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. A 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 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. A standard pairwise meta-analysis, trial sequential analysis and Bayesian network meta-analysis will be used to compare the efficacy of different pharmacological interventions.

Strengths and limitations of this study

► To the best of our knowledge, this is the first network meta-analysis to comprehensively explore and compare the effect of different pharmacological interventions for prophylaxis against POAF after cardiac surgery.

► The results of this network meta-analysis will help clinicians and patients to select appropriate prophylaxis methods.

► Our results will be limited by both the quantity and quality of the trials available for this review.

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 $10000–11500 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
Atrial fibrillation, cardiac surgery and heart surgery. No limitation of language or publication date will be set during the search process. Our proposed prophylactic interventions for preventing POAF, all of them conducted a pairwise meta-analysis to compare the efficacy of one intervention with controls, or different durations and doses. Traditional pairwise meta-analyses of randomised clinical trials (RCTs) are used to obtain an overall estimate of treatment effect of one intervention relative to the control. Network meta-analysis (NMA) is increasingly used to evaluate healthcare interventions, and the advantage of NMA over pairwise meta-analysis is that it allows indirect comparisons of multiple interventions and rank ordering of the interventions that have not been studied in a head to head fashion.

Also, attention has been paid to developing NMA for AF prevention. Harenberg et al conducted an NMA for three medicines (dabigatran, rivaroxaban and apixaban) in the treatment of patients with AF. Fu et al and Lip et al investigated direct oral anticoagulants in patients with non-valvular AF. Chatterjee et al studied the timing and route of amiodarone for POAF prevention. Harenberg et al comprehensively compared treatments for prophylaxis against POAF after cardiac surgery using NMA.

This study is a comprehensive NMA on different pharmacological interventions for prophylaxis against POAF after cardiac surgery.

**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 study records will be abstracted: country of origin, year of publication, number of participants, intervention 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 c² and I² statistics. If the P value is ≥0.1 and I² ≤50%, we will search sources of heterogeneity by subgroup analysis and meta-regression. If no clinical heterogeneity is identified, the Mantel–Haenszel fixed effects model will be employed. If the P value is <0.1 and I² >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 Beggs’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. anohle 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.

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**Contributors**

Conception and design of research: WX, YL, LG and KY. Tested the feasibility of the study: LL, FL, OZ, Y-LC and YW. Wrote the manuscript: WX. All authors approved the final manuscript.

**Competing interests**

None declared.

**Provenance and peer review**

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