Pharmacological interventions for preventing post-operative atrial fibrillation in patients undergoing cardiac surgery: a network meta-analysis protocol

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ABSTRACT

Introduction Postoperative atrial fibrillation (POAF) is the most common complication following cardiac surgery, and randomised clinical trials (RCTs) and systematic reviews have been conducted to compare and evaluate different pharmacological interventions for preventing POAF. This study aimed to explore the effect of different pharmacological interventions for prophylaxis against POAF after cardiac surgery using network meta-analysis (NMA).

Methods and analysis A systematic search will be performed in PubMed, EMBASE and the Cochrane Library to identify RCTs, systematic reviews, meta-analyses or NMA of different pharmacological interventions for POAF. We will evaluate the risk of bias of the included RCTs according to the Cochrane Handbook V.5.1.0, and use GRADE to assess the quality of evidence. Standard pairwise meta-analysis, trial sequential analysis and Bayesian network meta-analysis will be used to compare the efficacy of different pharmacological interventions.

Ethics and dissemination Ethics approval and patient consent are not required as this study is a meta-analysis based on published studies. The results of this NMA and trial sequential analysis will be submitted to a peer-reviewed journal for publication.

Protocol registration number CRD42017067492.

INTRODUCTION

Postoperative atrial fibrillation (POAF) is the most common complication following cardiac surgery, with an incidence of 15–50%1–5 depending on the cardiac surgical procedure, patient population and exposure to prophylactic interventions. The rate reported in 2009 was even higher in valve surgery (64%).6 POAF normally occurs between days 2 and 4 after surgery, with the maximum incidence seen on postoperative day 2, with 80% and 94% of patients suffering POAF having it by day 4 and by the end of day 6, respectively.7 Furthermore, a substantial impact of POAF on hospital resources was observed. It was estimated that POAF lengthened hospital stay by 4.9 days, with an extra cost of $10 000–11 500 in hospital stay in the USA.7

In addition to directly causing discomfort and leading to haemodynamic compromise, this complication is associated with major adverse consequences, including an increased rate of death, postoperative stroke and other complications,8–10 hospitalisations and inflated costs.11 12 Contemporary studies show that 20–30% of patients with an ischaemic stroke have atrial fibrillation (AF) diagnosed before, during or after the initial event. Cognitive impairment,13–15 decreased quality of life16 17 and depressed mood18 are common in AF patients, and between 10% and 40% of AF patients are hospitalised each year.19 20

Increasing research has assessed various interventions for preventing POAF21 based on the multifactorial aetiology, including pharmacological or non-pharmacological interventions (eg, bi-atrial pacing). Pharmacological interventions aim to reduce the dispersion of...
**Box Detailed search strategy**

**Pubmed**
#1. “Atrial Flutter” [Mesh]
#2. “Arrhythmias, Cardiac” [Mesh]
#3. “Atrial Fibrillation” [Mesh]
#4. AF [Title/Abstract]
#5. “atrium fibrillation” [Title/Abstract]
#6. “atrial flutter” [Title/Abstract]
#7. “atrial arrhythmia” [Title/Abstract]
#8. “heart fibrillation” [Title/Abstract]
#9. “heart atrium fibrillation” [Title/Abstract]
#10. “Thoracic Surgery” [Mesh]
#11. “cardiac surgery” [Title/Abstract]
#12. “heart surgical” [Title/Abstract]
#13. “heart surgery” [Title/Abstract]
#14. “heart surgical” [Title/Abstract]
#15. “cardiac surgery procedures” [Title/Abstract]
#16. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#17. #10 or #11 or #12 or #13 or #14 or #15
#18. #16 and #17

**The Cochrane Library**
#1. MeSH descriptor: [Atrial Fibrillation] explode all trees
#2. MeSH descriptor: [Atrial Flutter] explode all trees
#3. MeSH descriptor: [Arhythmias, Cardiac] explode all trees
#4. atrium fibrillation:ti,ab,kw (Word variations have been searched)
#5. atrial flutter:ti,ab,kw (Word variations have been searched)
#6. atrial arrhythmia:ti,ab,kw (Word variations have been searched)
#7. atrial flutter:ti,ab,kw (Word variations have been searched)
#8. heart fibrillation:ti,ab,kw (Word variations have been searched)
#9. heart atrium fibrillation:ti,ab,kw (Word variations have been searched)
#10. Thoracic Surgery - [Mesh]
#11. heart surgery:ti,ab,kw (Word variations have been searched)
#12. heart surgical:ti,ab,kw (Word variations have been searched)
#13. heart surgery procedures:ti,ab,kw (Word variations have been searched)
#14. heart surgical procedures:ti,ab,kw (Word variations have been searched)
#15. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#16. #10 or #11 or #12 or #13 or #14 or #15
#17. #16 and #17

**Embase**
#1. ‘atrial fibrillation’/exp
#2. ‘heart fibrillation’/exp
#3. ‘atrial arrhythmia’:ab,ti
#4. ‘atrium fibrillation’:ab,ti
#5. ‘atrial flutter’:ab,ti
#6. ‘heart fibrillation’:ab,ti
#7. ‘heart’/exp
#8. ‘cardiac surgery’:ab,ti
#9. ‘heart surgery’:ab,ti
#10. ‘heart surgical’:ab,ti
#11. ‘cardiac surgical’:ab,ti
#12. ‘cardiac surgery procedures’:ab,ti
#13. #1 OR #2 OR #3 OR #4 OR #5 OR #6
#14. #7 OR #8 OR #9 OR #10 OR #11 OR #12
#15. #13 AND #14
#16. #15 AND[embase]/lim NOT [medline]/lim

**OBJECTIVE**
To comprehensively explore the effect of different pharmacological interventions for prophylaxis against POAF after cardiac surgery using NMA.

**METHODS AND ANALYSIS**

**Design**
A Bayesian NMA will be carried out in this study.

**Information source**
A systematic search will be performed in PubMed, EMBASE, and the Cochrane Library. Two librarians (LL and JHT) will be consulted to work on the search strategy. We will use the following search terms: atrial fibrillation, heart fibrillation, atrial fibrillation, cardiac surgery and heart surgery. No limitation of language or publication date will be set during the search process. Our detailed search strategy for the different databases is outlined in box.
Eligibility criteria

Patients: adult patients (≥18 years old) undergoing heart surgery, such as coronary artery bypass graft surgery, valvular surgery, or both, with no history of chronic AF.

Study designs: RCTs, systematic reviews, meta-analyses or NMA will be included for their references.

Interventions: any pharmacological intervention aimed at preventing POAF after cardiac surgery.

Outcomes: primary outcome is incidence of AF, including inhospital AF, and AF up to 2 weeks after discharge; secondary outcomes are incidence of stroke (measured within the same period as AF) or cerebrovascular accident, mortality rate, length of hospital stay, cost of treatment during hospital stay and adverse events.

Other criteria: we will include RCTs published in English. There will be no limitations on duration of study follow-up, year of publication or publication status.

Study records

ENDNOTE X7 literature management software will be used to screen and manage search records, while a standard data abstraction form will be developed with Microsoft Excel 2013 (Microsoft Corp, Redmond, Washington, USA). Pilot tests will be performed for literature screening and data extraction, and remarks will be made to ensure high inter-rater reliability among the reviewers.

Study eligibility will be assessed in two stages. First, pairs of reviewers will independently examine the titles and abstracts in ENDNOTE to identify related studies. Then, each full text article from the screening stage will be obtained and evaluated. Excluded trials and the reasons will be recorded and any disagreement will be resolved through discussion or consultation with an independent third adjudicator.

Data extraction

A rigorous process will be applied to extract the data. To start, the initial data extraction form will be created. Then, a random sample of 3–5 included RCTs will be pilot tested. If necessary, the form will be revised to complete the final data extraction. Finally, two independent reviewers will extract the data of interest, and conflicts will be resolved through discussion or a third reviewer. The following descriptive data from eligible studies will be abstracted: country of origin, year of publication, type of surgery, interventions, treatment schema and doses, number of participants, patient characteristics, background therapies, type of surgery, outcomes measurement or monitoring, length of follow-up, definition of primary outcome and end points of AF, stroke, mortality, length of stay and cost.

Assessment of risk of bias of included studies

Two reviewers will evaluate the risk of bias of the selected RCTs according to the criteria and technique proposed in the Cochrane Handbook V.5.1.0, which includes random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. Each study will be assigned a level of risk of bias (high risk, unclear risk, low risk) for each item. Any disagreement will be resolved through discussion or consultation with an independent third adjudicator.

Geometry of the network

A network plot will be drawn to present the geometry of the network of comparisons across trials to ensure a NMA is feasible. Trials will be excluded if they are not connected by interventions. Nodes in network geometry represent different interventions and edges represent head to head comparisons. The size of nodes and thickness of edges are associated with sample sizes and numbers of RCTs, respectively.

Pairwise meta analysis

Pairwise meta analyses will be performed using Review Manager 5.3.3 (Cochrane Collaboration, Denmark). OR with 95% CI will be used for incidence of AF or supraventricular tachycardia, incidence of stroke or cerebrovascular accident, and mortality rate. Mean differences (MDs) or standard mean differences (SMDs) with 95% CI will be used for length of hospital stay and cost of treatment during hospital stay. We will assess clinical and methodological heterogeneity through examination of the characteristics of the included trials. Heterogeneity across trials will be assessed by $\chi^2$ and $I^2$ statistics. If the P value is ≥0.1 and $I^2$ ≤50%, which suggests there is no statistical heterogeneity, then the Mantel–Haenszel fixed effects model will be employed. If the P value is <0.1 and $I^2$ >50%, we will explore sources of heterogeneity by subgroup analysis and meta-regression. If no clinical heterogeneity is identified, the Mantel–Haenszel random effects model will be used. Pub- lication bias will be examined using Begg’s and Egger’s funnel plot method when applicable. In addition, the contour-enhanced funnel plot will be obtained as an aid to distinguish asymmetry due to publication bias.

Network meta-analysis

We will perform Bayesian NMAs with the package ‘gemtc’ V.0.8.1 of R-3.3.2 software to compare the effects of different prophylactic agents. The Markov Chains Monte Carlo sampler will be used to generate samples. A total of 5000 simulations for each chain will be set as the ‘burn-in’ period. Then, posterior summaries will be based on 100 000 subsequent simulations. Model convergence will be assessed using the Brooks–Gelman–Rubin plots method. Global heterogeneity will be assessed on the bias of the...
magnitude of heterogeneity variance parameter ($I^2$ or $\tau^2$) estimated from the NMA models using the mtc. anohe command of the ‘gemtc’ package. A node splitting method will be used to examine the inconsistency between direct and indirect comparisons when a loop connecting three arms exists. The ranking probabilities for all treatments will be estimated, and a treatment hierarchy using the probability of being the best treatment can be obtained. This process will be performed using the cumulative ranking curve (SUCRA). SUCRA values are expressed as percentages—100% for the best treatment, 0% for the worst treatment. We will also try to use the frequentist approach to compare stability if necessary.

**Assessment of the quality of evidence**
The quality of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) using four levels—high quality, moderate quality, low quality and very low quality. This process will be performed with the online guideline development tool (GD, http://gd3.guidelinedevelopment.org/).

**ETHICS AND DISSEMINATION**
**Publication plan**
This protocol has been registered on the international prospective register of systematic reviews (PROSPERO). The procedures of NMA will be conducted and reported according to the PRISMA extension statement for network meta-analyses. The results of this NMA and trial sequential analyses (TSA) will be submitted to a peer reviewed journal for publication.

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Conception and design of research: XW, YL, LG and KY. Tested the manuscript: XW. All authors approved the final manuscript.

**Competing interests**
None declared.

**Provenance and peer review**
Not commissioned; externally peer reviewed.

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**REFERENCES**
1. Echahidi N, Pibarot P, O’Hara G, et al. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 2008;51:793–801.
2. Jongnarangsin K, Oral H. Postoperative atrial fibrillation. Cardioi Clin 2006;27:69–78.
3. Nair SG. Atrial fibrillation after cardiac surgery. Ann Card Anaesth 2010;13:196–205.
4. Chelazzi C, Villa G, De Gaudio AR, et al. Postoperative atrial fibrillation. ISRN Cardiol 2011;2011:1–10.
5. Raiten JM, Ghadimi K, Augoustides JG, et al. Atrial fibrillation after cardiac surgery: clinical update on mechanisms and prophylactic strategies. J Cardiothorac Vasc Anesth 2015;29:806–16.
6. Rho RW. The management of atrial fibrillation after cardiac surgery. Heart 2009;95:422–9.
7. Avanki SP, Shaw D, Adams DH, et al. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. Circulation 1996;94:390–7.
8. Almassi GH, Schowalter T, Nicolosi AC, et al. Atrial fibrillation after cardiac surgery: a major morbidity event? Ann Surg 1997;226:501.
9. Reed GL, Singer DE, Ricard E, et al. Stroke following coronary-artery bypass surgery. A case-control estimate of the risk from carotid bruits. N Engl J Med 1988;319:1246–50.
10. Creswell LL, Schuessler RB, Rosenbloom M, et al. Hazards of postoperative atrial arrhythmias. Ann Thorac Surg 1993;56:539–49.
11. Mathew JP, Parks R, Salvaggio JS, et al. Atrial fibrillation following coronary artery bypass graft surgery: predictors, outcomes, and resource utilization. JAMA 1996;276:300–6.
12. Mathew JP, Fontes ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 2004;291:1720–9.
13. Chh T, Breteler MM, de Bruyne MC, et al. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. Stroke 1997;28:316–21.
14. Knecht S, Oelschläger C, Duning T, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. Eur Heart J 2008;29:2125–32.
15. Ball J, Carrington MJ, Stewart S. Mild cognitive impairment in high-risk patients with chronic atrial fibrillation: a forgotten component of clinical management? Heart 2013;99:542–7.
16. Marzona I, O’Donnell M, Teo K, et al. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. CMAJ 2012;184:E329–36.
17. Thrall G, Lane D, Carroll D, et al. Quality of life in patients with atrial fibrillation: a systematic review. Am J Med 2006;119:448.e1–448.e19.
18. von Eisenhart Rothe A, Hutt F, Baumert J, et al. Depressed mood amplifies heart-related symptoms in persistent and paroxysmal atrial fibrillation patients: a longitudinal analysis-data from the German Competence Network on Atrial Fibrillation. Europace 2015;17:1354–62.
19. Steinberg BA, Kim S, Fonarow GC, et al. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Am Heart J 2014;167:735–42.
20. Kirchhof P, Schmalowski J, Pittrow D, et al. Management of patients with atrial fibrillation by primary-care physicians in Germany: 1-year results of the ATRIUM registry. Clin Cardiol 2014;37:277–84.
21. Chung MK. Cardiac surgery: postoperative arrhythmias. Crit Care Med 2000;28(Suppl):N136–44.
22. Arsenaux KA, Yusuf AM, Crystal E, et al. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database Syst Rev 2013:1:1201–6.
23. Raiten J, Patel PA, Gutsche J. Management of postoperative atrial fibrillation in cardiac surgery patients. Semin Cardiothorac Vasc Anesth 2015;19:122–9.
24. Mitchell LB, Crystal E, Heilbron B, et al. Atrial fibrillation following cardiac surgery. Can J Cardiol 2005;21(Suppl B):45B.
25. Gillinov AM, Bagiella E, Moskowitz AJ, et al. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. N Engl J Med 2016;374:1911–21.
26. Li L, Li Q, Lin L, et al. Efficacy and safety of left lateral for prevention of atrial fibrillation after cardiac surgery: a meta-analysis of randomized controlled trials. Int J Clin Exp Med 2015;8:10265–73.
27. Liu S, Bian C, Zhang Y, et al. Landiolol hydrochloride for prevention of atrial fibrillation after cardiac surgery: a meta-analysis. Pacing Clin Electrophysiol 2014;37:691–6.
28. Tsu LV, Lee S. Use of ranolazine in the prevention and treatment of postoperative atrial fibrillation in patients undergoing cardiac surgery. Ann Pharmacother 2014;48:633–7.
29. Chen WT, Krishnan GM, Sood N, et al. Effect of statins on atrial fibrillation after cardiac surgery: a duration- and dose-response meta-analysis. J Thorac Cardiovasc Surg 2010;140:364–72.
30. Patti G, Bennett R, Seshasai SR, et al. Statin pretreatment and risk of in-hospital atrial fibrillation among patients undergoing cardiac surgery: a collaborative meta-analysis of 11 randomized controlled trials. Europace 2015;17:855–63.
31. Liakopoulos OJ, Choi YH, Kuhn EW, et al. Statins for prevention of atrial fibrillation after cardiac surgery: a systematic literature review. J Thorac Cardiovasc Surg 2009;138:678–86.
32. Bagshaw SM, Galbraith PD, Mitchell LB, et al. Prophylactic amiodarone for prevention of atrial fibrillation after cardiac surgery: a meta-analysis. Ann Thorac Surg 2006;82:1927–37.
33. de Fruutos F, Gea A, Hernandez-Estefania R, et al. Prophylactic treatment with coenzyme Q10 in patients undergoing cardiac surgery: could an antioxidant reduce complications? A systematic review and meta-analysis. Interact Cardiovasc Thorac Surg 2015;20:254–9.
34. Trivedi C, Sadadia M. Colchicine in prevention of atrial fibrillation following cardiac surgery: systematic review and meta-analysis. Indian J Pharmacol 2014;46:590–5.
35. Polymeropoulos E, Bagos P, Papadimitriou M, et al. Vitamin C for the prevention of postoperative atrial fibrillation after cardiac surgery: a meta-analysis. Adv Pharm Bull 2016;6:243–50.
36. Cook RC, Yamashita MH, Kearns M, et al. Prophylactic magnesium does not prevent atrial fibrillation after cardiac surgery: a meta-analysis. Ann Thorac Surg 2013;95:533–41.
37. Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. BMC Med 2013;11:159.
38. Harenberg J, Marx S, Diener HC, et al. Comparison of efficacy and safety of dabigatran, rivaroxaban and apixaban in patients with atrial fibrillation using network meta-analysis. Int Angiol 2012;31:330.
39. Fu W, Guo H, Guo J, et al. Relative efficacy and safety of direct oral anticoagulants in patients with atrial fibrillation by network meta-analysis. J Cardiovasc Med 2014;15:873–9.
40. Lip GY, Mitchell SA, Liu X, et al. Relative efficacy and safety of non-Vitamin K oral anticoagulants for non-valvular atrial fibrillation: Network meta-analysis comparing apixaban, dabigatran, rivaroxaban and edoxaban in three patient subgroups. Int J Cardiol 2016;204:88–94.
41. Zhao BC, Huang TY, Deng QW, et al. Prophylaxis against atrial fibrillation after general thoracic surgery: Trial sequential analysis and network meta-analysis. Chest 2017;151:149.
42. Higgins JPT GS. Cochrane handbook for systematic reviews of interventions version 5.1.0[EB/OL]: The Cochrane Collaboration, 2011. http://www.cochrane-handbook.org
43. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088.
44. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
45. Peters JL, Sutton AJ, Jones DR, et al. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008;61:991–6.
46. van Valkenhoef G, Kuiper J. gemtc: network meta-analysis using Bayesian methods. https://rdrr.io/cran/gemtc/
47. Wu HY, Huang JW, Lin HJ, et al. Comparative effectiveness of rexin-angiotensin system blockers and other antihypertensive drugs in patients with diabetes: systematic review and bayesian network meta-analysis. BMJ 2013;347:f6008.
48. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004;23:3105–24.
49. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163–71.
50. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value Health 2011;14:429–37.
51. Comparing bayesian and frequentist approaches for network meta-analysis: An empirical study. https://www.globalevidencesummit.org/abstracts/comparing-bayesian-and-frequentist-approaches-network-meta-analysis-empirical-study (accessed 17 Sep 2017).
52. Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ 2014;349:g6530.