Systematic Review

Surgical ablation of atrial fibrillation during mitral valve surgery: a systematic review and meta-analysis

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Background: Atrial fibrillation (AF) is a common tachyarrhythmia, affecting approximately 33 million people worldwide, and is frequently associated with mitral valve disease. Surgical ablation during mitral valve surgery provides an opportune circumstance for arrhythmia correction. The results of recent randomized trial data are promising, demonstrating both safety and efficacy. The aim of this systematic review is to report the efficacy and morbidity of concomitant surgical ablation for AF during mitral valve surgery.

Methods: Five electronic databases were searched from inception to March 2023. All studies reporting the primary outcome, freedom from AF (FFAF), for patients with a history of AF undergoing concomitant mitral valve surgery were identified. Studies with patient cohorts less than 100 were excluded. Relevant data were extracted and a meta-analysis of proportions was conducted using a random-effects model. Survival data were pooled from original Kaplan-Meier curves and reconstructed, reporting aggregate FFAF and survival.

Results: Thirty-six studies with a total of 8,340 patients were included in the systematic review. All 36 papers reported postoperative FFAF with a pooled result of 76.9% [95% confidence interval (CI): 73.8–79.9%] at a weighted mean follow-up of 40.2 months, however this result was associated with significant heterogeneity (I^2=89%). A total of 31 studies reported postoperative short-term mortality, with a pooled result of 1.68% (95% CI: 1.15–2.29%). Aggregate survival at 1 to 5 years was 93.7%, 92.5%, 91.3%, 89.4%, and 87%, respectively, and aggregate FFAF for 1 to 5 years was 90.2%, 83.5%, 79.5%, 76.4% and 73.2%, respectively.

Conclusions: Evaluation of the evidence suggests that concomitant ablation for AF during mitral valve surgery is both safe and efficacious. The results were associated with significant heterogeneity, reflective of variable institutional protocols, patient characteristics, and lesion sets. Randomized data with longer term follow-up would help validate these results.

Keywords: Atrial fibrillation (AF); mitral valve surgery; MAZE; ablation; freedom from atrial fibrillation

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Introduction

Atrial fibrillation (AF) is a common tachyarrhythmia, affecting approximately 33 million people worldwide (1,2). Mitral valve disease, in particular, has a strong association with AF, with 30–40% of patients developing AF in the context of mitral valve disease (3). The most common association is with mitral stenosis, which produces dilatation and fibrosis of the left atrium due to volume overload (4). Left atrial dilatation produces a further challenge, as it is resistant to ablation, particularly if the diameter exceeds 60 mm (5). There are a number of benefits associated with performing AF ablation at the same time as mitral valve

surgery, including improved freedom from AF (FFAF), and quality of life (6,7) It provides an opportune moment for direct epicardial and endocardial lesion sets on the atria. Furthermore, the left atrial appendage (LAA) may be ligated concurrently, further reducing the incidence of thromboembolism (8).

A number of surgical approaches enable AF ablation concomitantly with mitral valve surgery. The gold standard approach is the Cox-Maze procedure, developed in 1992, which utilizes a series of lesions on the left and right atrium. The creation of a "maze" of incisions on both the atria interrupt the circuits responsible for the creation and propagation of AF (9). Earlier iterations of the Cox-Maze procedure utilized "cut and sew" lesions, whereas later iterations (namely the Cox-Maze IV procedure) utilise energy sources to create lesions. The Cox-Maze IV procedure reports excellent long-term (10-year) FFAF of 77% (10). Utilizing the Cox-Maze procedure in conjunction with mitral valve surgery has been the topic of recent randomized control trials, with one notable trial demonstrating a significantly higher FFAF when compared to mitral valve surgery alone (11). Concomitant surgical ablation of AF during valvular surgery has also been shown to be safe, with large registry data demonstrating that it does not increase operative mortality but may in fact be associated with a reduction in relative mortality compared to patients who do not undergo concomitant ablation (12).

Despite the large body of evidence supporting AF ablation during mitral valve surgery, the American Heart Association (AHA) provided a 2a recommendation in 2020 for surgical correction of AF during valvular heart surgery (13). This was echoed by the 2021 European Society of Cardiology (ESC) providing level 2a evidence for concomitant ablation and LAA exclusion (14). The aim of this systematic review and meta-analysis is to evaluate the efficacy of concomitant AF ablation during mitral valve surgery. The primary outcome was FFAF. The secondary aim is to evaluate the safety profile of concomitant ablation.

Methods

Literature search strategy

Five electronic databases were used to perform the literature search, including MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews (CDSR) and SCOPUS. These databases were searched from inception to the 5th of March 2023. The search strategy included a combination of keywords and Medical Subject Headings (MeSH), including "Ablation" OR "Maze" OR "Cryomaze" OR "Cryo" AND "Atrial Fibrillation" AND "Mitral Valve". Predefined criteria for selection were used to assess all articles. The article was written in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (15). The PRISMA flowchart is outlined in Figure S1. Two reviewers (A.E and B.M) independently screened the abstracts of all identified records. Included titles were then reviewed with a full-text copy by the same two reviewers. Any conflicts were resolved with a third independent reviewer (A.W.S.). The reference list of selected studies was manually searched to identify any additional titles, not identified by the electronic search.

Selection criteria

Studies were eligible for inclusion if they included a patient population that underwent AF ablation concomitantly with mitral valve surgery. Mitral valve surgery was deemed to be any operation involving the mitral valve as the primary pathology (e.g., mitral stenosis or regurgitation), through an open chest approach (sternotomy or thoracotomy). AF ablation was defined as any cut/sew lines, radiofrequency, or cryoablation performed on the heart (i.e., either epicardial or endocardial). In order to minimise the risk of publication bias associated with smaller studies, only those with 100 or more patients were included. The inclusion criteria were: (I) AF ablation concurrently with mitral valve surgery; (II) mitral valve surgery as the primary pathology and indication for surgery; (III) cohort sizes >100 patients; (IV) open chest procedure through either a sternotomy or thoracotomy; (V) FFAF reported; (VI) published after 2000. Studies which reported concomitant aortic valve surgery and coronary artery bypass grafting (CABG) were included as long as mitral valve surgery was the primary indication. Studies that had mixed populations that did not delineate between pathologies were excluded. Studies which performed mitral valve surgery through a closed chest approach (robotic mitral valve surgery) were also excluded. When trials/registries/institutions published duplicate studies with extended length of follow-up or larger study populations, the most updated and complete study was included. Included studies were limited to those in English and only involving human subjects. Abstracts, case reports, conference presentations, editorials, and reviews were excluded.

Outcomes

The primary outcome was defined as FFAF (i.e., sinus rhythm maintenance postoperatively). Subgroup analysis was performed based on study design, rheumatic etiology, type of AF, lesion sets utilized, and enlarged left atria (LA; greater than 60 mm). Secondary endpoints were short-term mortality (in-hospital or 30-day mortality), postoperative stroke, reoperation for bleeding, and pacemaker insertion over the follow-up period.

Data extraction and statistical analysis

Two independent reviewers (A.E and B.M) extracted data directly from publication texts, tables, and figures. A third reviewer (A.W.S.) independently reviewed and confirmed the integrity of all extracted data. Attempts were made to clarify missing data with the authors. For baseline variables, nominal data was recorded as number of events (n) and expressed as a percentage. Continuous variables were either expressed as a mean and standard deviation (SD) or median and interquartile ranges (IQR). For statistical analysis, medians and IQR were first converted to mean and SD utilising the method outlined by Wan *et al.* (16). When data was exactly uniform, the SD was listed as zero. Statistical analysis was carried out using Stata® (Version 17.0, StataCorp, Texas, USA). Baseline continuous data was collated using the "metan" function and the pooled result expressed as a weighted mean (n) and 95% confidence interval (CI). Nominal data was collated and expressed as a proportion and percentage. To summarize outcome data, a meta-analysis of proportions was performed using the "metaprop" function, with a Freeman-Tukey arcsine transformation. A random effects model was utilized to account for varied study design, experience of the surgeons, center protocol, and population. Results were expressed as forest plots where appropriate, with cumulative proportion expressed as a single percentage. The influence of energy source and lesions sets on the primary outcome was explored utilizing the "metaprop", "by(group)" function. Heterogeneity was assessed using the I^2 test statistic. Low heterogeneity was denoted by I^2<50%, moderate heterogeneity by I^2=50–74%, and high heterogeneity by I^2≥75%. Statistical significance was denoted by P<0.05. Kaplan-Meier survival curves were digitized where numbers at risk were presented, and an algorithmic computational tool was utilized to derive individual patient data as outlined by Guyot *et al.* (17). Event and censoring data were compiled for 5 years, and overall survival curves were produced with Stata® (Version 17.0, StataCorp).

Assessment of bias and heterogeneity

Publication bias was assessed through visual inspection of funnel plots and Begg's rank correlation test in Stata MP®. A trim-and-fill analysis was performed in the instance of publication bias. An influential study analysis with adjusted effect sizes and heterogeneity was computed after the omission of each study. The risk of bias was performed utilising two tools: the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for cohort studies and the Risk of Bias in Randomized trials (RoB2) tool for randomized studies.

Results

Study characteristics

The literature search identified a total of 4,365 studies (Figure S1). No additional articles were identified after manual searches of reference lists. After removing duplicates, a total of 3,266 articles were screened. After full review, 36 studies with 8,340 patients were included in the systematic review (*Table 1*). The majority of papers were cohort studies, of which six were prospective, 28 were retrospective, and two were randomized trials. The cohort sizes ranged from 100 to 812 patients. The recruitment years for patients ranged from 1994 to 2021. The majority of papers examined a cohort of patients with AF and mitral valve disease in general, whereas seven papers examined a cohort of patients with AF and rheumatic mitral valve disease exclusively (19,23,24,26,29,39,40). The weighted mean follow-up period was 42.2 months (95% CI: 33.0–51.4), with a weighted mean reported follow-up of 40.2 months (95% CI: 32.8–47.6). Study data was is summarized in *Table 1*.

Baseline demographic data

All studies reported baseline demographic data. The weighted mean age of patients was 57.2 years (95% CI: 54.7–59.8) and 46.5% were male. The majority of patients had persistent AF (82.5%), and 17.5% of patients had paroxysmal AF. The weighted mean duration of AF preoperatively was 50 months (95% CI: 46.1–53.9), and weighted mean ejection fraction (EF) of 55.5% (95% CI: 53.7–57.1%). The weighted mean LA diameter was

Table 1 Study details

Primary author	Study period	Country	Study design	Patient cohort	Total patients	Mean follow up time (months)	Reported follow up time (months)	Method of monitoring
Ad *et al.* (18)	2005	United States of America	PCS	AF and mitral valve surgery	473	52.0±37	36.0±0	Holter
Baek *et al.* (19)	2000–2004	Republic of Korea	RCS	AF and rheumatic mitral valve surgery	170	26.6±15.2	26.6±15.2	ECG/Holter
Bando *et al.* (20)	1992–2000	Japan	RCS	AF and mitral valve surgery	258	36.0±0	36.0±0	ECG
Bogachev-Prokophiev *et al.* (21)	2012–2020	Russia	RCS	AF and mitral valve surgery	242	43.9±23.8	43.9±23.8	Holter
Brick *et al.* (22)	2016	Brazil	PCS	AF and mitral valve surgery	100	60.0±0	60.0±0	Holter
Chavez *et al.* (23)	2013–2014	Brazil	RCS	AF and rheumatic mitral valve surgery	103	12.0±0	12.0±0	ECG/Holter
Chen *et al.* (24)	2009–2012	China	RCS	AF and rheumatic mitral valve surgery	324	12.0±0	12.0±0	Holter
Churyla *et al.* (25)	2004–2014	United States of America	RCS	AF and mitral valve surgery	616	38.0±58.4	38.0±58.4	ECG/Holter
Dong *et al.* (26)	2009–2011	China	PCS	AF and rheumatic mitral valve surgery	191	17.4±11.8	12.0±0	ECG
Ezelsoy *et al.* (27)	2001–2015	Turkey	RCS	AF and mitral valve surgery	167	136±29.6	136±29.6	ECG/Holter
Funatsu *et al.* (28)	1998–2006	Japan	RCS	AF and mitral valve surgery	268	45.6	45.6	ECG/Holter
Garcia-Villarreal (29)	1998–2007	Mexico	RCS	AF and rheumatic mitral valve surgery	100	60.0±0	60.0±0	Holter/ echocardiography
Gatti *et al.* (30)	2005–2017	Italy	RCS	AF and mitral valve surgery	118	79.2±45.6	79.2±45.6	Holter
Geidel *et al.* (31)	2001–2006	Germany	PCS	AF and mitral valve surgery	109	36.0±19.0	36.0±19.0	ECG
Gelsomino *et al.* (32)	2003–2012	Netherlands	RCS	AF and mitral valve surgery	685	56.5±18.3	56.5±18.3	ECG/Holter
Gillinov *et al.* 2006 (33)	1993–2004	United States of America	RCS	AF and mitral valve surgery	152	12.0±0	12.0±0	ECG
Gillinov *et al.* 2015 (11)	2010–2013	United States of America	RCT	AF and mitral valve surgery	133	12.0±0	12.0±0	Holter
Goette *et al.* (34)	2009–2012	Germany	RCS	AF and mitral valve surgery	120	20.0±13.0	20.0±13.0	Holter
Han *et al.* (35)	2016–2018	China	RCT	AF and mitral valve surgery	200	12.0±0	12.0±0	Holter
Hwang *et al.* (36)	1997–2012	Republic of Korea	RCS	AF and mitral valve surgery	362	40.4±51.8	40.4±51.8	ECG/Holter
Jiang *et al.* (37)	2009–2020	China	RCS	AF and mitral valve surgery	168	3–6	3–6	ECG

Table 1 (*continued*)

Table 1 (*continued*)

Primary author	Study period	Country	Study design	Patient cohort	Total patients	Mean follow up time (months)	Reported follow up time (months)	Method of monitoring
Kasemsarn *et al.* (38)	2004–2011	Thailand	RCS	AF and mitral valve surgery	236	41.0 (median)	41.0 (median)	ECG
Kim *et al.* (39)	1994–2004	Republic of Korea	RCS	AF and rheumatic mitral valve surgery	127	86.4±32.4	86.4±32.4	ECG
Kim *et al.* (40)	1997–2016	Republic of Korea	RCS	AF and rheumatic mitral valve surgery	812	64.5±67.5	36.0±0	Holter
Labin *et al.* (41)	2001–2015	United States of America	PCS	AF and mitral valve surgery	245	41.0±37.0	36.0±0	ECG/Holter
Lavalle *et al.* (42)	2008–2017	Italy	RCS	AF and mitral valve surgery	100	24.0±0	24.0±0	ECG/Holter
Lawrence *et al.* (43)	2002–2012	United States of America	RCS	AF and mitral valve surgery	184	32.4±28.8	24.0±0	ECG/Holter
Loardi *et al.* (44)	2005–2012	Italy	RCS	AF and mitral valve surgery	122	24.0±0	24.0±0	Holter/ echocardiography
McCarthy *et al.* (45)	2013–2021	United States of America	RCS	AF and mitral valve surgery	277	33.6±24.0	33.6±24.0	Holter/device
Nardi *et al.* (46)	1999–2010	United States of America	RCS	AF and mitral valve surgery	128	108±0	108±0	Echocardiography
Rahmanian *et al.* (47)	2003–2006	United States of America	RCS	AF and mitral valve surgery	141	9.96±6.36	9.96±6.36	ECG
Rostagno *et al.* (48)	2003–2011	Italy	PCS	AF and mitral valve surgery	301	96.0	96.0	ECG/Holter
Wang *et al.* (49)	2013–2018	China	RCS	AF and mitral valve surgery	129	24.0±0	24.0±0	Holter/ echocardiography
Wang *et al.* (50)	1999–2006	China	RCS	AF and mitral valve surgery	122	19.0±16.0	19.0±16.0	Echocardiography
Wu *et al.* (51)	1995–2011	Taiwan	RCS	AF and mitral valve surgery	207	101±50.9	101±50.9	ECG/Holter
Yao *et al.* (52)	2016–2019	China	RCS	AF and mitral valve surgery	150	24.0±0	24.0±0	ECG/Holter

PCS, prospective cohort study; AF, atrial fibrillation; RCS, retrospective cohort study; RCT, randomised control trial; ECG, electrocardiogram.

55.7 mm (95% CI: 42.5–59.1) and four studies reported a mean LA diameter greater than 60 mm (19,21,29,50). These results are summarized in *Table 2*.

Operative data

Operative data was variably reported. The majority of patients underwent a sternotomy (94.7%) and 5.3% underwent a mini-access procedure through a thoracotomy. A slight majority of patients (54.8%) underwent a mitral valve replacement, and 45.2% of patients underwent a mitral valve repair; 56.9% of patients had rheumatic etiology for mitral valve disease. In terms of concomitant procedures, 8.7% of patients underwent CABG and 14.9% underwent an aortic valve replacement (AVR). The energy source used was reported by all studies. Ten studies utilized cryoablation alone, and 17 studies utilized radiofrequency ablation alone. One study utilized a harmonic scalpel, and two studies utilized cut and sew lesions. The remaining studies used a combination of energy sources. A bi-atrial lesion set or bi-atrial maze (BAM) was exclusively utilized by 19 studies, whereas a left atrial maze (LAM) was utilized by 7 studies. An isolated pulmonary vein isolation (PVI) was performed by two studies. The remaining studies used a combination of lesion sets within their patient cohorts. Left atrial reduction was performed by only eight studies. The main indication for this was an enlarged left atrium. Finally, LAA exclusion was reported by most studies, and performed in the entire cohort in 21 studies. The cardiopulmonary bypass time (CPBT) and cross clamp times (CCT) were variably reported, with a weighted mean of 142 min (95% CI: 132–152) and 98 min (95% CI: 92.7–103.3) respectively. Procedural characteristics are summarized in *Table 3*. In terms of postoperative protocol, the use of antiarrhythmic drugs (AADs) and anticoagulation varied greatly and remained study specific. The majority of studies utilised amiodarone and continued it for at least 3 months. The most common oral anticoagulation agent used was warfarin. Only two studies specified the cessation of warfarin if patients were in sinus rhythm (18,38) (Table S1).

Primary endpoint

All 36 papers reported postoperative FFAF. The pooled freedom from AF (FFAF) was 76.9% (95% CI: 73.8–79.9%) at a weighted mean follow-up of 40.2 months (95% CI: 32.8–47.6). This result was associated with large heterogeneity (I^2=89%; *Figure 1*). The corresponding FFAF off AAD was 75.9% (95% CI: 68.7–82.5%), with significant heterogeneity (I^2=92.7%). Seven studies reported long-term data (greater than 5 years) with a weighted mean follow-up of 103.8 months (95% CI: 91.5–116.2), and an FFAF of 66.9% (95% CI: 57.1–76.0%). This result was associated with significant heterogeneity (I^2=91%).

Subgroup analysis did not demonstrate a significant difference in FFAF between studies opting to use cryoablation and radiofrequency only. Based on lesion sets, a BAM demonstrated the highest FFAF (80.6%), followed by LAM (69.8%) followed by PVI (53.7%) which was statistically significant (P<0.001). When stratified based on LA volume reduction, studies which performed LA volume reduction demonstrated higher FFAF of 83.2% compared to cohorts which did not (74.9%) (P<0.001).

Secondary endpoints

A total of 31 studies reported postoperative short-term mortality, with a pooled result of 1.68% (95% CI:

Table 2 Demographic details

Primary author	n	Males	Age ± SD (years)	Paroxysmal AF (%)	Persistent AF (%)	Length of AF ± SD (months)	LVEF ± SD (%)	LA diameter ± SD (mm)
Ad *et al.* (18)	473	261	65.3±11.4	68	405	25.6±40.15	54.6±11	53±10
Baek *et al.* (19)	170	62	46.3±12.2	0	170	94.6±56	54.7±10.3	63.1±9.5
Bando *et al.* (20)	258	125	59.1±9.5	NR	NR	NR	NR	NR
Bogachev-Prokophiev *et al.* (21)	242	104	54.8±0.65	78	164	43.2±3.72	61±0.62	66±0.5

Table 2 (*continued*)

Table 2 (*continued*)

Primary author	n	Males	Age ± SD (years)	Paroxysmal AF (%)	Persistent AF (%)	Length of AF ± SD (months)	LVEF ± SD (%)	LA diameter ± SD (mm)
Brick *et al.* (22)	100	37	43.56±4.94	0	100	NR	NR	NR
Chavez *et al.* (23)	103	25	50.76±10.7	13	90	39.9±4.68	58.3±11.6	55±8
Chen *et al.* (24)	324	136	50.67±18.3	0	324	NR	56.6±9.67	57.48±15
Churyla *et al.* (25)	616	315	68.3±11.2	309	307	32±40.1	55.3±8.17	47.3±8.2
Dong *et al.* (26)	191	78	46±9.1	0	191	43.7±15.4	57.3±6.7	56.7±11
Ezelsoy *et al.* (27)	167	67	56.8±6.9	0	167	NR	53.7±6.2	53±5
Funatsu *et al.* (28)	268	145	60.6±10.2	22	246	67.2±58.8	NR	57±12
Garcia-Villarreal (29)	100	30	52.8±12.6	0	100	42.2±78	47.6±7.2	74±10.8
Gatti *et al.* (30)	118	60	66.5±9	42	76	21.3±33.3	55.9±11.2	51.3±9.3
Geidel *et al.* (31)	109	55	69±9	0	109	72±75	54±13	57±6
Gelsomino *et al.* (32)	685	454	65±9.3	0	685	35.6±40.3	49.7±10.4	52.4±7
Gillinov *et al.* 2006 (33)	152	75	4±11	152	0	47.7±78.6	61±16	48.8±7.6
Gillinov *et al.* 2015 (11)	133	76	69.7±10.4	0	133	NR	55.1±7.6	NR
Goette *et al.* (34)	120	78	68±10	48	72	61.2±96	NR	52±8
Han *et al.* (35)	200	82	58.8±7.5	0	100	NR	55±3	54.8±7.6
Hwang *et al.* (36)	362	182	52.2±13.8	47	315	34±49.1	56.7	NR
Jiang *et al.* (37)	168	77	55±8	NR	NR	53.5±63.5	62.7±7.2	57±9
Kasemsarn *et al.* (38)	236	89	50.9±11.1	0	236	NR	58.1±9.4	54.1±7.6
Kim *et al.* (39)	127	45	49±10	0	127	76.8±74.4	54±10	58±10
Kim *et al.* (40)	812	235	53.6±11.7	NR	NR	NR	NR	NR
Labin *et al.* (41)	245	109	66.1±10.9	107	138	119.1±81.8	NR	55±11
Lavalle *et al.* (42)	100	36	65±12	31	69	30.8±1.6	55.9±11	NR
Lawrence *et al.* (43)	184	79	65±12	79	105	69±80	53±11	55±12
Loardi *et al.* (44)	122	59	62±8.5	53	69	69.4±42.6	57±9	56±12
McCarthy *et al.* (45)	277	161	67.2±10.4	169	108	52.8±75.7	59.3±7.45	47.2±8.2
Nardi *et al.* (46)	128	71	66±8.3	0	128	NR	57±9	55±7.6
Rahmanian *et al.* (47)	141	64	65.9±13.3	NR	NR	35±39	48±13	46±9
Rostagno *et al.* (48)	301	126	69.1±9.0	0	301	36.9±49.7	51.6±9.8	53.7±8
Wang *et al.* (49)	129	53	58.4±7.2	0	129	NR	56±4	58.9±10.1
Wang *et al.* (50)	122	51	43.1±12.1	0	122	48.5±81	44.2±10.6	71±17.1
Wu *et al.* (51)	199	95	54±12.4	0	199	45.8±55.3	62.5±12.5	54.2±9.8
Yao *et al.* (52)	150	75	63±9	0	150	NR	59±9	53±4

N, number; SD, standard deviation; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; LA, left atrial; NR not reported.

Table 3 Procedural details

Primary author	Sternotomy	Mini-access	MV-repair	MV-replacement	Rheumatic aetiology	CABG	AVR	Energy source	Lesion set	LAA exclusion	LAA exclusion method	CPBT	CCT
Ad *et al.* (18)	421	52	NR	NR	NR	82	47	Radiofrequency and cryoablation	BAM/ LAM/PVI	473/473	Amputation/ clip/suture	NR	NR
Baek *et al.* (19)	170	0	17	153	170	2	34	Cryoablation	BAM	129/170	NS	205±62	154±43
Bando *et al.* (20)	NR	NR	147	111	NR	NR	NR	Cryoablation	BAM	179/258	NS	NR	NR
Bogachev-Prokophiev *et al.* (21)	171	71	93	149	148	NR	NR	Cryoablation	BAM	242/242	Suture	137.7±3.9	96±2.3
Brick *et al.* (22)	100	0	10	90	100	0	0	Other (harmonic)	BAM	NS	NS	72.5±41.5	NR
Chavez *et al.* (23)	NR	NR	7	96	103	0	0	Radiofrequency	BAM/ LAM/PVI	93/103	Suture	125.5±30.5	NR
Chen *et al.* (24)	NR	NR	76	248	324	NR	NR	Radiofrequency	BAM	324/324	Suture	106.8±25.7	65.9±20
Churyla *et al.* (25)	NR	NR	363	253	NR	NR	NR	Radiofrequency and cryoablation	BAM/ LAM	NS	NS	127.7±37.9	95±32.7
Dong *et al.* (26)	191	0	0	191	191	NR	59	Radiofrequency	BAM	191/191	Suture	139.4±39.1	84±25.5
Ezelsoy *et al.* (27)	167	0	167	0	NR	0	0	Radiofrequency	LAM	167/167	NS	136.4±11.9	91.4±9.9
Funatsu *et al.* (28)	268	0	98	170	NR	15	70	Cryoablation	BAM	NS	NS	165±52	121±40
Garcia-Villarreal (29)	100	0	31	69	100	0	0	C&S	PVI	100/100	Amputation	104±37.6	78.2±23
Gatti *et al.* (30)	118	0	71	47	26	30	0	Cryoablation	LAM	43/118	Suture	163.8±43.4	126.6±30.9
Geidel *et al.* (31)	NR	NR	65	43	37	20	4	Radiofrequency	PVI	NS	NS	132±23	94±19
Gelsomino *et al.* (32)	685	0	316	369	50	97	145	Radiofrequency	BAM/ LAM/PVI	685/685	Amputation/ suture	96.4±14.3	74.2±13.1
Gillinov *et al.* 2006 (33)	152	0	115	37	24	38	18	Radiofrequency	BAM/ LAM/PVI	152/152	NS	NR	NR
Gillinov *et al.* 2015 (11)	133	0	79	54	NR	27	14	Cryoablation	BAM/PVI	133/133	Amputation/ clip	132.5±31	95.9±36.3
Goette *et al.* (34)	0	120	120	0	NR	NR	NR	Cryoablation	LAM	120/120	Suture	NR	105±32
Han *et al.* (35)	NR	NR	31	169	149	14	NR	C&S and cryoablation	BAM	200/200	Amputation	155.1±38.7	90.7±25.1
Hwang *et al.* (36)	362	0	362	0	128	0	0	Cryoablation	BAM	NS	NS	169.6±51.2	113.2±31.1

Table 3 (*continued*)

Table 3 (*continued*)

Primary author	Sternotomy	Mini-access	MV-repair	MV-replacement	Rheumatic aetiology	CABG	AVR	Energy source	Lesion set	LAA exclusion	LAA exclusion method	CPBT	CCT
Jiang *et al.* (37)	168	0	0	168	87	0	0	Radiofrequency	BAM	168/168	Suture	131.5±41.4	79.1±35.9
Kasemsarn *et al.* (38)	236	0	88	148	175	8	23	Radiofrequency	BAM	236/236	Amputation/ suture	NR	NR
Kim *et al.* (39)	NR	NR	21	106	127	4	25	C&S	BAM	NS	NS	228±64	140±39
Kim *et al.* (40)	NR	NR	143	669	812	36	219	C&S and cryoablation	BAM/ LAM	392/812	NS	NR	NR
Labin *et al.* (41)	245	0	144	101	92	27	12	Radiofrequency and cryoablation	BAM	245/245	Amputation/ suture/clip	193.1±44.3	101.4±28.5
Lavalle *et al.* (42)	100	0	61	39	NR	NR	NR	Radiofrequency	LAM	52/100	Suture	90±23	71±14
Lawrence *et al.* (43)	NR	NR	111	73	NR	NR	NR	Radiofrequency	BAM/ LAM	NS	NS	189±41	93±29
Loardi *et al.* (44)	NR	NR	76	46	NR	NR	NR	Radiofrequency	LAM	122/122	NS	121±43	95±38
McCarthy *et al.* (45)	277	0	194	83	NR	37	32	Cryoablation	BAM	277/277	Clip/suture	115±35.5	88.6±25.1
Nardi *et al.* (46)	NR	NR	NR	NR	86	0	NR	Radiofrequency	LAM	128/128	Amputation	NR	NR
Rahmanian *et al.* (47)	141	0	119	22	45	30	11	Cryoablation	BAM/ LAM	34/128	NS	191±68	138±60
Rostagno *et al.* (48)	NR	NR	177	124	143	44	56	Radiofrequency	LAM	NS	NS	NR	NR
Wang *et al.* (49)	NR	NR	31	98	84	0	14	C&S and cryoablation	BAM	129/129	Amputation	164.1±30	87±12.8
Wang *et al.* (50)	122	0	8	114	NR	5	21	Radiofrequency	BAM	122/122	Amputation	NR	NR
Wu *et al.* (51)	NR	NR	NR	NR	109	NR	41	Radiofrequency	BAM	199/199	NS	NR	NR
Yao *et al.* (52)	NR	NR	65	85	NR	4	52	Radiofrequency	BAM	150/150	Suture	108.5±18	82±17.5

MV, mitral valve; CABG, coronary artery bypass graft; AVR, aortic valve replacement; LAA, left atrial appendage; CPBT, cardiopulmonary bypass time; CCT, cross clamp time; NR, not reported; BAM, bi-atrial maze; LAM, left atrial maze; PVI, pulmonary vein isolation; NS, not specified; C&S, cut and sew.

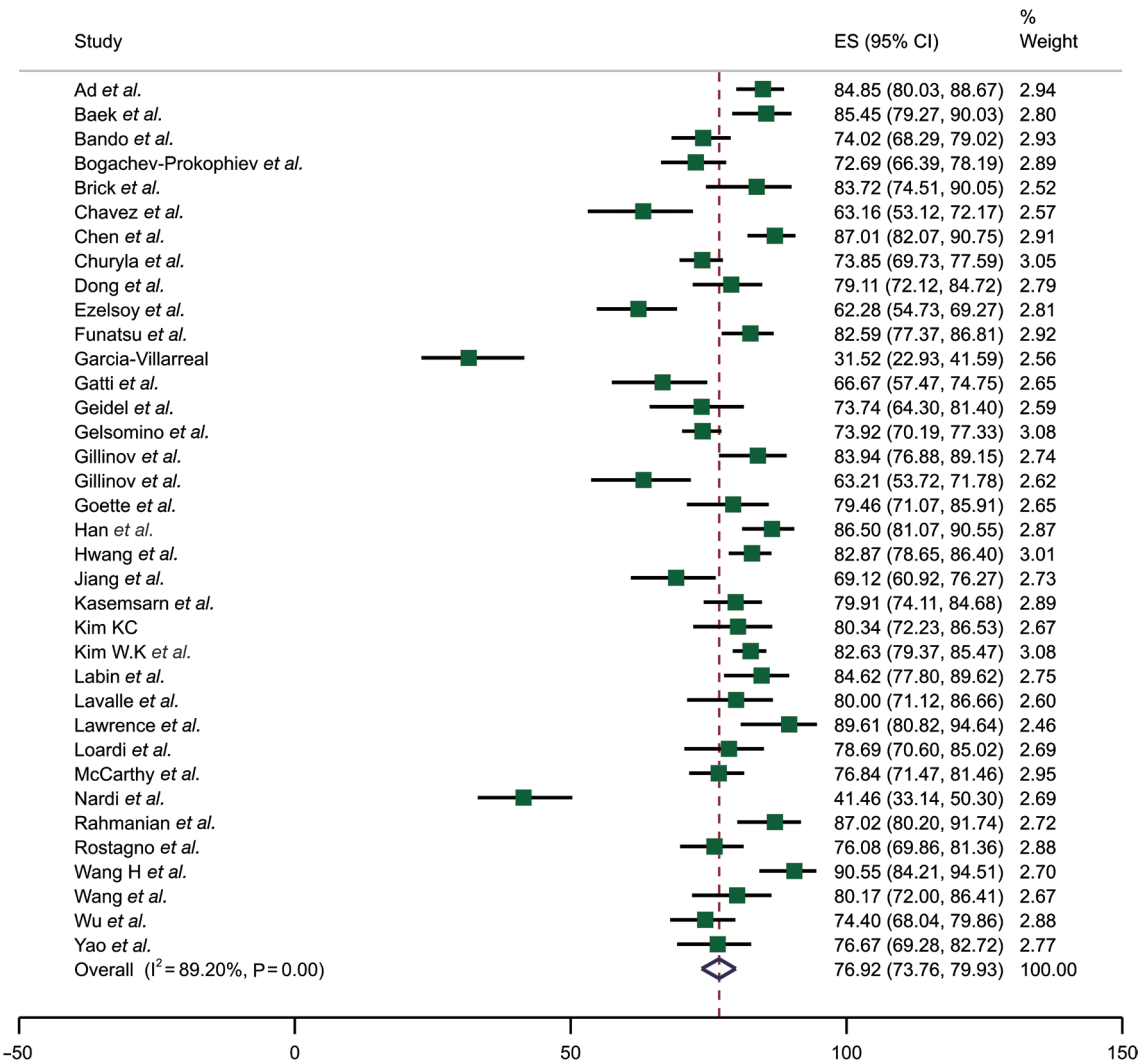

Figure 1 Freedom from atrial fibrillation. ES, effect size; CI, confidence interval.

1.15–2.29%). This result was associated with moderate heterogeneity (I^2=67%; *Figure 2*). Twenty-eight studies reported postoperative stroke with a pooled result of 0.99% (95% CI: 0.60–1.46%), This result was associated with moderate heterogeneity (I^2=56%; Figure S2). Twenty-five studies reported postoperative return to theater for bleeding, with a pooled result of 2.78% (95% CI: 1.78–3.97%). This result was associated with high heterogeneity (I^2=82%, Figure S3). Thirty-three studies reported pacemaker insertion postoperatively, with a pooled incidence of 3.99% (95% CI: 2.64–5.58%). This result is associated with high heterogeneity (90.2%; Figure S4). Outcome data is summarized in *Table 4*.

Survival curve analysis

Aggregation of overall survival was performed on six of the included studies. Overall survival at 1 to 5 years was 93.7%, 92.5%, 91.3%, 89.4% and 87% respectively (*Figure 3*). Aggregate FFAF was performed in 10 of the included studies. Overall FFAF at 1 to 5 years was 90.2%, 83.5%, 79.5%, 76.4% and 73.2% respectively (*Figure 4*).

Study quality and bias assessment

Leave-one-out analysis highlighted the potential effects of two studies (29,46) (Figure S5). As such, the omission of

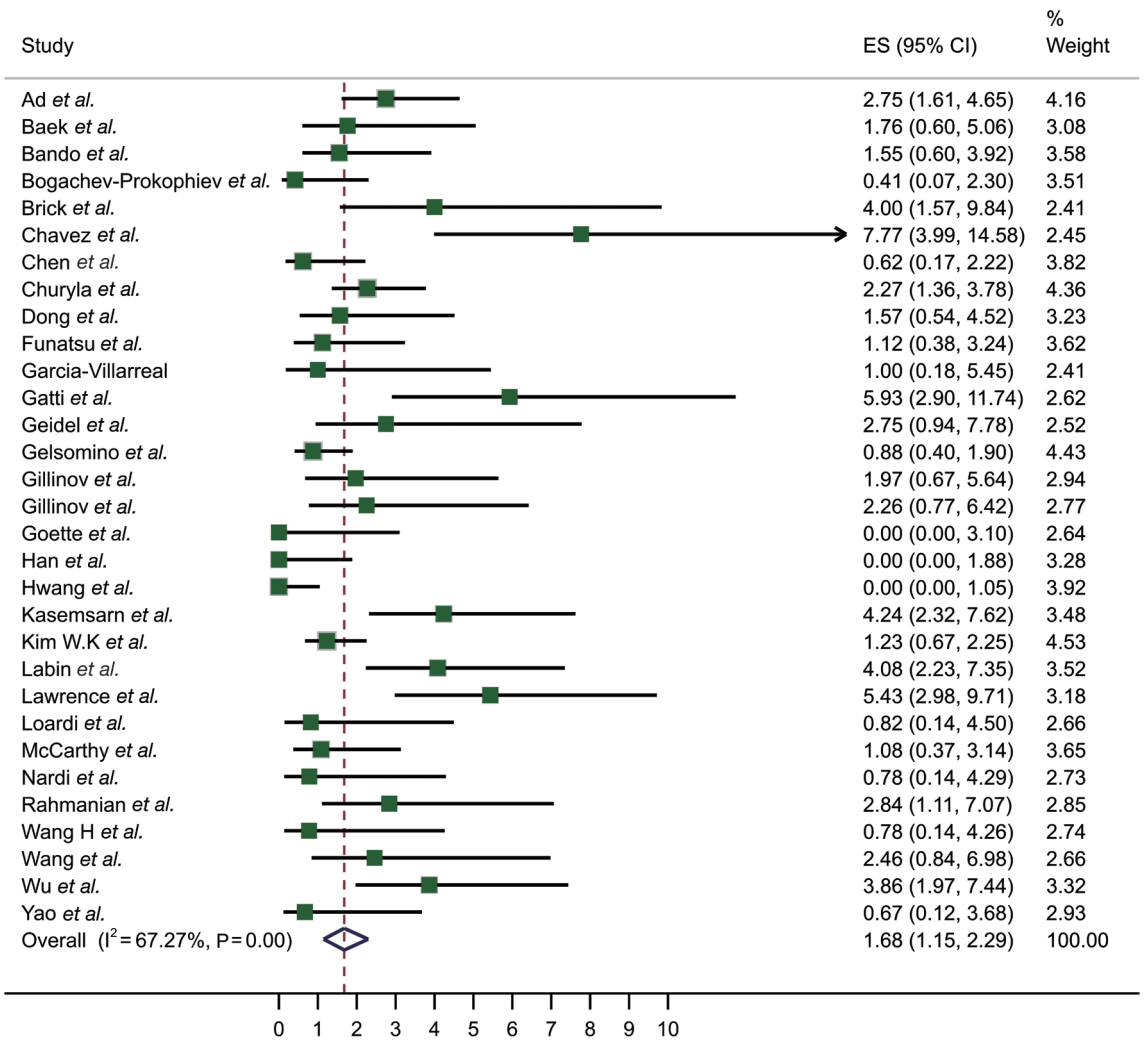

Figure 2 Short term mortality. ES, effect size; CI, confidence interval.

Table 4 Postoperative outcomes

Parameter	Events/total	N	Weighted pooled estimate (%) (95% CI)	Heterogeneity I^2 (%)
Freedom from AF	5,465/6,942	36	76.9 (73.8–79.9)	89.2
Freedom from AF off AAD	1,650/2,236	9	75.9 (68.7–82.5)	92.7
Long-term freedom from AF	765/1,140	7	66.9 (57.1–76.0)	91.4
Short-term mortality	140/8,117	31	1.68 (1.15–2.29)	67.3
CVA (short-term)	75/6,443	28	0.99 (0.60–1.46)	55.8
Takeback for bleeding	164/5,791	25	2.78 (1.78–3.97)	82.3
PPM insertion	401/7,771	33	3.99 (2.64–5.58)	90.2

N, number of studies; CI, confidence interval; AF, atrial fibrillation; AAD, antiarrhythmic drugs; CVA, cerebrovascular accident; PPM, permanent pacemaker.

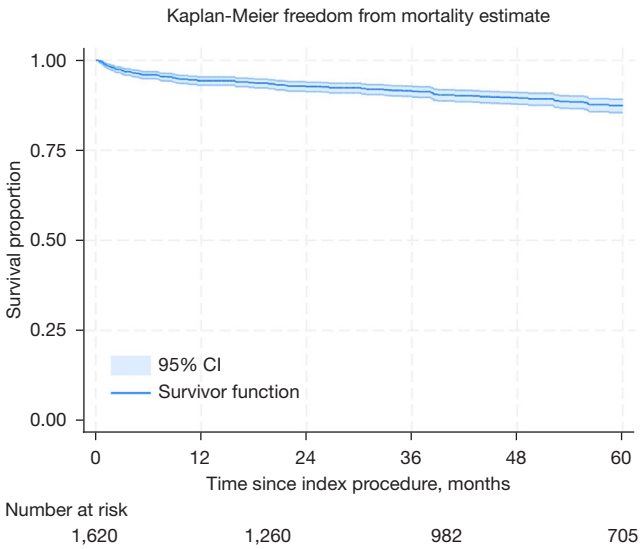

Figure 3 Survival curve for mortality. CI, confidence interval.

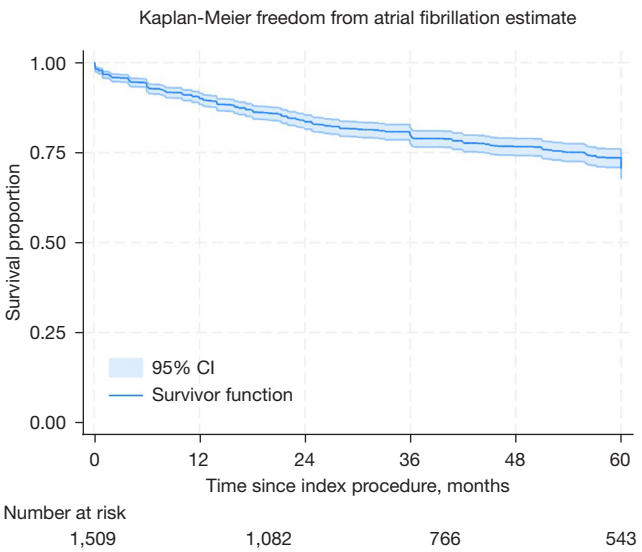

Figure 4 Survival curve for freedom from AF. CI, confidence interval; AF, atrial fibrillation.

these two studies increased FFAF to 78.9%, and marginally improved heterogeneity (I^2=80%). There was potential evidence of publication bias on visual inspection of funnel plots for the primary outcome, with two smaller studies producing a smaller effect size (Figure S6). This result was not significant on Egger's test for small-study effects (P=0.163). There was no evidence of publication bias on visual inspection of funnel plots for short-term mortality (Figure S7). The ROBINS-I tool was applied to 34 studies, with the majority of studies scoring "moderate" in terms of risk of bias. Five studies scored a "serious" risk of bias and four studies scored a "low" risk of bias, reflecting the largely retrospective nature of the cohort studies included. The RoB2 tool was applied to the two randomized studies included within this analysis, with one study demonstrating a "low" risk and the second demonstrating "some concerns" with respect to bias. These results are visually represented in Figures S8,S9.

Discussion

AF has a significant association with mitral valve disease. Surgical ablation during mitral valve surgery provides an opportune circumstance for simultaneous arrhythmia correction. Randomised trial evidence demonstrates that it is both efficacious and safe. Gillinov *et al.* demonstrated an FFAF at 63.2% 12 months postoperatively, compared to 29.4% in those receiving mitral valve surgery alone (11). This was associated with a mortality rate of 6.8%, which did not vary significantly from mitral valve surgery alone (8.7%). A Cochrane review of 22 randomised control trials demonstrated a freedom from atrial tachyarrhythmia of 51% in patients undergoing concomitant ablation compared to 24.1% in those who underwent mitral valve surgery alone (6). AF ablation may also be associated with a long-term survival benefit. One multicentre study demonstrated a 5-year survival advantage in patients undergoing concomitant AF ablation during cardiac surgery, adjusted for baseline covariates (53). Despite the body of evidence supporting AF ablation during mitral valve surgery in patients with AF, there remains poor uptake among surgeons, with 61.5% of surgical ablations being performed concomitantly with mitral valve surgery in the United States (54,55). Currently, the Society of Thoracic Surgeons (STS) provides a class 1 indication for surgical ablation at the time of concomitant mitral operations, isolated AVR, isolated CABG, and AVR plus CABG (56). Both the AHA and ESC provide level 2a evidence for concomitant ablation during cardiac surgery (13,14).

The results of this study demonstrate an FFAF of 76.9% at a mean follow-up of 40.2 months. This result suggests a superior FFAF at a later time point than previously reported in systematic reviews (6,7). This study also demonstrates that the success of the procedure may be sustained, with an FFAF of 66.9% at 103.8 months and an aggregate FFAF of 73.2% at 5 years on analysis of survival

data. An explanation for this result may be the inclusion of a number of contemporary studies, with newer iterations of the maze procedure and lesion sets. These results were associated with significant heterogeneity, which is indicative of the different experience of the involved surgeons, lesion sets utilized, baseline characteristics of the patients, and variable follow-up protocols. We attempted to mitigate this as much as feasible by the inclusion of larger studies (>100 patients). Concomitant AF ablation is also safe, with a pooled short-term mortality of 1.68% This result also demonstrates a lower mortality than previously reported; Phan *et al.* reported a pooled 30-day mortality of 4.4%, and Huffman *et al.* reported 2.3% (6,7). Complications are also uncommon, with a pooled stroke rate of 1% and pacemaker rate of 3.99%. Pacemaker insertion is significantly higher amongst patients undergoing surgical ablation with mitral valve surgery than mitral valve surgery alone (7). Contemporary randomised data with long-term follow up can further verify these results.

The Cox-Maze procedure remains the gold standard for the surgical treatment of AF, employing a bi-atrial lesion set (57). Key components of the maze procedure include en-bloc isolation of the pulmonary veins, a connecting lesion to the mitral annulus, extensive right atrial lesions, and excision of the LAA (58). In order to reduce procedural times and postoperative conduction issues, less extensive lesion sets have been adopted to target the left atrium only, with varying levels of efficacy (58). The addition of the right atrial lesions of the maze procedure reduces the occurrence of both AF and typical right atrial flutter (58). Issues with right-sided lesions include increased CPBT, and increased incidence of pacemaker implantation (6,7). This study demonstrated a statistically significant benefit in employing a BAM when compared to an LAM. Of note, a PVI alone conferred a poor FFAF, especially in the context of persistent AF (29). Two of the included studies within this review compared BAM to left-atrial maze, and one study compared BAM to PVI alone (11,25,32). Churyla *et al.* did not demonstrate a significant improvement in FFAF after the addition of a right atrial lesion set, whereas Gelsomino *et al.* did, demonstrating that a left atrial lesion s*et alo*ne is independently associated with failure patients with persistent AF (25,32). Gillinov *et al.* demonstrated that PVI alone is associated with a significantly worse FFAF in a cohort of patients with persistent AF (11). Other studies which employed PVI alone in this cohort of patients demonstrated a poor FFAF (29). Paroxysmal AF is associated with higher frequency pulmonary vein activity than permanent AF, supporting the notion that focal triggers in the pulmonary vein are less important in patients with permanent AF (59). Therefore, in this cohort of patients, isolation of the pulmonary veins alone may not be efficacious. Further randomised evidence is required to discern the true long-term benefit of BAM.

The size of the left atrium affects the success of concomitant AF ablation. One theory alludes to the "critical mass" of the left atrium, whereby the greater the tissue surface area, the higher the possibility of sustaining AF (60). In addition, atrial remodelling most commonly seen in patients with AF with rheumatic heart disease reduces the refractory period of AF, which increases the probability of sustained AF (50). In this cohort of patients, concomitant left atrial reduction is important to ensure success. The findings of this review support this, with a higher FFAF recorded in patients undergoing volume reduction surgery. Of the included studies, Wang *et al.* demonstrated a FFAF of 76% at one year after aggressive bi-atrial reduction with a full maze, in a cohort of patients with giant LA (8.6 cm). It has been suggested by other studies that this strategy needs to be adopted when the maximal left atrial dimension exceeds 5.5 cm (61). The optimal energy source is a complex consideration. In this study, there was no significant difference between studies utilizing cryoablation *vs.* radiofrequency. In short, radiofrequency utilizes heat energy to apoptose cells, thus creating scar. It has been shown to be as effective as "cut and sew" lesions (62). A bipolar energy source has greater efficacy than unipolar devices. Cryoablation, on the other hand, creates ice crystals which produce acute disruption of cell membranes and local tissue ischemia. This mechanism has the benefit of preserving the fibrous skeleton and collagen structures and is safe around valvular tissue (30). This is consistent with previously published data, and highlights that regardless of energy source, transmural lesions are key (63).

A final consideration is the role of LAA closure at the time of surgery. This was variably conducted across the studies included within this review, with a total of 21 studies excluding the LAA in the entire patient cohort. Closure of the LAA has been demonstrated to reduce the incidence of thromboembolism in the postoperative setting and confers a class 2a recommendation with concomitant ablation in patients with a CHA_2DS_2-VASc score greater than two (8,14). There are a number of ways that the appendage can be excluded, including internal suture ligation, external ligation, or surgical excision. Despite this, echocardiographic evidence demonstrates that LAA

elimination remains incomplete and goes undetected (64). Randomized evidence does not demonstrate a significant difference between these methods; however, it does advocate for the use of echocardiography at the time of operation to assess effectiveness (64). One potential benefit of AF surgery and LAA closure is the cessation of anticoagulation. The majority of studies continued anticoagulation in the postoperative period however we found these study protocols to be heterogenous and unclear if the indication was AF or mechanical/biological valves. Only two studies specified that they stopped oral anticoagulation if patients remained in sinus rhythm (18,38). There remains a paucity of evidence assessing the incidence of stroke risk following LAA exclusion/AF surgery *vs.* anticoagulation alone.

There are a number of important limitations to consider when interpreting the results described in this study. Firstly, the heterogeneity of the data. This could represent a number of different factors, such as the variable ablation lines, experience of operator(s), patient comorbidities, different energy sources and post-operative protocols. We also noted that studies inconsistently reported loss of follow-up, whereby some studies completed follow-up of 100% of patients and others demonstrated significant attrition. This leads to survivor bias and can skew results. There were also varying definitions of success across the studies; some utilized continuous monitoring, whereas others employed electrocardiograms (ECGs) which are snapshots in time. Single ECGs may be less sensitive in picking up atrial tachyarrhythmias and therefore underreport FFAF. Very few studies utilized AF burden calculations or continuous loop recorders. Lastly, the majority of studies were retrospective in nature and this is reflected in the risk of bias analysis with only four cohort studies being classified as a "low" risk of bias. Five studies demonstrated a "severe" risk of bias, particularly with regards to patient selection bias, reporting and loss of follow up. These issues can be ameliorated with further prospective or randomized data.

Conclusions

In summary, concomitant ablation of AF during mitral valve surgery is effective at maintaining FFAF, both in the mid- and long-term. It can be performed concomitantly to mitral valve surgery with low mortality and morbidity. The addition of right atrial lesion sets, in addition to atrial volume reduction surgery, may confer greater efficacy. There does not seem to be correlation between energy source and FFAF. Further high-quality randomized data is required to evaluate the long-term efficacy of concomitant ablation, especially comparing different lesion sets.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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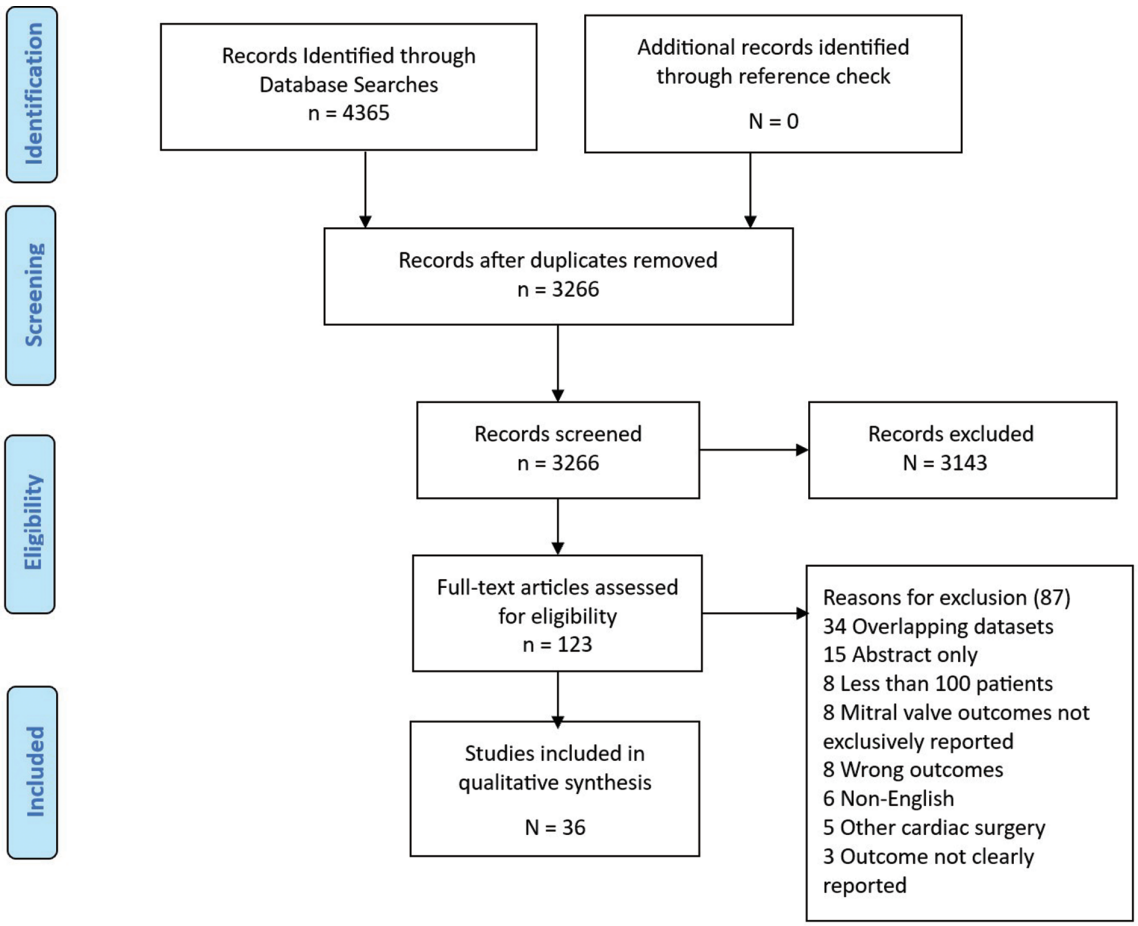

Figure S1 PRISMA flow-chart summarizing the search strategy for relevant publications.

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Table S1 Postoperative drug protocols

Primary author	Antiarrhythmic drug	Anticoagulation
Ad *et al.* (18)	Amiodarone for 3 months, stopped if in SR	Warfarin (INR 2-2.5) for 6 months, stopped if in SR/No LAA excluded on TTE
Baek *et al.* (19)	Amiodarone for 3 months, stopped if in SR	Anticoagulation (not specified) for 3-6 months. Aspirin 100mg/day after
Bando *et al.* (20)	Digoxin	Warfarin
Bogachev-Prokophiev *et al.* (21)	Amiodarone 200mg/day for 3 months, stopped if in SR	Warfarin (lifetime for mechanical, 6 months for biological)
Brick *et al.* (22)	Amiodarone 200mg/day for 6 months	Not Specified
Chavez *et al.* (23)	Not Specified	Not Specified
Chen *et al.* (24)	Amiodarone 200 mg once daily for 3-6 months	Not Specified
Churyla *et al.* (25)	Not Specified	Warfarin
Dong *et al.* (26)	Amiodarone 200mg/day for 3 months, stopped if in SR	Warfarin (INR 1.5-2)
Ezelsoy *et al.* (27)	Amiodarone 200 mg and metoprolol 50 mg per oral for 3 months	Warfarin for 3 months
Funatsu *et al.* (28)	Unspecified class 1a or 1c AADs	Warfarin (lifetime for mechanical, 3 months for biological)
Garcia-Villarreal (29)	Amiodarone 200mg/day for 3 months, stopped if in SR	Not specified
Gatti *et al.* (30)	Amiodarone 200 or 400mg/day until SR	Warfarin 3-6 months with INR 2.0-3.0
Geidel *et al.* (31)	Amiodarone 200mg daily for 3 months	Warfarin (lifetime for mechanical, 3 months for biological)
Gelsomino *et al.* (32)	Amiodarone 200mg BD for 1 week, then 200mg daily for 6 months	Warfarin for 6 months, INR target of 2.5-3.5
Gillinov *et al.* 2006 (33)	Not Standardized	Not Standardized
Gillinov *et al.* 2015 (11)	Not Standardized	Not Standardized
Goette *et al.* (34)	Amiodarone 400mg for 48 hours	Anticoagulation for 3 months
Han *et al.* (35)	Amiodarone 200mg daily for 3 months	Warfarin for 6 months, INR 2-2.5
Hwang *et al.* (36)	Not standardized	Warfarin 3-6 months with INR 1.5-2.5
Jiang *et al.* (37)	Amiodarone 200mg TDS 1 week, BD 1 week, daily until 3 months. If not in SR, then continued to 6 months	Not Specified
Kasemsarn *et al.* (38)	Amiodarone for 6 months	Warfarin for 1 year and aspirin for life if Holter monitor proved no AF.
Kim (39)	Not Specified	Not Specified
Kim *et al.* (40)	Not Specified	Warfarin with INR 2-3 (mechanical). Warfarin 3-6 months with INR 1.5-2.5 (bioprosthetic)
Labin *et al.* (41)	Class I/III AADs, for 2 months	Warfarin 3-6 months
Lavalle *et al.* (42)	Amiodarone 200mg TDS 1 week, BD 1 week, daily until SR	Warfarin
Lawrence *et al.* (43)	Class I/III AADs, for 2 months	Warfarin
Loardi *et al.* (44)	Amiodarone 200mg TDS until discharge, then 200mg daily for 6 months	Not specified
McCarthy *et al.* (45)	Not Specified	Not specified
Nardi *et al.* (46)	Amiodarone 200mg daily 4-6wks. After this, 200mg daily for 5 days per week until SR	Warfarin 3 months, INR 2.5-3.5
Rahmanian *et al.* (47)	Amiodarone given at cardiologist's discretion	Warfarin lifelong (mechanical), 2 months (bioprosthetic)
Rostagno *et al.* (48)	Amiodarone 200mg BD until discharge, then 200mg daily for 3 months	Warfarin lifelong (mechanical), 6 months (bioprosthetic) INR 2.5-3.5
Wang *et al.* (49)	Amiodarone 3 months	Warfarin 3 months, INR 2-2.5
Wang *et al.* (50)	Amiodarone (dose not specified)	Warfarin 3 months for pts with LA diameter >50mm
Wu *et al.* (51)	AADs not used	Heparin 2 weeks, warfarin for 6 weeks
Yao *et al.* (52)	Amiodarone 200mg daily for 3 months	Warfarin

AADs, anti-arrhythmic drugs; SR, sinus rhythm; TTE; transthoracic echocardiogram; BD, twice a day; TDS, three times a day; INR, international normalised ratio; LA, left atrial.

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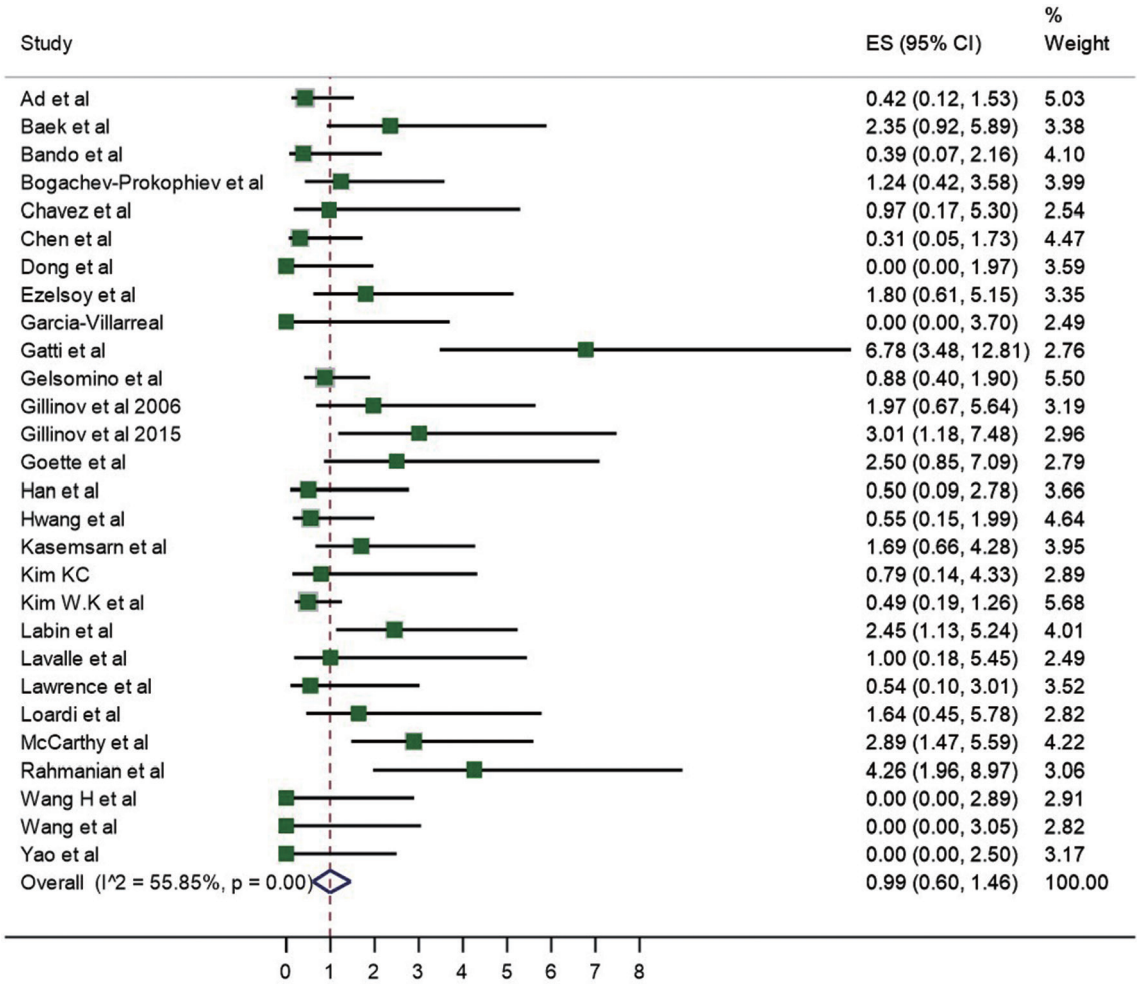

Figure S2 Postoperative stroke.

https://dx.doi.org/10.21037/acs-2023-afm-0131

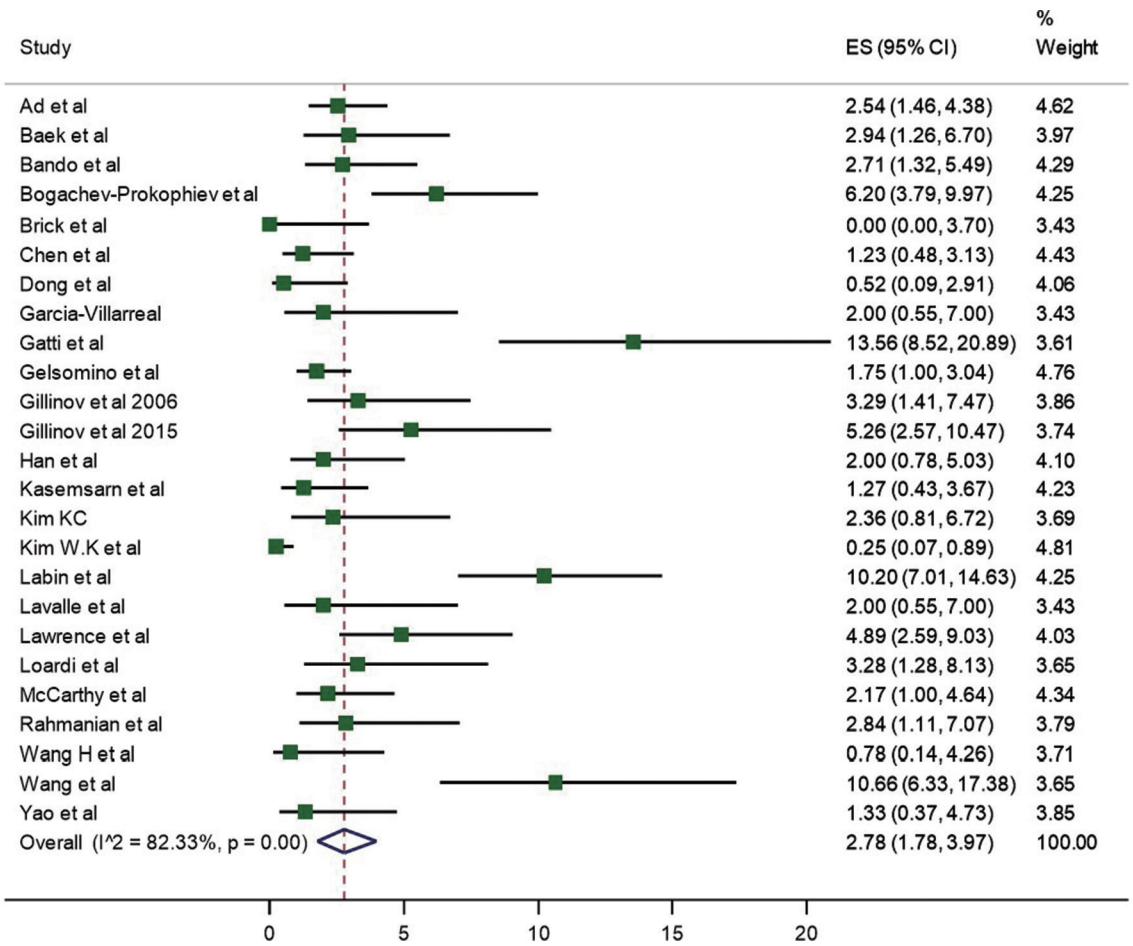

Figure S3 Postoperative re-exploration.

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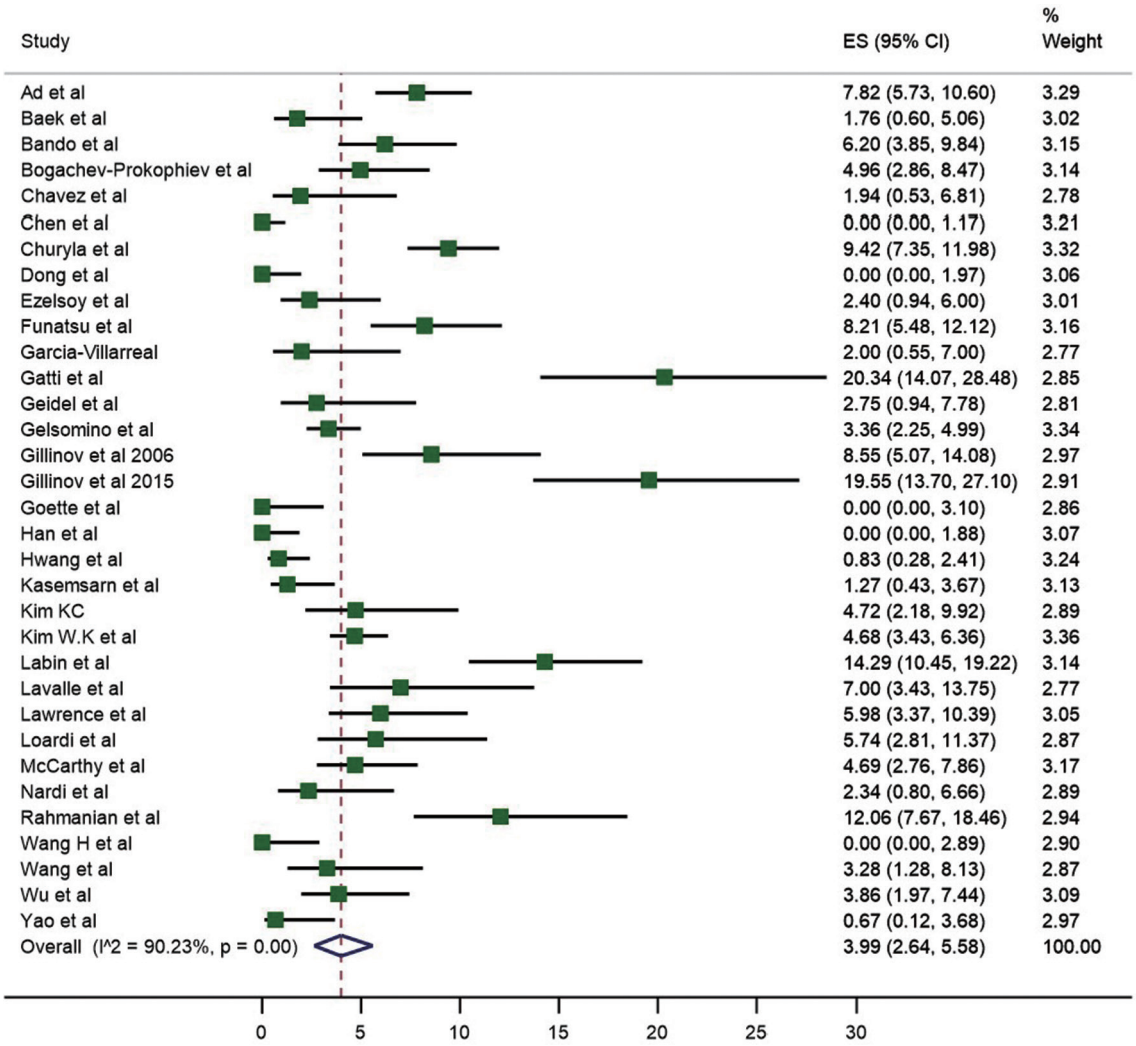

Figure S4 Postoperative PPM insertion.

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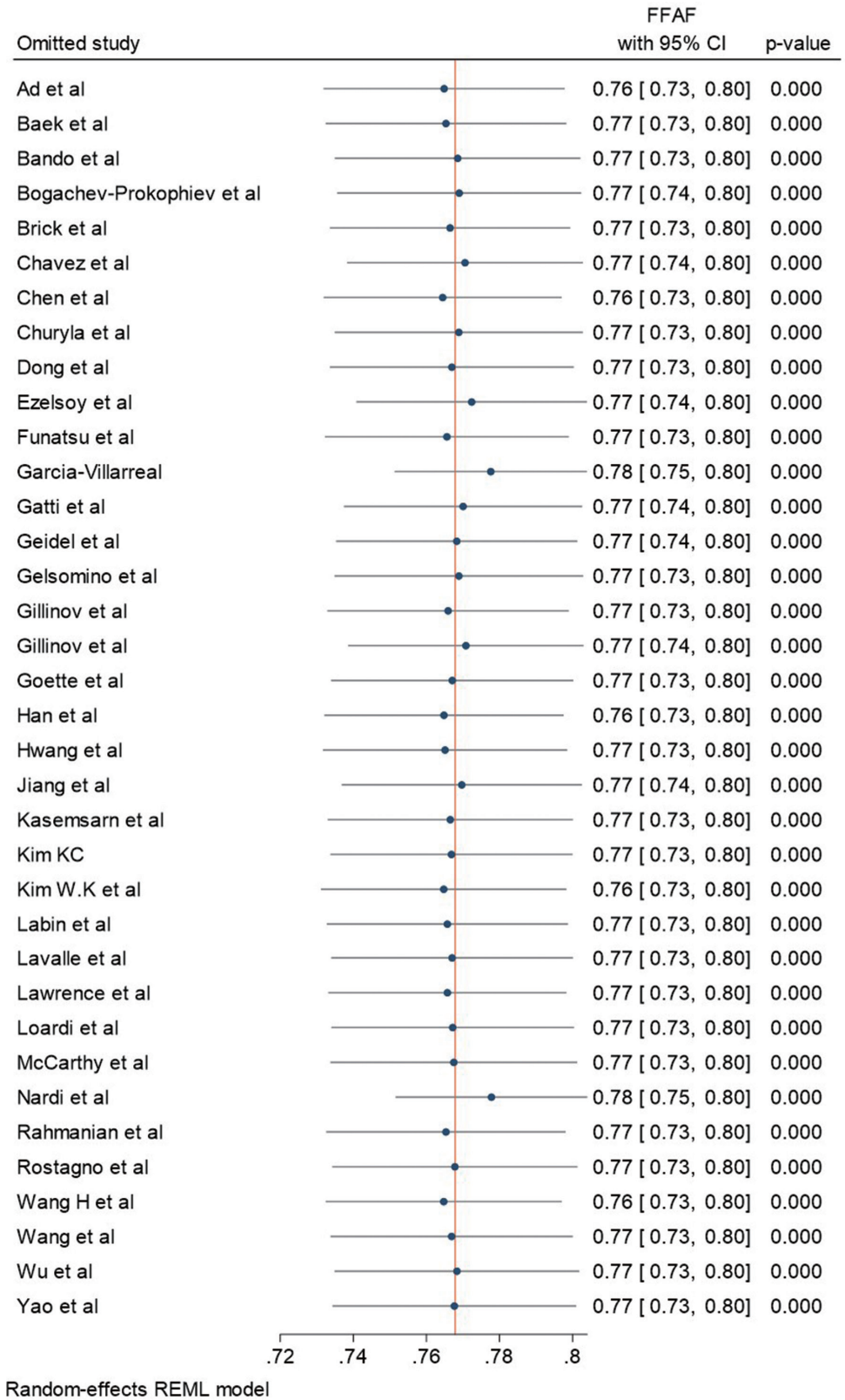

Figure S5 Leave one out analysis.

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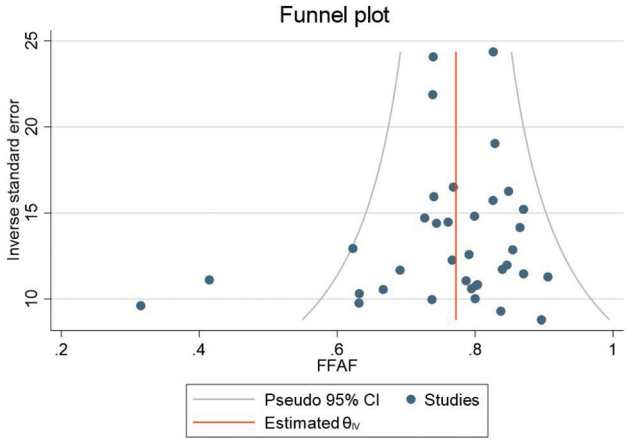

Figure S6 Funnel plot for freedom from AF.

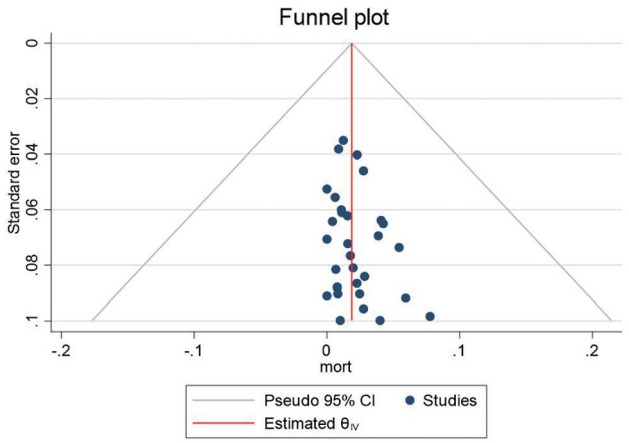

Figure S7 Funnel plot for mortality.

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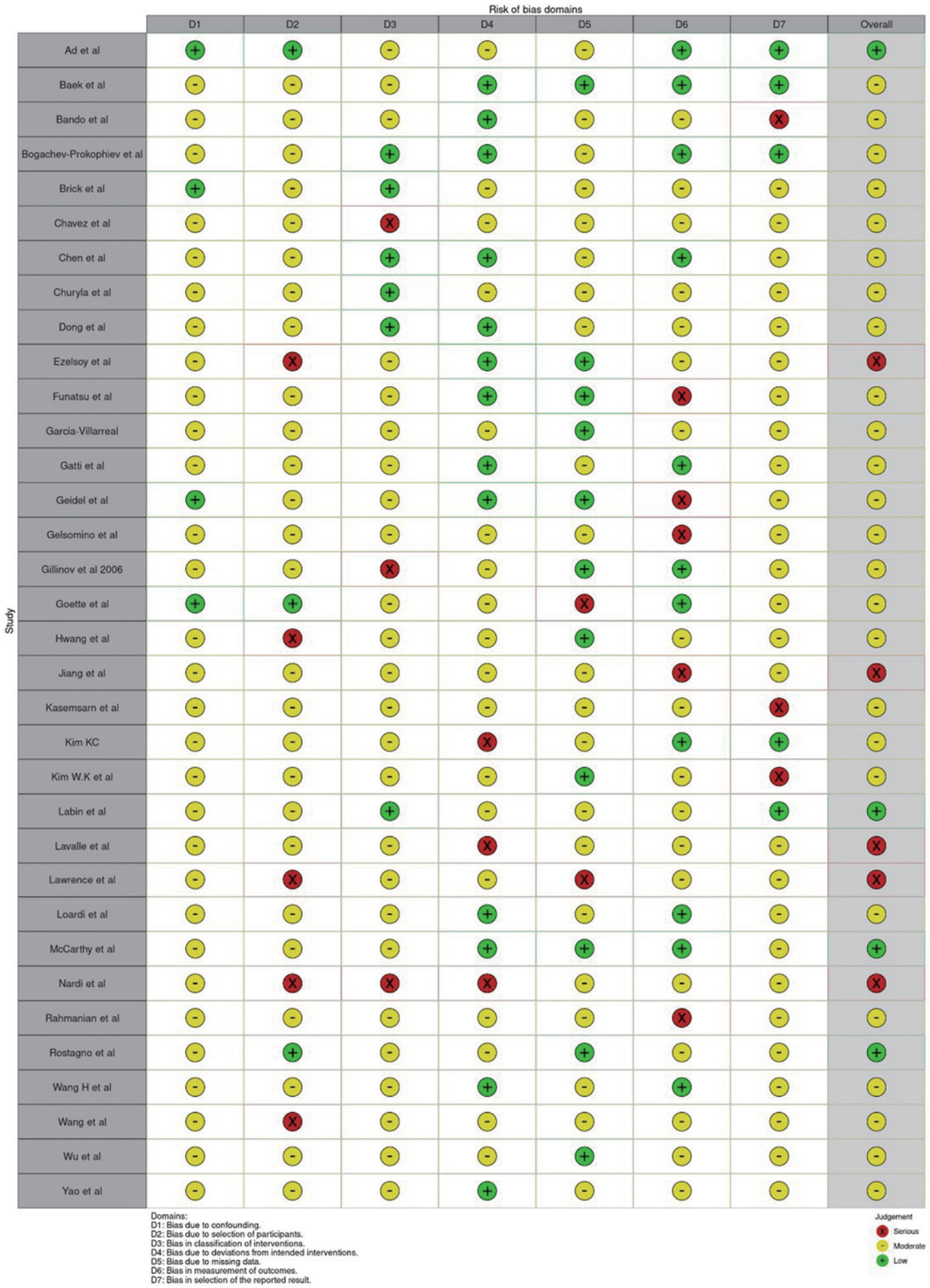

Figure S8 Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I).

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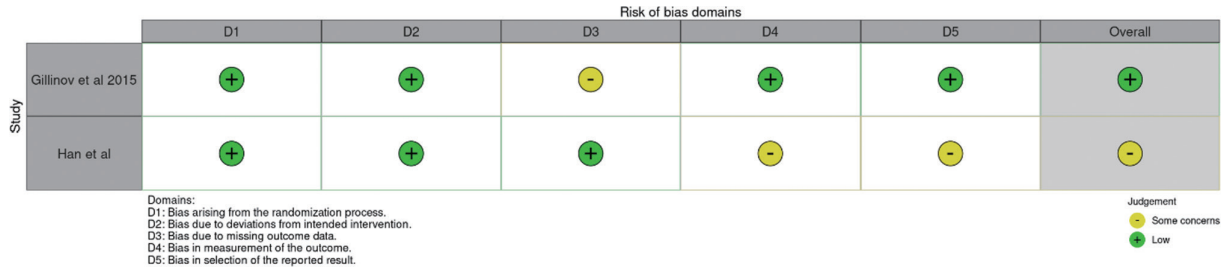

Figure S9 Risk of Bias in Randomised Trials (RoB2).

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