Left atrial appendage exclusion during open cardiac surgery in patients without atrial fibrillation reduces 4-year ischemic stroke and mortality

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Patrick M. McCarthy, MD,[a] Roxana Mehran, MD,[b] Marc Gerdisch, MD,[c] Basel Ramlawi, MD,[d] Randall J. Lee, MD, PhD,[e,f] Michael A. Ferguson, PhD,[f] Jane Kruse, BSN,[a] and Richard P. Whitlock, MD[g,h]

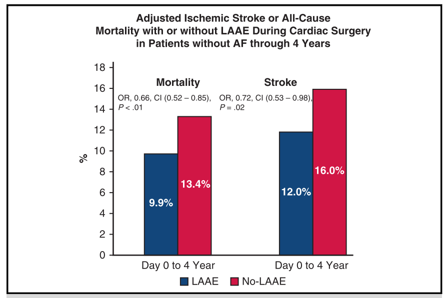
ABSTRACT

Objective: This study assessed the influence of surgical left atrial appendage exclusion (LAAE) during cardiac surgery in patients with no preoperative history of atrial fibrillation (AF).

Methods: Real World Data Insights, an all-payers' claims database, with approximately 90% Medicare patients was utilized. Patients with no preoperative history of AF (older than age 65 years) undergoing open coronary artery bypass or valve procedures with/without concomitant surgical LAAE with an epicardial clip between 2015 and 2020 and a minimum of 2-year follow-up were included. Inverse probability treatment weighting and logistic regression were used.

Results: Open coronary artery bypass represented 48.8% (n = 29,954) and valve 51.2% (n = 31,466) of procedures after adjustment. Thirty-day postoperative AF was present in 12.2% patients (n = 175) for LAAE and 5.8% (n = 3485) for no-LAAE ($P < .01$). By day 90 after surgery, rates of new AF were similar between groups through 4-year follow-up. During 4 years of follow-up more patients received oral anticoagulation with LAAE ($P < .01$). LAAE had 28% lower adjusted ischemic stroke odds (odds ratio, 0.72; 95% CI, 0.53-0.98; $P = .02$) and 34% lower adjusted all-cause mortality (odds ratio, 0.66; 95% CI, 0.52-0.85; $P < .01$). In patients who developed postoperative AF, LAAE + oral anticoagulation showed 74% lower odds of adjusted ischemic stroke (odds ratio, 0.26; 95% CI, 0.10-0.70; $P = .01$) and 58% lower odds of adjusted all-cause mortality (odds ratio, 0.42; 95% CI, 0.18-1.01; $P = .05$) than no-LAAE + oral anticoagulation therapy alone.

Conclusions: LAAE during open cardiac surgery in patients without AF was safe, associated with higher postoperative AF, and lower ischemic stroke and all-cause mortality. Randomized controlled studies are ongoing in a similar population. (JTCVS Structural and Endovascular 2024;4:100032)



Four-year ischemic stroke and mortality benefit with LAAE in surgical patients without AF.

CENTRAL MESSAGE

LAAE was associated with a 28% reduction in odds of ischemic stroke and 34% reduction in odds of mortality over 4 years in cardiac surgery patients without preoperative AF.

PERSPECTIVE

Surgical LAAE is a Class I Guideline for patients with AF undergoing cardiac surgery. An all-payor data set was used to assess the influence of surgical LAAE during cardiac surgery in patients without preoperative AF. Four years postsurgery, the odds of ischemic stroke and all-cause mortality were reduced by 28% and 34%, respectively.

From the [a]Division of Cardiac Surgery, Department of Surgery, Northwestern University Feinberg School of Medicine and Northwestern Medicine, Chicago, Ill; [b]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [c]Department Cardiothoracic Surgery, Franciscan Health Indianapolis, Indianapolis, Ind; [d]Department of Cardiac Surgery, Lankenau Heart Center, Mainline Health, Wynnewood, Pa; [e]Department of Cardiac Electrophysiology, University of California, San Francisco, San Francisco, Calif; [f]Healthcare Economics and Reimbursement, AtriCure, Mason, Ohio; [g]Division of Cardiac Surgery, Department of Surgery, McMaster University, Hamilton, Ontario, Canada; and [h]Population Health Research Institute, Hamilton, Ontario, Canada.

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Address for reprints: Patrick M. McCarthy, MD, Division of Cardiac Surgery, Department of Surgery, Northwestern University Feinberg School of Medicine and Northwestern Medicine, 676 N Saint Clair St, Suite 730, Chicago, IL 60611-2908 (E-mail: Patrick.McCarthy@nm.org).

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Abbreviations and Acronyms

- AF = atrial fibrillation
- CAB = coronary artery bypass
- $CHADS_2$ = congestive heart failure, hypertension, age, diabetes, gender
- CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female)
- IPTW = inverse probability of treatment weighting
- LAA = left atrial appendage
- LAAE = left atrial appendage exclusion
- LeAAPS = LAAE for Stroke Prevention in Cardiac Surgery Patients
- NoAF = no atrial fibrillation
- OAC = oral anticoagulant
- POAF = postoperative atrial fibrillation

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Atrial fibrillation (AF) after cardiac surgery occurs in approximately 20% to 40% of patients without AF[1,2] typically in the first 2 to 5 days following surgery,[3,4] but may appear asymptomatically as late as 30 days after surgery.[5] Postoperative AF (POAF) triggers are believed to be surgically related or from patient risk factors.[6,7] Older age is an independent risk factor for POAF,[8] which has been associated with an increased risk of stroke and mortality.[3,9] Preoperative $CHADS_2$ (congestive heart failure, hypertension, age, diabetes, gender) and CHA_2DS_2-VASc (congestive heart failure, hypertension, age 75 years or older [doubled], diabetes, stroke [doubled], vascular disease, age 65-74 and sex category [female]) are predictive of POAF,[10] early and late stroke risk,[2] and bleed risk while anticoagulated.[11,12] Nonpharmacologic strategies to protect against stroke risk is important to balance the risk of oral anticoagulation (OAC) use.

For patients with AF, approximately 75% of embolic events result from thrombi from the left atrial appendage (LAA), and even in patients with no history of AF (NoAF) the LAA may be a source of embolic material in the absence of AF.[13,14] Exclusion of the LAA (LAAE) during cardiac surgery has shown reduction of stroke and thromboembolism.[14-17] Whitlock and colleagues[15] in a randomized study found a 33% relative risk reduction in ischemic stroke at 3.8 years after cardiac surgery ($P < .05$). As a result, Class I guidelines recommend LAAE during concomitant cardiac surgery in those with AF and CHA_2DS_2-VASc score >2.[14,18] Evidence regarding the surgical benefit of LAAE in NoAF patients is sparse. A recent randomized study found a trend for lower stroke benefit in POAF patients with surgical LAAE, but was not designed to study this end point.[19] In a propensity score matched cardiac surgery study of 1232 NoAF patients treated with LAAE, there were fewer postsurgery cerebral vascular events 30 days after surgery.[20] Although these results are hypothesis generating, more information is required to assess the influence of LAAE in NoAF patients. A contemporary, nationally representative cohort from an all-payor database was used to compare surgical LAAE[21] with the AtriClip LAA Exclusion System (AtriCure) versus No-LAAE among NoAF patients.

MATERIALS AND METHODS

This retrospective study utilized data from STATinMED Real World Data Insights, an all-payer claims database representing 80% of the US health care system (Appendix E1). Procedures were evaluated using International Classification of Diseases 10th edition diagnosis and procedure codes as well as pharmacy claims.

Because the aggregate data used in this analysis were deidentified, publicly available, and not human subjects research as defined in 45 CFR 46.102, the study was exempt from institutional review board review.

Patient Selection

Patients aged 65 years or older undergoing cardiac surgery between October 1, 2015, and September 30, 2020, were selected for the study (Figure 1). Study design was based on the LAAE for Stroke Prevention

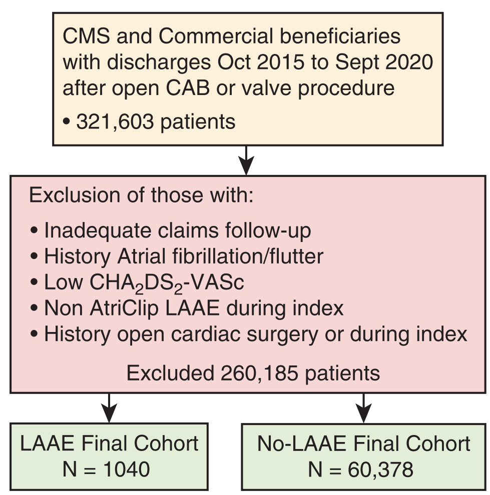


FIGURE 1. Consolidated Standards of Reporting Trials diagram. Patients aged 65 years or older who had open cardiac surgery performed between October 1, 2015, and September 30, 2020, were included. Patients with missing claims follow-up, history of atrial fibrillation/flutter, inadequate congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female) (*CHA_2DS_2-VASc*) score, no AtriClip (AtriCure) appendage exclusion, or prior open cardiac surgery, including ablation were excluded. The final adjusted cohort included 1040 patients in the left atrial appendage exclusion (*LAAE*) group compared with 60,378 in the No-LAAE group. *CMS*, Centers for Medicare and Medicaid Services; *CAB*, coronary artery bypass.

in Cardiac Surgery Patients (LeAAPS) Investigational Device Exemption randomized trial (National Clinical Trial No. 05478304). Patients with an index procedure of coronary artery bypass (CAB), valve repair/replacement (mitral, aortic, tricuspid, or pulmonic) were included, including combination procedures. All patients had a minimum of CHA_2DS_2-VASc score $\geq$ 4 and aged 65 years or older or had a CHA_2DS_2-VASc score of 3 with an age 75 years or older. Patients had continuous capture with medical benefits for the 12-month pre- and at least 24-month postindex date. Surgical LAAE was performed with an AtriClip device.

Exclusion criteria during the 12-month preindex period were (including day of surgery): AF or atrial flutter diagnosis, cardiac surgery, mechanical valve, open/percutaneous LAA closure, or surgical ablation.

Clinical Outcomes

The primary study end points were first event 4-year ischemic stroke and all-cause mortality. Secondary end points included perioperative safety (bleeding, pericardial effusion, sternal wound infection, or myocardial infarction), and mortality (within 30 days of surgery), long-term systemic embolism, thromboembolism (first occurrence of ischemic stroke, transient ischemic attack, or systemic embolism), hospital emergency department visits and readmissions. AF and heart failure admissions were assessed. Estimated OAC use was available from prescriptions filled in 70% to 75% (years 1-4) of patients in follow-up. Given the incompleteness of data, OAC analyses were limited.

Statistical Analysis

Baseline characteristics were described using proportions and means with SD. Differences between groups were tested with χ^2 and Student *t* test. Baseline differences were controlled with inverse probability treatment weighting (IPTW).[22] IPTW variable inclusion was based on univariate differences and a standardized mean difference < 0.20 was considered a match (Appendix E1). After adjustment, group comparisons were analyzed with univariable logistic regression.[23] Odds ratios (OR) and 95% CIs were reported. Forest plots were used for select outcomes. Analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing).

RESULTS

After exclusions, 61,447 were included in the study before adjustment (Figure 1). The average age was 74.4 years (LAAE) and 75.3 years (No-LAAE). Mean CHA_2DS_2-VASc score was 4.8 for both groups (Table 1).

CAB represented 48.8% of procedures and valves 52.3%. Group percentages for total valvular procedures were well matched, although there were more mitral procedures (21.3% vs 2.8%) performed in LAAE and more aortic procedures performed in No-LAAE patients (49.0% vs 33.2%). Average last mean follow-up was 3.2 years for LAAE and 3.3 years for No-LAAE patients, although 4-year event rates were analyzed in those who completed follow-up without imputation.

There was no difference for 30-day mortality, bleeding, pericardial effusion, sternal wound infection, or myocardial infarction (Table E1). After surgery 12.2% (129 out of 1056) LAAE patients developed POAF versus 5.8% (3485 out of 60,391) in the No-LAAE group (P < .01) (Table E2). By day 90 after surgery new rates of any AF

TABLE 1. Presurgery demographic, antithrombotic therapy, and surgical treatments in patients without atrial fibrillation undergoing cardiac surgery with and without left atrial appendage exclusion (LAAE)

Variable	Unweighted sample LAA (n = 1056)	Unweighted sample No-LAAE (n = 60,391)	Unweighted sample *P* value	IPTW sample* LAAE (n = 1040)	IPTW sample* No LAAE (n = 60,379)	SMD
Patients						
Mean age	74.2 (5.1)	75.3 (5.1)	<.01	74.4 (6.6)	75.3 (1.1)	0.19
Men	610 (57.8)	33,384 (55.3)	.11	597 (56.6)	33,410 (55.3)	0.04
Medical history and presurgery OAC use						
CHA_2DS_2-VASc†	4.7 (1.2)	4.8 (1.2)	<.01	4.8 (0.3)	4.8 (0.2)	0.04
Previous MI	304 (28.8)	15,429 (25.5)	.01	282 (26.7)	15,463 (25.6)	0.03
Previous stroke (ischemic or hemorrhagic)	97 (9.2)	4385 (7.3)	.02	93 (8.8)	4405 (7.3)	0.06
Diabetes	496 (47.0)	28,237 (46.8)	.92	496 (47.0)	28,237 (46.8)	0.00
PAD	328 (31.1)	21,381 (35.4)	<.01	382 (36.2)	21,336 (35.3)	0.02
History CHF	415 (39.3)	24,511 (40.6)	.41	399 (37.8)	24,497 (40.6)	0.04
PVD	324 (30.7)	20,810 (34.5)	.01	367 (34.8)	20,771 (34.4)	0.01
Hypertension	943 (89.3)	55,309 (91.6)	<.01	955 (90.5)	55,286 (91.5)	0.01
Renal failure/dialysis	205 (19.4)	8440 (14.0)	<.01	161 (15.2)	8497 (14.1)	0.03
COPD	242 (22.9)	15,301 (25.3)	.07	261 (24.7)	15,276 (25.3)	0.00
Filled OAC prescription	48 (4.5)	1631 (2.7)	<.01	31 (2.9)	1650 (2.7)	0.00
Cardiac surgery performed						
Isolated CAB	659 (62.4)	29,279 (48.5)	<.01	530 (50.1)	29,424 (48.7)	0.03
Valve(s)	223 (21.1)	26,447 (43.8)	<.01	433 (41.0)	26,212 (43.4)	0.01
Valve(s) + CAB	174 (16.5)	4652 (7.7)	<.01	78 (7.4)	4743 (7.9)	0.03

Values are presented as n (%). *IPTW*, Inverse probability treatment weighting; *SMD*, standard mean difference; *OAC*, oral anticoagulant; *CHA_2DS_2-VASc score*, congestive heart failure, hypertension, age $\geq$75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female); *MI*, myocardial infarction; *PAD*, peripheral artery disease; *CHF*, congestive heart failure; *PVD*, peripheral vascular disease; *COPD*, chronic obstructive pulmonary disease; *CAB*, coronary-artery bypass grafting. *IPTW counts are rounded to whole numbers. †Scores on the CHA_2DS_2-VASc calculated from congestive heart failure, hypertension, age 75 years or older (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 years, and sex category (female) status.

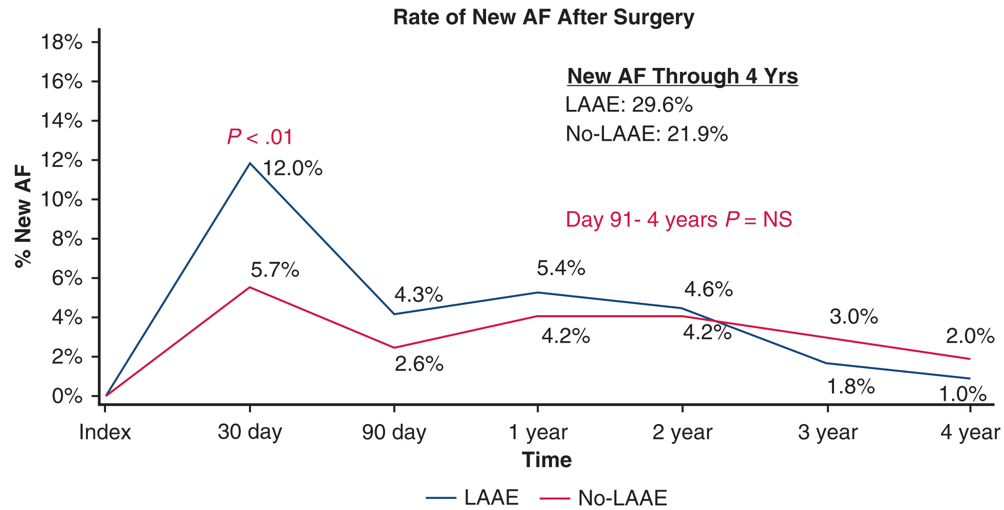


FIGURE 2. Postoperative atrial fibrillation (*AF*) over time. Postoperative AF occurred more for patients with left atrial appendage exclusion (*LAAE*) during the first 30 to 90 days after surgery, but over time, the incidence of new AF decreased and was similar between groups.

became similar between groups and through 4 years did not differ (Figure 2).

Before adjusting for which valve was operated on, LAAE was associated with a lower adjusted risk (28%) of ischemic stroke and OR of 0.72 (95% CI, 0.53-0.98; $P = .02$) (Table 2). After adjusting for valvular approach, the OR indicated that LAAE was associated with a more reduced risk (35%) of ischemic stroke (OR, 0.65; 95% CI, 0.49-0.86; $P < .01$). In the first 30 days after the operation, the LAAE group had a 28% reduction in odds for ischemic stroke (4.3% vs 5.9%; $P = .03$) and 26% lower odds between days 31 through 4 years (7.7% vs 10.1%; $P < .01$). Major bleed (0.1% vs 0.5%; $P = .01$), and other embolic events had lower odds through 4 years for LAAE, including ischemic stroke plus systemic embolism (4.3% vs 5.9%; $P = .03$), and thromboembolism (18.3% vs 23.4%; $P < .01$). Mortality from any cause had 34% lower odds occurring with LAAE through 4 years (10.0% vs 13.1%; $P < .01$), although the Medicare denominator file does not allow for causality. Similar to ischemic stroke, when post hoc analysis was performed to control for differences in valvular approach by group, LAAE demonstrated 42% lower odds of all-cause mortality ($P < .01$).

During postoperative year 1, OAC use was greater for LAAE (24.8% vs 17.4%; $P < .01$) and remained higher through follow-up (Table E3). In patients with LAAE + OAC use compared with No-LAAE + OAC the differences in adjusted ischemic stroke through 4 years did not reach statistical significance (9.5% vs 14.1%; $P = .17$) (Figure 3), although a 64% reduction in odds of

TABLE 2. Comparison of cerebral vascular events, all-cause mortality, and secondary outcomes through 4 years in patients without atrial fibrillation undergoing open cardiac surgery*

Outcome	Unweighted sample: LAAE (n = 1056)	Unweighted sample: No-LAAE (n = 60,391)	Unweighted sample: *P* value	IPTW sample†: LAAE (n = 1040)	IPTW sample†: No LAAE (n = 60,379)	IPTW sample†: Adjusted OR comparison (95% CI)	IPTW sample†: *P* value
Primary outcome through 4 y							
Ischemic stroke	103 (9.7)	6182 (10.2)	.64	127 (12.0)	9660 (16.0)	0.72 (0.53-0.98)	.02
Ischemic stroke or systemic embolism	111 (10.5)	6459 (10.7)	.88	137 (13.0)	10,063 (16.7)	0.75 (0.57-0.98)	.03
Thromboembolism‡	160 (15.2)	9382 (15.5)	.76	193 (18.3)	14,119 (23.4)	0.73 (0.59-0.92)	<.01
All-cause mortality	106 (10.0)	7941 (13.1)	.00	104 (9.9)	8104 (13.4)	0.66 (0.52-0.85)	<.01
Early stroke, late stroke, and bleed through 4 y							
Ischemic stroke within first 30 d	33 (3.1)	1097 (1.8)	.00	45.7 (4.3)	3566 (5.9)	0.72 (0.53-0.98)	.03
Ischemic stroke 31 d after surgery through 4 y	70 (6.6)	5085 (8.4)	.04	81 (7.7)	6094 (10.1)	0.74 (0.58-0.93)	<.01
Major bleed	2 (0.2)	306 (0.5)	.21	1 (0.1)	306 (0.5)	0.17 (0.04-0.71)	.01

Values are presented as n (%); patients with at least 1 event. *IPTW*, Inverse probability treatment weighting; *LAAE*, left atrial appendage exclusion; *OR*, odds ratio. *All adjusted comparisons were completed with logistic regression with OR and 95% CI. †IPTW counts rounded to whole numbers. ‡Thromboembolism is a composite measure consisting of ischemic stroke, systemic embolism, and transient ischemic attack.

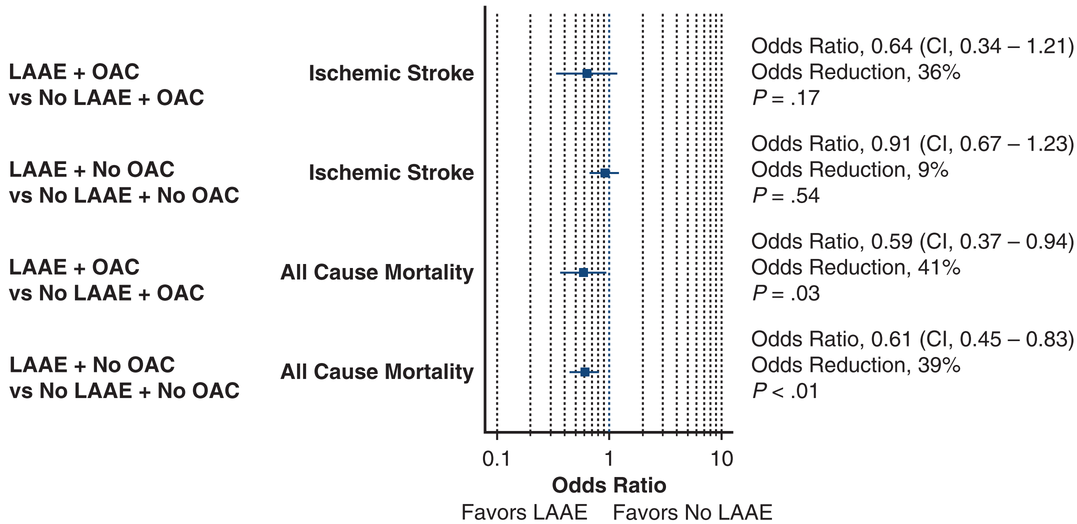


FIGURE 3. Adjusted ischemic stroke and mortality with/without oral anticoagulant (*OAC*) use following cardiac surgery through 4 years in all patients. Odds ratios with 95% CI comparisons. *LAAE*, Left atrial appendage exclusion.

ischemic stroke was present in late follow-up for LAAE + OAC (31 days to 4 years) (4.6% vs 11.7%; $P < .00$). LAAE + OAC use demonstrated a 41% reduction in odds of all-cause mortality (10.3% vs 16.3%; $P = .03$) compared with No-LAAE + OAC. Without OAC, LAAE alone demonstrated a 9% reduction in odds of stroke through 4 years (8.7% vs 9.6%; $P = .54$) and 39% reduction in odds of all-cause mortality (7.6% vs 11.9%; $P < .01$).

In those who developed POAF within 30 days, LAAE + OAC demonstrated 74% lower 4-year odds of ischemic stroke compared to No-LAAE + OAC (4.9% vs 16.2%; $P = .01$) (Figure 4). The same LAAE group demonstrated a trend for reduced all-cause mortality odds (50%) than No-LAAE without OAC (6.9% vs 15.0%; $P = .05$). Other long-term clinical events did not differ between groups through 4 years. AF-related admission was 1.5% and 1.4% in LAAE and No-LAAE.

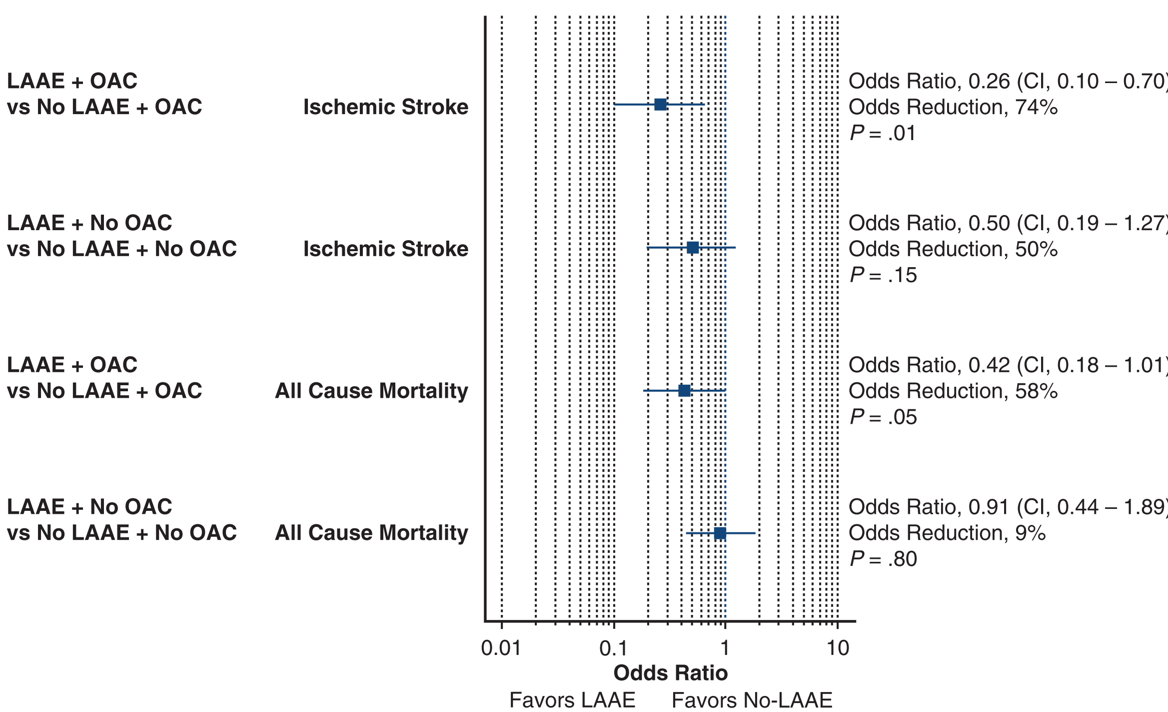


FIGURE 4. Adjusted ischemic stroke and mortality with/without oral anticoagulant (*OAC*) use following cardiac surgery through 4-years in 30-day postoperative atrial fibrillation patients. Odds ratio with 95% CI comparisons. *LAAE*, Left atrial appendage exclusion.

To ensure there was limited impact from unmeasured variables, we performed a sensitivity analysis with E-values to assess the magnitude of confounding bias.[24] The E-values for ischemic stroke (2.45) and all-cause mortality (2.26) suggested our findings are relatively robust against unmeasured confounding.

DISCUSSION

These findings add to the scarce body of knowledge of LAAE in NoAF patients. In the LAAE group, POAF was more prevalent, possibly from an acute inflammatory response from surgery and LAAE.[4] The occurrence of 30-day POAF was unusually low and may indicate underreporting or an AF event not requiring a provider encounter and not being reported with claims submission. New AF diagnosis stabilized by day 90 and remained similar for both groups through the rest of follow-up. TheAtriClip Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures (ATLAS) trial (ClinicalTrials.gov ID NCT02701062) findings were similar, but the rates of AF were much higher (47% LAAE vs 38% No-LAAE).[19] Unlike many reports of late morbidity and mortality associated with POAF,[3,9,25] we found no signal that POAF in the LAAE group had a deleterious effect. In fact, for POAF patients late ischemic stroke was lower in the LAAE group with OAC (74% reduction) and reduced by 50% in the no OAC use group.

All cardiac surgery patients are at risk for POAF, stroke, and mortality even with the use of OAC. Presurgery CHA_2DS_2-VASc score suggested that patients in the current study were at high risk for stroke even in the absence of AF. Perioperative stroke risk is multifactorial and is partially attributed to the surgery itself (eg, aortic and intracardiac manipulation),[26] factors against which LAAE is ineffective. A greater proportion of late strokes are related to LAA thrombus with or without AF, for which LAAE is effective. Some of the protective benefits from ischemic stroke for AF patients likely resulted from OAC use, but the difference in embolic protection between groups suggests incremental benefit of LAAE + OAC use. Our findings are consistent with Kim and colleagues[20] who found a reduction in cerebral vascular events following prophylactic LAA closure during concomitant surgery. The AtriClip Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures (ATLAS) trial (ClinicalTrials.gov ID NCT02701062) also observed a trend of lower stroke rate following surgery in those who developed POAF.[19] The method used for LAAE

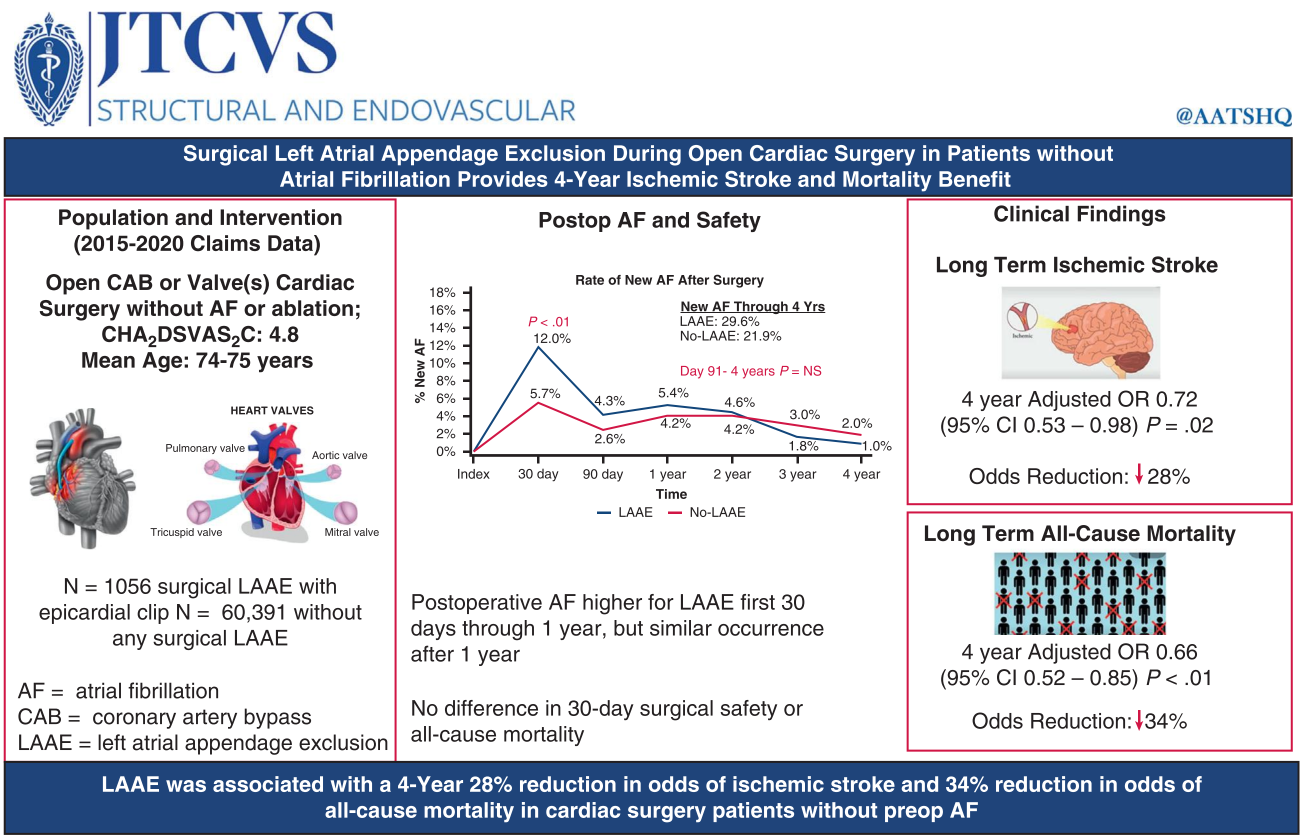


FIGURE 5. Prophylactic left atrial appendage exclusion (*LAAE*) during cardiac surgery. LAAE showed a significant decrease in long-term cerebral vascular event rate and lower all-cause mortality in primarily elderly Medicare beneficiaries without atrial fibrillation (*AF*) undergoing cardiac surgery. *CHA_2DS_2-VASc score*, Congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female).

during concomitant surgery was an epicardial exclusion clip. Although imaging was not available, others have reported epicardial exclusion clip closure efficacy as high as 98%.[21,27] In this study the combination of LAAE + OAC had the greatest reduction in stroke risk, with no incremental benefit of adding OAC to LAAE for POAF after the 30-day postoperative period. Confirmation of this combination in the Left Atrial Appendage Exclusion for Stroke Prevention clinical trial (NCT05478304) in Cardiac Surgery Patients randomized trial may suggest a clinical protocol for stroke reduction without exposing the patient to the long-term risks of bleeding with OACs.

An additional finding was lower odds of all-cause mortality for the LAAE group with/without POAF during the 4-year follow-up period. Claims data does not allow the assessment of causality, but it is possible that lower embolic event rates contributed to lower patient mortality. A recent administrative data set analysis with AF patients undergoing CAB with LAAE without ablation found a 45% risk reduction in all-cause mortality after 90 days,[16] which is consistent with findings from this study. Left Atrial Appendage Occlusion Study III (LAAOS III) ClinicalTrials.gov ID NCT01561651 failed to demonstrate a mortality benefit, but the trial was not powered to do so.[15] These results have important implications for the use of nonpharmacologic therapies to prevent embolic stroke in NoAF patients who are at risk for stroke following cardiac surgery.

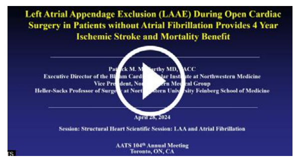
This analysis is subject to several limitations associated with retrospective studies, including selection bias, even with the most robust analysis. First, although IPTW can minimize differences in comorbidity status, the analysis may not entirely account for severity or even the influence of difference in valve procedure by group. Second, OAC documentation may have been incomplete. OAC use could influence embolic event rates independently, although our data indicate the LAAE had a significant effect with or without OAC. An analysis of patients with missing OAC data demonstrated differences of between 0% and 3% in aggregate stroke and mortality outcomes (Table E4). Third, the accuracy of POAF early, and late AF, is always difficult, and asymptomatic episodes may be undetected. But that is likely true for both groups. Fourth, the lack of adjudication of events such as stroke, and variability in stroke definition was a limitation in this and all database studies. Finally, this cohort was older with comorbidities and high CHA_2DS_2-VASC scores as in the Left Atrial Appendage Exclusion for Prophylactic Stroke Reduction. Trial Sponsor Name: AtriCure, Inc. NCT Number: NCT05478304 for Stroke Prevention in Cardiac Surgery Patients trial. These results may be less relevant in a younger population.

CONCLUSIONS

Prophylactic LAAE was associated with a significant reduction in odds of long-term cerebrovascular event rate and lower all-cause mortality in primarily elderly NoAF Medicare beneficiaries undergoing cardiac surgery in a real-world setting (Figure 5). These results suggest that LAAE may provide protective benefit against stroke incremental to that of OAC. Additional randomized trials are needed to verify these findings.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/surgical-left-atrial-appendage-7263.



Conflict of Interest Statement

Dr McCarthy receives royalties from Edwards Lifesciences, speaking fees and a advisory board position from AtriCure, and is a surgical primary investigator REPAIR-MR (unpaid) for Abbott. Dr Mehran has received institutional research payments from Abbott, Abiomed, Affluent Medical, Alleviant Medical, Amgen, AM-Pharma, Arena, AstraZeneca, AtriCure Inc, Biosensors, Biotronik, Boston Scientific, Bristol-Myers Squibb, CardiaWave, CeloNova, CERC, Chiesi, Cleerly Health Inc, Concept Medical, Cytosorbents, Daiichi Sankyo, Duke, Element Science, Essential Medical, Faraday, Idorsia Pharmaceuticals, Janssen, MedAlliance, Mediasphere, Medtelligence, Medtronic, MJH Healthcare, Novartis, OrbusNeich, Penumbra, PhaseBio, Philips, Pi-Cardia, PLx Pharma, Population Health Research Institute, Protembis, RecCor Medical Inc, RenalPro, RM Global, Sanofi, Shockwave, Vivasure, and Zoll; has received personal fees from Affluent Medical, Boehringer Ingelheim, Cardiovascular Research Foundation, Cordis, Daiichi Sankyo Brasil, E.R. Squibb & Sons, Esperion Science/Innovative Biopharma, Europa Group/Boston Scientific, Gaffney Events, Educational Trust, Henry Ford Health Cardiology, Ionis Pharmaceuticals, Lilly and Company, MedCon International, Novartis, NovoNordisk, PeerView Institute for Medical Education, TERUMO Europe N.V., Vectura, VoxMedia, WebMD, IQVIA, Radcliffe, and TARSUS Cardiology; and holds equity (<1%) in Elixir Medical, Stel, and CntrolRad (spouse). Dr Gardisch is a paid consultant with Edwards. Dr Ramlawi is a consultant for Boston Scientific, Medtronic, LivaNova, and AtriCure. Dr Lee is an employee and stock-holder with AtriCure. Dr Ferguson is an employee and stock-holder with AtriCure. Dr Whitlock has grants from Boehringer Ingelheim, Abbott, Cytosorbents, AtriCure, and Bayer; receives consultant or speaking fees from AtriCure, Edwards Life

Sciences, Artivian, and Cytosorbents. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: epicardial, left atrial appendage exclusion, prophylactic, stroke, cardiac surgery, atrial fibrillation

APPENDIX E1. SUPPLEMENTAL METHODS

Data Source

Data licensed from public data sources were aggregated into STATinMED Real World Data Insights, a privately held payer medical and pharmacy claims dataset. The database provides claims data from approximately 80% of the US health care system (Medicare, Medicare Advantage, Medicaid, and commercial insurance). These data are sourced directly from claims clearing houses, which are responsible for managing claims transactions as they go between payers and providers. Ninety-nine percent of the data were from Centers for Medicare and Medicaid Services (CMS) and Veterans Administration (VA) sources due to completeness of records and mortality data, including greater availability of long-term follow-up. More than 99% of data were linked to the CMS National Death Index. Data were de-identified, and data use complied with the requirements of the Health Insurance Portability and Accountability Act for the privacy and security of protected health information. Index data were used from the 2015 to 2020 period and follow-up ranged from a minimum of 2 years to a maximum of 5 years. Because retrospective data, initially available in the public and anonymized, do not meet the Health and Human Service Services definition as human research (as defined in 45 CFR 46.102), the study was exempt from institutional review board review.

Statistical Methods

Baseline characteristics of the study population by interventional group (left atrial appendage exclusion [LAAE] vs no-LAAE) were described using proportions for categorical variables and means with SDs for continuous variables. Differences between groups were tested using the χ^2 test for categorical variables and Student *t* test for continuous variables.

Given the significant differences in baseline characteristics and the nonrandomized design of the study, inverse probability treatment weighting (IPTW) was used to balance baseline characteristics between LAAE and no-LAAE groups. IPTW has been widely used in observational studies for causal inference and is a methodological tool that attempts to reconstruct a randomized controlled trial retrospectively, to control for confounders that are overrepresented in either the treatment or control groups. Using the propensity scores, the IPTW method assigns weights to each individual based on the inverse of their probability of receiving the treatment given their observed covariates. Through weighting, a pseudopopulation is created that is well balanced in terms of confounders. This process mimics the exchangeability of groups after random treatment assignment.

The propensity score was estimated using a multivariate logistic regression, with the receipt of LAAE as the dependent variable and observed baseline characteristics as independent variables. The variables included in the final logistic model were based on univariate group differences ($P < .1$) as well as additional clinically relevant indices. Variables included in the IPTW model were age, gender, race, US geographic surgical region, payer channel, congestive heart failure, hypertension, age, diabetes, gender (CHA_2DS_2-VASc) score, open cardiac surgery type (valve group or coronary artery bypass group), history of acute myocardial infarction, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, previous stroke, current oral anticoagulant use, hypertension, renal failure/on dialysis, peripheral arterial disease, and heart failure. Good matching was considered if variables had a standard mean difference less than 0.20. After IPTW adjustment, preplanned comparisons between LAAE and non-LAAE patients for all primary and secondary outcomes of interest were analyzed using multivariable logistic regression. Odds ratios (ORs) and their 95% CI were reported. Adjusted counts were rounded to nearest whole number. Logistic regression was chosen given its appropriateness for case-control type analyses with retrospective treatment and longitudinal assessment. Time intervals for analysis were initially planned as index through 4 years. The last actual follow-up was used in analysis, and imputation was not performed. Post hoc analysis included 30 days and 30 days through 4 years. New atrial fibrillation occurrence was assessed at 90 days after index and then yearly intervals to determine if each group developed new atrial fibrillation at a similar rate. Analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing) and the atrial fibrillation plot over time was built with Excel (Microsoft Corp).

TABLE E1. Thirty-day safety events*

Variable	Unadjusted event rate LAAE (n = 1056)	No LAAE (n = 60,391)	Adjusted odds ratio comparison (95% CI)†
Patients with at least 1 event			
Safety outcomes			
Operative mortality	9 (0.9)	285 (0.5)	1.86 (0.86-4.04)
Pericardial effusion	13 (1.2)	758 (1.3)	1.47 (0.69-3.11)
Sternal wound infection	18 (1.7)	1207 (2.0)	0.74 (0.42-1.28)
Major bleed	1 (0.1)	113 (0.2)	0.19 (0.03-1.39)
Myocardial infarction	109 (10.3)	5564 (9.2)	0.91 (0.72-1.15)

Values are presented as n (%). *LAAE*, Left atrial appendage exclusion. *Adjustment denotes inverse probability treatment weighting. Perioperative period is index surgery through 30 days' follow-up. †All adjusted comparisons were completed with logistic regression.

TABLE E2. Any new atrial fibrillation (AF) diagnosis in patients after cardiac surgery

Variable	LAAE (n = 1056)	No LAAE (n = 60,391)	*P* value
AF first 30 d through 1 y			
AF after surgery through 30 d	129 (12.2)	3485 (5.8)	<.01
AF 31 d after surgery through 1 y	104 (9.8)	4174 (6.9)	<.01
AF first 90 d through 1 y			
AF after surgery through 90 d	175 (16.5)	5102 (8.4)	<.01
AF 91 d after surgery through 1 y	58 (5.4)	2557 (4.2)	.05
AF 1 year through 4 y			
AF 1 y after surgery through 2 y	49 (4.6)	2591 (4.3)	.63
AF 2 y after surgery through 3 y	19 (1.8)	1824 (3.0)	.02
AF 3 y after surgery through 4 y	12 (1.1)	1200 (2.0)	.06
Total	313 (29.6)	13,274 (21.9)	

Values are presented as n (%). *LAAE*, Left atrial appendage exclusion.

TABLE E3. Oral anticoagulant prescription status in patients after cardiac surgery

Variable	LAAE (n = 1056)	No LAAE (n = 60,391)	*P* value
Any postoperative anticoagulation filled during time period*			
Prescription filled first year after surgery	186 (24.8)	7459 (17.4)	<.01
Prescription filled second year after surgery	175 (23.7)	7224 (17.2)	<.01
Prescription filled third year after surgery	153 (22.5)	6144 (16.0)	<.01

Values are presented as n (%). *LAAE*, Left atrial appendage exclusion. *N = 751, 739, and 679 for LAAE group and 42,825 and 42,098, and 39,432 for no-LAAE group, respectively, for patient prescription status available at years 1, 2, and 3 postsurgery.

TABLE E4. Unadjusted rates over 4 years

Variable	Unadjusted rates over 4 y LAAE OAC/No-OAC data available	No LAAE OAC/No-OAC data available
Ischemic stroke	9%/11%	10%/10%
All-cause mortality	11%/9%	14%/11%

LAAE, Left atrial appendage exclusion; *OAC*, oral anticoagulation.