Systematic review and meta-analysis of left atrial appendage closure's influence on early and long-term mortality and stroke

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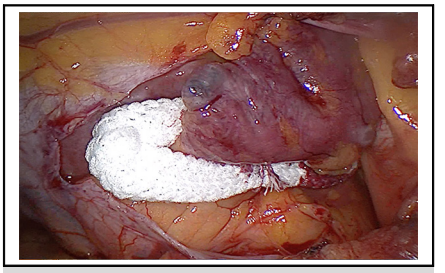
ABSTRACT

Objective: Left atrial appendage closure (LAAC) concomitant to heart surgery in patients with underlying atrial fibrillation (AF) has gained attention because of long-term reduction of thromboembolic complications. As of mortality benefits in the setting of non-AF, data from both observational studies and randomized controlled trials are conflicting.

Methods: On-line databases were screened for studies comparing LAAC versus no LAAC concomitant to other heart surgery. End points assessed were all-cause mortality and stroke at early and longest-available follow-up. Subgroup analyses stratified on preoperative AF were performed. Risk ratios (RR) with 95% CIs served as primary statistics.

Results: Electronic search yielded 25 studies (N = 660 [158 patients]). There was no difference between LAAC and no LAAC in terms of early mortality. In the overall population analysis, LAAC reduced long-term mortality (RR, 0.86; 95% CI, 0.74-1.00; $P = .05$; $I^2 = 88\%$), reduced early stroke risk by 19% (RR, 0.81; 95% CI, 0.72-0.93; $P = .002$; $I^2 = 57\%$), and reduced late stroke risk by 13% (RR, 0.87; 95% CI, 0.84-0.90; $P < .001$; $I^2 = 58\%$). Subgroup analysis showed lower mortality (RR, 0.85; 95% CI, 0.72-1.01; $P = .06$; $I^2 = 91\%$), short-, and long-term stroke risk reduction only in patients with preoperative AF (RR, 0.81; 95% CI, 0.71-0.93; $P = .003$; $I^2 = 71\%$ and RR, 0.87; 95% CI, 0.84-0.91; $P < .001$; $I^2 = 70\%$, respectively). No benefit of LAAC in patients without AF was found.

Conclusions: Concomitant LAAC was associated with reduced stroke rates at early and long-term and possibly reduced all-cause mortality at the long-term follow-up but the benefits were limited to patients with preoperative AF. There is not enough evidence to support routine concomitant LAAC in non-AF settings. (JTCVS Open 2024;19:131-63)



LAAC reduces stroke incidence in patients with preoperative AF.

CENTRAL MESSAGE

This systematic review and meta-analysis found LAAC was associated with reduced stroke rates, both early and long-term, and reduced long-term mortality. These benefits were confined to preoperative AF.

PERSPECTIVE

Left atrial appendage closure concomitant to heart surgery in patients with underlying atrial fibrillation has gained attention because of long-term reduction of thromboembolic complications in the pivotal LAAOS III trial. As of mortality benefits of LAAC and efficacy in the setting of non-AF, data from both observational studies and randomized controlled trials are conflicting.

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Abbreviations and Acronyms

AF	= atrial fibrillation
CHA_2-DS_2-VASc	= Congestive heart failure, Hypertension, Age (>65 = 1 point, > 75 = 2 points), Diabetes, previous Stroke/transient ischemic attack (2 points)
LAA	= left atrial appendage
LAAC	= left atrial appendage closure
LAAOS	= Left Atrial Appendage Occlusion Study III
OAC	= oral anticoagulation
POAF	= postoperative atrial fibrillation
PRISMA	= Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	= randomized controlled trials

Cardiovascular disease remains a leading cause of morbidity and mortality worldwide, with atrial fibrillation (AF) and stroke being significant contributors to this burden.[1,2] The left atrial appendage (LAA) is a known site for thrombus formation, especially in patients with AF, with as little as only 0.07% of atrial clots found outside the LAA in nonvalvular AF.[3,4] The formation of blood clots in the LAA poses a considerable risk for embolic events, primarily strokes.[5] As a preventive strategy, the use of anticoagulants has been the gold standard for stroke prevention in patients with AF.[6,7] In recent years, concomitant LAA closure (LAAC) procedures during other heart surgeries have emerged as a potential alternative approach to reduce stroke risk in patients with AF.[8-10] The Left Atrial Appendage Occlusion Study III (LAAOS III) provided definitive evidence supporting LAAC in patients with AF and elevated Congestive heart failure, Hypertension, Age (>65 = 1 point, > 75 = 2 points), Diabetes, previous stroke/transient ischemic attack (2 points) (CHA_2-DS_2-VASc) score undergoing cardiac surgery because it reduced the long-term incidence of stroke. Data regarding mortality benefits remain inconclusive and derive primarily from observational studies.[11-13]

Although studies have explored the benefits of LAAC in patients with AF, there remains a paucity of evidence regarding its efficacy in patients without underlying AF.[14-16] This gap in knowledge is critical because many patients undergoing cardiac surgery may not have documented AF preoperatively, yet at the same time, may have elevated CHA_2-DS_2-VASc score and thromboembolic risk. It has been also speculated that LAAC may serve as bailout for patients developing postoperative AF (POAF) after cardiac surgery to reduce embolic risk and POAF-related stroke burden.[17,18]

This systematic review and meta-analysis aimed to synthesize the existing evidence on concomitant LAA closure at the time of other heart surgery, with a specific focus on its influence on mortality and stroke outcomes.

METHODS

Data Sources and Search Strategy

Established methods were used in compliance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in Health Care Interventions statement as well as the Meta-analysis of Observational Studies in Epidemiology guidelines.[19,20] PRISMA and Meta-analysis of Observational Studies in Epidemiology checklists are available in Tables E1 and E2, respectively. We conducted a database screening for relevant studies up to May 31, 2023, through PubMed, EMBASE (Table E3) the Cumulative Index of Nursing and Allied Health Literature, the Web of Science, the Cochrane Register of Controlled Clinical Trials, Clinical Key, and Google Scholar registries, as well as published proceedings from major cardiac, thoracic, cardiothoracic, and cardiology society meetings. Search terms included *left atrial appendage closure/*, *occlusion/*, *removal/*, *amputation/*, *ligation/*, *stapling/*, *clipping/*, *occlusion/*, *exclusion/*, and *heart/cardiac surgery.*

No language, publication date, or publication status restriction was imposed. Both blinded and open-label trials were considered eligible. The most updated or inclusive data for each study were used for abstraction. The references of original and review articles were cross-checked.

Selection Criteria and Quality Assessment

Studies were considered eligible when comparing concomitant LAAC versus no LAAC at time of heart surgery for another indication. Citations were screened at the title/abstract level and retrieved as full reports if they

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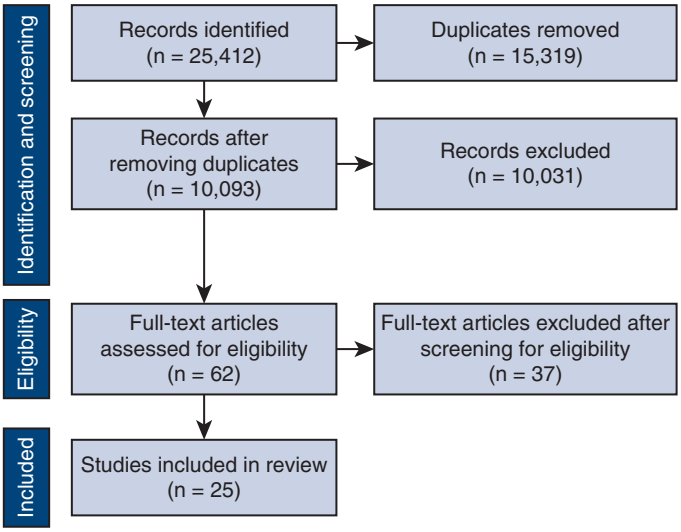

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

fulfilled the inclusion criteria: human studies, randomized controlled trials (RCTs) or observational studies with a control group, and the reporting of a prespecified outcome of mortality and/or stroke. We excluded studies in which no data of interest were provided, there was no control group, different techniques of LAAC at time of heart surgery were compared but without a no-LAAC control group, LAAC was performed as standalone procedure, and heart surgery with concomitant LAAC was compared with transcatheter coronary or valve intervention with transcatheter LAAC.

We extracted data for the included studies using a prespecified datasheet. Variables in the prespecified datasheet included study characteristics, demographic data, clinical characteristics, interventions, and outcomes.

Two independent reviewers (M.S. and E.J.D.) selected the studies for inclusion and extracted studies and patient characteristics of interest and relevant outcomes. Conflicts were resolved by consensus after discussion with a third reviewer (M.K.). Two authors (M.S. and E.J.D.) independently assessed the trials' eligibility and risk of bias. The risk of bias for randomized studies was assessed using the components recommended by the Cochrane Collaboration,[21] including random sequence generation and random allocation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias.

For each selected observational study, the risk of bias was evaluated independently by 2 authors (M.S. and E.J.D.) using the 7 domains (confounding, participant selection, intervention classification, intervention deviation, missing data, outcome measurement, and selective reporting) of the Risk of Bias in Non-Randomized Studies of Interventions scale for observational studies and risk of bias scale for randomized trials.[22] Certainty of evidence was assessed by 4 main factors (risk of bias, inconsistency, indirectness, and imprecision)[23] using the Grading of Recommendations Assessment, Development, and Evaluations approach. The certainty of the evidence was rated from high (ie, we are very confident that the true effect lies close to that of the effect estimate) to very low (ie, we have very little confidence in the effect estimate: the true effect is likely to be substantially different).[24] Any discrepancies in bias assessment between the assessors were recorded.

Outcome Measures

The end points assessed were all-cause mortality and stroke at early (in-hospital/30 days) and longest available follow-up. Definitions were adopted as were in the included studies.

Statistical Analysis

Data were analyzed according to the intention-to-treat principle. Randomized and observational studies providing any kind of adjustment were assessed separately as sensitivity analysis. Risk ratios (RRs) and 95% CIs were used as summary statistics. Heterogeneity was assessed by the Cochran Q test.[25] The statistical inconsistency test was $I^2 = [(Q\_df)/Q] \times 100\%$, where Q is the χ^2 statistic and *df* is its degrees of freedom. Thresholds for the interpretation of I^2 for low, moderate, and considerable degree of heterogeneity were values of 25%, 50%, and 75%, respectively.[26] Pooled RRs were calculated using a random-effects model with the DerSimonian-Laird method as the most conservative approach. Observational studies and RCTs were analyzed separately. Potential publication bias was examined for the primary end point constructing a funnel plot in which the SE of the log RR was plotted against the RR. The asymmetry of the plot was estimated both visually and by a linear regression approach. To better account for studies reporting 0 events, calculations were repeated with log RR as primary statistics using Haldane continuity correction.[27] To account for differences in follow-up, events and person-years were calculated and meta-analyses of long-term stroke and mortality reported as rate ratios (RateRs) with corresponding 95% CIs. Analyses were primarily carried out as subgroups analysis divided by presence of underlying AF (<50% AF vs >50% AF in the study population). We addressed the influence of each study and potential publication bias by testing whether deleting each study in turn would have significantly changed the pooled results of the meta-analysis for the primary end point. Review Manager 5.4 (The Nordic Cochrane Center) and Comprehensive Meta-Analysis, version 2 (Biostat) were used for statistical computations.

RESULTS

PRISMA flow diagram presenting the study selection process is available in Figure 1. Electronic search returned 25 studies (N = 660 [158 patients])[8-13,15,18,28-35,E1-E9] to be included in the systematic review. Seven studies were RCTs[10,15,18,33,34,E3,E4]; of the remaining, 8[9,12,29,32,35,E2,E7] provided adjusted estimates. Table 1 lists baseline characteristics of included studies. Of the totality of patients, 15.9% (67,238) underwent LAAC. Patients were predominantly men older than age 70 years. Information regarding CHA_2DS_2-VASC and Hypertension, Abnormal

TABLE 1. Studies baseline characteristics and bias analysis

Study	Blinding	LAAC method	Index surgery	Follow-up (mo)	Risk of bias	Protocol mandated OAC postdischarge
RCTs						
Gerdisch and colleagues[15] 2022 [ATLAS]	No	AtriClip (100%)	CABG (83.27%) Mitral valve (5.34%) Aortic valve (23.31%) Other (6.23%)*	12	Some concerns	According to patients' individual situations
Healey and colleagues[33] 2005 [LAAOS]	No	Suturing (21.15%) Stapling (63.46%) Mixed (15.38%)	CABG ± valve surgery (100%)	13	High risk	No
Jiang and colleagues[34] 2020	Yes	Suturing (100%)	MVR (100%) ± AVR (14.92%)/ Tricuspid valve surgery (77.9%)/CABG (7.73%)	N/D	High risk	Yes
Nagpal and colleagues[E3] 2009	Yes	Suturing (100%)	Isolated mitral valve surgery (100%)	N/D	High risk	No
Park-Hansen and colleagues[18] 2018 [LAACS]	Yes	Purse string and running suture recommended	Isolated CABG (48.12%) AVR ± other (41.71%) AVR + MVR (1.06%) MVR ± other (8.02%) Tricuspid valve only (0.53%) Aortic surgery only (0.53%)	44.4	Low risk	No
Whitlock and colleagues[E4] 2013 [LAAOS II]	Yes	Stapling (3.85%) Cut and sew (96.15%)	Isolated CABG (47.06%) Isolated valve (41.18%) Other (11.76%)	12	Low risk	No
Whitlock and colleagues[10] 2021 [LAAOS III]	Yes	Cut and sew (55.7%) Stapling (11.2%) Closure device (15.1%) Closure from within (13.8%) Other (4.1%)	Isolated CABG (21.02%) Isolated valve (22.91%) Other (55.35%) Any valve surgery (66.65%) – Mitral (35.53%)/Aortic (35.53%)/Tricuspid (17.27%)/ Pulmonic (0.13%) SA (32.75%)	3.8	Low risk	Yes
Observational	Adjustments					
Abrich and colleagues[28] 2018	No	Ligation (52.7%) Excision (41%) Stapling (9%)	Mitral valve (100%) ± CABG (2.5%)/SA (55.2%)	47.16	Moderate risk	No
Elbadawi and colleagues[29] 2017	Yes	N/D	CABG (100%)	N/D	Moderate risk	No
Elbadawi A and colleagues[30] 2017	Yes	N/D	Valve (100%)	N/D	Moderate risk	No
Enginoev and colleagues[31] 2020	No	Ligation (100%)	OPCAB (100%)	41	Moderate risk	No
Friedman and colleagues[8] 2018	No	N/D	Isolated CABG (35%) Mitral valve ± CABG (30%) Aortic valve ± CABG (35%)	31.2	Moderate risk	No
Hadaya and colleagues[32] 2022	Yes	N/D	Isolated CABG (40.57%) Mitral valve ± CABG (21.16%) Aortic valve ± CABG (23.21%) Other valve/multivalve ± CABG (15.06%)	25.2	Moderate risk	No

(Continued)

TABLE 1. Continued

Study	Blinding	LAAC method	Index surgery	Follow-up (mo)	Risk of bias	Protocol mandated OAC postdischarge
Johnsrud and colleagues[35] 2018	Yes	Ligation (71%) Amputation (29%)	Isolated CABG (4.03%) CABG + valve (14.52%) CABG + valve + other (13.71%) Isolated valve (16.94%) Valve + other (33.87%) Other (7.26%)	68.4	Low risk	No
Juo and colleagues[E9] 2018	Yes	Ligation (100%)	Isolated CABG (73.52%) CABG + valve (26.48%)	N/D	Serious risk	No
Kato and colleagues[E1] 2015	No	Suturing (N/D) Ligation (N/D)	Isolated CABG (43.53%) Valve (43.26%) CABG + valve (13.16%)	6	Serious risk	Yes
Kim and colleagues[E8] 2013	Yes	Ligation (N/D) Excision (N/D) Stapling (N/D)	Isolated CABG (82.1%) Isolated valve (8.8%) CABG + valve (8.6%) Other (0.5%)	1	Moderate risk	No
Lee and colleagues[E2] 2014	Yes	N/D	Mitral valve + other (100%)	62.6	Moderate risk	Yes
Mahmood and colleagues[11] 2020	No	N/D	Isolated CABG (100%)	1	Serious risk	No
Mehaffey and colleagues[13] 2023	No	N/D	Open atrial (Mitral/tricuspid valve ± CABG) – 16.6% Closed atrial (Aortic valve/ CABG) – 83.4%	36	Serious risk	No
Melduni and colleagues[12] 2017	Yes	Suturing (N/D) Amputation (N/D) Ligation (N/D) Stapling (N/D)	Mitral valve (62.26%) CABG + valve/other (20.5%) Aortic valve (11.39%) Isolated CABG (3.36%) Tricuspid valve (2.49%)	109.2	Low risk	No
Wilbring and colleagues[E5] 2016	No	Ligation (65.8%) Amputation (34.2%)	Mitral valve (62.8%) Aortic valve (26%) Tricuspid valve (18.3%) CABG (41%) Atrial septal defect closure (10.8%)*	12	Serious risk	Yes
Yao and colleagues[9] 2018	Yes	N/D	CABG (45.75%) Valve (71.73%) CABG + valve (17.49%) Aortic (28.22%) Mitral (43.51%) Tricuspid or pulmonary (9.94%) Both mitral and aortic (2.95%)*	25	Moderate risk	No
Zapolanski and colleagues[E6] 2013	No	Ligation (100%)	Isolated CABG (49.18%) Isolated valve (14.63%) CABG + valve (15.31%) CABG + valve + other (4.45%) Other (16.43%)	1	Serious risk	No
Zheng and colleagues[E7] 2020	Yes	Ligation (N/D) Suturing (N/D) Amputation (minority)	Isolated MVR (67%) DVR (27.16%) Tricuspid valve surgery (82.69%) Concurrent CABG (9.86%)	1	Moderate risk	Yes

LAAC, Left atrial appendage closure; *OAC*, oral anticoagulation; *RCT*, randomized clinical trial; *ATLAS*, AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures; *CABG*, coronary artery bypass grafting; *LAAOS*, Left Atrial Appendage Occlusion Study; *MVR*, mitral valve replacement; *AVR*, aortic valve replacement; *N/D*, no data; *LAACS*, The Left Atrial Appendage Closure by Surgery; *SA*, surgical ablation; *DVR*, double valve replacement. *Multiple procedures were permitted. Patients may be represented more than once.

TABLE 2. Patients' baseline characteristics

Study	Group	No. of patients	Age	LVEF (%)	Preoperative AF (%)	POAF (%)	Male (%)	DM (%)	CKD (%)	CHA_2-DS_2-VASC	HAS-BLED	OAC at baseline (%)	AAD at baseline (%)	OAC postdischarge (%)
Abrich and colleagues[28] 2018	LAAC	188	70	< 40 EF – 4.3	100	N/D	51.1	8	N/D	2.6	N/D	82.4	N/D	N/D
	No-LAAC	93	70.1	<40 EF – 3.2	100		37.6	21.5	N/D	2.9		85		
Elbadawi and colleagues[29] 2017	LAAC	2520	71.3	N/D	100	N/D	77.71	59.6	17.9*	4	N/D	N/D	N/D	N/D
	No-LAAC	12,595	70.6		100		69.2	60	12.6*	4				
Elbadawi and colleagues[30] 2017	LAAC	652	70.8	N/D	100	N/D	59	3.1	N/D	N/D	N/D	N/D	N/D	N/D
	No-LAAC	652	71.2		100		49.7	3.9						
Enginoev and colleagues[31] 2020	LAAC	57	63.5	55	100	N/D	89.5	26.3	N/D	3	2	N/D	N/D	19.3
	No-LAAC	68	61	55	100		83.8	14.7		2	2			27.9
Friedman and colleagues[8] 2018	LAAC	3892	75	<3 0 EF –5.1	100	N/D	59.8	30.1	35.4	3.9	N/D	N/D	N/D	68.9
	No-LAAC	6632	76.4	< 30 EF –7.3	100		62.4	36.4	39.5	4.1				60.3
Gerdisch and colleagues[15] 2022 [ATLAS]	LAAC	376	69.2	57.3	0†	47.3	69.9	N/D	N/D	3.4	2.8	N/D	N/D	23.7
	No-LAAC	186	68.9	58.7	0†	38.2	69.9	N/D	N/D	3.4	2.9			16.1
Hadaya and colleagues[32] 2022	LAAC	8792	69.8	N/D	21	N/D	67.9	33.3	4.7*	N/D	N/D	N/D	N/D	N/D
	No-LAAC	9642	69.1				70.6	42.7	7.9*					
Healey and colleagues[33] 2005 [LAAOS]	LAAC	52	72	N/D	17	44.2	73	N/D	N/D	N/D	N/D	N/D	N/D	N/D
	No-LAAC	25	71		8	52	72							
Jiang and colleagues[34] 2020	LAAC	521	53	59	68.1	N/D	43.8	8.3	N/D	N/D	N/D	N/D	N/D	100%
	No-LAAC	339	52	60	53.7		54.9	8.3						N/D

(Continued)

TABLE 2. Continued

Study	Group	No. of patients	Age	LVEF (%)	Preoperative AF (%)	POAF (%)	Male (%)	DM (%)	CKD (%)	CHA_2-DS_2-VASC	HAS-BLED	OAC at baseline (%)	AAD at baseline (%)	OAC postdischarge (%)
Johnsrud and colleagues[35] 2018	LAAC	62	71.9	N/D	100	N/D	60	79	N/D	N/D	N/D	37	N/D	90
	No-LAAC	62	75.9		100		63	79				45		81
Juo and colleagues[E9] 2018	LAAC	20,664	72	N/D	100	N/D	75.2	65.1	84.2	3	N/D	N/D	N/D	N/D
	No-LAAC	213,978	70.4		100		76.3	67.8	86.2	3				
Kato and colleagues[E1] 2015	LAAC	369	65.4	60.9	25.5	49.3	57.7	18.2	N/D	$\geq$ 2 – 79.6	N/D	N/D	N/D	N/D
	No-LAAC	1462	67.1	57.6	9.1	39.1	72.1	39.1						
Kim and colleagues[E8] 2013	LAAC	1405	66.6	N/D	N/D	23	67.9	34.1	N/D	N/D	N/D	N/D	N/D	N/D
	No-LAAC	662	65.8			18.4	67.52	35.3						
Lee and colleagues[E2] 2014	LAAC	187	55.98	56.3	100	N/D	32.6	11.8	0.5	N/D	N/D	N/D	N/D	100
	No-LAAC	192	50.7	56.1	100		38.5	5.7	0					100
Mahmood and colleagues[11] 2020	LAAC	17,763	65-74 – 40.8	N/D	100	N/D	77.9	42.2	2.4	N/D	N/D	N/D	N/D	N/D
	No-LAAC	235,524	65-74 – 39.2		100		75.8	43.3	2.4					
Mehaffey and colleagues[13] 2023	LAAC	23,338	69.78	N/D	100	N/D	65.6	34.2	24.6	N/D	N/D	N/D	N/D	N/D
	No-LAAC	80,044	70.81		100		63.4	37.9	28.4					
Melduni and colleagues[12] 2017	LAAC	461	67.4	58.4	45	68.6	61	13	N/D	N/D	N/D	N/D	8	N/D
	No-LAAC	461	67.6	58.3	47	31.9	63	13					9	

(Continued)

TABLE 2. Continued

Study	Group	No. of patients	Age	LVEF (%)	Preoperative AF (%)	POAF (%)	Male (%)	DM (%)	CKD (%)	CHA_2-DS_2-VASC	HAS-BLED	OAC at baseline (%)	AAD at baseline (%)	OAC postdischarge (%)
Nagpal and colleagues[E3] 2009	LAAC	22	57.8	N/D	18.2	18	50	4.5	N/D	N/D	N/D	N/D	N/D	N/D
	No-LAAC	21	59.2		19	29	57.1	0						
Park-Hansen and colleagues[18] 2018 [LAACS]	LAAC	101	67.6	N/D	12.8	60.5	83.2	30.7	14.9%	2.9	N/D	37.62	17.8	N/D
	No-LAAC	86	69.3		16.8	50	87.2	22.1	16.3%	2.9		32.56	26.7	
Whitlock and colleagues[E4] 2013 [LAAOS II]	LAAC	26	77.4	< 50 EF –26.92	100	N/D	76.92	26.92	N/D	N/D	N/D	65.38	N/D	68
	No-LAAC	25	74.6	< 50 EF –40	100		76	28				68		50
Whitlock and colleagues[10] 2021 [LAAOS III]	LAAC	2379	71.3	< 50 EF – 30.8	100	N/D	68	32.4	N/D	4.2	N/D	51.1	N/D	83.4
	No-LAAC	2391	71.1	< 50 EF – 30.6	100		67	32		4.2		52.2		81
Wilbring and colleagues[E5] 2016	LAAC	240	68.45	51.65	100	N/D	51.67	36.25	17.5	3.43	N/D	N/D	N/D	100
	No-LAAC	87	70	54	100		48.3	39.1	13.8	3.6				100
Yao and colleagues[9] 2018	LAAC	4295	68.2	N/D	74.9	N/D	64.9	35.1	13.9	≥ 2– 89.3	≥ 3 – 63.6	30.5	1.7	N/D
	No-LAAC	4295	68.4		74.9		64.7	35.8	14	≥ 2 – 89.3	≥ 3 – 65.4	30.5	1.7	
Zapolanski and colleagues[E6] 2013	LAAC	808	>75 – 34.7%	< 35 EF – 14.4	19.9	19.4	73.8	34.9	7.4	N/D	N/D	N/D	N/D	N/D
	No-LAAC	969	>75 – 38.3%	< 35 EF – 9.4	10.7	22.9	73.8	28.3	6%					
Zheng and colleagues[E7] 2020	LAAC	137	55.3	60.4	100	N/D	38.7	5.1	15.3	2.2	N/D	N/D	N/D	100
	No-LAAC	360	56.2	61.2	100		38.1	9.4	17.8	2.2				100

LVEF, Left ventricle ejection fraction; *AF*, atrial fibrillation; *POAF*, postoperative atrial fibrillation; *DM*, diabetes mellitus; *CKD*, chronic kidney disease; *CHA_2-DS_2-VASC*, Congestive heart failure, Hypertension, Age (>65 = 1 point, > 75 = 2 points), Diabetes, previous Stroke/transient ischemic attack (2 points); *HAS-BLED*, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; *OAC*, oral anticoagulation; *AAD*, antiarrythmic drugs; *LAAC*, left atrial appendage closure; *N/D*, no data; *CABG*, coronary artery bypass graft; *ATLAS*, AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures; *LAAOS*, Left Atrial Appendage Occlusion Study; *LAACS*, The Left Atrial Appendage Closure by Surgery. *End-stage renal disease. †Documented preoperative AF.

Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly scores were seldom reported, as was information on background baseline medication. The prevalence of AF varied across studies and ranged from 0%[15] to 100%.[8,10,11,13,28-31,35,E2,E4,E5,E7] Yao and colleagues[9] provide outcome data for patients with AF and those without separately. In studies labeled as predominantly AF, 99.7% of patients had preoperative AF. Preoperative AF frequency in the predominantly non-AF group was 32.5%. Table 2 lists patient and procedure-related characteristics.

LAA ligation was preferred method for LAAC across the included studies,[28,31,34,35,E3,E5,E6] stapling and amputation together with device closure were adopted as well. The AtriClip device (AtriCure) was used exclusively in 1 study.[15] However, data of LAAC technique and associated outcomes were largely missing.

Bias analysis revealed that most observational studies were of moderate quality driven by excess in selection bias; signs of reporting bias were seen across included RCTs (Table 1). Detailed bias assessment is available as Tables E4 and E5. Follow-up of the included studies ranged from in-hospital/30 days to 109 months.[12]

Mortality

Seventeen studies (403,691 patients) were included in the analysis of early mortality. Overall, 8150 (2.02%) patients died in-hospital or within 30-days postoperative with mortality rates of 2.04% and 2.02% for LAAC and no LAAC, respectively. In random effects model, there was no difference between LAAC and no LAAC in terms of mortality (RR, 0.94; 95% CI, 0.73-1.21; $P = .61$; $I^2 = 84\%$). Similarly, no differences were seen when stratified according to preoperative AF (P value for subgroup differences = .27) (Figure 2). Twenty-five studies (432,318 patients) were included in the analysis of longest available follow-up. Mean weighted follow-up duration was 14.7 months; 24,918 patients accounting for 5.8% of the total population died: 6.52% versus 5.64% in the LAAC and no LAAC groups, respectively. Statistically, there was a borderline statistical significance in favor of LAAC in the overall analysis (RR, 0.86; 95% CIs, 0.74-1.00; $P = .05$; $I^2 = 88\%$), which was driven by lower mortality in subgroup of patients with underlying preoperative AF (RR, 0.85; 95% CI, 0.72-1.01; $P = .06$; $I^2 = 91\%$) (Figure 3). When adjusted for the duration of follow-up, the magnitude and direction of the estimates were maintained in the analysis of RateRs (RateR, 0.83; 95% CI, 0.71-0.97; $P = .02$; $I^2 = 89\%$), again driven by the benefit in patients with preoperative AF (RateR, 0.85; 95% CI, 0.71-1.01; $P = .07$; $I^2 = 90\%$) (Figure E1).

Stroke

Seventeen studies (634,774 patients) were included in the analysis of early stroke. Overall, 27,197 (4.28%) patients experienced in-hospital or within 30-days postoperative stroke with corresponding rates of 3.00% and 4.46% for LAAC and no LAAC, respectively. In the random effects model, this was associated with statistically significant, nearly 20% reduction of stroke risk with LAAC compared with no LAAC (RR, 0.81; 95% CI, 0.72-0.93; $P = .002$; $I^2 = 57\%$). LAAC was associated with reduced risk of stroke in patients with underlying AF (RR, 0.81; 95% CI, 0.71-0.93; $P = .003$; $I^2 = 71\%$), whereas such a benefit was absent in patients without previously diagnosed AF (RR, 0.81; 95% CI, 0.54-1.20; $P = .45$; $I^2 = 0\%$) (P for subgroup differences = .11) (Figure 4). For the analysis of longest available follow-up for stroke, 24 studies (640,100 patients) provided data of interest. Analysis of publication bias is available as Figure 5, *A*, and revealed no big-study effect. Egger test returned at $P = .005$. At weighted mean follow-up of 9.47 months, 29,887 patients (4.66%) experienced a stroke: 3.77% versus 4.80% in the LAAC and no LAAC groups, respectively, which translated to statistically significant benefit of 13% RR (RR, 0.87; 95% CI, 0.84-0.90; $P < .00001$; $I^2 = 58\%$). When patients were analyzed according to AF status before surgery; in those who had preoperative AF, the benefit was sustained (RR, 0.87; 95% CI, 0.84-0.91; $P < .00001$; $I^2 = 70\%$), whereas there was no statistical significance in the subgroup of patients without prior AF (RR, 0.83; 95% CI, 0.63-1.09; $P = .17$; $I^2 = 0\%$) (Figure 5, *B*). When adjusted for the duration of follow-up, the magnitude and direction of the estimates were maintained in the analysis of RateRs (RateR, 0.79; 95% CI, 0.70-0.88; $P \leq .0001$; $I^2 = 56\%$), again driven by the benefit in patients with preoperative AF (RateR, 0.78; 95% CI, 0.69-0.88; $P < .0001$; $I^2 = 68\%$) (Figure E2).

Sensitivity Analyses

Meta-analyses limited to RCTs and propensity score-matched studies showed no difference in the direction and magnitude of the estimates; LAAC was associated with significantly reduced all-cause mortality at longest available follow-up (RR, 0.83; 95% CI, 0.70-0.98; $P = .03$; $I^2 = 57\%$) with marked differences between estimates in preoperative AF and no preoperative AF subgroups (RR, 0.76; 95% CI, 0.60-0.95; $P = .02$; $I^2 = 67\%$ vs RR, 0.99; 95% CI, 0.83-1.19; $P = .95$; $I^2 = 1\%$) ($P_{\text{subgroups}} = .07$) (Figure E3). LAAC was further associated with significantly reduced (by 36%) risk of stroke at longest available follow-up (RR, 0.64; 95% CI, 0.53-0.77; $P < .00001$; $I^2 = 21\%$) with marked differences between estimates in

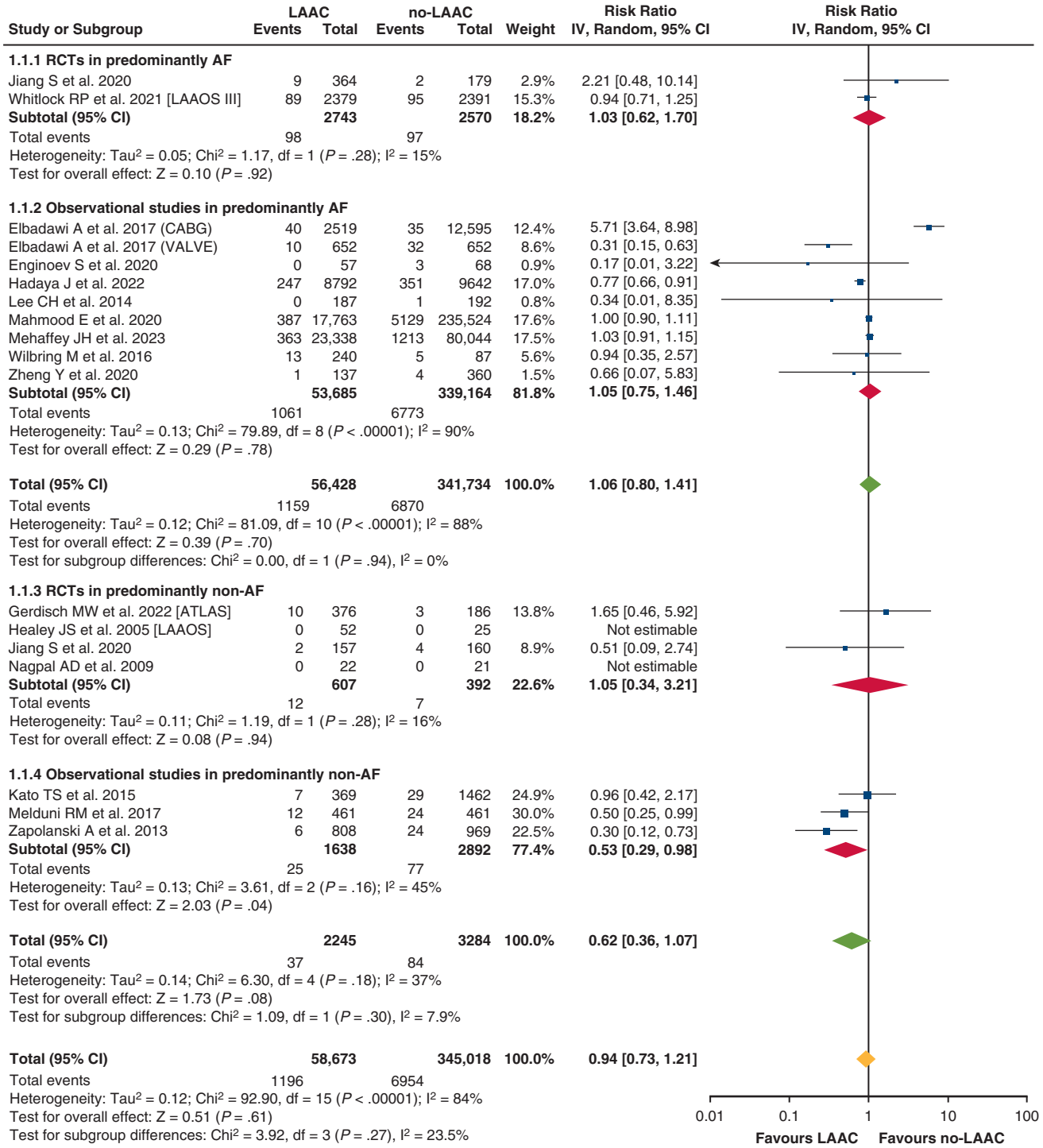

FIGURE 2. Meta analysis of early (in-hospital/30-day) mortality for the comparison of left atrial appendage closure (*LAAC*) versus no-LAAC stratified by presence or not of preoperative atrial fibrillation (*AF*). *Blue squares* correspond to single studies' point estimates with 95% CI; *red diamonds* are the risk ratios (RRs) results of meta-analysis for subgroups of randomized controlled trials and observational studies; *blue squares* represent the LAAC effect in the subgroups of AF and non-AF, whereas red square is the overall result. *IV*, Inverse variance; *CI*, confidence interval; *RCT*, randomized clinical trial; *LAAOS*, Left Atrial Appendage Occlusion Study; *CABG*, coronary artery bypass grafting.

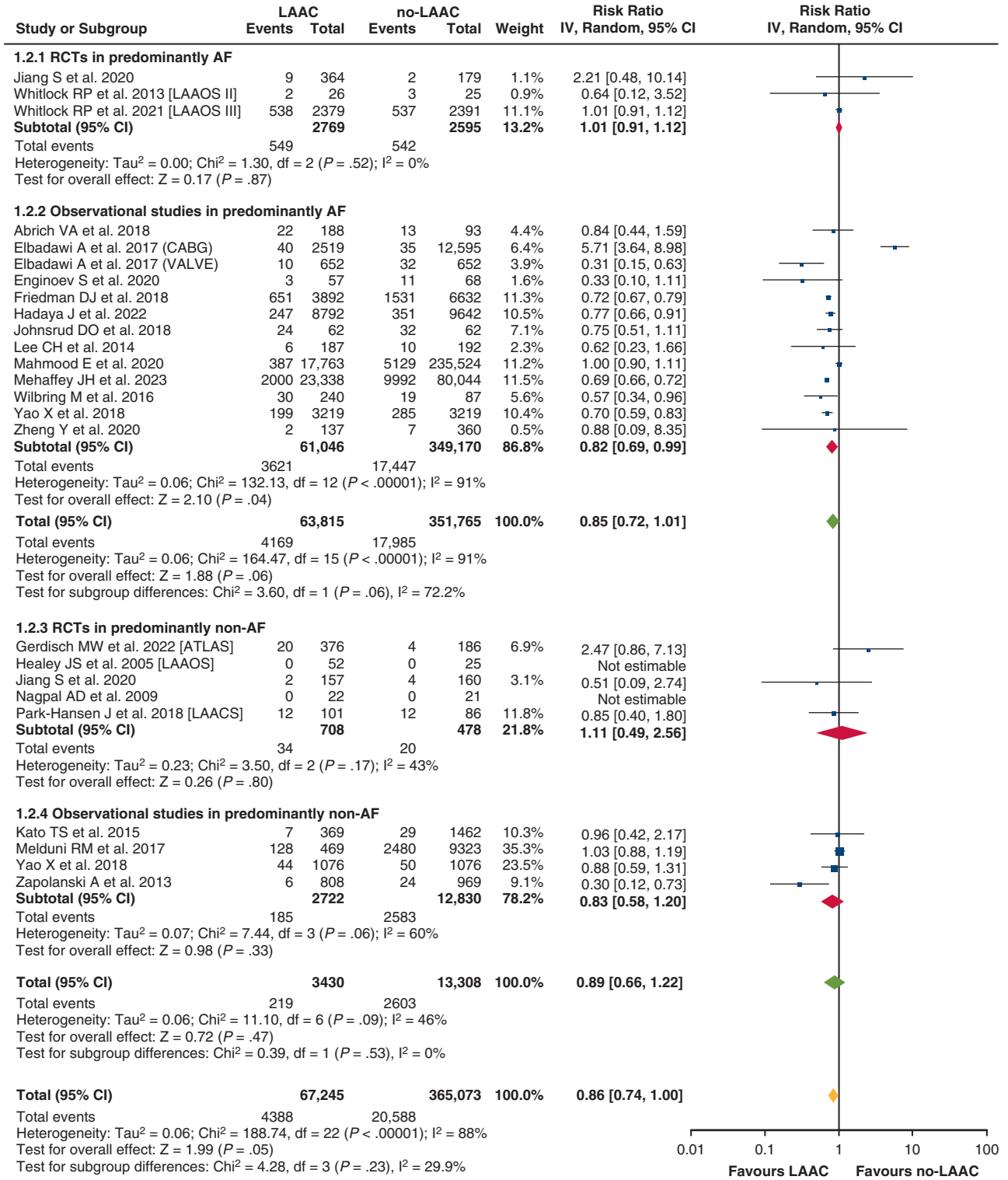

FIGURE 3. Meta analysis of longest available follow-up mortality for the comparison of LAAC versus no-LAAC stratified by presence- or no of preoperative atrial fibrillation. Remaining information as in the Figure 2 legend. *LAAC*, Left atrial appendage closure; *IV*, inverse variance; *CI*, confidence interval; *RCT*, randomized clinical trial; *LAAOS*, Left Atrial Appendage Occlusion Study; *CABG*, coronary artery bypass grafting.

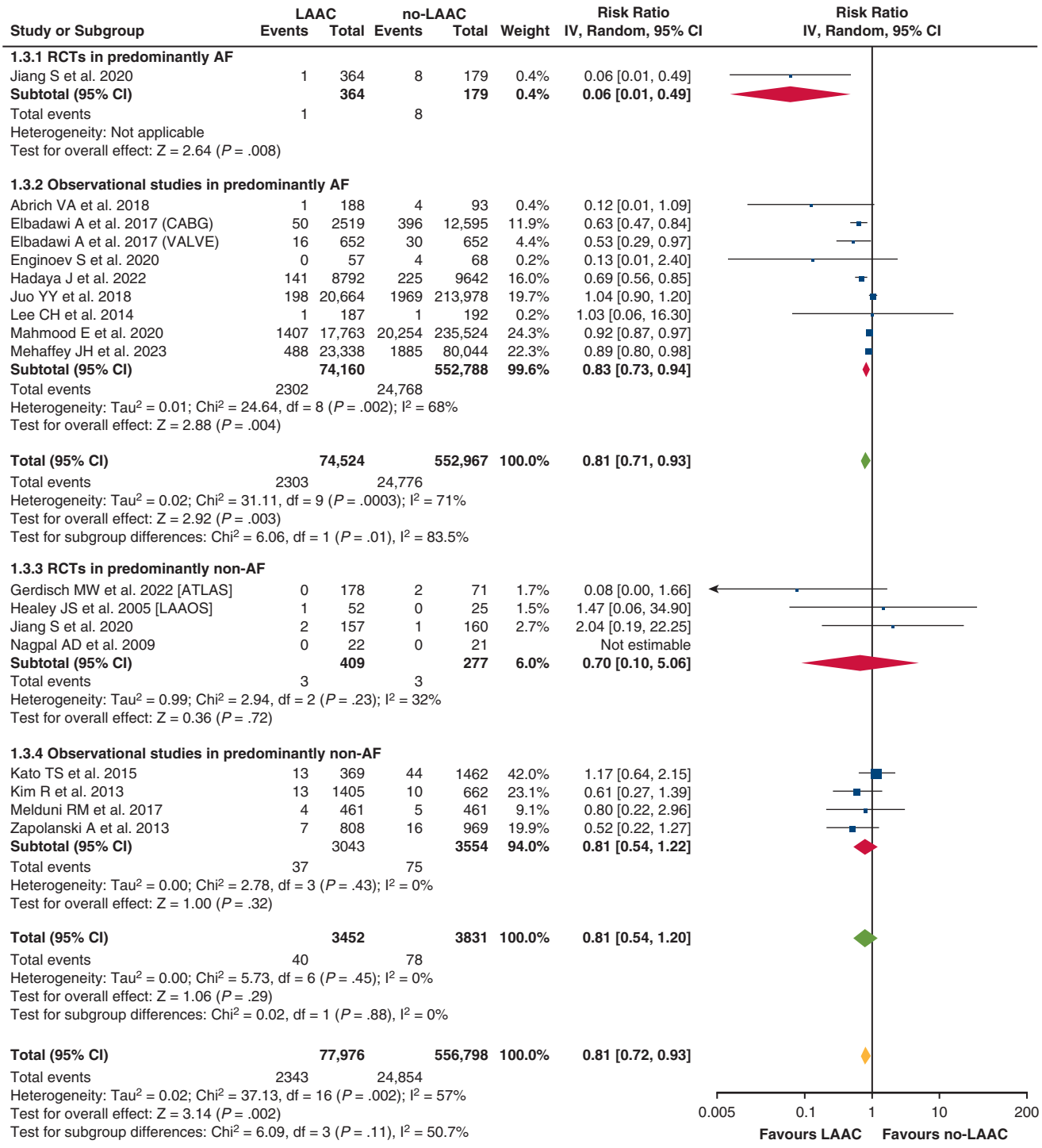

FIGURE 4. Meta analysis of early (in-hospital/30-day) stroke for the comparison of left atrial appendage closure (*LAAC*) versus no-LAAC stratified by presence- or not of preoperative atrial fibrillation. Remaining information as in the Figure 2 legend. *IV*, Inverse variance; *CI*, confidence interval; *RCT*, randomized clinical trial; *CABG*, coronary artery bypass grafting; *LAAOS*, Left Atrial Appendage Occlusion Study.

preoperative AF and no preoperative AF subgroups (RR, 0.58; 95% CI, 0.47-0.71; $P < .00001$; $I^2 = 20\%$ vs RR, 0.87; 95% CI, 0.64-1.17; $P = .63$; $I^2 = 0\%$) ($P_{\text{subgroups}} = .03$) (Figure E4). Estimates of log RR to account for studies reporting 0 events are available in Figures E5-E8 for all-cause mortality and stroke at early- and long-term follow-up, respectively; these reflect the findings of RRs of the meta-analyses in full. Removing single

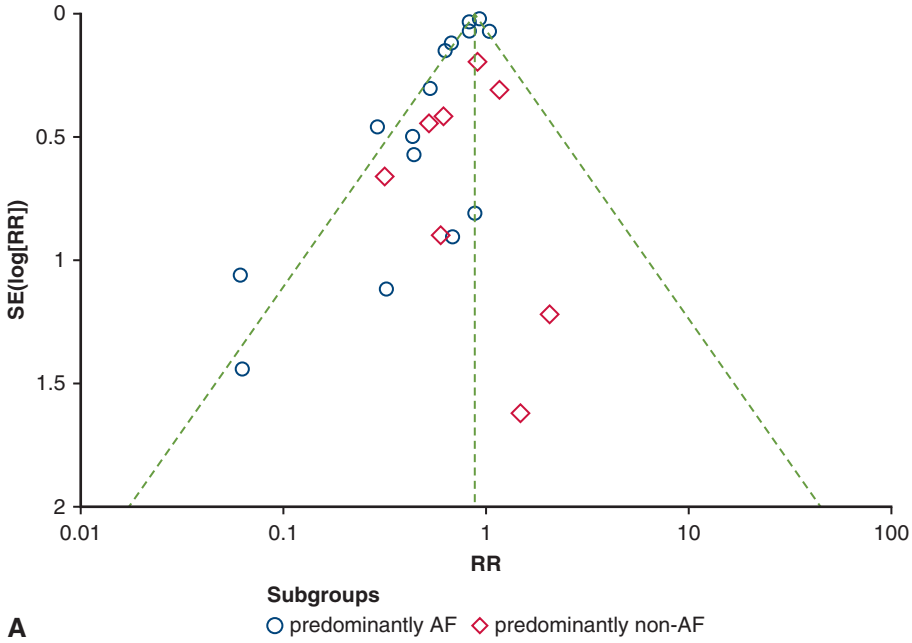

FIGURE 5. A, Funnel plot for the assessment of publication bias. B, Meta-analysis of longest available follow-up stroke for the comparison of left atrial appendage closure (*LAAC*) versus no-LAAC stratified by presence or not of preoperative atrial fibrillation. Remaining information as in the Figure 2 legend. *SE*, standard error; *RR*, risk ratios; *AF*, atrial fibrillation; *IV*, inverse variance; *CI*, confidence interval; *RCT*, randomized clinical trial; *LAAOS*, Left Atrial Appendage Occlusion Study; *CABG*, coronary artery bypass grafting.

studies, 1 at a time, and repeating the calculations did not alter the direction of the estimates.

DISCUSSION

The current systematic review and meta-analysis has investigated the associations between concomitant LAAC with all-cause mortality and stroke in patients undergoing cardiac surgery for another indication with or without preoperative AF. Its main findings are as follows: concomitant LAAC was associated with borderline statistically significant reductions in long-term mortality that were limited to patients with underlying AF, early mortality was unaltered, and both 30-day/in-hospital and long-term stroke rates were significantly reduced with the strategy of LAAC but these were limited to patients with preoperative AF (Figure 6).

Pathophysiology Beyond Clot Formation and Rationale Behind LAAC

The LAA is a small, pouch-like extension located in the left atrium of the heart. It is a remnant of the embryonic left atrium and has a complex internal structure with trabeculations and recesses.[E10] This complex structure provides an ideal environment for blood stasis and turbulence, facilitating the formation of blood clots or thrombi.[3,E11,E12] On the other hand, LAA has, indeed, reservoir, contractile, and endocrine functions as well, and its occlusion at the time of cardiac surgery is not without consequences. Because the LAA is a more distensible chamber than the left atrium,[E13] it serves as a decompression chamber for the LA and protects it from acute pressure increases.

Factors that influence rates of surgical LAAC include the type of performed procedure, geographic region and associated reimbursement policies.[E14] Recently, knowing the encouraging results in patients with preoperative AF, LAAC is becoming of interest also in patients without AF for prevention of thromboembolic events early after surgery and in case POAF develops in the long-term. LAAOS was the first study to address LAAC for patients with high risk of developing postoperative stroke rather than those who had preoperative AF.[33] Although limited in sample size and underpowered for events assessment, it paved the way for the future studies.

LAAC and Mortality

The current meta-analysis found that LAAC was associated with borderline significant reduction in all-cause mortality observed at longest available follow-up. Furthermore, although this benefit was solely present in patients with underlying AF, there were no differences between LAAC and no LAAC within the first 30 days postoperatively. One plausible explanation for the observed reduction in long-term all-cause mortality associated with concomitant LAAC in patients with preexisting AF is the potential role of thromboembolic events burden. By closing off the LAA,

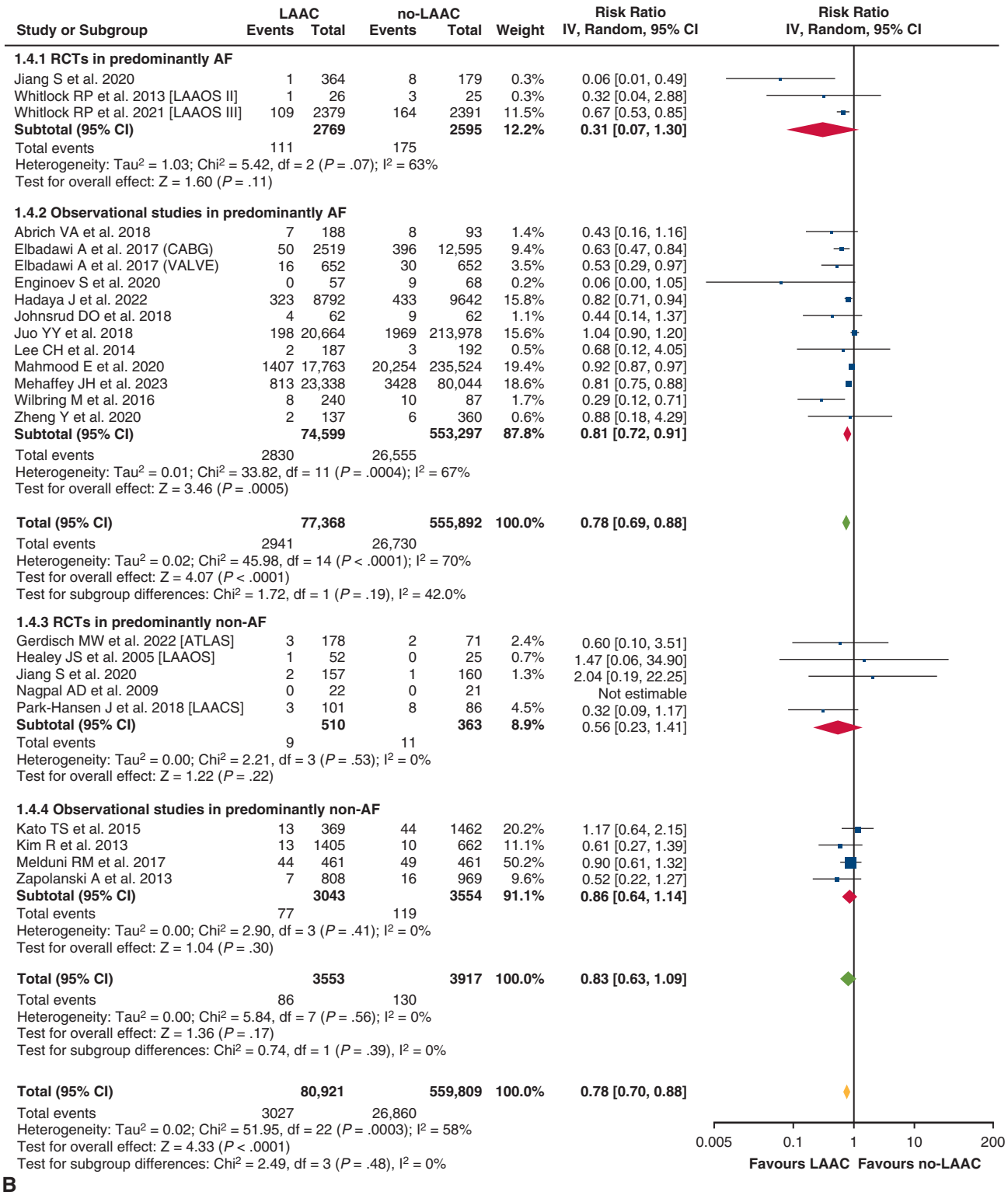

FIGURE 5. (Continued).

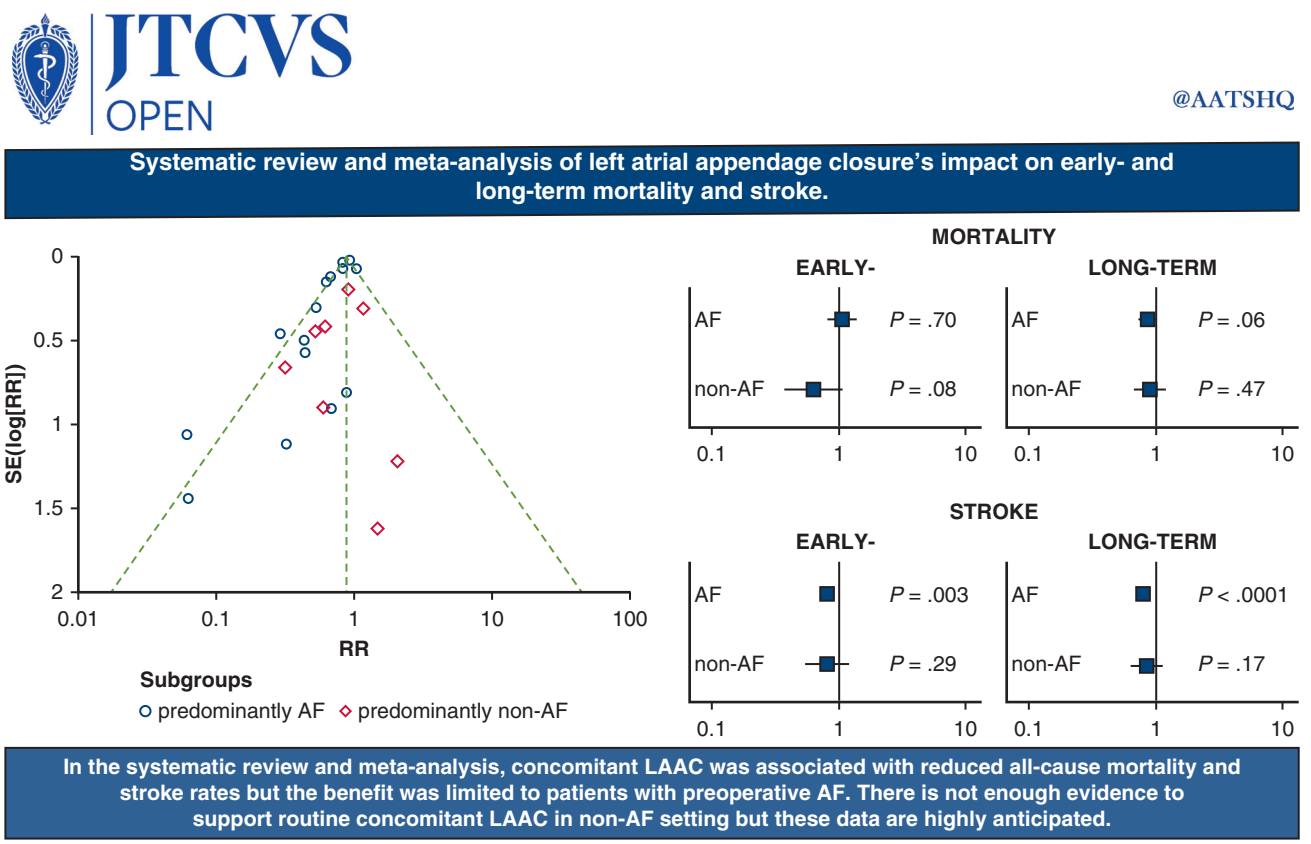

FIGURE 6. Graphical Abstract. *SE*, standard error; *RR*, risk ratios; *AF*, atrial fibrillation; *LAAC*, left atrial appendage closure.

concomitant LAAC effectively mitigates the risk of embolic events, including stroke, which in turn could contribute to improved long-term survival rates in these patients. The LAAOS III study found that, at 3.8 years, all-cause mortality was unchanged with either approach. Another explanation of mortality reductions beyond LAAC in long-term seems to be oral anticoagulation (OAC) compliance; indeed, 1 interesting finding available from Yao and colleagues[9] and addressing relationship between OAC, AF, LAAO, and long-term mortality rates found gradient rates of 1.42, 2.55, 2.75, and 3.69 for no AF and OAC, no AF and no OAC, AF and OAC, and AF and no OAC, respectively, in the LAAC group; in patients in whom LAAC was not performed, the corresponding rates were 1.30, 2.77, 4.53, and 5.32, suggesting mortality differences favor OAC regardless of AF status and higher mortality reductions with LAAC in patients with underlying AF were even higher when OAC was continued; of note, 77% of LAAOS III patients had their OAC maintained throughout the study period, which may have contributed to the neutral findings on mortality.

Melduni and colleagues[12] reported on the first propensity score-matched analysis and demonstrated that survival was not different between patients who underwent surgical exclusion of the LAA during non–AF-related cardiac surgery and those who did not. However, the decision regarding long-term anticoagulation following LAA closure was left to the discretion of the treating physicians in this study and whether it was safe to discontinue OAC in patients without AF after LAAC regardless their high CHA_2DS_2VASc indices remains to be elucidated.

LAAC and Stroke

The main rationale behind LAAC is stroke-risk reduction. Although the results are overall inconsistent, the majority of observational studies reported a reduction in stroke incidence, and the recently published results of the landmark LAAOS III trial confirmed that occlusion of LAA is safe and results in reduction of thromboembolic burden in patients with AF.[10,E15] Our study confirmed that LAAC reduces the risk of early and late stroke by 19% and 13%, respectively. However, similarly to the mortality analysis, the benefit was mainly driven by the group of patients with preoperative AF because the reduction in stroke incidence was not apparent nor statistically significant in patients without AF.

Due to the fact that the concept of LAAC is well grounded in patients with AF and recent studies have

brought evidence of its efficacy and safety, clinicians started to advocate for the addition of the procedure to the overall group of patients undergoing cardiac surgery. Justification of such an approach includes the fact that postoperative AF may occur in up to one-third of patients undergoing heart surgery and, concurrently, introduce significantly increased risk of future AF and cerebral infarction.[E16,E17] The Left Atrial Appendage Closure by Surgery trial, which investigated the addition of LAAC to the concomitant surgery, reported the significant reduction of composite end point rates, including ischemic stroke, transient ischemic attack, or imaging abnormalities. However, the stroke-alone rate difference between the 2 groups in this study was only numerical.[18] Recently, the AtriClip Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures trial confirmed the high success and low complication rates of LAAC performance with the AtriClip device in patients with CHA_2DS_2VASc score ≥ 2 and no history of AF.[15] Once again, no significant reduction in stroke incidence was reported. The benefit of LAAC addition was confirmed by Kim and colleagues[E8] and Endo and colleagues[E18] in the corresponding subgroup analysis. Both studies confirmed that LAAC decreases the risk of stroke, but only in patients who developed POAF. Hopefully, the currently ongoing The Left Atrial Appendage Exclusion for Prophylactic Stroke Reduction trial will shed more light on the issue of prophylactic LAAC in patients without a history of AF.[E19] Similarly the randomized prospective multicenter trial for stroke prevention by prophylactic surgical closure of the left atrial appendage in patients undergoing bioprosthetic aortic valve surgery (LAA-CLOSURE trial), aims to investigate outcomes of prophylactic surgical LAAC in patients undergoing surgical aortic valve replacement.[E20] The study's secondary end points include hospitalization for decompensated heart failure, which will shed more light on the controversies regarding decrease in natriuretic peptide concertation, leading to fluid retention and heart failure decompensation.[E19]

In terms of stroke reduction in patients with AF, our results confirm previous findings by Gutierrez and colleagues.[E15] The authors showed that the benefit of LAAC was only reported in studies that enrolled >70% of patients with AF and no effect was seen in studies with <30% rate of preoperative AF.[E15] Although the reduction in embolism risk in patients with AF after surgical LAAC is apparent, the question regarding optimal technique remains unanswered. Concerns remain regarding the risk of incomplete occlusion and residual flow making the procedure ineffective. According to Jang and colleagues,[E21] the incidence of unsuccessful LAAC varies from 0% with the epicardial clipping device up to 30% with the surgical ligation technique. With this fact is related the problem of the anticoagulation regimen. Currently the data on the safety of OAC cessation after surgical LAAC are inconclusive.

Limitations

The current analysis shares and reflects the limitations of the included single studies. There was a high proportion of observational studies in which the selection bias cannot be ruled out; some studies report on in-hospital outcomes only. We observed high degree of heterogeneity in both the analyses of stroke and mortality. Although we accounted for between- and within-study variability with random effects models employed in the meta-analysis that assigns wider CIs to final point estimates, certain differences between studies remain and therefore the results cannot be generalized to the entire population; that is, the presence of underlying AF, protocol-mandated OAC, history of prior cerebrovascular events, heart failure status, and type of surgical procedures. None of the studies reported on outcomes depending on LAAC technique in case more than 1 was adopted, making inferences about recanalization with simple purse string suture impossible. Moreover, only 8 out of 25 included studies reported rates of POAF. Finally, patients at different risks for developing stroke were included in the single studies and thus the meta-analysis; only half of the studies provided CHA_2DS_2VASc score, 6 studies provided information regarding OAC at baseline, 12 provided information regarding OAC at discharge, and 3 provided information on OAC compliance at follow-up, making the associations of LAAC with reduced mortality limited. On the other hand, we conducted a series of sensitivity analyses, including those accounting for durations of follow-up and excluding observational nonadjusted studies,[E21-E54] and found the direction and magnitude of estimates to support the main results.

CONCLUSIONS

Concomitant LAAC was associated with reduced stroke rates at early, long-term, and possibly reduced all-cause mortality, but the benefits were limited to patients with preoperative AF. There is not enough evidence to support routine concomitant LAAC in non-AF settings.

Conflict of Interest Statement

Dr Maesen reports Medtronic grants paid to institute and consultant fees from Atricure and Medtronic paid to institute. Dr Litwinowicz, is consultant to Medtronic, Getinge, and LivaNova, and member of the Medical Advisory Board of Eurosets, Hemocue, and Xenios. Dr Whitlock reports grants from Bayer and Roche, grants and personal fees from Boehringer Ingelheim and AtriCure, and personal fees from PhaseBio; Dr La Meir is a consultant for Atricure; Dr de Asmundi receives research grants on behalf of the center from Biotronik, Medtronic, Abbott, LivaNova, Boston Scientific, AtriCure, Philips, and Acutus and compensation for teaching purposes and proctoring from Medtronic, Abbott, Biotronik, Livanova, Boston Scientific, Atricure,

and Acutus Medical Daiichi Sankyo. Dr Cox discloses a financial relationship with Adagio Medical, Atricure, PAVmed, Lucid Diagnostics, and PotentiaMetrics; Dr Suwalski, is a consultant for Atricure. The remaining authors reported no conflict of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

References

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation*. 2014;129(8):837-847.
2. De Backer O, Arnous S, Ihlemann N, et al. Percutaneous left atrial appendage occlusion for stroke prevention in atrial fibrillation: an update. *Open Heart*. 2014;1(1):e000020.
3. Cresti A, García-Fernández MA, Sievert H, et al. Prevalence of extra-appendage thrombosis in non-valvular atrial fibrillation and atrial flutter in patients undergoing cardioversion: a large transoesophageal echo study. *EuroIntervention*. 2019;15(3):E225-E230.
4. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg*. 1996;61(2):755-759.
5. Regazzoli D, Ancona F, Trevisi N, et al. Left atrial appendage: physiology, pathology, and role as a therapeutic target. *BioMed Res Int*. 2015;2015:205013.
6. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society in Collaboration with the Society of Thoracic Surgeons. *Circulation*. 2019;140(2):e125-e151.
7. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373-498.
8. Friedman DJ, Piccini JP, Wang T, et al. Association between left atrial appendage occlusion and readmission for thromboembolism among patients with atrial fibrillation undergoing concomitant cardiac surgery. *JAMA*. 2018;319(4):365-374.
9. Yao X, Gersh BJ, Holmes DR, et al. Association of surgical left atrial appendage occlusion with subsequent stroke and mortality among patients undergoing cardiac surgery. *JAMA*. 2018;319(20):2116-2126.
10. Whitlock RP, Belley-Cote EP, Paparella D, et al. Left atrial appendage occlusion during cardiac surgery to prevent stroke. *N Engl J Med*. 2021;384(22):2081-2091.
11. Mahmood E, Matyal R, Mahmood F, et al. Impact of left atrial appendage exclusion on short-term outcomes in isolated coronary artery bypass graft surgery. *Circulation*. 2020;142(1):20-28.
12. Melduni RM, Schaff HV, Lee HC, et al. Impact of left atrial appendage closure during cardiac surgery on the occurrence of early postoperative atrial fibrillation, stroke, and mortality: a propensity score-matched analysis of 10 633 patients. *Circulation*. 2017;135(4):366-378.
13. Mehaffey JH, Hayanga JWA, Wei L, Mascio C, Rankin JS, Badhwar V. Surgical ablation of atrial fibrillation is associated with improved survival compared with appendage obliteration alone: an analysis of 100,000 Medicare beneficiaries. *J Thorac Cardiovasc Surg*. May 7, 2023 [Epub ahead of print]. https://doi.org/10.1016/j.jtcvs.2023.04.021
14. Waterford SD. Left atrial appendage exclusion in patients without atrial fibrillation undergoing cardiac surgery. *Innovations (Phila)*. 2022;17(6):461-462.
15. Gerdisch MW, Garrett HE, Mumtaz MA, et al. Prophylactic left atrial appendage exclusion in cardiac surgery patients with elevated CHA2DS2-VASc Score: results of the randomized ATLAS trial. *Innovations (Phila)*. 2022;17(6):463-470.
16. Whitlock RP, Belley-Côté EP. The ATLAS trial: a look before we LeAAPS. *Innovations (Phila)*. 2022;17(6):459-460.
17. Madsen CL, Park-Hansen J, Irmukhamedov A, et al. The left atrial appendage closure by surgery-2 (LAACS-2) trial protocol rationale and design of a randomized multicenter trial investigating if left atrial appendage closure prevents stroke in patients undergoing open-heart surgery irrespective of preoperative atrial fibrillation status and stroke risk. *Am Heart J*. 2023;264:133-142.
18. Park-Hansen J, Holme SJV, Irmukhamedov A, et al. Adding left atrial appendage closure to open heart surgery provides protection from ischemic brain injury six years after surgery independently of atrial fibrillation history: the LAACS randomized study. *J Cardiothorac Surg*. 2018;13(1):53.
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
20. Stroup DF, Berlin JA, Morton SC, 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(15):2008-2012.
21. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343(7829):d5928.
22. Cochrane handbook for systematic reviews of interventions. Cochrane training. Accessed August 17, 2023. https://training.cochrane.org/handbook
23. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ*. 2015;350:h870.
24. Santesso N, Glenton C, Dahm P, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *J Clin Epidemiol*. 2020;119:126-135.
25. Cohen JF, Chalumeau M, Cohen R, Korevaar DA, Khoshnood B, Bossuyt PMM. Cochran's Q test was useful to assess heterogeneity in likelihood ratios in studies of diagnostic accuracy. *J Clin Epidemiol*. 2015;68(3):299-306.
26. Ioannidis JPA, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. *BMJ*. 2007;335(7626):914-916.
27. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
28. Abrich VA, Narichania AD, Love WT, Lanza LA, Shen WK, Sorajja D. Left atrial appendage exclusion during mitral valve surgery and stroke in atrial fibrillation. *J Interv Card Electrophysiol*. 2018;53(3):285-292.
29. Elbadawi A, Ogunbayo GO, Elgendy IY, et al. Impact of left atrial appendage exclusion on cardiovascular outcomes in patients with atrial fibrillation undergoing coronary artery bypass grafting (from the National Inpatient Sample Database). *Am J Cardiol*. 2017;120(6):953-958.
30. Elbadawi A, Olorunfemi O, Ogunbayo GO, et al. Cardiovascular outcomes with surgical left atrial appendage exclusion in patients with atrial fibrillation who underwent valvular heart surgery (from the National Inpatient Sample Database). *Am J Cardiol*. 2017;119(12):2056-2060.
31. Enginoev S, Koz'min D, Magomedov G, et al. Ligation of left atrial appendage during off-pump coronary surgery. *Thorac Cardiovasc Surg*. 2020;68(8):695-699.
32. Hadaya J, Hernandez R, Sanaiha Y, et al. Left atrial appendage closure during cardiac surgery: safe but underutilized in California. *J Thorac Cardiovas Surg Open*. 2022;13:150-162.
33. Healey JS, Crystal E, Lamy A, 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(2):288-293.
34. Jiang S, Zhang H, Wei S, et al. Left atrial appendage exclusion is effective in reducing postoperative stroke after mitral valve replacement. *J Card Surg*. 2020;35(12):3395-3402.
35. Johnsrud DO, Melduni RM, Lahr B, Yao X, Greason KL, Noseworthy PA. Evaluation of anticoagulation use and subsequent stroke in patients with atrial fibrillation after empiric surgical left atrial appendage closure: a retrospective case-control study. *Clin Cardiol*. 2018;41(12):1578-1582.

Key Words: atrial fibrillation, left atrial appendage closure, heart surgery, arrhythmia, systematic review, meta-analysis

E-References

E1. Kato TS, Iwamura T, Endo D, et al. Left atrial appendage closure reduces the incidence of postoperative cerebrovascular accident in patients undergoing cardiac surgery. *Circ J*. 2015;79(12):2591-2597.

E2. 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(1):124-132.

E3. 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(3):553-557.

E4. Whitlock RP, Vincent J, Blackall MH, et al. Left atrial appendage occlusion study II (LAAOS II). *Can J Cardiol*. 2013;29(11):1443-1447.

E5. Wilbring M, Jung F, Weber C, Matschke K, Knaut M. Reduced incidence of thromboembolic events after surgical closure of left atrial appendage in patients with atrial fibrillation. *Innovations (Phila)*. 2016;11(1):24-30.

E6. Zapolanski A, Johnson CK, Dardashti O, et al. Epicardial surgical ligation of the left atrial appendage is safe, reproducible, and effective by transesophageal echocardiographic follow-up. *Innovations (Phila)*. 2013;8(5):371-375.

E7. Zheng Y, Rao CF, Chen SP, He L, Hou JF, Zheng Z. Surgical left atrial appendage occlusion in patients with atrial fibrillation undergoing mechanical heart valve replacement. *Chin Med J (Engl)*. 2020;133(16):1891-1899.

E8. 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(2):582-589.

E9. Juo YY, Lee Bailey K, Seo YJ, Aguayo E, Benharash P. Does left atrial appendage ligation during coronary bypass surgery decrease the incidence of postoperative stroke? *J Thorac Cardiovasc Surg*. 2018;156(2):578-585.

E10. Handke M, Harloff A, Hetzel A, Olschewski M, Bode C, Geibel A. Left atrial appendage flow velocity as a quantitative surrogate parameter for thromboembolic risk: determinants and relationship to spontaneous echocontrast and thrombus formation–a transesophageal echocardiographic study in 500 patients with cerebral ischemia. *J Am Soc Echocardiogr*. 2005;18(12):1366-1372.

E11. Nishikii-Tachibana M, Murakoshi N, Seo Y, et al. Prevalence and clinical determinants of left atrial appendage thrombus in patients with atrial fibrillation before pulmonary vein isolation. *Am J Cardiol*. 2015;116(9):1368-1373.

E12. Hoit BD, Walsh RA. Regional atrial distensibility. *Am J Physiol*. 1992;262(5 Pt 2):H1356-H1360.

E13. Hoit BD, Shao Y, Tsai LM, Patel R, Gabel M, Walsh RA. Altered left atrial compliance after atrial appendectomy. Influence on left atrial and ventricular filling. *Circ Res*. 1993;72(1):167-175.

E14. Hadaya J, Sanaiha Y, Tran Z, Shemin RJ, Benharash P. Defining value in cardiac surgery: a contemporary analysis of cost variation across the United States. *J Thorac Cardiovasc Surg Open*. 2022;10:266-281.

E15. Gutiérrez EM, Castaño M, Gualis J, et al. Beneficial effect of left atrial appendage closure during cardiac surgery: a meta-analysis of 280 585 patients. *Eur J Cardiothorac Surg*. 2020;57(2):252-262.

E16. Steinberg BA, Zhao Y, He X, et al. Management of postoperative atrial fibrillation and subsequent outcomes in contemporary patients undergoing cardiac surgery: insights from the society of thoracic surgeons CAPS-Care Atrial Fibrillation Registry. *Clin Cardiol*. 2014;37(1):7-13.

E17. Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. *Eur J Cardiothorac Surg*. 2010;37(6):1353-1359.

E18. Endo D, Kato TS, Iwamura T, et al. The impact of surgical left atrial appendage amputation/ligation on stroke prevention in patients undergoing off-pump coronary artery bypass grafting. *Heart Ves*. 2017;32(6):726-734.

E19. Left atrial appendage exclusion for prophylactic stroke reduction trial - full text view - ClinicalTrials.gov. Accessed August 17, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT05478304

E20. Jang SJ, Wong SC, Mosadegh B. Leaks after left atrial appendage closure: ignored or neglected? *Cardiology*. 2021;146(3):384-391.

E21. Branzoli S, Guarracini F, Marini M, et al. Heart team for left atrial appendage occlusion: a patient-tailored approach. *J Clin Med*. 2021;11(1):176.

E22. Franciulli M, De Martino G, Librera M, et al. Stand-alone thoracoscopic left atrial appendage closure in nonvalvular atrial fibrillation patients at high bleeding risk. *Innovations (Phila)*. 2020;15(6):541-546.

E23. Cartledge R, Suwalski G, Witkowska A, et al. Standalone epicardial left atrial appendage exclusion for thromboembolism prevention in atrial fibrillation. *Interact Cardiovasc Thorac Surg*. 2022;34(4):548-555.

E24. Min XP, Zhu TY, Han J, Li Y, Meng X. Left atrial appendage obliteration in atrial fibrillation patients undergoing bioprosthetic mitral valve replacement. *Herz*. 2016;41(1):87-94.

E25. Gong Z, Jiang S, Li B, et al. Early results of left atrial appendage closure in cerebral ischemic stroke reduction in patients with mitral valve replacement. *Zhonghua Wai Ke Za Zhi*. 2014;52(12):934-938.

E26. García-Fernández MA, Pérez-David E, Quiles 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(7):1253-1258.

E27. Rhee Y, Park SJ, Lee JW. Epicardial left atrial appendage clip occlusion in patients with atrial fibrillation during minimally invasive cardiac surgery. *J Thorac Cardiovasc Surg*. 2023;166(2):468-474.

E28. Ohtsuka T, Nonaka T, Hisagi M, Ninomiya M, Masukawa A, Ota T. Thoracoscopic stapler-and-loop technique for left atrial appendage closure in nonvalvular atrial fibrillation: mid-term outcomes in 201 patients. *Heart Rhythm*. 2018;15(9):1314-1320.

E29. Yoshimoto A, Suematsu Y, Kurahashi K, Takahashi H, Inoue T. A comparison between stand-alone left atrial appendage occlusion and resection as a method of preventing cardiogenic thromboembolic stroke. *Gen Thorac Cardiovasc Surg*. 2024;72(3):157-163.

E30. Wang Z, Wang K, Lu S, et al. Surgical and percutaneous left atrial appendage intervention: silent cerebral embolism considerations. *Eur J Cardiothorac Surg*. 2023;63(6):ezad074.

E31. Caliskan E, Sahin A, Yilmaz M, et al. Epicardial left atrial appendage AtriClip occlusion reduces the incidence of stroke in patients with atrial fibrillation undergoing cardiac surgery. *Europace*. 2018;20(7):e105-e114.

E32. Endo D, Kinoshita T, Lee J, et al. Left atrial appendage closure during coronary bypass surgery in patients on hemodialysis. *Circ J*. 2023;87(7):982-989.

E33. Deshmukh A, Bhatia A, Sayer GT, et al. Left atrial appendage occlusion with left ventricular assist device decreases thromboembolic events. *Ann Thorac Surg*. 2019;107(4):1181-1186.

E34. Fu M, Qin Z, Zheng S, et al. Thoracoscopic left atrial appendage occlusion for stroke prevention compared with long-term warfarin therapy in patients with nonvalvular atrial fibrillation. *Am J Cardiol*. 2019;123(1):50-56.

E35. Noseworthy PA, Van Houten HK, Krumholz HM, et al. Percutaneus left atrial appendage occlusion in comparison to non-vitamin K antagonist oral anticoagulant among patients with atrial fibrillation. *J Am Heart Assoc*. 2022;11(19):e027001.

E36. Korsholm K, Valentin JB, Damgaard D, et al. Clinical outcomes of left atrial appendage occlusion versus direct oral anticoagulation in patients with atrial fibrillation and prior ischemic stroke: a propensity-score matched study. *Int J Cardiol*. 2022;363:56-63.

E37. Nielsen-Kudsk JE, Korsholm K, Damgaard D, et al. Clinical outcomes associated with left atrial appendage occlusion versus direct oral anticoagulation in atrial fibrillation. *JACC Cardiovasc Interv*. 2021;14(1):69-78.

E38. Gloekler S, Fürholz M, de Marchi S, et al. Left atrial appendage closure versus medical therapy in patients with atrial fibrillation: the APPLY study. *EuroIntervention*. 2020;16(9):e767-e774.

E39. Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial [published correction appears in *J Am Coll Cardiol*. 2014 Sep 16;64(11):1186]. *J Am Coll Cardiol*. 2014;64(1):1-12.

E40. Godino C, Melillo F, Bellini B, et al. Percutaneous left atrial appendage closure versus non-vitamin K oral anticoagulants in patients with non-valvular atrial fibrillation and high bleeding risk. *EuroIntervention*. 2020;15(17):1548-1554.

E41. Ding WY, Rivera-Caravaca JM, Fazio-Eynullayeva E, et al. Outcomes of left atrial appendage occlusion vs. non-vitamin K antagonist oral anticoagulants in atrial fibrillation. *Clin Res Cardiol*. 2022;111(9):1040-1047.

E42. Osmancik P, Herman D, Neuzil P, et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol*. 2020;75(25):3122-3135.

E43. Paiva L, Coelho J, Barra S, et al. Non-vitamin K antagonist oral anticoagulation versus left atrial appendage occlusion for primary and secondary stroke prevention after cardioembolic stroke. *Rev Port Cardiol (Engl Ed)*. 2021;40(5):357-365.

E44. Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial [published correction appears in *JAMA*. 2015;313(10):1061]. *JAMA*. 2014;312(19):1988-1998.

E45. Blackshear JL, Johnson WD, Odell JA, et al. Thoracoscopic extracardiac obliteration of the left atrial appendage for stroke risk reduction in atrial fibrillation. *J Am Coll Cardiol*. 2003;42(7):1249-1252.

E46. Aryana A, Singh SK, Singh SM, et al. Association between incomplete surgical ligation of left atrial appendage and stroke and systemic embolization. *Heart Rhythm*. 2015;12(7):1431-1437.

E47. Wolf RK, Schneeberger EW, Osterday R, et al. Video-assisted bilateral pulmonary vein isolation and left atrial appendage exclusion for atrial fibrillation [published correction appears in *J Thorac Cardiovasc Surg*. 2006;131(4):772]. *J Thorac Cardiovasc Surg*. 2005;130(3):797-802.

E48. Alqaqa A, Martin S, Hamdan A, Shamoon F, Asgarian KT. Concomitant left atrial appendage clipping during minimally invasive mitral valve surgery: technically feasible and safe. *J Atr Fibrillation*. 2016;9(1):1407.

E49. Salzberg SP, Plass A, Emmert MY, et al. Left atrial appendage clip occlusion: early clinical results. *J Thorac Cardiovasc Surg*. 2010;139(5):1269-1274.

E50. Suwalski G, Emery R, Gryszko L, et al. Early operative comparison of two epicardial left atrial appendage occluding systems applied during off-pump coronary revascularisation in patients with persistent atrial fibrillation. *Kardiochir Torakochirurgia Pol*. 2016;13(1):10-14.

E51. Ad N, Massimiano PS, Shuman DJ, Pritchard G, Holmes SD. New approach to exclude the left atrial appendage during minimally invasive cryothermic surgical ablation. *Innovations (Phila)*. 2015;10(5):323-327.

E52. Ellis CR, Aznaurov SG, Patel NJ, et al. Angiographic efficacy of the atriclip left atrial appendage exclusion device placed by minimally invasive thoracoscopic approach. *JACC Clin Electrophysiol*. 2017;3(12):1356-1365.

E53. Ailawadi G, Gerdisch MW, Harvey RL, et al. Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial. *J Thorac Cardiovasc Surg*. 2011;142(5):1002-1009.e1.

E54. van Laar C, Verberkmoes NJ, van Es HW, et al. Thoracoscopic left atrial appendage clipping: a multicenter cohort analysis. *JACC Clin Electrophysiol*. 2018;4(7):893-901.

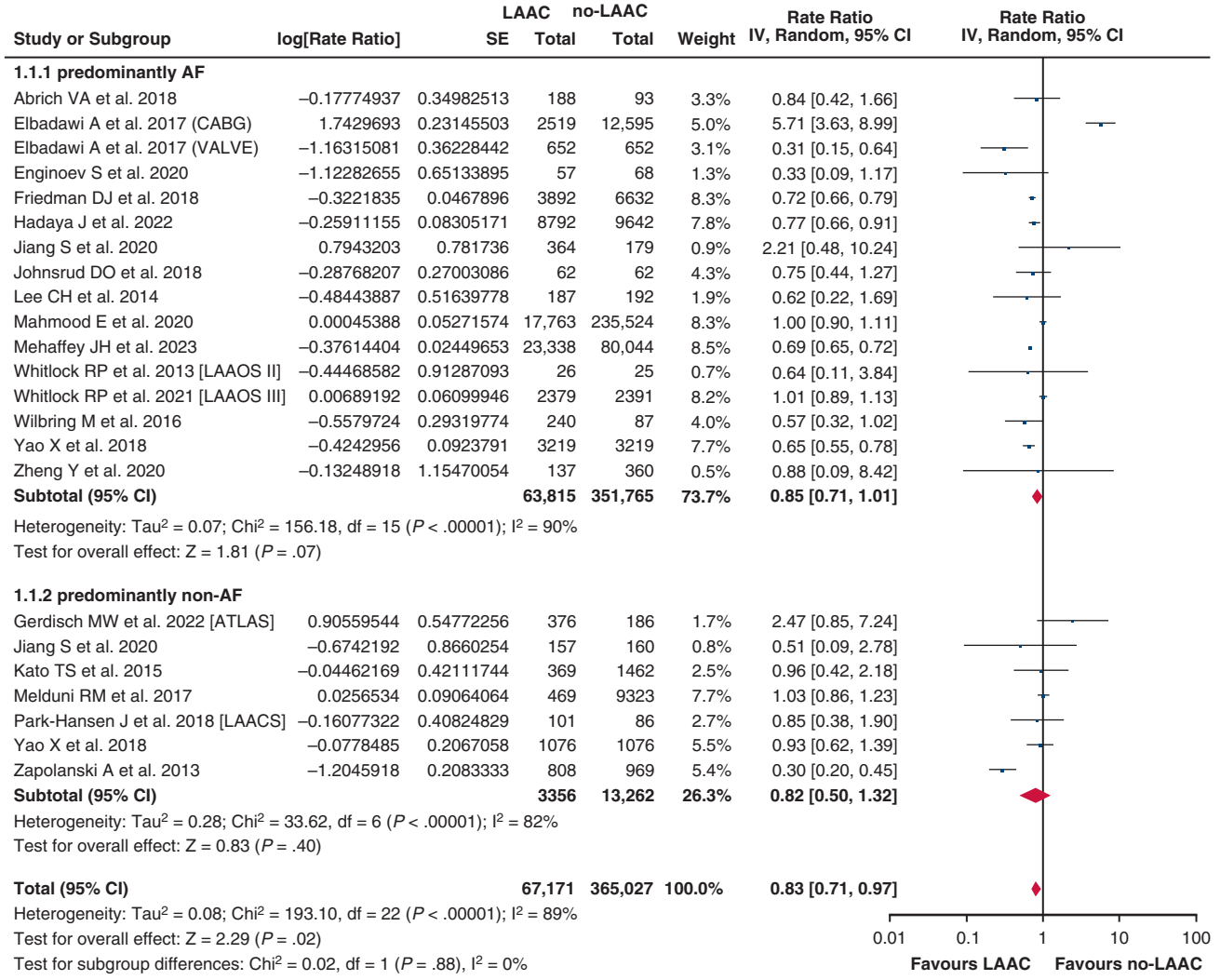

FIGURE E1. Morality at longest follow-up adjusted for the duration of follow-up. *LAAC*, Left atrial appendage closure; *SE*, standard error; *IV*, inverse variance; *CI*, confidence interval; *AF*, atrial fibrillation; *CABG*, coronary artery bypass grafting; *LAAOS*, Left Atrial Appendage Occlusion Study; *ATLAS*, AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures; *LAACS*, The Left Atrial Appendage Closure by Surgery.

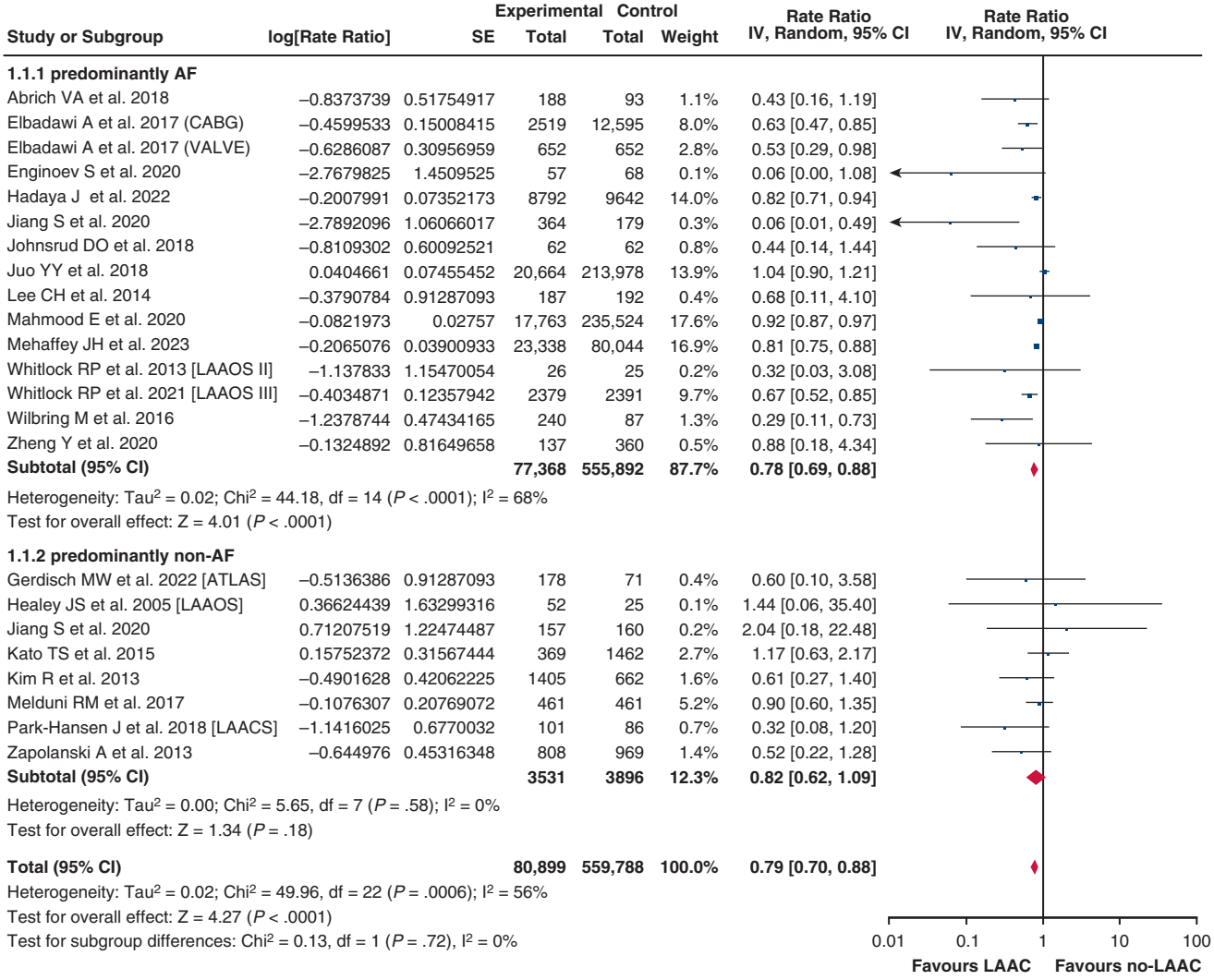

FIGURE E2. Stroke at longest follow-up adjusted for the duration of follow-up. *SE*, standard error; *IV*, inverse variance; *CI*, confidence interval; *AF*, atrial fibrillation; *CABG*, coronary artery bypass grafting; *LAAOS*, Left Atrial Appendage Occlusion Study; *ATLAS*, AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures; *LAACS*, The Left Atrial Appendage Closure by Surgery.

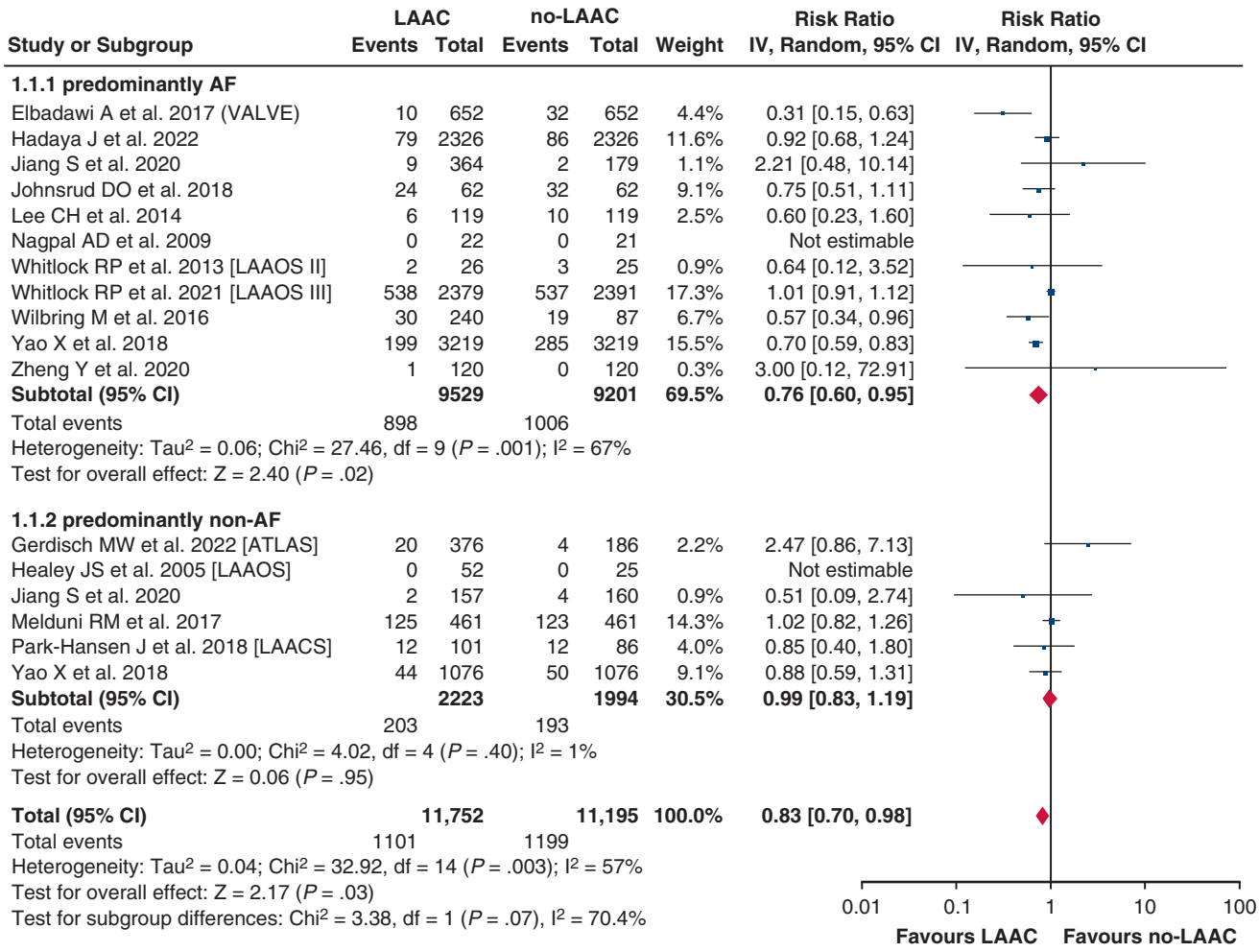

FIGURE E3. Mortality at longest follow-up. Randomized controlled trials and propensity score-matched studies only. *LAAC*, Left atrial appendage closure; *IV*, inverse variance; *CI*, confidence interval; *AF*, atrial fibrillation; *LAAOS*, Left Atrial Appendage Occlusion Study; *ATLAS*, AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures; *LAACS*, The Left Atrial Appendage Closure by Surgery.

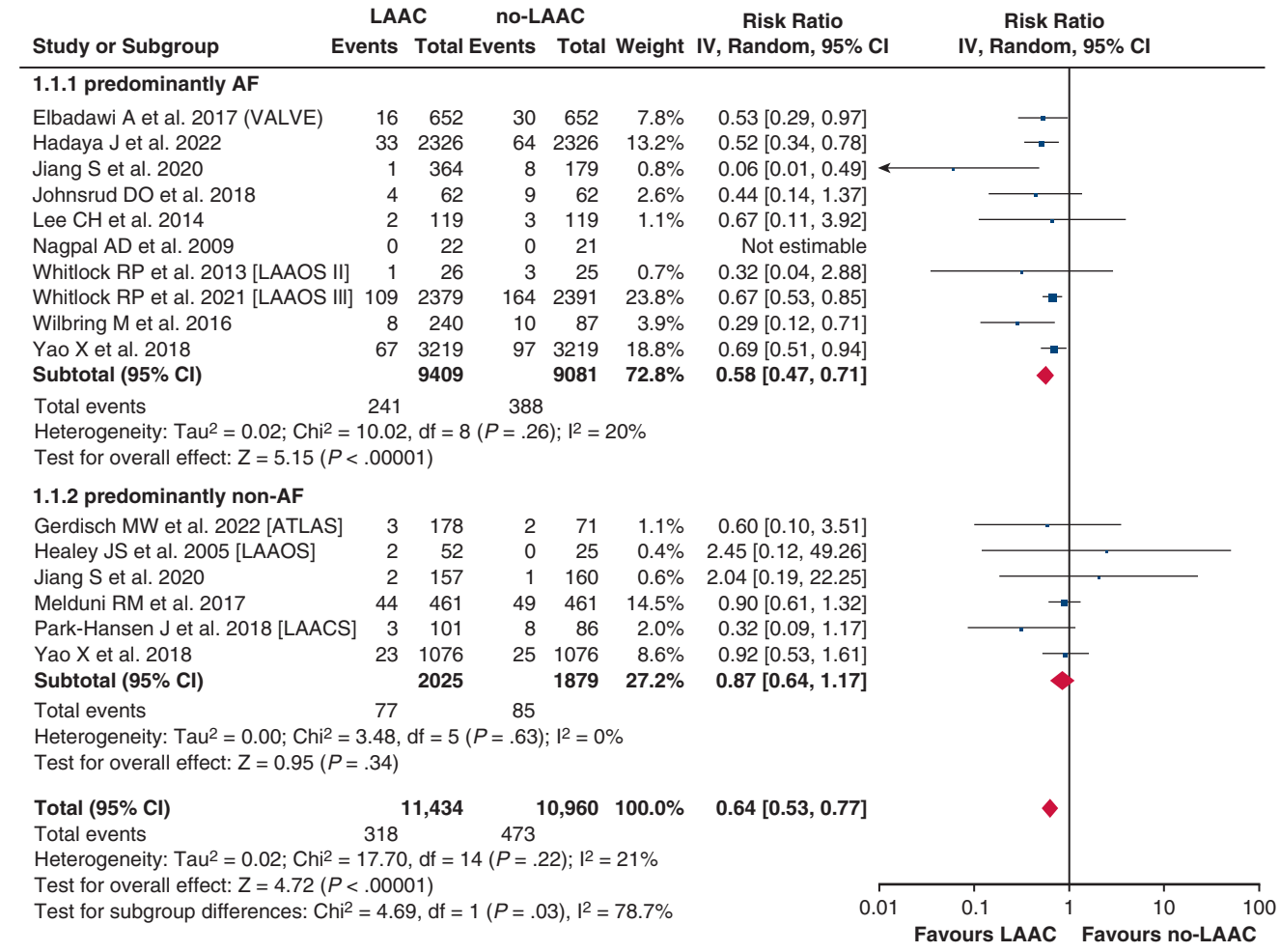

FIGURE E4. Stroke at longest follow-up. Randomized controlled trials and propensity score-matched studies only. *LAAC*, Left atrial appendage closure; *IV*, inverse variance; *CI*, confidence interval; *AF*, atrial fibrillation; *LAAOS*, Left Atrial Appendage Occlusion Study; *ATLAS*, AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures; *LAACS*, The Left Atrial Appendage Closure by Surgery.

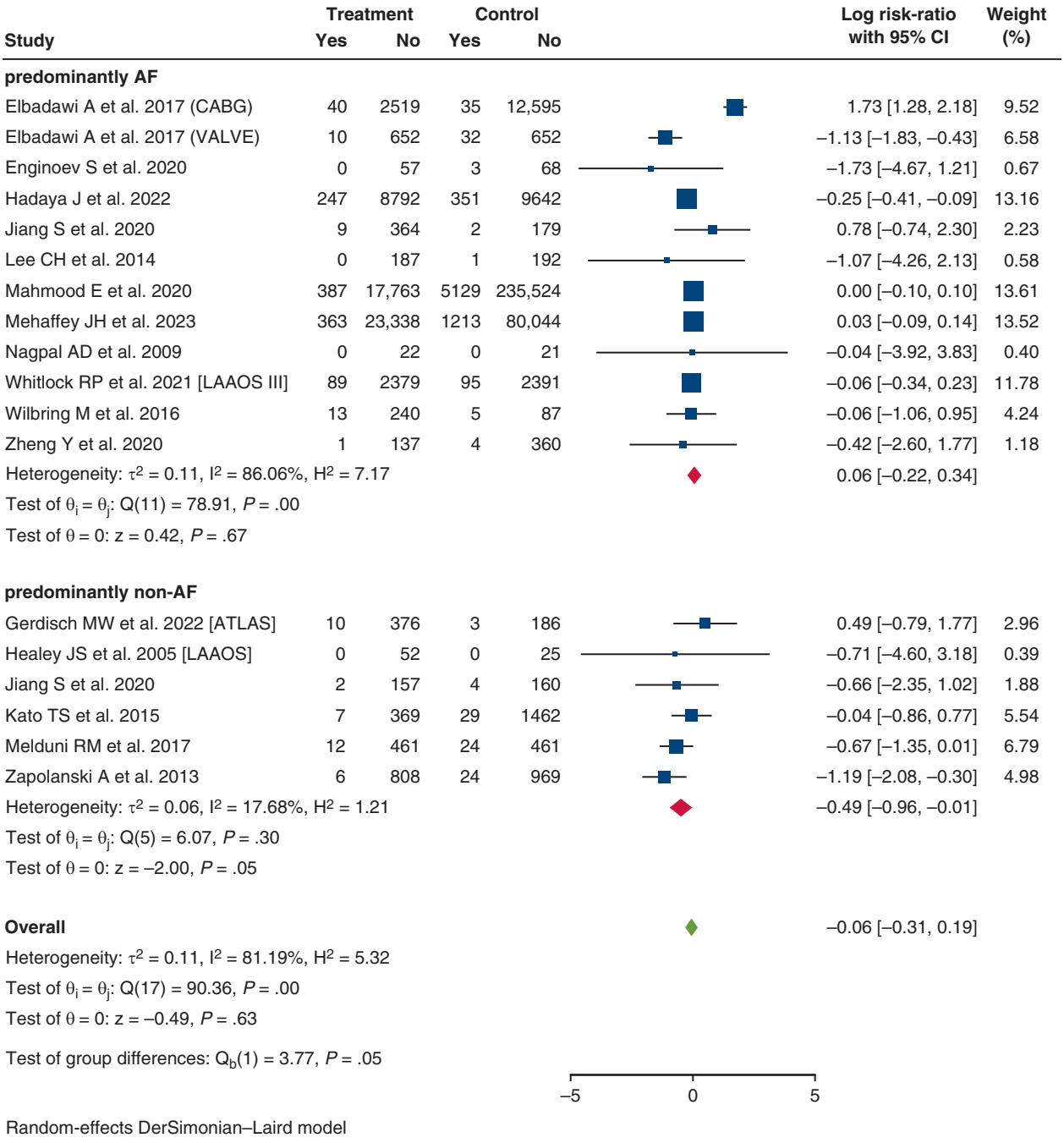

FIGURE E5. Mortality at early follow-up. Log risk ratio. *CI*, confidence interval; *AF*, atrial fibrillation; *CABG*, coronary artery bypass grafting; *LAAOS*, Left Atrial Appendage Occlusion Study; *ATLAS*, AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures.

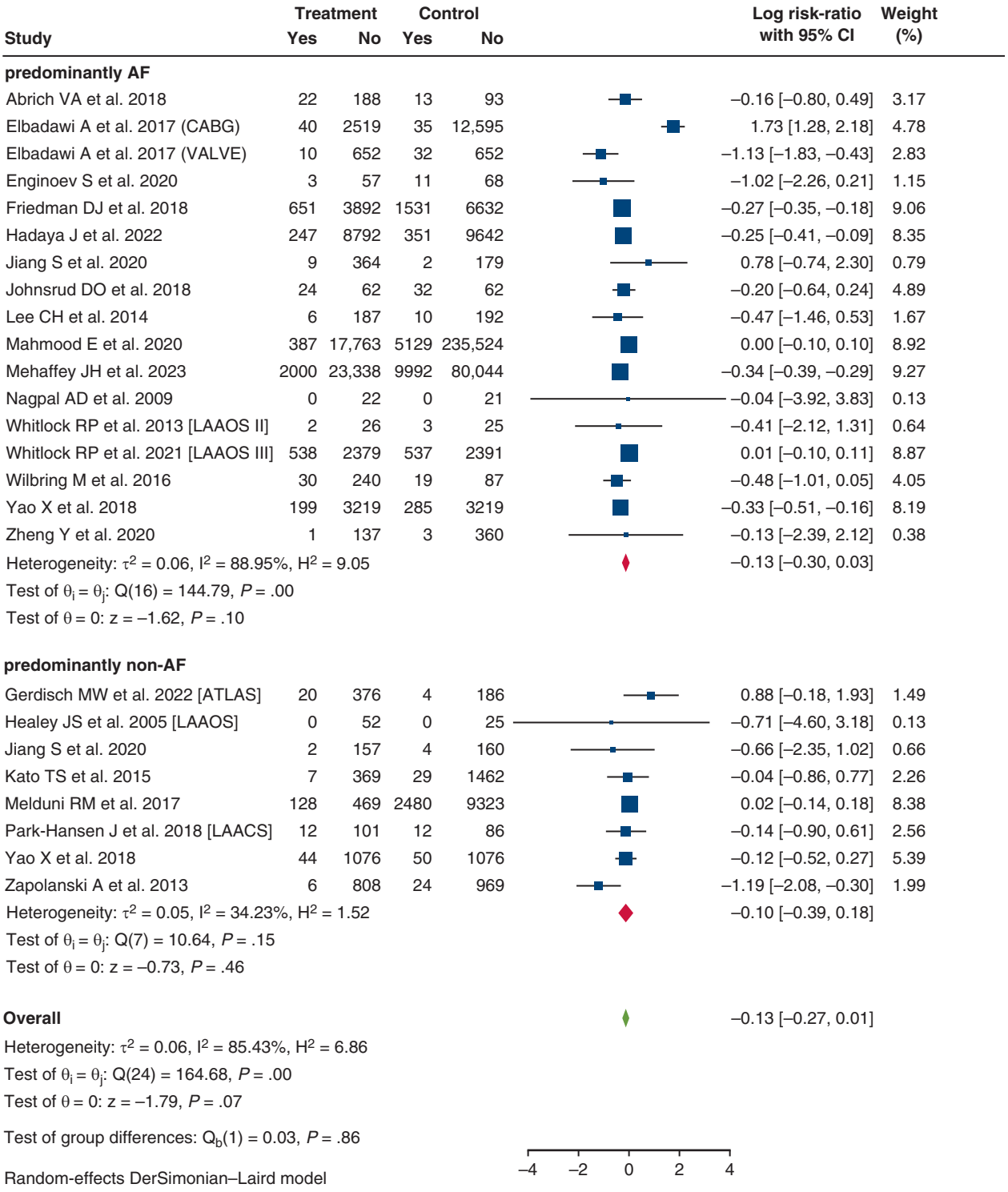

FIGURE E6. Mortality at long-term follow-up. Log risk ratio. *CI*, confidence interval; *AF*, atrial fibrillation; *CABG*, coronary artery bypass grafting; *LAAOS*, Left Atrial Appendage Occlusion Study; *ATLAS*, AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures.

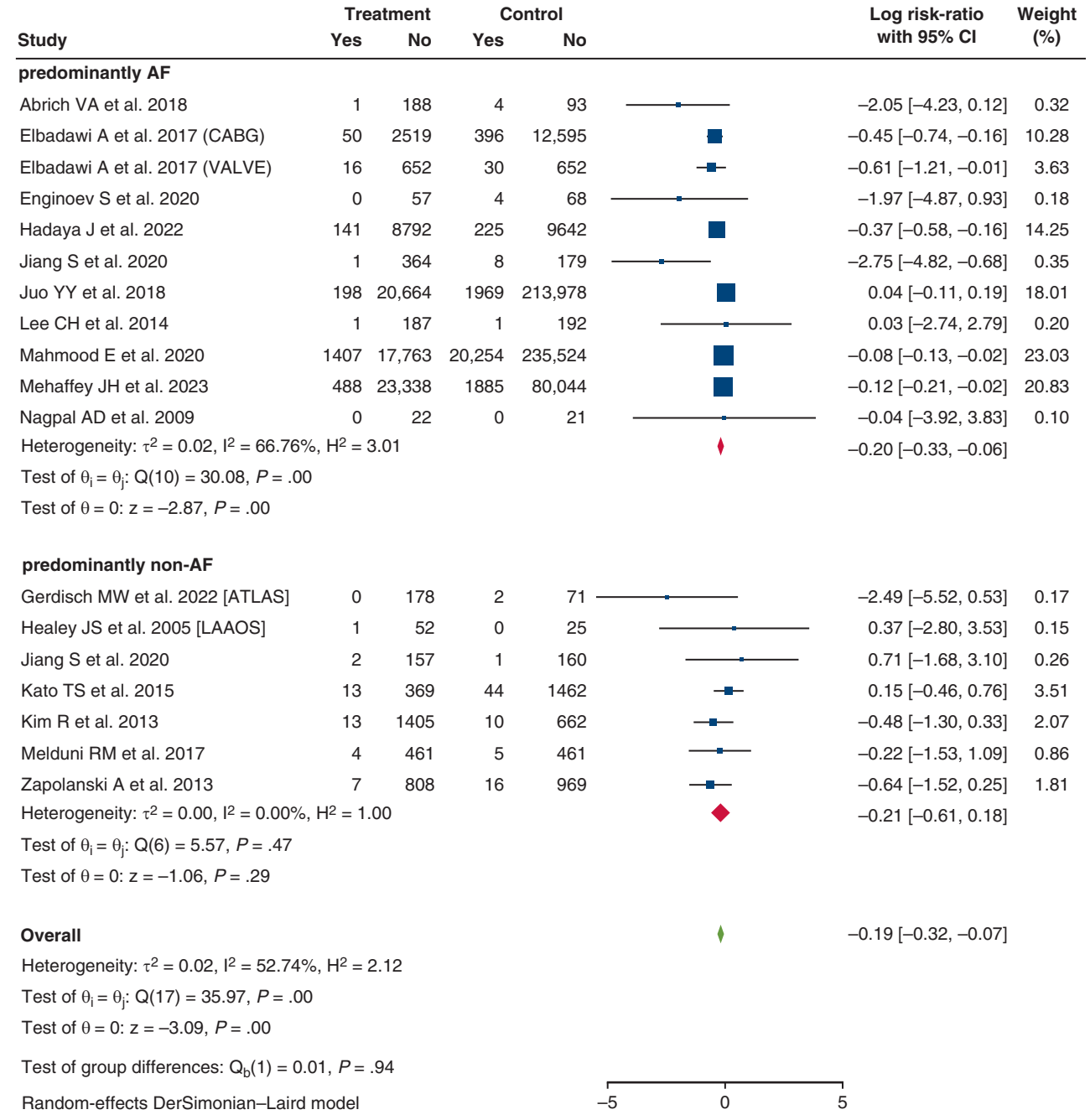

FIGURE E7. Stroke at early follow-up. Log risk ratio. *CI*, confidence interval; *AF*, atrial fibrillation; *CABG*, coronary artery bypass grafting; *LAAOS*, Left Atrial Appendage Occlusion Study; *ATLAS*, AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures.

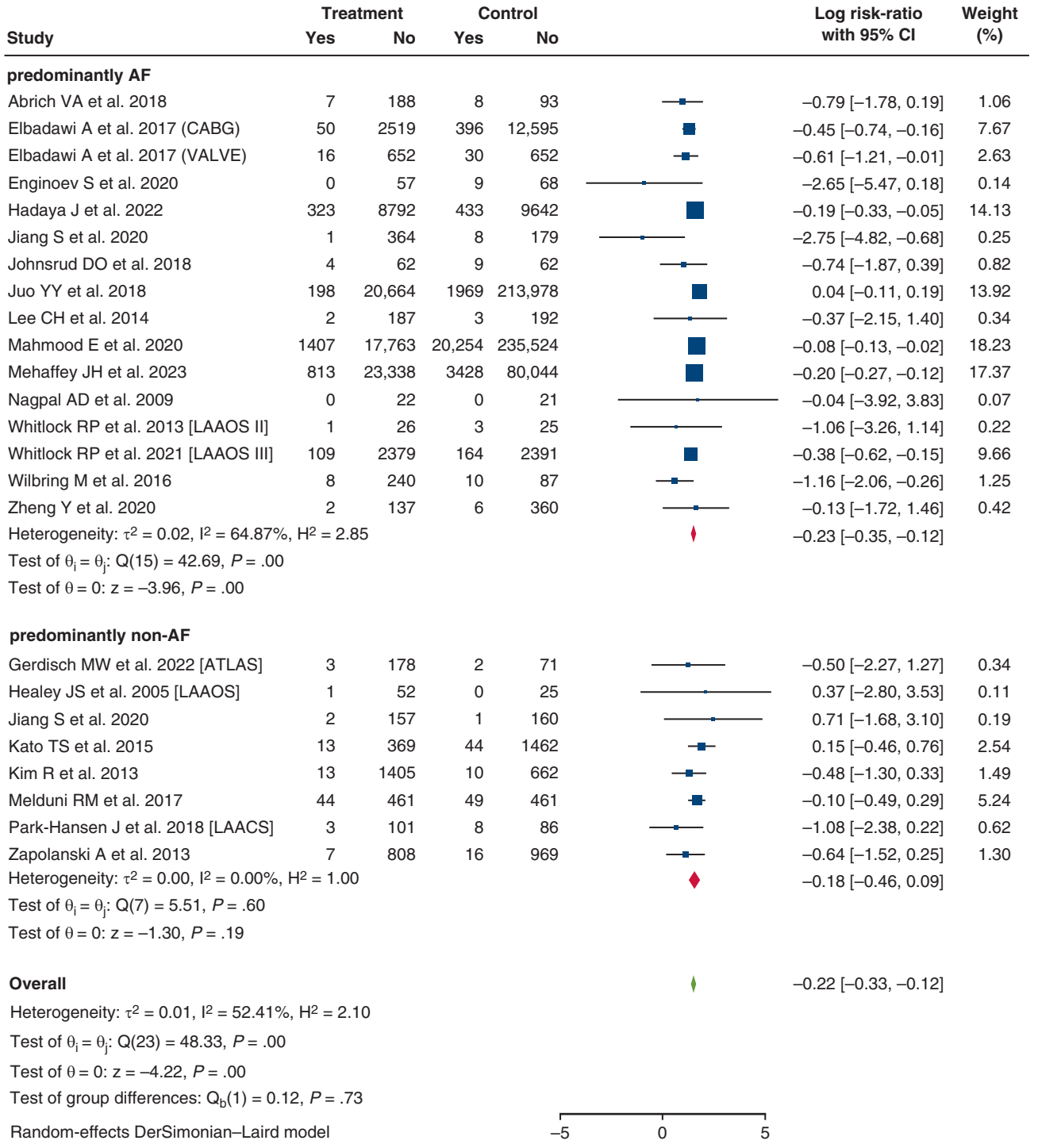

FIGURE E8. Stroke at long-term follow-up. Log risk ratio. *CI*, confidence interval; *AF*, atrial fibrillation; *CABG*, coronary artery bypass grafting; *LAAOS*, Left Atrial Appendage Occlusion Study; *ATLAS*, AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures.

TABLE E1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRSMA) checklist

Section and topic	Item #	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review.	1
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (eg, for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5-6
	10b	List and define all other variables for which data were sought (eg, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Effect measures	12	Specify for each outcome the effect measure(s) (eg, risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (eg, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5-7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5-7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5-7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (eg, subgroup analysis, meta-regression).	5-7

(Continued)

TABLE E1. Continued

Section and topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	5-7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5-7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	5-7
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary References
Study characteristics	17	Cite each included study and present its characteristics.	8, Supplementary Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8, Supplementary Table 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (eg, confidence/credible interval), ideally using structured tables or plots.	Figures 2, 3, 4 5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (eg, confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8-10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11-12, Supplementary Figures 4-6
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplementary Table 4 and 5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	9-12, Figures 2-4, 5b, Supplementary Figures 1-6
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10-15
	23b	Discuss any limitations of the evidence included in the review.	15-16
	23c	Discuss any limitations of the review processes used.	15-16
	23d	Discuss implications of the results for practice, policy, and future research.	10-15
Other information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	16
Competing interests	26	Declare any competing interests of review authors.	16
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	16

TABLE E2. Meta-analysis of observational studies in epidemiology checklist

Item No.	Recommendation	Reported on page No.
Reporting of background should include		
1	Problem definition	
2	Hypothesis statement	5-6
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5-6
5	Type of study designs used	5-6
6	Study population	5-6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	7
8	Search strategy, including time period included in the synthesis and key words	6-7
9	Effort to include all available studies, including contact with authors	6-7
10	Databases and registries searched	6-7
11	Search software used, name and version, including special features used (eg, explosion)	N/A
12	Use of hand searching (eg, reference lists of obtained articles)	6-7
13	List of citations located and those excluded, including justification	Table 1, References E21-E54
14	Method of addressing articles published in languages other than English	6
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	N/A
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7-8
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	7-8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7-8, Table 1, Tables E4 and E5
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7-8
22	Assessment of heterogeneity	8
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8-9
24	Provision of appropriate tables and graphics	6-9; Figure 1, Table E3
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 5, *B*
26	Table giving descriptive information for each study included	Tables 1-2
27	Results of sensitivity testing (eg, subgroup analysis)	Figures 2-5, *A*, Figures E1-E6
28	Indication of statistical uncertainty of findings	NA
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Figure 5, *A*
30	Justification for exclusion (eg, exclusion of non-English language citations)	Figure 1, 7-8
31	Assessment of quality of included studies	Table E4
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	13-16
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	17
34	Guidelines for future research	13-17
35	Disclosure of funding source	17

TABLE E3. Search strategy

No.	Search	Results
PubMed		
1.	left atrial appendage* closure [Title/Abstract] OR left atrial appendage* occlusion [Title/Abstract] OR left atrial appendage* removal [Title/Abstract] OR left atrial appendage* amputation [Title/Abstract] OR left atrial appendage* ligation [Title/Abstract] OR left atrial appendage* stapling [Title/Abstract] OR left atrial appendage* clipping [Title/Abstract] OR left atrial appendage* occlusion [Title/Abstract] OR left atrial appendage* exclusion [Title/Abstract]	2698
2.	left atrial appendage* [Title/Abstract] AND ((cardiac [Title/Abstract] OR heart [Title/Abstract]) AND surgery [Title/Abstract])	581
3.	#1 AND #2	232
Medline		
1.	(left atrial appendage* closure or left atrial appendage* occlusion or left atrial appendage* removal or left atrial appendage* amputation or left atrial appendage* ligation or left atrial appendage* stapling or left atrial appendage* clipping or left atrial appendage* occlusion or left atrial appendage* exclusion).ab.	1844
2.	((cardiac or heart) and surgery).ab.	171,115
3.	#1 AND #2	176

TABLE E4. ROB risk of bias analysis in the randomized controlled trials

Study	Randomization	Deviation	Missing data	Outcome assessment	Selective reporting	Overall
Gerdisch and colleagues[15] 2022 [ATLAS]	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Healey and colleagues[33] 2005 [LAAOS]	Low risk	High risk	Low risk	High risk	Some concerns	High risk
Jiang S and colleagues[34] 2020	Some concerns	Low risk	Low risk	High risk	Some concerns	High risk
Nagpal and colleagues[E3] 2009	Low risk	High risk	Low risk	Some concerns	Some concerns	High risk
Park-Hansen and colleagues[18] 2018 [LAACS]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Whitlock and colleagues[E4] 2013 [LAAOS II]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Whitlock and colleagues[10] 2021 [LAAOS III]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

TABLE E5. ROBINS I risk of bias analysis in the observational studies

Study	Confounding	Participant selection	Intervention classification	Intervention deviation	Missing data	Outcome measurement	Selective reporting	Overall
Abrich and colleagues[28] 2018	Moderate risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias	Moderate risk of bias
Elbadawi and colleagues[29] 2017	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias	Low risk of bias	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias
Elbadawi and colleagues[30] 2017	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias	Low risk of bias	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias
Enginoev and colleagues[31] 2020	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias	Moderate risk of bias	Low risk of bias	Moderate risk of bias
Friedman and colleagues[8] 2018	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias
Hadaya and colleagues[32] 2022	Moderate risk of bias	Low risk of bias	Moderate risk of bias	No information	Low risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias
Johnsrud and colleagues[35] 2018	Low risk of bias	Low risk of bias	Low risk of bias	No information	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Juo and colleagues[E9] 2018	Serious risk of bias	Serious risk of bias	Moderate risk of bias	Moderate risk of bias	Serious risk of bias	Low risk of bias	Moderate risk of bias	Serious risk of bias
Kato and colleagues[E1] 2015	Moderate risk of bias	Low risk of bias	Serious risk of bias	No information	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias	Serious risk of bias
Kim and colleagues[E8] 2013	Moderate risk of bias	Low risk of bias	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias	Low risk of bias	Moderate risk of bias	Moderate risk of bias
Lee and colleagues[E2] 2014	Moderate risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias
Mahmood and colleagues[11] 2020	Serious risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias
Mehaffey and colleagues[13] 2023	Serious risk of bias	Low risk of bias	Serious risk of bias	No information	Low risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias
Melduni and colleagues[12] 2017	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Wilbring and colleagues[E5] 2016	Serious risk of bias	Low risk of bias	Serious risk of bias	Serious risk of bias	Moderate risk of bias	Low risk of bias	Moderate risk of bias	Serious risk of bias

(Continued)

TABLE E5. Continued

Study	Confounding	Participant selection	Intervention classification	Intervention deviation	Missing data	Outcome measurement	Selective reporting	Overall
Yao and colleagues[9] 2018	Moderate risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias
Zapolanski and colleagues[E6] 2013	Serious risk of bias	Moderate risk of bias	Serious risk of bias	Serious risk of bias	Serious risk of bias	Moderate risk of bias	Moderate risk of bias	Serious risk of bias
Zheng and colleagues[E7] 2020	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias