Safety and efficacy of left atrial appendage closure in non-valvular atrial fibrillation patients with peripheral arterial disease.

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Abstract

Objective: To investigate the clinical characteristics, safety and efficacy of left atrial appendage closure (LAAC) in non-valvular atrial fibrillation (NVAF) patients with peripheral arterial disease (PAD).

Background: LAAC is an alternative therapy to prevent thromboembolism in NVAF patients. The safety and efficacy of LAAC in NVAF patients with PAD remain unclear.

Methods: Retrospective analysis was performed in 148 NVAF patients after LAAC who were categorized into two groups: 86 patients with PAD and 62 patients without PAD.

Results: The total procedural success rate was 97.3%. There was significant higher thromboembolism risk based on the CHA2DS2-VASc score in patients with PAD (4.7 ± 1.4 vs. 3.0 ± 1.5, p<0.001). The bleeding risk based on the HAS-BLED score was similar between groups (2.6 ± 1.0 vs. 2.3 ± 1.1, p=0.122). There were no significant differences in thromboembolism rate (3.7% vs. 1.7%, p = 0.849), severe bleeding rate (2.5% vs. 1.7%, p=1.000), and mortality (3.5% vs. 0%, p = 0.371) between groups. Estimated annual thromboembolism rate adjusted for warfarin use reduced by 39% in PAD group, while reduced by 50% in non-PAD group after LAAC. Estimated annual severe bleeding rate among those taking warfarin reduced by 54% in PAD group, while reduced by 65% in non-PAD group after LAAC.

Conclusion: LAAC was a safe procedure in NVAF patients with PAD. Compared with warfarin, LAAC was associated with a lower risk of thromboembolism as well as severe bleeding in NVAF patients with PAD during follow-up.

Keywords: Atrial fibrillation, Peripheral arterial disease, Left atrial appendage closure, Thromboembolism.

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Introduction

It is well-known that non-valvular atrial fibrillation (NVAF) shares lots of risk factors with PAD, such as obesity, hypertension, diabetes, heart failure and so on. Previous studies have shown that the prevalence of PAD in NVAF ranges from 2.9% to 21% [1-3]. Concomitant PAD in NVAF may increase the risk of stroke [3]. Actually, PAD are significant predictors of thromboembolism and mortality in subjects with NVAF [3]. Left atrial appendage closure (LAAC) has been developed as an alternative treatment to oral anticoagulation (OAC) for stroke prevention in NVAF patients in whom OAC therapy is ineffective or contraindicated [4]. To date, the study about LAAC in NVAF patients with PAD is limited. This study was aimed to investigate the safety and efficacy of LAAC in this special population.

Methods

Patient selection

LAAC was performed in 148 consecutive patients with NVAF with the Watchman (Boston Scientific, USA) or Amplatzer Cardiac Plug (ACP, Abbott; Abbott Park, IL) device during May 2017 and January 2019 in our center. The LAAC procedures with Watchman or ACP were described previously [5,6]. This study was approved by the ethics committee of our hospital and was complied with the Declaration of Helsinki and all relevant Chinese laws. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

The cohort was divided into 2 groups: Patients with PAD and patients without PAD. PAD was defined as vascular ultrasound suggesting carotid, or femoral artery plaque formation.

Follow-up

Clinical follow-up was carried out in patients who were successfully implanted occluder by patient visits or phone contact. Transesophageal echocardiography (TEE), transthoracic echocardiography or cardiac computed tomography angiography were performed during post-procedure to assess for device-related thrombus (DRT) and peri-device leaks according to patients' condition and the preference of physicians.

Post-procedure antithrombotic strategies

According to an updated expert consensus [7], the post-procedure antithrombotic strategies in this study were as followed: anticoagulant for 1.5-3 months followed by dual antiplatelet therapy until 6 months after LAAC and a lifelong single antiplatelet therapy; dual antiplatelet therapy for 1.5-12 months followed by a lifelong single antiplatelet therapy; anticoagulant for 1.5-9 months followed by a lifelong single

antiplatelet therapy; various variants due to coexisted diseases or complications.

Study Outcomes

Peri-procedural and post-procedure major adverse events based on the Munich consensus document [8] were recorded, including death, stroke/transient ischemic attack (TIA), systemic embolism, device embolization, DRT, peri-device leaks and bleeding. In this study, thromboembolism event included ischemic stroke, TIA, systemic embolism. Additionally, major bleeding, fatal bleeding and hemorrhagic stroke were regarded as severe bleeding.

Procedure efficacy to prevent thromboembolism was tested by comparing the actual event rate with the estimated thromboembolism rate adjusted for warfarin use per year by the CHA2DS2-VASc score [9]. Procedure safety to reduce severe bleeding event was assessed by comparing the actual event rate with the estimated severe bleeding rate among those taking warfarin only per year by the HAS-BLED score [10].

Statistical Analysis

Continuous variables were shown as mean ± standard deviation. For the continuous variables, the normality was performed by Shapiro-Wilk test. To assess the differences between two continuous variables, the independent samples Student's t test (for normally distributed values), or the Mann-Whitney U-test (for non-normally distributed values) were used. Categorical variables were expressed as counts and percentages, which were compared with the chi-square test. If the value of p obtained by chi-square test is near 0.05, Fisher's exact test should be used. For the data of group variable unordered and result variable ordinal, the nonparametric test of rank transformation should be adopted. Statistical analysis was performed with SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). A two-sided $p<0.05$ was considered statistically significant.

Results

Study population

The LAAC procedure was performed in 148 NVAF patients: 86 patients with PAD and 62 patients without PAD. As presented in Table 1, patients with PAD were older (72.7 ± 8.0 *vs.* 68.2 ± 9.6 years, p=0.008) and presented a higher prevalence of hypertension (74.4% *vs.* 59.7%, p=0.043), diabetes mellitus (39.5% *vs.* 17.7%, p=0.004) and coronary artery disease (44.2% *vs.* 6.5%, <0.001*). At enrollment, PAD patients were more commonly treated with dual antiplatelet therapy (15.1% *vs.* 4.8%, p=0.047).

Procedural characteristics

As shown in Table 2, procedural success was achieved in 144 patients (97.3%), without significant differences between the PAD group and non-PAD group. The left atrial appendage (LAA) anatomy was not suitable to device closure because of the size of the LAA orifice >35 mm in 4 patients. There were no significant differences in LAA dimension, the type and size of occlusion device between groups. Combined procedures of atrial septal defect occlusion during LAAC were more common in patients without PAD (1.2% *vs.* 9.7%, p=0.044).

As displayed in Table 3, one patient died from acute left heart failure at twelve hours after LAAC in PAD group. In addition, one minor bleeding, referring to pacemaker pocket hematoma, was observed in PAD group in which the pacemaker and Watchman device were implanted at the same term operation. Furthermore, two cardiac tamponades occurred in PAD patients: one occurred at 3 days following a 22 mm ACP device implantation, which was managed with pericardiocentesis; the other one occurred before the Watchman device implantation due to coronary sinus perforation, which was managed with immediate occlusion. There were also two cardiac tamponades in non-PAD patients: one occurred at 3 days following a 24 mm ACP device implantation, which was managed with pericardiocentesis and transfusion; the other occurred at 1 day after a 28 mm ACP device implantation, which required immediate surgical intervention. Beyond that, one case of device embolization occurred at 1 day following an ACP device implantation in non-PAD group, which was managed with surgery.

Long-term outcomes

As presented in Table 4, this study total fellow up 140 out of 144 patients who successfully implanted occluder, with 1 patient dropping out due to device embolization and 1 patient losing his life during peri-procedure, and 2 patients lost during post-procedure. The average follow-up time in PAD group and non-PAD group were 12.2 ± 5.2 months and 11.6 ± 5.3 months, respectively (p=0.508). There was significant higher thromboembolism risk based on the CHA2DS2-VASc score in patients with PAD (4.7 ± 1.4 *vs.* 3.0 ± 1.5, p<0.001). However, the bleeding risk based on the HAS-BLED score was similar between the two groups (2.6 ± 1.0 *vs.* 2.3 ± 1.1, p=0.122). Patients with PAD were more commonly treated with dual antiplatelet therapy for 1.5-12 months followed by a lifelong single antiplatelet therapy after LAAC (51.9% *vs.* 35.6%, p=0.056). Patients without PAD were more commonly treated with anticoagulant for 1.5-3 months followed by dual antiplatelet therapy until 6 months after LAAC and a lifelong single antiplatelet therapy after LAAC (29.6% *vs.* 50.8%, p=0.011).

As shown in Table 5, two patients died in PAD group: one patient died without any definite cause at 5 months after LAAC; another died of cardiovascular factors at 8 months after LAAC, who had acute myocardial infarction within 1.2 month before LAAC. There were no significant differences in thromboembolism between groups. Significantly, all observed thromboembolism in our study were ischemic strokes: 3 cases on single antiplatelet therapy and 1 case secondary to peri-device leak. The incidence of minor bleeding events during post-procedure was slightly higher in PAD than that in non-PAD: 18 episodes minor bleeding events in PAD patients and 5 minor bleeding events in non-PAD patients (21% *vs.* 10.2%, p=0.030). However, there were no significant differences in severe bleeding (2.5% *vs.* 1.7%, p=1.000). Of note, all observed severe bleeding events in our study were hemorrhagic strokes: 2 cases in patients on dual antiplatelet therapy, and 1 case on single antiplatelet therapy. Besides, DRT was detected in 3 patients: 2 patients due to discontinuous antithrombotic therapy, 1 patient on single antiplatelet therapy. Furthermore, dense spontaneous echo contrast was observed in LA or LAA on TEE in 2 patients.

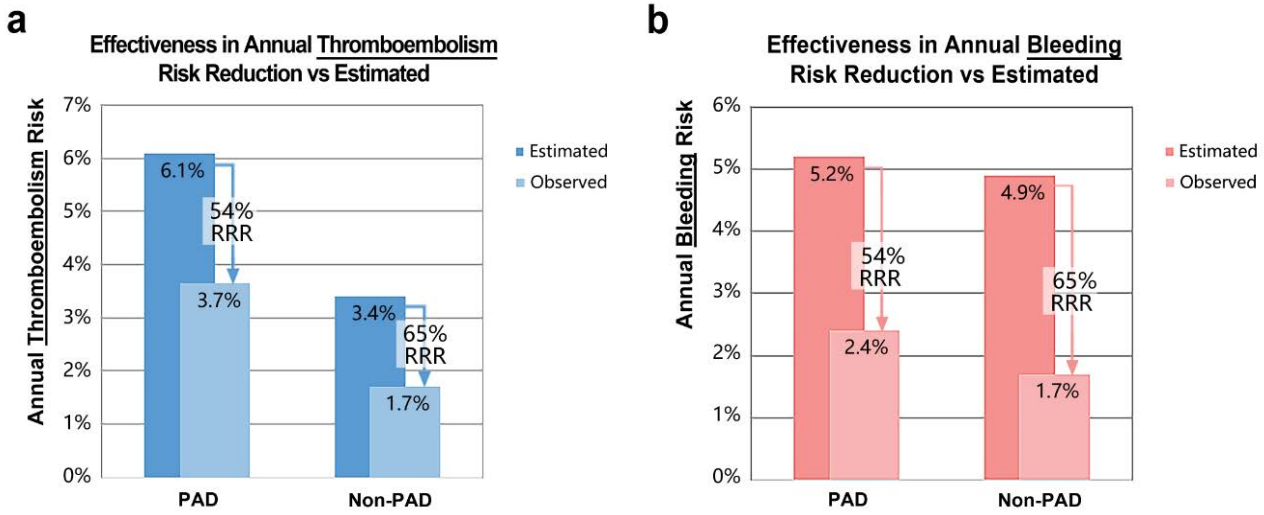

Figure 1. *Reduction in annual thromboembolism a) and bleeding risk b) after left atrial appendage closure.*

Table 1. *Baseline patients' characteristics.*

Variable	Patients with PAD (n=86)	Patients without PAD (n=62)	p value
Baseline characteristics			
Age, years	72.7 ± 8.0	68.2 ± 9.6	0.008*
Gender			0.41
Male (%)	57/86 (66.3)	37/62 (59.7)	
Female (%)	29/86 (33.7)	25/62 (40.3)	
Atrial fibrillation			0.42
Paroxysmal (%)	40/86 (46.5)	33/62 (53.2)	
Chronic (%)	46/86 (53.5)	29/62 (46.8)	
Hypertension (%)	64/86 (74.4)	37/62 (59.7)	0.043*
Diabetes mellitus (%)	34/86 (39.5)	11/62 (17.7)	0.004*
Coronary artery disease	38/86 (44.2)	4/62 (6.5)	<0.001*
Pre-procedure antithrombotic medications			
Anticoagulant (%)	36/86 (41.9)	30/62 (48.4)	0.431
Single antiplatelet (%)	15/86 (17.4)	11/62 (17.7)	0.962
Dual antiplatelets (%)	13/86 (15.1)	3/62 (4.8)	0.047*
Anticoagulant + Single antiplatelet (%)	2/86 (2.3)	1/62 (1.6)	1
No treatment (%)	21/86 (24.4)	17/62 (27.4)	0.68
Note: * indicates p<0.05.			

Table 2. *Procedural characteristics.*

Variable	Patients with PAD (n=86)	Patients without PAD (n=62)	p value
Procedural success (%)	84/86 (97.7)	60/62 (96.8)	1
LAA dimension			
Width, mm	2.3 ± 0.4	2.3 ± 0.4	0.461
Length, mm	2.8 ± 0.6	2.8 ± 0.4	0.932
Occlusion device type			0.223
ACP (%)	4/84 (4.8)	7/60 (11.7)	
Watchman (%)	80/84 (95.2)	53/60 (88.3)	
Occlusion device size, mm	27.2 ± 3.9	27.9 ± 3.9	0.48
Combined procedures			
CAG/PCI (%)	3/86 (3.5)	2/62 (3.2)	1
Atrial septal defect occlusion (%)	1/86 (1.2)	6/62 (9.7)	0.044*
RFCA (%)	4/86 (4.7)	4/62 (6.5)	0.913
Cardiac pacemaker implantation (%)	1/86 (1.2)	1/62 (1.6)	1
Note: * indicates p<0.05. NA=Not Available; CAG=Coronary Arteriography; PCI=Percutaneous Coronary Intervention; RFCA=Radio Frequency Catheter Ablation; TIA=Transient Ischemic Attack.			

The estimated annual risk of thromboembolism based on the CHA2DS2-VASc score adjusted for warfarin use in patients with non-PAD was 3.4%, while the actual annual rate of thromboembolism was 1.7%, reducing by 50% (Figure 1a). The actual annual rate of thromboembolism in PAD group as we observed was 3.7%, reducing by 39% compared with estimated thromboembolism incidence of 6.1% (Figure 1a). Estimated severe bleeding rate reduced by 65% in patients without PAD, while reduced by 54% in patients with PAD compared with estimated severe bleeding rate among those taking warfarin per year by the HAS-BLED score (Figure 1b).

Table 3. *Major adverse events during peri-procedure.*

Variable	Patients with PAD (n=86)	Patients without PAD (n=62)	p value
Death (%)			
Cardiovascular mortality (%)	1/86 (1.2)	0/62 (0.0)	1
Non-cardiovascular mortality (%)	0/86 (0.0)	0/62 (0.0)	NA
TE			
Stroke/TIA (%)	0/86 (0.0)	0/62 (0.0)	NA
Systemic embolism (%)	0/86 (0.0)	0/62 (0.0)	NA
Bleeding			
Minor bleeding (%)	1/86 (1.2)	0/62 (0.0)	1
Severe bleeding (%)	0/86 (0.0)	0/62 (0.0)	NA
Cardiac tamponade (%)	2/86 (2.3)	2/62 (3.2)	1
Device embolization (%)	0/86 (0.0)	1 /62 (1.6)	0.419

Note: * indicates p<0.05.
TE=Thromboembolism; TIA=Transient Ischemic Attack; NA=Not Available.

Table 4. *Follow-up information.*

Variable	Patients with PAD (n=83)	Patients without PAD (n=59)	p value
FU			
Number of patients (%)	81/83 (97.6)	59/59 (100)	0.511
months	12.2 ± 5.2	11.6 ± 5.3	0.508
Risk score			
CHA_2DS_2-VaSc score	4.7 ± 1.4	3.0 ± 1.5	<0.001*
Estimated annual risk of stroke, %	6.1 ± 2.6	3.4 ± 2.1	<0.001*
HAS-BLED score	2.6 ± 1.0	2.3 ± 1.1	0.122
Estimated annual risk of major bleeding, %	5.2 ± 1.8	4.9 ± 2.1	0.198
Post-procedure antithrombotic strategies			
OAC (1.5-3M) + DAPT (6M) + SAPT (Lifelong)	24/81 (29.6)	30/59 (50.8)	0.011*
DAPT (1.5-12M) + SAPT (Lifelong)	42/81 (51.9)	21/59 (35.6)	0.056
OAC (1.5-9M) + SAPT (Lifelong)	8/81 (9.9)	4/59 (6.8)	0.518
Others	7/81 (8.6)	4/59 (6.8)	0.931

*indicates p<0.05.
FU=Follow Up; OAC=Oral Anticoagulant; DAPT=Dual Antiplatelet Therapy; SAPT=Single Antiplatelet Therapy.

Table 5. *Major adverse events during post-procedure.*

Variable	Patients with PAD (n=81)	Patients without PAD (n=59)	p value
All causes mortality			
Cardiovascular mortality (%)	1/81 (1.2)	0/59 (0.0)	1
Non-cardiovascular mortality (%)	1/81 (1.2)	0/59 (0.0)	1
TE			
Stroke/TIA (%)	3/81 (3.7)	1/59 (1.7)	0.849
Systemic embolism (%)	0/81 (0)	0/59 (0)	NA
Bleeding			
Minor bleeding (%)	18/81 (21.0)	5/59 (10.2)	0.030*
Severe bleeding (%)	2/81 (2.5)	1/59 (1.7)	1
Device-related thrombus (%)	1/81 (1.2)	2/59 (3.4)	0.781
Peri-device leak (%)	1/81 (1.2)	0/59 (0.0)	1

* indicates p<0.05.
TE=Thromboembolism; TIA=Transient Ischemic Attack; NA=Not Available.

Discussion

The main findings of this single center study were as followed. LAAC is a safe procedure with similar procedural success rate in NVAF patients with PAD and without PAD. There was higher thromboembolism risk based on the CHA2DS2-VASc score in PAD group. However, there were no significant differences in thromboembolism rate between groups, suggesting that the LAAC procedure obviously reduced the risk of thromboembolism for NVAF patients with PAD. Compared with warfarin, LAAC was associated with a lower risk of thromboembolism as well as severe bleeding in NVAF patients with PAD during follow-up.

It was reported that 50% - 80% of patients with CHA2DS2-VASc score ≥ 2 were taking OAC therapy in developed countries, while only 36.5% of those received OAC in Beijing, China [11]. An improvement of OAC use among Chinese patients with NVAF was observed in recent years. However, AF remains frequently under-recognized in patients who experienced an acute stroke. In this study, 25.7% NVAF patients still did not take any antithrombotic drugs. In this regard, LAAC contributes to standardized treatment in NVAF patients in a certain degree.

Actually, the optimal antithrombotic strategy after LAAC is still controversial at present. The most solid scientific antithrombotic strategy after receiving a Watchman device is warfarin for 45 d followed by dual antiplatelet therapy for 6 months and a lifelong single antiplatelet therapy. A single-center retrospective analysis showed that there was no significant difference in the incidence of all-cause mortality, major cardiovascular events and bleeding events between the new oral anticoagulation group

and the dual antiplatelets group within 45 days after LAAC [12]. In September 2017, dual antiplatelet therapy, as well as new oral anticoagulant plus aspirin were approved as antithrombotic options for at least 3 months following Watchman implantation [7]. However, the optimal duration of dual antiplatelet therapy is still uncertain. According to Bergmann et al. study, most of major bleeding events occurred in the first 6 month after LAAC with Watchman, the treatment phase with dual antiplatelets; after switching to single antiplatelet therapy, the incidence of bleeding events decreased obviously [13]. In fact, in this study, 67% severe bleeding events occurred on dual antiplatelet therapy, 67% occurred during the first 6 month and 100% occurred in Watchman implanted cases. In Weise' report, their antithrombotic strategy was short-term dual antiplatelets for six weeks followed by a single antiplatelet therapy lifelong, if complete endothelialization of the device surface, no significant peri-device leak and DRT were observed through TEE after 6 weeks of implantation. The results of 6-month follow-up showed that the short-term dual antiplatelet therapy did not increase thromboembolism and DRT risk [14]. It was reported that device-related thrombus was associated with prior thromboembolism, larger left atrial appendage, heart failure, deeper implantation, permanent AF, vascular disease, and larger occluder size [15,16]. Therefore, randomized control studies to explore the feasibility of short-term dual antiplatelet therapy after the LAAC procedure are urgent.

An interesting point to consider was that the occurrence of several severe adverse events in this study, such as cardiac tamponade and device embolization, were highly correlated with ACP device, which might be due to lack of experience for ACP in our center. In this study, 3 cardiac tamponades and 1 device embolization occurred with ACP. Actually, several studies have revealed that ACP is prone to cause device embolization than Watchman after LAAC. A recent systematic review included a total of 31 cases of device embolization after LAAC: 13 cases with Watchman and 18 cases with ACP. The device embolization incidence was 1.1% and 3.6%, respectively. Among the 31 cases, 20 cases occurred during peri-procedure [17]. In a multicenter prospective study with ACP including a total of 1047 patients, there were 52 (5.0%) periprocedural major adverse events: 8 deaths (0.8%), 9 strokes (0.9%), 1 myocardial infarction (0.1%), 13 cardiac tamponades (1.2%), 13 major bleedings (1.2%), 8 device embolization (0.8%) [18]. In the multicenter EWOLUTION registry study with Watchman including a total of 1021 patients, there were 31 (3.0%) periprocedural major adverse events:

7 major bleedings (0.6%), 4 pericardial effusions (0.4%), 1 cardiac tamponade (0.1%), 4 vascular damages to the groin (0.4%), 3 procedural air embolisms (0.3%), 2 device embolization (0.2%), 2 reinterventions (0.2%), and several singular events [19].

In the year of 2009, the CHA2DS2-VASc score was first put forward and PAD was considered as an independent predictor factor for thromboembolism among patients with NVAF [20]. However, this study indicated that there were no significant differences in thromboembolism, severe bleeding, and mortality between PAD and non-PAD group after LAAC. Compared with warfarin, LAAC was associated with a lower risk of thromboembolism as well as severe bleeding during follow-up. Therefore, LAAC has important clinical significance in preventing thromboembolism to NVAF patients with PAD.

Concomitant diabetes mellitus and NVAF may increase the risk of thromboembolism based on the CHA2DS2-VASc score [9]. However, in Litwinowicz et al. study, which included patients with CHA2DS2-VASc score of 3.5 ± 1.6, the estimated risks in thromboembolic and bleeding decreased by 77% and 100% respectively in patients with diabetes mellitus after LAAC [21]. In addition, previous intracranial bleeding in NVAF may increase the risk of bleeding based on the HAS-BLED score [10]. Moreover, patients with AF also face an increased risk of ischemic stroke after intracranial hemorrhage [22]. However, in a multicenter prospectively study, which included patients with CHA2DS2-VASc score of 4.5 ± 1.5, the observed annual stroke/TIA rate was 1.4% (75% relative risk reduction), while the observed annual major bleeding rate was 0.7% (89% relative risk reduction) for AF patients with previous intracranial bleeding after LAAC [23]. Additionally, these 5-year outcomes of the PREVAIL trial, combined with the PROTECT AF trial, which was performed in a relative low thromboembolism risk population with CHA2DS2-VASc score of 2.3 ± 1.1, demonstrated that LAAC with Watchman provides stroke prevention in NVAF comparable to warfarin, with additional reductions in major bleeding, particularly hemorrhagic stroke, and mortality [24]. To sum up, the LAAC may receive more benefits in high-risk NVAF patients which need to be further generalized in clinical practice.

Conclusion

In summary, LAAC was a safe procedure with similar procedural success rate in NVAF patients with PAD and without PAD. Although the thromboembolism risk was higher in PAD group, thromboembolism rate after LAAC was similar between groups. Compared with warfarin, LAAC was associated with a lower risk of thromboembolism as well as severe bleeding in NVAF patients with PAD during follow-up.

Limitation

Our study is a non-randomized, retrospective, observational, small-size sample, single centered study. The major limitation for estimating the overall value of LAAC is the lack of a control group and using only an estimated thromboembolism or bleeding risk score for analysis. The number of patients in each group was unequal. Besides, not all the patients received regular follow-up.

Acknowledgment

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Conflict of Interest

The authors declare that they have no conflicts of interest.

References

1. Olesen JB, Lip GY, Lane DA, et al. Vascular disease and stroke risk in atrial fibrillation: A nationwide cohort study. Am J Med. 2012;125:826e813-23.

2. Violi F, Davi G, Proietti M, et al. Ankle-Brachial index and cardiovascular events in atrial fibrillation. Thromb Haemost. 2016;115:856-63.

3. Proietti M, Raparelli V, Laroche C, et al. Adverse outcomes in patients with atrial fibrillation and peripheral arterial disease: A report from the Eurobservational research programme pilot survey on atrial fibrillation. Europace. 2016;19:1439-48.

4. Camm AJ, Lip GY, De-Caterina R, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: An update of the 2010 ESC guidelines for the management of atrial fibrillation developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33:2719-47.

5. Sick PB, Schuler G, Hauptmann KE, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2007;49:1490-5.

6. Park JW, Bethencourt A, Sievert H, et al. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: Initial European experience. Catheter Cardiovasc Interv. 2011;77:700-6.

7. Chen S, Weise FK, Chun KRJ, et al. Antithrombotic strategies after interventional left atrial appendage closure: An update. Expert Rev Cardiovasc Ther. 2018;16:675-8.

8. Tzikas A, Holmes DR, Gafoor S, et al. Percutaneous left atrial appendage occlusion: The Munich consensus document on definitions, endpoints, and data collection requirements for clinical studies. Europace. 2017;19:4-15.

9. Lip GY, Frison L, Halperin JL, et al. Identifying patients at high risk for stroke despite anticoagulation: A comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. Stroke. 2010;41:2731-8.

10. Lip GY, Frison L, Halperin JL, et al. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. J Am Coll Cardiol. 2011;57:173-80.

11. Chang SS, Dong JZ, Ma CS, et al. Current status and time trends of oral anticoagulation use among chinese patients with nonvalvular atrial fibrillation: The chinese atrial fibrillation registry study. Stroke. 2016;47:1803-10.

12. Bosche LI, Afshari F, Schone D, et al. Initial experience with novel oral anticoagulants during the first 45 days after left atrial appendage closure with the watchman device. Clin Cardiol. 2015;38:720-4.

13. Bergmann MW, Ince H, Kische S, et al. Real-world safety and efficacy of Watchman Laa closure at one year in patients on dual antiplatelet therapy: Results of the DAPT subgroup from the Evolution all-comers study. Euro Intervention. 2018;13:2003-11.

14. Weise FK, Bordignon S, Perrotta L, et al. Short-term dual antiplatelet therapy after interventional left atrial appendage closure with different devices. Euro Intervention. 2018;13:e2138-e46.

15. Pracon R, Bangalore S, Dzielinska Z, et al. Device thrombosis after percutaneous left atrial appendage occlusion is related to patient and procedural characteristics but not to duration of postimplantation dual antiplatelet therapy. Circ Cardiovasc Interv. 2018;11:e005997.

16. Garot P, Cormier B, Horvilleur J. Device-related thrombus after left atrial appendage closure. Interv Cardiol. 2019;14:42-4.

17. Aminian A, Lalmand J, Tzikas A, et al. Embolization of left atrial appendage closure devices: A systematic review of cases reported with the watchman device and the amplatzer cardiac plug. Catheter Cardiovasc Interv. 2015;86:128-35.

18. Tzikas A, Shakir S, Gafoor S, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: Multicentre experience with the AMPLATZER Cardiac Plug. Euro Intervention. 2016;11:1170-9.

19. Boersma LV, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: Peri-procedural outcomes from the EWOLUTION registry. Eur Heart J. 2016;37:2465-74.

20. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. Chest. 2010;137:263-72.

21. Litwinowicz R, Bartus M, Ceranowicz P, et al. Left atrial appendage occlusion for stroke prevention in diabetes mellitus patients with atrial fibrillation: Long-term results. J Diabetes. 2019;11:75-82.

22. Lerario MP, Gialdini G, Lapidus DM, et al. Risk of ischemic stroke after intracranial hemorrhage in patients with atrial fibrillation. PLOS One. 2015;10:e0145579.

23. Tzikas A, Freixa X, Llull L, et al. Patients with intracranial bleeding and atrial fibrillation treated with left atrial appendage occlusion: Results from the Amplatzer Cardiac Plug registry. Int J Cardiol. 2017;236:232-6.

24. Reddy VY, Doshi SK, Kar S, et al. 5-Year outcomes after left atrial appendage closure: From the prevail and protect af trials. J Am Coll Cardiol. 2017;70:2964-75.

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