Left atrial concomitant surgical ablation for treatment of atrial fibrillation in cardiac surgery: A meta-analysis of randomized controlled trials

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Abstract

Introduction

Surgical ablation is a generally established treatment for patients with atrial fibrillation undergoing concomitant cardiac surgery. Left atrial (LA) lesion set for ablation is a simplified procedure suggested to reduce the surgery time and morbidity after procedure. The present meta-analysis aims to explore the outcomes of left atrial lesion set versus no ablative treatment in patients with AF undergoing cardiac surgery.

Methods

A literature research was performed in six database from their inception to July 2017, identifying all relevant randomized controlled trials (RCTs) comparing left atrial lesion set versus no ablative treatment in AF patient undergoing cardiac surgery. Data were extracted and analyzed according to predefined clinical endpoints.

Results

Eleven relevant RCTs were included for analysis in the present study. The prevalence of sinus rhythm in ablation group was significantly higher at discharge, 6-month and 1-year follow-up period. The morbidity including 30 day mortality, late all-cause mortality, reoperation for bleeding, permanent pacemaker implantation and neurological events were of no significant difference between two groups.

Conclusions

The result of our meta-analysis demonstrates that left atrial lesion set is an effective and safe surgical ablation strategy for AF patients undergoing concomitant cardiac surgery.
Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and associated with reduced survival and increased risk of stroke, with a prevalence of 30 to 50% in patients undergoing mitral valve surgery\cite{1–6}. The pathology of AF is supposed to be abnormal re-entry circuits existing in atrial walls. The first surgical procedure called Cox-Maze III procedure was introduced by Dr James L Cox in 1992\cite{7}. The Cox-Maze III operation is a complex procedure which involves a series of endocardial incisions in both atria. The aim of Cox-Maze procedure is to interrupt the multiple, disorganized re-entrant circuits\cite{8}. This procedure is usually performed with other cardiac surgery including mitral valve repair/replacement or coronary artery bypass graft. Recent researches renewed the pathophysiological mechanisms underlying AF and found the pulmonary veins and left atrium were the main “triggers” of AF\cite{9}. This discovery lead to the innovation of the traditional Cox-Maze III procedure and limited the incisions to left atrium even just pulmonary veins instead of both atria. On the other hand, the advent of new energy sources for maze operation including radiofrequency, cryo-energy and microwaves also reduced the complex of the procedure. Previous meta-analysis has demonstrated that surgical ablation is an effective and safe procedure for AF patients undergoing cardiac surgery or mitral valve surgery only\cite{10, 11}. However, the direct evidence respecting to outcomes of left atrial surgical ablation for AF patients were not established. In order to make a supplement to this field, the present meta-analysis aims to summarize the available randomized evidence about the clinical outcomes of left atrial surgical ablation in patients undergoing concomitant surgery.

Materials and methods

Literature search strategy

Electronic searches were performed using PubMed, Ovid Medline, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Review of Effectiveness (DARE) and ACP Journal Club from their date of inception to July 2017. To achieve the maximum sensitivity of the search strategy, we combined the terms: ‘atrial fibrillation’ AND ‘ablation’ AND ‘randomized controlled trial’ as either key words or medical subject headings (MeSH) terms. The reference lists of all retrieved articles were checked for further identification of extra relevant studies assessed using the inclusion and exclusion criteria.

Selection criteria

Inclusion criteria for the present systematic review and meta-analysis were as follows:

1. Randomized controlled trial.
2. Patients underwent any cardiac surgery concomitantly with surgical ablative treatment of atrial fibrillation.
3. All patients were diagnosed with permanent or persistent atrial fibrillation.
4. Surgery ablation techniques included the left atrial surgical ablation.
5. A direct comparison between cardiac surgery with or without left atrial surgical ablation.
6. The endpoints of study were sinus rhythm or AF-free survival.

Exclusion criteria for the present systematic review and meta-analysis were as follows:
1. Not a randomized controlled trial.
2. Catheter ablation without concomitant cardiac surgery.
3. Comparison between other ablation techniques or different ablation energy, such as Cox-maze, modified Cox-maze, biatrial surgical ablation, cut and sew, cryoablation, radiofrequency, microwave, bipolar and unipolar.
4. Patients with paroxysmal AF were included.
5. Duplicate data from the same study.

Data extraction and quality assessment
All data were extracted from article texts, tables and figures. Two investigators independently reviewed every retrieved article (XW and QH). A disagreement was solved by discussion and consensus with a third investigator (CW) if necessary. The risk of bias was assessed according to the Cochrane Collaboration for risk of bias, by two reviewers (JL and JJ). The final results were reviewed by senior investigators (MY and BC).

Statistical analysis
Clinical outcomes were assessed with a standard meta-analysis technique. The hazard ratio (HR) and odds ratio (OR) was used as a summary statistic. \( \chi^2 \) tests were used to examine heterogeneity between trials. I\(^2\) statistic was used to estimate the heterogeneity and I\(^2\) > 50% was considered as substantial heterogeneity. In the present meta-analysis, the results were analyzed with the random-effects model considering the possible clinical diversity and methodological variation between studies. HR and the corresponding 95% CI were used for freedom from atrial fibrillation indirectly calculated using the method of Tierney and colleagues[12] in each study. If there was a substantial heterogeneity, the possible reasons for this were explored qualitatively. Meta-regression was used to investigate the effects of covariates, especially variations in patient characteristics. Publication bias of the major outcomes of this meta-analysis was detected by Egger’s regression test. All P values were two-sided. All statistical analyses were conducted with Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata (version 12.0; StataCorp, College Station, TX).

Results
Literature search
A total of 1430 references were identified through six electronic database searches. Manual search of reference lists yielded two extra studies. After exclusion of duplicate or irrelevant references, 696 potentially relevant articles were retrieved. After detailed evaluation of these articles, 32 studies remained for assessment. After applying the selection criteria, 11 RCTs were selected for analysis (Fig 1). In these eleven studies, 666 patients underwent procedures that involved cardiac surgery with left atrial ablation (CS + LA group; \( n = 333 \)) or without surgical ablation (CS group; \( n = 333 \)). The study characteristics of these trials are summarized in Table 1.

Quality assessment
These eleven studies were all RCTs[13–23]. One study had more than 50 patients[13], while the remaining ten studies had less than 50 patients (range, 10–49 patients). Five studies used
cut-and-sew[13, 14, 18, 19, 23], two studies used radiofrequency ablation[20, 21], two studies used cryoablation[15, 22] and two studies used microwave[16, 17]. All studies reported patients undergoing left atrial ablation and left appendage amputation. A little variant existed among studies with regarding to ablation or cut-and-sew lines on the left atrial wall. All studies except one[17] reported a line connecting pulmonary veins and mitral valve annulus. Eight studies made a line connecting pulmonary veins and appendage amputation site[13–18, 21, 22]. Six studies isolated the pulmonary veins in one circle[14–17, 19, 23]. Four studies isolated the left and right pulmonary veins in pair[13, 18, 21, 22]. One study isolated the pulmonary veins in pair or one by one[20]. The five studies which isolated the pulmonary veins in pair or one by one made a connection line between two pairs. Only two studies reported performing cryoablation or electrocauterization to coronary sinus[15, 23]. The lesion set description of included studies were summarized in Table 2. All studies focused on permanent or persistent AF. SR was the primary endpoint in nine studies, while AF-free survival was the primary endpoint in two studies. The data of SR at discharge was reported in 8 of 11 studies. Preoperative data for co-variates, which were available for both groups, were variable between the studies in Table 3. Out of the 8 studies, age and gender were reported in 8, LVEF in 7, LAD in 8, AF duration in 7, NYHA III/IV in 2, hypertension in 4, stroke and diabetes in 3. As such, the NYHA, stroke and diabetes were excluded from meta-regression analysis for sinus rhythm at discharge. The data of freedom from atrial fibrillation were extracted indirectly from 7 of 11 studies. Out of the 7 studies, age, gender, LVEF and LAD were reported in 7, AF duration in 6, NYHA III/IV, hypertension, stroke and diabetes in 3. As such, the NYHA, stroke and diabetes were excluded from meta-regression analysis for freedom from atrial fibrillation at 1 year follow up. 30-day mortality was reported by all eleven studies. The 11 RCTs were also assessed qualitatively using tools recommended by the Cochrane Collaboration for the risk of bias. A graph and summary of selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias identified in each individual RCT is shown in Fig 2.
Baseline patient and operational characteristics

The baseline patient and operational characteristics were observed in Table 3. Similar baseline characteristics were observed in both groups. Males accounted for 24–83% of patients undergoing CS + LA and 41–83% undergoing CS alone (weighted mean: 52% vs. 57%; P > 0.05). The average age ranged between 35–75 years for both CS + LA and CS groups (weighted mean: 59 vs. 59; P = 0.71) for CS + LA and CS groups respectively. There were also no differences between CS+LA and CS groups in terms of LVEF (P = 0.33), LA diameter (LAD) (P = 0.26), NYHA III/IV (P = 0.24), prior stroke (P = 0.09) and diabetes (P = 0.99). CBP and aortic cross clamp time was significantly longer when cardiac surgery was performed concomitantly with left atrial surgical ablation (P <0.01). Five studies reported valvular surgery with
Table 3. Summary of baseline patient characteristics and risk factors in studies comparing CS+LA with CS alone in surgical treatment for atrial fibrillation.

| First author          | Age (y) | Male (%) | LVEF (%) | LAD (mm) | AF duration (mo) | NYHA III-IV (%) | Hypertension (%) | Prior stroke (%) | Diabetes (%) |
|-----------------------|---------|----------|----------|----------|------------------|-----------------|-----------------|-----------------|-------------|
|                       | CS+LA   | CS       | CS+LA    | CS       | CS+LA            | CS              | CS+LA           | CS              | CS          |
| Wang                  | 52±10   | 54±10    | 40       | 41       | 61±7            | 54±7            | 51±9            | 35±21           | 43          |
| Vasconcelos           | 50±10   | 51±10    | 27       | 43       | 69±9            | 55±5            | 55±5            | 24±20           | 43          |
| Srivastava            | 36±8    | 37±10    | 55       | 59       | 60±7            | 54±5            | 49±6            | 12              | 30          |
| Schuetz               | 65±10   | 70±8     | 50       | 74       | 63±13           | 54±17           | 55±11           | 46±34           | 111±11      |
| Knaut                 | 74±4    | 75±6     | 58       | 67       | 56±14           | 45±4            | 47±6            | 71±53           | 52±96       |
| Doukas                | 67±9    | 67±8     | 63       | 50       | 57±6            | 58±7            | 58±7            | 60±11           | 57±55       |
| De Lima               | 54±9    | 50±15    | 30       | 60       | 64±12           | 53±9            | 62±12           | 23±4           | 17±3        |
| Chevalier             | 70±6    | 66±10    | 24       | 50       | 60±9            | 55±11           | 53±11           | 161             | 89.2        |
| Cherniavsky           | 62±7    | 64±8     | 83       | 74       | 56±14           | 49±55           | 49±50           | NR              | NR          |
| Blomstrom-Lundqvist   | 70±8    | 66±8     | 83       | 83       | 54±9            | 61±11           | 58±7            | 26±33           | 33±54       |
| Albrecht              | 55±5    | 51±15    | 30       | 50       | 62±11           | 53±8            | 62±12           | 32±32           | 25±32       |
| Minimum               | 36      | 37       | 24       | 41       | 54              | 45              | 47              | 12              | 45          |
| Maximum               | 74      | 75       | 83       | 83       | 69              | 61              | 61              | 161             | 70          |
| Weighted average      | 59      | 59       | 52       | 57       | 59              | 54              | 54              | 46              | 55          |
| P                     | 0.71    | 0.22     | 0.33     | 0.26     | 0.85            | 0.24            | 0.85            | 0.09            | 0.99        |

CS: cardiac surgery; LA: left atrial ablation; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; AF, atrial fibrillation; NYHA, New York Heart Association Functional Classification; NR, not reported; M, median

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The CS + LA group also had a significantly higher proportion of patients in SR compared to CS group at 6-month (55.8% vs. 24.4%; OR, 5.00; 95% CI, 3.18–7.88; P < 0.00001; I² = 0%) and 1-year (55.1% vs. 20.8%; OR, 7.40; 95% CI, 3.97–13.79; P < 0.00001; I² = 16%) follow-up periods. The results are summarized in Fig 3. Meta-regression models found no significant effects exerted by patient age (P = 0.166), gender (P = 0.939), LVEF (P = 0.226), AF duration (P = 0.138), hypertension (P = 0.252), or LAD (P = 0.145) upon sinus rhythm at discharge in Fig 4. Subgroup analysis of different ablation energy including cut and sew radiofrequency ablation, Fig 2.

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Table 4. Summary of perioperative characteristics and complications.

| First author   | CBP time (min) | Cross-clamp time (min) | CABG (%) | Valvular surgery (%) | 30-day mortality (%) | Reoperation for bleeding (%) |
|----------------|----------------|------------------------|----------|----------------------|----------------------|-----------------------------|
|                | CS+LA          | CS                     | CS+LA    | CS                   | CS+LA                | CS+LA                       | CS+LA                      | CS           |
| Wang           | 101.0 ± 34.0   | 85.3 ± 34.7            | 72.1 ± 28.3 | 61.9 ± 29.3          | NR                   | NR                          | 100                        | 100          | 0            | 0           | NR          | NR          |
| Vasconcelos    | 106 ± 17       | 78 ± 24                | NR       | NR                   | 0                    | 0                           | 100                        | 0            | 6.7          | 0           | 6.7         | 0           |
| Srivastava     | NR             | NR                     | NR       | 0                    | 0                    | 100                         | 100                        | 6.7          | 0            | 0           | 5           | 5           |
| Schuetz        | 121 ± 27       | 104 ± 45               | 100 ± 25 | 74 ± 44              | 12.5                 | 26                          | 66.7                       | 36.8         | 4.2          | 5.3         | NR          | NR          |
| Knaut          | NR             | NR                     | NR       | NR                   | 54                   | 57                          | NR                         | NR           | 8.3          | 0           | NR          | NR          |
| Doukas         | 106 ± 34       | 99 ± 37                | 70 ± 26  | 64 ± 28              | 12.5                 | 12.5                        | 100                        | 6.1          | 8.3          | NR          | NR          | NR          |
| De Lima        | 97.8 ± 3       | 68.3 ± 22              | NR       | 49.1 ± 19            | 0                    | 100                         | 0                          | 0            | 0            | 0           | 10          |
| Chevalier      | NR             | NR                     | 93 ± 32  | 74 ± 19              | 0                    | 100                         | 4.8                        | NR           | 0            | 0           | NR          | NR          |
| Cherniaevsky   | 105.2 ± 37.2   | 70.8 ± 40.6            | 73.1 ± 28 | 47.5 ± 32.9          | 100                  | 100                         | 0                          | 0            | 0            | 0           | 0           | 0           |
| Blomstrom-Lundqvist | 147 ± 23 | 119 ± 33                | 87 ± 95  | 84 ± 23              | 20                   | 14.3                        | 100                        | 3.3          | 0            | 5.9         | 5.7         |
| Albrecht       | 99.85 ± 23.8   | 62.0 ± 23.8            | 74.7 ± 19 | 45.10 ± 21.1         | 0                    | 0                           | 100                        | 5            | 0            | 0           | 0           | 0           |
| Minimum        | 97.8           | 62                    | 70       | 45.1                 | 0                    | 0                           | 0                          | 0            | 0            | 0           | 0           | 0           |
| Maximum        | 147            | 119                   | 100      | 84                   | 100                  | 100                         | 8.3                        | 8.3          | 6.7          | 10          |
| Weighted average | 110.1    | 89.1                   | 78.4     | 64.1                 | 21.7                 | 23.5                        | 87.7                       | 85.2         | 3            | 1.5         | 3.3         | 3.3         |

Wang 101.0 ± 34.0 85.3 ± 34.7 72.1 ± 28.3 61.9 ± 29.3 NR NR 100 100 0 0 NR NR
Vasconcelos 106 ± 17 78 ± 24 NR NR 0 0 100 100 6.7 0 6.7 0
Srivastava NR NR NR 0 0 100 100 0 0 5 5
Schuetz 121 ± 27 104 ± 45 100 ± 25 74 ± 44 12.5 26 66.7 36.8 4.2 5.3 NR NR
Knaut NR NR NR 54 57 NR NR NR 8.3 0 NR NR
Doukas 106 ± 34 99 ± 37 70 ± 26 64 ± 28 10.2 12.5 100 100 6.1 8.3 NR NR
De Lima 97.8 ± 3 68.3 ± 22 NR 49.1 ± 19 0 0 100 100 0 0 0 10
Chevalier NR NR 93 ± 32 74 ± 19 0 0 100 100 4.8 0 NR NR
Cherniaevsky 105.2 ± 37.2 70.8 ± 40.6 73.1 ± 28.2 47.5 ± 32.9 100 100 0 0 0 0 0 0
Blomstrom-Lundqvist 147 ± 23 119 ± 33 87 ± 95 84 ± 23 20 14.3 100 100 3.3 0 5.9 5.7
Albrecht 99.85 ± 23.8 62.0 ± 23.8 74.7 ± 19.2 45.10 ± 21.1 0 0 100 100 5 0 0 0
Minimum 97.8 62 70 45.1 0 0 0 0 0 0 0 0
Maximum 147 119 100 84 100 100 100 100 8.3 8.3 6.7 10
Weighted average 110.1 89.1 78.4 64.1 21.7 23.5 87.7 85.2 3 1.5 3.3 3.3

CS: cardiac surgery; LA: left atrial ablation; CBP, cardiopulmonary bypass time; NR, not reported; CAGB, coronary artery bypass grafting

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CS: cardiac surgery; LA: left atrial ablation; CBP, cardiopulmonary bypass time; NR, not reported; CAGB, coronary artery bypass grafting

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microwave and cryoablation demonstrated no significant difference affecting SR at discharge. Subgroup analysis according to the included number of patients or concomitant cardiac surgery type didn’t make a difference regarding SR at discharge. The results are summarized in Figs 5–7. Left atrial surgical ablation showed a good benefit in terms of freedom from atrial fibrillation at 1-year follow up (Hazard Ratio, 0.41; 95% CI, 0.37–0.46; P < 0.00001; I² = 92%; Fig 8). Meta-regression models found no significant effects exerted by patient age (P = 0.07), gender (P = 0.08), LVEF (P = 0.42), AF duration (P = 0.14), or LAD (P = 0.31) upon freedom from atrial fibrillation at 1 year follow up in Fig 9.

Assessment of safety

Mortality. Mortality outcomes at 30 days were reported in all studies. The risk of 30-day all-cause mortality was not significantly different between CS + LA and CS groups at 30 days (2.7% vs. 2.3%; OR, 1.06; 95% CI, 0.43–2.60; P = 0.90; I² = 0%; Fig 10). Furthermore, all-cause late mortality was also not significantly different (1.7% vs. 2.4%; OR, 1.25; 95% CI, 0.30–5.29; P = 0.76; I² = 0%; Fig 11). No significant heterogeneity was observed in these two comparisons.

Neurological events. All but one study reported outcomes for neurological events. The rates of neurological events ranged from 0 to 10.3% in the studies. 4 of 10 studies with a total of 329 patients reported no neurological events. 3 of 10 studies with a total of 137 patients reported a rate of neurological events above 9%. Overall there was a comparable results between CS + LA and CS groups with no significant heterogeneity (3.2% vs. 3.2%; OR, 1.05; 95% CI, 0.41–2.67; P = 0.92; I² = 0%; Fig 12).

Permanent pacemaker implantations. Permanent pacemaker implantations were reported in nine out of eleven included studies. The permanent pacemaker implantation percentage was 4.7% on average in these studies with a range from 0 to 16.9%. 3 of 9 studies reported no permanent pacemaker implantation with 164 patients included. 3 of 9 studies reported a percentage over 11% with a total of 153 patients. Overall, there was no difference in pacemaker implantations whether left atrial ablation was performed or not (5.5% vs. 5.1%; OR, 1.08; 95% CI, 0.48–2.40; P = 0.85; I² = 5%; Fig 13).
Reoperation for bleeding. Reoperation for bleeding were reported in six out of eleven included studies. The average reoperation for bleeding rate was 1.5%, ranging from 0 to 6.2%. 2 of 6 studies reported no reoperation for bleeding with a total of 104 patients. Overall, there was no difference in reoperation for bleeding between CS + LA and CS groups (5.3% vs. 5.1%; OR, 1.05; 95% CI, 0.31–3.55; P = 0.94; I² = 0%; Fig 14).

**Table 4. Meta-regression analysis assessing the effect of various patient characteristics on sinus rhythm at discharge.** LVEF: left ventricular ejection fraction; LAD: left atrial diameter.

| Study or Subgroup | CS+LA | CS | Odds Ratio | M-H, Random, 95% CI |
|-------------------|-------|----|------------|---------------------|
| **4.1.1 Discharge SR** |       |    |            |                     |
| Albrecht 2009      | 16    | 20 | 12.4%      | 22.67 [4.37, 117.47]|
| Cherniavsky 2014   | 30    | 34 | Not estimable |                     |
| Chevalier 2009     | 16    | 22 | 8.3%       | 67.20 [7.13, 633.37]|
| Doukas 2005        | 24    | 28 | 13.5%      | 22.08 [4.82, 101.21]|
| Schaeuf 2003       | 13    | 19 | 14.0%      | 8.30 [1.45, 27.45]  |
| Srivastava 2008    | 21    | 40 | 19.8%      | 3.81 [1.45, 10.02]  |
| Vasconcelos 2004   | 13    | 14 | 9.1%       | 1.08 [0.13, 8.95]   |
| Wang 2014          | 44    | 60 | 22.9%      | 5.71 [2.73, 11.96]  |
| **Subtotal (95% CI)** | 269   | 267 | 100.0%     | 8.04 [3.74, 17.20]  |
| **Total events**   | 177   | 80 |            |                     |

Egger's test detected no publication bias for the major outcomes of this meta-analysis: 30 days mortality (P = 0.52), permanent pacemaker implantations (P = 0.23), neurological events (P = 0.73), and reoperations for bleeding (P = 0.22). Publication bias was found regarding sinus
rhythm prevalence at 1 year (P = 0.02). After excluding the study of Chevalier or Wang, no publication bias was detected with P value of 0.09 and 0.06, respectively.

Discussion

AF has been supposed to be caused by the multiple and disorganized re-entrant circuits in atrial walls. Cox-Maze III procedure firstly applied by Dr James L Cox in 1992 was the gold standard treatment for AF. During the past two decades, modified Cox-Maze procedures and multiple ablation energy improved the outcomes of surgical ablation compared with traditional Cox-Maze III procedure. A recent meta-analysis has confirmed the cardiac surgery with concomitant surgical ablation is an effective and safe strategy for AF[10]. However, the efficacy and safety of simplified left atrial surgical ablation were not established. Thus, our study aims to report the clinical outcomes of CS+LA versus CS through a meta-analysis of RCTs.

AF has been consistently proved to be an independent predictor of life and survival, which suggests that the restoration of SR in AF patients is a critical therapeutic strategy[24–27]. For example, the AFFIRM study proved that the prevalence of SR was an important, independent predictor of survival, after adjustment for clinical variables such as age and comorbidities[26]. The risk to die among patients in SR was almost half of those who did not improve from AF (adjusted hazard ratio, 0.53; 99% CI, 0.39 to 0.72; P < 0.0001). In the present meta-analysis, we demonstrated that a higher SR prevalence in the CS+LA group at discharge (65.8% vs. 30.0%), 6-month (55.8% vs. 24.4%) and 1-year (55.1% vs. 20.8%) follow-up compared to CS group. Surgical ablation also improved the freedom from atrial fibrillation at 1-year follow up (HR, 0.41, 95% CI, 0.37–0.46; P < 0.00001; I² = 92). Previous meta-analyses had proved that
concomitant surgical ablation was a safe and effective at restoring rhythm during cardiac surgery with no exception for mitral valve surgery[10, 11]. The surgical ablation group had a higher prevalence of sinus rhythm at all 12 month follow up (OR, 6.72; 95% CI 4.88 to 9.25; P < 0.00001). The mortality, pacemaker implantation and neurological events were similar compared with no surgical ablation group. Another meta-analysis comparing biatrial ablation (BA) and left atrial ablation for AF found that the superiority of BA for restoring SR only maintained in 1 year with no difference beyond 1 year[28]. The SR prevalence in BA and LA group was similar for patients with follow-up beyond 1 year (59 vs 64%; OR 1.03; 95% CI 0.70–1.51; P = 0.87; I^2 = 26%). Our meta-analysis proved that left atrial ablation was an effective therapeutic strategy to restore SR in persistent or permanent AF patients, which was a good supplement to the previous studies.

The present meta-analysis found acceptable 30-day mortality (range: 0–8.3%) and all-cause late mortality rates (range: 0–7.5%) in included RCTs with no significant difference between CS+LA and CS group. Considering five of eleven studies underwent the traditional cut-and-sew techniques, the low mortality justified the safety of cut-and-sew in left atrial maze surgery. However, the small number of patients in RCTs suggested this result should be treated with caution.

Performing surgical atrial fibrillation in conjunction with cardiac surgery was supposed to increase the risk for postoperative permanent pacemaker requirement[29]. The adjusted odds of permanent pacemaker implantation was higher in surgical ablation group than that in patients with no history of AF who underwent cardiac surgery (OR 2.7; 95% CI 1.7–4.4). In the present meta-analysis, permanent pacemaker implantations were similar in CS+LA and CS group with a proportion of 5.5% and 5.1%, which was lower than the 5.94 to 7.10%
reported by a large retrospective study of the Society of Thoracic Surgeons National Cardiac Database[30]. This result suggested that LA lesion set was a safe procedure in terms of pacemaker implantation. It was consistent with a recent retrospective study which found that not left atrial but biatrial lesion set was the only statistically significant predictor of permanent pacemaker implantation after concomitant surgical ablation for AF through a univariate and multivariate analysis of 594 patients[31]. Demographic data, type of surgical procedure, and type of energy source did not have a significant impact of pacemaker implantation rate. The enhanced SR outcomes may reduce the incidence of permanent pacemaker implantation. However, this speculation should be taken with caution as studies reported different indications for pacemaker implantations.

No significant difference was found between CS+LA and CS group in terms of neurological events. Previous studies reported a protective effect from neurological events after Cox-Maze technique in AF patients undergoing concomitant cardiac surgery[32–35]. The negative outcome in our meta-analysis may be as a result of mixed factors including prosthetic valve

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Fig 7. Meta-regression analysis assessing the effect of various patient characteristics on freedom for atrial fibrillation at 1 year follow-up. LVEF: left ventricular ejection fraction; LAD: left atrial diameter.

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Fig 8. Forest plot of 1-year freedom from atrial fibrillation at 1 year follow-up, showing summary of HRs with 95% confidence intervals for included studies.

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implantation, oral anti-coagulant or anti-platelet drugs, and the interaction between antiarhythmic and anti-coagulant drugs. We also found a similar reoperation rates for bleeding in these two groups. This result was logically reasonable as the reoperation for bleeding was similar in mixed BA and LA surgical ablation compared with cardiac surgery alone[10].

There are several limitations to our meta-analysis. Firstly, the RCTs included in this meta-analysis were small sample size studies. Secondly, the variant ablation or cut-and-sew lines in left atrial among RCTs may had influence on the efficacy of surgical ablation. Thirdly, the follow-up results beyond 1 year were not reported in most RCTs which cast doubts on the long-term efficacy of surgical ablation. Fourthly, AF monitoring in RCTs were based on ECG or 24h Holter at specific time point which may not be effective to detect the paroxysmal or

Fig 9. Meta-regression analysis assessing the effect of various patient characteristics on freedom for atrial fibrillation at 1 year follow up. LVEF: left ventricular ejection fraction; LAD: left atrial diameter.

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| Study or Subgroup | CS+LA Events | Total | CS Events | Total | Weight | Odds Ratio M.H, Random, 95% CI |
|-------------------|--------------|-------|-----------|-------|--------|-----------------------------|
| Albrecht 2009     | 0            | 70    | 0         | 70    |        | Not estimable               |
| Blomstrom Lundqvist 2007 | 3 | 49    | 4         | 48    | 33.3%  | 0.72 [0.15, 3.39]            |
| Cherniavsky 2014  | 0            | 30    | 0         | 34    |        | Not estimable               |
| Chevalier 2009    | 1            | 21    | 0         | 22    | 7.6%   | 3.29 [0.13, 85.44]          |
| de Lima 2004      | 0            | 10    | 0         | 10    |        | Not estimable               |
| Doukas 2005       | 3            | 49    | 4         | 48    | 33.3%  | 0.72 [0.15, 3.39]           |
| Knaut 2010        | 2            | 24    | 0         | 21    | 8.4%   | 4.78 [0.22, 105.36]         |
| Schuetz 2003      | 1            | 24    | 1         | 19    | 10.0%  | 0.78 [0.05, 13.39]          |
| Srivastava 2008   | 0            | 40    | 0         | 40    |        | Not estimable               |
| Vasconcelos 2004  | 1            | 15    | 0         | 14    | 7.5%   | 3.00 [0.11, 79.91]          |
| Wang 2014         | 0            | 70    | 0         | 70    |        | Not estimable               |
| Total (95% CI)    | 402          | 396   | 100.0%    |       | 1.06   | [0.43, 2.60]                |

Total events 11

Heterogeneity: Tau² = 0.00; Chi² = 2.32, df = 5 (P = 0.89), I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)

Fig 10. Forest plot of 30-day mortality, showing summary ORs with 95% confidence intervals for included studies.

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### Fig 11. Forest plot of late mortality, showing summary ORs with 95% confidence intervals for included studies.

![Forest plot of late mortality](https://doi.org/10.1371/journal.pone.0191354.g011)

| Study or Subgroup | CS+LA Events | Total | CS Events | Total | Weight | M-H, Random, 95% CI | Odds Ratio |
|-------------------|--------------|-------|-----------|-------|--------|-------------------|------------|
| Albrecht 2009     | 0            | 20    | 0         | 20    | Not estimable |                  |            |
| Cherniavsky 2014  | 0            | 30    | 0         | 34    | Not estimable |                  |            |
| de Lima 2004      | 0            | 10    | 0         | 10    | Not estimable |                  |            |
| Knaust 2010       | 1            | 24    | 0         | 21    | 19.6%  | 2.74 [0.11, 71.04] |            |
| Srivastava 2008   | 3            | 40    | 2         | 40    | 61.1%  | 1.54 [0.24, 9.75]  |            |
| Vasconcelos 2004  | 0            | 15    | 1         | 14    | 19.3%  | 0.29 [0.01, 7.74]  |            |
| Wang 2014         | 0            | 70    | 0         | 70    | Not estimable |                  |            |

Total (95% CI): 209 / 209 = 100.0%

Heterogeneity: $\tau^2 = 0.00$, $\text{Chi}^2 = 1.04$, df = 2 ($p = 0.60$), $I^2 = 0$

Test for overall effect: $Z = 0.30$ ($p = 0.78$)

### Fig 12. Forest plot of neurological events, showing summary ORs with 95% confidence intervals for included studies.

![Forest plot of neurological events](https://doi.org/10.1371/journal.pone.0191354.g012)

| Study or Subgroup | CS+LA Events | Total | CS Events | Total | Weight | M-H, Random, 95% CI | Odds Ratio |
|-------------------|--------------|-------|-----------|-------|--------|-------------------|------------|
| Albrecht 2009     | 0            | 20    | 1         | 20    | 8.3%   | 0.32 [0.01, 8.26]  |            |
| Blomstrom Lundqvist 2007 | 4        | 40    | 2         | 35    | 27.9%  | 2.54 [0.43, 14.95] |            |
| Cherniavsky 2014  | 0            | 30    | 0         | 34    | Not estimable |                  |            |
| Chevalier 2009    | 3            | 21    | 1         | 22    | 15.9%  | 3.50 [0.33, 36.87] |            |
| de Lima 2004      | 0            | 10    | 1         | 10    | 0.0%   | 0.30 [0.01, 8.33]  |            |
| Doukas 2006       | 2            | 49    | 3         | 48    | 28.1%  | 0.64 [0.10, 4.00]  |            |
| Knaust 2010       | 0            | 24    | 0         | 21    | Not estimable |                  |            |
| Srivastava 2008   | 0            | 40    | 0         | 40    | Not estimable |                  |            |
| Vasconcelos 2004  | 1            | 15    | 2         | 15    | 13.9%  | 0.46 [0.04, 5.75]  |            |
| Wang 2014         | 0            | 70    | 0         | 70    | Not estimable |                  |            |

Total (95% CI): 309 / 315 = 100.0%

Heterogeneity: $\tau^2 = 0.00$, $\text{Chi}^2 = 3.71$, df = 5 ($p = 0.59$), $I^2 = 0$

Test for overall effect: $Z = 0.10$ ($p = 0.92$)

### Fig 13. Forest plot of permanent pacemaker implantations, showing summary ORs with 95% confidence intervals for included studies.

![Forest plot of permanent pacemaker implantations](https://doi.org/10.1371/journal.pone.0191354.g013)

| Study or Subgroup | CS+LA Events | Total | CS Events | Total | Weight | M-H, Random, 95% CI | Odds Ratio |
|-------------------|--------------|-------|-----------|-------|--------|-------------------|------------|
| Blomstrom Lundqvist 2007 | 7         | 30    | 4         | 35    | 32.3%  | 2.38 [0.62, 9.02]  |            |
| Cherniavsky 2014  | 0            | 30    | 0         | 34    | Not estimable |                  |            |
| Chevalier 2009    | 3            | 21    | 2         | 22    | 18.6%  | 1.87 [0.25, 11.13] |            |
| de Lima 2004      | 0            | 10    | 0         | 10    | Not estimable |                  |            |
| Doukas 2006       | 2            | 49    | 4         | 48    | 13.8%  | 0.47 [0.08, 2.68]  |            |
| Knaust 2010       | 2            | 24    | 4         | 21    | 18.5%  | 0.39 [0.06, 2.36]  |            |
| Srivastava 2008   | 0            | 40    | 0         | 40    | Not estimable |                  |            |
| Vasconcelos 2004  | 0            | 15    | 1         | 14    | 5.8%   | 0.29 [0.01, 7.74]  |            |
| Wang 2014         | 2            | 70    | 0         | 70    | 8.7%   | 5.15 [0.24, 109.15]|            |

Total (95% CI): 289 / 294 = 100.0%

Heterogeneity: $\tau^2 = 0.05$, $\text{Chi}^2 = 5.24$, df = 5 ($p = 0.39$), $I^2 = 5$

Test for overall effect: $Z = 0.18$ ($p = 0.85$)
asymptomatic recurrent episodes. Fifthly, publication bias was found in the present meta-analysis. However, the main outcomes were robust in sensitive analysis.

Conclusion

We draw a conclusion that concomitant left atrial surgical ablation and cardiac surgery for persistent or permanent AF has a good efficacy for restoration of SR in 1 year following surgery. The 30 day mortality, late all-cause mortality, neurological events and permanent pacemaker implantation are of no significant difference between two groups. Thus, our meta-analysis demonstrates that left atrial surgical ablation is an effective therapeutic strategy for AF patients undergoing concomitant cardiac surgery without increased risk of mortality and morbidity.

Supporting information

S1 File. PRISMA checklist.

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