Meta-Analysis Evaluating Outcomes of Surgical Left Atrial Appendage Occlusion During Cardiac Surgery

Abdisamad M. Ibrahim, MD[a,*], Nitin Tandan, MD[a], Cameron Koester, DO[a], Mohammad Al-Akchar, MD[a], Bishal Bhandari, DO[a], Albert Botchway, PhD[b], Jumana Abdelkarim, MD[a], Ruby Maini, MD[a], and Mohamed Labedi, MD[c]

Surgical left atrial appendage occlusion (S-LAAO) has become a common procedure performed in patients undergoing cardiac surgery; however, evidence to support this procedure remains inconclusive. This meta-analysis aims to assess the efficacy of S-LAAO in terms of ischemic stroke, postoperative atrial fibrillation, and all-cause mortality. A thorough literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. We identified 10 relevant studies for our meta-analysis. It included 6,779 patients who underwent S-LAAO and 6,573 who did not undergo LAAO. In terms of ischemic stroke, the S-LAAO cohort had a lower events (pooled odds ratio [OR] 0.655 (0.518 to 0.829), p = 0.0004) compared with the non-LAAO cohort. S-LAAO cohort also had lower events of all-cause mortality (pooled OR 0.74 (95% confidence interval 0.55 to 0.99), p = 0.0408) when compared with the non-LAAO cohort. In regards to postoperative atrial fibrillation, there was no difference between the 2 groups (pooled OR 1.29 (95% confidence interval 0.81 to 2.06), p = 0.2752). In conclusion, S-LAAO was associated with lower events of ischemic stroke or systemic embolism and all-cause mortality when compared to the non-LAAO group. **(Am J Cardiol 2019;124:1218−1225)**

Left atrial appendage (LAA) has a high propensity for thrombus formation in patients with atrial fibrillation (AF) and mitral valve disease.[1] The pathogenesis of left atrial thrombus formation is not well elucidated, but it is thought that the relative stasis that occurs in the LAA during AF leads to thrombus formation. Approximately 90% of left atrial thrombi are found in the LAA.[1] Thrombi in the left atrial appendage account for the majority of cardioembolic strokes in AF.[2] In addition, many patients may have some form of contraindication or limitation to anticoagulation, including personal history of bleeding, nonadherence, or they wish to avoid anticoagulation. Therefore, surgical occlusion of the LAA is often performed as an adjunct procedure in patients who underwent cardiac surgery in order to reduce the risk of thromboembolic events.

The data about the effectiveness of surgical left atrial appendage occlusion (S-LAAO) is limited. Postoperative AF is a well-known complication of cardiac surgery and carries a significant risk of thromboembolic events[3]; thus, any residual communication between the LAA and the left atrium has the potential to increase the risk of cerebrovascular events.[4] In a recent study, S-LAAO was noted to be associated with reduced risk of stroke and mortality.[2] S-LAAO was also found to have high rates of AF related outpatient visits and hospitalizations compared with non-LAAO, in propensity score-matched patients.[2] Although different studies have been performed to evaluate the success of LAAO,[5−12] the power of these studies by themselves are too low to generalize to a large population. The question with respect to S-LAAO becomes how it affects a patient's likelihood of experiencing a stroke, developing AF, or even causing death.

The safety of utilizing S-LAAO as a means of primary prevention for ischemic stroke in patients with AF remains equivocal. This meta-analysis aims to assess the efficacy of S-LAAO in terms of ischemic stroke or systemic embolism, postoperative AF, and all-cause mortality.

Methods

A thorough publication review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement utilizing electronic bibliographic databases including Cochrane Central Register of Controlled Trials, Google Scholar, MEDLINE, PubMed publisher, and Web of Science. To ensure that our search was comprehensive, we utilized multiple search key terms and all synonyms including: "left atrial appendage", "atrial appendage occlusion", "cardiac surgery". The bibliography section of selected studies, as well as previously published review articles and meta-analyses, were manually searched for additional publications that were not initially identified on preliminary search. The abstracts were subsequently screened to identify select manuscripts for full text review and inclusion in this meta-analysis.

Studies were included that compared all forms of cardiac surgery performed with or without left atrial appendage

[a]Department of Internal Medicine, SIU School of Medicine, Springfield, Illinois; [b]Center for Clinical Research, SIU School of Medicine, Springfield, Illinois; and [c]Division of Cardiology, Department of Internal Medicine, SIU School of Medicine, Springfield, Illinois. Manuscript received May 26, 2019; revised manuscript received and accepted July 18, 2019.

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*Corresponding author: Tel: (217) 545-8000.

E-mail address: Aibrahim0912@gmail.com (A.M. Ibrahim).

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occlusion. Additionally, to be included in our meta-analysis, articles had to be published in a peer-reviewed journal and written in English. To ensure studies included in this meta-analysis were applicable to current practice and utilized the most current procedural techniques, we included studies conducted between January 2000 and March 2019 (Figure 1). All of the identified articles were independently reviewed by the investigators for outcomes including ischemic stroke or systemic embolism, postoperative AF, and all-cause mortality. Studies that did not include these outcomes were excluded from this meta-analysis. Abstracts without full text publications were also excluded. Previously published meta-analyses, studies from the national inpatient sample, and STS registry were excluded to avoid evaluation of duplicate data. Final decisions regarding a studies inclusion or exclusion from this meta-analysis were made by consensus of all involved investigators.

The meta-analysis was conducted using studies that reported number of events and the total sample for both S-LAAO and non-LAAO cohorts. Studies that had no events were excluded. Random effects were used to pool the odds ratios (OR) and confidence intervals (CI) using the DerSimonian and Laird method.[13] Statistical analysis was conducted using StatsDirect software, England.[14]

Results

Ten studies were included in our meta-analysis (Table 1). Out of 13,352 patients included in the study, 6,779 of them received S-LAAO while the remaining 6,573 were in the non-LAAO cohort. The cardiac surgery varied widely between patients and they included (coronary artery bypass graft, mitral valve, or aortic valve repair). The method of the surgical technique for LAAO varied between studies. The latest follow up ranged from 1 month to 9 years.

The S-LAAO group was associated with a reduced risk of stroke (pooled OR 0.655 [0.518 to 0.829], p = 0.0004) compared with the non-LAAO group (Figure 2). Incidence

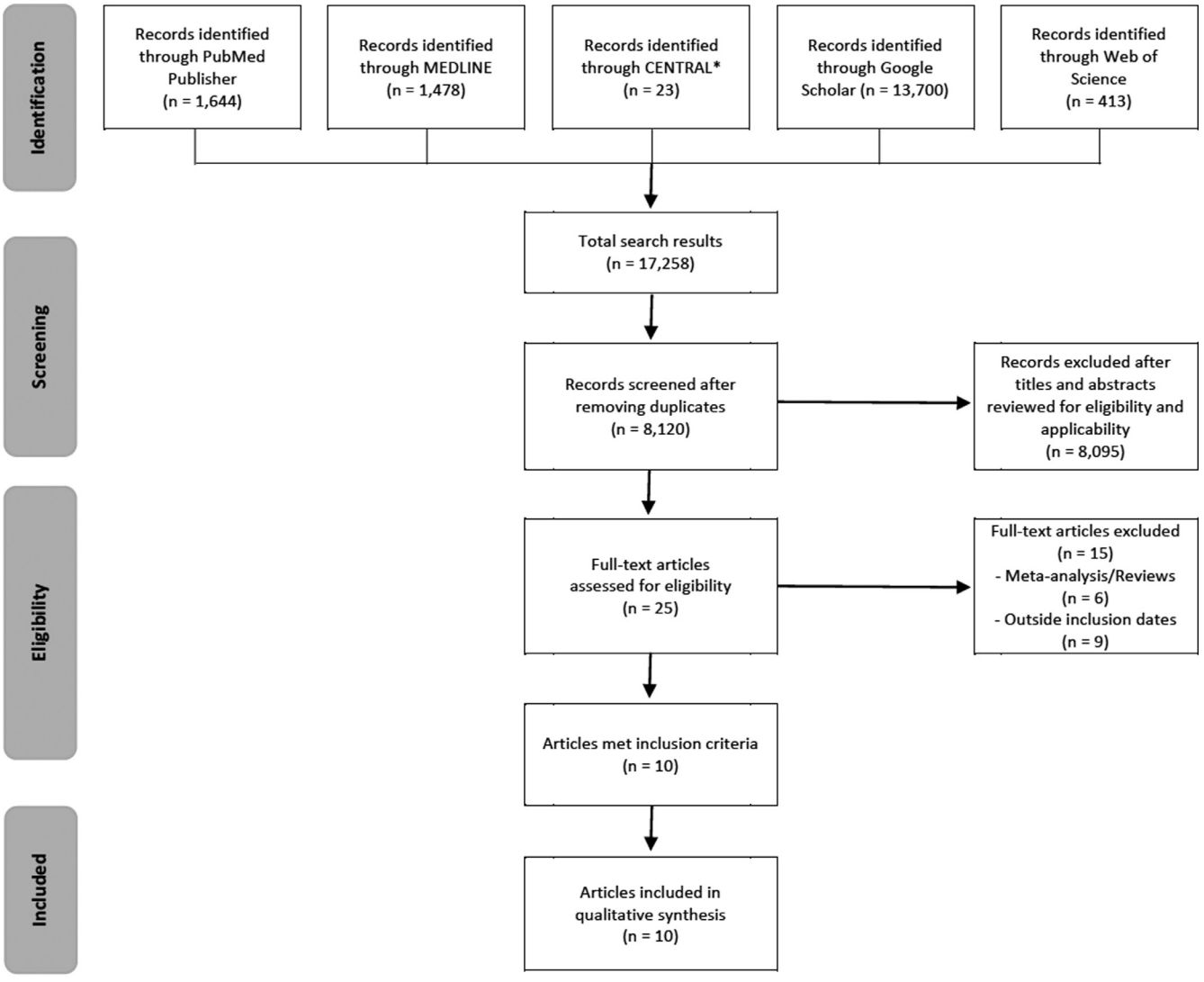

Figure 1. Literature search process outlined according to preferred reporting items of systematic review and meta-analysis flow diagram.

Table 1
Baseline characteristics of included studies

Authors	Year	Sample size	**LAAO**	Non-LAAO	Cardiac surgery	Follow up (months)
Garcia-Fernandez	2003	205	**58**	147	Mitral valve surgery	69.4 +/− 67
Healey	2005	77	**52**	25	Coronary artery bypass grafting	13 +/− 7
Nagpal	2009	43	**22**	21	Mitral valve surgery	48
Kim	2013	2,067	**631**	631	Coronary artery bypass grafting, Valvular surgery	1
Whitlock	2013	51	**26**	25	Coronary artery bypass grafting, Valvular surgery	12
Zapolanski	2013	3,195	**808**	969	Coronary artery bypass grafting, Valvular surgery	1
Lee	2014	379	**119**	119	Mitral valve surgery	37.2 +/− 33.6
Melduni	2017	461	**461**	461	Coronary artery bypass grafting, Valvular surgery	109.2
Park-Hensen	2018	187	**86**	101	Coronary artery bypass grafting, Valvular surgery	44.4 +/− 19.2
Yao	2018	8,590	**4295**	4295	Coronary artery bypass grafting, Valvular surgery	25.2 +/− 22.8

MVS = mitral valve surgery; CABG = coronary artery bypass grafting; VS = valvular surgery.

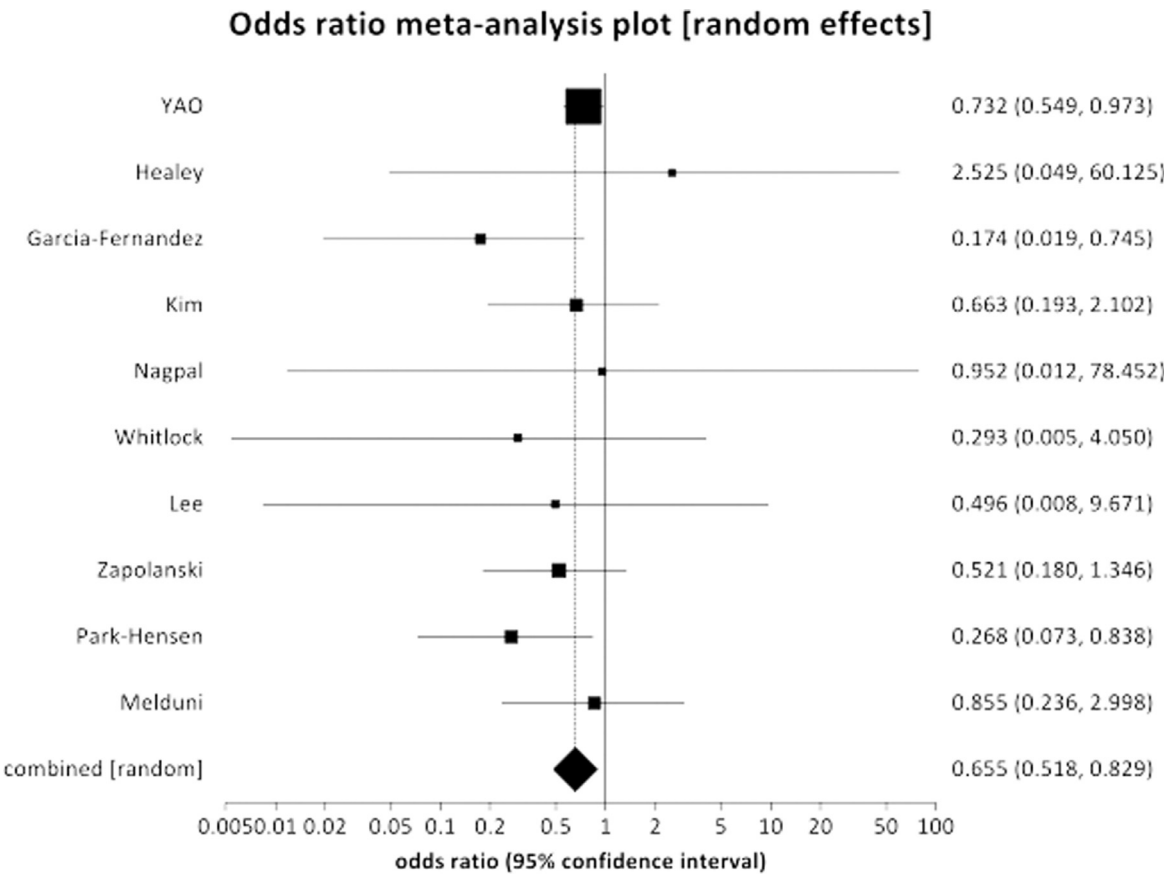

Figure 2. Forest plot of the odds ratio (OR) of ischemic stroke and systemic embolism in LAAO cohort versus non-LAAO cohort. The S-LAAO group has a lower OR for latest follow-up, (0.655 [0.518 to 0.829], p = 0.0004) compared with non-LAAO.

ratio was reported in the appendix and had similar outcomes (Appendix 1).

There was no difference of postoperative AF between S-LAAO and non-LAAO (pooled OR 0.1.29 [95% CI 0.81 to 2.06], p = 0.2752) (Figure 3). Incidence ratio was reported in the appendix and had similar outcomes (Appendix 2).

S-LAAO group was associated with reduced risk of all-cause mortality in terms of the (pooled OR 0.74 [95% CI 0.55 to 0.99], p = 0.0408) compared with the non-LAAO group (Figure 4). In terms of incidence ratio, there is a trend toward lower events in the S-LAAO cohort, but it was not statistically significant (pooled 0.76 [95% CI 0.57 to 1.00), p = 0.0493) (Appendix 3).

Heterogeneity was assessed using the I^2 statistic. The conventional threshold of <50% was used as an acceptable cut-off. Presenting the analyses that used ORs, all 3 outcomes were acceptable except for postoperative AF; ischemic stroke or systemic embolism I^2 0% (CI = 0% to 52.7%); postoperative AF I^2 94% (CI = 90.7% to 95.8%), all-cause mortality I^2 43.5% (CI = 0% to 76.1%). A visual inspection of bias using funnel plots shows that the plots are reasonably symmetrical in shape. To complement the

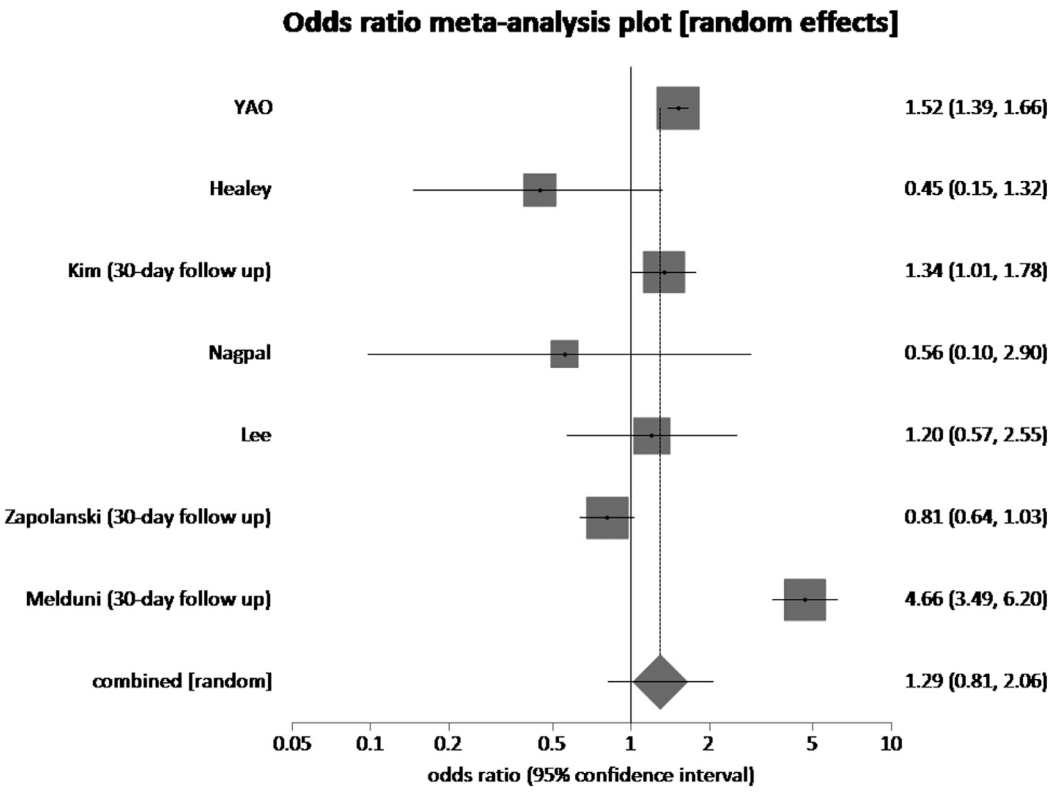

Figure 3. Forest plot of the odds ratio (OR) of postoperative AF in S-LAAO cohort versus non-LAAO cohort. There was no difference between the S-LAAO and non-LAAO group in terms of the OR 0.1.29 (95% CI 0.81 to 2.06), p = 0.2752.

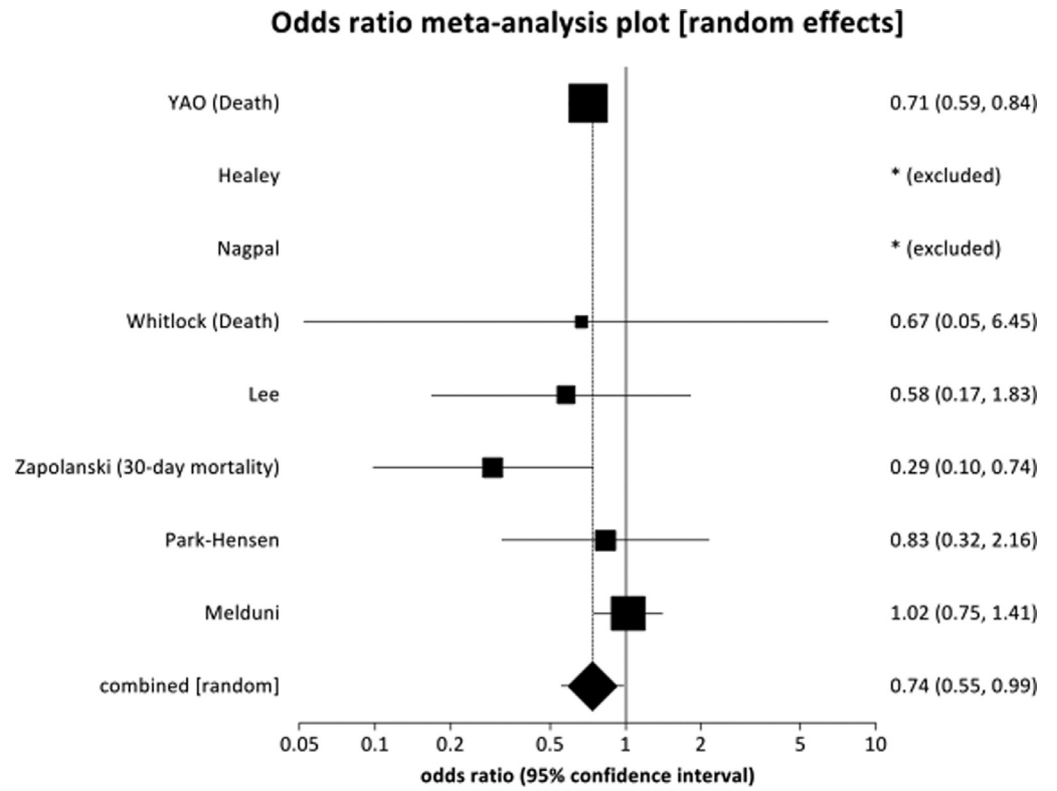

Figure 4. Forest plot of the odds ratio (OR) of all-cause mortality in S-LAAO cohort versus non-LAAO cohort. There is lower mortality in the S-LAAO group in terms of the OR, (0.74 [95% CI 0.55 to 0.99], p = 0.0408) compared with the non-LAAO.

funnel plots, we conducted Eggers and Harbord Eggers bias tests. Both tests were statistically nonsignificant indicating the absence of bias (Figures 5−7). Risk of bias was also assessed using the recommended Cochrane review qualitative guide. A risk of bias table, performed with the assistance of the ROBINS-I (2016) tool, shows low risk as per the analysis results with low-to-moderate risk of bias, which may be attributable to the selection of studies as specified in "Methods" (Appendix 4).[15]

Discussion

In the United States, the prevalence of AF is around 1%[16] and it continues to increase with time.[17,18] AF increases the risk of stroke, transient ischemic attack, and mortality.[19] Thrombi in the LAA accounts for the most of cardioembolic strokes in AF.[2] Therefore, surgical occlusion of the LAA has been proposed to decrease the risk of stroke, systemic embolism, and all-cause mortality.[2] Given the limited data available regarding the effects of LAAO on these outcomes, this meta-analysis was performed to assess the clinical significance of LAAO during routine cardiac surgery.

Previous studies have shown different results in terms of the incidence of stroke with S-LAAO.[20] In this meta-analysis, lower incidence and OR of ischemic stroke were observed in the S-LAAO group compared with the non-LAAO group. These findings have been seen in many studies that included stroke as an outcome as well as a previous meta-analysis comparing S-LAAO versus non-LAAO.[21] However, our study included a larger sample size compared with the previous meta-analysis and with a larger sample size, the CIs of the data assessed were narrower. Since 90% of left atrial thrombi are found in the LAA, exclusion from the systemic circulation should reduce the incidence of ischemic stroke or systemic embolism.[4] With consideration that less than 50% of patients adhere to the prescribed anticoagulation regimen, S-LAAO may be an option as intervention that would reduce the risk of ischemic stroke.[22] In the 2016 ESC/EACTS guidelines, it was recommended to continue anticoagulation post S-LAAO in AF patients for stroke prevention (Class 1B).[23]

S-LAAO also had lower events of all-cause mortality when compared with the non-LAAO group, in terms of the OR. Although reviewing the incidence ratios, there is a trend toward lower mortality events in the S-LAAO cohort, but it was not statistically significant. Yao et al and Zapolanski et al studies have shown mortality benefit.[2,7] In contrast, Whitlock et al, Lee et al, Park-Hensen et al, and Melduni showed no significant difference in mortality between the S-LAAO and non-LAAO groups.[4,6,11,12] Most complications from the S-LAAO were associated with incorrect or incomplete S-LAAO.[6,24] The results of this meta-analysis showed that S-LAAO is at least comparable, if not beneficial, in terms of all-cause mortality. Thus, it supports the safety of performing S-LAAO in patients undergoing cardiac surgery.

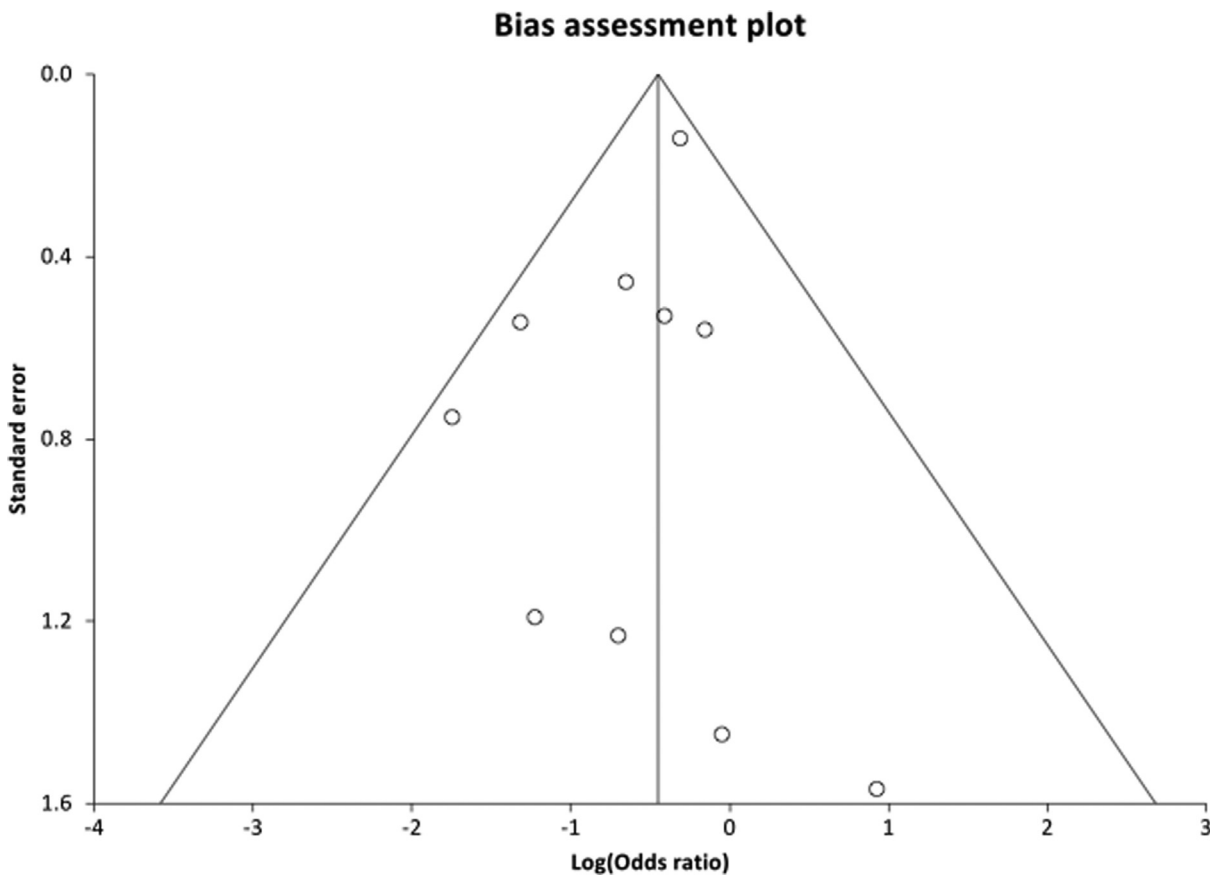

Figure 5. Funnel plot for ischemic stroke or systemic embolism (Odd ratio analysis). Egger: bias = −0.508 (95% CI −1.499 to 0.483), p = 0.2712 Harbord-Egger: bias = −0.421 (92.5% CI −1.370 to 0.528), p = 0.3906.

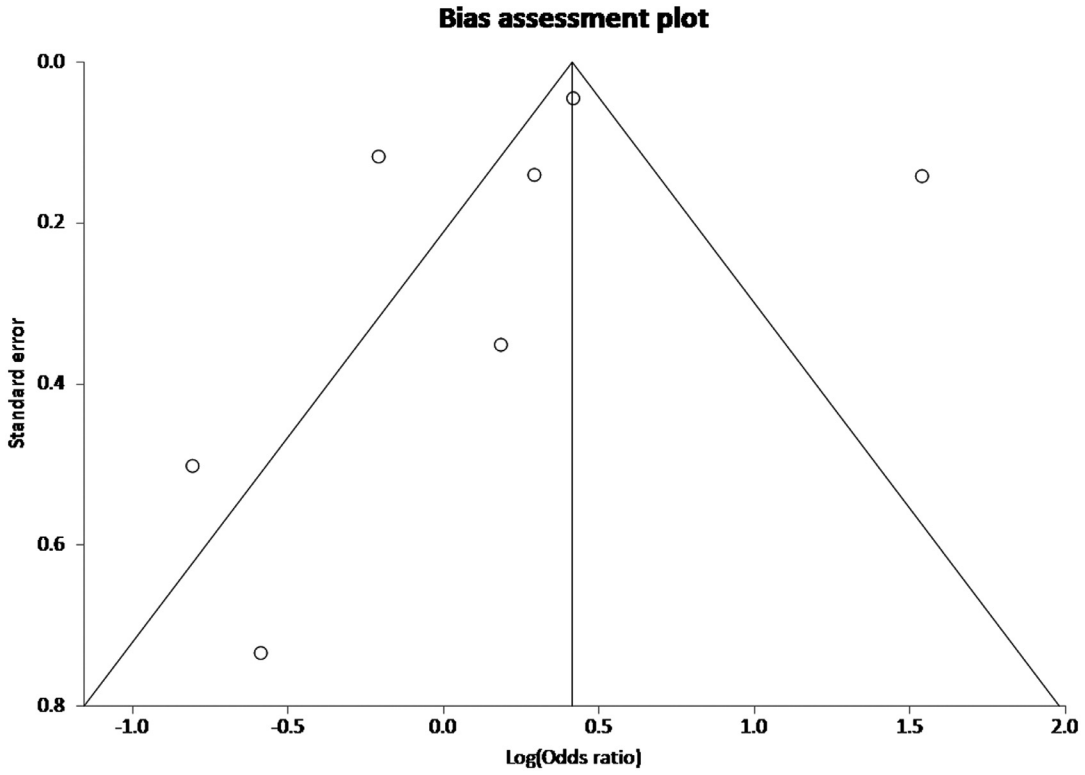

Figure 6. Funnel plot for postoperative atrial fibrillation (Odds ratio analysis). Egger: bias = −0.77 (95% CI −7.17 to 5.63), p = 0.7697. Harbord-Egger: bias = −0.872 (92.5% CI −6.521 to 4.777), p = 0.7433.

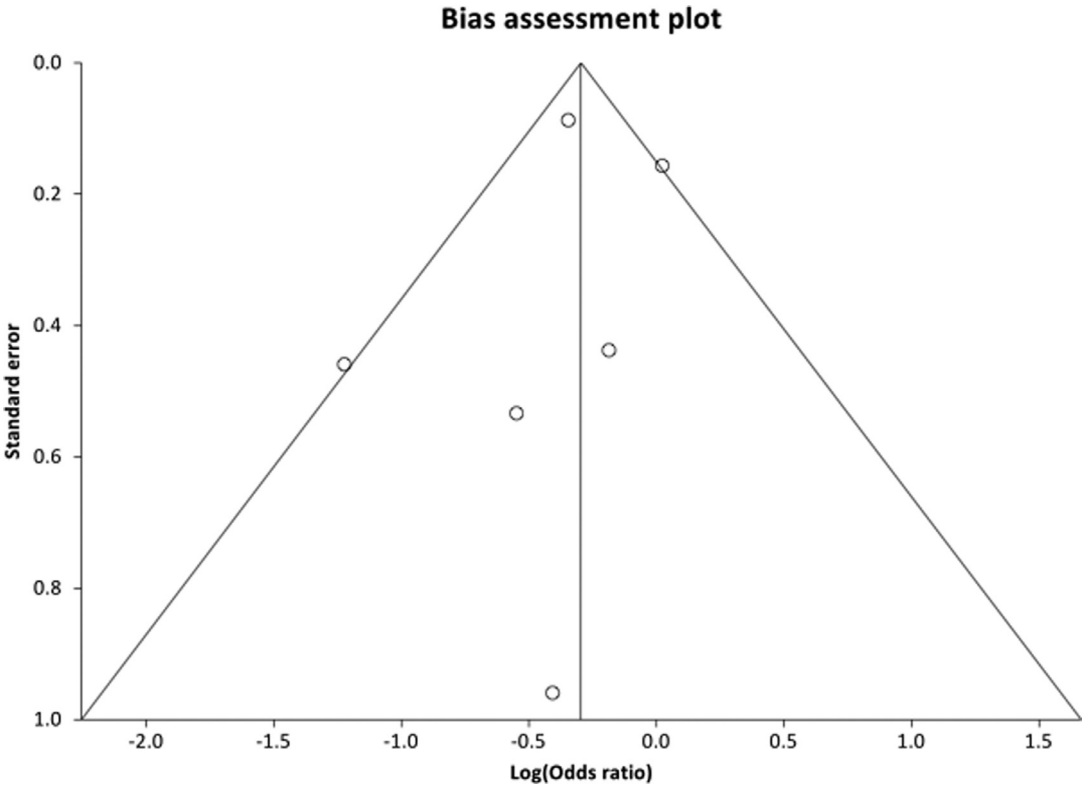

Figure 7. All-cause mortality (Odds ratio analysis) Egger: bias = −0.429 (95% CI −2.924 to 2.065) P = 0.6575 Harbord-Egger: bias = −0.387 (92.5% CI −2.588 to 1.815), p = 0.6959.

In regards to postoperative AF, there was no difference between the S-LAAO and non-LAAO groups. The incidence of postoperative AF postcardiac surgery is estimated to be 30% to 40%.[25–27] Melduni et al showed that S-LAAO was associated with an increased risk of postoperative AF, after adjusting for confounders.[4] Risk factors that were associated with postoperative AF were increased age or previous history of AF, whereas antiarrhythmic drugs were seen as protective.[4]

One major question that may influence whether or not S-LAAO should be performed during cardiac surgery is, if specific surgical techniques can influence morbidity and mortality. Though S-LAAO provides theoretical protection from thrombus formation, surgical occlusion is often ineffective in eliminating the communication between the LAA and the left atrium. Multiple studies have shown that a significant percentage of patients have residual flow between the appendage and the atrium visualized on postprocedure transesophageal echocardiogram.[5,8] A study performed by Katz et al demonstrated a proportion of 22% of embolic events in 36% of in-patients with incomplete LAA ligation during cardiac surgery.[28] In contrast, as study performed by Garcia-Hernandez showed incomplete LAA ligation in approximately 10% of patients with one known embolic event postcardiac surgery.[5] The reported difference in the outcomes was purported to be secondary to techniques of the S-LAAO. Since the theoretical risk of subsequent thromboembolic events increases with failed S-LAAO, further evidence is needed to identify the most effective mode of S-LAAO. Although surgical techniques still remain a question mark, greater experience with the surgery can lead to safer patient outcomes.[8]

There are several limitations to consider when analyzing the results of this meta-analysis. First, there are variations of surgical techniques when it comes to S-LAAO. Some studies have used double ligation with sutures, whereas others have used stapler closure, epicardial clip, or resection of the LAA. Second, the successful closure of the LAA varies between different techniques. It was reported that 40% of S-LAAO might be incomplete at the time of follow up.[21] Given the uncertainty of successful closure of the LAA between different surgical techniques, further studies are needed to address this issue. Third, it is not well documented if S-LAAO adds significant operation time to the planned procedure and how that affects the outcome. Fourth, there were only 3 randomized control trials with small sample sizes in this meta-analysis.

In conclusion, S-LAAO has shown to be an effective technique in preventing ischemic stroke or systemic embolism and all-cause mortality when compared with the non-LAAO cohort. Further randomized trials are needed with long-term follow-up to evaluate the clinical benefits of LAAO.

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Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.032.

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