ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2018 November 26; 10(11): 191-249

Published by Baishideng Publishing Group Inc

W J C
World Journal of
Cardiology

Contents

Monthly Volume 10 Number 11 November 26, 2018

ABOUT COVER

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AIM AND SCOPE

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJC covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, nursing, and health promotion. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJC*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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World Journal of Cardiology (*WJC*) is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

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NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORIAL BOARD MEMBERS
All editorial board members resources online at http://www.wjgnet.com/1949-8462/editorialboard.htm

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PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
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PUBLICATION DATE
November 26, 2018

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Cardiology

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World J Cardiol 2018 November 26; 10(11): 242-249

DOI: 10.4330/wjc.v10.i11.242

ISSN 1949-8462 (online)

META-ANALYSIS

Surgical left atrial appendage occlusion during cardiac surgery: A systematic review and meta-analysis

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Supported by no external funding. Dr. Benditt is supported in part by a grant from the Dr. Earl E Bakken family in support of heart-brain research.

Author contributions: Atti V, Anantha-Narayanan M contributed equally to this work and performed the analysis. Turagam MK designed the research. Koerber S, Rao S, Viles-Gonzalez JF, Suri R, Velagapudi P, Lakkireddy D and Benditt DG supervised the research. All the authors had role in writing the manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Manuscript source: Invited Manuscript

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Received: August 9, 2018
Peer-review started: August 9, 2018
First decision: August 24, 2018
Revised: September 8, 2018
Accepted: October 12, 2018
Article in press: October 12, 2018
Published online: November 26, 2018

Abstract

AIM

To evaluate the safety and efficacy of surgical left atrial appendage occlusion (s-LAAO) during concomitant cardiac surgery.

METHODS
We performed a comprehensive literature search through May 31st 2018 for all eligible studies comparing s-LAAO *vs* no occlusion in patients undergoing cardiac surgery. Clinical outcomes during follow-up included: embolic events, stroke, all-cause mortality, atrial fibrillation (AF), reoperation for bleeding and postoperative complications. We further stratified the analysis based on propensity matched studies and AF predominance.

RESULTS
Twelve studies (n = 40107) met the inclusion criteria. s-LAAO was associated with lower risk of embolic events (OR: 0.63, 95%CI: 0.53-0.76; P < 0.001) and stroke (OR: 0.68, 95%CI: 0.57-0.82; P < 0.0001). Stratified analysis demonstrated this association was more prominent in the AF predominant strata. There was no significant difference in the incidence risk of all-cause mortality, AF, and reoperation for bleeding and postoperative complications.

CONCLUSION
Concomitant s-LAAO during cardiac surgery was associated with lower risk of follow-up thromboembolic events and stroke, especially in those with AF without significant increase in adverse events. Further randomized trials to evaluate long-term benefits of s-LAAO are warranted.

Key words: Left atrial appendage; Left atrial appendage occlusion; Embolic events; Stroke; Adverse events

Core tip: Surgical left atrial appendage occlusion (s-LAAO) is performed during cardiac surgeries in patients with atrial fibrillation. However, evidence to perform routinely during cardiac surgeries is conflicting and contrasting. It is currently given a class Ⅱb recommendation in the professional medical society guidelines. We sought to perform a meta-analysis of all the studies published to date to evaluate the safety and efficacy of s-LAAO.

Atti V, Anantha-Narayanan M, Turagam MT, Koerber S, Rao S, Viles-Gonzalez JF, Suri RM, Velagapudi P, Lakkireddy D, Benditt DG. Surgical left atrial appendage occlusion during cardiac surgery: A systematic review and meta-analysis. *World J Cardiol* 2018; 10(11): 242-249 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i11/242.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i11.242

INTRODUCTION

The left atrial appendage (LAA) is considered to be the dominant source of embolism (> 90%) in patients with non-valvular atrial fibrillation (AF)[1]. Occlusion or resection of the left atrial appendage occlusion (LAAO) remains an important intervention for prevention of recurrent emboli in patients who are at risk of stroke. LAAO provides an opportunity to avoid systemic anti-coagulation, thereby minimizing the risk of bleeding.

Surgical LAAO (s-LAAO) usually involves LAA closure while performing other cardiac surgeries. With the increasing prevalence of AF[2], there is a growing interest in the surgical community for s-LAAO. Prior studies assessing the clinical impact of surgical occlusion of the LAA during cardiac surgery have shown contradictory results[3-14]. Furthermore, there are no large scale randomized controlled trials evaluating routine s-LAAO during cardiac surgery. Therefore s-LAAO remains a class IIb recommendation in professional medical society guidelines[15,16]. Despite this recommendation, s-LAAO is routinely performed in patients with AF undergoing cardiac surgery. Therefore, we sought to perform a meta-analysis of the available studies published to date to evaluate the safety and efficacy of concomitant s-LAAO *vs* no occlusion during cardiac surgery[3,4,6-14].

MATERIALS AND METHODS

Search strategy

The systematic review and meta-analysis was done in compliance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines[17]. The PRISMA checklist is presented in Supplementary Table 1. The initial search strategy was developed by two authors (V.A and M.A.N). We performed a systematic search, without language restriction, using PubMed, EMBASE, SCOPUS, Google Scholar, and ClinicalTrials.gov from inception to May 31st, 2018 for studies comparing s-LAAO *vs* no occlusion- only in patients undergoing concomitant cardiac surgery. We used the following keywords and medical subject heading: "Cardiac surgeries" OR "Heart surgeries" OR "Cardiac surgical procedures" AND "Left atrial appendage" OR "occlusion" OR "ligation" OR "resection" OR "excision" OR "amputation".

Study selection and data extraction

Only studies comparing s-LAAO *vs* no occlusion during any cardiac surgery were included in our analysis. The reference lists of original studies, conference abstracts and relevant review articles were further reviewed. Two investigators (V.A and M.A.N) independently performed the literature search, reviewed the originally identified titles and abstracts and selected studies for pooled analysis based on the inclusion criteria. Any divergence was resolved through discussion with a third independent reviewer (M.K.T). The quality of observational studies was assessed using the Newcastle Ottawa scale, Supplementary Table 2.

Clinical outcomes

We evaluated the following clinical outcomes during follow-up in each report: (1) embolic events; (2) stroke; (3) all-cause mortality; (4) AF; (5) postoperative complications; and (6) reoperation for bleeding. We further performed stratified meta-analysis to evaluate the potential source of heterogeneity across the included studies. Stratification factors are inclusion of only propensity matched studies and studies with AF predominant cohort (> 50% of study population having AF). The ischemic events attributed to embolic causes in the included studies were included in the embolic events. Complications included in the analysis are appendage tears, myocardial infarction, major bleeding, septicemia, pacemaker implants, renal failure, pericardial effusion, cardiac tamponade, and stroke.

Statistical analysis

The meta-analysis was done using Review Manager (RevMan), Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014. Due to methodological and clinical heterogeneity between the included studies, a random-effects model estimating the odds ratio (OR) and the estimated 95% confidence interval (CI) of the above-mentioned outcomes were used. The OR estimate of each study was calculated by the random-effects model obtained by the DerSimonian-Lariad method[18].

Heterogeneity was assessed using Higgins' and Thompson's I2 statistic, with I2 values of > 50% was considered significant. Publication bias was visually estimated by funnel plots. A 2-tailed $P < 0.05$ was considered statistically significant for all analyses.

RESULTS

Search results

A total of 1328 reports were retrieved during the initial search (Supplementary figure 1). 1049 reports were selected after removing 279 duplicates. 387 reports were screened and 354 were excluded. 33 reports were assessed for eligibility. Finally, after excluding 21 reports (no comparison groups-14, others-7) 12 studies were included. Among these 12 studies, three were randomized controlled trials (RCTs) and nine were observational studies. Among these nine observational studies, four were propensity matching studies[5,6,10,13]. one was case matching study[12]. The inter-reviewer agreement on study eligibility was 100%.

Study characteristics

The characteristics of the included studies are presented in Table 1 and Table 2. Out of 40107 patients included, 13535 patients received s-LAAO during cardiac surgery while the remaining 26572 patients did not receive s-LAAO. The mean (SD) age of the study population ranged from 50.7 (12.4) years to 77.4 (6.8) years. The primary cardiac operation varied widely. The surgical procedures were primarily valve surgery in the studies by Garcia-Fernandez, Nagpal, Lee and Elbadawi[3,5,8,12], while they were primarily coronary artery bypass grafting (CABG) in the studies by Healey, and Elbadawi[7,11]. Remaining studies included a combination of valve surgery and CABG. Lee *et al*[5] also performed ablation of AF together with mitral valve surgery. The prevalence of AF varied in the study cohorts. The s-LAAO techniques varied; the methods variously included double suturing, exclusion, amputation, resection and stapling (Table 2). The follow-up period ranged from in-hospital only to 109.2 mo.

Clinical outcomes

s-LAAO was associated with lower risk of embolic events (OR: 0.63, 95%CI: 0.53-0.76; $P < 0.001$) and a lower risk of stroke (OR: 0.68, 95%CI: 0.57-0.82; $P < 0.0001$) (Figure 1A and 1B). There was no significant difference in all-cause mortality between the two groups (OR: 0.83, 95%CI: 0.51-1.36; $P = 0.46$) (Figure 1C). There was no significant difference in the incidence of follow-up AF between the two groups (OR: 1.41, 95%CI: 0.79-2.52, $P = 0.24$) (Figure 1D).

With regard to postoperative complications, there was no significant difference between the groups (OR: 1.44, 95%CI: 0.91-2.25; $P = 0.12$) (Figure 1F). Similarly, there was no significant difference in the incidence of reoperation for bleeding between the two groups (OR: 0.98, 95%CI: 0.57-1.69; $P = 0.94$) (Figure 1G).

Test of heterogeneity and publication bias

Test of heterogeneity was not significant for follow-up embolic events (*P* heterogeneity = 0.60, I2 = 0%) and stroke ($P = 0.84$, I2 = 0%), while it was significant for all-cause mortality ($P < 0.001$, I2 = 92%), AF ($P < 0.001$, I2 = 95%), postoperative complications ($P = 0.004$, I2 = 66%) and reoperation for bleeding ($P = 0.20$, I2 = 36%).

Subgroup analysis

In subgroup analysis including only propensity matched studies, s-LAAO group had a trend towards lower risk of stroke (OR: 0.78, 95%CI: 0.60-1.00; $P = 0.05$), Supplementary Figure 2A. Test of heterogeneity was not significant ($P = 0.63$, I2 = 0%). There was no significant difference in the incidence of all-cause mortality (OR: 1.10, 95%CI: 0.34-3.60; $P = 0.87$), Supplementary Figure 2B**.** In subgroup analysis including only AF predominant studies (> 50%), s-LAAO was associated with lower risk of stroke (OR: 0.60, 95%CI: 0.46-0.78; $P = 0.0002$) (Supplementary Figure 3A). There was no significant difference in all-cause mortality (OR: 0.87, 95%CI: 0.11-7.12; $P = 0.89$) (Supplementary Figure 3B). Test of heterogeneity was not significant for stroke ($P = 0.86$, I2 = 0%) while it was significant for all-cause mortality ($P < 0.001$, I2 = 94%).

Funnel plot for visual inspection of publication bias is shown in Supplementary Figure 4.

DISCUSSION

The main findings of our meta-analysis of patients un-

Table 1 Characteristics of the included studies

Study, yr	Country	Study period	Study design	Sample size		Cardiac surgery type	Follow up period (mo)
				s-LAAO	No occlusion		
García-Fernández *et al*, 2003[3]	Spain	2003	retrospective	58	147	MVS	69.4 ± 67
Healey *et al*, 2005[7]	Germany	2001-2002	RCT	52	25	CABG	13 ± 7
Nagpal *et al*, 2009[8]	Canada	2007-2007	RCT	22	21	MVS	<1
Whitlock *et al*, 2013[9]	Canada	2009-2010	RCT	26	25	CABG and VS	1
Zapolanski *et al*, 2013[4]	United States	2005-2012	retrospective	808	969	CABG and VS	NR
Kim *et al*, 2013[6]	United States	2001-2010	retrospective	631	631	CABG and MVS	1
Lee *et al*, 2014[1][5]	Korea	1999-2011	retrospective	119	119	MVS with AF ablation	63 ± 44
Melduni *et al*, 2017[1][10]	United States	2000-2005	prospective	461	461	CABG and VS	109.2
Elbadawi *et al*, 2017[2][11]	United States	1998-2013	retrospective	652	652	VS	In-hospital
Elbadawi *et al*, 2017[12]	United States	2004-2013	retrospective	2519	12595	CABG	In-hospital
Friedman *et al*, 2018[14]	United States	2011-2012	retrospective	3892	6632	CABG, MVS, AVS	31.2
Yao *et al*, 2018[1][13]	United States	2009-2017	retrospective	4295	4295	CABG, VS	25.2 ± 22.8

RCT: Randomized controlled trial; CABG: Coronary artery bypass grafting; VS: Valvular surgery; MVS: Mitral valve surgery; AVS: Aortic valve surgery; AF: Atrial fibrillation. [1]Propensity match studies. [2]Case matching study.

Table 2 Baseline and procedural characteristics of included studies

Study	Age (mean ± SD)		Hypertension		AF (%)		Technique of s-LAAO
	s-LAAO	No occlusion	s-LAAO	No occlusion	s-LAAO	No occlusion	
García-Fernández *et al*, 2003[3]	63 ± 12	62 ± 10	NR	NR	NR		Double suturing
Healey *et al*, 2005[7]	72 ± 6	71 ± 5	75	92	17	8	Suture or stapler
Nagpal *et al*, 2009[8]	57.8 ± 13.3	59.2 ± 11.9	NR	NR	18	29	Resection
Whitlock *et al*, 2013[9]	77.4 ± 6.8	74.6 ± 7.6	92.3	92	100	100	Amputation and closure or stapler
Zapolanski *et al*, 2013[4]	70.52 ± 11.83		83.9	80.6	19.9	10.7	Double ligation
Kim *et al*, 2013[6]	66.6 ± 11.4	65.8 ± 11.6	80.9	73.1	NR	NR	Ligation and excision
Lee *et al*, 2014[5]	55.9 ± 12.2	50.7 ± 12.4	19.8	14.5	100	100	Amputation
Melduni et *al*, 2017[10]	67.4 ± 12.7	67.6 ± 13.5	59	61	47	45	Amputation, suturing or stapler
Elbadawi *et al*, 2017[11]	70.8 ± 10.2	71.2 ± 11.1	70.6	52.8	100	100	NR
Elbadawi *et al*, 2017[12]	71.3 ± 9	70.6 ± 8.7	78.5	76.1	100	100	NR
Friedman *et al*, 2018[14]	75 ± 5.9	76.4 ± 6.4	14.5	12.7	50.5	43.4	Any technique
Yao *et al*, 2018[13]	68.2 ± 10.6	65.8 ± 11.3	88.6	90.4	75.4	31.4	

dergoing s-LAAO during concomitant cardiac surgery are the following: (1) s-LAAO was associated with lower rates of embolic events and stroke; and (2) there was no significant difference in the incidence of all-cause mortality, postoperative complications or reoperations for bleeding between the two groups. The reduced risk of embolic events and stroke with s-LAAO was retained in the subgroup analysis including only studies with AF predominant population (Table 3).

The estimated global prevalence of AF is on the rise due to a demographic shift with more prevalent ageing population carrying a higher burden of comorbidities[19]. About 25% of the strokes in the United States are related to AF and about 90% of the strokes in non-valvular AF are caused by thrombi originating in LAA[20]. Anticoagulants, both warfarin and direct acting oral anticoagulants (DOACs) reduce the incidence of stroke by more than 60%[21,22] but they are associated with increasing risk of bleeding, and significant drug-drug interactions[16]. The benefits of anticoagulants are also limited by other issues including underutilization, poor compliance and cost[16].

The higher risk of stroke in the ageing population with AF has led to the increased adoption of LAA occlusion in clinical practice[23]. The two largest RCTs - PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) showed percutaneous LAAO being non-inferior to warfarin with respect to stroke rates and embolic events[24,25]. Following the success with percutaneous LAAO, there has been a resurgence of interest in s-LAAO within the surgical community, especially with increase in the aging population and rising prevalence of AF[6,10,14].

Our findings show that s-LAAO was associated with lower risk of follow-up embolic events and stroke. The association of lower risk of stroke was more prominent in subgroup with AF predominant population. S-LAAO theoretically prevents formation of thrombus in LAA. However, successful s-LAAO is largely influenced by LAA morphology, occlusion technique and also operator

A

Study or subgroup	Surgical occlusion Events	Surgical occlusion Total	No surgical occlusion Events	No surgical occlusion Total	Weight	Odds ratio M-H,random,95%CI	Yr
Garcia-fernandez 2003	2	58	25	147	1.5%	0.17 [0.04, 0.76]	2003
Healey 2005	2	52	0	25	0.3%	2.52 [0.12, 54.28]	2005
Nagpal 2009	1	22	1	21	0.4%	0.95 [0.06, 16.28]	2009
Zapolanski 2013	7	808	16	969	4.1%	0.52 [0.21, 1.27]	2013
Whitlock 2013	1	26	3	25	0.6%	0.29 [0.03, 3.03]	2013
Lee 2014	1	119	2	119	0.6%	0.50 [0.04, 5.54]	2014
Friedman 2018	157	3892	402	6632	92.4%	0.65 [0.54, 0.79]	2018
Total (95%CI)		4977		7938	100%	0.63 [0.53, 0.76]	
Total events	171		449				

Heterogeneity. $Tau^2 = 0.00$; $Chi^2 = 4.54$, df = 6 ($P = 0.60$); $I^2 = 0\%$

Test for overall effect: $Z = 4.94$ ($P < 0.00001$)

B

Study or subgroup	Surgical occlusion Events	Surgical occlusion Total	No surgical occlusion Events	No surgical occlusion Total	Weight	Odds ratio M-H,random,95%CI	Yr
Healey 2005	1	52	0	25	0.3%	1.49 [0.06, 37.76]	2005
Nagpal 2009	1	22	1	21	0.4%	0.95 [0.06, 16.28]	2009
Whitlock 2013	1	26	3	25	0.6%	0.29 [0.03, 3.03]	2013
Kim 2013	13	631	10	631	4.7%	1.31 [0.57, 3.00]	2013
Zapolanski 2013	6	808	14	969	3.5%	0.51 [0.20, 1.33]	2013
Lee 2014	1	119	1	119	0.4%	1.00 [0.06, 16.18]	2014
Elbadawi 2017a	50	2519	396	2595	36.8%	0.62 [0.46, 0.84]	2017
Elbadawi 2017	16	652	30	652	8.6%	0.52 [0.28, 0.97]	2017
Melduni 2017	4	461	5	461	1.9%	0.80 [0.21, 2.99]	2017
Yao 2018	90	4295	122	4295	42.8%	0.73 [0.56, 0.96]	2018
Total (95%CI)		9585		19793	100.0%	0.68 [0.57, 0.82]	
Total events	183		582				

Heterogeneity. $Tau^2 = 0.00$; $Chi^2 = 4.93$, df = 9 ($P = 0.84$); $I^2 = 0\%$

Test for overall effect: $Z = 4.18$ ($P < 0.0001$)

C

Study or subgroup	Surgical occlusion Events	Surgical occlusion Total	No surgical occlusion Events	No surgical occlusion Total	Weight	Odds ratio M-H,random,95%CI	Yr
Healey 2005	0	52	0	25		Not estimable	2003
Nagpal 2009	0	52	0	21		Not estimable	2009
Zapolanski 2013	6	808	9	969	10.4%	0.80 [0.28, 2.25]	2013
Whitlock 2013	2	26	3	25	5.1%	0.61 [0.09, 4.01]	2013
Lee 2014	0	119	1	119	2.1%	0.33 [0.01, 8.20]	2014
Elbadawi 2017a	40	2549	35	12595	16.6%	5.79 [3.67, 9.13]	2017
Elbadawi 2017	10	652	32	652	13.7%	0.30 [0.15, 0.62]	2017
Melduni 2017	12	461	24	461	13.9%	0.49 [0.24, 0.99]	2017
Friedman 2018	651	3892	1531	6632	19.2%	0.67 [0.60, 0.74]	2018
Yao 2018	243	4295	335	4295	19.0%	0.71 [0.60, 0.84]	2018
Total (95%CI)		12846		25794	100%	0.83 [0.51, 1.36]	
Total events	964		1970				

Heterogeneity. $Tau^2 = 0.32$; $Chi^2 = 89.60$, df = 7 ($P < 0.00001$); $I^2 = 92\%$

Test for overall effect: $Z = 0.74$ ($P = 0.46$)

D

Study or subgroup	Surgical occlusion Events	Surgical occlusion Total	No surgical occlusion Events	No surgical occlusion Total	Weight	Odds ratio M-H,random,95%CI	Yr
Healey 2005	12	52	4	25	10.7%	1.57 [0.45, 5.49]	2005
Nagpal 2009	4	22	6	21	9.2%	0.56 [0.13, 2.34]	2009
Zapolanski 2013	157	808	222	969	20.8%	0.81 [0.64, 1.02]	2013
Lee 2014	27	119	28	119	17.4%	0.95 [0.52, 1.74]	2014
Melduni 2017	316	461	147	461	20.5%	4.66 [3.53, 6.14]	2017
Yao 2018	1190	4295	868	4295	21.4%	1.51 [1.37, 1.67]	2018
Total (95%CI)		5757		5890	100.0%	1.41 [0.79, 2.52]	
Total events	1706		1275				

Heterogeneity. $Tau^2 = 0.40$; $Chi^2 = 95.32$, df = 5 ($P < 0.00001$); $I^2 = 95\%$

Test for overall effect: $Z = 1.18$ ($P = 0.24$)

E

Study or subgroup	Surgical occlusion Events	Surgical occlusion Total	No surgical occlusion Events	No surgical occlusion Total	Weight	Odds ratio M-H,random,95%CI	Yr
Healey 2005	8	52	1	25	3.8%	4.36 [0.51, 37.00]	2005
Nagpal 2009	14	22	11	21	9.0%	1.59 [0.47, 5.39]	2009
Zapolanski 2013	3	808	5	969	7.2%	0.72 [0.17, 3.02]	2013
Whitlock 2013	1	26	2	25	3.0%	0.46 [0.04, 5.42]	2013
Lee 2014	22	119	22	119	17.0%	1.00 [0.52, 1.92]	2014
Elbadawi 2017a	1030	2519	903	2595	26.1%	2.31 [2.11, 2.53]	2017
Melduni 2017	32	461	32	461	19.8%	1.00 [0.60, 1.66]	2017
Elbadawi 2017	17	652	9	652	14.2%	1.91 [0.85, 4.32]	2017
Total (95%CI)		4659		14867	100%	1.44 [0.91, 2.25]	
Total events	1127		2985				

Heterogeneity. $Tau^2 = 0.20$; $Chi^2 = 20.64$, df = 7 ($P = 0.004$); $I^2 = 66\%$

Test for overall effect: $Z = 1.57$ ($P = 0.12$)

F

Study or subgroup	Surgical occlusion Events	Surgical occlusion Total	No surgical occlusion Events	No surgical occlusion Total	Weight	Odds ratio M-H,random,95%CI	Yr
Nagpal 2009	0	22	0	21		Not estimable	2009
Whitlock 2013	2	26	1	25	4.5%	2.00 [0.17, 23.56]	2013
Zapolanski 2013	23	808	38	969	42.7%	0.72 [0.42, 1.22]	2013
Lee 2014	13	119	6	119	20.7%	2.31 [0.85, 6.30]	2014
Melduni 2017	14	461	18	461	32.1%	0.77 [0.38, 1.57]	2017
Total (95%CI)		1436		1595	100.0%	0.98 [0.57, 1.69]	
Total events	52		63				

Heterogeneity. $Tau^2 = 0.11$; $Chi^2 = 4.69$, df = 3 ($P = 0.20$); $I^2 = 36\%$

Test for overall effect: $Z = 0.07$ ($P = 0.94$)

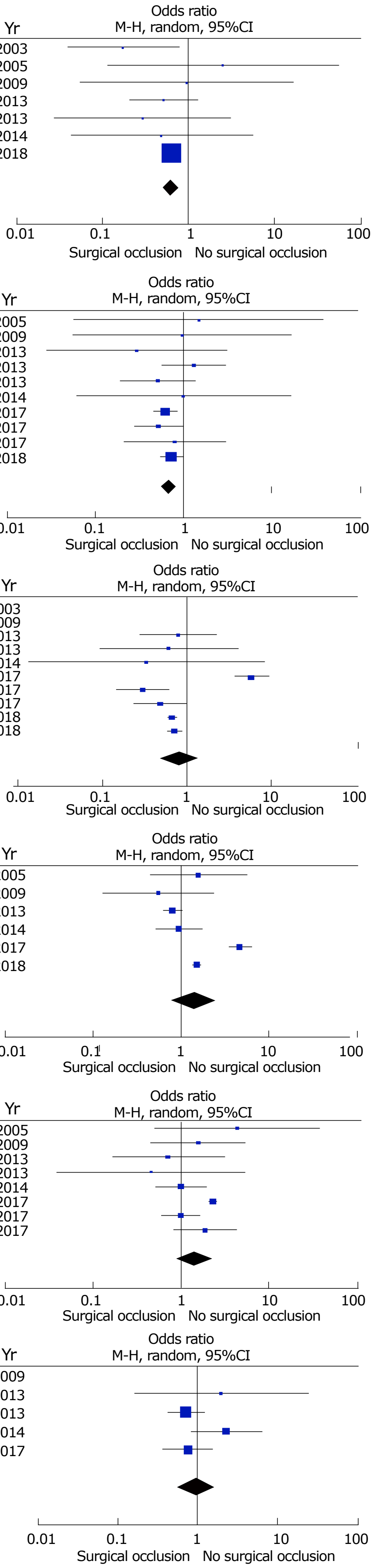

Figure 1 Forest plots for study outcomes. A: Embolic events; B: Stroke; C: All-cause mortality; D: Atrial fibrillation; E: Postoperative complications; F: Reoperation for bleeding.

Table 3 Complications reported in the individual studies

Study	Total complications s-LAAO (%) *vs* No occlusion (%)	Type of complications s-LAAO	No occlusion
Healey *et al*, 2005[7]	8 (52) *vs* 1 (4)	8- intraoperative LAA tears	1- LAA tear
Nagpal *et al*, 2009[8]	14 (63.6) *vs* 11 (52.3)	1- septicemia 1- myocardial infarction 2- RBC transfusion 8- temporary pacemaker 2- permanent pacemaker	1- RBC transfusion 7- temporary pacemaker 3- permanent pacemaker
Whitlock *et al*, 2013[9]	1 (3.8) *vs* 2 (25)	1- major bleeding	2- major bleeding
Zapolonski *et al*, 2013[4]	3 (0.3) *vs* 5 (0.6)	3- myocardial infarction	5- myocardial infarction
Lee *et al*, 2014[5]	22 (18.4) *vs* 22 (18.4)	9- requirement of dialysis 4- permanent pacemaker insertion 1- wound revision 8- pericardial effusion	1- low cardiac output syndrome 10- dialysis 2- permanent pacemaker insertion 1- mediastinitis 2- wound revision 6- pericardial effusion
Melduni *et al*, 2017[10]	32 (6.9) *vs* 32 (6.9)	14- pneumonia 18- acute renal failure	14- pneumonia 18- acute renal failure
Elbadawi *et al*, 2017[11]	17 (3.1) *vs* 9 (1.6)	17- pericardial effusion	7- pericardial effusion 2- hemorrhage
Elbadawi *et al*, 2017[12]	1030 (40.8) *vs* 2903 (23)	16- cardiac tamponade 68- pericardial effusion 917- hemorrhage 29- postoperative shock	19- cardiac tamponade 151- pericardial effusion 2687- hemorrhage 46- postoperative shock

RBC: Red blood cell; LAA: Left atrial appendage.

skill. A previous study showed that a complete LAA occlusion was achieved in only 40%-50% of the patient population[10,26]. The techniques of s-LAAO varied widely amongst the included studies as summarized in Table 2. The excision technique to exclude LAA has been shown to have a higher success rate than the other modalities of s-LAAO[24]. Currently, concomitant LAA closure is given a Class Ⅱb (level of evidence B) by the European Society of Cardiology (ESC)/European Society for Cardio-Thoracic Surgery (EACTS) guidelines and a Class IIb (level of evidence C) by the 2017 Society of Thoracic Surgeons guidelines (STS)[16]. Therefore, there is a wide practice level variation in the utilization of s-LAAO during cardiac surgery. The number of studies with a particular technique is inadequate to perform individual technique based meta-analysis so we combined all different techniques of s-LAAO in our meta-analysis. It should be noted that none of the other studies except the study from Friedman *et al*[14] reported long-term benefits. However, Friedman *et al*[14] showed a remarkable reduction in postoperative embolism at follow up. Further studies with long-term follow up of embolic events are essential. Our results are similar to a previous meta-analysis comparing s-LAAO vs no occlusion[27,28]. However, we included additional studies by Friedman *et al*[14], Elbadawi *et al*[11] and Yao *et al*[13] yielding a larger sample size. In addition, we performed a subgroup analysis of the included studies to identify the patient population that is most likely to benefit from this procedure.

In the current study, we found no significant difference in the risk of postoperative complications and reoperation for bleeding. s-LAAO is associated with inherent risk of procedural complications including LAA tears as observed in the study by Healey *et al*[7] and so learning curve plays an essential role in success of the procedure. Hypothetically, avoidance of aggressive anticoagulation after s-LAAO might have contributed to some of the benefits observed with s-LAAO. However, only few studies reported the long-term details of anticoagulation. Lee *et al*[5] reported no difference in the utilization of anticoagulation between the two groups (62.2% *vs* 55.4%). In the study by Friedman *et al*[14], anticoagulation was prescribed to 68.9% of the patients in the s-LAAO group compared to only 60.3% in the group without s-LAAO. In contrast to percutaneous LAAO, evidence regarding the utilization of anticoagulation after s-LAAO is not clear. The 2016 ESC/EACTS guidelines still recommend therapeutic anti-coagulation in all patients despite s-LAAO (Class Ⅰ, level of evidence B)[15]. With lack of long term data, there is need for prospective trials to address this issue. The ongoing LAAOS-Ⅲ (left atrial appendage occlusion study Ⅲ) and the ATLAS (AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures) trials should be able to provide further insights into the benefits of s-LAAO.

LIMITATIONS

Our study should be viewed in the context of following limitations. First, due to the small number of studies with small sample sizes, except the study by Friedman *et al*[14], the results might be underpowered to detect the true clinical benefits of certain clinical outcomes. Second, there was a wide variation of surgical techniques of LAAO, so we were not able to address the effect of individual techniques. Third, only Friedman *et* *al*[14] reported long-term embolic events, whereas the other studies did not report long term outcomes. The study by Friedman *et al*[14] reported readmissions for embolic events, so some of the events which did not require hospitalization were not included. The effect of anticoagulation on postoperative outcomes remains unclear due to inadequate reporting in the included studies. Fourth, it is unclear if s-LAAO increases the duration of the surgical procedure as it was only reported in two studies. Fifth, the burden of AF varied among the included studies, thus carrying risk of a selection bias. Finally, publication bias is an inherent limitation of any meta-analysis.

CONCLUSION

In conclusion, our results support the safety of s-LAAO and favor its continued use in conjunction with concomitant cardiac surgery, especially in patients with AF. Randomized controlled trials are essential to evaluate the long-term benefits of s-LAAO.

ARTICLE HIGHLIGHTS

Research background

The left atrial appendage (LAA) is a common site for intracardiac thrombus formation in patients with atrial fibrillation (AF). Surgical left atrial appendage occlusion (s-LAAO) during concomitant cardiac surgery has been evaluated as an effective treatment approach to reduce the risk of stroke and embolic events.

Research motivation

Percutaneous LAAO has been shown to be non-inferior compared with warfarin in reducing the risk of stroke and embolic events in two large randomized controlled trials, PROTECT-AF and PREVAIL. However, data regarding s-LAAO is conflicting and contrasting. So, we performed a systematic review and meta-analysis of all the studies published to date to evaluate if concomitant s-LAAO during cardiac surgery is safe and effective.

Research objectives

The purpose of this study is to evaluate the safety and efficacy of concomitant s-LAAO during cardiac surgery.

Research methods

We searched five databases for studies comparing concomitant s-LAAO with no occlusion during cardiac surgery. We obtained a total of 12 studies for inclusion and performed a meta-analysis. The outcomes of interest were embolic events, stroke, all-cause mortality, AF, postoperative complications and reoperation for bleeding.

Research results

Concomitant s-LAAO during cardiac surgery was associated with lower risk of embolic events and stroke. This was evident in the AF predominant strata as well. There was no significant difference in the risk of all-cause mortality, AF, postoperative complications and reoperation for bleeding.

Research conclusions

Our meta-analysis including all the studies published to date comparing concomitant s-LAAO against no occlusion during cardiac surgery supports the use of concomitant s-LAAO during cardiac surgeries. It was associated with lower risk of stroke and embolic events.

Research perspectives

From this meta-analysis, it could be seen that concomitant s-LAAO during cardiac surgeries was associated with lower risk of stroke and embolic events compared with no occlusion. This association was prominent amongst the AF predominant strata as well. These beneficial effects could be seen due to the occlusion of LAA which is the source of 90% thrombi in non-valvular AF. Future randomized trials are needed to evaluate the long term benefits of s-LAAO.

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P- Reviewer: Vermeersch P, Said SAM **S- Editor**: Dou Y
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