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Original Article

Stroke Prevention With Left Atrial Appendage Closure in Patients With Atrial Fibrillation and Prior Intracranial Hemorrhage

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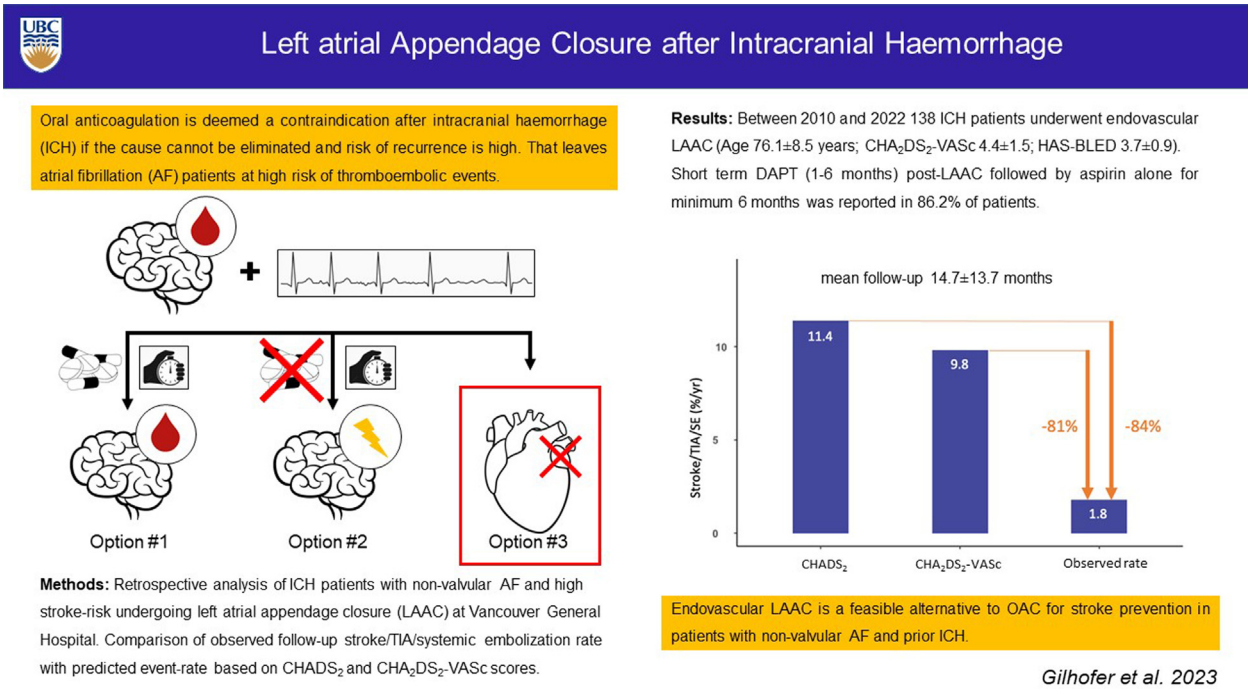

ABSTRACT

Background: Oral anticoagulation (OAC) is deemed a relative contraindication after intracranial hemorrhage (ICH) if the cause cannot be eliminated and the risk of recurrence is high. That leaves atrial fibrillation (AF) patients at high risk of thromboembolic events. Endovas-

RÉSUMÉ

Contexte : L'anticoagulation par voie orale (ACO) est considérée comme une contre-indication relative après une hémorragie intracrânienne (HIC) si la cause ne peut être éliminée et si le risque de récidive est élevé. Les patients souffrant de fibrillation auriculaire (FA)

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cular left atrial appendage closure (LAAC) can be an alternative to OAC for patients requiring stroke prevention.

Methods: We performed a retrospective single-centre analysis of 138 consecutive ICH patients with nonvalvular AF and high stroke risk who underwent LAAC between 2010 and 2022 at Vancouver General Hospital. We report the baseline characteristics, procedural results, and follow-up data, comparing the observed stroke/transient ischemic attack (TIA) rate with the predicted event rate based on their CHA_2DS_2-VASc scores.

Results: The average age was 76.1 ± 8.5 years; the mean CHA_2DS_2-VASc score was 4.4 ± 1.5; and the mean HAS-BLED score was 3.7 ± 0.9. The procedural success rate was 98.6%, and the complication rate was 3.6% with no periprocedural death, stroke, or TIA. The antithrombotic regimen post-LAAC consisted of short-term dual antiplatelet therapy (1-6 months) followed by aspirin alone for a minimum of 6 months in 86.2%. At mean follow-up of 14.7 ± 13.7 months, 9 deaths (6.5%, 7 cardiovascular, 2 noncardiovascular), 2 strokes (1.4%), and 1 TIA (0.7%) had occurred. The annualized observed stroke/TIA rate was 1.8%, which was lower than the adjusted predicted stroke rate of 7.0% (95% confidence interval: 4.8%-9.2%). Two patients (1.5%) suffered another ICH (both on aspirin monotherapy). One device-related thrombus (0.7%) was confirmed and treated with OAC without sequelae.

Conclusion: Endovascular LAAC is a feasible alternative to OAC for stroke prevention in patients with nonvalvular AF and prior ICH.

sont donc exposés à un risque élevé d'événements thromboemboliques. La technique de fermeture percutanée de l'appendice auriculaire gauche (AAG) peut être une solution de rechange aux anticoagulants oraux en prévention des accidents vasculaires cérébraux (AVC).

Méthodologie : Nous avons réalisé une analyse rétrospective unicentrique auprès de 138 patients consécutifs qui étaient atteints d'une HIC accompagnée d'une FA non valvulaire ainsi que d'un risque élevé d'AVC et qui ont subi une fermeture de l'AAG entre 2010 et 2022 à l'hôpital général de Vancouver. Nous présentons ici les caractéristiques initiales, les résultats de l'intervention et les données de suivi, en comparant le taux d'AVC/AIT (accident ischémique transitoire) observé avec le taux prédit d'événements sur la base de leurs scores CHA_2DS_2-VASc.

Résultats : L'âge moyen était de 76,1 ± 8,5 ans. Le score CHA_2DS_2-VASc moyen était de 4,4 ± 1,5, et le score HAS-BLED moyen de 3,7 ± 0,9. Le taux de réussite de l'intervention a été de 98,6 % et le taux de complications de 3,6 %, sans décès périopératoires, ni AVC ou AIT. Le traitement antithrombotique après la fermeture de l'AAG consistait en une bithérapie antiplaquettaire de courte durée (de 1 à 6 mois), suivie de la prise d'aspirine seule pendant au moins 6 mois dans 86,2 % des cas. Après un suivi moyen de 14,7 ± 13,7 mois, 9 décès (6,5 %, 7 d'origine cardiovasculaire et 2 d'origine non cardiovasculaire), 2 AVC (1,4 %) et 1 AIT (0,7 %) sont survenus. Le taux annualisé d'AVC/AIT observé était de 1,8 %, ce qui est inférieur au taux prédit d'AVC après ajustement, soit 7,0 % (intervalle de confiance à 95 % : 4,8 % à 9,2 %). Deux patients (1,5 %) ont souffert d'une autre HIC (tous deux sous aspirine en monothérapie). Un thrombus lié au dispositif (0,7 %) a été confirmé et traité par anticoagulathérapie orale sans séquelles.

Conclusion : La technique de fermeture de l'AAG représente une solution de rechange à l'anticoagulation par voie orale dans la prévention des AVC chez les patients souffrant de FA non valvulaire et ayant déjà subi une HIC.

Atrial fibrillation (AF) affects 1%-2% of the general population, and the prevalence increases to 18% in patients aged > 85 years.[1] AF increases the risk of stroke by 5-fold, and lifelong oral anticoagulation (OAC) treatment is recommended for patients at high stroke risk according to the $CHADS_2$ [**C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75, **D**iabetes, and Prior **S**troke/Transient Ischemic Attack [doubled]) and CHA_2DS_2-VASc [**C**ongestive Heart Failure, **H**ypertension, **A**ge (≥ 75 Years) (doubled), **D**iabetes Mellitus, **S**troke (doubled), **V**ascular Disease, **A**ge (65-74) Years, **S**ex **C**ategory (Female)] scores. However, OAC increases bleeding risk, with rates of fatal (0.6%/y) and major (3.0%/y) bleeding being approximately 5 times higher with warfarin vs without.[2] The most-feared bleeding complication is intracranial hemorrhage (ICH), which accounts for 58% of all bleeding-associated deaths in anticoagulated patients.[3] Even with the use of direct OAC (DOAC), the risk of ICH is still significant (apixaban, 0.3%/y; dabigatran, 0.2%-0.3%/y; edoxaban, 0.2%-0.3%/y; rivaroxaban, 0.4%/y), compared with that of warfarin (0.3%-1.8%/y).[4] Furthermore, ICH in patients on OAC is associated with a significantly poorer prognosis, compared to ICH in patients not on OAC (52% vs 26% 3-month mortality, respectively[5]), independent of the type of OAC.[4,6,7] This poorer prognosis is most likely due to more rapid hematoma expansion as a result of the coagulopathy.[5]

The risk of recurrent bleeding after ICH can vary based on the pathophysiology, reported at 4.4% per patient-year in patients with cerebral amyloid angiopathy (CAA) vs 2.1% per patient-year after hypertensive ICH. Even without further OAC use, the rate of recurrent ICH is high, at 2.3%/y with CAA, and 2.1%/y with hypertensive ICH.[5] Patients with prior lobar ICH and the detection of microbleeds in cerebral imaging are reported to have a risk of recurrent lobar ICH of 10%/y.[5] In CAA-associated ICH, the recurrence rate increases to ∼27% in patients with extensive cortical superficial siderosis.[5] OAC after the index ICH can triple the risk of recurrence (hazard ratio [HR] 3.0).[8] Nevertheless, nonvalvular AF patients who suffered an ICH can be at significant risk of ischemic stroke and may benefit from restarting OAC. via reduction of ischemic stroke and mortality, despite risk of recurrent ICH.[9] The American College of Chest Physicians guidelines, as well as the American Heart Association/American Stroke Association secondary stroke prevention guidelines, indicate that the decision on resuming antithrombotic therapy in patients after ICH should be individualized

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See page 410 for disclosure information.

Table 1. Baseline demographics of intracranial haemorrhage (ICH) patients

Characteristic	Mean ± SD or n (%) (N = 138)
Age, y	76.1 ± 8.5
Men	96 (69.6)
BMI, kg/m^2	26.2 ± 5.0
Hypertension	113 (81.9)
Dyslipidemia	89 (64.5)
Diabetes mellitus	34 (24.6)
Smoking history (active or remote)	67 (49.0)
COPD	14 (10.1)
Coronary artery disease	41 (29.7)
Previous MI	26 (18.8)
Previous PCI	27 (19.6)
CABG	11 (8.0)
Heart failure	30 (21.7)
LVEF < 40%	18 (13.0)
History of valve surgery	8 (5.8)
Previous stroke/TIA	78 (56.5)
Systemic embolization	6 (4.3)
Permanent/persistent AF	84 (60.9)
Paroxysmal AF	54 (39.1)
Pacemaker/AICD	26 (18.8)
Creatinine, μmol/L	109.3 ± 64.7
eGFR, mL/kg per 1.73 m^2	63.3 ± 22.1
Hemoglobin at baseline	134.3 ± 16.6
Platelet count at baseline	201.8 ± 66.8
$CHADS_2$ score	2.9 ± 1.3
CHA_2DS_2-VASc score	4.4 ± 1.5
HAS-BLED score	3.7 ± 0.9
Bleeding	
Previous major	138 (100)
Previous major while on OAC	108 (78.3)
Intracranial	138 (100)
Epidural	0 (0)
Subdural	57 (41.3)
Subarachnoid	16 (11.6)
Intracerebral	64 (46.4)
Cerebral amyloid angiopathy	17 (12.3)
Additional major bleeding	13 (9.4)

AF, atrial fibrillation; AICD, automated implantable cardioverter defibrillator; BMI, body mass index; CABG, coronary artery bypass grafting; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75, **D**iabetes, and Prior **S**troke/Transient Ischemic Attack [doubled]; CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge [≥ 75 Years] [doubled[, **D**iabetes Mellitus, **S**troke (doubled), **V**ascular Disease, **A**ge [65-74] Years, **S**ex **C**ategory [Female]; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HAS-BLED, **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile International Normalized Ratio, **E**lderly [>65 Years], **D**rugs/Alcohol Concomitantly; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; SD, standard deviation; TIA, transient ischemic attack.

according to their risk of subsequent arterial or venous thromboembolism and the risk of recurrent ICH, respectively.[9]

Endovascular left atrial appendage closure (LAAC) is increasingly performed as an alternative to OAC in patients with nonvalvular AF who are considered poor candidates for long-term OAC. In particular, a few series have shown that LAAC may be safe and feasible in ICH patients, with the use of (single or dual) antiplatelet therapy (SAPT; DAPT) or short-term OAC (45 days) post-LAAC.[10,11] In the randomized **Re**start or **St**op **A**ntithrombotics **R**andomised **T**rial (RESTART) study, the continued use of antiplatelet therapy for secondary prevention after cardiac procedures did not lead to an increased rate of recurrent ICH, compared to the rate in patients in whom the antiplatelet medication was stopped after ICH.[12] Although the 2016 AF guidelines by the European Society of Cardiology provided a list of factors supporting the withholding or reinitiation of OAC after ICH, independent of the option of LAAC, the updated version of 2020 highlights the consideration that AF acts as a risk marker, and withholding OAC after LAAC could result in undertreating the overall risk of stroke related to atrial cardiomyopathy.[1] Nonetheless, a recent ICH is still considered an absolute contraindication against OAC; nonvalvular AF patients with a high bleeding risk need to be carefully evaluated, modifiable risk factors must be addressed, and the decision of an adequate stroke prevention strategy must be based on an individual assessment.[1]

In our institution, we have been performing LAAC for ICH patients for stroke prevention for over a decade, and we herein report our single-centre consecutive case series.

Materials and Methods

We performed a retrospective analysis of consecutive ICH patients with noonvalvular AF and at high risk of stroke ($CHADS_2 \geq 1$ or CHA_2DS_2-VASc ≥ 2) who underwent endovascular LAAC at Vancouver General Hospital. We included ICH from any etiology. Although either cranial computed tomography or cranial magnetic resonance imaging (MRI) was sufficient for the diagnosis of ICH, the diagnosis of CAA was based on cranial MRI. Indication for LAAC was confirmed in regular interdisciplinary meetings with colleagues from neurology, neuroradiology, and neurosurgery for all patients. A minimum of 4 weeks was recommended between the neurologic event and LAAC. However, the timing of LAAC was primarily dependent on the timing of referral.

Baseline characteristics, bleeding risk, baseline and discharge antithrombotic therapy, procedural results, periprocedural complications, and follow-up events data were collected. Device surveillance imaging post-LAAC was performed at 3 months with transoesophageal echocardiography (TOE) and/or cardiac computed tomography angiography. Clinical in-person or telephone follow-ups were performed at 3 and 12 months post-LAAC, and annually thereafter. Institutional research ethics board approval was obtained for our retrospective study.

Table 2. Medications at baseline for intracranial hemorrhage patients

Medication	n (%) (N = 138)
Aspirin	56 (40.1)
Clopidogrel	2 (1.4)
DAPT	6 (4.3)
OAC (DOAC/VKA)	24 (17.4)
DOAC	14 (10.1)
Aspirin + AC (DOAC/VKA/LMWH)	4 (2.9)
None	45 (32.6)

AC, anticoagulation; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulation; LMWH, low-molecular weight heparin; OAC, oral anticoagulation; VKA, vitamin K antagonist.

Table 3. Left atrial appendage closure procedural characteristics, for intracranial hemorrhage patients

Characteristic	n (%) or mean ± SD (N = 138)
WATCHMAN	50 (36.2)
Device size, mm	29.0 ± 3.3
WATCHMAN FLX	20 (14.5)
Device size, mm	30.0 ± 3.7
ACP	15 (10.9)
Device size, mm	26.1 ± 3.7
Amulet	53 (38.4)
Device size, mm	27.3 ± 4.7
Overall device size, mm	28.2 ± 4.2
Procedural success	136 (98.6)
First device implanted	105 (76.1)
General anaesthesia	125 (90.6)
Combined intervention	5 (3.6)
Total procedural time, min	83.7 ± 37.7
Fluoroscopy time, min	17.5 ± 12.1
Contrast dye used, mL	110.2 ± 80.6
Successful transseptal puncture	138 (100)
Procedural TOE	125 (90.6)
Procedural ICE	13 (9.4)

Amplatzer cardiac plug (ACP) and Amulet (second-generation ACP; both St. Jude Medical, St. Paul, MN). WATCHMAN and WATCHMAN FLX (both Boston Scientific, Natick, MA).

ICE, intracardial echocardiography; SD, standard deviation; TOE, transoesophageal echocardiography.

LAAC procedure

LAAC was performed with Amplatzer cardiac plug (ACP) (St. Jude Medical, St. Paul, MN), Amulet (second generation ACP), WATCHMAN or WATCHMAN FLX (Boston Scientific, Natick, MA) devices. Patients were given loading doses of aspirin and clopidogrel prior to entering the procedure room. LAAC was performed under general anaesthesia with TOE guidance, or under conscious sedation using intracardiac echocardiography. Detailed implantation steps have been described previously.[13] Heparin was administered to achieve an activated clotting time > 250 seconds. Every patient was loaded with aspirin 325 mg, and clopidogrel 300 mg, if they were not already on one of these medications. Standard antithrombotic therapy on discharge included aspirin 81 mg/d for at least 6 months, and clopidogrel 75 mg/d for 1 to 3 months.

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of patients. Continuous variables were reported as mean ± standard deviation, or median and interquartile range. Categorical variables were reported as absolute frequency and percentage. The efficacy of LAAC in preventing thromboembolic events was tested by comparing the predicted event rate by the $CHADS_2$ and CHA_2DS_2-VASc scores with the observed event rate at follow-up. The average annual risk for the whole study population was calculated from the predicted individual patient annual risk. The observed annualized thromboembolic event rate (stroke, transient ischemic attack [TIA], and systemic embolism) was subtracted from the predicted event rate and divided by the predicted event rate x 100, to obtain the % relative risk reduction (RRR). For comparison of the predicted and the observed event rates, we demonstrated the 95% confidence interval (CI) of the predicted rate. Statistical significance was achieved if the observed event rate was outside of the 95% CI of the predicted rate. Statistical analysis was performed using SPSS 21 (IBM, Armonk, NY).

Results

We included 138 consecutive ICH patients who underwent LAAC between September 2010 and February 2022. Baseline demographics and the types of ICH are described in Table 1. The average age was 76.1 ± 8.5 years; 69.6% were men; the mean CHA_2DS_2-VASc score was 4.4 ± 1.5; and the mean HAS-BLED [**H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile International Normalized Ratio, **E**lderly, **D**rugs/Alcohol Concomitantly] score was 3.7 ± 0.9. The types of ICH included subdural hematoma (41.3%), intracerebral hemorrhage (46.4%), subarachnoid hemorrhage (11.6%), and CAA (12.3%), although cranial MRI was not performed in all patients. Therefore, CAA could be underestimated. In 108 patients (78.3%), the ICH occurred while they were on OAC. The average time between ICH and LAAC was 27.2 ± 49.7 months. Prior to the procedure, 24 patients (17.4%) were on OAC, 1 (1.4%) was on low-molecular weight heparin (due to the presence of left atrial appendage thrombus on pre-procedural TOE), 4 had aspirin plus OAC, 6 (4.3%) were on dual antiplatelet therapy (DAPT), and 58 (41.5%) were on SAPT (56 on aspirin, 2 on clopidogrel); 45 (32.6%) were not on any antithrombotic therapy (Table 2). LAAC devices implanted were ACP in 10.9% of cases, Amulet in 38.4%, WATCHMAN in 36.2% and WATCHMAN FLX in 14.5% (Table 3). Procedural success was 136 of 138 (98.6%), with 2 cases of device embolization (1.4%) in our early experience with the ACP device that were both percutaneously retrieved without sequelae. The majority of procedures (90.6%) were performed under general anaesthesia with TOE guidance. Few LAAC procedures were performed under conscious sedation using intracardiac echocardiography guidance, mainly because of the presence of esophageal strictures. Additional gastrointestinal bleeding or neurologic sequelae post-ICH were not a reason for the decision to use conscious sedation instead of general anaesthesia. Combined invasive procedures were performed in 3.6% of cases (1 coronary angiogram, 1 percutaneous coronary intervention, 1 atrioventricular-nodal ablation, 1 cardioversion, and 1 AF ablation). After device release, peri-device leaks were observed in 13 patients (9.4%) on TOE, with a mean leak size of 1.8 mm (range: 1-4 mm), but no leak was ≥ 5 mm. Procedural complications included

Table 4. Follow-up events, for intracranial hemorrhage patients with clinical follow-up

Event	Mean ± SD or n (%) (N = 134)
Mean duration of follow-up, mo	14.7 ± 13.7
Stroke	2 (1.4)
TIA	1 (0.7)
Death	9 (6.5)
CV death	7 (5.1)
Non-CV death	2 (1.4)
Bleeding, major	6 (4.0)
Bleeding, minor	7 (5.1)

CV, cardiovascular; TIA, transient ischemic attack.

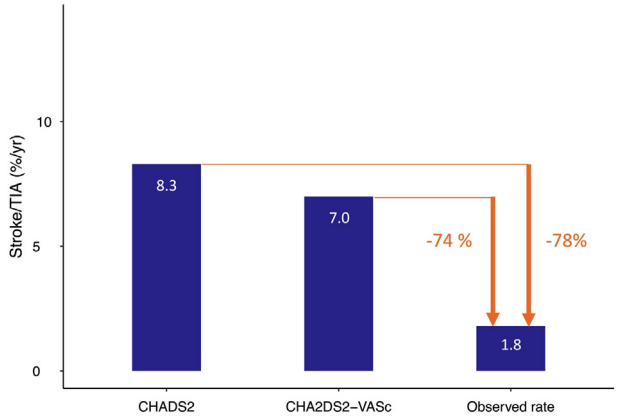

Figure 1. The predicted annual rate of stroke and transient ischemic attack (TIA) in our study cohort, based on $CHADS_2$ [**C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75, **D**iabetes, and Prior **S**troke/TIA (doubled)] and CHA_2DS_2-VASc [**C**ongestive Heart Failure, **H**ypertension, **A**ge (≥ 75 Years) (doubled), **D**iabetes Mellitus, **S**troke (doubled), **V**ascular Disease, **A**ge (65-74) Years, **S**ex **C**ategory (Female)] scores, compared with the cumulative observed rate of stroke/TIA during the study period. The observed annual event rates were 78% and 74%, respectively, lower than predicted.

one pericardial tamponade (0.7% of patients; this occurred several hours postprocedure and was successfully drained percutaneously) and one mild pericardial effusion (0.7% of patients) that did not require intervention. No periprocedural death, stroke, TIA, or myocardial infarction occurred. One (0.7% of patients) periprocedural major bleeding event (gastrointestinal bleed from esophageal ulcers due to the TOE probe) and one (0.7% of patients) minor bleeding event (gastrointestinal bleed followed by polypectomy during hospitalization) occurred.

Postprocedure, the majority of patients (92.5%) were discharged on DAPT (70.9% for 1 month, 14.9% for 3 months, 3.0% for 6 months, and 3.7% for longer than 6 months), with a median duration of 1 month (interquartile range [IQR], 1 to 1; minimum 6 days; maximum 24 months). Five patients (3.7%) received SAPT for at least 6 months, but one stopped aspirin after 42 days for unclear reasons. One patient (0.7%) received DOAC and aspirin for 1 year post-LAAC after a left ventricular thrombus was diagnosed. The 2 patients with device embolization who were successfully retrieved and were not deemed candidates for another closure attempt were continued on warfarin, which they were on prior to the procedure. One patient who initially received DAPT for 1 month was switched to warfarin by the family physician in the first year after LAAC, for unclear reasons.

Patients were followed for a mean duration of 14.7 ± 13.7 months post-LAAC (Table 4). Three patients were lost to follow-up. Of the 9 deaths that occurred (6.5% of patients), 7 (5.1%) were presumed to be cardiovascular, and 2 (1.4%) were noncardiovascular. None of the deaths was related to the LAAC procedure. Two strokes (1.4%) and one TIA (0.7%) occurred, and device imaging of these patients did not reveal any device-related thrombus (DRT) or other complication related to the LAAC. No change in antithrombotic therapy was undertaken in any of the 3 patients after the neurologic event, and all 3 remained on SAPT. The annualized observed stroke/TIA rate was 1.8%, which was lower than the adjusted predicted stroke rate based on their $CHADS_2$ score (8.3%, 95% CI: 5.8%-10.8%) as well as their CHA_2DS_2-VASc score (7.0%, 95% CI: 4.8%-9.2%; Fig. 1). No systemic embolization following LAAC occurred. The annualized observed rate of stroke, TIA, and systemic embolization was lower than the adjusted predicted rate for stroke, TIA, and systemic embolization according to the $CHADS_2$ score (11.4%, 95% CI: 8.2%-14.6%) and the CHA_2DS_2 VASc scores (9.8%, 95% CI: 6.8%-12.8%; Fig. 2). This resulted in the following: an RRR in stroke of 78.3% and a number needed to treat (NNT) of 13; an RRR in stroke, TIA, and systemic embolization of 84.2% and an NNT of 10 based on the $CHADS_2$ score; an RRR in stroke of 74.3% and an NNT of 19; and an RRR in stroke, TIA, and systemic embolization of 81.6%, and an NNT of 13 based on the CHA_2DS_2 VASc score. Seven patients (5.1%) had minor bleeding (mostly gastrointestinal bleeding, with one scleral bleed). Major bleeding events occurred in 6 cases (4.0%). Although 4 patients had gastrointestinal bleeding, 2 (1.4%) had another ICH (both occurred on aspirin monotherapy; one was fatal). Supplemental Figures S1 and S2 illustrate cumulative event curves.

Device surveillance postprocedure was performed using TOE in 65 patients (47.1%) and/or with cardiac computed tomography angiography in 93 patients (67.4%). Only one confirmed case of DRT (0.7% of patients) occurred, on top of a well-seated Amulet device while the patient was on aspirin; initially, the patient was treated with a 2-month regimen of full-dose apixaban in addition to aspirin. but the DRT reappeared after stopping DOAC, and therefore, the patient had another 3-month regimen with full-dose apixaban, with complete resolution of the nonmobile thrombus. So far, the patient has had no ischemic or bleeding events since the LAAC. In 5 patients with follow-up TOE after a median of

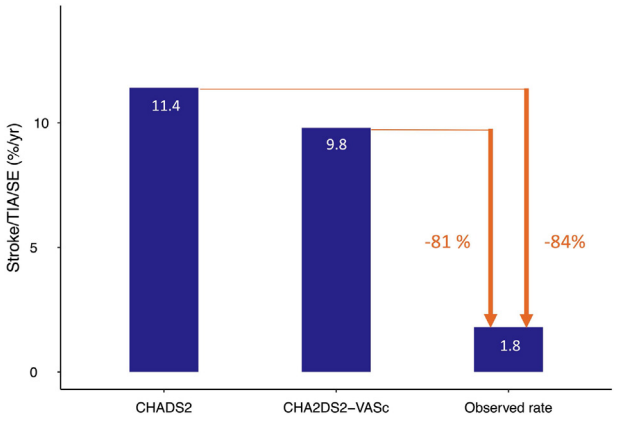

Figure 2. The predicted annual rate of stroke, transient ischemic attack (TIA) and systemic embolization (SE) in our study cohort, based $CHADS_2$ [**C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75, **D**iabetes, and Prior **S**troke/TIA (doubled)] and CHA_2DS_2-VASc [**C**ongestive Heart Failure, **H**ypertension, **A**ge (≥ 75 Years) (doubled), **D**iabetes Mellitus, **S**troke (doubled), **V**ascular Disease, **A**ge (65-74) Years, **S**ex **C**ategory (Female)] scores, compared with the cumulative observed rate of stroke, TIA, and SE during the study period. The observed annual event rates were 84% and 81%, respectively, lower than predicted.

3 months, a moderate peri-device leak (3-5 mm) was detected, and in 1 patient, a major peri-device leak (> 5 mm) was detected.

Discussion

In our retrospective real-world case series, we report high procedural success and safety in 138 patients with ICH who underwent percutaneous LAAC. The annualized stroke/TIA event rate at follow-up was 1.8%, which was lower than the expected rate based on their baseline CHA_2DS_2-VASc score (RRR, 74.3%). Patients were discharged predominantly on DAPT postprocedure, with no recurrent ICH while on this regimen post-LAAC, and a low incidence of DRT post-LAAC.

The optimal stroke preventative therapy for patients with prior ICH is not established. AF trials with DOAC reported lower rates of ICH, compared with warfarin.[6,14,15] However, patients with a history of ICH were excluded from these trials. Thus, administering DOAC in this high-risk population remains an unstudied strategy, and the recurrent bleeding risk is unknown. Without OAC, the incidence of recurrent ICH varied between 2.3% and 14.0% in several neuropathologic studies, and the reported mortality rate after recurrent ICH was 23.5%-32.0%.[16-18] The level of risk of recurrent ICH if anticoagulation is resumed is unclear, and registry-based observational studies reported rates of 4.3% during a mean of 43-month follow-up, 7.5% during a median 16.5-month follow-up, and 8.2% during a median 9.9-month follow-up.[19,20]

Although OAC cessation exposes patients to a significantly higher risk of thromboembolism, a history of ICH is considered a contraindication for resumption of OAC if the cause for the bleed could not be identified.[1] Aneurysmal bleeds that can be clipped or coiled, or ICH that occurs in the setting of an overdose of vitamin K antagonists, should be viewed differently from ICH that occur while patients are on adequately dosed DOAC, or multiple microbleeds in patients with CAA. However, many physicians as well as patients are reluctant to resume OAC after such a dramatic event, irrespective of the cause of the ICH.

Endovascular LAAC has become an established alternative to OAC in patients with nonvalvular AF who are at high bleeding risk. However, published randomized controlled trials included only patients eligible to take warfarin.[21] Ongoing randomized trials that are including patients who have a contraindication to OAC are slow in enrolling patients; in fact, the **As**sessment of the W**A**TCHMAN FLXTM Device in **P**atients Unsui**t**able f**or** **O**ral Anticoagulation (ASAP-TOO) study was stopped prematurely because of very slow enrollment.[22] The Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Hemorrhage (STROKE-CLOSE) study randomizing ICH patients to LAAC vs medical therapy is also facing enrollment issues. Thus, data on ICH patients with LAAC is unlikely to be derived from adequately powered randomized trials. Our study adds to the current literature that contains a few small case series showing LAAC to be safe and effective in ICH patients.[11]

Pouru et al. reported a series of 104 AF patients with a prior ICH who were treated with LAAC, which resulted in a 69% RRR of thromboembolic events, compared to their predicted risk without any stroke prophylaxis according to the CHA_2DS_2-VASc score.[10] In our study, we confirmed a similar RRR of 74%, with an annualized rate of stroke or TIA of 1.8%.

The ideal antithrombotic therapy post-LAAC in the ICH population is currently undefined. One observational study found that antiplatelet use after ICH did not appear to be associated with an increased risk of ICH recurrence in 127 survivors of lobar hemorrhage (HR 0.8; 95% CI: 0.3-2.3; $P = 0.73$) and 80 survivors of deep hemorrhage (HR 1.2; 95% CI: 0.1-14.3; $P = 0.88$).[23] In a Spanish observational LAAC registry including 160 patients with a history of ICH, the recurrent rate of ICH was 0.8% at a mean follow-up of 22.9 months.[24] Their patients received aspirin for at least 6-12 months and clopidogrel for 3-6 months.[24] In our series, the majority of patients were treated with DAPT for 1 month (70.9%) to 3 months (14.9%), and subsequently were treated with aspirin for at least 6 months post-LAAC. We did not observe significant bleeding or DRT related to this regimen. Despite our reporting of our safe strategy with short-term DAPT after LAAC, further studies are necessary to evaluate the optimal postprocedural antithrombotic strategy.

A systematic review on 407 LAAC patients with a history of ICH was published by Garg et al., reporting a periprocedural bleeding risk of almost 0% and a minimal rate of recurrent ICH of 0.05%, as well as a very low rate of ischemic stroke of 0.54% after a mean follow-up period of 14 months.[25] With a similar follow-up timeframe, we saw 2 recurrent ICHs in our cohort, resulting in a recurrence rate of 1.7%, which was higher than that reported by Garg et al. One patient had a fatal ICH 17 months post-LAAC while on aspirin alone. She had CAA and a high risk of stroke, with a CHA_2DS_2-VASc score of 4. She tolerated DAPT with aspirin and clopidogrel for 1 month without any side-effects post-LAAC. The second patient with recurrent ICH had a CHA_2DS_2-VASc score of 5, with recurrent strokes and TIAs. He suffered an ICH while on OAC 8 months before LAAC. Post-LAAC, he was treated with DAPT with aspirin and clopidogrel for 1 month, before switching to aspirin alone. Unfortunately, 2 months after LAAC he suffered a recurrent non-fatal ICH while on aspirin, which was then stopped. He recovered from this event, and had had no further events at 3 years post-LAAC.

The optimal timing of LAAC after an ICH is also not established. The American Heart Association guidelines acknowledge that the optimal time to resume OAC in patients after an ICH is not clear, but that for most patients, waiting for 1 week might be reasonable (class IIb, level of evidence B).[8] Based on currently available data, da Silva and Frontera suggest that OAC can be safely restarted in select groups of patients within 4 weeks after ICH, after careful assessment of risks for ICH recurrence and thromboembolism, in case the cause of the bleeding could be eliminated.[26] The European Society of Cardiology guidelines also recommend either restarting OAC or planning LAAC after at least 4 weeks following the index bleeding event.[1] In our cohort, 111 of 138 patients with AF and previous ICH did not have adequate stroke prevention prior to LAAC. As many patients from our cohort were referred by physicians outside our institution or other centres in the province, we had limited influence in the timing of referrals and

LAAC. We typically wait at least 1 month after ICH before performing LAAC, in keeping with the above recommendations. The long average time between ICH and LAAC in our cohort is due mostly to delayed referrals. However, we are convinced that adequate stroke prevention, either with OAC or LAAC, is essential, even if it is delayed.

Limitations

Given the relatively small sample size and the nonrandomized design of our single-centre retrospective series, bias potential is present in patient selection and outcomes. Patients referred for LAAC may represent a healthier and more robust group, which may explain the low incidence of long-term bleeding and cardiovascular complications in our cohort. Conversely, patients who were severely disabled post-ICH may not be referred for LAAC. In terms of antithrombotic regimen post-LAAC, we preferentially used DAPT post-LAAC in our ICH cohort; we were not able to compare the safety of other antithrombotic strategies.

Conclusion

Endovascular LAAC is a feasible alternative to OAC for stroke prevention in patients with nonvalvular AF and prior ICH. Further studies are necessary to assess the long-term outcomes and the optimal antithrombotic therapy post-LAAC in this challenging patient cohort.

Ethics Statement

Institutional research ethics board approval was obtained for our retrospective study.

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Supplementary Material

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