

openheart Risk and protective factors for atrial fibrillation after cardiac surgery and valvular interventions: an umbrella review of meta-analyses

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ABSTRACT

Objective Postoperative atrial fibrillation (POAF) is a common complication affecting approximately one-third of patients after cardiac surgery and valvular interventions. This umbrella review systematically appraises the epidemiological credibility of published meta-analyses of both observational and randomised controlled trials (RCT) to assess the risk and protective factors of POAF.

Methods Three databases were searched up to June 2021. According to established criteria, evidence of association was rated as convincing, highly suggestive, suggestive, weak or not significant concerning observational studies and as high, moderate, low or very low regarding RCTs.

Results We identified 47 studies (reporting 61 associations), 13 referring to observational studies and 34 to RCTs. Only the transfemoral transcatheter aortic valve replacement (TAVR) approach was associated with the prevention of POAF and was supported by convincing evidence from meta-analyses of observational data. Two other associations provided highly suggestive evidence, including preoperative hypertension and neutrophil/lymphocyte ratio. Three associations between protective factors and POAF presented a high level of evidence in meta-analyses, including RCTs. These associations included atrial and biatrial pacing and performing a posterior pericardiectomy. Nineteen associations were supported by moderate evidence, including use of drugs such as amiodarone, b-blockers, glucocorticoids and statins and the performance of TAVR compared with surgical aortic valve replacement.

Conclusions Our study provides evidence confirming the protective role of amiodarone, b-blockers, atrial pacing and posterior pericardiectomy against POAF as well as highlights the risk of untreated hypertension. Further research is needed to assess the potential role of statins, glucocorticoids and colchicine in the prevention of POAF. **PROSPERO registration number** CRD42021268268.

INTRODUCTION

Acute or new-onset atrial fibrillation (AF) in the immediate postoperative period is

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Postoperative atrial fibrillation (POAF) is a common complication after cardiac surgery and valvular interventions.
- ⇒ Numerous risk factors for POAF have been identified, but there is no credibility assessment.

WHAT THIS STUDY ADDS

- ⇒ Only a few identified risk factors and protective factors of POAF were supported by high-level evidence; namely, amiodarone, b-blockers, atrial pacing and posterior pericardiectomy against POAF as protective factors and untreated hypertension as a risk factor.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This study provides a broad picture of the non-genetic risk factors associated with the risk for POAF and evaluates their level of evidence across published meta-analyses.
- ⇒ These findings allow for robust classifications that can be used for future policymaking and future studies on POAF prevention.

classified as postoperative AF (POAF).¹ POAF is a common complication affecting over 30% of patients following cardiac surgery or valvular intervention.^{2,3} AF episodes after cardiac surgery are typically brief and self-terminating,⁴ with the highest incidence occurring between days 2 and 4 after cardiac surgery.⁵ POAF is an independent risk factor for numerous adverse events, including increased risk of stroke, prolonged hospital stays and a doubling of all-cause mortality.^{3,6}

Identifying and targeting modifiable risk factors may reduce the risk of POAF. However, risk prediction for POAF is complex. Propensity for POAF is due to a combination of preoperative, perioperative and postoperative factors.³ Predisposing factors such as age,

left ventricular dysfunction, hypertension and left atrial enlargement are strongly associated with POAF.^{5,7} Local inflammation associated with surgical lesions and post-operative pericarditis,^{3,8,9} prolonged mechanical ventilation, pulmonary infections and electrolyte imbalances also appear to be linked to POAF.^{4,5,7} Moreover, adrenergic activation seems to be involved: the use of inotropic drugs increases the risk for POAF, while b-blockers reduce this risk.^{5,10}

Although numerous meta-analyses on risk factors for POAF have been published, there is still no complete and concise summary of the research. Thus, the prevention and management of POAF after cardiac surgery and cardiac interventions remain a major challenge.

We aimed to summarise the existing evidence on risk and protective factors associated with POAF among published meta-analyses through an umbrella review. An umbrella review is a systematic collection, evaluation and synthesis of the existing systematic reviews and meta-analyses on a specific topic.¹¹ It can be applied to provide a comprehensive picture of risk and protective factors for a specific disease and has already been implemented in several clinical entities.^{12,13} Using standardised methods used in umbrella review, we ranked the evidence from existing meta-analyses on POAF according to sample size, strength of the association and the presence of various biases.^{11,14}

METHODS

Data selection, search strategy and selection criteria

In this study, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses¹⁵ reporting guidelines and the Meta-Analysis of Observational Studies in Epidemiology guidelines¹⁶ (online supplemental appendix 1) were followed. An a priori protocol was registered in the PROSPERO database.

Bibliographic databases (PubMed, Web of Science, Cochrane review and Cochrane database of clinical trials) were searched from inception through 28 May 2021, to identify systematic reviews with meta-analysis of observational or randomised controlled trials (RCT) examining associations between non-genetic risk or protective factors and risk for POAF. The search algorithm used was broad to identify all eligible studies with terms related to AF and meta-analysis and is presented in online supplemental appendix 2. Reference lists from eligible studies were also hand searched to identify additional studies.

Two researchers (DK and MS) independently searched for eligible articles. The same researchers examined the full texts of the recovered articles for eligibility. Any discrepancies were resolved through discussions with a third researcher (EC).

We included only meta-analyses of observational studies with a cohort, case-control or nested case-control study design and RCTs. Whenever multiple meta-analyses assessed the same risk or protective factor, we included

only the meta-analysis with more studies.¹⁷ All reported outcomes were considered for inclusion.

We excluded meta-analyses with (1) study designs other than the ones stated before (eg, cross-sectional), (2) a non-systematic selection of the included studies, or non-systematic reviews, (3) examining genetic variants of AF, (4) studies published in non-English language, (5) insufficient data for quantitative synthesis or (6) study-specific effect estimates for continuous exposures were reported as mean difference rather than relative risk (RR) measures, such as OR, HR, RR. The reasons for exclusion after a full-text review are presented in the supplementary material (online supplemental table 1, Appendix 3).

Data extraction

Data extraction was performed independently by two researchers (DK and MS) using a predefined extraction form (EXCEL 365). Any disagreements were resolved through discussion. The extracted data included information on the first author's name, year of publication, journal, standard identifier (DOI), number of component studies, total sample size and the risk or protective factors assessed, with the RR estimate (such as OR, HR, RR), alongside with their 95% CIs. For each component study, we collected the first author's name, year of publication, study design, sample size (exposure and non-exposure) and the RR estimates (ie, HR, OR, RR) with the corresponding 95% CI.

Quality assessment

The RoB per included meta-analysis was assessed using the MeaSurement Tool to Assess systematic Reviews (AMSTAR2) tool (available at <https://amstar.ca/Amstar-2.php>). This tool appraises randomised and non-randomised studies and evaluates criteria within 10 original domains. Two reviewers (DT and MS) performed the quality assessment and checked by a third investigator in case of disagreement (EC).¹⁸

Data synthesis and analysis

We used standardised methods and state-of-the-art approaches for data synthesis and analysis in this umbrella meta-analysis.^{13,19} Specifically, the effect size (ES) of different studies reported in each meta-analysis were extracted, for each association, and the pooled ESs and 95% CIs were recalculated, using random-effects models.²⁰ This was because of the expected heterogeneity, in particularly observational studies.²⁰

Between-study heterogeneity was evaluated using the I^2 metric.²¹ I^2 varies between 0% and 100% and measures the variability of ES due to heterogeneity rather than sampling error.²¹ An I^2 value greater than 50% corresponds to substantial heterogeneity. The small study effect bias (ie, whether small studies tend to yield more significant ES than the larger ones) was evaluated using the Egger regression asymmetry test.²² A p value <0.10

was considered to provide adequate evidence for small study effects.

Finally, the excess significance bias was measured to evaluate whether more studies had statistically significant results than anticipated.²³ The anticipated number of statistically significant studies per association was calculated by adding the statistical power estimates for each component study. The ES of the larger study was used (ie, the study with the smallest SE) in each meta-analysis to calculate the power of each study using a non-central t distribution. A p value ≤ 0.10 was considered significant for excess significance bias.²³ All analyses were performed using Stata V.17.0 (StataCorp, College Station, Texas).

Assessment of epidemiological credibility

Relevant associations of risk and protective factors with POAF derived from observational studies were classified into five categories according to the evidentiary power of their associations: convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV) and not significant (NS) (online supplemental table 1, appendix 4). Following previous umbrella reviews,¹³ we considered as convincing the associations with >1000 cases a highly significant association ($p\text{-value} < 1 \times 10^{-6}$), no large between-study heterogeneity, no evidence of excess significance bias or small study effects, and a 95% prediction interval excluding the null value. Highly suggestive evidence needed >1000 cases, a highly significant association ($p\text{ value} < 1 \times 10^{-6}$ by random-effects model), and a statistically significant effect in the largest study. Suggestive evidence required >1000 cases and $p\text{ value} < 0.001$ by random-effects model. Associations with a $p\text{ value} > 0.05$ in the random-effects meta-analysis were considered non-significant.

In RCTs, the credibility of evidence was categorised according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) levels of evidence (GLE) using a standardised set of rules.^{24 25} The evaluated areas included: (1) imprecision, by the sample size in the pooled analysis (if 100–199 participants, GLE was downgraded by one level; if < 100 participants, downgraded by two levels); (2) RoB of trials, by the proportion of participants in the pooled measured to have low RoB for randomization and observer blinding (if $< 75\%$ of participants had low RoB or RoB not reported, GLE was downgraded by one level); (3) inconsistency, by heterogeneity (if $I^2 > 75\%$, downgraded by one level) and (4) RoB of the systematic review, based on AMSTAR 2 questionnaire (if moderate quality, downgraded by one level; if low or critically low quality, downgraded by two levels). Then, the associations were graded as high, moderate, low or very low by GLE (online supplemental table 2, appendix 4).

Patient and public involvement

No participants were involved in the design, conduct, reporting, or dissemination plans of the research question or outcome measures.

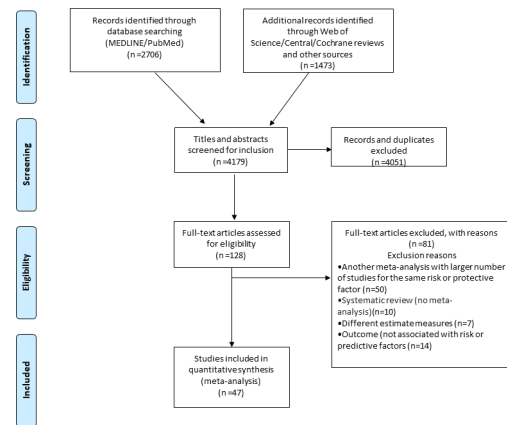


Figure 1 PRISMA flowchart diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

RESULTS

Literature search

The initial search yielded 4179 publications. After evaluating titles and abstracts, 128 eligible articles were identified. Eighty-one articles were excluded after a full-text review (online supplemental table 1, appendix 3), and 47 articles were subsequently included for analysis (13 meta-analyses of observational studies and 34 meta-analyses of RCTs, reported overall 49 associations; figure 1; online supplemental table 1, appendix 5).

Meta-analyses of observational studies

The median number of meta-analyses included in meta-analyses of observational studies was 7.5 (IQR=4.3–11.8), the median number of participants was 4349 (IQR=1219–30 273) and the median number of cases were 1036 (IQR=343–7373).

In the meta-analyses of observational studies, 10 of the 13 studied associations (77%) had a nominally statistically significant effect ($p \leq 0.05$) under the random-effects models, and three of those (23%) achieved a $p\text{ value} < 10^{-6}$. Seven associations (54%) had more than 1000 cases per association. Significant heterogeneity ($I^2 > 50\%$) was found in eight associations (62%), and only three associations (23%) had a 95% prediction interval that excluded the null value. In 10 associations (77%), the ES of the largest study had a nominally statistically significant effect ($p \leq 0.05$). Finally, small study effects were found for two associations (15%), and excess significance bias was found for four (31%).

The quality of meta-analyses of observational studies assessed by AMSTAR2 was high in five meta-analyses, moderate in five and low or critically low in three (table 1; online supplemental table 1, appendix 5).

When the criteria for the credibility of evidence were applied, one (8%) association presented convincing evidence (table 1; online supplemental table 1, appendix 5) concerning the use of non-transfemoral transcatheter aortic valve replacement (TAVR) versus transfemoral TAVR. Two other associations (15%) presented highly suggestive evidence for risk factors:

Table 1 Predictors for postoperative AF, in meta-analyses of observational studies

Author, year	Predictor	Exposed/unexposed as included in MA	k	n/N	Metric	ES (95% CI)	P	PI include null value	I ²	SSE	ESB	LS sign	CE	CES2 (n>1000)	AMSTAR 2 quality
Angsubhakorn 2020	Non-transfemoral transcatheter AVR	Transfemoral transcatheter AVR or non-transfemoral AVR	7	1262/5681	RR	2.95 (2.43 to 3.58)	8.2×10 ⁻²⁸	No	40.62	No	No	Yes	I	I	Critically low
Liu 2020	Neutrophil/lymphocyte ratio	High or low neutrophil/lymphocyte ratio	12	1330/9262	OR	1.39 (1.26 to 1.53)	1.9×10 ⁻¹¹	No	95.15	No	Yes	Yes	II	II	High
Zhou 2017	Preoperative hypertension	Preoperative hypertension or normotension	25	92658/130087	RR	1.07 (1.05 to 1.09)	9.1×10 ⁻¹⁵	No	54.88	No	Yes	Yes	II	II	Moderate
Litton 2012	Preoperative BNP/NT-proBNP	High BNP/NT-proBNP or low BNP/NT-proBNP	4	530/1115	OR	2.89 (1.04 to 8.04)	0.041	Yes	91.23	No	No	Yes	IV	IV	Critically low
Phan 2016	Obesity	Obese or not	32	16608/86984	OR	1.21 (1.06 to 1.38)	0.006	Yes	89.36	No	Yes	No	IV	IV	High
Liu 2018	Blood transfusion	Blood transfusion or not	8	7491/31069	OR	1.55 (1.08 to 2.21)	0.016	Yes	97.09	No	Yes	Yes	IV	IV	High
Qaddoura 2014	OSAS	OSAS or not	7	264/700	OR	1.84 (1.14 to 2.96)	0.012	Yes	51.69	No	No	Yes	IV	IV	Moderate
Sun 2020	RAASI	RAASI use in TAVR or not	2	280/1532	RR	0.73 (0.59 to 0.91)	0.004	NP	0.45	NP	No	Yes	IV	IV	Moderate
Chen 2020	CHA2DS2-VASC SCORE	CHA2DS2-VASC≥2 or CHA2DS2-VASC<2	8	NA/NA	OR	1.46 (1.25 to 1.72)	3.2×10 ⁻⁶	Yes	0.000	Yes	NA	Yes	IV	III	Moderate
Athanasios 2004	Off-pump elderly	Off-pump or not	8	809/3017	OR	0.70 (0.51 to 0.95)	0.022	Yes	49.07	No	NP	Yes	IV	IV	Critically low
Guan 2020	Off-pump	On- or off-pump CABG	13	6431/31039	OR	0.94 (0.79 to 1.12)	0.515	Yes	0.073	No	NP	No	NS	NS	High
Yousuf Salmasi 2020	Mini sternotomy	Mini-sternotomy or right anterior thoracotomy	5	616/2234	OR	0.67 (0.25 to 1.78)	0.425	Yes	91.00	No	No	No	NS	NS	Moderate
Chen 2019	RAASI	RAASI use in cardiac surgery or not	11	7018/27885	OR	1.06 (0.93 to 1.2)	0.368	Yes	67.29	Yes	NP	Yes	NS	NS	High

CHADS2-VASC: congestive heart failure, hypertension, age >75 years, diabetes, stroke, vascular disease, age >65, female sex.
OSAS: obstructive sleep apnea syndrome; AF: atrial fibrillation; AVR: aortic valve replacement; BNP: brain natriuretic peptide; CE: class of evidence; CES, class of evidence sensitivity analysis; ES: effect size; ESB, excess significance bias; I²: heterogeneity; K: number of studies for each factor; LS: largest study with significant effect; n: total number of cases; N: total number of cohorts per factor; NA: not assessable; NP: not pertinent, because the number of observed studies is less than the expected; NR: not reported; NT-proBNP, N-terminal pro B-natriuretic peptide; PI, prediction interval; PCT, randomised controlled trial; RR, risk ratio; SSE, small study effects.

preoperative hypertension and neutrophil/lymphocyte ratio. The remaining seven (54%) statistically significant associations between risk or protective factors and POAF presented weak evidence (table 1; online supplemental table 1, appendix 5), while three associations (23%) were NS (table 1; online supplemental table 1, appendix 5). The three factors with convincing and highly suggestive evidence in the principal analysis did not change their class of evidence when the criterium with greater than 1000 cases per association was excluded (table 1).

Meta-analyses of randomised studies

The median number of studies included in meta-analyses of RCTs was 10 (IQR=4.8–13), the median number of cases was 344 (IQR=201–707) and the median number of participants was 1692 (IQR=834–2526) (table 2; online supplemental appendix).

Overall, 30 of the 48 (63%) associations reported a nominally significant summary result at $p < 0.05$ (19 had $p \leq 0.001$). Twenty-one (44%) did not show considerable heterogeneity ($I^2 < 50\%$), and only seven associations (15%) had a 95% prediction interval that excluded the null value. Nineteen (40%) showed small study effects, and 21 (44%) showed excess significance bias. The ES of the largest study had a nominally statistically significant effect ($p \leq 0.05$) in 19 (40%) associations.

The quality of included meta-analyses of RCTs was scored as high in 20, moderate in 5 and low or critically low in 9 (online supplemental appendix 5).

By applying the credibility criteria for meta-analyses of RCTs, three (6%) associations between protective factors and POAF presented a high GLE (tables 2 and 3; online supplemental table 1, appendix 5): atrial or biatrial pacing and the performance of a posterior pericardiotomy. Twenty associations (42%) of protective factors and the risk for POAF presented a moderate GLE, for instance, the use of amiodarone, beta-blockers, colchicine and glucocorticoid as well as TAVR as compared with surgical aortic valve replacement (SAVR) (tables 2 and 3; online supplemental table 1, appendix 5). The remaining seven (14%) statistically significant associations between protective factors and POAF presented low GLE, while 18 associations (38%) were not statistically significant (table 2; Online supplemental table 1, appendices 5 and 6).

DISCUSSION

This study reviewed 47 meta-analyses of observational and randomised design and found 40 significant associations of preoperative and postoperative risk and protective factors for POAF. Few of these were supported by convincing evidence or high GLE evidence, namely, the transfemoral TAVR versus non-transfemoral approach, the use of atrial or biatrial pacing and the choice of posterior pericardiotomy.

This study is the first umbrella review that systematically assesses the potential risk and protective factor

associated with POAF across broad spectrum of meta-analyses of observational and randomised studies and grade the evidence by using well-established criteria of credibility.^{19 25 26} Umbrella review methods have been previously used to assess the associations between other adverse health conditions with potential risk and protective factors, such as AF,¹³ adiposity²⁷ and vitamin D concentration.²⁶ This method is appropriate for a research area that is undoubtedly complex and ambiguous.^{3 6} The large number of included patients (more than 400 000) in combination with the high number of cases per association enabled robust classifications. Furthermore, the AMSTAR 2 tool for quality assessment of the included meta-analyses allowed for a confident interpretation of our results. Hence, our proposed grading needs to be considered when planning future studies on preventive models of POAF.

POAF is a common complication after repair of severe aortic stenosis.²⁸ Data from a meta-analysis of observational studies²⁹ showed that non-transfemoral TAVR versus transfemoral TAVR increases the risk of POAF threefold, a finding supported by convincing evidence. Contrary to the transfemoral approach, patients undergoing transapical TAVR require a pericardiotomy and several studies have shown that pericardial injury can lead to postoperative inflammation and the subsequent development of POAF. Furthermore, meta-analyses of RCTs³⁰ for patients at low and intermediate surgical risk showed a significant risk reduction for POAF using TAVR compared with SAVR. This finding is to be expected since an open procedure is associated with more postoperative inflammation, enhanced sympathetic stimulation and oxidative stress as opposed to a minimally invasive procedure such as TAVR.^{28 31}

One of the modifiable preoperative factors associated with POAF, supported by highly convincing evidence, was hypertension.³² Hypertension is a well-established risk factor for AF,³³ and its adequate management during the preoperative period may protect against POAF by reducing both high left ventricular filling pressures and easing atrial stretch.^{32–34}

In our study, the most critical perioperative protective factors for POAF prevention, that did not involve medical therapy, were atrial or biatrial pacing and posterior pericardiotomy, both supported by high GLE.³⁵ Overdrive atrial pacing might prevent POAF by reducing the risk of bradycardia and bradycardia-mediated atrial ectopic beats.³ In the meta-analysis by Ruan *et al*,³⁵ the reduction in POAF risk with moderate heterogeneity and high quality according to AMSTAR 2 was meaningful. Posterior pericardiotomy is a risk-reducing procedure for postoperative pericarditis by making an incision in the posterior pericardium and connecting the pericardial to the left pleural space.³ We found that about two-thirds as many patients undergoing cardiac surgery were protected from POAF when posterior pericardiotomy was used compared with not, at the expense of more pleural effusions.³⁶

Table 2 Statistical significant predictors for postoperative AF, in meta-analyses of RCTs

Author, year	Predictor	Exposed/unexposed as included in MA	k	n/N	Metric	ES (95% CI)	P	PI include null value	I ² %	SSE	ESB	LS sign	High RoB	GLE	AMSTAR 2 quality
Ruan 2020	Atrial pacing	Atrial pacing or not	21	511/2002	OR	0.57 (0.43 to 0.76)	0.0002	Yes	35.04	No	Yes	No	≤25%	High	High
Ruan 2020	Bi-atrial pacing	Bi-atrial pacing or not	10	235/1014	OR	0.44 (0.26 to 0.76)	0.002	Yes	57.55	No	Yes	No	≤25%	High	High
Hu 2016	Posterior pericardiectomy	Posterior pericardiectomy or not	10	329/1648	OR	0.36 (0.23 to 0.56)	0.0000	Yes	56.36	No	Yes	Yes	≤25%	High	High
Liu 2019	Dexmedetomidine	Dexmedetomidine use or not	13	335/1684	OR	0.70 (0.49 to 0.98)	0.037	Yes	29.82	No	No	No	>25%	Moderate	High
Guerra 2017	Ranolazine	Ranolazine use or not	3	176/700	OR	0.30 (0.13 to 0.69)	0.004	Yes	66.00	No	No	Yes	>25%	Moderate	High
Patti 2015	Statin pre-treatment	Statin pre-treatment or not	11	303/1106	OR	0.41 (0.32 to 0.53)	0.000	Yes	0.00	No	NP	Yes	≤25%	Moderate	High
Putzu 2016	Perioperative statin therapy	Perioperative statin therapy or not	19	1255/4737	OR	0.53 (0.35 to 0.81)	0.003	Yes	90.90	No	Yes	Yes	>25%	Moderate	High
Guo 2014	PUFAs alone and in combination therapy with vitC+vitE	PUFAs alone and in combination therapy with vitC+vitE or not	11	956/3137	OR	0.61 (0.44 to 0.86)	0.005	Yes	68.84	Yes	Yes	No	>25%	Moderate	Moderate
Guo 2014	EPA/DHA ratio 1:2	EPA/DHA ratio 1:2 or 1:2	11	956/3137	OR	0.61 (0.44 to 0.86)	0.005	Yes	68.84	Yes	Yes	No	>25%	Moderate	Moderate
Gillespie 2005	Amiodarone	Amiodarone or not	15	762/2941	OR	0.5 (0.42 to 0.60)	0.0000	No	0.00	No	NP	Yes	≤25%	Moderate	Moderate
DiNicolantonio 2014	Carvedilol use	Carvedilol or metoprolol use	4	135/497	OR	0.50 (0.28 to 0.90)	0.020	Yes	45.88	No	No	No	≤25%	Moderate	High
Li 2015	Landioliol	Landioliol use or not	9	217/807	RR	0.40 (0.30 to 0.53)	0.0000	No	20.15	Yes	Yes	Yes	>25%	Moderate	High
Ho 2009	Hydrocortisone	Hydrocortisone use or not	18	455/1509	RR	0.74 (0.63 to 0.86)	0.0002	No	0.00	No	No	Yes	>25%	Moderate	High
Geng 2017	Perioperative antioxidant therapy	Perioperative antioxidant therapy use or not	11	464/1544	RR	0.55 (0.42 to 0.72)	0.0000	Yes	54.44	Yes	Yes	Yes	>25%	Moderate	High
Lernerz 2017	Colchicine	Colchicine use or not	5	354/1744	RR	0.66 (0.52 to 0.85)	0.001	Yes	24.68	No	No	No	>25%	Moderate	Moderate
Liu 2014	Prophylactic MAC use	Prophylactic MAC use or not	10	253/1026	OR	0.56 (0.38 to 0.83)	0.004	Yes	14.06	No	No	No	≤25%	Moderate	Critically low
Langlois 2017	PUFA	PUFA supplementation or not	17	1074/3614	OR	0.67 (0.49 to 0.90)	0.008	Yes	62.14	No	Yes	No	>25%	Moderate	High
Liu 2014	Low dose glucocorticoids	Low dose glucocorticoids use or not	5	285/843	RR	0.71 (0.55 to 0.92)	0.008	Yes	31.82	No	No	Yes	>25%	Moderate	High
Liu 2015	Medium dose glucocorticoids	Medium dose glucocorticoids use or not	19	1915/5968	RR	0.76 (0.60 to 0.96)	0.020	Yes	49.57	Yes	Yes	No	>25%	Moderate	High
Liu 2015	Glucocorticoids	Glucocorticoids use or not	27	2255/7019	RR	0.77 (0.66 to 0.90)	0.001	Yes	40.08	Yes	Yes	No	>25%	Moderate	High
Khan 2020	TAVR in patients with aortic stenosis with low risk	TAVR or SAVR	3	563/2633	OR	0.13 (0.09 to 0.18)	0.0000	Yes	48.84	No	No	Yes	>25%	Moderate	High
Khan 2020	TAVR in patients with aortic stenosis with intermediate risk	TAVR or SAVR	2	812/3692	OR	0.23 (0.16 to 0.33)	0.0000	NP	76.17	NP	No	Yes	>25%	Moderate	High
Khan 2020	TAVR in patients with low and intermediate risk	TAVR or SAVR	4	1375/6325	OR	0.17 (0.12 to 0.24)	0.0000	No	82.84	Yes	No	Yes	>25%	Moderate	High
Chatterjee 2013	Oral amiodarone	Oral amiodarone or not	8	472/1906	RR	0.58 (0.47 to 0.72)	0.0000	No	36.28	No	No	Yes	≤25%	Low	Low
Chatterjee 2013	IV amiodarone	IV amiodarone or not	15	598/2044	RR	0.57 (0.43 to 0.75)	0.0001	Yes	68.26	Yes	Yes	Yes	≤25%	Low	Low
Chatterjee 2013	Preoperative amiodarone	Preoperative amiodarone or not	11	585/2231	RR	0.55 (0.46 to 0.64)	0.0000	No	18.49	No	No	Yes	≤25%	Low	Low
Chatterjee 2013	Peri/postoperative amiodarone p	Peri/postoperative amiodarone or not	12	482/1717	RR	0.55 (0.38 to 0.80)	0.001	Yes	57.85	Yes	Yes	Yes	≤25%	Low	Low

Continued

Table 2 Continued

Author, year	Predictor	Exposed/unexposed as included in MA	k	n/N	Metric	ES (95% CI)	P	PI include null value	I ² %	SSE	ESB	LS sign	High RoB	GLE	AMSTAR 2 quality
Miller 2005	Magnesium	Magnesium administration or not	20	577/2490	OR	0.53 (0.38 to 0.74)	0.0002	Yes	59.67	Yes	Yes	No	>25%	Low	Critically low
Wiesbauer 2007	B-blockers	B-blockers use or not	26	1019/3959	OR	0.38 (0.29 to 0.49)	0.0000	No	45.04	Yes	Yes	Yes	>25%	Low	Critically low
Violi 2014	Antioxidants	Antioxidants use or not	15	481/1738	RR	0.58 (0.45 to 0.76)	0.0001	Yes	54.39	Yes	Yes	No	>25%	Low	Critically low

AF, atrial fibrillation; CE, class of evidence; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ES, effect size; ESB, excess significance bias; GLE, GRADE level of evidence; GRADE, Grading of Recommendations Assessment, Development and Evaluation; I², heterogeneity; K, number of studies for each factor; LS, largest study with significant effect; n, number of cases; N, total number of cohort per factor; NA, not assessable; NAC, N-acetylcysteine; NP, not pertinent, because the number of observed studies is less than the expected; NR, not reported; OSAS, obstructive sleep apnea syndrome; PI, prediction interval; PUFAs, polyunsaturated fatty acids; RCT, randomised controlled trial; RoB, risk of bias; RR, risk ratio; SAVR, surgical aorta valve replacement; SSE, small study effects; TAVR, transcatheter aorta valve replacement; vit, vitamin.

Table 3 Summary of associations with high epidemiological credibility of risk and protective factors with the risk of postoperative atrial fibrillation

Level of credibility	Associations
Meta-analyses including Observational studies	
Convincing	Transfemoral transcatheter AVR
High suggestive	Preoperative hypertension, high neutrophil/lymphocyte ratio
Grade level of evidence	
Meta-analyses including RCTs	
High	Atrial pacing, biatrial pacing, posterior pericardiectomy
Medium	Dexmedetomidine, glucocorticoids (general, low, medium doses), hydrocortisone, ranolazine, statin (pre-treatment and perioperative), antioxidant, PUFAs (alone or in combinations with Vitamin C and E), amiodarone, colchicine, TAVR compared with SAVR, landiolol, carvedilol, prophylactic NAC use
AVR, aortic valve replacement; NAC, N-acetylcysteine; PUFAs, polyunsaturated fatty acids; RCT, randomised controlled trial; SAVR, surgical aorta valve replacement; TAVR, transcatheter aorta valve replacement.	

More than 10 pharmacological treatments have been studied as preventive treatment options against POAF. Drugs provided statistically significant prevention of POAF in meta-analyses of RCTs with at least moderate GLE included amiodarone,³⁷ statins,³⁸ colchicine,³⁹ b-blockers (carvedilol and landiolol)⁴⁰⁻⁴¹ and glucocorticoids.⁴² Amiodarone and b-blockers are established treatments for AF and POAF, recommended in the current European Society of Cardiology (ESC) guidelines (Class I, level of evidence A),³³ a recommendation supported by our results. However, the use of statins, colchicine and glucocorticoids can also be considered, even if they are not directly recommended by the current ESC guidelines.³³ Due to their anti-inflammatory actions,³ these medications may play a protective role against POAF in the preoperative management of patients undergoing cardiac surgery, as shown by our results based on meta-analyses of RCTs, supported by a moderate level of evidence.

Furthermore, ranolazine appears to have a protective role against POAF. However, the results are based on meta-analysis with few events.⁴³ Controversial results have also been shown for the effects of fish oils⁴⁴⁻⁴⁵ and antioxidants⁴⁶⁻⁴⁷ and should not be broadly recommended before cardiac surgery, according to our analysis.

In this study, we described the broad picture of risk and protective factors that have been studied for POAF. However, our study has several limitations that should be reported. First, asymmetry and excess significance

tests offer bias clues but not definitive proof. Second, even we appraised the quality of the included meta-analyses, we did not assess the quality of their off-studies. Component studies should be qualitatively assessed in the original meta-analyses. Third, although we evaluated many risks and protective factors, there might be other factors of POAF that have not yet been evaluated in published meta-analyses, such as chronic obstructive pulmonary disease and severe heart failure. Fourth, the associations supported by convincing or highly suggestive evidence based on observational data can be considered strong but are not evidence of causality. Fifth, the grading criteria applied in the credibility assessment are not validated in empirical studies. However, they are proposed by expert panels of well-renowned epidemiologists.^{25 48}

CONCLUSIONS

Although POAF is a common complication after cardiac surgery and has been thoroughly studied over the last decades, only 6 of the 61 (9.8%) associations reported here were supported by high-level evidence. While some associations might be genuine, there is still a degree of uncertainty. In our study, we were able to confirm the protective role of TAVR versus non-TAVR or SAVR, along with the protective role of amiodarone, B-blockers, atrial pacing and posterior pericardiotomy against POAF, and the risk of untreated hypertension. In addition, our analysis suggests that statins, glucocorticoids and colchicine may play a role in preventing POAF. Further investigation by meta-analyses of individual participant data may facilitate the study of sources of between-study heterogeneity and identify risk and protective factors of POAF in specific subpopulations.⁴⁹

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Supplementary content

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Appendix 2 Search Strategy

Pubmed

(auricular fibrillation OR atrial fibrillation OR AF OR AFib) AND (“meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR metaanaly*[tiab] OR meta-analy*[tiab])

Web of science

(TS=(atrial fibrillation AND TS= (meta-analysis OR metaanaly* OR meta-analy*)) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article)

Cochrane review

Keyword:

Atrial fibrillation

Embase (Cochrane central database of triasls (373)

(auricular fibrillation OR atrial fibrillation) AND (meta-analysis OR metaanaly* OR meta-analy*)

Appendix 3 List of studies excluded after full-text evaluation with reasoning

eTable 1 List of studies excluded after full-text evaluation with reasoning

Author, Year	Reason for exclusion
Zhang, 2016 ¹	Different estimate measures
Disertori, 2012 ²	Another outcome
Schneider, 2010 ³	Another outcome
Bhuriya, 2011 ⁴	Another outcome
White, 2007 ⁵	Systematic review (no meta-analysis)
Samokhvalov, 2010 ⁶	Another outcome
Kodama, 2011 ⁷	Another outcome
Shiga, 2004 ⁸	Another meta-analysis with larger number of studies with same risk or protective factor
Alghamdi, 2005 ⁹	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Mak, 2009 ¹⁰	Another outcome
Leong, 2016 ¹¹	Another outcome
Tanboga, 2016 ¹²	Another outcome
Liu, 2016 ¹³	Another outcome
Shepherd, 2008 ¹⁴	Systematic review (no meta-analysis)
Nomani, 2020 ¹⁵	Systematic review (no meta-analysis)
Kontogiorgis, 2016 ¹⁶	Systematic review (no meta-analysis)
Madrid, 2004 ¹⁷	Another outcome
Yang, 2014 ¹⁸	Another outcome
Patel, 2007 ¹⁹	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Zhou, 2013 ²⁰	Another outcome
Kulik, 2009 ²¹	Systematic review (no meta-analysis)
Winchester, 2010 ²²	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Dong, 2011 ²³	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Liakopoulos, 2012 ²⁴	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Chen, 2010 ²⁵	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Liakopoulos, 2008 ²⁶	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Elgendy, 2015 ²⁷	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Goh, 2015 ²⁸	Systematic review (no meta-analysis)
Rezaei, 2016 ²⁹	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
An, 2017 ³⁰	Another meta-analysis with larger number of studies for the same risk or protective factor of AF

Yuan, 2017 ³¹	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Zhen-Han, 2017 ³²	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Ma, 2018 ³³	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Zhang, 2019 ³⁴	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Zhang, 2011 ³⁵	Different estimate measures
Baker, 2007 ³⁶	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Whitlock, 2020 ³⁷	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Baker, 2016 ³⁸	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Hill, 2019 ³⁹	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Polymeropoulos, 2016 ⁴⁰	Systematic review (no meta-analysis)
Shi, 2018 ⁴¹	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Bagshaw, 2006 ⁴²	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Buckley, 2007 ⁴³	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Sakamoto, 2014 ⁴⁴	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Ji, 2016 ⁴⁵	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Kim 2021 ⁴⁶	Overlapping meta-analysis of risk or protective factors of AF
Thein, 2018 ⁴⁷	Overlapping meta-analysis of risk or protective factors of AF
Weymann, 2017 ⁴⁸	Different estimate measures
Kuhn, 2015 ⁴⁹	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Cheng, 2005 ⁵⁰	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Wijeyesundera, 2005 ⁵¹	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Zimmer, 2003 ⁵²	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Sedrakyan, 2005 ⁵³	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Trivedi, 2017 ⁵⁴	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Khan, 2013 ⁵⁵	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Harling, 2011 ⁵⁶	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Ali-Hassan-Sayegh, 2014 ⁵⁷	Another meta-analysis with larger number of studies for the same risk or protective factor of AF

Lee, 2016 ⁵⁸	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Salih, 2017 ⁵⁹	Different estimate measures
Harrison, 2013 ⁶⁰	Another outcome
De Oliveira, 2012 ⁶¹	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Fairley, 2017 ⁶²	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Athanasίου, 2004 ⁶³	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Armaganijan, 2011 ⁶⁴	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Benedetto, 2013 ⁶⁵	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Costanzo, 2013 ⁶⁶	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Mozaffarian, 2013 ⁶⁷	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Xin, 2013 ⁶⁸	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Zhang, 2014 ⁶⁹	Different estimate measures
Wu, 2018 ⁷⁰	Other design
De Frutos, 2014 ⁷¹	Different estimate measures
Cappabianca, 2011 ⁷²	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Viviano, 2014 ⁷³	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Hu, 2017 ⁷⁴	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Burgess, 2006 ⁷⁵	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Lowres, 2018 ⁷⁶	Another outcome
Öztürk, 2020 ⁷⁷	Different estimate measures
Walter, 2020 ⁷⁸	Another meta-analysis with larger number of studies for the same risk or protective factor of AF
Bjerrum, 2020 ⁷⁹	Systematic review (no meta-analysis)
Chokesuwattanaskul, 2020 ⁸⁰	Systematic review (no meta-analysis)
Norhayati, 2020 ⁸¹	Another meta-analysis with larger number of studies for the same risk or protective factor of AF

Appendix 4 Criteria for evaluation of the credibility of evidence

eTable 1. Criteria for evaluation of the credibility of the evidence of observational studies

Classification	Criteria
Convincing evidence (Class I)	<ol style="list-style-type: none"> 1. More than 1000 cases 2. Significant summary associations ($p < 1 \times 10^{-6}$) per random-effects calculations 3. No evidence of small-study effects 4. No evidence of excess of significance bias 5. Prediction intervals not including the null value 6. Largest study nominally significant ($p < 0.05$) 7. No large heterogeneity (i.e., $I^2 < 50\%$)
Highly Suggestive evidence (Class II)	<ol style="list-style-type: none"> 1. More than 1000 cases 2. Significant summary associations ($p < 1 \times 10^{-6}$) per random-effects calculation 3. Largest study nominally significant ($p < 0.05$)
Suggestive Evidence (Class III)	<ol style="list-style-type: none"> 1. More than 1000 cases 2. Significant summary associations ($p < 1 \times 10^{-3}$) per random-effects calculations
Weak evidence (Class IV)	<ol style="list-style-type: none"> 1. All other associations with $p \leq 0.05$
Non-significant associations (NS)	<ol style="list-style-type: none"> 1. All associations with $p > 0.05$

eTable 2. Criteria for evaluation of the credibility of the evidence of RCTs

Grade level of evidence	Number of downgrades
High	0 downgrades
Moderate	1 -2 downgrades
Low	3-4 downgrades
Very Low	5-6 downgrades

Note: GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Appendix 5 List of studies included in the umbrella meta-analysis with baseline characteristics

eTable 1 List of studies included in the umbrella meta-analysis with baseline characteristics

Study	Type of studies included	Risk or protective factors of recurrence post cardiac surgery or intervention	Exposures	Non-exposures (comparator)	No of included studies estimates	Population (s)	AMSTAR 2
Liu, 2019 ⁸²	RCTs	Dexmedetomidine	Dexmedetomidine use	No use	13	Patients undergoing cardiac surgery	High quality
Miller, 2005 ⁸³	RCTs	Magnesium	Low/high Magnesium dose administration	No administration	20	Patients undergoing cardiac surgery	Critically low quality
Henyan, 2005 ⁸⁴	RCTs	Magnesium	Pre/intra/postoperative magnesium administration	No administration	5	Patients undergoing cardiothoracic surgery	Critically low quality
Guerra, 2017 ⁸⁵	RCTs	Ranolazine	Ranolazine use	No use	5	Patients undergoing cardiac surgery	High quality
Patti, 2015 ⁸⁶	RCTs	Statin pre-treatment	Statin use	No use	11	Patients undergoing	High quality

						cardiac surgery	
Putzu, 2016 ⁸⁷	RCTs	Perioperative statin treatment	Statin use	No use	19	Patients undergoing cardiac surgery	High quality
Mariani, 2013 ⁸⁸	RCTs	n-3 PUFAs	n-3 PUFA use	No use	8	Patients undergoing cardiac surgery	High quality
Liu, 2011 ⁸⁹	RCTs	Omega-3 fatty acids	Omega-3 fatty acids use	No use	10	Patients undergoing cardiac surgery	Critically low quality
Guo, 2014 ⁹⁰	RCTs	Omega-3 fatty acids combined with vitamin C and vitamin D	Use of omega-3 fatty acids combined with vitamin C and vitamin D	No use	11	Patients undergoing cardiac surgery	Moderate quality
Gu, 2012 ⁹¹	RCTs	Thoracic epidural anaesthesia post coronary artery bypass grafting	Use of thoracic epidural anaesthesia post coronary artery bypass grafting	No use	5	Patients undergoing coronary artery bypass grafting	Critically low quality
Li, 2020 ⁹²	RCTs	Perioperative Glucose-Insulin-Potassium	Perioperative Glucose-Insulin-Potassium use	No use	13	Patients undergoing cardiac surgery	Moderate quality

Gillespie, 2005 ⁹³	RCTs	Postoperative amiodarone	Postoperative Amiodarone use	No use	15	Patients undergoing cardiac surgery	Moderate quality
Chatterjee, 2013 ⁹⁴	RCTs	Amiodarone	Oral, iv, pre- and peri-operative amiodarone use	No use	15	Patients undergoing cardiac surgery	Low quality
Ali-Hassan-Sayegh, 2015 ⁹⁵	RCTs	Glucose–insulin–potassium treatment	Glucose–insulin–potassium treatment	No treatment	14	Patients undergoing cardiac surgery	High quality
Espinosa, 2016 ⁹⁶	RCTs	Clevidipine	Clevidipine use	No use	4	Patients undergoing cardiac surgery	High quality
Violi, 2014 ⁹⁷	RCTs	Antioxidants use	Antioxidants use	No use	15	Patients undergoing cardiac surgery	Critically low quality
Ling, 2018 ⁹⁸	RCTs	Dexmedetomidine	Dexmedetomidine use	No use	9	Patients undergoing cardiac surgery	High quality
DiNicolantonio, 2014 ⁹⁹	RCTs	Carvedilol use	Carvedilol use	Metoprolol use	4	Patients undergoing cardiac surgery	High quality
Li, 2015 ¹⁰⁰	RCTs	Landiolol	Landiolol use	No use	9	Patients undergoing	High quality

						cardiac surgery	
Ho, 2009 ¹⁰¹	RCTs	Corticosteroids	Corticosteroids use	No use	18	Patients undergoing cardiac surgery	High quality
Athanasίου, 2004 ¹⁰²	Retrospective cohorts	Off-pump technic	Off-pump technic	No Off-pump technic	8	Elderly patients undergoing cardiac surgery	Critially low quality
Wiesbauer, 2007 ¹⁰³	RCTs	B-blockers	B-blocker use	No use	26	Patients undergoing cardiac surgery	Critially low quality
Litton, 2012 ¹⁰⁴	Prospective cohorts, Retrospective cohorts	BNP or NT-proBNP	High BNP/NT-proBNP	Low BNP/ NT-proBNP	4	Patients undergoing cardiac surgery	Critially low quality
Phan, 2016 ¹⁰⁵	Prospective cohorts, Retrospective cohorts	Obesity	Obese	Non-obese	32	Patients undergoing cardiac surgery	High quality
Liu, 2018 ¹⁰⁶	Prospective cohort	blood transfusion	blood transfusion	No blood transfusion	8	Patients undergoing cardiac surgery	High quality
Rabi, 2010 ¹⁰⁷	RCTs	Peri-operative GI/GIK infusion	Peri-operative GI/GIK infusion use	No use	12	Patients undergoing	Critially low quality

						cardiac surgery	
Liu, 2015 ¹⁰⁸	RCTs	Anterior fat pad removal	Anterior fat pad removal	Anterior fat pad left intact	7	Patients undergoing CABG	Moderate quality
Geng, 2017 ¹⁰⁹	RCTs	Perioperative antioxidant vitamin administration	Perioperative antioxidant vitamin administration	No administration	11	Patients undergoing cardiac surgery	High quality
Lennerz, 2017 ¹¹⁰	RCTs	Colchicine	Colchicine use	No use	5	Patients undergoing cardiac surgery	Moderate quality
Zhu, 2018 ¹¹¹	RCTs	Dexmetomidine	Dexmetomidine use	No use	5	Patients undergoing cardiac surgery	High quality
Kaw, 2016 ¹¹²	RCTs	Diastolic dysfunction	Diastolic dysfunction	Normal diastolic function	3	Patients undergoing cardiac surgery	Moderate quality
Liu, 2014 ¹¹³	RCTs	N-acetylcysteine	N-acetylcysteine use	No use	10	Patients undergoing cardiac surgery	Critically low quality
Qaddoura, 2014 ¹¹⁴	Prospective cohorts	OSAS	OSAS	No OSAS	7	Patients undergoing CABG	Moderate quality

Hu, 2016 ¹¹⁵	RCTs	posterior pericardiotomy	posterior pericardiotomy	No posterior pericardiotomy	10	Patients undergoing CABG	High quality
Zhou, 2017 ¹¹⁶	Prospective cohort, Case-control	preoperative hypertension treatment	preoperative hypertension treatment	No preoperative hypertension treatment	25	Patients undergoing cardiac surgery	Moderate quality
Langlois, 2017 ¹¹⁷	RCTs	PUFA	PUFA use	No use	17	Patients undergoing cardiac surgery	High quality
Chen, 2019 ¹¹⁸	RCTs, Prospective cohorts	RAASi	RAASi use	No use	11	Patients undergoing cardiac surgery	High quality
Liu, 2014 ¹¹⁹	RCTs	Glucocorticoids	Use of different dose-schemes of glucocorticoids	No glucocorticoids	19	Patients undergoing cardiac surgery	High quality
Chen, 2020 ¹²⁰	Prospective cohorts, Retrospective cohorts and Case controls	CHA2DS2-VASc	CHA2DS2-VASc ≥ 2	CHA2DS2-VASc < 2	8	Patients undergoing cardiac surgery	Moderate quality
Guan, 2020 ¹²¹	Prospective cohorts, Retrospective cohorts	off-pump CABG	off-pump CABG	on-pump CABG	13	Patients with HF undergoing cardiac surgery	High quality

Liu, 2020 ¹²²	Prospective cohorts, Retrospective cohorts	Postoperative	High Neutrophil/Lymphocyte Ratio	Low Neutrophil/Lymphocyte Ratio	12	Patients undergoing cardiac surgery	High quality
Ruan, 2020 ¹²³	RCTs	Atrial pacing	Atrial pacing	No atrial pacing	21	Patients undergoing cardiac surgery	High quality
Yusuf Salmasi, 2020 ¹²⁴	Retrospective cohort	Mini-sternotomy	Mini-sternotomy	Right anterior thoracotomy	5	Patients undergoing aortic valve replacement	Moderate quality
Khan, 2020 ¹²⁵	RCTs	TAVR	TAVR	SAVR	5	Patients undergoing aortic valve replacement	High quality
Sun, 2020 ¹²⁶	Retrospective cohort	RAASi	RAASi use	No use	2	Patients undergoing TAVR	Moderate quality
Angsubhakorn, 2020 ¹²⁷	Retrospective cohorts	Transfemoral	Transfemoral	No transfemoral	7	Patients undergoing TAVR	Critically low quality
Reynolds, 2021 ¹²⁸	RCTs	HTK	HTK	multidose cardioplegia	4	Patients undergoing cardiac surgery	Moderate quality

AF: Atrial Fibrillation; BMI: Body mass index; CABG: coronary artery bypass graft; CHADS VASc: Congestive heart failure, Hypertension, Age>75 years, DHA: docosahexaenoic acid; Diabetes, Stroke, Vascular disease, Age>65, female Sex; BNP: B-natriuretic peptide; CPAP: continuous positive airway pressure; DC: direct current; EPA: eicosapentaenoic acid; GIK: glucose insulin potassium infusion; HF: heart failure; HTK: Histidine-Tryptophan-Ketoglutarate; NAC: N-acetylcysteine; NT-proBNP: N-terminal pro B-natriuretic peptide; PUFAs: Polyunsaturated fatty acids; RAASi: renin angiotensin aldosterone system

inhibitors OSAS: obstructive sleep apnea syndrome; RCT: randomized controlled trial; SAVR: surgical aorta valve replacement; TAVR: transcatheter aorta valve replacement

Appendix 6 Non-significant risk/protective factors for postoperative AF, in meta-analyses of RCTs

eTable 1. Non-significant risk/protective factors for postoperative AF, in meta-analyses of RCTs

Author, Year	Predictor	Exposed/Unexposed as included in MA	k	n/N	Metric	ES (95% CI)	p	PI include null value	I ² %	SSE	ESB	LS sign	High RoB	GLE	AMSTAR 2 Quality
Reynolds 2021	HTK	HTK or multidose cardioplegia	4	76/363	OR	1.18(0.39, 3.57)	0.768	Yes	74.23	Yes	NP	No	>25%	NS	Moderate
Ruan 2020	left atrial pacing	left atrial pacing or not	3	85/224	OR	0.59(0.34, 1.02)	0.06	Yes	3.30	No	NP	No	≤25%	NS	High
Ruan 2020	right atrial pacing	right atrial pacing or not	8	191/764	OR	0.76(0.49, 1.18)	0.225	Yes	24.70	No	No	No	≤25%	NS	High
Liu 2015	High dose glucocorticoids	High dose glucocorticoids or not	3	55/208	RR	0.90(0.57, 1.42)	0.653	Yes	0.01	No	NP	No	>25%	NS	High
Zhu 2018	Dexmetomidine	Dexmetomidine or not	5	56/698	RR	0.70(0.26, 1.87)	0.481	Yes	55.14	No	No	No	>25%	NS	High
Kaw 2016	Diastolic dysfunction	Diastolic dysfunction or not	3	195/733	OR	2.67(0.45, 15.80)	0.276	Yes	91.66	No	No	No	>25%	NS	Moderate
Rabi 2010	GI/GIK infusion	GI/GIK infusion or not	12	688/1952	OR	1.04(0.36, 2.98)	0.940	Yes	95.06	No	Yes	No	>25%	NS	Critically low
Liu 2015	Anterior fat pad removal	Anterior fat pad removal or not	7	216/991	RR	1.41(0.85, 2.32)	0.180	Yes	70.38	Yes	Yes	No	>25%	NS	Moderate
Ling 2018	Sedation by Dexmetomidine	Sedation by Dexmetomidine compared to propofol, morphin and placebo	9	251/1295	OR	0.73(0.4, 1.33)	0.303	Yes	60.55	No	No	No	>25%	NS	High
Ali-Hassan-Sayegh 2015	GIK therapy	GIK therapy or not	14	277/1799	OR	0.72(0.48, 1.07)	0.108	Yes	56.20	No	Yes	No	≤25%	NS	High
Espinosa 2016	clevidipine	clevidipine or not	4	74/1820	RR	1(0.45, 2.25)	0.989	Yes	60.72	No	NP	No	≤25%	NS	High
Li 2020	Glucose-Insulin-Potassium Therapy	Glucose-Insulin-Potassium Therapy or not	13	203/1700	RR	0.8(0.63, 1.02)	0.074	Yes	1.43	Yes	No	Yes	>25%	NS	Moderate
Gu 2012	Epidural anaesthesia	Epidural anaesthesia or not	5	155/540	RR	0.57(0.27, 1.22)	0.149	Yes	83.03	Yes	Yes	No	>25%	NS	Critically low
Hemila 2017	Vitamin C use	Vitamin C use or not	5	268/889	RR	0.93(0.64, 1.35)	0.690	Yes	63.17	Yes	No	Yes	≤25%	NS	High
Henyan 2005	Intra-operative and postoperative initiation of magnesium administration	Intra-operative and postoperative initiation of magnesium administration or not	4	133/528	OR	1.02(0.68, 1.52)	0.942	Yes	1.38	No	NP	No	>25%	NS	Critically low

Henyan 2005	Preoperative initiation of magnesium administration	Preoperative initiation of magnesium administration or not	4	154/706	OR	0.38(0.14, 1.03)	0.06	Yes	81.56	Yes	No	No	>25%	NS	Critically low
Mariani 2013	n-3 PUFAs	n-3 PUFAs use or not	8	859/2687	RR	0.83(0.64, 1.06)	0.136	Yes	73.80	Yes	Yes	No	>25%	NS	High
Liu 2011	Omega-3 fatty acids	Omega-3 fatty acids use or not	10	903/1955	OR	0.81(0.57, 1.15)	0.240	Yes	64.68	No	No	No	>25%	NS	Critically low

Abbreviations: AF, Atrial Fibrillation; CE, class of evidence; CI, confidence interval; ES, effect size; ESB, excess significance bias; GIK, glucose insulin potassium infusion; GLE, GRADE level of evidence; GRADE: GRADE, Grading of Recommendations Assessment, Development and Evaluation; HTK, Histidine-Tryptophan-Ketoglutarate; I², heterogeneity; K, number of studies for each factor; LS, largest study with significant effect; n, number of cases; N, total number of cohort per factor; NA, not assessable; NP, not pertinent, because the number of observed studies is less than the expected; NR, not reported; OR, odds ratio; PI, prediction interval; PUFAs: Polyunsaturated fatty acids; RoB, risk of bias; RR, risk ratio; SSE, small study effects; RCT, randomized controlled trial; vit, vitamin.

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