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 protocol 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 $10000–11 500 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 life,16 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
# 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]
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: [Arrhythmias, 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 arrhythmia:ti,ab,kw (Word variations have been searched)
8. heart fibrillation:ti,ab,kw (Word variations have been searched)
9. “heart atrium fibrillation” [Title/Abstract]
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

## Embase

1. “atrial fibrillation”/exp
2. “heart fibrillation”/exp
3. “atrial arrhythmia”:ab,ti
4. “atrial arrhythmia”:ab,ti
5. “atrial flutter”:ab,ti
6. “heart fibrillation”:ab,ti
7. “heart surgery”: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

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**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 $c^2$ 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. Publication 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 (GDT, http://gdt.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.

REFERENCES
46. van Valkenhoef G, Kuiper J. gemtc: network meta-analysis using Bayesian methods. https://cran.r-project.org/web/packages/gemtc/