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Left atrial appendage closure in patients with atrial fibrillation and acute ischaemic stroke despite anticoagulation

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ABSTRACT

Background The occurrence of acute ischaemic stroke (AIS) while using oral anticoagulants (OAC) is an increasingly recognised problem among nonvalvular atrial fibrillation (NVAF) patients. We aimed to elucidate the potential role of left atrial appendage closure (LAAC) for stroke prevention in patients with AIS despite OAC use (AIS-despite-OAC).

Methods We retrospectively collected baseline and follow-up data from consecutive NVAF patients who had AIS-despite-OAC and subsequently underwent endovascular LAAC, between January 2015 and October 2021. The primary outcome measure was the occurrence of AIS after LAAC, and the safety outcome was symptomatic intracerebral haemorrhage (ICH).

Results 29 patients had LAAC specifically because of AIS-despite-OAC. The mean age at the time of the procedure was 73.4±8.7, 13 were female (44.82%). The mean CHA_2DS_2-VASc score was 5.96±1.32, with an expected AIS risk of 8.44 per 100 patient-years. 14 patients (48%) had two or more past AIS-despite-OAC. After LAAC, 27 patients (93.10%) were discharged on OAC which was discontinued in 17 (58.62%) after transoesophageal echocardiogram at 6 weeks. Over a mean of 1.75±1.0 years follow-up after LAAC, one patient had an AIS (incidence rate (IR) 1.97 per 100 patient-years). One patient with severe cerebral microangiopathy had a small ICH while on direct OAC and antiplatelet 647 days after LAAC.

Conclusions LAAC in AIS-despite-OAC patients demonstrated a low annual AIS recurrence rate in our cohort (1.97%) compared with the expected IR based on their CHA_2DS_2-VASc scores (8.44%) and to recent large series of AIS-despite-OAC patients treated with OAC/aspirin only (5.3%–8.9%). These hypothesis-generating findings support randomised trials of LAAC in AIS-despite-OAC patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While oral anticoagulants (OAC) remain the cornerstone of stroke prevention in patients with non-valvular atrial fibrillation (NVAF), patients who sustain an acute ischaemic stroke (AIS) despite OAC use are often seen in clinical practice.

⇒ Large-scale studies showed that patients who had AIS-despite-OAC have a high risk of AIS recurrence with continuation of the same OAC, switching to a different OAC or addition of aspirin.

WHAT THIS STUDY ADDS

⇒ Left atrial appendage closure, a non-pharmacological FDA-approved stroke prevention method in NVAF patients, resulted in low ischaemic stroke recurrence rates in our cohort of patients with AIS-despite-OAC.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings support the need for large-scale randomised controlled studies of patients with AIS-despite-OAC in order to address the clinical challenge of stroke prevention in this patient population.

INTRODUCTION

Oral anticoagulants (OACs) are recommended by the American Heart Association guidelines for the prevention of cardioembolic stroke in patients with non-valvular atrial fibrillation (NVAF).[1] Compared with placebo, vitamin K antagonists (VKA) reduce the risk for acute ischaemic stroke (AIS) and systemic embolism by 67%.[2] Direct OACs (DOACs) were found to be non-inferior to VKA for AIS prevention and proved to have lower intracerebral haemorrhage (ICH) risk, and therefore, are now adopted as first-line drugs in many patients with NVAF.[3–6] However, OACs do not provide full protection from embolism even in low-risk patient populations and some patients still experience AIS while adequately taking their prescribed OAC. The risk of AIS in patients taking OAC is approximately 1.7% per year for VKA and 1.4% per year for non-VKA OACs over 2.2 years follow-up in a population with the mean CHA_2DS_2-VASc (Cardiac failure or dysfunction, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled]—Vascular disease, Age 65–74 and Sex category [Female]) of 2.6.[7] The risk of having a recurrent AIS in patients who had an AIS-despite-OAC was 8.9 per 100 patient-years in a large multicentre study, about 7–10 folds higher than outcomes reported in DOAC arms of the randomised controlled trials (RCTs)

of the 4 DOACs.[8 9] Changing the type of OAC was not proven to affect the risk of recurrent stroke in this population.[9] Therefore, patients who had an AIS-despite-OAC remain a challenging population for secondary stroke prevention. Left atrial appendage closure (LAAC) with the Watchman device (Boston Scientific, Marlborough, Massachusetts, USA) was approved by the Food and Drug Administration (FDA) in 2015 and serves as an alternative stroke prevention method in patients with atrial fibrillation (AF) at increased risk of stroke who have a rationale to avoid long term anticoagulation.[10 11] In this study, we aimed to elucidate the effects of LAAC on AIS recurrence among patients who had AIS-despite-OAC.

METHODS

Patient selection

In this retrospective, observational study, we included consecutive NVAF patients who had endocardial LAAC with either Watchman 2.5/Watchman-FLX or Amplatzer Amulet (Abbott, Minneapolis, Minnesota, USA) devices within single health system network specifically for AIS-despite-OAC, between January 2015 and October 2021. A thorough review of electronic medical records was performed by a neurologist and patients who were referred to LAAC specifically because of AIS(s) while adequately taking OAC as prescribed by their physician, were collected. All AIS on OAC happened while using DOAC regularly or while on warfarin with INR>2. Patients who were not using their OAC at the time of index AIS and patients who were not specifically referred because of AIS-despite-OAC were not included in this study.

Outcomes

The primary outcome measure was the occurrence of symptomatic AIS during the follow-up period after LAAC. The safety outcome was the occurrence of symptomatic ICH during the same period.

Data collection and statistical analysis

Baseline data were collected including patient demographics and clinical characteristics at the time of LAAC. Cardiac imaging data before the LAAC, at the time of the procedure and at 6 weeks follow-up visit were collected. Periprocedural complications were defined as the occurrence of pericardial effusion/tamponade, vessel/cardiac perforation, device migration, major bleeding, stroke, death or any condition that required surgical or other intervention within 7 days of LAAC. Device-related thrombus and peridevice leak (including the size of the leak) were documented through review of cardiac imaging at all time points. Interval history from LAAC to last follow-up visit was reviewed for any event of AIS, symptomatic ICH including traumatic ICH, myocardial infarction, systemic embolism and major bleeding. Antithrombotic medication use was recorded at the time of discharge after LAAC, at 6 weeks after discharge, 3 months, 6 months, 12 months after discharge and during the last available follow-up visit. Detailed information related to all AISs before and after LAAC was registered. Clinical data as well as brain imaging, vascular imaging, cardiac imaging and lab results for each stroke were collected and reviewed. AIS pattern was determined based on diffusion-weighed imaging findings into the following subtypes: single lesion (cortico-subcortical lesion, cortical lesion, subcortical lesion ≥15 mm or subcortical lesion <15 mm), two or more scattered lesions in one vascular territory and multiple lesions in multiple vascular territories.[12] Presumed cause of each AIS was concluded based on patient's clinical characteristics, aetiological workup and the imaging pattern of AIS on brain MRI, by consensus of a neurologist and a stroke neurologist. For patients who had single subcortical infarcts of greatest diameter less than 15 mm, we also provided the location of the infarct. Such small infarcts might be more likely related to cerebral small vessel disease (cSVD) if they are located in classical deep locations such as internal capsule, basal ganglia, thalamus or pons whereas NVAF-related embolism might be the cause if they are in other subcortical locations such as corona radiata or centrum semiovale although cSVD remains in the differential in these patients as well.[13 14] There were three patients who did not have a brain MRI available to review for all of their past strokes and the presence/absence of an embolic infarct was obtained from review of head CT and the official clinical/imaging reports. Categorical variables are reported as counts and corresponding percentage while continuous variables are reported as mean±SD or median (IQR) depending on their distribution. Based on already published data, the baseline characteristics, and the occurrence of AIS in follow-up of patients who did or did not have LAAC after AIS-despite-OAC, were presented in tables 3 and 4.

RESULTS

Between January 2015 and October 2021, 29 patients were specifically referred for the LAAC procedure because they had AIS(s) while taking OAC as prescribed by their physicians. All patients were evaluated by stroke neurology physicians. The mean age at the time of LAAC was 73.4±8.7 years and 13 of the patients were female (44.82%). All patients had a diagnosis of NVAF (44.82% paroxysmal, 55.18% permanent) for a median duration of 4.83 years (IQR 1.52–10.11) at the time of LAAC. Patients' characteristics and vascular risk factors are further described in table 1.

Detailed characteristics pertaining to the patients' AIS before LAAC as well as their management and outcome events during follow-up are provided in online supplemental table S1. 14 patients (48.3%) had more than one AIS prior to LAAC. Five patients had an AIS before LAAC while they were treated with VKA, 21 while treated with DOAC and 3 patients while they were treated with either VKA or DOAC at different time points as shown in online supplemental table S1. On detailed review of potential aetiologies of AIS-despite-OAC, only one patient (patient #16 in online supplemental table S1) had one

Table 1 Baseline patient characteristics of the study population (n=29)

Age, mean±SD, years	73.4±8.7
Female, n (%)	13 (44.8)
AF, paroxysmal, n (%)	13 (44.8)
AF, permanent, n (%)	16 (55.2)
Hypertension, n (%)	28 (96.9)
Diabetes mellitus, n (%)	15 (51.7)
Dyslipidaemia, n (%)	29 (100)
CAD, n (%)	9 (31)
PVD, n (%)	6 (20.7)
DVT/PE, n (%)	4 (13.8)
Heart failure, n (%)	10 (34.5)
Chronic renal disease, n (%)	12 (41.4)
Smoking, n (%)	1 (3.4)
Past carotid endarterectomy/stenting, n (%)	3 (10.3)
Multiple prior ischaemic strokes, n (%)	14 (48.3)
2 ischaemic strokes	11 (37.9)
4 ischaemic strokes	2 (6.9)
5 ischaemic strokes	1 (3.4)
CHA_2DS_2-VASc, mean±SD	5.96±1.32
HAS-BLED, mean±SD	4.24±0.93
LAAC device type	
Watchman	16 (55.2)
Watchman-FLX	13 (44.8)

AF, atrial fibrillation; CAD, coronary artery disease; CHA_2DS_2-VASc, Cardiac failure or dysfunction, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled)—Vascular disease, Age 65–74 and Sex category (Female); DVT, deep vein thrombosis; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; LAAC, left atrial appendage closure; PE, pulmonary embolism; PVD, peripheral artery disease.

AIS consisting of a single small infarct in a classical deep location (thalamus) that could have been related to cSVD although embolism cannot be ruled out in the presence of NVAF. All other patients sustained clearly embolic-looking infarcts while on OAC at least once, leading up to their referral to LAAC. No patient had proximal large vessel atherosclerotic disease or other classical cause for their AIS. The potential additional aetiological factors in three patients are provided in online supplemental table S1. The mean CHA_2DS_2-VASc score was 5.96±1.32, with a calculated annual ischaemic stroke risk of 8.44 per 100 patient-years. Mean HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly) score was 4.24±0.93. 16 patients (55.2%) had the Watchman 2.5 implanted while the other 13 patients had the new generation Watchman-FLX (44.8%). There were no periprocedural complications for any of the patients. Patients were followed up for a mean of 1.75±1.0 years after LAAC. During follow-up, no patient had peridevice leak of more than 5 mm, however, four patients had peridevice leak of 3–5 mm. One of those patients had coiling of the leak with complete closure. None of the patients had device-related thrombus. Post-LAAC antithrombotic treatment was individualised to the patients' perceived needs and varied as described in table 2. 27 patients were discharged on OAC. After the 6 weeks post-LAAC trans0esophageal echocardiogram (TEE) was performed, 12 (41.4%) patients remained on OAC treatment. At 1-year follow-up, one patient died and two were lost to follow-up. Among the remaining 26 patients, 18 patients were using antiplatelet monotherapy, 1 was not taking any antithrombotic treatment and 7 patients were still using OAC (24.1%).

For the primary outcome of recurrent symptomatic AIS, one patient had a small subcortical infarct in the centrum semiovale (<15 mm) despite continued OAC use, 190 days after LAAC (patient #11 in online supplemental table S1). This patient had a prior medical history significant for monoclonal gammopathy of unknown significance

Table 2 Antithrombotic treatment after left atrial appendage closure (n=29)

Antithrombotic treatment	Discharge	6 weeks p/LAAC	3 months p/LAAC	6 months p/LAAC	1-year p/LAAC
AP monotherapy	0	7 (24.1%)	15 (51.7%)	20 (69.0%)	18 (62.2%)
DAPT	2 (6.9%)	10 (34.5%)	4 (13.8%)	0	0
VKA	1 (3.4%)	0	0	0	0
VKA+AP	9 (31.0%)	4 (13.8%)	2 (6.9%)	2 (6.9%)	2 (6.9%)
DOAC	5 (17.3%)	0	0	0	1 (3.4%)
DOAC+AP	12 (41.4%)	8 (27.6%)	7 (24.2%)	5 (17.3%)	4 (13.8%)
None	0	0	0	1 (3.4%)	1 (3.4%)
Died	0	0	0	0	1 (3.4%)
Lost to follow-up	0	0	1 (3.4%)	1 (3.4%)	2 (6.9%)

AP, antiplatelet; DAPT, dual antiplatelet; DOAC, direct oral anticoagulation; p/LAAC, post left atrial appendage closure; VKA, vitamin K antagonist.

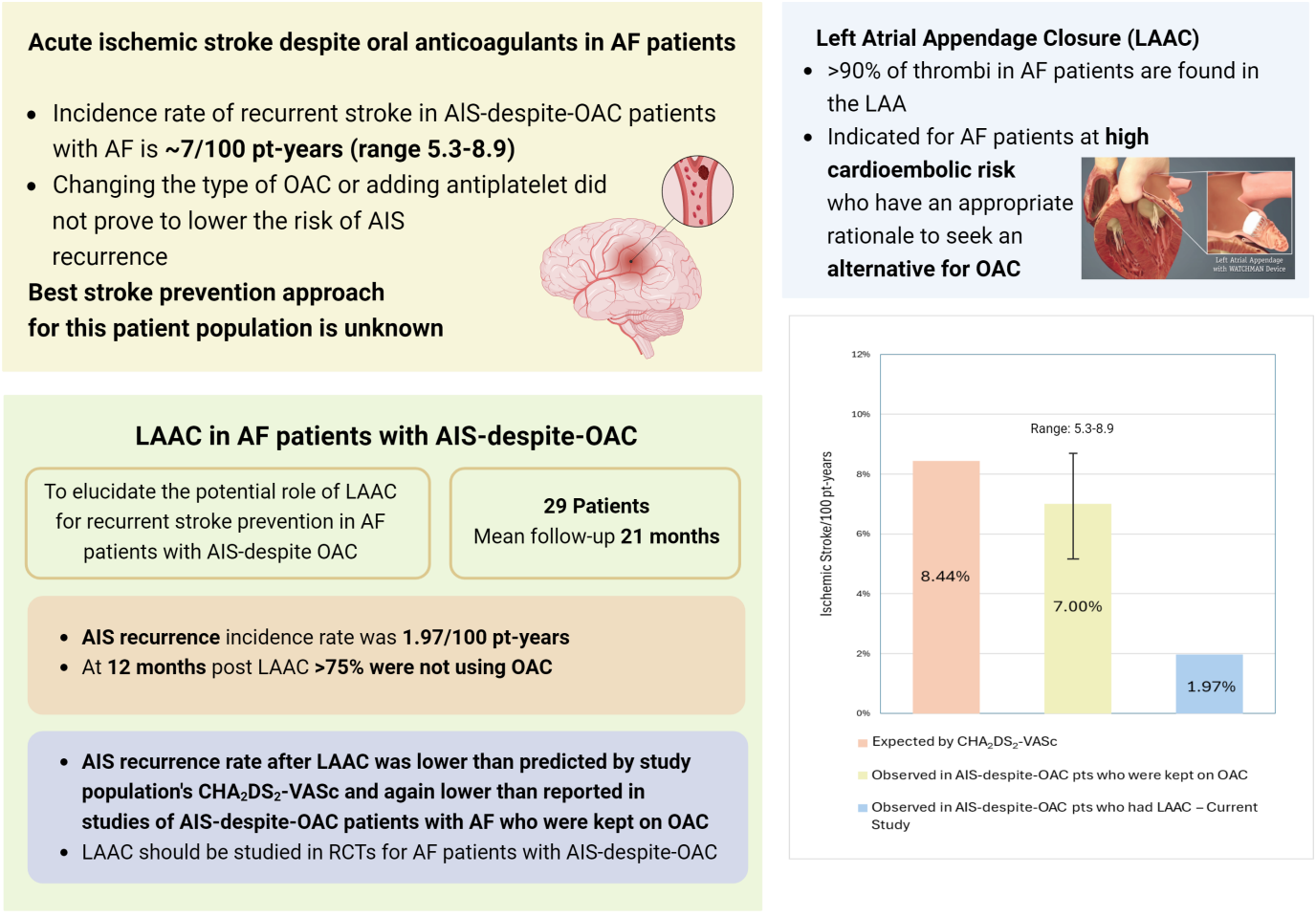

Figure 1 Left atrial appendage closure in patients with atrial fibrillation and acute ischaemic stroke despite anticoagulation. AF, atrial fibrillation; AIS, acute ischaemic stroke; NVAF, non-valvular atrial fibrillation; RCT, randomised controlled trial; OAC, oral anticoagulant.

(MGUS) and five ischaemic strokes prior to LAAC, four of those while taking DOAC. Accordingly, incidence rate (IR) for recurrent AIS after LAAC in our study population was 1.97 per 100 patient-years (see figure 1). For the safety outcome of symptomatic ICH, one patient had a small cerebellar ICH while taking DOAC and aspirin (IR 1.97 per 100 patient-years) 647 days after LAAC (patient #18 in online supplemental table S1). This patient had four ischaemic strokes (two while using DOAC and two while using VKA) leading up to the decision to perform LAAC, and a prior brain MRI also showed multiple mixed location (deep and lobar) cerebral microbleeds. There was no systemic embolism in any patient during follow-up. None of the patients suffered myocardial infarction or major bleeding.

DISCUSSION

We performed a retrospective analysis of patients who had endocardial LAAC due to AIS-despite-OAC, in order to investigate the role of LAAC in this high-risk patient population. During a 1.75 years follow-up period, only one patient experienced an AIS after LAAC resulting in an IR of 1.97 per 100 patient-years. Our study did not have a control arm, but AIS IR was lower compared with the expected rate based on the mean CHA_2DS_2-VASc (8.44 per 100 patient-years) and compared with previously published large series of patients who had AIS-despite-OAC and were kept on OAC without LAAC (5.3–8.9 per 100 patient-years) as shown in figure 2. Outcome data from our consecutive case series support the view that LAAC might be a useful approach to decrease the risk of AIS in this high-risk population.

We report detailed information on index strokes, LAAC procedure and follow-up events within a well-defined patient population with NVAF who had LAAC specifically because they had one or more AIS-despite-OAC. NVAF patients with AIS-despite-OAC pose a therapeutic dilemma regarding the best secondary stroke prevention method. Multiple studies focused on longitudinal follow-up of large NVAF patient populations who had AIS-despite-OAC have been recently published (table 3).[9 15–20]

These patients were all kept on OAC (change in type/brand allowed) with or without the addition of antiplatelet. These studies consistently showed high AIS recurrence rates ranging between 5.3 and 8.9 per 100 patient-years. Changing the type of OAC, the OAC brand

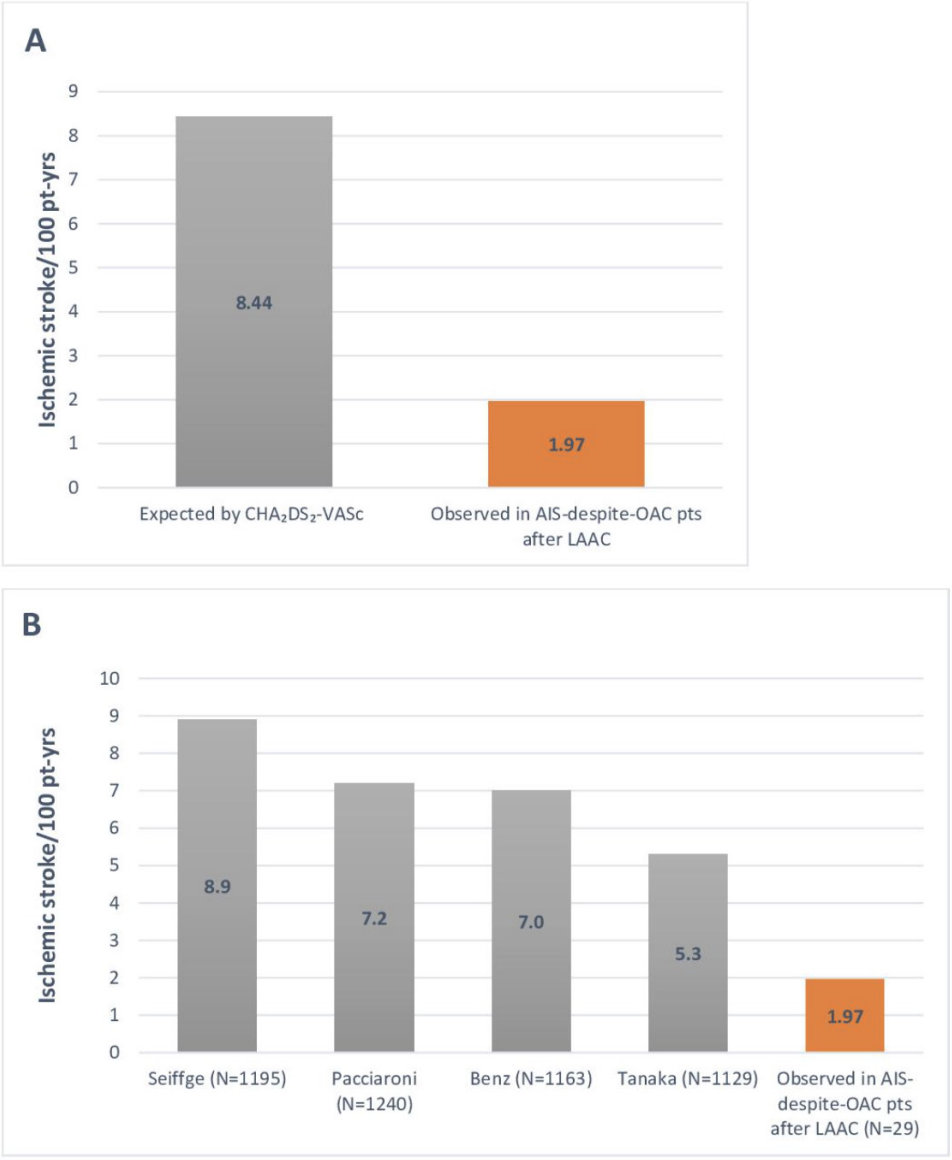

Figure 2 Recurrent ischaemic stroke risk in patients with AIS-despite-OAC was lower after LAAC compared with expected by CHA_2DS_2-VASc (A) and compared with data from previous publications on AIS-despite-OAC patients who were kept on OAC without LAAC as further described in table 3 (B). AIS, acute ischaemic stroke; OAC, oral anticoagulant; LAAC, left atrial appendage closure; CHA_2DS_2-VASc, Cardiac failure or dysfunction, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled)—Vascular disease, Age 65–74 and Sex category (Female)

Table 3 Published data on baseline characteristics and outcomes in patients who had AIS-despite-OAC and kept on OAC without left atrial appendage closure

Author, year	Study design	No. of pts.	Age (years)	CHA_2DS_2-VASc	HAS-BLED	Follow-up	Recurrent AIS risk	Recurrent ICH risk
Seiffge *et al*[9] 2020	Pooled analysis from prospective, observational registries	1195	79 (73–84)	5 (4–6)	3 (3–4)	318 days	8.9 per 100 patient-years	2.0 per 100 patient-years
Benz *et al*[15] 2023	Individual participant data from five randomised trials	1163	73 (67–78)	4 (3–6)	N/A	337 days	7 per 100 patient-years	N/A
Tanaka *et al*[16] 2020	Pooled analysis from prospective, observational registries	1129	75 (70–80)	N/A	N/A	1 year	5.3 per 100 patient-years	0.6 per 100 patient-years
Pacciaroni *et al*[18] 2022	Prospective, observational	1240	78.9±9.1	77.1%≥4	38.1%≥3	15 months	7.2 per 100 patient-years	1.5 per 100 patient-years

AIS, acute ischaemic stroke; ICH, intracerebral haemorrhage; N/A, not available; OAC, oral anticoagulant.

or adding aspirin did not reduce the risk of recurrent AIS.[9] Our study included a high embolic risk NVAF population with half of our patients having sustained more than one AIS-despite-OAC. Despite the high embolic risk patient population included (mean CHA_2DS_2-VASc: 5.96), the IR of 1.97 per 100 patient-years represents a 77% relative reduction in AIS risk based on the expected annual AIS rate in a patient population with similar mean risk score (8.44 per 100 patient-years). LAAC is not commonly performed in AIS-despite-OAC hence our relatively small study population, but we have been able to report very detailed data on the index strokes and follow-up thanks to the design of our study that was performed in a single hospital system composed of multiple hospitals. RCTs are needed to evaluate whether LAAC is superior to simple OAC continuation in patients with AIS-despite OAC. Based on a conservative 2 years cumulative IR of ischaemic stroke of 10.3% in an NVAF patient population who had AIS-despite-OAC and kept on OAC, and on an IR of 4% in patients who had LAAC after AIS-despite-OAC based on our findings, an RCT including 698 patients would have 90% power to show superiority of LAAC over OAC-only approach.[15]

Although it is difficult to confirm that an AIS is directly related to embolism from NVAF, the review of the stroke imaging for location/size/pattern of infarct(s) and ruling out alternative aetiologies increase our confidence in the stroke aetiology. Such review is difficult in large-scale studies including RCT because of the bulk of the data that needs to be obtained and reviewed. Thanks to the design of our study based on a single healthcare system, we have been able to review and report clinical details as well as imaging data of 50 AIS that our 29 patients sustained before LAAC as well as the one AIS after LAAC. There was only one patient who suffered from one subcortical infarct less than 15 mm in diameter prior to LAAC, whereas the other patients had at least one clearly embolic infarct. The location of the small infarct in this patient was the thalamus, which could have been due to either cSVD or NVAF-related embolism. Despite having very high embolic risk (high CHA_2DS_2-VASc scores and past AIS-despite-OAC), our cohort exhibited low rates of AIS recurrence after LAAC, similar to recent studies that explored the role of LAAC in patients with AIS-despite-OAC (table 4). With respect to the aetiology of the only one recurrent AIS after LAAC in our cohort, it is possible that the patient's pre-existing MGUS might have played a role as a competing aetiology for the patient's pre-LAAC ischaemic strokes as well as post-LAAC stroke.[21] It is indeed important to perform a thorough stroke aetiological investigation among NVAF patients who had AIS-despite-OAC but there are many situations in which the relative contribution of a potential aetiological factor is unknown. If such a potential additional aetiology is found, specific treatment can be planned, if available, in the hope to reduce the risk of further strokes. Aetiological evaluation and treatment decisions require a multidisciplinary approach based on the complexity of the patient's other medical conditions, as was the case for patients enrolled in this study. All patients were evaluated by stroke neurology and cardiology specialists. Our findings suggest that in NVAF patients with AIS-despite-OAC mainly without a concurrent aetiology, LAAC is associated with a low risk of recurrent embolic events in follow-up.

Current FDA approval allows the use of either VKA or DOAC or dual antiplatelets during the first 6 weeks immediately following LAAC with Watchman 2.5 or Watchman-FLX devices.[1] The great majority of patients are taken off of anticoagulant therapy after the first follow-up TEE at 6 weeks, provided that there is no significant peridevice leak or device-related thrombus. Again, based on current FDA-approval, most patients are kept on lifelong daily aspirin. The optimal duration of anticoagulant use in NVAF patients who undergo LAAC for AIS-despite-OAC, is hotly debated. Some experts argue that these high embolic risk patients should remain on long-term OAC after LAAC in order to reduce recurrent embolic stroke risk. The LAAOS III study showed a 33% reduction in AIS risk when surgical LAAC was performed in addition to long-term OAC use in a patient population with NVAF who underwent cardiac surgery.[22] Although a different surgical patient population, LAAOS III provided proof of concept that the combination of LAAC and long-term OAC is superior to OAC-only approach. In our study, 24.1% of NVAF patients who had LAAC after AIS-despite-OAC were kept on OAC at 1 year after the procedure. The rate of AIS recurrence was low at an average of 1.75 years follow-up and only two patients were lost to follow-up before 12 months. The recent FDA-required study, Primary Outcome Evaluation of a Next-Generation Left Atrial Appendage Closure Device that resulted in approval of Watchman-FLX device showed that the majority of embolic events occur within the first year after LAAC, a finding in line with other published data.[23] Among NVAF patients who sustained one or more embolic AIS-despite-OAC, our study shows low AIS rate despite conservative use of OAC after LAAC, over a relatively long follow-up compared with the other case series (table 4). The only patient who had an ICH in follow-up was on DOAC and aspirin therapy, 21.9 months after LAAC. Anti-thrombotic treatment after LAAC might be a challenging decision, especially in high ischaemic risk NVAF patients who also carry a high haemorrhagic risk. The patient who experienced ICH in follow-up had mixed location (deep and lobar) cerebral microbleeds on brain MRIs at the time of past AIS-despite-OAC. Mixed location cerebral microbleeds typically represent a more severe form of hypertensive cSVD.[24 25] Such patients might undergo LAAC to be able to discontinue OAC in the absence of past AIS-despite-OAC. This patient was kept on DOAC and aspirin because of the history of four AIS-despite-OAC. Post-LAAC antithrombotic regimens varied in our cohort and such variability has been the rule rather than the exception in previous reports as well.[26] Among patients who received Watchman for LAAC between 2016 and 2018 included in the large LAAC Registry of

Table 4 The efficacy and safety of Left atrial appendage closure in patients with AIS-despite-OAC

Author, year	Study design	No. of patients	Inclusion criteria	Age (years)	CHA_2DS_2-VASc	HAS-BLED	Follow-up (years)	OAC discontinuation	AIS during follow-up (events/100 patient-years)	Antithrombotic therapy at time of incident AIS	Major bleeding incl. ICH during follow-up (events/100 patient-years)
(Current study)	Retrospective observational	29 (5 VKA, 21 DOAC, 3 both DOAC and VKA)	NVAF patients with previous stroke despite adequate OAC use	73.4±8.7	6.0±1.3	4.2±0.9	1.75±1.00	19 (65.5%)	1 (1.97%)	DOAC	1 (1.97%)
Cruz-González *et al*,[28] 2020	Retrospective observational	115 (mostly VKA)	NVAF patients with previous stroke on OAC	73.8±10.2	5.5±1.5	3.9±1.3	1.35±1.02	Individualised depending on the patient history, indication for LAAC and physician preference	3 (1.93%)	Unknown	0 (0%)
Galloo *et al*[29] 2020	Retrospective observational	15 (40% DOAC, 60% VKA)	NVAF patients with previous stroke on OAC after excluding alternative causes of stroke	78.1±5.8	6±1.2	5.0±1.2	3.1±2.7	4 (26.7%)	2 (4.30%)	1 VKA, 1 on no OAC	0 (0%)
Freixa *et al*[30] 2019	Retrospective observational	22 (13 VKA, 6 DOAC, 3 OAC+ASA)	AF patients with cardioembolic events despite optimal OAC	68.9±9.1	4.5±1.3	2.6±1.1	1.8 (0.7–2.8)	3 (13.6%)	1 (2.52%)	Antiplatelet	1 (2.52%) haematuria
Masjuan *et al*[31] 2019	Prospective observational	19 (9 VKA, 10 DOAC)	AF patients with a history of at least two recurrent cardioembolic strokes in the previous year despite adequate OAC and after excluding alternative causes of stroke	72.1±9.6	5.3±1.5	1.7±1.2	1.45±0.96	0	0	–	0 (0%)
Pracoń *et al*[32] 2022	Prospective registry	39 (18 DOAC, 18 VKA, 3 both DOAC and VKA)	NVAF who had AIS/TIA/peripheral embolism/LAA thrombus while on OAC	73 (62–77)	5.0 (3.0–6.0)	2.0 (1.0–3.0)	1.02 (0.98–1.07)	All discharged on DAPT after LAAC	3 (7.54%)	Antiplatelet	0 (0%)

Variables are expressed as mean ±SD or median (IQR).
AIS, acute ischaemic stroke; DOAC, direct oral anticoagulant; ICH, intracranial haemorrhage; LAA, left atrial appendage; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant; TIA, transient ischaemic attack; VKA, vitamin-K anticoagulant.

the National Cardiovascular Data Registry, only 12.2% received the full post procedure antithrombotic treatment protocol studied in pivotal trials.[27] As the question about the optimal antithrombotic treatment after LAAC in AIS-despite-OAC patients remains unanswered, assessing the individualised ischaemic and haemorrhagic stroke risks for each patient might be the right approach until we have data from randomised trials. Based on our results, future clinical trials involving AF patients who had AIS-despite-OAC should mandate a thorough evaluation for concomitant stroke aetiologies. Patients without a clear other aetiology can be randomised to LAAC with either lifelong anticoagulation or one of the currently FDA-approved post-LAAC regimens versus continuation of OAC without LAAC.

Study limitations

The main limitations of our study include its retrospective, observational nature and the relatively small sample size. Despite these potential weaknesses, 93% of our patients had thorough follow-up for at least 1 year with a mean duration of 1.75 years follow-up. We made all efforts to obtain information about the two patients who were lost to follow-up, but we were not able to find follow-up data. Thorough review of existing sources and databases did not provide any evidence that they expired. The current study also provides a high level of relevant detail for AIS-despite-OAC including detailed imaging review. Our sample size is average when compared with the other studies reported in table 4, but it should be remembered that LAAC is uncommonly performed after AIS-despite-OAC. Very detailed patient review and inclusion of patients who had LAAC specifically for AIS-despite-OAC are strengths of our study. About half of the patients had more than one AIS-despite-OAC and all were compliant with OAC use. Few of our patients had other potential aetiologies for AIS (MGUS, heart failure, haemochromatosis, cSVD) but this would only elevate recurrent AIS risk and further emphasise the success of LAAC as reflected by the low incidence AIS rates. A selection bias of patients who could tolerate the LAAC procedure could have influenced our results, but from an embolic and haemorrhagic prospective, the mean CHA_2DS_2-VASc and HAS-BLED of 5.96 and 4.24, respectively, represent a very high-risk population who could reasonably be compared with previous studies which included patients with even lower risk scores (table 3). Although we did not have a control group without LAAC, we compared our results to the expected AIS rates based on CHA_2DS_2-VASc scores of our own patients. We also reported relevant data from the previously published studies of AIS-despite-OAC who were maintained on anticoagulant therapy without LAAC as shown in figure 2.

CONCLUSIONS

Our hypothesis-generating results show that the primary outcome of AIS after LAAC in a high embolic risk NVAF population who had AIS-despite-OAC was lower (1.97 per 100 patient-years) than the expected AIS rates calculated based on our cohort's CHA_2DS_2-VASc scores (8.44 per 100 patient-years) and it was also lower than the rates previously reported in multiple studies that included patients who were kept on OAC as stroke prevention method (5.3–8.9 per 100 patient-years) as shown in figure 2. LAAC might be beneficial to this population along with personalised post-LAAC antithrombotic treatment. RCTs are needed to confirm whether LAAC is a superior treatment approach for NVAF patients who had AIS-despite-OAC and identify the optimal post-LAAC antithrombotic regimen in this population.

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