Comparative effects of off-pump and multiple cardiopulmonary bypass strategies in coronary artery bypass grafting surgery: protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction: Multiple revascularisation strategies with or without cardiac arrest have been developed to minimise the negative effects of cardiopulmonary bypass interventions during coronary artery bypass grafting (CABG) surgery. Several observational and randomised studies have evaluated the efficacy of these interventions. This study aims to compare the efficacy and safety of four prevalent revascularisation strategies with/without cardiopulmonary bypass interventions in CABG surgery.

Methods and analysis: We will search on PubMed, Embase, Cochrane Library, Web of Science and ClinicalTrials.gov for randomised controlled trials and observational cohort studies comparing outcomes of CABG surgery under conventional on-pump, off-pump, on-pump beating heart and minimal extracorporeal circulation technology. All English articles published before 30 November 2022 will be considered. The primary outcome will be 30-day mortality. The secondary outcomes will be various early and late adverse events after CABG surgery. The Revised Cochrane Risk of Bias Tool and Newcastle-Ottawa Scale will be used to assess the quality of included articles. A random-effects pairwise meta-analysis will be performed to report the head-to-head comparison. Then, the network meta-analysis will be performed using a Bayesian framework with random-effects models.

Ethics and dissemination: This research does not require the approval of an ethics committee as it relies on reviewing literature and does not involve dealing with humans or animals. The findings of this review will be published in a peer-reviewed journal.

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INTRODUCTION

Cardiovascular diseases are the primary cause of death worldwide, accounting for about 18 million deaths annually (31% of all deaths). Atherosclerotic coronary heart disease is the leading cause of death from cardiovascular disease, accounting for nearly 45% of all cases. Despite the ongoing debate on different revascularisation strategies, coronary artery bypass grafting (CABG) is generally accepted to provide survival benefits for patients with multivessel coronary artery disease. Those with more advanced coronary artery disease, left ventricular dysfunction or diabetes are particularly likely to benefit from CABG.

For decades, the heart is typically arrested with cardioplegia undergoing cardiopulmonary bypass (CPB) to ensure a bloodless surgical field for CABG. However, this conventional on-pump CABG (ONCAB) is often associated with potentially negative effects, including activation of systemic inflammatory responses, excessive haemodilution, haemodynamic instability and risk of air embolism or atherosclerotic debris. These adverse events often lead to subsequent multiorgan dysfunction.

Whereafter in the 1990s, off-pump CABG (OPCAB) was developed as an alternative technique to avoid the use of CPB and reduce the ischaemic/reperfusion injury attributed to cardiac arrest. Though there appear to
be trends in some studies that OPCAB may be related to better short-term outcomes, particularly in high-risk groups, definitive conclusions about the relative merits of ONCAB and OPCAB are difficult to reach. Besides, long-term prognosis and graft patency rates remain concerns behind the initial enthusiasm for OPCAB.6–12 For it is more difficult to achieve complete revascularisation, more excellent surgical skills are needed to operate on a beating heart.13

Hence, an intermediary option combining the advantages of ONCAB and OPCAB appeared. In on-pump beating heart (ON-BH) CABG, surgeons carry out the ONCAB on a beating heart, which does not need aortic cross-clamping.14 This procedure has been observed to be associated with lower early morbidity and mortality, but the clinical benefit is still under discussion.15 16 Another strategy to decrease the side effects of CPB, the minimal extracorporeal circulation (MiECC) technology, was born in the early 2000s.17 MiECC makes it possible to reduce haemodilution while permitting optimal surgical conditions, but it is not only a miniaturised CPB system. MiECC has been observed to attenuate systemic inflammatory response, postoperative bleeding and postoperative atrial fibrillation. It can also offer improved renal function and myocardial protection.18–23

Over the last two decades, many studies have been dedicated to proving the safety of these strategies by comparing them with conventional ONCAB.25–29 Few studies directly compared the effectiveness of CABG surgery under off-pump, ON-BH and MiECC to power for convincing clinical benefits in short-term and long-term outcomes of these three interventions. Network meta-analysis (NMA), as an extension of pairwise meta-analysis, allows the evaluation of multiple treatments in a single analysis.30 31 Hence, the main aim of this study is to provide a synthesis of evidence on the effectiveness of these four different revascularisation strategies with/without CPB interventions (on-pump, off-pump, ON-BH and MiECC) in CABG surgery.

METHODS AND ANALYSIS

Design
This protocol is reported following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)32 and has been registered in the International Prospective Register of Systematic Reviews (PROSPERO). Any amendments to this protocol will be updated on PROSPERO registration. The final review will be reported according to the appropriate PRISMA extension for NMA31 and Meta-analysis of Observational Studies in Epidemiology.33 The PRISMA-P checklist of this study is included in online supplemental table 1.

Eligibility criteria
Patients
Adults (≥18 years old) undergoing isolated CABG surgery.

Interventions/ comparators
Any comparison involving on-pump, off-pump, ON-BH and MiECC in isolated CABG surgery. Figure 1 displays the network of all possible pairwise comparisons between the eligible interventions.

Outcomes
Primary outcome will be 30-day mortality; secondary outcomes will be any adverse cardiac and cerebrovascular events: atrial fibrillation, myocardial infarction (MI), stroke, neurological complications, and renal failure needing haemodialysis, perioperative bleeding, use of blood products, reoperation for bleeding, mean rate of complete revascularisation, length of intensive care unit stay and hospital stay. The time point for the analysis of short-term outcomes will be a 30-day follow-up. Mid-term will be defined as 1–3 years after surgery and long term as >3 years after surgery.

Study designs
Randomised controlled trials (RCTs) and observational cohort studies will be included.

Other limitations
Only studies reported in English will be included. Single-arm studies not presenting a comparison will be excluded.

Search strategy
A systematic search will be performed on PubMed, Embase, Cochrane Library, Web of Science and ClinicalTrials.gov. All English articles published before 30 November 2022 will be considered.

Search strategies include mesh terms and various entry terms and combinations of the following search terms: ‘extracorporeal circulation’, ‘cardiopulmonary bypass’,
We will rerun our search prior to the final analysis. We will also search for additional references by hand-searching the included studies’ bibliographies, relevant systematic reviews and meta-analyses to identify any studies missed in our literature search. A search strategy (PubMed) is presented in online supplemental table 2.

Two researchers will work on the literature search by screening their titles and abstracts to examine their eligibility for inclusion. Disagreements on study inclusion will be resolved through discussion. If necessary, a senior reviewer will be consulted. The proposed flow diagram of the study selection is illustrated in figure 2.

**Data extraction**

The following data will be extracted by two researchers independently:

- Study characteristics, such as the first author of the study, year of publication, country, study type, interventions and sample size.
- Patient characteristics, such as sex, mean age, preoperative cardiac function (eg, left ventricular ejection fraction (LVEF), New York Heart Association class and European System for Cardiac Operative Risk Evaluation (EuroSCORE)) and preoperative comorbidities (eg, peripheral vascular disease, diabetes, chronic obstructive pulmonary disease, prior MI, atrial fibrillation, previous stroke, unstable angina, heart failure, shock, renal failure, left main disease and left ventricular dysfunction).
- Intervention and surgery characteristics, such as urgent or emergent surgery.
- Primary and secondary outcomes.

**Quality assessment**

The methodological quality of RCTs will be evaluated by two reviewers independently based on the Revised Cochrane Risk of Bias Tool 2.0. The following items will be assessed: bias derived from the randomisation process, bias due to deviations from planned interventions, bias due to lack of results data, bias in the measurement of the result and bias in the selection of the reported
results. For each domain, the possible risk of bias judgements will be low risk of bias, some concerns and high risk of bias.

The Newcastle-Ottawa Scale will be used to assess the quality of the included cohort studies. A ‘star system’ will be used for each study to judge on three broad perspectives: the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or outcome of interest.

A summary of the risk of bias will be presented graphically. The conflicts will be resolved through discussion or with a third investigator.

Synthesis of included studies

Pairwise meta-analysis

A random-effects pairwise meta-analysis will be conducted with pooled results reported in terms of the mean difference (MD) for continuous outcomes or risk ratio (RR) for dichotomous outcomes, together with the corresponding 95% CIs. Forest plots will be presented.

Cochrane’s Q test and the I² statistic will be used to evaluate between-study heterogeneity. Generally, p>0.1 and I²≤50% are considered to indicate the absence of statistical heterogeneity.

Network meta-analysis

Data synthesis

The NMA will be performed using a Bayesian framework with random-effects models to account for the underlying variation across studies. Similar to the pairwise meta-analysis, results will be reported in terms of RR and MD, together with corresponding 95% CIs.

For each outcome, the network plots of network geometry will be established to test the feasibility of a network. League plots will demonstrate the estimated relative effect sizes for all interventions. Besides, interventions will be ranked for the probability of being the best option according to their surface under the cumulative ranking curve (SUCRA) probabilities. A higher SUCRA value is considered to lead to a more significant effect in the relevant outcome.

Transitivity analysis

As the extension of clinical and methodological homogeneity to comparisons across groups of studies, transitivity refers to the validity of indirect comparisons of a network of treatments. To meet the transitivity assumption, we will evaluate the included studies by comparing the characteristics of the population, intervention and study design.

Inconsistency analysis

The consistency will be evaluated using node splitting analysis to assess the extent of disagreement between the direct and indirect evidence. P<0.05 will be considered to indicate an inconsistency between direct and indirect evidence.

Additional analysis

Subgroup analysis

For the primary outcome, we expect to perform the subgroup analysis based on the following if sufficient studies are available:

- Types of study design: RCTs only and observational studies only.
- Risk of patients: the risk factors will be determined by preoperative cardiac function (such as LVEF and EuroSCORE), preoperative comorbidities (such as chronic obstructive pulmonary disease, recent MI, atrial fibrillation, previous stroke, unstable angina, heart failure, shock, renal failure and left main disease) and emergency of surgery.
- Length of follow-up: short term (<30 days after surgery), mid-term (1–3 years after surgery) and long term (>3 years after surgery).

Sensitivity analysis

Sensitivity analysis will help to evaluate the impact of the trials’ quality by excluding studies at high risk of bias.

Meta-regression

Meta-regression will be conducted to evaluate the potential influence of study-level covariates in the NMA model.

Reporting bias and small study effects

For comparisons involving at least 10 studies, comparison-adjusted funnel plots and the Egger regression test will be generated to test publication bias. Publication bias is considered to be significant with small study effects when p<0.05.

All analyses and plots will be generated in Stata V.15.0 and R V.3.4.0 (www.r-project.org) using the appropriate R packages. We will narratively describe the results when quantitative analysis cannot be conducted.

Quality of evidence

The quality of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation. This approach is based on four steps: presenting of direct and indirect treatment estimates, rating of quality of direct and indirect effect estimates, and presenting and rating of quality of NMA effect estimates.

Patient and public involvement

Patients or the public will not be involved in the design or conduct of this study.

Ethics and dissemination

This research does not require the approval of an ethics committee as it relies on reviewing of literature and does not involve dealing with humans or animals. Findings of this review will be published in a peer-reviewed journal.
DISCUSSION
Undoubtedly, the emergence of CPB brings more possibilities for the development of cardiac surgery. However, with the improvement of surgical techniques and pursuit of better postoperative quality of life, more alternatives have been developed in CABC surgery to minimise the adverse effects of CPB.\textsuperscript{4, 47} In this analysis, we seek to explore the efficacy and safety of on-pump, off-pump, ON-BH and MiECC in CABC surgery.

Several limitations are expected. First, including observational studies will introduce variability between studies and groups, and therefore bias. Thus, careful assessment of the quality of observational studies will be needed to select for well-designed, high-quality studies. Second, comparisons of long-term outcomes may not be reached or be objective if the data are insufficient, for long-term results have seldom been reported. Third, additional confounders could not be accounted for in the analysis, such as surgeon’s experience. Finally, limiting our searches to English language studies may increase the risk of selection bias. We will use the risk of bias assessment tools to screen the included studies rigorously. Besides, publication bias will be reported as a part of the results in the final analysis.

Despite the limitations, there still exists a role for evaluating well-designed, high-quality observational studies as it can address certain limitations of RCTs, such as short follow-up time, small sample size and highly selected population. Besides, to our knowledge, this is the first study to compare four different revascularisation strategies in a single NMA. The results will provide the comparative effectiveness of these four strategies concerning the risk of different postoperative outcomes and facilitate evidence-informed decision-making for patients undergoing CABC surgery.

Contributors JT and YL developed the initial idea of this study and the strategies for study selection. JT and XL searched for the studies. JT and SG designed and wrote the original draft. LD, BJ and YL provided consultations about clinical issues and revised the draft. All authors contributed to the revision of the final manuscript and approved the submitted version.

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Competing interests None declared.

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