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Improved outcomes in CABG patients with atrial fibrillation associated with surgical left atrial appendage exclusion

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Abstract

Background: We sought to determine the impact of left atrial appendage clip exclusion (LAACE) on coronary artery bypass grafting (CABG) outcomes among patients with pre-existing atrial fibrillation (AF).

Methods: From October 1, 2015 to October 1, 2017, 4210 Medicare beneficiaries with pre-existing AF underwent isolated CABG (i.e., without ablation) with (n = 931) or without (n = 3279) LAACE. Inverse probability of treatment weighting was used to evaluate the effect of concomitant LAACE on short- and long-term outcomes after CABG. Long term risks of thromboembolism and mortality were assessed using competing-risk regression and Cox proportional hazard models.

Results: Operative mortality, length of stay, and 30-day readmission did not differ between groups. Thromboembolism risk was 26% lower for the CABG + LAACE group compared with isolated CABG over a 2-year time-to-event analysis (sub hazard ratio [sHR] 0.74, 95% confidence interval [CI] 0.54–1.00, p = .049). There were no differences in ischemic stroke rates. All-cause mortality risk was 45% lower for CABG + LAACE during the late follow-up period (91–730 days; HR 0.55, 95% CI 0.32–0.95, p = .031). The late period annual absolute all-cause mortality rate was 3.7% for CABG + LAACE and 6.9% for isolated CABG. There were lower readmission rates (31% vs. 43%, p < .001) and total inpatient days (4.0 days vs. 7.2 days, p < .01.) for the CABG + LAACE during follow-up. Total hospital in and out-patient treatment costs were similar between groups through one year.

Conclusions: Concomitant LAA exclusion via an epicardial closure device is associated with reduced CABG mortality, thromboembolic events, and readmissions in patients with pre-existing atrial fibrillation.

KEYWORDS

atrial fibrillation, CABG, embolism, left atrial appendage, stroke

Abbreviations: AF, atrial fibrillation; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; ICD-10-PCS, International Classification of Diseases, 10th Revision – Procedure Coding System; IPT, inverse probability of treatment; LAA, left atrial appendage; LAACE, left atrial appendage clip exclusion; OAC, oral anticoagulation; sHR, sub hazard ratio; STS, Society of Thoracic Surgery; TIA, transient ischemic attack.

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1 | INTRODUCTION

Approximately 5%–11% of all patients requiring cardiac surgery and up to 28% of older surgical patients have pre-existing atrial fibrillation (AF).[1–5] Preoperative AF contributes significantly to mortality, stroke, length of stay, and readmission after cardiac surgery.[1–4] Non-AF related cardiac surgery presents a unique opportunity to concurrently address comorbid AF and improve outcomes.

Among patients with AF, 90% of strokes can be attributed to thrombi originating from the left atrial appendage (LAA).[6] Concomitant surgical LAA management is recommended both by the revised 2019 American College Cardiology (Class IIB)[7] and 2017 Society of Thoracic Surgeons (Class IIA)[8] guidelines. This can be achieved by excision of the appendage and suture closure of the stump, suture ligation at the base, internal suture exclusion, staple excision at the base, or LAA clip exclusion (LAACE) at the base.

Trials of concomitant suture and staple left atrial appendage occlusion with coronary artery bypass grafting (CABG) demonstrated incomplete occlusion, subsequent increased risk of thromboembolism, and high incidence of procedure-related adverse events.[9,10] However, the EXCLUDE (AtriCure Exclusion of the LAA in Patients Undergoing Concomitant Cardiac Surgery) trial demonstrated successful occlusion at 1 year in over 98% of patients with no device-related mortalities or adverse events when using an epicardially placed clip (AtriClip® LAA Exclusion System, AtriCure Inc.).[11] While subsequent studies have confirmed the safety and feasibility of the procedure, there is a paucity of contemporary data to demonstrate the impact of LAA exclusion via an epicardial clip on outcomes when added to isolated CABG in patients with AF when compared with CABG alone.

Therefore, a contemporary, nationally representative cohort of beneficiaries from the Medicare administrative database was used to evaluate the effect of adding LAACE to isolated CABG among patients with AF on patient outcomes and healthcare resource use.

2 | MATERIAL AND METHODS

2.1 | Data source and study population

Data were obtained from the Medicare Standard Analytic Files (SAF) data set of hospital inpatient and outpatient claims. Medicare is a federal health insurance program in the United States, provides coverage for legal residents more than or equal to 65 years of age, patients less than 65 years of age with certain disabilities, and those with end-stage renal disease requiring dialysis or transplant. Because this is a publicly available data set without any direct patient identifiers, this study was exempt from review by our institutional review board.

Patients with AF undergoing CABG were identified among patients treated at an acute inpatient care facility and discharged between October 1, 2015 and September 30, 2017 using International Classification of Diseases, 10th Revision – Procedure Coding System (ICD-10 PCS) codes (Table S1). Surgical epicardial LAACE via clip device insertion was identified with ICD-10 PCS code 02L70CK.

Study patients were aged more than or equal to 65 at the time of CABG admission and presented with either persistent or paroxysmal AF. Patients not continuously eligible for Medicare 2015–2017 or with missing records were excluded. Patients who underwent a major cardiac procedure (including surgical ablation) concomitant to or one year before the index CABG were excluded. ICD-10 codes for surgical ablation can be found in Table S2.

Baseline characteristics were identified from ICD diagnoses on claims during the 12-months before the CABG index event. The sensitivity and specificity of using ICD-9 and 10 codes to document AF have been established.[12] Because of the transition to ICD-10 code set in 2015, the definition of baseline persistent or paroxysmal AF depended on the baseline claims dates. For baseline claims before October 1, 2015, ICD-9 diagnosis code 427.31 was used to identify AF. AF was defined as persistent if there were two or more inpatient or outpatient hospital encounters for AF at least 7 days apart during the 12 months before CABG. AF was defined as paroxysmal if there was one inpatient or outpatient encounter for AF in previous 12 months before CABG. While there has been no formal validation study, these criteria are consistent with existing published claims data.[13,14] For baseline claims after October 1, 2015, persistent and paroxysmal AF were defined by ICD-10 codes I481 and I480.

2.2 | Clinical outcomes and healthcare resources

Outcomes assessed included perioperative events and mortality, hospital length of stay, thromboembolic events, ischemic stroke, all-cause mortality, hospital costs, and hospital readmissions. Events were identified from the primary diagnosis indicated for hospital inpatient or outpatient encounters. Event dates were the admission dates.

Operative mortality was defined as all-cause mortality during the index stay or within 30-days from date of index admission, per the Society Thoracic Surgery (STS) guidelines.[15] Thromboembolism was defined as the first occurrence of ischemic stroke, transient ischemic attack (TIA), or peripheral embolism (Tables S3–S5). We analyzed ischemic stroke separately. Both inpatient and outpatient hospital costs were estimated from charges and each hospital's cost-to-charge ratio. Costs were divided into 29 “cost centers” as per CMS coding where each cost center represents a unit of the hospital that contributes to the total cost (i.e., room and board, laboratory, supplies, radiology, etc.). These can be found in Table S6. Costs were not adjusted for inflation.

2.3 | Follow-up

Follow-up was through September 30, 2017 or death, if earlier. All patients were included in the analysis of index event, thromboembolic events, and all-cause mortality outcomes over 2 years when data was available. To ensure complete follow-up, patients with admission dates before August 31, 2017, June 30, 2017, and September 30, 2016 were included in the 30-day, 90-day, and 1-year analyses, respectively. Average postoperative follow-up was 341 days (Table S7) in the time-to-event analyses,

Postdischarge all-cause hospital inpatient readmissions, hospital inpatient costs, hospital outpatient costs, and total hospital costs were analyzed during index and through 1-year after index admission date.

2.4 | Statistical analysis

Baseline categorical variables were described with counts and proportions, compared with a Fisher's exact or Person's χ^2 test. Continuous variables were described with means and standard variations and compared using analysis of variance.

Thromboembolism and ischemic stroke outcomes were analyzed with competing risk regression using the method of Fine and Gray, a survival analysis method that estimates the cumulative incidence of the outcome of interest, recognizing that patients are exposed to a competing risk.[16] Competing risks in our study were the outcome of interest, for example, thromboembolism, and mortality. Competing risk regression estimates a sub hazard ratio (sHR), which measures the effect of LAACE on the cumulative incidence of the outcome of interest.

All-cause mortality was analyzed with Cox proportional hazards models. Validity of the proportionality of hazards assumption was tested with interaction of treatment and durations, 90-days and 180-days. We used Schoenfeld residuals to test the proportionality assumption and included a time-varying covariate if the proportionality assumption was violated. If proportional hazards were not satisfied, follow-up comparisons were divided into two intervals: 0–90 days (early follow-up) and 91–730 days (late follow-up).

Negative binomial, logistic, and generalized linear models were used for all-cause hospital inpatient admissions, hospital inpatient costs, hospital outpatient costs, and total hospital costs depending on the distribution of the outcome.

Because study patients were not randomized, treatment groups may have had systematic differences that could have biased comparisons. Propensity scoring is a balancing methodology which was used to account for those systematic differences.[17] The propensity score was estimated using multivariate logistic regression, with the treatment received as the dependent variable and observed baseline characteristics as independent variables. The propensity score model was evaluated by comparing baseline characteristics across treatment groups with similar propensity scores. Baseline variables for the propensity model included age, gender, AF status, CHA_2DS_2-VASc score, HAS-BLED score, prior stroke history, heart failure status, prior acute myocardial infarction (AMI), prior renal failure, chronic lung disease status, prior TIA, prior peripheral and pulmonary embolism, hypertension status, endocarditis, prior percutaneous coronary intervention history, aortic stenosis, and aortic/mitral insufficiency. Patients with common support were identified as those with an overlap of propensity scores. The propensity score model was evaluated with standardized differences of the covariates (Figure S1).[18] Inverse probability of treatment (IPT) weighting was used in regression analyses of the outcome of interest.

3 | RESULTS

3.1 | Demographics and patient characteristics

From October 1, 2015 to September 30, 2017, 97,661 Medicare patients underwent isolated CABG. After excluding patients without AF, aged under 65, those receiving a concomittant ablation, or those who had a nonclip method of LAA exclusion, 3279 patients (78%) underwent isolated CABG and 931 (22%) CABG + LAACE (Figure 1). Both cohorts were comparable in age (74.3 vs. 74.0 years), but isolated CABG patients had higher CHA_2DS_2-VASc stroke risk and HAS-BLED bleed scores, rates of paroxysmal AF, hypertension, renal failure, chronic lung disease, heart failure, and prior AMI ($p < .05$). The CABG + LAACE cohort had a higher percentage of male patients, greater incidence of persistent AF, and prior TIA ($p < .05$; Table 1).

3.2 | Clinical findings

IPT-weighted operative mortality (5.2% vs. 5.3%, $p = .31$), length of stay (10.3 days vs. 10.9 days, $p = .63$), 30-day readmission rates (23% vs. 23%, $p = .31$), and incidence of perioperative complication (ischemic stroke, hemorrhagic stroke, peripheral embolism, TIA, and bleed) did not differ between groups (30-day mortality, length of stay, and readmission Table 2; postoperative complications Table S8).

In the IPT-weighted 2-year time-to-event analysis thromboembolism risk was reduced by 26% in the CABG + LAACE group (sHR 0.74, 95% confidence interval (CI) 0.54–1.00, $p = .049$; Figure 2). Annual risk for thromboembolism was 4.4% for CABG + LAACE and 5.9% for isolated CABG. Thromboembolism event distributions were similar between groups (CABG vs. CABG + LAACE); 55% versus 56% for ischemic strokes, 30% versus 28% for peripheral embolisms, and 21% versus 24% for TIA. In both cohorts 7% of patients had multiple thromboembolic events during follow-up.

IPT weighted ischemic stroke did not differ (sHR 0.74, 95% CI 0.49–1.11, $p = .144$; Figure 3). Annual risk of ischemic stroke was 2.3% for the CABG + LAACE group and 3.1% for isolated CABG. CABG + LAACE patients had 38% lower predicted annual ischemic stroke risk based on CHA_2DS_2-VASc scores versus 16% lower risk for isolated CABG. When combining ischemic and hemorrhagic stroke (total stroke) there were no differences between groups (sHR 0.72, 95% CI 0.49–1.06, $p = .096$).

Because proportional hazards were not satisfied with all-cause mortality, follow-up was divided into two-time intervals: 0–90 days (early follow-up) and 91–730 days (late follow-up). In the early follow-up period there was no difference in

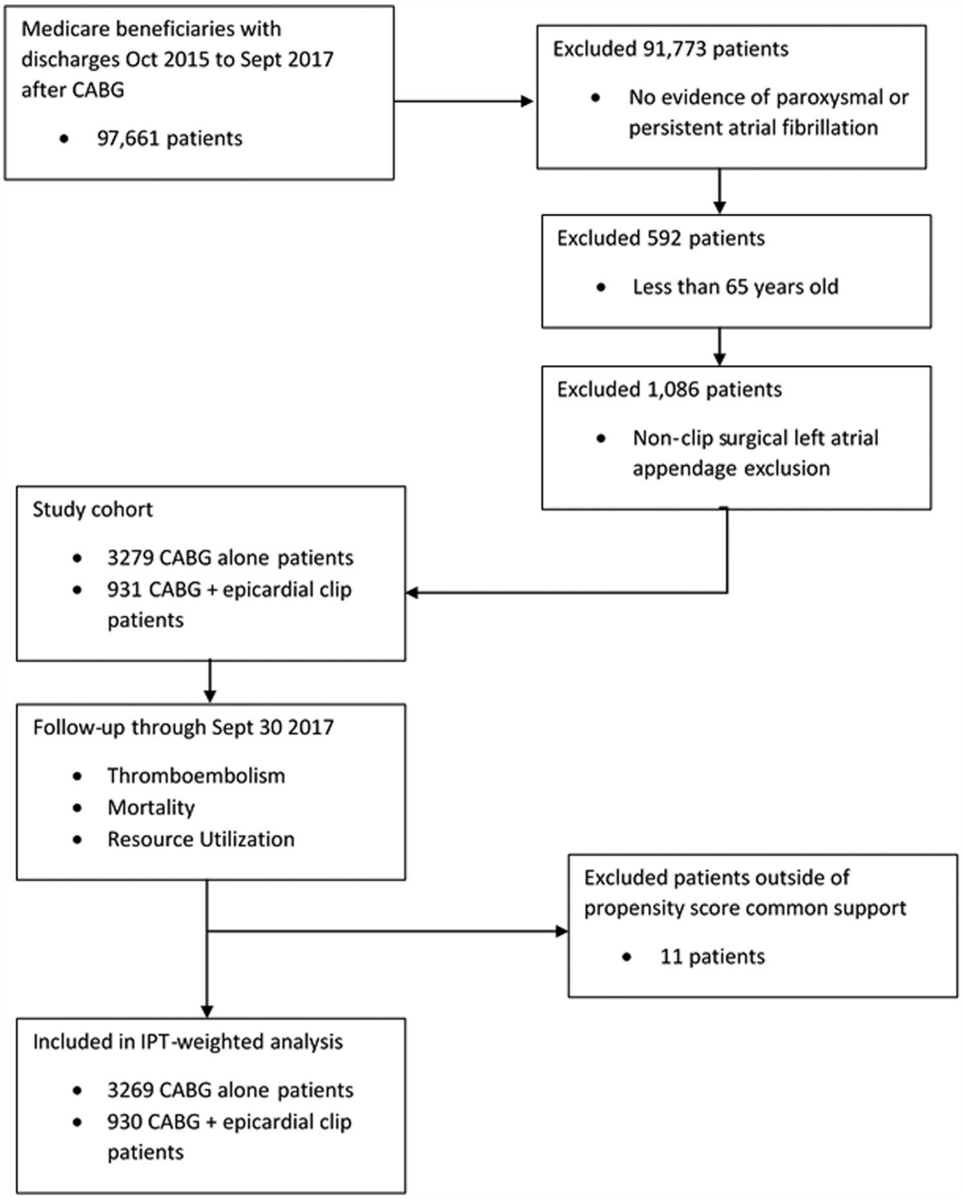

FIGURE 1 Patient flow diagram. CABG, coronary artery bypass grafting

IPW-weighted all-cause mortality between groups (HR 1.05, 95% CI 0.79–1.40, $p = .733$). However, in the late follow-up period IPW-weighted mortality was significantly lower for the CABG + LAACE group (HR 0.55, 95% CI 0.32–0.95, $p = .031$; Figure 4). The annual risk of mortality in the late period for CABG + LAACE was 3.7% and for isolated CABG 6.9%.

There were lower IPT-weighted hospital readmission rates over 1 year for CABG + LAACE (31% vs. 43%, $p < .001$). Total readmission days were lower for CABG + LAACE (4.0 days vs. 7.2 days, $p < .01$), with the biggest difference between groups occurring post 90-day treatment period (2.4 days vs. 0.9 days, $p = .013$; Table 2). Hospital readmission drivers for both groups were hypertension (8%), heart failure (7%), and atrial fibrillation/flutter (4%).

IPT-weighted adjusted total hospital index costs were similar between groups ($p = .132$; Table 2). Before IPT-weighting adjustment, there were higher costs for OR and supplies for CABG + LAACE ($p < .001$), significant after Hochberg adjustment for multiple comparisons (Table S6).[19] During 1-year follow-up, total inpatient and outpatient hospital costs, including index costs were comparable between groups ($p = .771$).

4 | DISCUSSION

In a Medicare cohort of patients with AF undergoing cardiac surgery without concomitant ablation, CABG + LAACE compared with isolated CABG was associated with a significantly lower risk of thromboembolism, all-cause mortality, and hospital readmissions. While observational in nature, this analysis supports the use of LAACE in patients with AF at the time of CABG surgery.

TABLE 1 Characteristics of CABG patients with and without surgical LAACE

Patient characteristics	CABG (n = 3279) Mean ± *SD* or %	CABG + LAACE (n = 931) Mean ± *SD* or %	p value
Age, years	74.3 ± 5.8	74.0 ± 5.6	.11
Male	73	77	**.02**
CHA_2DS_2-VASc score	3.7 ± 1.6	3.3 ± 1.6	**<.001**
CHA_2DS_2-VASc patients ≥ 2	94	89	**<.001**
HAS-BLED score	1.7 ± 0.9	1.5 ± 0.8	**<.001**
HAS-BLED patients ≥ 2	51	41	**<.001**
Comorbid conditions	N/%	N/%	
Persistent AF	751 (23)	252 (27)	**.009**
Paroxysmal AF	2528 (77)	679 (73)	**.009**
Hypertension	1051 (32)	197 (21)	**<.001**
Heart failure	1337 (41)	318 (34)	**<.001**
Renal failure/dialysis	198 (6)	26 (3)	**<.001**
Chronic lung disease	878 (27)	194 (21)	**<.001**
Prior AMI	892 (27)	185 (20)	**<.001**
Prior ischemic stroke	290 (9)	86 (9)	.70
Prior hemorrhagic stroke	14 (<1)	***	.07
Prior TIA	81 (3)	36 (4)	**.03**
Prior pulmonary embolism	129 (4)	34 (4)	.77
Prior peripheral embolism	77 (2)	17 (2)	.38

Note: Bold values indicate $p < .05$. Counts < 11 masked for privacy.

Abbreviations: AF, atrial fibrillation; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; LAACE, left atrial appendage clip exclusion; *SD*, standard deviation; TIA, transient ischemic attack.

TABLE 2 Unweighted and IPT-weighted comparison of resource use between CABG and CABG + LAACE at index and one-year

	Unweighted Mean ± *SD* or %			IPT-Weighted
Index outcome	**CABG** (N = 3279)	**CABG + LAACE** (N = 931)	**p value**	**p value**
Total inpatient days	10.9 ± 8.0	10.3 ± 6.4	**.01**	.63
ICU days	5.4 ± 6.8	5.1 ± 5.9	.18	.96
Operative mortality	5.3	5.2	.89	.31
Inpatient costs	$52,557 ± $37,734	$53,363 ± $30,224	.55	.13
Total resource use and admissions over 1 year	**N = 1796 Mean ± *SD* or %**	**N = 374 Mean ± *SD* or %**		
Patients with at least 1 hospital readmission	43.0	31.0	**<.001**	**<.001**
Inpatient days post index period through 1 year	7.2 ± 16.7	4.0 ± 9.6	**<.001**	**<.01**
Total inpatient costs	$65,469 ± $60,373	$60,849 ± $46,891	.11	.74
Total outpatient costs	$17,167 ± $53,846	$12,205 ± $36,975	**.05**	.90
Total inpatient and outpatient costs	$82,637 ± $83,441	$73,055 ± $62,145	**<.001**	.77

Note: Bold values indicate $p < .05$.

Abbreviations: CABG, coronary artery bypass grafting; ICU, intensive care unit; IPT, inverse probability weighting; LAACE, left atrial appendage clip exclusion.

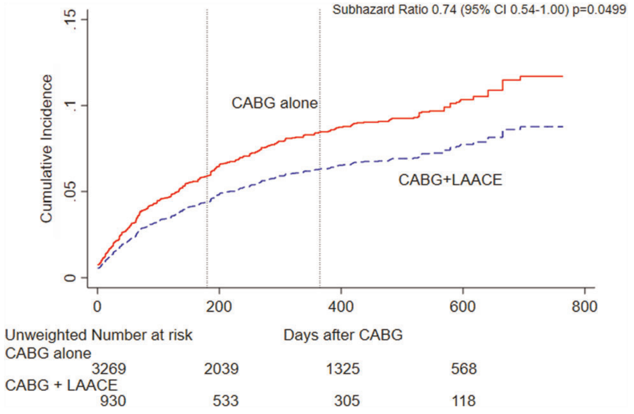

FIGURE 2 Adjusted cumulative risk of thromboembolism over time. Confidence intervals in Table S9. CABG, coronary artery bypass grafting; LAACE, left atrial appendage clip exclusion

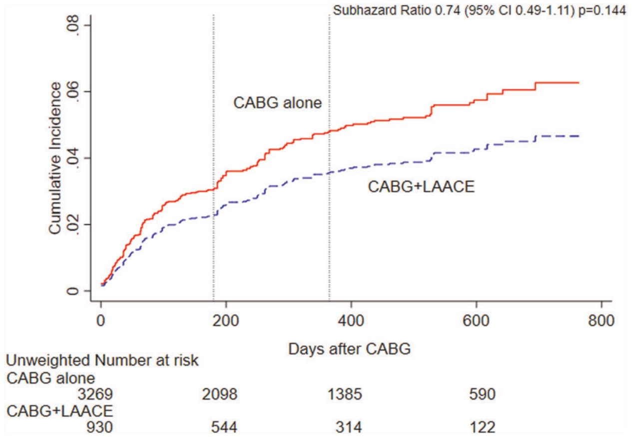

FIGURE 3 Adjusted cumulative risk of ischemic stroke over time. Confidence intervals in Table S10. CABG, coronary artery bypass grafting; LAACE, left atrial appendage clip exclusion

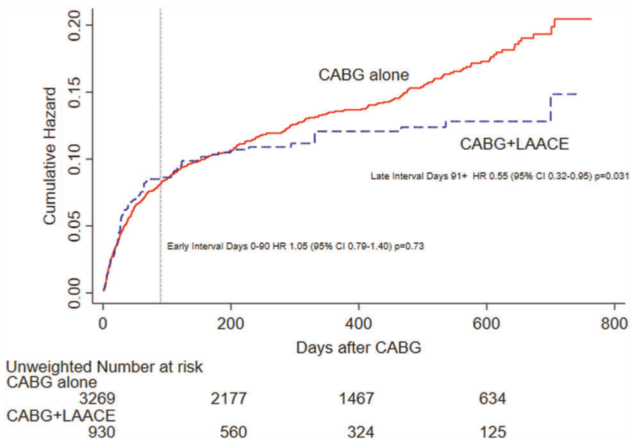

FIGURE 4 Adjusted Nelson–Aalen IPT-weighted cumulative hazard of all-cause mortality over time. Values less than 0.20 are indistinguishable from cumulative incidence. Confidence intervals in Table S11. CABG, coronary artery bypass grafting; LAACE, left atrial appendage clip exclusion

These results are consistent with previous findings of surgical LAA exclusion reported by others. Following baseline adjustment, 10,524 Medicare beneficiaries with various types of cardiac surgical procedures with concomitant LAA exclusion had a significantly lower rate of thromboembolism (sHR 0.67; 95% CI, 0.56–0.81; $p < .001$) and all-cause mortality (HR 0.88; 95% CI, 0.79–0.97; $p = .001$) compared with matched patients with various types of cardiac surgeries without surgical LAA exlcusion.[20]

Similarly, in a recent administrative claims study with propensity matched AF patients undergoing cardiac surgery ($n = 8590$) the risk of stroke was 1.14 versus 1.59 events per 100 person-years (HR, 0.73, $p = .003$) and risk of mortality was 3.01 versus 4.30 events per 100 person-years (HR, 0.71, $p < .001$) in patients who had any type of surgical left atrial appendage management compared with those who did not.[21] Our results are similar in that ischemic stroke was a major contributor to thrombogenic events and probably mortality risk, and excluding the LAA appears to offer protection against future stroke risk. Our results suggest that CABG + LAACE patients demonstrated a significant thromboembolism and mortality risk reduction compared to patients undergoing isolated CABG. One recent study did not find benefit of surgical LAA exclusion with concomitant surgery, but these patients did not present with preoperative AF.[22]

In addition to large registries, other studies report benefits of surgical LAA exclusion. A meta-analysis with AF patients undergoing cardiac surgery found stroke incidence to be reduced in LAA exclusion patients at 30-day follow-up (odds ratio [OR] 0.46; $p = .005$) and at the latest follow-up (OR 0.48; $p = .01$) compared with the group without LAA exclusion.[19] Incidence of all-cause mortality was significantly decreased with LAA exclusion (OR 0.38; $p = .0003$), while postoperative AF and reoperation for bleeding was comparable.[23]

One additional consideration is the impact of surgical ablation for AF in combination with surgical LAACE. Patients with surgical AF ablation were excluded in the current study. However, clinical practice guidelines from the STS have Level I recommendations for the treatment of AF concomitantly with cardiac surgery, and substantial evidence exists on the symptom reduction and mortality benefit of surgical ablation.[8,14,24] It is likely that the addition of surgical ablation with LAACE would have had an additive effect to clinical outcome, but the current study did not assess the additive impact of surgical ablation.

Oral anticoagulation (OAC) may have had an effect on the current study results. The presence of AF and the absence of concomitant AF ablation most likely increased the likelihood of patients in both study arms remaining on OACs. A recent cohort analysis observed that approximately 60% of patients remained on OAC after concomitant surgical LAA management.[20] The same study demonstrated that surgical LAA management when compared with no-LAA management was associated with a lower risk of thromboembolism among patients discharged without anticoagulation (sHR, 0.26; 95% CI, 0.17–0.40; $p < .001$), but not among patients discharged with anticoagulation (sHR, 0.88; 95% CI 0.56–1.39; $p = .59$). However, additional prospective, controlled studies are needed to better understand the effect or LAACE in presence or absence of OACs.

Another significant finding from the current study is the impact of surgical LAACE on hospital economics. After reviewing 29 cost centers from the index procedure, there were no differences in overall procedure costs, but operating room and supply costs were greater for surgical LAACE ($p < .0001$). Lower costs in other hospital cost centers explained the cost neutrality finding. During follow-up there were no difference between groups in early readmit rates, but after 90 days there were more readmits and average days in hospital for the isolated CABG group. Following IPT-weighted adjustment, there was a small ($1501) nonsignificant difference in overall in/outpatient hospital costs in favor of CABG + LAACE over a 1-year period.

Because of the limited evidence on the benefit of surgical LAACE, societal recommendations have not been robust. Most recently, the 2019 ACC/AHA/HRS Focused Update on Guidelines for Management of Patients with Atrial Fibrillation (Class IIb, B-NR) updated the level of evidence for surgical LAACE from C to B-NR because of new evidence.[7] Our current study demonstrating the reduced risk of thromboembolic events associated with surgical LAACE in CABG patients with pre-existing AF adds to this body of evidence. Awaited are the results from Left Atrial Appendage Occlusion Study (LAAOS) III (NCT 01561651), a randomized study of 4700 AF patients with or without surgical LAA exclusion to assess the long-term rates of stroke or systemic arterial embolism, which will also likely have an impact when the treatment guidelines are revised.[25]

This study is subject to several limitations associated with all retrospective observational studies including selection bias. Though propensity score methods are effective at mitigating the impact of differences in the frequency of preoperative confounders, they may not entirely account for their severity. Randomized trials are needed to support the findings of this observational study and others with similar findings. Second, there was no documentation of OAC use in either group. Most likely both groups utilized OAC during follow-up, but it is unclear if use was greater in either group. Third, LAACE was examined in comparison to no concomitant intervention. Further studies should compare clip exclusion with other commonly used surgical LAA techniques, as closure rates and efficacy could vary. In addition, by excluding any patient who received a concomitant ablation, this study cannot comment on the cumulative effect of LAACE and ablation and whether the addition of LAACE to CABG with ablation would be any more effective than CABG with ablation along without LAACE. Lastly, the cohort were older Medicare beneficiaries, with many comorbidities. These results may not be generalizable to younger, less sick patients.

5 | CONCLUSION

In conclusion, CABG + LAACE showed a significant decrease in thromboembolic event rate, fewer hospital readmits and lower all-cause mortality in Medicare beneficiaries with AF compared with isolated CABG patients in a real-world setting. Treatment costs over time were similar between groups suggesting CABG + LAACE is a cost-effective treatment strategy. These findings suggest that clip exclusion of the LAA during cardiac surgery may provide protective benefit in patients with pre-existing AF. Additional randomized trials should be completed to verify these findings.

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CONFLICT OF INTERESTS

Dr. Gillinov: consultant, AtriCure, Medtronic, Edwards Lifesciences, Abbott, CryoLife, and ClearFlow. Dr. Anderson: company received funding from AtriCure to support statistical analysis hours and data access fees. Dr. Ferguson: employee of AtriCure, stock ownership. Dr. Soltesz and Dr. Dewan: none

AUTHOR CONTRIBUTIONS

Edward G. Soltesz, Krish C. Dewan, A. Marc Gillinov, and Michael A Ferguson developed the study concept. Michael A Ferguson supported funding of work. Louise H. Anderson acquired data and performed analysis. All authors helped craft and critically revise the manuscript. All authors approved the final version of the manuscript and can be held accountable for the integrity of the work.

DATA AVAILABILITY STATEMENT

The initial data files that support the findings of this study period are openly available from CMS at https://www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/LimitedDataSets/StandardAnalyticalFiles. Restrictions apply to the availability of analysis files created from the initial CMS files due to data use agreements with CMS.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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