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

Emmanouil Charitakis ,[1] Dimitrios Tsartsalis,[2,3] Dafni Korela,[4] Maria Stratinaki,[4] Farkas Vanky,[1] Efstratios I Charitos,[5] Joakim Alfredsson,[1] Lars O Karlsson,[1] Emmanouil Foukarakis,[4] Constantina Aggeli,[3] Costas Tsioufis,[3] Håkan Walfridsson,[1] Elena Dragioti[6]

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For numbered affiliations see end of article.

Correspondence to
Dr Emmanouil Charitakis; emmanouil.charitakis@liu.se

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 pericardiotomy. 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 pericardiotomy 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.

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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 pericardiotomy 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.

INTRODUCTION

Acute or new-onset atrial fibrillation (AF) in the immediate postoperative period is 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 postoperative 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-Analyses[15] reporting guidelines and the Meta-Analysis of Observational Studies in Epidemiology guidelines[16] (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 etable 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 etable 1, appendix 4). Following previous umbrella reviews,[13] we considered as convincing the associations with>1000 cases a highly significant association (p-value<1 × 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 value <1×10^{-6} by random-effects model), and a statistically significant effect in the largest study. Suggestive evidence required>1000 cases and p value <0.001 by random-effects model. Associations with a p 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 etable 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.

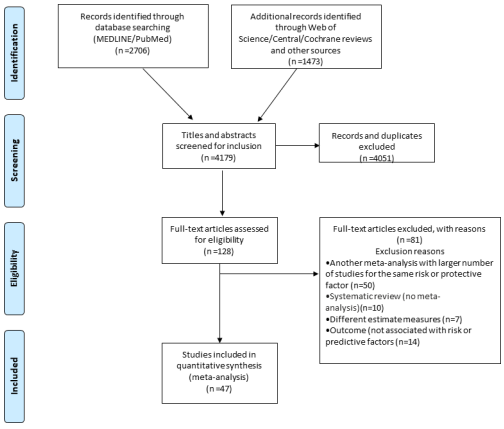

Figure 1 PRISMA flowchart diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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 etable 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 etable 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≤0.05) under the random-effects models, and three of those (23%) achieved a p 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≤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 etable 1, appendix 5).

When the criteria for the credibility of evidence were applied, one (8%) association presented convincing evidence (table 1; online supplemental etable 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 (1.0.5 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
Athanasiou 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

CHADS 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; I^2, heterogeneity; K, number of studies for each factor; LS, largest study with significant effect; n, 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; RCT, 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 etable 1, appendix 5), while three associations (23%) were NS (table 1; online supplemental etable 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≤0.001). Twenty-one (44%) did not show considerable heterogeneity (I2<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≤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 etable 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 etable 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 etable 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] adiposity[27] 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 studies[29] 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 RCTs[30] 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 pericardiotomy	Posterior pericardiotomy 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 ratio1:2	EPA/DHA ratio1:2 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	Landiolol	Landiolol 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
Lennerz 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 NAC use	Prophylactic NAC 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 glucocrorticoids	Low dose glucocrorticoids 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 glucocrorticoids	Medium dose glucocrorticoids 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	Glucorticoids	Glucorticoids 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; I^2, 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 pericardiotomy
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, ranolasine 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 oils[44 45] and antioxidants[46 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]

Author affiliations
[1]Department of Cardiology and Department of Health, Medicine and Caring Sciences, Linköping University, Linkoping, Sweden
[2]Department of Emergency Medicine, Hippokration Hospital, Athens, Greece
[3]First Department of Cardiology, Hippokration Hospital, Athens Medical School, Athens, Greece
[4]Department of Cardiology, Venizeleio General Hospital, Heraklion, Greece
[5]Department of Cardiac Surgery, Kerckhoff Hospital, Bad Nauheim, Hessen, Germany
[6]Pain and Rehabilitation Centre and Department of Health, Medicine and Caring Sciences, Linköping University, Linkoping, Sweden

Contributors EC, DT and ED designed the study. MS and DK performed a comprehensive screening of the literature, selected the studies included in the meta-analysis and abstracted the data items. ED and DT performed the statistical analysis. EC drafted the manuscript and is the guarantor of the paper. EC, ED, DT, MS, DK, LOK, FV, EIC, JA, EF, CA, CT, and HW interpreted the results and edited the manuscript critically. All the co-authors have read and accepted this version of the manuscript.

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ORCID iD
Emmanouil Charitakis http://orcid.org/0000-0002-2514-5324

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