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Prophylactic Left Atrial Appendage Exclusion in Cardiac Surgery Patients With Elevated CHA_2DS_2-VASc Score: Results of the Randomized ATLAS Trial

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Abstract

Objective: Patients with elevated CHA_2DS_2-VASc scores are at high risk for atrial fibrillation (AF) and thromboembolic events (TE) after cardiac surgery. Left atrial appendage exclusion (LAAE) is a permanent, continuous approach to stroke prevention in AF, overcoming limitations of oral anticoagulation (OAC). We report ATLAS trial results focused on LAAE technical success and perioperative safety and TE rates with and without LAAE in cardiac surgery patients who developed postoperative AF (POAF). **Methods:** ATLAS (NCT02701062) was a prospective, multicenter, feasibility trial. Patients age ≥18 years, undergoing structural heart procedure, with no preoperative AF, CHA_2DS_2-VASc ≥2, and HAS-BLED ≥2 were randomized 2:1 to LAAE or no LAAE. Patients who developed POAF and/or received LAAE were followed for 1 year. LAAE was evaluated with intraoperative transesophageal echocardiography. **Results:** A total of 562 patients were randomized to LAAE (n = 376) or no LAAE (n = 186). Mean CHA_2DS_2-VASc (3.4 vs 3.4) and HAS-BLED (2.8 vs 2.9) scores were similar for LAAE and no LAAE groups. LAAE success (no flow nor residual stump >10 mm) was 99%. One LAAE-related serious adverse event (0.27%) occurred and was resolved without sequelae. There were 44.3% of patients who developed POAF. Through 1 year, 3.4% of LAAE patients and 5.6% of no LAAE patients had TE. OAC was used by 32.5% of POAF patients. Bleeding was higher with OAC than without (16.1% vs 5.4%, P = 0.008). **Conclusions:** ATLAS demonstrated a high rate of successful LAAE with low LAAE-related serious adverse events in cardiac surgery patients. Study results should be considered in future trial design to further evaluate prophylactic LAAE for stroke prevention in cardiac surgery patients with elevated stroke risk.

Central Message
Elevated CHA_2DS_2-VASc score and POAF increase AF recurrence and stroke risk. ATLAS demonstrated prophylactic LAAE was feasible with a low rate of safety events and resulted in a numerically lower thromboembolic rate in cardiac surgery patients who developed POAF.

Keywords
postoperative atrial fibrillation, left atrial appendage, stroke, bleeding, anticoagulation

Introduction

Postoperative atrial fibrillation (POAF) occurs in approximately 20% to 40% of patients following open cardiac surgery and is the most common arrhythmia that occurs after coronary artery bypass graft (CABG).[1–4] POAF typically develops within 2 to 5 days following the surgical procedure, with the highest risk for POAF reportedly at 2 days post-procedure,[3–5] and it can extend hospital stay by 2 to 5 days.[6] POAF, including asymptomatic, has been shown to continue out to at least 30 days.[7] The majority of in-hospital POAF is paroxysmal, and patients are in sinus rhythm at discharge. However, POAF is associated with a 5- to 8-fold increased risk of future development of AF.[3,8] Furthermore, several studies have reported an increased stroke rate in patients who develop POAF.[6,9–11] POAF has also been associated with increased perioperative and long-term mortality.[3,6,9,11]

Increased age, diabetes, hypertension, male sex, systolic and diastolic dysfunction, obesity, and left atrial enlargement have been identified as risk factors for the development of POAF.[12,13] In addition, there is a considerable amount of published data that CHA_2DS_2-VASc score is a predictor of stroke (with and without AF) and future development of AF itself. Chua et al. reported $CHADS_2$ and CHA_2DS_2-VASc scores ≥2 predict

POAF and suggested these scores as a tool to identify cardiac surgery patients at high risk of developing AF.[4] A meta-analysis found that higher CHA_2DS_2-VASc score was an independent predictor of POAF.[14] In addition, CHA_2DS_2-VASc score independently identifies increased the risk of stroke early and late after cardiac surgery, irrespective of preoperative or new-onset in-hospital AF.[15] In non-AF CABG patients, the risks of stroke or transient ischemic attack (TIA) at 5 years with low (0 to 1), high (2 to 4), and very high (5 to 9) CHA_2DS_2-VASc scores are 4.1%, 5.6%, and 9.2%, respectively.[16] In non-AF surgical aortic valve replacement patients with low, high, and very high CHA_2DS_2-VASc scores, rates of stroke or TIA at 5 years are 5.2%, 14.0%, and 21.9%, respectively.[17]

In addition to the risk of ischemic stroke, elevated CHA_2DS_2-VASc score is also associated with major bleeding while anticoagulated[18,19] and frailty.[20] Therefore, patients with elevated CHA_2DS_2-VASc scores are at high risk of not only developing AF and stroke but also major bleeding if anticoagulated.

Because of the increased risk of stroke with POAF and elevated CHA_2DS_2-VASc score, oral anticoagulation (OAC) may be prescribed,[21] particularly if POAF episodes are frequent or prolonged, such as greater than 48 hours. However, the benefit of anticoagulation must be weighed against the risk of bleeding, particularly in patients with higher HAS-BLED scores[22] and a recent cardiac surgical procedure. A large Swedish registry reported that 24% of patients with POAF were treated with OAC within 30 days. There was no association between OAC use and reduced thromboembolic event rate or mortality;[1] however, there was an increased risk of bleeding in patients who received OAC. Studies analyzing the Society of Thoracic Surgeons (STS) database have also shown increased bleeding in POAF patients on anticoagulation without a statistically significant reduction in 30-day stroke.[23,24]

The left atrial appendage (LAA) is the predominant site of thrombus formation during AF.[25] Surgical management of the LAA focuses on exclusion to prevent blood flow between the left atrium and LAA. Cox et al. observed a low stroke rate (0.7%) in AF patients who underwent surgical maze procedures with LAA excision, even though approximately two-thirds of the patients did not take anticoagulation after the procedure.[26] This suggested that eliminating the LAA as a thrombus source may have contributed to the low incidence of stroke. A propensity-matched study reported a 0% stroke rate in patients with POAF who had LAA ligation compared with 6.1% in patients with POAF and no LAA ligation ($P = 0.003$).[27] Recently, the Left Atrial Appendage Occlusion Study (LAAOS) III trial reported a significantly decreased rate of ischemic stroke and systemic embolism in cardiac surgery patients with preexisting AF who underwent surgical LAA occlusion compared with patients who did not have LAA occlusion.[28]

The AtriClip Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures (ATLAS) trial was a feasibility study monitoring a subset of cardiac surgery patients for whom the risks of thromboembolic events and bleeding intersected and thus had equipoise regarding LAA management and anticoagulation. ATLAS evaluated standard-of-care medical management versus mechanical LAA exclusion (LAAE) with an implantable clip device (AtriClip, AtriCure, Inc., Mason, OH, USA) in addition to the standard-of-care medical management in patients undergoing cardiac surgery with elevated risks of thromboembolic events and bleeding.

Methods

ATLAS was a prospective, randomized, multicenter, unblinded pilot study (NCT02701062 at clinicaltrials.gov). Patients were randomized into 2 arms: (1) those who received surgical LAAE with the AtriClip device and (2) those who did not receive LAAE (or LAA occlusion by any other method). The study protocol was approved by each participating center's institutional review board. Written informed patient consent was obtained for all patients prior to enrollment.

Inclusion criteria were ≥18 years of age (male or female), scheduled for any nonmechanical valve and/or CABG (structural heart) procedure in which direct access to the LAA was expected, no documented preoperative AF, CHA_2DS_2-VASc score ≥2, HAS-BLED score ≥2, acceptable surgical candidate based on age, medical history, and surgical procedure (including use of general anesthesia), willing and able to provide written informed consent, non-childbearing potential or negative pregnancy test within 7 days prior to procedure (for females), and willing and able to return for follow-up visits. Exclusion criteria

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were redo cardiac surgery, mechanical heart valve or other anticipated or current requirement for anticoagulation therapy during the postoperative (30-day) period, hypercoagulability conditions that may have confounded the study, ejection fraction <30%, left atrium >6 cm, severe diastolic dysfunction, requirement for chronic anticoagulation therapy, any known reason that the patient would be unable to tolerate post-surgical anticoagulants, patient had a stroke/cerebrovascular accident within the 30 days prior to signing informed consent, any medical condition or finding for which the investigator used medical discretion to determine the subject should be excluded, patient was currently participating or had participated in a clinical study in the 30 days prior to signing informed consent (participating in survey clinical studies with no treatment was not an exclusion criterion), and the patient had a condition that, in the opinion of the investigator, may have jeopardized the patient's well-being or the soundness of the clinical study or could have interfered with provision of informed consent, completion of tests, therapy, or follow-up.

Intraoperative exclusion criteria included the presence of a thrombus in the left atrium or LAA, LAA tissue was deemed friable or had significant adhesions (as evaluated by the surgeon) near or on the LAA making clip placement risky, LAA was outside of the manufacturer-recommended range (width <29 mm or >50 mm), direct visualization access was not available for clip placement, and any medical condition or finding for which the investigator used medical discretion to determine patient exclusion. All inclusion/exclusion criteria, including intraoperative exclusion criteria, were met prior to patient enrollment and randomization.

Enrolled patients were randomized 2:1 to either receive the clip device for LAAE or no LAAE and evaluated for POAF development. Randomization was generated by the sponsor's statistician using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA) and stratified by site. A blocking scheme was used for randomization for each surgeon to ensure equal and balanced treatment group allocations and to avoid bias. Treatment group was provided via sealed envelope. The AtriClip LAA Exclusion system is cleared by the Food and Drug Administration 510(k) and indicated for occlusion of the LAA, under direct visualization, in conjunction with other open cardiac procedures. It was used in accordance with its Instructions for Use. All patients were monitored per hospital standard of care for POAF after the index procedure. POAF diagnosis was based on telemetry/continuous monitoring during hospitalization per institutional standard of care. Patients who did not develop POAF prior to hospital discharge were exited from the study at the 30-day assessment. All patients who received the AtriClip regardless of POAF occurrence were followed for adverse events out to 365 days as part of the device safety assessment. Only those who developed POAF were included in the comparative data. All patients who developed POAF received treatment per the institution's standard of care. The decision to administer anticoagulation postoperatively and during follow-up was at the discretion of the investigator/institution accounting for the patient's individual situation. All patients who developed POAF were followed to 1 year. Thromboembolic and hemorrhagic events, as well as deaths, were adjudicated by an independent physician who was not involved in the ATLAS trial.

The effectiveness endpoints reported in this analysis are (1) perioperative complications associated with the AtriClip placement (defined as stroke, major bleeding that required reoperation and/or transfusion of >2 units of packed red blood cells within any 24-hour period during the first 2 days after the index procedure, myocardial infarction, or death), (2) intraoperative successful exclusion of the LAA (defined as no flow [0 mm] between the LAA and left atrium and ≤5 mm LAA remnant by intraoperative transesophageal echocardiography [TEE] with Doppler), and (3) composite thromboembolic event (ischemic stroke with or without major disability, peripheral ischemia, TIA) rates between the group of patients diagnosed with POAF (LAAE vs no LAAE) through 365 days after the index procedure. Composite event rates were compared using Fisher's exact test. Significance was considered at $P < 0.05$. Since ATLAS was a feasibility study, P values were exploratory in nature and should be interpreted carefully as they were calculated post hoc. Adverse events were adjudicated for relatedness by investigators and an independent physician.

Results

Baseline Patient Characteristics

A total of 562 patients from 23 sites were enrolled in the study. The first patient was treated in February 2016, and the last patient had their final follow-up visit in April 2019. All patients received medical management according to institutional standard of care. After randomization, 376 patients had LAAE and 186 patients did not have their LAA closed. Baseline patient characteristics are described in Table 1. Baseline parameters were similar between groups, except for left ventricular ejection fraction, which was 58.7% ± 6.9% in the no LAAE arm compared with 57.3% ± 8.4% in the LAAE arm ($P = 0.041$).

Cardiac Surgical Procedure Characteristics

Cardiac surgery approaches and procedures were similar between the 2 arms (Table 2). The majority had a sternotomy (97.0%, 545 of 562), and CABG was performed in 83.3% (468 of 562). Fourteen (2.5%) intraoperative complications related to the structural heart procedures occurred, including major bleeding requiring transfusion and sinoatrial node dysfunction. The incidence of these complications was not significantly different between the LAAE and no LAAE arms (2.7% [10 of 376] vs 2.2% [4 of 186], $P > 0.999$).

LAAE Outcomes

LAAE was performed per device Instructions for Use. The outcomes of LAAE are shown in Table 3. LAAE with the clip was attempted in all 376 patients randomized to the LAAE

Table 1. Demographic and Baseline Patient Characteristics.

Parameter	LAAE ($n = 376$)	No LAAE ($n = 186$)	*P* value[a]
Age, years	69.2 ± 7.8	68.9 ± 8.7	0.683
Sex			0.490
Female	30.1 (113/376)	26.9 (50/186)	
Male	69.9 (263/376)	73.1 (136/186)	
Race			
American Indian or Alaskan Native	0.0 (0/376)	0.5 (1/186)	0.331
Asian	1.3 (5/376)	1.6 (3/186)	0.724
Black or African American	3.7 (14/376)	3.8 (7/186)	>0.999
Native Hawaiian or other Pacific Islander	0.0 (0/376)	0.5 (1/186)	0.331
White	94.4 (355/376)	91.9 (171/186)	0.275
Other	0.8 (3/376)	2.2 (4/186)	0.227
Ethnicity			0.311
Hispanic or Latino	1.3 (5/376)	2.7 (5/186)	
Not Hispanic or Latino	98.4 (370/376)	96.8 (180/186)	
Body mass index, kg/m^2	31.0 ± 5.6	30.0 ± 5.9	0.052
CHA_2DS_2-VASc score	3.4 ± 1.2	3.4 ± 1.1	0.933
HAS-BLED score	2.8 ± 0.7	2.9 ± 0.6	0.576
Left atrial diameter, cm	4.0 ± 0.7	3.9 ± 0.6	0.556
	3.9 (2.1, 6.0)	3.9 (1.9, 5.6)	
Left ventricular ejection fraction, %	57.3 ± 8.4	58.7 ± 6.9	0.041
	60.0 (30.0, 81.0)	60.0 (35.0, 72.0)	

Abbreviation: LAAE, left atrial appendage exclusion.
Categorical variables are reported as % (*n*/*N*), and continuous variables are reported as mean ± SD and median (min, max) where applicable.
[a]*P* values reflect Fisher's exact tests for categorical variables and *t* tests for continuous variables.

Table 2. Surgical Characteristics and Postoperative Medications.

Parameter	LAAE ($n = 376$)	No LAAE ($n = 186$)	*P* value[a]
Surgical approach			>0.999
Right minithoracotomy	0.3 (1/376)	0.0 (0/186)	
Sternotomy	96.8 (364/376)	97.3 (181/186)	
Other	2.9 (11/376)	2.7 (5/186)	
Cardiac procedure(s)[b]			
CABG	82.2 (309/376)	85.5 (159/186)	0.340
Mitral valve	5.9 (22/376)	4.3 (8/186)	0.551
Aortic valve	24.5 (92/376)	21.0 (39/186)	0.397
Other	6.6 (25/376)	5.4 (10/186)	0.711
Postoperative atrial fibrillation	47.3 (178/376)	38.2 (71/186)	0.047
Antiarrhythmic therapy administered	45.7 (172/376)	37.6 (70/186)	0.677
Anticoagulation therapy administered	23.7 (89/376)	16.1 (30/186)	0.326

Abbreviations: CABG, coronary artery bypass graft; LAAE, left atrial appendage exclusion.
Data are reported as % (*n*/*N*).
[a]Fisher's exact test was used for categorical variables.
[b]Multiple procedures were permitted. Patients may be represented more than once.

arm, and the clip was implanted in 373 patients (99.2%). Three patients did not receive the clip implant due to (1) inability of the surgeon to directly visualize the LAA (via minithoracotomy), (2) LAA adhesion to the heart, and (3) physician judgment due to concomitant surgical procedure complications. No other methods of LAA closure or exclusion were used in any patient. Of the 373 patients who received the clip, intraoperative TEE assessments could not be verified postoperatively for 2 patients, and 1 patient did not have flow assessment. Therefore, 370 patients had complete intraoperative TEE data to assess LAAE success by both residual stump size and residual flow. Of these 370 patients, 366 had stump size ≤10 mm and no flow between the left atrium and LAA (98.9%, 95% CI: 92.7% to 97.3%), and 353 had stump size ≤5 mm and no flow between the left atrium and the LAA (95.4%, 95% CI: 97.3% to 99.7%).

Table 3. Results of LAAE With Clip Device.

Parameter	LAAE ($n = 376$)
Successful implantation of clip device	99.2 (373/376)
Surgeon inability to directly visualize the LAA (minithoracotomy)	0.27 (1/376)
Adhesion of LAA to heart	0.27 (1/376)
Surgeon decision due to concomitant surgical complication	0.27 (1/376)
Intraoperative exclusion success[a,b]	
No flow with stump ≤10 mm	98.9 (97.3–99.7, 366/370)
No flow with stump ≤5 mm	95.4 (92.7–97.3, 353/370)
Protocol-specified perioperative complications related to clip[c]	0 (0/376)
All events related to clip device/application[d]	
Intraoperative torsion of the heart (serious)	0.27 (1/376)
Post-pericardiotomy syndrome (nonserious)	0.27 (1/376)

Abbreviations: LAAE, left atrial appendage exclusion; TEE, transesophageal echocardiography.
Data are reported as % (*n*/*N*) or % (95% confidence interval, *n*/*N*).
[a]Assessed by intraoperative TEE and Doppler flow.
[b]Three patients with successful implantation did not have complete TEE data available for residual stump and flow.
[c]Stroke, major bleeding that required reoperation and/or transfusion of >2 units packed red blood cells within any 24-hour period during the first 2 days after the index procedure, myocardial infarction, or death.
[d]Both events were managed without sequelae.

Table 4. Total Thromboembolic Events Through 1 Year in Patients With Postoperative Atrial Fibrillation.

Parameter	LAAE ($n = 178$)	No LAAE ($n = 71$)
Ischemic stroke	1.7 (3/178)	2.8 (2/71)
Transient ischemic attack	0 (0/178)	2.8 (2/71)[a]
Peripheral ischemia	1.7 (3/178)	1.4 (1/71)
Thromboembolic event rate (total events/total patients)[b]	3.4 (6/178)	7.0 (5/71)
Thromboembolic event rate (total patients with events/total patients)[b]	3.4 (6/178)	5.6 (4/71)

Abbreviation: LAAE, left atrial appendage exclusion.
Data are reported as % (*n*/*N*).
[a]Two events occurred in 1 patient.
[b]The comparison between the LAAE and no LAAE groups was not significant.

No perioperative complications defined by the study protocol occurred that were related to the clip or its placement. One serious adverse event, intraoperative torsion of the heart, related to application of the clip was reported, which was resolved by the operating surgeon during the case without sequelae. Acute post-pericardiotomy syndrome occurred in another patient, which was not considered serious and resolved with medication without sequalae. No LAAE-related renal failures were reported. The 30-day mortality rate in the LAAE arm was 2.6% (10 of 376, 95% CI: 1.2% to 4.8%), which is consistent with published data in cardiac surgery patients.[29] No deaths were attributed to the study device or procedure.

POAF Development

POAF developed during hospital stay in 47.3% of patients (178 of 376) in the LAAE arm compared with 38.2% of patients (71 of 186) in the no LAAE arm ($P = 0.047$, Table 2). Patients in the no LAAE arm who did not develop POAF were exited from the study at 30 days but were included for safety assessment. The thromboembolic event rate within 30 days for all patients who received LAAE was 1.3% (4 of 376). In patients who did not receive LAAE, the rate was 3.8% (7 of 186). There were no significant differences in antiarrhythmic drug and anticoagulation therapy administration between the 2 arms.

Thromboembolic Events in Patients Who Developed POAF

Patients who developed POAF were followed through 1 year for thromboembolic events, which included ischemic stroke, TIA, and peripheral ischemia (Table 4). In the LAAE arm, 3 ischemic strokes occurred at days 2, 5, and 339 post-procedure, and 3 peripheral ischemia events occurred at days 41, 62, and 156 post-procedure. No TIAs occurred in the LAAE arm during follow-up. In the no LAAE arm, 2 ischemic strokes occurred at 6 and 8 days post-procedure, 2 TIAs were reported in 1 patient at 5 and 20 days post-procedure, and 1 peripheral ischemic event occurred at approximately 3 months post-procedure. The thromboembolic event rate by total patients who experienced events (total patients

with events/total patients) was 3.4% (6 of 178) in the LAAE arm compared with 5.6% (4 of 71) in the no LAAE arm. The thromboembolic event rate by total events (total events/total patients) through 1 year after the procedure was 3.4% in the LAAE arm compared with 7.0% in the no LAAE arm.

Bleeding Rates

In patients who developed POAF, OAC was permitted per institutional standard of care. In the LAAE arm, 31.5% of patients (56 of 178) with POAF received OAC and 35.2% of patients (25 of 71) in the no LAAE arm received OAC. The mean durations of OAC use in those patients were 3.9 months in the LAAE arm and 3.3 months in the no LAAE arm. The bleeding rate on OAC was 16.1% (13 patients with events out of 81 patients) versus 5.4% (9 patients with events out of 168 patients) without OAC ($P = 0.008$) in patients with POAF. Bleeding rates were also higher with OAC use when analyzed in each arm.

Discussion

There is a population of cardiac surgery patients without preoperative AF for whom the risks of developing AF, stroke, and bleeding coincide, making the benefit–risk of OAC unclear. The CHA_2DS_2-VASc score, which is easily calculated, is frequently used to identify at-risk patients. As described in the previous sections, abundant published data demonstrate that the CHA_2DS_2-VASc score is a predictor of AF and ischemic stroke.

ATLAS aimed to evaluate the feasibility and safety of LAAE in non-AF cardiac surgery patients with elevated CHA_2DS_2-VASc scores and thromboembolic event rates in patients with or without LAAE. Specifically, patients who developed POAF, and hence were at high risk of future AF, were followed for 12 months for thromboembolic event outcomes. Of the LAAE arm, 47% developed POAF compared with 38% of the no LAAE arm ($P = 0.047$). The difference may be related to inflammation in the presence of the clip. However, an increase in POAF after surgical LAA closure by nonclip methods such as ligation, stapling, or excision has also been reported.[30–32] Local atrial inflammation, sterile pericarditis, and an acute decrease in left atrial volume and compliance resulting in stretching of the left atrium and pulmonary veins have been postulated as contributing to POAF after LAA closure. In the current study, the incidence of POAF was significantly higher in the LAAE group, but the incidence of perioperative stroke was 1.1% (2 of 178) in the LAAE group and 2.8% (2 of 71) in the no LAAE group.

ATLAS demonstrated the safe and effective exclusion of the LAA with the clip device for study patients. Previous studies have shown high rates of LAAE with the clip device, as evidenced by lack of Doppler flow and stump size $\leq$10 mm.[33] Results herein confirm those findings with 99% LAAE efficacy by TEE. No protocol-specified perioperative complications, including stroke, occurred due to LAAE. One serious and 1 nonserious adverse event attributed to clip application resolved without sequalae. Of 376 patients, 3 (0.8%) were unable to have the clip applied, showing that most patients deemed eligible for the procedure have successful clip placement. While follow-up imaging to confirm long-term exclusion was beyond the scope of this feasibility trial, previous studies have demonstrated durable LAA exclusion with the clip.[34,35] Mortality rates between the LAAE arm and no LAAE arms were similar through 30 days (all patients) and through 1 year (patients with POAF). No deaths that occurred in the LAAE arm were attributed to the clip.

In ATLAS, which by study design comprised patients with higher bleeding risk, there was a significantly increased incidence of major bleeding with OAC compared with patients who did not take OAC. Of POAF patients on OAC, 16% had hemorrhagic stroke, gastrointestinal, neurologic, or other major bleeding. Two recent studies utilizing the STS database found a significantly increased 30-day rate of rehospitalization for major bleeding/cardiac tamponade in patients with POAF treated with OAC after cardiac surgery, without a significant decrease in 30-day readmission for stroke/TIA compared with POAF patients who did not receive OAC.[23,24] These findings support a careful assessment of bleeding risk when prescribing anticoagulation to reduce thromboembolic risk after cardiac surgery.

Since the LAA is the predominant site of thrombus formation in AF, it follows that exclusion of the LAA may help prevent strokes that originate from LAA thrombi. In a retrospective analysis, Caliskan et al. found the observed stroke rate in cardiac surgery patients with existing AF who received LAAE with the clip device and discontinued OAC was significantly reduced compared with that predicted by the CHA_2DS_2-VASc score.[34] This strategy could be particularly relevant for patients at increased risk of bleeding on OAC, like those in ATLAS. The LAAOS III trial demonstrated a statistically significant reduction in ischemic stroke and systemic embolism rates in cardiac surgery patients with preexisting AF who received surgical LAA occlusion.[28] At 1 year, there was a 22% reduction in ischemic stroke/systemic embolism with LAA occlusion compared with no LAA occlusion, when added to standard of care. The groups were equally anticoagulated with 76.9% of patients who received LAA occlusion and 78.9% of patients who did not receive LAA occlusion who were on OAC. Similarly, the incidence of patients with thromboembolic events (ischemic stroke, TIA, and peripheral ischemia) through 1-year postprocedure in the ATLAS study was numerically lower (3.4%) compared with POAF patients who did not have LAAE (5.6%), although this was not significantly different.

In ATLAS, 65% of patients without LAAE who developed POAF did not receive OAC. Because ATLAS was a postmarket, feasibility pilot study, the protocol could not dictate postoperative medical management. The finding is consistent with data derived from real-world experience revealing approximately 50% to 60% of patients with AF start OAC and continued adherence is less than 50%.[11] A 2.5- to 4-fold increased risk of major bleeding complications within 30 days with use of

anticoagulation for POAF after cardiac surgery has been reported.[23,24] The 3-fold increase in bleeding event rate observed in ATLAS for POAF patients on OAC aligned with this range.

Some patients who received LAAE in ATLAS were administered anticoagulation. There is no consensus on whether anticoagulation should be discontinued after LAAE, and recently, LAAOS III demonstrated that the combined effect of LAAE and anticoagulation for stroke reduction is higher as compared with anticoagulation alone.[28] Larger studies will be needed to evaluate whether LAAE in the absence of OAC shows a benefit of both reduced thromboembolic and bleeding events compared to standard-of-care OAC alone, specifically in patients at high risk of bleeding.

One of the key study limitations is that the number of patients who developed POAF and number of overall events were limited, which impacted robust comparisons between arms and subgroups. It is possible that POAF was underdetected in this population particularly given the requirement of CHA_2DS_2-VASc score ≥ 2. POAF was evaluated only through hospital discharge in ATLAS. A recent study using continuous monitoring found a POAF rate of 19.6% through 30 days after discharge.[7] While there is an association between POAF and late strokes, most observed strokes in ATLAS were perioperative. It cannot be assumed that the impact of LAAE on the stroke rate in patients with POAF is the same as the impact of LAAE on late strokes. As ATLAS was a feasibility trial, the recognized limitations and study results are important to inform future trials for evaluating the role of LAAE for thromboembolic event prevention relative to OAC.

Conclusions

ATLAS demonstrated a 99% successful LAAE with a serious adverse event rate related to the clip application of $<0.3\%$ in patients undergoing prophylactic LAAE during cardiac surgery. While the POAF rate was higher in the LAAE group, these patients had a numerically lower thromboembolic event rate compared with those treated with standard of care without LAAE, which potentially points to the protective effect of LAAE. Future studies are warranted to explore these and additional endpoints with study design refinements based on this feasibility trial.

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Ethics Statement

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