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ORIGINAL ARTICLE

Efficacy and safety of left atrial appendage closure in non-valvular atrial fibrillation in patients over 75 years

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Abstract

Percutaneous left atrial appendage closure (LAAC) may decrease risks of stroke and bleeding in elderly patients with non-valvular atrial fibrillation (NVAF), but it is still lacking of evidence. The present study aimed at evaluating the efficacy and safety of LAAC in patients with NVAF over 75 years. 351 patients with NVAF who underwent LAAC were retrospectively analyzed on the LAAC procedure characteristics and the clinical follow-up according to age (age ≥ 75 years or < 75 years). Out of the 351 patients, LAA were successfully closed in 347 patients (98.9%), including 341 with Watchman (WM) device and 6 with Amplatzer cardiac plug (ACP) device because of the WM device-incompatible anatomy. There were no significant differences in total LAAC success rate and procedure-related major complications within 7 days between the groups aged ≥ 75 years and aged < 75 years. After a nearly 2-year follow-up, there was an increased trend of major bleedings and all bleedings in the group aged ≥ 75 years, but there were no significant differences between both groups in all-cause death, cardiovascular death, stroke/TIA/system embolism, device thrombus and device gap (> 5 mm). Kaplan–Meier analysis revealed that the relative risk of annual thromboembolic events between the observed values and the expected ones based on CHA_2DS_2-VASc score in the group aged ≥ 75 years decreased more obviously (61.9% vs. 54.3%); however, the relative risk of bleedings between the observed values and the expected ones based on HAS-BLED score in the younger group aged < 75 years decreased more significantly (59.6% vs. 29.2%). LAAC in patients with advanced age (age ≥ 75 years), has the same level of efficacy, safety and feasibility as in the younger patients aged < 75 years. Thus, LAAC may be an ideal choice to prevent stroke in NVAF patients with advanced age.

Keywords Left atrial appendage closure · Non-valvular atrial fibrillation · Elderly · Efficacy · Safety

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Introduction

There is a high risk of stroke and thromboembolic events in atrial fibrillation (AF) patients [1]. The risk of stroke in patients with AF is estimated to be fivefold higher than those without AF [2]. Conventional oral anticoagulants (OACs) such as warfarin are documented to decrease the risk of stroke by 64%, [3] and are therefore recommended to prevent cardioembolic stroke [4]. Warfarin is very effective in the prevention of stroke but also has many limitations, especially in increasing the risk of bleeding, which is an important cause of mortality [5]. Recently, novel oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban and edoxaban have been approved for prevention of stroke in patients with non-valvular atrial fibrillation (NVAF) [6]. But there are still some concerns on NOACs, such as side effects in gastrointestinal complaints especially gastrointestinal bleeding, renal function, cost and patients' quality of life [7, 8]. Due to the limitations of OACs mentioned as above, there is an increasing demand to develop technologies that can prevent stroke and improve the quality of life in patients with AF.

Percutaneous left atrial appendage closure (LAAC) is established as a promising alternative to OACs in patients with NVAF to prevent stroke because of its acceptable safety of procedure and the long-term efficiency [9–12]. Currently, several closure devices have been developed such as PLAATO, WATCHMAN (WM), Amplatzer cardiac plug (ACP)/Amulet, WaveCrest, LAmbre and Lariat [13], however, only the WATCHMAN device has been well-evaluated in randomized controlled trials, [9–12, 14] and was therefore approved for prevention of stroke in patients with NVAF in Europe, China, and the United States [4, 15]. Advanced age is not only a key risk factor of thromboembolic events in patients with AF, but also increases the risk of bleedings especially when patients are administered with OACs. Although LAAC has been proven reliable, safe and efficient in preventing stroke in NVAF, few reports evaluated the efficacy and safety of LAAC in patients with advanced age. In the present study, the efficacy and safety of LAAC were analyzed by comparing the procedure characteristics and the clinical follow-up between patients ≥ 75 years or < 75 years.

Materials and methods

Patients

The study adhered to international rules for scientific studies, the Helsinki principles, with the institutional review board approval in our hospital. All patients involved in this study gave their informed consent.

From February 2012 to December 2017, a total of 351 NVAF patients with high stroke risk and contraindications for long-term OAC were selected for LAAC operation according to the ESC guidelines for the management of AF [4, 6] in Helmut-G.-Walther hospital, Lichtenfels, Germany. All patients who underwent LAAC were categorized into 2 groups according to age, namely, the advanced-age group (≥ 75 years) or the non-advanced-age group (< 75 years). Data, including demographic and clinical characteristics, procedural success rate, peri-operation complications or adverse events and long-term follow-up were collected and analyzed.

Procedure and follow-up

Left atrial appendage closure was performed by implanting the WM left atrial appendage device (Boston Scientific, Marlborough, MA, USA) as planned under general anesthesia with the guidance of transesophageal echocardiography (TEE) and fluoroscopy. The procedure was only performed by the well-trained physician with certificate or board license of the program. A LAAC procedure was declared unsuccessful if repeated thrombosis in left atrial and other adjacent tissues occurred and could not be resolved by conventional means (e.g. GP IIb/IIIa receptor inhibitor injection and increased dose of heparin), or if a complete closure of the LAA (residual leak < 5 mm) could not be obtained with alternative devices or methods (e.g. using additional WM devices, ACP device, or the special 'Kissing-Watchman' technology [16]) because of the complex anatomy. A successful LAAC procedure was defined as complete closure of the LAA or closure with minor residual leak < 5 mm under TEE imaging as described in the report [10]. After the procedure, patients stayed in the hospital for 1 or 2 days and were then discharged after exclusion of tamponade/significant pericardial effusion by transthoracic echocardiography (TTE) examination, procedure-related major bleedings, and other severe periprocedural complications. TEE follow-up was scheduled at 45 days and at 6 months. Post-implantation drug regimens consist of either warfarin or NOAC, or in patients with contraindications for warfarin, combined enoxaparin or heparin with aspirin till 45 days. If TEE showed complete closure of the LAA, no residual peri-device flow (jet > 5 mm in width), or no device-related thrombus, the antithrombotic therapy was then switched to the duplex antiplatelet treatment with aspirin and clopidogrel until the second TEE exam at 6 months, and eventually to aspirin alone. If thrombi were detected, anticoagulation regimen would restart with warfarin or NOAC and aspirin till complete resolution of the thrombus by repeated TEE exams.

In addition, all patients received a long-term outpatient follow-up or were contacted by telephone to ask about clinical events, including stroke/TIA/systemic thromboembolism events, death, bleedings, etc.

Statistical analysis

Demographic, echocardiographic, procedural, and clinical follow-up data were collected and analyzed. Data are presented as frequencies and percentages for categorical variables and continuous variables are expressed as mean ± standard deviation. Significant differences for continuous variables between two groups were tested by using two-sided Student's *t* test, and categorical variables were compared using a Fisher's exact test or Chi-squared analysis. A P value < 0.05 was considered statistically significant. Analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, Illinois).

Results

Baseline characteristics

Characteristics of all patients who underwent LAAC were documented at baseline. As shown in Table 1, the advanced-age group ($n = 206$) were much older (80.1 ± 3.9 vs. 67.7 ± 6.5 years, $P < 0.001$) and accounted for a higher proportion of female (38.8% vs. 25.5%, $P = 0.009$). The mean values of $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores in the advanced-age group were higher than those in the non-advanced-age group, and the OAC refusal rate was higher in the non-advanced-age group (27.6% vs. 18.0%, $P = 0.036$). However, there were no significant differences in the pattern of AF or clinical comorbidities such as hypertension, chronic heart failure, diabetes, coronary heart diseases, previous stroke/TIA and previous major bleedings between the two groups.

Procedural results

All 351 patients initially underwent LAAC with the WM device as planned. Among them, 341 were successfully implanted with the WM device, including 7 double-device implantations using the 'Kissing Watchman' technology due to complex anatomy. 6 patients were implanted with the ACP device because of the WM device-incompatible anatomy. Successful LAAC was not obtained in 4 patients due to repeated thrombosis. Between the advanced-age group and the non-advanced-age group, there were no significant differences in the success rate of LAAC procedures (97.9% vs 99.5%, $P = 0.311$) and the WM-device success rate (96.6% vs 97.6%, $P = 0.747$). However, the X-ray dosage (9716.9 ± 9314.5 vs 6257.6 ± 6370.4 mGy, $P < 0.001$) in the non-advanced-age group were higher than that in the advanced-age group (Table 2).

Peri-procedural complications

Severe peri-procedural complications within 7 days were evaluated between the two groups. There were no significant differences in major procedure-related events including death, stroke, major bleeding, device thrombus, cardiac

Table 1 Baseline characteristics

Variable	Total	Non-advanced-age group (age < 75)	Advanced age-group (age ≥ 75)	*P* value
Patient number, *n* (%)	351 (100%)	145 (41.3%)	206 (58.7%)	–
Age, years (mean ± SD)	76.0 ± 8.0	67.7 ± 6.5	80.1 ± 3.9	< 0.001
Female sex, *n* (%)	117 (33.1%)	37 (25.5%)	80 (38.8%)	0.009
Chronic heart failure, *n* (%)	61 (17.4%)	21 (14.5%)	40 (19.4%)	0.255
Hypertension, *n* (%)	281 (80.1%)	115 (79.3%)	166 (80.6%)	0.787
Diabetes mellitus, *n* (%)	99 (28.2%)	40 (27.6%)	59 (28.6%)	0.904
Coronary heart disease, *n* (%)	184 (52.4%)	68 (46.9%)	116 (56.3%)	0.084
Previous TIA/stroke, *n* (%)	61 (17.4%)	22 (15.2%)	39 (18.9%)	0.393
Previous major bleeding, *n* (%)	130 (37.0%)	49 (33.8%)	81 (39.3%)	0.314
Refusal of OAC, *n* (%)	77 (21.9%)	40 (27.6%)	37 (18.0%)	0.036
CHA_2DS_2 score (mean ± SD)	2.5 ± 1.2	1.9 ± 1.1	2.9 ± 1.1	< 0.001
CHA_2DS_2-VASc score (mean ± SD)	3.9 ± 1.5	3.0 ± 1.3	4.5 ± 1.4	< 0.001
HAS-BLED score (mean ± SD)	3.5 ± 1.1	3.2 ± 1.2	3.7 ± 1.0	< 0.001
Atrial fibrillation pattern				
Permanent, *n* (%)	228 (65.0%)	88 (60.7%)	140 (68.0%)	0.174
Persistent or paroxysmal, *n* (%)	123 (35.0%)	57 (39.3%)	66 (32.0%)	0.174

tamponade/ pericardial effusion, and severe vascular complications (Table 3).

Follow-up results of clinical events

All 351 patients were followed up after LAAC, including at least one TEE evaluation of LAAC device implantation and clinical follow-up by outpatient visit or telephone. The mean follow-up period was similar (23.8 ± 16.2 months in the non-advanced-age group vs. 21.6 ± 14.8 months in the advanced-age group, $P = 0.19$). As shown in Table 4, except for an increased trend of major bleeding and all bleedings in the advanced-age group, there were no significant differences in all-cause death, cardiovascular death,

Table 2 Procedural characteristics of LAAC

Variable	Total ($n = 251$)	Non-advanced-age group (age < 75)	Advanced age-group (age ≥ 75)	*P* value
Patient number, *n* (%)	351(100%)	145(41.3%)	206(58.7%)	–
Total procedure success rate, *n* (%)	347(98.9%)	142(97.9%)	205(99.5%)	0.311
Procedure success rate with WM device, *n* (%)	341(97.2%)	140(96.6%)	201(97.6%)	0.747
X-ray time, min (mean ± SD)	11.5 ± 9.7	11.3 ± 7.5	11.7 ± 11.1	0.73
X-ray dose, mGy (mean ± SD)	7694.8 ± 7905	9716.9 ± 9314.5	6257.6 ± 6370.4	< 0.001
Contrast volume, ml (mean ± SD)	101.3 ± 64.8	108.2 ± 82.6	96.4 ± 48.1	0.09

LAAC left atrial appendage closure, *WM* Watchman

Table 3 Peri-procedural complications

Variable	Total ($n = 351$)	Non-advanced-age group (age < 75) ($n = 145$)	Advanced age-group (age ≥ 75) ($n = 206$)	*P* value
Death, *n* (%)	0 (0%)	0 (0%)	0 (0%)	1.000
Stroke, *n* (%)	1 (0.3%)	1 (0.7%)	0 (0%)	1.000
Major bleeding, *n* (%)	2 (0.57%)	0 (0%)	2 (1.0%)	0.514
Device thrombus, *n* (%)	7 (2.0%)	4 (2.8%)	3 (1.5%)	0.933
Pericardial effusion, *n* (%)	11 (3.1%)	6 (4.1%)	5 (2.4%)	0.372
Cardiac tamponade, *n* (%)	3 (0.9%)	2 (1.4)	1 (0.5%)	0.572
Severe vascular complication, *n* (%)	2 (0.6%)	1 (0.7%)	1 (0.5%)	0.513

Table 4 Follow-up outcomes

Variable	Total ($n = 351$)	Non-advanced-age group (age < 75) ($n = 145$)	Advanced age-group (age ≥ 75) ($n = 206$)	*P* value
Mean follow-up, months	22.5 ± 15.4	23.8 ± 16.2	21.6 ± 14.8	0.19
Stroke/TIA, *n* (%)	18 (5.1%)	6 (4.1%)	12 (5.8%)	0.625
All-cause death, *n* (%)	47 (13.4%)	16 (11.0%)	31 (15.0%)	0.340
Cardiovascular death, *n* (%)	9 (2.6%)	4 (2.8%)	5 (2.4%)	1.000
Non-cardiovascular death, *n* (%)	38 (10.8%)	12 (8.3%)	26 (12.6%)	0.225
All bleeding, *n* (%)	45 (12.8%)	13 (9.0%)	32 (15.5%)	0.076
Major bleeding, *n* (%)	25 (7.1%)	6 (4.1%)	19 (9.2%)	0.091
Cerebral hemorrhage, *n* (%)	8 (2.3%)	2 (1.4%)	6 (2.95)	0.478
Gastrointestinal bleeding, *n* (%)	6 (1.7%)	1 (0.7%)	5 (2.4%)	0.407
Other bleeding, *n* (%)	11 (3.1%)	3 (2.1%)	8 (3.9%)	0.536
System embolism, *n* (%)	4 (1.1%)	1 (0.7%)	3 (1.5%)	0.645
Device thrombus, *n* (%)	14 (4.0%)	5 (3.4%)	9 (4.4%)	0.786
Device Gap (> 5 mm), *n* (%)	5 (1.4%)	4 (2.8%)	1 (0.5%)	0.164

TIA transient ischemic attack

stroke/TIA, systemic embolism, device thrombus or device gap (> 5 mm) between the two groups.

According to Kaplan–Meier estimates, the expected rates of annual thromboembolic events based on CHA_2DS_2-VASc scores in the non-advanced and advanced-age groups were 4.6% and 8.4%, respectively, whereas the observed values in our study were 2.1% and 3.2%. In other words, the relative risk of annual thromboembolic events in the advanced-age group reduced much more than that in the non-advanced-age group (61.9% vs 54.3%) (Fig. 1). However, compared with the expected annual bleeding rate based on HAS-BLED score, the observed value decreased by 29.2% in the group aged ≥ 75 and 59.6% in the group aged < 75, demonstrating a greater decline in relative risk of bleedings in the group aged < 75 (Fig. 2).

Discussion

LAAC is now widely accepted as an effective alternative to OAC for stroke prevention in aged patients with atrial fibrillation at high risk of thromboembolic events and major bleedings [17]. Although several implantation devices e.g. the WM device have been approved for clinical use in many countries, few reports have identified the efficacy and safety of this procedure in elderly patients, especially those aged ≥ 75 who are frailer and more prone to complications [18]. It is necessary to clarify whether there are any differences or not between patients with advanced age (≥ 75 years) and those less than 75 years.

In the current study, we collected and analyzed data from 351 patients who underwent LAAC procedure according

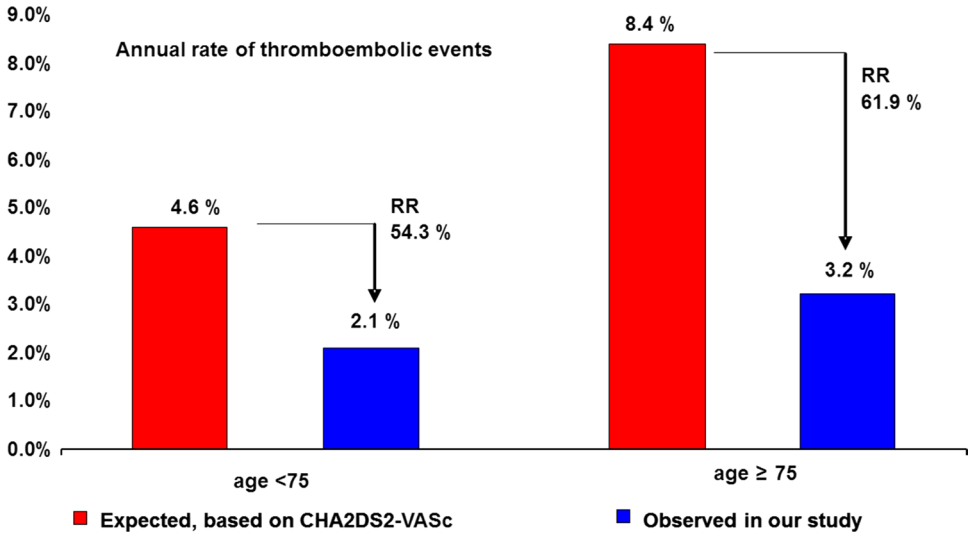

Fig. 1 Observed rate of annual thromboembolic events vs. the expected rate based on the CHA_2DS_2-VASc score. *RR* relative risk

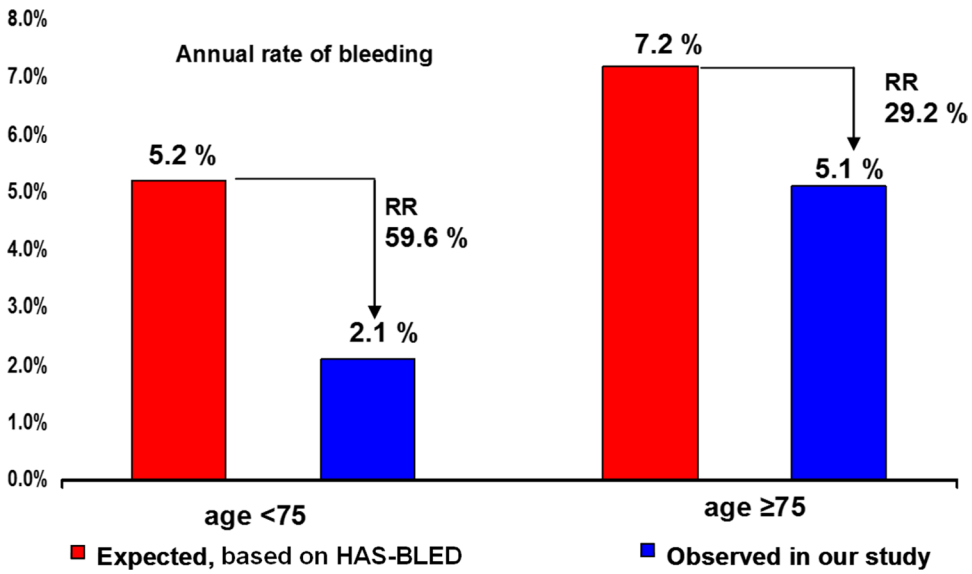

Fig. 2 Observed rate of annual bleeding events vs. the expected rate based on the HAS-BLED score. *RR* relative risk

to age (≥ 75 years or < 75 years). Out of the 351 patients, 341 (97.2%) underwent successful planned LAA closure by implanting 348 WM devices (7 patients received double WM devices using kissing-WM technology). 6 patients were implanted with ACP devices due to WM-incompatible LAA anatomy. Only 4 patients did not obtain successful LAAC procedures due to repeated thrombosis. In terms of the total LAAC procedure success rate, there were no apparent statistical differences between the advanced-age group and the non- advanced-age group. Consistent with our results, Davtyan and colleagues [19] recently also reported that there were no significant differences in LAAC success rate between patients aged ≥ 75 years and those less than 75; however, the sample size of that study was small with only 72 patients, and over half of them used the ACP device.

Besides the much older age, patients in the advanced-age group (age ≥ 75) had a higher proportion of women and higher mean CHA_2DS_2, CHA_2DS_2-VASc, and HAS-BLED scores than those in the non-advanced-age group (age < 75), which revealed higher risks of stroke, major bleeding and other high-risk clinical conditions [17, 18] in the advanced-age group. These risks may occur anytime during the peri-LAAC procedure and post-LAAC management, such as procedure-related major bleeding due to slowdown of heparin metabolism from renal inadequacy, procedure-related thromboembolism, acute heart failure, and anesthesia complications, etc. In the current study, however, there were no significant statistical differences in procedure-related major complications within 7 days including death, stroke, cardiac tamponade/pericardial effusion, major bleeding and severe vascular complication between the two groups. Recently, a study also showed no significant difference in the total procedure complications between patients aged ≥ 75 years or < 75 [19]. In other words, it might be deducted from our study that LAAC procedure is feasible and safe in elderly patients aged ≥ 75 years.

In addition, long-term efficacy in terms of the nearly 2-year clinical follow-up was also compared between the two groups. Based on our results, there were no significant differences in all-cause death, cardiovascular death, stroke/TIA, systemic embolism, device thrombus, and device gap (> 5 mm) after LAAC between the two groups. However, an increased trend of major bleedings and all bleedings was observed in the advanced-age group in comparison with the non-advanced-age group, this result is reasonable since patients with advanced age are prone to bleeding and have more complicated clinical conditions including renal impairment, falls and other geriatric syndromes [17, 18, 20–23].

Despite higher $CHADS_2$ score and CHA_2DS_2-VASc score, as previously discussed, patients with advanced age (≥ 75 years) had higher expected risks of stroke/TIA/systemic thromboembolism than those aged less than 75 years; however, the rates of stroke/TIA within the nearly 2-year clinical follow-up were similar between the two groups. As reported [24, 25], according to the Kaplan–Meier estimates, the expected rates of annual thromboembolic events, including stroke, TIA and other systemic thromboembolisms were obtained based on CHA_2DS_2-VASc score and compared with our observed results in both groups. Our results showed that the relative risk of annual thromboembolic events in the advanced-age group decreased much more than that in the non-advanced-age group (61.9% vs 54.3%), which means LAAC might be more useful in preventing stroke/TIA and other thromboembolic events in older patients with AF. Considering the high risk of bleedings in older patients, we also evaluated the long-term relative risk of bleedings between the observed and the expected values based on HAS-BLED scores. According to our results, the observed rate of annual bleedings decreased by 29.2% in the group aged ≥ 75 and 59.6% in the group aged < 75 compared with the expected values based on HAS-BLED score. Thus, there was a greater decline in the relative risk of bleedings in the group aged < 75. Among patients registered in the EWOLUTION study, the mean CHA_2DS_2-VASc score was 4.5 ± 1.6 (72% of them over ≥ 4), the average HAS-BLED score was 2.3 ± 1.2 (40% of them ≥ 3), and over 50% patients were over 75 years, which were high-risk factors of stroke and bleedings, in terms of 1-year follow-up; however, the study still observed a decreased ischemic stroke rate (1.1%) and a decreased rate of major bleedings (2.6%) compared with the expected values based on CHA_2DS_2-VASc and HAS-BLED scores [26]. In a sense, these results from the EWOLUTION study also confirmed the efficacy and safety of LAAC in older patients with AF.

As it is well known that device-related thrombus and residual leakage are the key concerns of LAAC, these parameters were identified at TEE follow-up. As expected, there were no significant differences in device thrombus or obvious device gap (> 5 mm) in both groups. Overall, these results confirmed the long-term safety of LAAC procedure in NVAF patients regardless of the advanced age.

We recognize that there are some limitations in our study. The present study is a real-world retrospective analysis of patients who underwent LAAC in a single center from February 2012 to December 2017. The sample size is only 351, which is not a large one for a retrospective study. Plus, the nearly 2-year follow-up time in average might not be enough to deduct the differences on clinical events after LAAC between the advanced-age and the non-advanced-age groups.

In summary, the procedural success rate of LAAC and safety in the peri-procedure period within 7 days were similar in the advanced-age group (age ≥ 75 years) and the non-advanced-age group (age < 75 years). According to the nearly 2-year follow-up, there were no significant statistical differences in major events, including death, ischemic

stroke or bleeding, between the two groups despite an increased tendency for major bleeding and all bleedings in the advanced-age group. Overall, percutaneous LAAC is efficient, safe, and feasible in elderly patients, even in those aged over 75 years, and therefore may be an ideal choice to prevent stroke and other thrombotic complications in NVAF patients with advanced age.

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Compliance with ethical standards

Conflict of interest Jiangtao Yu received proctor fees from Boston Scientific. The other co-authors have no conflicts of interest.

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