAA orifice diameter was 25.3 ± 5.3 mm, and the mean LAA depth was 29.3 ± 6.7 mm. The procedure time, X-ray exposure time and X-ray exposure dose were 71.9 ± 21.8 min, 8.4 ± 5.8 min, and 193.4 ± 150.9 mGy, respectively. One hundred and seven (70.4%) patients underwent

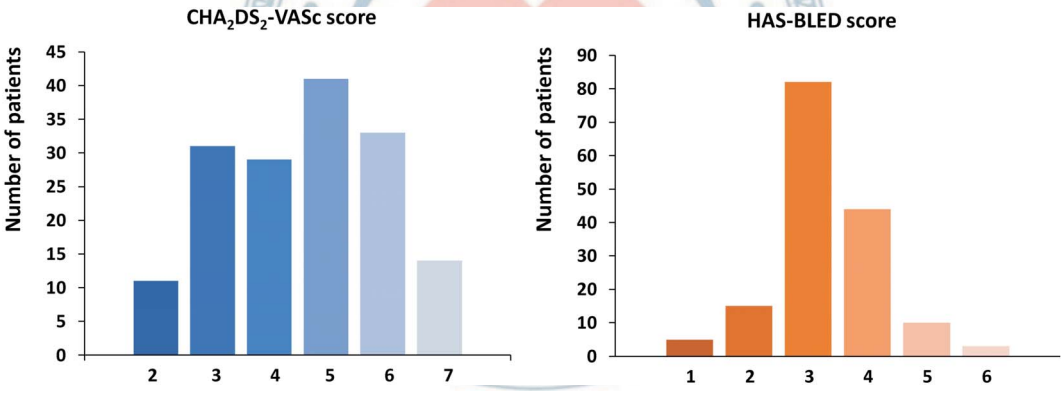

Figure 1. *Distributions of CHA_2DS_2-VASc score and HAS-BLED score in the study population.*

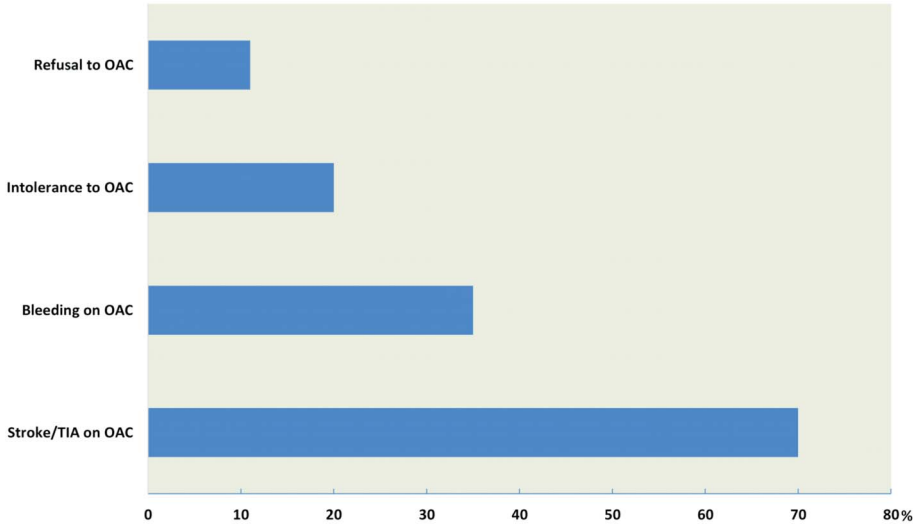

Figure 2. *Indications for left atrial appendage closure (LAAC) (for some patients > 1 indication was reported). OAC, oral anticoagulant. TIA, transient ischemic attack.*

Table 2. Peri-procedural data (n = 152)

Variable	
LAA orifice diameter, mm	25.3 ± 5.3
LAA depth, mm	29.3 ± 6.7
LAA closure device	
Watchman	87 (57.2)
Amplatzer Cardiac Plug	47 (30.9)
LAmbre	18 (11.8)
Success at first attempt	107 (70.4)
LAA leakage	16 (10.5)
Residual flow < 1 mm	6 (3.9)
Residual flow 1-3 mm	10 (6.6)
Residual flow > 3 mm	0 (0.0)
Procedure time, min	71.9 ± 21.8
X-ray exposure time, min	8.4 ± 5.8
X-ray exposure dose, mGy	193.4 ± 150.9
Major complications	
Death	0 (0.0)
Stroke	0 (0.0)
Device embolization	0 (0.0)
Cardiac tamponade	2 (1.3)
Minor complications	
Minor bleeding	0 (0.0)
Arteriovenous fistula	0 (0.0)
Femoral hematoma	1 (0.7)
Pseudoaneurysm	1 (0.7)

Values are mean ± SD or n (%). LAA, left atrial appendage.

direct device implantation without additional device repositioning, and 16 (10.5%) patients had a residual flow ≤ 3 mm.

The new method for LAAC implantation was tolerable in all of the patients. The judgement of the operators during the procedure was not affected by LA in the present study. Two patients suffered cardiac tamponade and complained of chest tightness. Both patients were confirmed with echocardiography and treated immediately. Therefore, the LAAC approach under LA may allow for instantaneous monitoring of patient discomfort, which can be an indication of some complications.

Periprocedural complications

There were major complications documented in 2 (1.3%) patients. Both patients experienced cardiac tamponade and were treated with pericardiocentesis. The minor complications were hematoma at the puncture site of the femoral vein in 1 patient and pseudoaneurysm in 1 patient. No patients experienced death, stroke, or device embolization.

Follow-up

Table 3 displays the follow-up data. The median follow-up period was 522 days (IQR, 250-755 days), resulting in a total of 216 patient-years. Ischemic stroke occurred in 4 patients and was conservatively managed, and all of these patients recovered with only slight sequelae. The annual ischemic stroke rate was 1.9/100 person-years, resulting in a 75% reduction compared with the expected annual risk (Figure 3). One patient suffered a cerebral hemorrhage 5 months post-procedure and died. Gastrointestinal bleeding was documented in 1 patient. His condition improved with conservative treatment. The annual major bleeding rate (including both periprocedural and follow-up events) was 1.9/100 person-years, which translated into a 72% reduction (Figure 3). A total of 142 (93.4%) patients underwent TEE (n = 137) or CT (n = 5). The median number of days after implantation was 48 days (IQR 44-55 days). LAAs were completely sealed with the absence of flow or with minimal flow (≤ 3 mm) around the device in all patients. Thrombus formation on the atrial surface of the device was documented in 2 (1.4%) patients, one of whom was noncompliant with anticoagulation treatment starting early after device implantation. Neither patient had any neurological symptoms and were treated with dabigatran until the thrombus dissolved. Ten patients did not undergo TEE or CT due to intolerance or refusal to undergo the examinations. However, none of the patients suffered thromboembolic events.

Table 4 summarizes the antithrombotic medications. At baseline, 20 (13.2%) patients were treated with DAPT, 30 (19.7%) with warfarin, 67 (44.1%) with dabigatran, and 35 (23.0%) with rivaroxaban. During the follow-up period, the patients received anticoagulants or DAPT for 6 weeks, DAPT between 6 weeks and 6 months, and aspirin or clopidogrel only after 6 months. Only one person discontinued the drugs by himself. However, he did not suffer any thromboembolic or bleeding events during follow-up. At the end of the follow-up period, 18 (11.9%) patients had been treated with DAPT, 57 (37.7%) with aspirin only, and 76 (48.4) with clopidogrel only.

DISCUSSION

To the best of our knowledge, this is the first study

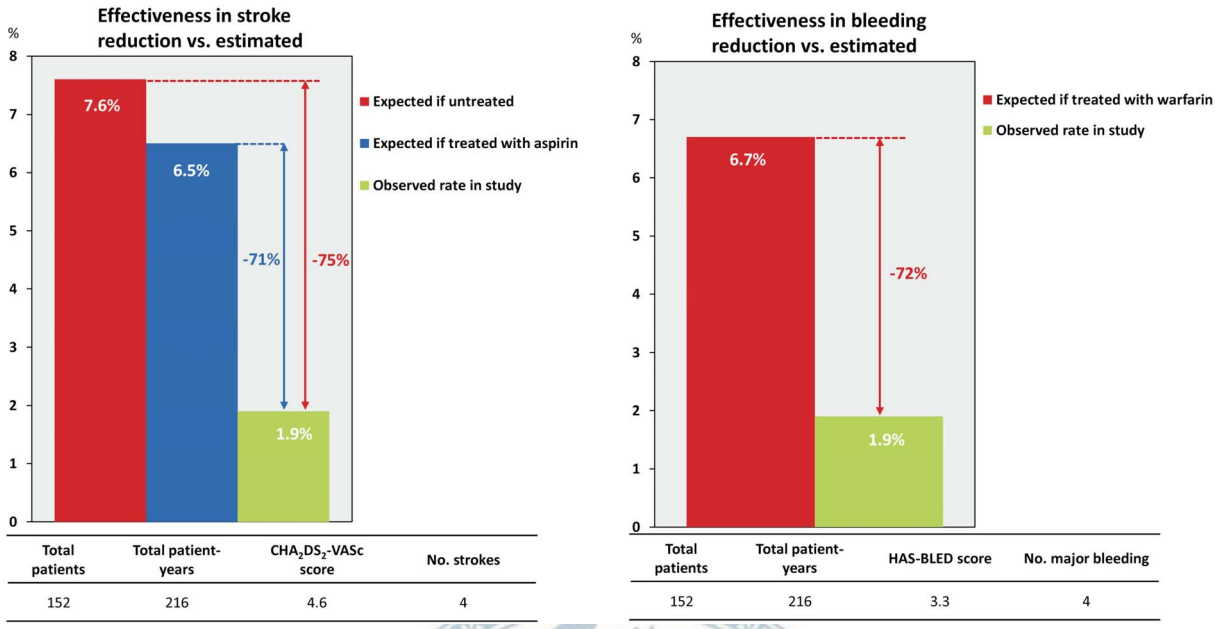

Figure 3. *Effectiveness of percutaneous left atrial appendage closure (LAAC) in reduction of stroke and bleeding based on annual rate predicted by CHA_2DS_2-VASc score and HAS-BLED score, respectively. Both periprocedural and follow-up events are included in the analysis.*

Table 3. Follow-up data

Variable	
Adverse events (n = 152, 100 person-year)	
Death	1 (0.5)
Ischemic stroke	4 (1.9)
TIA	0 (0.0)
Systemic embolism	0 (0.0)
Cerebral hemorrhage	1 (0.5)
Gastrointestinal bleeding	1 (0.5)
TEE follow-up (n = 137)	
Thrombus formation on the device	2 (1.5)
Residual flow < 1 mm	5 (3.6)
Residual flow 1-3 mm	7 (5.1)
Residual flow > 3 mm	0 (0.0)
CT scan follow-up (n = 5)	
Thrombus formation on the device	0 (0.0)

Values are n (%).
CT, computed tomography; TEE, transesophageal echocardiography; TIA, transient ischemia attack.

Table 4. Antithrombotic medication

Antithrombotic medication	
Baseline (n = 152)	
DAPT	20 (13.2)
Warfarin	30 (19.7)
Dabigatran	67 (44.1)
Rivaroxaban	35 (23.0)
End of follow-up (n = 151)	
DAPT	18 (11.9)
Aspirin only	57 (37.7)
Clopidogrel only	76 (48.4)

Values are n (%). DAPT, dual antiplatelet therapy.

to assess the safety and clinical efficacy of percutaneous LAAC with TEE under LA. The main finding of this investigation is that LAAC under LA was safe and showed a favorable outcome for stroke prevention in non-valvular AF patients, with a high procedural success rate and a moderate number of periprocedural complications.

LAAC has been performed under GA or deep sedation in most prior studies to relieve discomfort and make patients compliant with TEE monitoring.[5,6,19] However, endotracheal tube intubation and mechanical ventilation are needed, which may result in airway damage. Yildirim et al. reported that anesthetics significantly prolonged the QT interval, which is an independent predictor of cardiac and all-cause mortality.[20,21] Hypotension after the induction of GA is common. Jor et al. reported that hypotension was observed at least once in 36.5% of their study population.[22] Moreover, GA has been associated with adverse cardiac events.[23] Therefore, LA may be more suitable than GA for LAAC procedures. An approach using LA with intraprocedural TEE guidance has been reported for other structural interventions, such as transcatheter

aortic valve replacement, to be noninferior or even superior to traditional transcatheter aortic valve replacement using GA.[24] The benefits of LAAC under LA include: (1) reduced procedural cost by obviating the need for anesthesiologists; (2) avoiding the risk of GA (e.g., esophageal thermal injury); (3) allowing for the instantaneous monitoring of neurologic changes or pain and discomfort that can be an indication of some complications; and 4) improved patient comfort and recovery time.

Several operators have reported LAAC using ICE to avoid GA.[12,13] However, ICE-guided LAAC was performed in a small series of patients. Thus, the safety and feasibility are still unclear and await further investigations. Additionally, it is sometimes technically challenging to obtain adequate imaging of the LAA to guide device implantation and evaluate device stability and peri-device leakage using ICE. Some cardiologists have advocated for fluoroscopy-guided LAAC without echocardiography guidance, which appears to be feasible and safe.[9,10] However, device repositioning or exchange often occurs during the procedure, which may not support such a strategy. A prior study showed that the rates of repositioning and device exchange were 43% and 12%, respectively.[6] In the present study, devices were repositioned in 30% of the patients based on the TEE findings.

For the development of a new method for LAAC, the patient's response, compliance, and tolerance are important considerations. To shorten the duration of TEE probe placement, TEE was performed at the end of the procedure to confirm the position and residual flow of the occluder device in this study. In addition, lidocaine hydrochloride mucilage was used to anesthetize the oropharynx to relieve the patient's discomfort. Moreover, all of the patients were compliant with the procedure and intraprocedural TEE examination.

The procedural success rate was high, and the number of periprocedural complications was moderate in the present study. There were 2 (1.3%) periprocedural major adverse events, but no stroke or device embolization events occurred. The rate of cardiac tamponade was reported to be 1.24% in a multicenter study that was performed under GA with TEE guidance.[7] However, the rate of cardiac tamponade reached 2.6% in the first published study regarding LAAC using LA and fluoroscopic guidance only. Additionally, the incidence of neurologic events and device embolization has been reported to be up to 2% and 4.6%, respectively.[10] The incidence of device embolization was high without the confirmation of TEE before device release. As mentioned above, device repositioning or exchange often occurs during the procedure. Therefore, we believe that echocardiography is necessary during the LAAC approach.

The expected annual risk of stroke based on the CHA_2DS_2-VASc score in this study was 7.6% (if untreated) or 6.5% (if treated with aspirin). However, the observed ischemic stroke rate was only 1.9%, resulting in fewer events than expected. The results appear generally comparable to those reported previously for Watchman, ACP, and LAmbre devices.[5-7] As shown in Figure 1, all of the patients included in our study had a CHA_2DS_2-VASc score ≥ 2, which is an indication for OAC therapy. However, 87.4% of the patients had an HAS-BLED score ≥ 3, indicating a high bleeding risk. The expected annual major bleeding rate based on the HAS-BLED score in this study was 6.7%, and the annual major bleeding rate (including both periprocedural and follow-up events) was 1.9/100 person-years, which translated into a 72% reduction. In fact, the annual risk was 1.0/100 person-years if only taking the events during follow-up into account. Table 3 shows that most patients were treated with only SAPT. Modifications of antithrombotic therapy after LAAC may result in a reduction in bleeding events.

Study limitations

The major limitation of this study is that this was a single-center, one-arm, observational study, and the sample size was small. There were no direct comparisons of the safety and efficacy of LAAC performed under LA vs. GA. The expected annual risk of stroke and major bleeding based on CHA_2DS_2-VASc and HAS-BLED scores was used for the comparisons, which is methodologically imperfect. TEE follow-up was not available for all patients. However, as a safety and efficacy assessment study for LAAC guided by TEE under LA, this is, to the best of our knowledge, the first cohort study to report peri-procedural and medium-term clinical results.

CONCLUSIONS

Percutaneous LAAC under LA had a high procedural success rate and a moderate number of periprocedural

complications. LAAC showed an encouraging outcome for stroke prevention. Modifications of antithrombotic therapy after LAAC may result in a reduction in bleeding events. Randomized investigations with a larger sample size are warranted.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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