European Journal of Cardio-Thoracic Surgery Advance Access published July 26, 2014

European Journal of Cardio-Thoracic Surgery (2014) 1–8
doi:10.1093/ejcts/ezu291

ORIGINAL ARTICLE

ADULT CARDIAC

Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: a meta-analysis

Yi-Chin Tsai[a,†], Kevin Phan[b,c,†], Stine Munkholm-Larsen[c,d], David H. Tian[b], Mark La Meir[e,f] and Tristan D. Yan[b,g,*]

[a] Department of Cardiothoracic Surgery, The Prince Charles Hospital, Chermside, Australia
[b] The Collaborative Research (CORE) Group, Macquarie University, Sydney, Australia
[c] Sydney Medical School, University of Sydney, Sydney, Australia
[d] Department of Cardiology, Hvidovre University Hospital, Copenhagen, Denmark
[e] Department of Cardiothoracic Surgery and Cardiology, Academic Hospital Maastricht and Cardiovascular Research Institute Maastricht, Maastricht, Netherlands
[f] University Hospital Brussels, Brussels, Belgium
[g] Department of Cardiothoracic Surgery, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia

* Corresponding author. The Collaborative Research (CORE) Group, Macquarie University, 2 Technology Place, Sydney, Australia. E-mail: tristanyan@annalscts.com (T.D. Yan).

Received 26 March 2014; received in revised form 6 June 2014; accepted 12 June 2014

Abstract

OBJECTIVES: Concomitant left atrial appendage occlusion (LAAO) during surgical ablation has emerged as a potential treatment strategy to reduce stroke and perioperative mortality in patients with atrial fibrillation (AF). The present meta-analysis aims to assess current evidence on the efficacy and safety between LAAO and LAA preservation cohorts for patients undergoing cardiac surgery.

METHODS: Electronic searches were performed using six electronic databases from their inception to November 2013, identifying all relevant comparative randomized and observational studies comparing LAAO with non-LAAO in AF patients undergoing cardiac surgery. Data were extracted and analysed according to predefined endpoints including mortality, stroke, postoperative AF and reoperation for bleeding.

RESULTS: Seven relevant studies identified for qualitative and quantitative analyses, including 3653 patients undergoing LAAO ($n = 1716$) versus non-LAAO ($n = 1937$). Stroke incidence was significantly reduced in the LAAO occlusion group at the 30-day follow-up [0.95 vs 1.9%; odds ratio (OR) 0.46; $P = 0.005$] and the latest follow-up (1.4 vs 4.1%; OR 0.48; $P = 0.01$), compared with the non-LAAO group. Incidence of all-cause mortality was significantly decreased with LAAO (1.9 vs 5%; OR 0.38; $P = 0.0003$), while postoperative AF and reoperation for bleeding was comparable.

CONCLUSIONS: While acknowledging the limitations and inadequate statistical power of the available evidence, this study suggests LAAO as a promising strategy for stroke reduction perioperatively and at the short-term follow-up without a significant increase in complications. Larger randomized studies in the future are required, with clearer surgical and anticoagulation protocols and adequate long-term follow-up, to validate the clinical efficacy of LAAO versus non-LAAO groups.

Keywords: Atrial fibrillation • Surgical occlusion • Left atrial appendage • Meta-analysis

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice, affecting 1–2% of the general population in developed countries [1, 2]. Patients with AF have a 5-fold increase in the risk of strokes, leading to significant long-term disability [3]. While oral anticoagulant therapy, in particular warfarin, has been established as the standard for stroke prevention in patients with AF, the complex therapeutic profile of anticoagulants has curtailed their clinical usage, with studies demonstrating that less than half of patients hospitalized with AF took warfarin as prescribed [4]. As such, surgical intervention has been viewed as a viable alternative to minimize stroke risk in AF patients.

[†]Both authors contributed equally to this work.

The left atrial appendage (LAA) is a tubular structure attached to the left atrium that is highly prone to stasis and thrombus formation during AF. Consequently, the LAA is responsible for the generation of at least 90% of left atrial thrombi, making it an attractive concomitant surgical target during cardiac operations in an attempt to reduce the risk of embolic stroke [5]. For this reason, LAA occlusion (LAAO) is often performed routinely during surgical ablation with variable levels of success. Surgical occlusion techniques include excision, stapler removal and running sutures, and, with more recent technological advances, occlusion via innovative devices such as AtriClip and TigerPaw [6]. However, the role of LAAO during routine cardiac surgery is not well established and may represent a possible prophylactic method of reducing stroke incidence [7, 8]. To summarize the available evidence and explore the benefits and risks of surgical LAAO, the present meta-analysis aims to compare the efficacy and safety of cardiac surgery with concomitant LAAO versus non-LAAO.

METHODS

Literature search strategy

Electronic searches were performed using Ovid MEDLINE, Cochrane Central Register of Controlled Trails, Cochrane Database of Systematic Reviews, ACP Journal club and Database of Abstracts of Review of Effectiveness from their date of inception to May 2014. To achieve the maximum sensitivity of the search strategy and identify all studies, we combined the terms: 'left atrial appendage' and 'cardiac surgery'. The reference list of all retrieved articles was reviewed for further identification of potentially relevant studies. All identified articles were systematically assessed using the inclusion and exclusion criteria. The outcome of embolic stroke events where neurological symptoms lasted more than 24 h were assessed in the present study.

Selection criteria

Eligible comparative studies for the present meta-analysis included those in which cardiac surgeries were performed with or without surgical LAAO. All forms of cardiac surgical procedures, such as coronary artery bypass grafting (CABG) and valvular surgery, were included. Studies that did not include stroke or cardiovascular events were excluded. All publications were limited to human subjects and in the English language. Abstracts, case reports, conference presentations, editorials and expert opinions were excluded. Review articles were omitted because of potential publication bias and possible duplication of results.

Data extraction and critical appraisal

All data were extracted from article texts, tables and figures. When insufficient data were available from publications, corresponding authors were contacted to provide additional records. Two investigators (Kevin Phan and Yi-Chin Tsai) independently reviewed each retrieved article. Agreement was measured by kappa statistics. Discrepancies between the two reviewers were resolved by discussion and consensus. Because quality scoring is controversial in the meta-analyses of observational studies, two reviewers (Kevin Phan and Yi-Chin Tsai) independently appraised each article included in our analysis according to a critical review checklist of the Dutch Cochrane Centre proposed by MOOSE [9]. The key points of this checklist include: (i) clear definition of the study population; (ii) clear definition of outcomes and outcome assessment; (iii) independent assessment of outcome parameters; (iv) sufficient duration of follow-up; (v) no selective loss during follow-up and (vi) important confounders and prognostic factors identified. The final results were reviewed by the senior investigators (Mark La Meir and Tristan D. Yan).

Statistical analysis

Meta-analysis was performed by combining all results of reported incidences or mortality, stroke, postoperative AF and reoperation for bleeding. The odds ratio (OR) was used as a summary statistic. Chi-squared tests were used to study heterogeneity between trials. I^2 statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance. I^2 can be calculated as $I^2 = 100\% \times (Q - \mathrm{df})/Q$, with Q defined as Cochrane's heterogeneity statistics and df as degrees of freedom. An I^2 value of greater than 50% was considered substantial heterogeneity, and necessitated further qualitative analysis.

Evidence of publication bias was sought using Egger and Begg methods. A contour-enhanced funnel plot was performed to aid in interpretation of the funnel plot. Possible asymmetry was investigated using trim-and-fill analysis.

All *P*-values were two-sided. All statistical analysis was conducted with Review Manager Version 5.2 (Cochrane Collaboration, Software Update, Oxford, UK) and Comprehensive Meta-Analysis 2.2 (Biostat, Englewood, NJ, USA).

RESULTS

Quantity and quality of trials

One thousand and sixty-nine references were identified through six electronic database searches. After exclusion of duplicate and irrelevant references, 51 potentially relevant articles were retrieved for detailed evaluation. After the inclusion and exclusion criteria were applied, seven studies remained for further analysis. The agreement kappa statistic for study inclusion was good [$\kappa = 0.664$; standard error = 0.129; 95% confidence interval (CI) 0.411–0.917]. Of the seven studies, two were randomized controlled trials (RCTs) [10, 11], two were retrospective propensity-score studies [12, 13] and the final three comprised a prospective cohort study [14], observation study [15] and a two-part study that included a cross-sectional and RCT component [8]. The study characteristics of these trials and surgical details are summarized in Tables 1 and 2.

In these seven studies, 3653 cardiac patients were included for analysis to compare LAA ($n = 1716$) versus non-LAAO ($n = 1937$). In three studies, the primary cardiac operation was mitral valve surgery [10, 12, 15], while CABG was the primary operation in one study [11]. The remaining studies included a mixture of CABG and valve procedures [8, 13, 14]. Sutures were used to occlude the LAA in four studies [10, 11, 14, 15], as was the stapler [8, 11]. One group underwent the cryo-maze procedure [12]. In terms of source of stroke, only Nagpal *et al*. [10] and Healey *et al*. [11] specified that it was of ischaemic origin, whereas none was specified in the rest of the included studies. Quality assessment using the MOOSE checklist criteria is summarized in Table 3. Based on this assessment, a remove-one-study sensitivity analysis was performed but any significant trends in the results were maintained.

Baseline and operative characteristics

Similar baseline characteristics were observed in both comparison arms (Table 2). Males accounted for 61.3% of the LAAO cohort and 59.7% of the non-occlusion cohort. The average age of the LAAO cohort (65.0 years) was comparable with that of the non-occlusion cohort (64.0%). Preoperative strokes were reported in five studies, with a weighted mean average of 8.5% in the LAAO group and 6.7% in the non-LAAO group. The proportion of patients with valvular disease was also similar between the LAAO and non-occlusion groups, with 39.1 and 44.3%, respectively.

Table 1: Study characteristics of relevant articles identified for meta-analysis comparing LAA versus non-LAA occlusion for AF patients with concomitant cardiac surgery

First author	Year	Country	Study period	Type of study	No. of LAA	No. of non-LAA	Concomitant procedure	Method for LAA occlusion	Indication
Lee	2014	Korea	1999–2011	PSM	119	119	MVS	LAA resection during cryo-maze procedure	Matched patients undergoing cryo-maze ablation for AF and MV surgery. LAAO treatment according to the surgeon's ablation technique
Whitlock	2013	Canada	2009–2010	Mixed*	26	25	CABG, VS	Amputation and stapler closure	Patients undergoing cardiac surgery with CPB, and with a history of AF with previous stroke/TIA or at least two of: age >65 years, HT, DM, HF/ LVEF <50%. Patients randomly assigned to LAAO
Kim	2013	USA	2001–2010	PSM	631	631	CABG, MVS	LAA resection or closure	Patients undergoing cardiac surgery, with or without LAAO according to the surgeon's standard practice
Zapolanski	2013	USA	2005–2012	OS	808	969	CABG, valvular	Double ligation with suture	Patients undergoing cardiac surgery. LAAO by double ligation or no LAAO was determined by the surgeon's decision
Nagpal	2009	Canada	2007–2007	RCT	22	21	MVS	LAA resection: suture	MV repair or replacement patients, with randomized LAAO treatment
Healey	2005	Germany	2001–2002	RCT	52	25	CABG	Sutures or staplers	Patients undergoing elective CABG and any of the following factors for AF and stroke: age >75 years, HT + age >65 years, previous stroke, history of AF. LAAO treatment randomized
Garcia-Fernandez	2003	Spain	1996–2001	OS	58	147	MVS	LAA ligation by endocardial sutures	MV surgery for regurgitation, endocarditis, investigation of embolic source, right/left ventricular function. Specific indication for LAAO not reported

RCT: randomized controlled trial; PSM: propensity-score matching; OS: observational study; *2 stages: cross-sectional OS and RCT; MVS: mitral valve surgery; CABG: coronary artery bypass surgery; VS: valvular surgery; TIA: transient ischaemic attack; LAA: left atrial occlusion; AF: atrial fibrillation; CPB: cardiopulmonary bypass; HT: hypertension; DM: diabetes mellitus; HF: heart failure; LVEF: left ventricular ejection fraction.

Cardiopulmonary bypass duration was only reported in one study [8] and was 17 min longer in the LAAO group. Cross-clamp duration was reported in two studies [8, 11]. Whitlock *et al.* reported a difference of 23 min, whereas Healey *et al*. demonstrated no significant difference in the cross-clamp duration.

Assessment of occurrence of postoperative stroke

Stroke incidence was significantly reduced in patients who underwent LAAO surgery compared with those who did not at Day 30 postoperatively (0.95 vs 1.9%; OR 0.46; 95% CI 0.27–0.79; $P = 0.005$; $I^2 = 0\%$) and at the latest follow-up (1.4 vs 4.1%; OR 0.48; 95% CI 0.24–0.98; $P = 0.04$; $I^2 = 0\%$; Fig. 1).

Assessment of incidence on postoperative atrial fibrillation at the 30-day and the latest follow-up

Application of surgical LAAO did not prevent patients from having postoperative AF compared with the LAA preservation group (22 vs 21.7%; OR 0.99; 95% CI 0.75–1.32; $P = 0.97$; $I^2 = 48\%$) on Day 30 and at the most recent follow-up (3.2 vs 4.0%; OR 0.60; 95% CI 0.17–2.14; $P = 0.43$; $I^2 = 57\%$; Fig. 2).

Assessment of all-cause mortality

Mortality was significantly lower in surgical LAAO compared with the LAA preservation group (1.9 vs 5%; OR 0.38; 95% CI 0.22–0.64; $P = 0.0003$; $I^2 = 0\%$) in the most recent follow-up (Fig. 3).

Assessment of reoperation for bleeding

The incidence of reoperation for bleeding in the LAA group is not higher than the LAA preservation group (2.4 vs 2.5%; OR 1.23; 95% CI 0.49–3.10; $P = 0.66$; $I^2 = 55\%$).

Publication bias

Inspection of the funnel plot (Fig. 4) did not show significant asymmetry for all-cause neurological events. Trim-and-fill analysis suggested that one study was missing; however, this did not significantly affect the overall effect size with Begg's test score of $P = 0.2597$ and Egger's test score of $P = 0.6994$. These results suggest that publication bias was not a significant influencing factor.

Table 2: Baseline characteristics of included studies for meta-analysis

First author	Age (mean ± SD)		Male (%)		Preoperative stroke (%)		Hypertension (%)		Valvular heart disease (%)		Cardiopulmonary bypass duration (min)		Cross-clamp duration (min)	
	LAA	Non-LAA	LAA	Non-LAA	LAA	Non-LAA	LAA	Non-LAA	LAA	Non-LAA	LAA	Non-LAA	LAA	Non-LAA
Lee	53.4 ± 12.5	54.1 ± 7.6	37.8	37.8	5.0	5.9	18.5	19.3	100	100	NR	NR	NR	NR
Whitlock	77.4 ± 6.8	74.6 ± 7.6	76.92	76	23.08	20	92.31	92	80.77	48	132.8 ± 48.4	115.5 ± 40.3	108 ± 43.6	85 ± 39.3
Kim	66.6 ± 11.4	65.8 ± 11.6	67.95	67.5	8.1	6.6	80.9	73.1	18.2	18.8	NR	NR	NR	NR
Nagpal	57.8 ± 13.3	59.2 ± 11.9	50	57.1	0	4.8	NR	NR	100	100	NR	NR	NR	NR
Healey	72 ± 6	71 ± 5	73	72	17	0	75	92	NR	NR	NR	NR	72 ± 27	75 ± 39
Garcia-Fernandez	63 ± 12	62 ± 10	24.1	39.5	NR	NR	NR	NR	100	100	NR	NR	NR	NR
Zapolanski	NR	NR	24.1	39.5	NR	NR	NR	NR	100	100	NR	NR	NR	NR
Weighted average mean	65.0	64.0	61.3	59.7	8.46	6.66	71.9	66.3	39.1	44.3	NA	NA	NA	NA

LAA: left atrial appendage; NR: not reported.

DISCUSSION

AF is a major health concern and continues to grow in its burden, being present in approximately one-sixth of patients admitted with stroke [7]. The current medical treatment, warfarin, has been the standard treatment regime for stroke prevention in patients with AF for many years [16]. However, the risk of life-threatening bleeding complications, drug interactions and narrow therapeutic windows constrain widespread usage of warfarin, while promising novel anticoagulants have been plagued by off-target toxicities and only offer modest improvements in bleeding risk [17]. As such, physicians have investigated other triggers of the stroke pathogenesis pathway in AF patients. Owing to its anatomical disposition for stasis and clotting during AF, the LAA is thought to be responsible for over 17% of atrial thrombi in rheumatic mitral valve disease and 91% of left atrial thrombi in non-rheumatic AF [18, 19]. Therefore, it is plausible that LAAO, particularly during routine cardiac surgery, would greatly curtail stroke incidence in patients with AF without additional procedural risks. Given the limited available evidence for surgical occlusion, the current meta-analysis aimed to summarize the evidence base and explore the risks and benefits of LAAO during routine cardiac surgery for prophylactic stroke prevention.

LAAO is often performed concomitantly during surgical ablation procedures where the heart is exposed and easier to access; however, the efficacy of this strategy in all routine cardiac surgery is not well established. Recent meta-analyses of randomized trials demonstrated no significant differences in neurological outcomes between AF patients undergoing surgical ablation versus no ablation [20, 21] or catheter ablation [22], with the majority of ablative procedures involving LAAO. While this suggests the ineffectiveness of LAAO for stroke prophylaxis, the influence of the maze procedure itself and sinus rhythm on stroke outcomes cannot be excluded. Contrasting results have been yielded in non-ablation populations, with a retrospective study examining 205 mitral valve replacement patients demonstrating that LAA ligation can reduce the risk of an embolic event by 6.7 times versus LAA preservation [15]. The present meta-analysis study suggests that surgical LAA resection with concomitant cardiac surgery is efficacious, with significantly reduced stroke incidence at the 30-day follow-up and at the latest follow-up. From the literature review (Table 3), incidence rate of stroke ranged 0–10.8%, embolism ranged 0–4%, while transient ischaemic attacks ranged 0–4.5%. Efficacy among studies appear quite variable, and thus findings should be viewed with caution as there are currently insufficient clinical data about the type and source of strokes and oral anticoagulant therapy protocol, which could affect the interpretation of results. Despite the limited evidence to date, this meta-analysis supports LAAO as a promising strategy for stroke prevention during cardiac surgery, and provides the rationale for future, adequately powered, randomized trials.

In order for LAAO to be used routinely, it must demonstrate at least comparable mortality rates compared with cardiac surgery without LAAO. Results from the current meta-analysis support the safety of LAAO during routine cardiac surgery, with no significant difference in mortality rates. A review of the literature (Table 4) shows that reported mortality rates range 0–40%, while rates of reoperation for bleeding risks range 0–10.9%. Higher rates of mortality reported by Nagpal *et al*. and Kanderian *et al*. may be attributed to increased bleeding risk, operative duration and risk of mortality due to extra surgical incisions of delicate, thin and fragile LAA tissue. These complications are associated with incorrect or

Table 3: Assessment of the quality of included studies

	First author						
	Lee	Whitlock	Kim	Nagpal	Healey	Garcia-Fernandez	Zapolanski
Clear definition of the study population	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clear definition of outcomes and outcome assessment	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Independent assessment of outcome parameters	No[a]	Yes	No[a]	Yes	Yes	No[a]	Yes
Sufficient duration of follow-up?	Yes	No	No	No	No	Yes	Yes
Sufficient sample size?	No	No	Yes	No	No	No	Yes
No selective loss during follow-up?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Important confounders and prognostic factors identified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[a]Lack of blinding during outcome assessment, not independently assessed by multiple investigators.

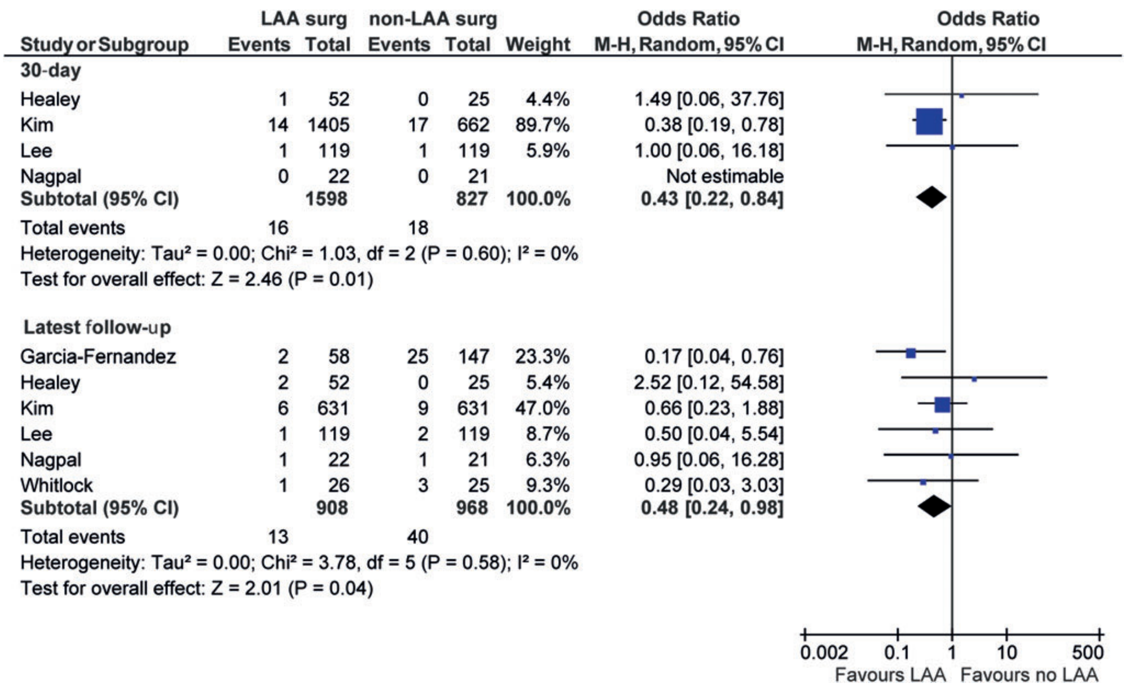

Figure 1: Forest plot of the odds ratio (OR) of embolic stroke incidence postoperatively on Day 30 and at the latest follow-up in the left atrial occlusion (LAA) group versus non-LAA group. The estimate of the OR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the number of events as a fraction of the total number is shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. M–H: Mantel–Haenszel.

incomplete LAAO [12, 23], given that LAAO success rates range 64–100% in the literature, and as such our meta-analysis findings should be interpreted with caution. Overall, there was no difference in terms of reoperations for bleeding between the LAAO and non-LAAO cohorts. The incidence of postoperative AF at the 30-day and latest follow-up was similar between LAA ligation and non-LAA cohorts. The literature review also suggested an overall low rate of postoperative myocardial infarctions, which ranged 0–2.5%. Overall, the current meta-analysis suggests that LAAO can be performed safely and concomitantly during cardiac surgery without additional complications or increased mortality.

Percutaneous approaches to LAAO have been studied in several prospective randomized studies including PROTECT-AF [17]. From the outcomes of 700 patients recruited in the PROTECT-AF trial, the efficacy of percutaneous LAAO was non-inferior to that of warfarin therapy. However, patients treated with the Watchman device had higher initial rates of pericardial effusions and procedure-related strokes, which arguably may be dependent on the learning curve [17]. Also, there are still concerns surrounding the small number of patients studied, 10-fold less than those in anticoagulant trials, and the fact that the apparent benefit in the LAAO arm which was driven by a reduction in haemorrhagic rather than ischaemic strokes. Furthermore, given that stroke is a systemic and not anatomical issue [1], LAAO is unlikely to be a complete strategy for stroke reduction or prevention. As such, the evidence supporting the prophylactic use of LAAO remains weak and requires further investigation.

Study or Subgroup	LAA Events	LAA Total	no LAA Events	no LAA Total	Weight	Odds Ratio M-H, Random, 95% CI
30 day						
Healey	12	52	4	25	4.6%	1.57 [0.45, 5.49]
Kim	324	1405	129	662	38.4%	1.24 [0.99, 1.56]
Lee	27	119	28	119	15.2%	0.95 [0.52, 1.74]
Nagpal	4	22	6	21	3.5%	0.56 [0.13, 2.34]
Zapolanski	157	808	222	969	38.3%	0.81 [0.64, 1.02]
Subtotal (95% CI)		**2406**		**1796**	**100.0%**	**0.99 [0.75, 1.32]**
Total events	524		389			
Heterogeneity: Tau² = 0.04; Chi² = 7.70, df = 4 (P = 0.10); I² = 48%						
Test for overall effect: Z = 0.04 (P = 0.97)						
Latest Follow-up						
Kim	0	631	7	631	14.8%	0.07 [0.00, 1.16]
Lee	21	119	18	119	51.2%	1.20 [0.60, 2.39]
Nagpal	4	22	6	21	34.0%	0.56 [0.13, 2.34]
Subtotal (95% CI)		**772**		**771**	**100.0%**	**0.60 [0.17, 2.14]**
Total events	25		31			
Heterogeneity: Tau² = 0.70; Chi² = 4.63, df = 2 (P = 0.10); I² = 57%						
Test for overall effect: Z = 0.78 (P = 0.43)						

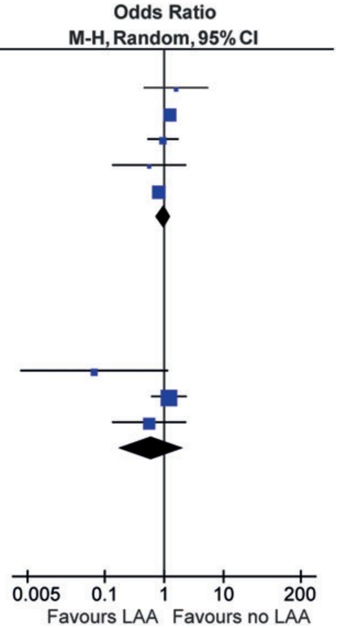

Figure 2: Forest plot of the odds ratio (OR) of occurrence of postoperative atrial fibrillation (AF) on Day 30 and at the latest follow-up in the left atrial occlusion (LAA) group versus non-LAA group. The estimate of the OR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the number of events as a fraction of the total number is shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. M–H: Mantel–Haenszel.

Study or Subgroup	LAA Events	LAA Total	no LAA Events	no LAA Total	Weight	Odds Ratio M-H, Random, 95% CI
Healey	0	52	0	25		Not estimable
Lee	6	119	11	119	26.0%	0.52 [0.19, 1.46]
Nagpal	0	22	0	21		Not estimable
Whitlock	2	26	3	25	7.8%	0.61 [0.09, 4.01]
Zapolanski	12	808	44	969	66.2%	0.32 [0.17, 0.60]
Total (95% CI)		**1027**		**1159**	**100.0%**	**0.38 [0.22, 0.64]**
Total events	20		58			
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%						
Test for overall effect: Z = 3.62 (P = 0.0003)						

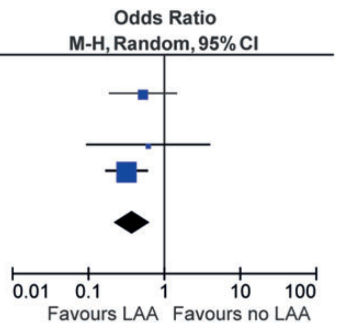

Figure 3: Forest plot of the odds ratio (OR) of all-cause mortality in the left atrial occlusion (LAA) group versus non-LAA group. The estimate of the OR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the number of events as a fraction of the total number is shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. M–H: Mantel–Haenszel.

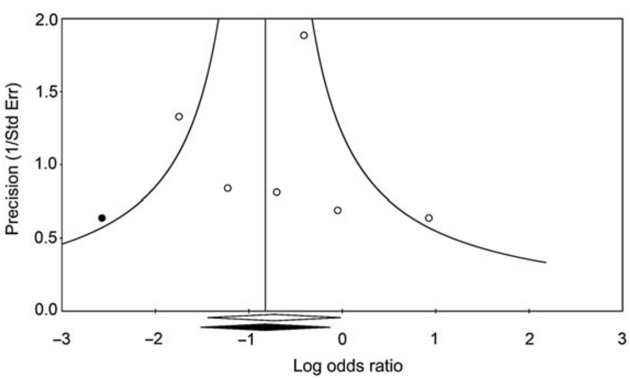

Figure 4: Funnel plot and trim-and-fill analysis of all-cause neurological outcomes for LAA occlusion versus non-occlusion cohorts. Open circles represent studies included in the current meta-analysis, while black-filled circles represent potential missing studies in the current literature. The lower white diamond represents log odd ratios of included studies, while the black diamond represents new log odds ratio after accounting for potential missing studies.

Limitations

Although the LAA is a well-documented incubator of thrombus formation during an AF episode, it has to be acknowledged that the LAA is not the only source of thrombi. Thrombi are also known to originate in aortic, carotid arteries as well as from venous sources entering the LA via a right–left shunt [7]. Current echocardiographic studies suggest that LAA occlusion only removes a cardiac-embolic source of thrombi from circulation but cannot achieve absolute effectiveness in stroke prevention. Thus, other interventions such as antithrombotic therapy may still be needed for different mechanisms of thrombi formation. However, the results from the current study did suggest that focused LAAO can be performed prophylactically and will be synergistic or additive in reducing stroke incidence.

The clinical effect of LAAO on operative time and effectiveness of various types of surgical techniques for successful LAAO have not been well evaluated. Most studies from the current evidence

Table 4: Systematic review of the literature for comparative and non-comparative studies reporting complication rates with LAA occlusion

Author	Year	No. of patients	LAA occlusion technique	Success (%)	Strokes (%)	Embolism (%)	TIA (%)	Reop bleeding (%)	MI (%)	Mortality (%)
Emmert (S1)	2014	40	Epicardial LAA clip	100	0	–	2.7	–	2.5	10
Zapolanski	2013	808	Double ligation with sutures	96	0.7	0	0.1	2.8	0.6	1.5
Whitlock	2013	26	Stapler closure	–	3.8	0	–	7.7	–	7.7
Lee	2013	119	LAA resection	–	0.8	–	0	10.9	0	5
Slater (S2)	2012	60	LAA occlusion device	93	0	2	–	5	1.7	–
Ailawadi (S3)	2011	70	Atrial clip device	95.7	1.6	–	1.6	–	–	0
Salzberg (S4)	2010	34	Epicardial LAA clip	100	0	–	0	–	0	8.8
Nagpal	2009	22	LAA resection	–	4.5	–	4.5	0	–	18
Bakhtiary (S5)	2008	259	LAA clamp ligation	100	1.5	–	1.2	0.8	–	0
Kanderian (S6)	2008	137	Surgical, stapler or suture occlusion	40	–	2.2	–	–	–	40
Almahameed (S7)	2007	136	LAA resection	–	–	–	–	–	–	–
Healey	2005	52	Sutures or staplers	–	3.8	–	1.9	–	–	0
Gillinov (S8)	2005	222	Buttressed stapling technique for LAA excision	–	2.3	–	–	3.2	–	–
Garcia-Fernandez	2003	58	Endocardial sutures	89.7	3.4	3.4	–	–	0	–
Katz (S9)	2000	50	LAA ligation	64	2	4	2	–	–	–
Orszulak (S10)	1995	285	LAA resection	–	10.8	–	–	–	–	15.5

LAA: left atrial appendage; TIA: transient ischaemic attack; reop: reoperative; MI: myocardial infarction.
Supplementary References S1–10 are included in Supplementary Material.

database did not analyse or report the duration of operative time when LAAO occlusion was performed. Two studies showed that LAAO can be successfully performed without increasing operation time [11], and the double ligation technique, which takes 2–3 min to perform, does not add significant time to the operation [14]. With regard to variations in surgical techniques, it is possible that successful occlusion occurred often with exclusion of the LAA compared with suture and stapler excision [24]. Furthermore, incomplete closure may occur in up to 40% of cases during follow-up. In the Left Atrial Appendage Occlusion Study (LAAOS), the technique of sutures oversewing the appendage without amputation produced successful exclusion only in 45%, whereas with a surgical stapler, it was 72% [11]. Different ligature and suture techniques failed in 36–60% of the patients, leaving the possibility of thrombus formation in the LAA and then stroke incidence [24, 25]. Given the limited available evidence, uncertainty surrounding the efficacy of different ligation techniques and the risks of incomplete LAA surgical ligation must be addressed in future randomized studies.

Only three RCTs with small study numbers and with an average short-term follow-up period of 12 months have been identified from the literature, thus limiting the data available to make definitive conclusions. Data on anticoagulation regimen, follow-up rhythm status and LAA closure were not well reported, and hence prevents a definitive interpretation of the current evidence base. Currently, a larger randomized trial (LAAOS III) is in the recruitment phase to evaluate the safety and efficacy of LAA removal in patients with AF undergoing heart surgery [7]. It is hoped that the result from this trial will clarify the role of concomitant LAAO in cardiac surgery for patients with AF.

CONCLUSION

In summary, the current meta-analysis supports surgical LAA resection during routine cardiac surgery as a promising strategy to decrease the incidence of stroke in short- and long-term follow-up, and provide the added advantage of reduced mortality risk. However, the current evidence base is very limited and thus warrants future prospective, randomized trials of adequate statistical power necessary to definitively and robustly assess the long-term benefits and risks of LAAO during cardiac surgery.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

REFERENCES

[1] Patel TK, Yancy CW, Knight BP. Left atrial appendage exclusion for stroke prevention in atrial fibrillation. Cardiol Res Pract 2012;2012:610827.

[2] Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med 2001;135:1061–73.

[3] Ngaage DL, Schaff HV, Mullany CJ, Sundt TM III, Dearani JA, Barnes S *et al.* Does preoperative atrial fibrillation influence early and late outcomes of coronary artery bypass grafting? J Thorac Cardiovasc Surg 2007;133: 182–9.

[4] Humphries KH, Jackevicius C, Gong Y, Svensen L, Cox J, Tu JV *et al.* Population rates of hospitalization for atrial fibrillation/flutter in Canada. Can J Cardiol 2004;20:869–76.

[5] Cox JL, Ad N, Palazzo T. Impact of the maze procedure on the stroke rate in patients with atrial fibrillation. J Thorac Cardiovasc Surg 1999;118: 833–40.

[6] Chatterjee S, Alexander JC, Pearson PJ, Feldman T. Left atrial appendage occlusion: lessons learned from surgical and transcatheter experiences. Ann Thorac Surg 2011;92:2283–92.

[7] Whitlock R, Healey J, Vincent J, Brady K, Teoh K, Royse A *et al.* Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. Ann Cardiothorac Surg 2014;3:45–54.

[8] Whitlock RP, Vincent J, Blackall MH, Hirsh J, Fremes S, Novick R *et al.* Left Atrial Appendage Occlusion Study II (LAAOS II). Can J Cardiol 2013;29: 1443–7.

[9] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
[10] Nagpal AD, Torracca L, Fumero A, Denti P, Cioni M, Alfieri O. Concurrent prophylactic left atrial appendage exclusion: results from a randomized controlled trial pilot study. Eur J Cardiothorac Surg 2009;36:553–7.
[11] Healey JS, Crystal E, Lamy A, Teoh K, Semelhago L, Hohnloser SH *et al*. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. Am Heart J 2005;150: 288–93.
[12] Lee CH, Kim JB, Jung SH, Choo SJ, Chung CH, Lee JW. Left atrial appendage resection versus preservation during the surgical ablation of atrial fibrillation. Ann Thorac Surg 2014;97:124–32.
[13] Kim R, Baumgartner N, Clements J. Routine left atrial appendage ligation during cardiac surgery may prevent postoperative atrial fibrillation-related cerebrovascular accident. J Thorac Cardiovasc Surg 2013;145:582–9; discussion 589.
[14] Zapolanski A, Johnson CK, Dardashti O, O'Keefe RM, Rioux N, Ferrari G *et al*. Epicardial surgical ligation of the left atrial appendage is safe, reproducible, and effective by transesophageal echocardiographic follow-up. Innovations (Phila) 2013;8:371–5.
[15] Garcia-Fernandez MA, Perez-David E, Quiles J, Peralta J, Garcia-Rojas I, Bermejo J *et al*. Role of left atrial appendage obliteration in stroke reduction in patients with mitral valve prosthesis—a transesophageal echocardiographic study. J Am Coll Cardiol 2003;42:1253–8.
[16] Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA *et al*. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol 2011;57:e101–98.
[17] Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. Circulation 2011;123: 417–24.
[18] Blackshear JL, Kusumoto F. Stroke prevention in atrial fibrillation: warfarin faces its challengers. Curr Cardiol Rep 2005;7:16–22.
[19] Leung DY, Black IW, Cranney GB, Hopkins AP, Walsh WF. Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. J Am Coll Cardiol 1994;24:755–62.
[20] Phan K, Xie A, La Meir M, Black D, Yan TD. Surgical ablation for treatment of atrial fibrillation in cardiac surgery: a cumulative meta-analysis of randomised controlled trials. Heart 2014;100:722–30.
[21] Phan K, Xie A, Tian DH, Shaikhrezai K, Yan TD. Systematic review and meta-analysis of surgical ablation for atrial fibrillation during mitral valve surgery. Ann Cardiothorac Surg 2014;3:3–14.
[22] Kearney K, Stephenson R, Phan K, Chan WY, Huang MY, Yan TD. A systematic review of surgical ablation versus catheter ablation for atrial fibrillation. Ann Cardiothorac Surg 2014;3:15–29.
[23] Roth P, Rahimi A, Boening A. The pericardium-reinforced technique of amputation of the left atrial appendage: quick, safe, and simple. Ann Thorac Surg 2010;90:e11–13.
[24] Dawson AG, Asopa S, Dunning J. Should patients undergoing cardiac surgery with atrial fibrillation have left atrial appendage exclusion? Interact CardioVasc Thorac Surg 2010;10:306–11.
[25] Katz ES, Tsiamtsiouris T, Applebaum RM, Schwartzbard A, Tunick PA, Kronzon I. Surgical left atrial appendage ligation is frequently incomplete: a transesophageal echocardiograhic study. J Am Coll Cardiol 2000;36: 468–71.