INTERNATIONAL JOURNAL OF SURGERY

OPEN

Comparative efficacy on outcomes of C-CABG, OPCAB, and ONBEAT in coronary heart disease: a systematic review and network meta-analysis of randomized controlled trials

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Importance: Coronary artery bypass grafting (CABG) remains the gold standard for the treatment of multivessel and left main coronary heart disease. However, the current evidence about the optimal surgical revascularization strategy is inconsistent and is not sufficient to allow for definite conclusions. Thus, this topic needs to be extensively discussed.
Objective: The aim of this present study was to compare the clinical outcomes of off-pump CABG (OPCAB), conventional on-pump CABG (C-CABG), and on-pump beating heart (ONBEAT) CABG via an updated systematic review and network meta-analysis of randomized controlled trials.
Data Sources: PubMed, Web of Science, and the Cochrane Central Registry were searched for relevant randomized controlled trials that were published in English before 1 December 2021.
Study Selection Published trials that included patients who received OPCAB, C-CABG, and ONBEAT CABG were selected.
Data Extraction and Synthesis: Two authors independently screened the search results, assessed the full texts to identify eligible studies and the risk of bias of the included studies, and extracted data. All processes followed the Preferred Reporting Items for Systematic Review and Meta-analysis of Individual Participant Data.
Main Outcomes and Measures: The primary outcome was postoperative mortality in patients who underwent C-CABG, OPCAB, or ONBEAT CABG. The secondary outcomes were postoperative myocardial infarction, stroke, and renal impairment in the three groups. The time point for analysis of outcomes was all time periods during the postoperative follow-up.
Results: A total of 39 385 patients (83 496.2 person-years) in 65 studies who fulfilled the prespecified criteria were included. In the network meta-analysis, OPCAB was associated with an increase of 12% in the risk of all-cause mortality when compared with C-CABG [odds ratio (OR): 1.12; 95% CI: 1.04–1.21], a reduction of 49% in the risk of myocardial infarction when compared with ONBEAT (OR: 0.51; 95% CI: 0.26–0.99), a reduction of 16% in the risk of stroke when compared with C-CABG (OR: 0.84; 95% CI: 0.72–0.99) and a similar risk of renal impairment when compared with C-CABG and ONBEAT.
Conclusions and Relevance: OPCAB was associated with higher all-cause mortality but lower postoperative stroke compared with C-CABG. OPCAB was associated with a lower postoperative myocardial infarction than that of ONBEAT. Early mortality was comparable among OPCAB, ONBEAT, and C-CABG.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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International Journal of Surgery (2023) 109:4263–4272

Received 5 June 2023; Accepted 12 August 2023

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/international-journal-of-surgery.

Published online 15 September 2023

http://dx.doi.org/10.1097/JS9.0000000000000715

Key Points

Question Which surgical revascularization strategy is better? Off-pump CABG (OPCAB), conventional on-pump CABG (C-CABG), or on-pump beating heart (ONBEAT) CABG?

Findings This systematic review and network meta-analysis included 65 clinical trials with 39 385 patients in total and found that early mortality rates were similar among the three groups, which shows satisfactory safety of OPCAB, C-CABG, and ONBEAT. C-CABG seems to have more advantages in long-term survival of patients than that of OPCAB, while it is associated with an increased risk of stroke as well. OPCAB is associated with less postoperative myocardial injury than ONBEAT. Renal impairment were comparable among the three groups.

Meaning The findings of this study provide compelling evidence comparing the three surgical revascularization strategies. Overall, the optimal surgical strategy should still be individualized for better outcomes in patients, which depends on the complexity of the lesions, comorbidities, and experience of the surgeons. Further work is required to verify these findings.

HIGHLIGHTS

- This systematic review and network meta-analysis included 65 clinical trials with 39 385 patients.
- This work found that early mortality is similar among the three groups, which shows satisfactory safety of OPCAB, C-CABG, and ONBEAT.
- C-CABG seems to have more advantages on long-term survival compared with OPCAB, while it is associated with an increased risk of stroke as well.
- OPCAB is associated with less postoperative myocardial injury compared with ONBEAT. And renal repairment is comparable among the three groups.
- The findings of this study provide compelling evidence comparing the three surgical revascularization strategies.

Introduction

Coronary artery bypass grafting (CABG) remains the gold standard for the treatment of multivessel and left main coronary heart disease, especially for patients with diabetes mellitus[1–3]. Conventional on-pump CABG (C-CABG) is performed with the use of cardiopulmonary bypass (CPB) and induces cardiac arrest to facilitate anastomosis, which may increase the incidence of several complications, including systemic inflammation, neurologic, and renal dysfunction and ischemic myocardial injury[4]. Off-pump CABG (OPCAB) avoids CPB and cardioplegic arrest, with less aortic manipulation, which could eliminate the complications caused by CPB and heart arrest. However, the fundamental problems of OPCAB depend on the experience level of the surgeons and the incomplete revascularization of lesions[5–8].

On-pump beating heart (ONBEAT) CABG is a hybrid procedure that combines the potential benefits of both C-CABG and OPCAB while avoiding their major drawbacks. It maintains hemodynamic stability by supporting CPB but without inducing cardioplegic arrest to reduce myocardial ischemia and preserve cardiac function while facilitating revascularization of posterior territories, and it has emerged as an effective substitute for high-risk populations[4,9].

Numerous randomized controlled trials (RCTs) and several meta-analyses have compared off-pump with on-pump CABG and concluded that OPCAB significantly reduced short-term rates of stroke and renal failure with no influence on the risk of mortality or myocardial infarction in low-risk and mixed-risk patients[10,11]. However, some data have shown the inferiority of off-pump CABG at longer follow-up periods[12,13]. Compared with ONBEAT, C-CABG was associated with similar[4,14] or inferior outcomes[9]. Few studies have investigated the results of OPCAB and ONBEAT, and the limited data have demonstrated comparable outcomes between the two procedures in patients with left ventricular dysfunction[15,16] or worse clinical outcomes in the ONBEAT population[17].

Overall, the current evidence is inconsistent and is not sufficient to allow for definite conclusions. The 2018 ESC/EACTS (European Society of Cardiology/European Association of Cardio-Thoracic Surgery) Guidelines on myocardial revascularization suggest that OPCAB and preferably no-touch techniques on the ascending aorta by experienced operators are recommended in patients with significant atherosclerotic aortic disease (1 B); OPCAB should be considered for subgroups of high-risk patients by experienced off-pump teams (2a B)[3]; and the 2021 ACC/AHA/SCAI (American College of Cardiology/Society for Cardiovascular Angiography and Interventions) Guideline for Coronary Artery Revascularization recommends that in patients with significant calcification of the aorta, the use of techniques to avoid aortic manipulation (off-pump techniques or beating heart) is reasonable to decrease the incidence of perioperative stroke when performed by experienced surgeons (2a, B)[18]. Thus, the optimal surgical revascularization strategy needs to be extensively discussed.

The aim of this present study was to compare the clinical outcomes of OPCAB, C-CABG, and ONBEAT via an up-to-date systematic review and network meta-analysis (NMA) of RCTs.

Methods

This study was fully compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Supplemental Digital Content 1, http://links.lww.com/JS9/B8) (Supplemental Digital Content 2, http://links.lww.com/JS9/B9): An updated guideline for reporting systematic reviews[19]. This study was conducted according to Assessing the methodological quality of systematic reviews (AMSTAR, Supplemental Digital Content 3, http://links.lww.com/JS9/B10) 2 criteria to self-evaluate the quality of this systematic review[20]. This study has been registered with a Research Registry unique identifying number (UIN): reviewregistry1679. (http://www.researchregistry.com). And it has also been registered at the International Prospective Register of Systematic Reviews (PROSPERO, CRD42022351746).

Search strategy and selection criteria

Included studies for this systematic review and NMAs were RCTs searched in PubMed, Web of Science, and the Cochrane Central Registry. Details of the literature search strategy are provided in the Appendix (Table S1 in Appendix 1, Supplemental Digital Content 3, http://links.lww.com/JS9/B11).

Two reviewers (L.Z. and D.J.L.) independently searched the literature and evaluated all articles. This systematic review included studies that met the following criteria: (1) RCTs in humans; (2) studies reporting baseline and postoperative results on on-pump, off-pump or ONBEAT CABG groups, including the essential outcome mortality and at least one of the following outcomes: myocardial infarction, stroke, and renal impairment; and (3) studies published in English.

The following exclusion criteria were applied: (1) studies that were not RCTs; (2) studies that did not include death as an endpoint; (3) studies that did not report the preoperative and postoperative data in the outcome measurements; (4) basic science or animal studies; and (5) unavailable full English texts.

Quality assessment

This systematic review and NMAs used the Jadad scale to assess the methodological quality of selected studies. Two reviewers (L. Z. and D.J.L.) performed the assessment of all included studies independently. Any discrepancies between the two reviewers were resolved by consensus with another reviewer (P.A.). The results of the Jadad scale are provided in the Appendix (Table S1–4 in Appendix 1, Supplemental Digital Content 3, http://links.lww.com/JS9/B11).

Outcomes

The primary outcome was postoperative mortality in patients with coronary heart disease who underwent C-CABG, OPCAB, or ONBEAT CABG. The secondary outcomes were postoperative myocardial infarction, stroke, and renal impairment in the three groups. The time point for analysis of outcomes was all time periods during the postoperative follow-up.

Data extraction

For each included randomized controlled trial, we collected the study characteristics (e.g. publication year, study design, number of participants in the intervention and control groups, and follow-up time), patient characteristics (e.g. sex, age, and comorbidities) and outcome in the compared groups. All data were extracted from article texts, tables, and figures. All the included articles were independently reviewed by two reviewers (L.Z. and D.J.L.). Discrepancies between the two reviewers were resolved by discussion and consensus with a third reviewer (P.A.).

Risk of bias assessment

The quality and bias risk of the included studies were assessed according to the Cochrane risk of bias tool (ROB2)[21] and Review Manager (version 5.4). Five domains were used to assess the risks of bias: randomization process; deviations from intended interventions; missing outcome data; measurement of the outcome; and selection of the reported result. For each source of bias, included studies were classified into a low, high, or unclear risk, and the discrepancies were discussed until a consensus was accepted. Details of the appraisal and quality score are provided in Appendix 2 (Supplemental Digital Content 3, http://links.lww.com/JS9/B11). A comparison-adjusted funnel plot (the symmetry of the funnel plot) was used to evaluate potential publication bias in the results among studies[22]. The results of the funnel plots are provided in Appendix 7 (Supplemental Digital Content 3, http://links.lww.com/JS9/B11).

Statistical analysis

This statistical analysis included five steps[23]. Step 1 was to provide an overview of the network relationship by drawing a network geometry. Step 2 was to check the assumption of consistency, whereby the treatment effects estimated from direct comparisons are consistent with those estimated from indirect comparisons. Step 3 was to illustrate the summary size of comparative effectiveness among all interventions by making the network forest plot. Step 4 was to identify the superiority among all interventions by calculating cumulative rankings. Step 5 was to evaluate the publication bias from the results.

Pairwise meta-analysis

We conducted the random effects model for pairwise meta-analysis following the Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021) (available from www.training.cochrane.org/handbook). All direct treatment outcomes were compared with odds ratios (ORs) and 95% CIs. There was no significant heterogeneity when $P > 0.05$ for Cochran's Q test (a statistical method to estimate heterogeneity by using Stata software) and I^2 (a statistical method to quantify heterogeneity by using Stata software) less than 50%. A fixed-effects model was applied to calculate the pooled value when $I^2 \leq 50\%$ or $P > 0.05$ for the Q test[24,25]. We also calculated τ^2 (DerSimonian & Laird estimator: a statistical approach to pool standardized mean differences) to determine the heterogeneity of sample size (Appendix 6, Supplemental Digital Content 3, http://links.lww.com/JS9/B11).

NMAs and rankograms

We performed a NMAs by the frequentist method to compare the superiority of different surgical revascularization strategies in patients with coronary heart disease[25]. Based on a random effects model, the dichotomous outcome variables were compared with ORs and 95% CIs. We estimated the probability of all possible ranks from being the best, second best, to the worst for each treatment via Salanti's method[26]. The 'rankograms' with surface under the cumulative ranking curve (SUCRA) probabilities were reported to provide a comparative hierarchy of procedural efficacy and safety. SUCRA was considered the more accurate estimation of cumulative ranking probabilities, and it reported that one treatment is among the best treatments based on the ranking of all interventions' probabilities[27]. A larger SUCRA value indicates a higher rank of the treatment and a safer or more effective treatment[28].

Examination of heterogeneity and consistency in the NMAs

Heterogeneity among individual studies and global inconsistency across different designs of treatment comparisons in the network were assessed with a generalized Q test based on a random effects model[29]. In addition, the local inconsistency between direct and indirect evidence within each treatment comparison was evaluated by node splitting analysis[30]. There were no significant differences between the results of the direct and indirect analyses when $P > 0.05$ for the node splitting analysis, while a consistency model was applied to pool the value.

Sensitivity analyses

The random effects consistency model (the symmetry of the plot) was used to further examine the pooled results in sensitivity analyses[31]. All analyses were conducted using STATA MP.16.0 (Stata) and STATA MP.17.0 (Stata), except for the risk assessment, which was conducted using Revman 5.4.

Certainty of evidence

We evaluated the quality of evidence included in network comparisons following the approach proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool (https://gdt.gradepro.org/). The system classifies the quality of evidence as high, moderate, low, or very low according to factors that include the study methodology, consistency and precision of the results, and the directness of the evidence[32]. The evidence was classified as very low if only one study was included. The quality of evidence was downgraded if the total risk of bias was more than 15%, substantial heterogeneity existed (I^2 >50% and $P_{\text{heterogeneity}}$ <0.1), 95% CIs overlapped the minimally important difference for benefit or harm (10% for mortality, myocardial infarction, stroke, and renal impairment), or publication bias was present (i.e. nonsymmetrical distribution of funnel plot; see Appendix 7, Supplemental Digital Content 3, http://links.lww.com/JS9/B11).

Results

Patient characteristics

A total of 2514 studies were identified through electronic database searching (Fig. 1). Duplicate, irrelevant, non-RCT studies and studies lacking accessibility of data were removed. Finally, 65 studies involving 39 385 patients (83 496.2 person-years) were included for further analysis. Among these patients, 19 626 received C-CABG, 19 457 received OPCAB, and 302 received ONBEAT. Study characteristics are summarized in Appendix 1 (Tables S1–1) (Supplemental Digital Content 3, http://links.lww.com/JS9/B11). The complete evidence networks for all outcomes are shown in Figure 2.

The quality of study assessment is summarized in Appendix 2 (Figs S2–1, S2–2) (Supplemental Digital Content 3, http://links.lww.com/JS9/B11). The funnel plot did not show significant asymmetry to suggest publication bias with mortality, myocardial infarction, stroke, and renal impairment selected outcomes (Appendix 7, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). Egger's test and sensitivity analysis were performed to verify the robustness of the primary and secondary outcomes in this study, which found that the literature included in this study was not at risk of bias (Appendix 9, Supplemental Digital Content 3, http://links.lww.com/JS9/B11).

Patients in the ONBEAT group had a similar age (64.20 ± 7.98 vs. 67.18 ± 6.71 vs. 67.47 ± 6.82) and ejection fraction (49.63 ± 11.42% vs. 54.78 ± 9.13 vs. 52.93 ± 9.55), a comparable proportion of patients with previous myocardial infarction (22.30 vs. 36.94% vs. 37.60%) and male patients (62.91 vs. 75.83% vs. 76.08%), and a higher proportion of patients with previous stroke (27.8 vs. 7.92% vs. 8.50%) compared with those of the OPCAB and C-CABG groups (Table 1). Nevertheless, these differences were not significant. The proportions of previous renal impairment between the OPCAB and C-CABG groups were also similar.

Mortality

In the NMAs, OPCAB was associated with a 12% increase in the risk of postoperative mortality compared with that of C-CABG (OR: 1.12; 95% CI: 1.04–1.21), and the quality of evidence was moderate according to the GRADE classification system. Comparisons between all other treatments were not significantly different. The league tables are shown in Figure 3A. The SUCRA values demonstrated that patients who underwent C-CABG had the highest probability of having the lowest rate of mortality (73.1%), followed by patients who underwent ONBEAT (58.5%) and OPCAB (18.4%) (Fig. 4A). No obvious publication bias in the included studies was revealed by the funnel plot (Figs S7–1 in Appendix 7, Supplemental Digital Content 3, http://links.lww.com/JS9/B11).

For the purpose of comparison, pairwise meta-analysis was also performed, and OPCAB was associated with an 11% increase in the risk of postoperative mortality compared with that of C-CABG (OR: 1.11; 95% CI: 1.03–1.20; $I^2 = 0.0\%$, $P = 0.919$) (Figure S6 c-1.1 in Appendix 6, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). Comparisons between all other treatments were not significantly different (Figure S6 c-1.1, 2, 3 in Appendix 6, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). Low heterogeneity was present.

In addition, the design of the ROOBY trial was severely criticized by surgeons' OPCAB experience and patients' selection[7]. Thus, we additionally analyzed the result of excluding the ROOBY trial, and it showed that OPCAB was associated with a similar risk of mortality compared with that of C-CABG (OR: 1.05; 95% CI: 0.96–1.14). No significant differences were found in the comparisons between all other treatments.

Myocardial infarction

In the NMAs, OPCAB was associated with a 49% reduction in the risk of myocardial infarction compared with that of ONBEAT (OR: 0.51; 95% CI: 0.26–0.99), and the quality of evidence was high according to the GRADE classification system. Comparisons between all other treatments were not significantly different. The league tables are shown in Figure 3B. The SUCRA values demonstrated that patients who underwent OPCAB had the highest probability of having the lowest rate of myocardial infarction (84.3%), followed by patients who underwent C-CABG (63.2%) and patients who underwent ONBEAT (2.6%) (Fig. 4B). No obvious publication bias in the included studies was revealed by the funnel plot (Figs S7–2 in Appendix 7, Supplemental Digital Content 3, http://links.lww.com/JS9/B11).

For the purpose of comparison, pairwise meta-analysis was also performed. OPCAB was associated with a reduction of 71% in the risk of postoperative myocardial infarction compared with that of ONBEAT (OR: 0.29; 95% CI: 0.11–0.75; $I^2 = 0.0\%$, $P = 0.507$) (Figure S6 c-2.3 in Appendix 6, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). Comparisons between all other treatments were not significantly different (Figure S6 c-2.1, 2, 3 in Appendix 6, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). Low heterogeneity was present.

Stroke

In the NMAs, OPCAB was associated with a 16% reduction in the risk of stroke compared with that of C-CABG (OR: 0.84; 95% CI: 0.72–0.99), and the quality of evidence was moderate

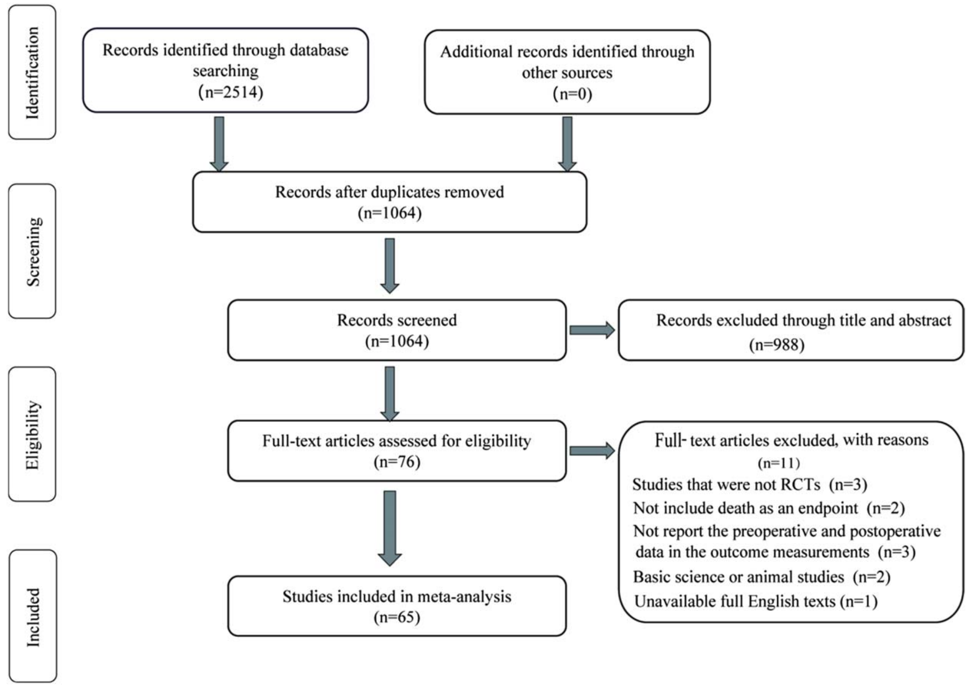

Figure 1. PRISMA flowchart for C-CABG, OPCAB, and ONBEAT. Literature search for network meta-analysis of C-CABG, OPCAB, and ONBEAT. C-CABG, conventional coronary artery bypass grafting; OPCAB, off-pump coronary artery bypass; ONBEAT, on-pump beating-heart coronary artery bypass grafting; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

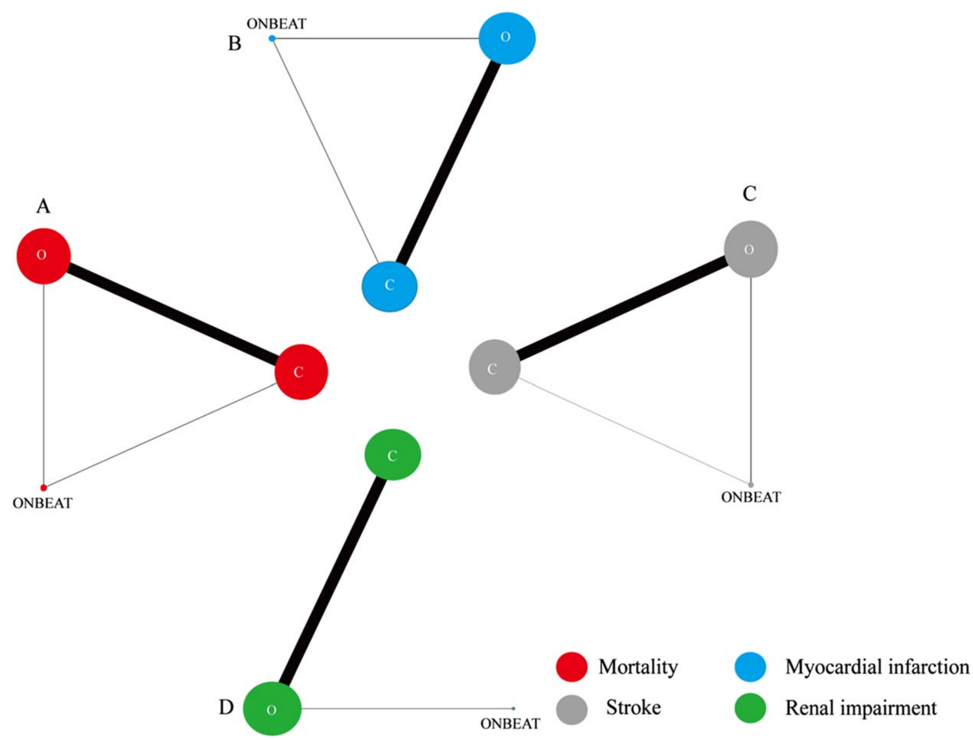

Figure 2. Network diagram for C-CABG, OPCAB, and ONBEAT. Network meta-analysis comparisons for: (A) mortality, (B) myocardial infarction, (C) stroke, (D) renal impairment. The node size is proportional to the number of participants engaged, and the thickness of the continuous line connecting nodes is proportional to the number of directly comparing participants between the two treatments. C, conventional coronary artery bypass grafting; O, off-pump coronary artery bypass; ONBEAT, on-pump beating-heart coronary artery bypass grafting.

Table 1

Baseline patient characteristics for the network meta-analysis between C-CABG, OPCAB, and ONBEAT.

				P		
	C-CABG	OPCAB	ONBEAT	C-CABG VS OPCAB	C-CABG VS ONBEAT	OPCAB VS ONBEAT
Male, %	76.08	75.83	62.91	0.5922	0.1658	0.3220
Age, years	67.47 ± 6.82	67.18 ± 6.71	64.20 ± 7.98	0.9393	0.9029	0.8792
Ejection fraction, %	52.93 ± 9.55	54.78 ± 9.13	49.63 ± 11.42	0.8477	0.9968	0.8940
Previous myocardial infarction, %	37.60	36.94	22.30	0.9594	0.1128	0.0605
Previous stroke, %	8.50	7.92	27.8	0.5310	–	–
Previous renal impairment, %	1.48	2.19	–	0.3727	–	–

C-CABG, conventional coronary artery bypass grafting; OPCAB, off-pump coronary artery bypass; ONBEAT, on-pump beating-heart coronary artery bypass grafting. *P*-value <0.05 means significant.

according to the GRADE classification system. Comparisons between all other treatments were not significantly different. The league tables are shown in Figure 3C. The SUCRA values demonstrated that patients who underwent OPCAB had the highest probability of having the lowest rate of stroke (83.4%), followed by patients who underwent ONBEAT (38.5%) and patients who underwent C-CABG (28.1%) (Fig. 4C). No obvious publication bias in the included studies was revealed by the funnel plot (Figs S7–3 in Appendix 7, Supplemental Digital Content 3, http://links.lww.com/JS9/B11).

For the purpose of comparison, pairwise meta-analysis was also performed. OPCAB was associated with a reduction of 15% in the risk of postoperative stroke compared with that of C-CABG (OR: 0.85; 95% CI: 0.73–0.99; $I^2 = 0.0\%$, $P = 0.992$) (Figure S6 c-3.1 in Appendix 6, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). Comparisons between all other treatments were not significantly different (Figure S6 c-3.1, 2, 3 in Appendix 6, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). Low heterogeneity was present.

Renal impairment

OPCAB was associated with a similar risk of renal impairment compared with that of C-CABG (OR: 0.89; 95% CI: 0.76–1.05). No significant differences were found in the comparisons between all other treatments. The league tables are shown in Figure 3D. The SUCRA values demonstrated that patients who underwent OPCAB had the highest probability of having the lowest rate of renal impairment (70.1%), followed by patients who underwent ONBEAT (52.7%) and patients who underwent C-CABG (27.2%) (Fig. 4D). No obvious publication bias in the included literatures was revealed by the funnel plot (Figs S7–4 in Appendix 7, Supplemental Digital Content 3, http://links.lww.com/JS9/B11).

For the purpose of comparison, pairwise meta-analysis was also performed. OPCAB was associated with a similar risk of postoperative renal impairment compared with that of C-CABG (OR: 0.88; 95% CI: 0.75–1.03; $I^2 = 0.0\%$, $P = 0.918$) (Figure S6 c-4.1 in Appendix 6, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). Comparisons between all other treatments were not significantly different (Figure S6 c-4.1, 2, 3 in Appendix 6, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). Low heterogeneity was present.

Subgroup analysis

A subgroup analysis was performed to explore the difference in postoperative mortality in the early (follow-up days, d ≤ 30) and long-term (d > 30) periods among the three groups. OPCAB was associated with a comparable risk of short-term (d ≤ 30) mortality compared with that of C-CABG (OR: 0.92; 95% CI: 0.76–1.11), and no significant differences were found in comparisons between that of OPCAB and that of ONBEAR or between that of ONBEAT and that of C-CABG (Fig. 5A). The SUCRA values demonstrated that patients who underwent

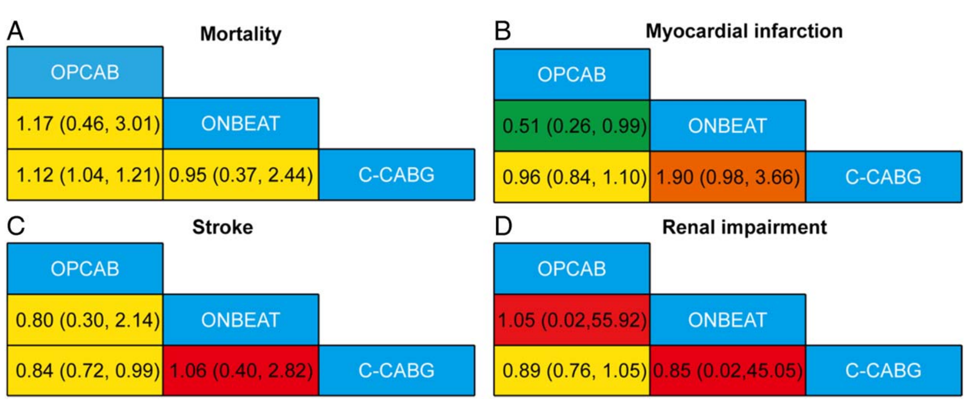

Figure 3. League tables for C-CABG, OPCAB, and ONBEAT. Outcomes shown for (A) mortality, (B) myocardial infarction, (C) stroke, (D) renal impairment following C-CABG, OPCAB, and ONBEAT. Results are OR (95% CI) from the network meta-analysis between the row defining intervention and the column defining intervention. Certainty of evidence is presented as green (high certainty evidence), yellow (moderate certainty evidence), orange (low certainty evidence), and red (very low certainty evidence). C-CABG, conventional coronary artery bypass grafting; OPCAB, off-pump coronary artery bypass; ONBEAT, on-pump beating-heart coronary artery bypass grafting.

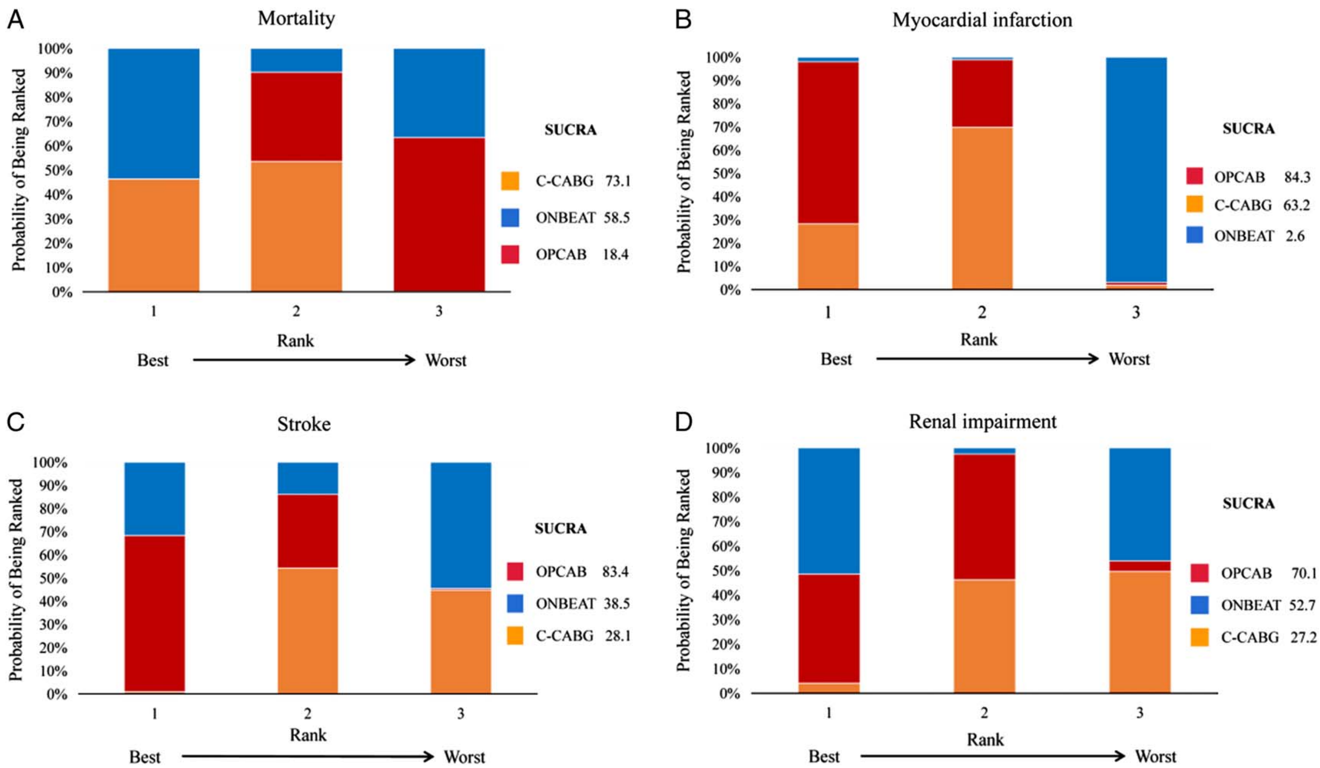

Figure 4. Rankograms for C-CABG, OPCAB, and ONBEAT. Outcomes shown for (A) mortality, (B) myocardial infarction, (C) stroke, (D) renal impairment following C-CABG, OPCAB, and ONBEAT. SUCRA, surface under the cumulative ranking; C-CABG, conventional coronary artery bypass grafting; OPCAB, off-pump coronary artery bypass; ONBEAT, on-pump beating-heart coronary artery bypass grafting.

ONBEAT had the highest probability of having the lowest rate of short-term ($d \leq 30$) mortality (64.5%), followed by patients who underwent OPCAB (59.5%) and patients who underwent C-CABG (26.0%). No obvious publication bias in the included studies was revealed by the funnel plot (Figs S7–5 in Appendix 7, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). For long-term ($d > 30$) mortality, OPCAB was associated with an increase of 17% in the risk of long-term ($d > 30$) mortality compared with that of C-CABG (OR: 1.17; 95% CI: 1.04–1.31) (Fig. 5B). The SUCRA values demonstrated that patients who underwent C-CABG had the highest probability of having the lowest rate of long-term mortality (99.6%), followed by patients who underwent OPCAB (0.4%) (Figure S4–7 in Appendix 4, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). No obvious publication bias in the included studies was revealed by the funnel plot (Figure S7-6 in Appendix 7, Supplemental Digital Content 3, http://links.lww.com/JS9/B11).

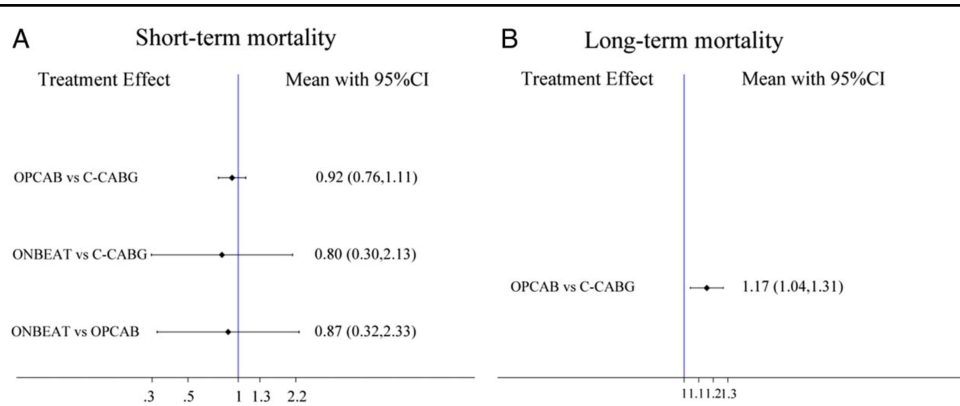

Figure 5. Subgroup meta-analysis forest plot for C-CABG, OPCAB, and ONBEAT. Outcomes shown for (A) Short-term mortality ($d \leq 30$; d, postoperative days), (B) Long-term mortality ($d > 30$; d, postoperative days) following C-CABG, OPCAB, or ONBEAT (OR and 95% CI). C-CABG, conventional coronary artery bypass grafting; OPCAB, off-pump coronary artery bypass; ONBEAT, on-pump beating-heart coronary artery bypass grafting.

For comparison purposes, pairwise meta-analysis was also performed. OPCAB was associated with an increase of 15% in the risk of long-term mortality compared with that of C-CABG (OR: 1.15; 95% CI: 1.06–1.24; $I^2 = 0.0\%$, $P = 0.636$) (Figure S6 c-6 in Appendix 6, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). Comparisons between all other treatments were not significantly different (Figure S6 c-5.1, 2, 3 in Appendix 6, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). Low heterogeneity was present.

Discussion

This study, which included the largest population ($n = 39\ 385$ participants) from RCTs to date, is the first NMAs to investigate the outcomes of C-CABG, CABG, and ONBEAT. OPCAB was associated with a 12% increase in the risk of postoperative all-cause mortality but a 16% reduction in the risk of postoperative stroke compared with those of C-CABG. OPCAB was associated with a 49% reduction in the risk of postoperative myocardial infarction compared with that of ONBEAT. The quality of all evidence of these results was moderate and high according to the GRADE classification system. Subgroup analysis showed comparable early mortality (≤ 30 days) among OPCAB, ONBEAT, and C-CABG. OPCAB was associated with an increase of 16% in the risk of mid-term and long-term (> 30 days) postoperative all-cause mortality compared with that of C-CABG.

We also summarized eight meta-analyses in the last 5 years to evaluate the safety and efficacy of C-CABG, OPCAB, and ONBEAT. Three studies showed that OPCAB was associated with significantly increased mortality compared with C-CABG, while comparisons between OPCAB and ONBEAT, C-CABG, and ONBEAT in other meta-analyses were unconvincing due to their inclusion of observational studies[13,33,34]. These studies indicated the superiority of ONBEAT in early mortality and postoperative complications compared with C-CABG and OPCAB. Details of the literature search and results are provided in the Appendix (Tables S1 and 2 in Appendix 1, Supplemental Digital Content 3, http://links.lww.com/JS9/B11). These comprehensive results reflected the existing inconsistency and uncertainty in the choice of surgical revascularization strategies.

The superiority of OPCAB and C-CABG has been continuously debated during the past decade. Numerous randomized trials have compared these two strategies. The CORONARY trial and GOPCABE trial indicated similar 1-year and 5-year rates of mortality, stroke, myocardial infarction, repeat revascularization, and composite end points of these events[35–38]. The ROOBY trial illustrated worse composite outcomes (all-cause death, repeat revascularization and nonfatal myocardial infarction) in the off-pump group at 1-year[35]. OPCAB led to lower rates of 5-year survival and event-free survival than those of C-CABG[12]. The ROOBY trial recently reported results at the 10-year follow-up, and no OPCAB advantages were found for 10-year death or revascularization endpoints[39]. Consequently, whether C-CABG or off-pump surgery has an impact on survival remains highly inconclusive. Consistent with the ROOBY trial, our study revealed increased mortality in patients who underwent OPCAB. However, the design of the ROOBY trial was severely criticized because too-low-risk patients were enrolled and the participating surgeons' off-pump experience was limited[7]. Thus, we additionally analyzed the result of excluding the ROOBY trial, and it showed similar mortality rates between patients who underwent OPCAB and C-CABG. This contradictory conclusion points to the importance of the surgeons' experience in off-pump procedure, and more rational, well-designed RCTs are warranted on this topic in the future.

The three large RCTs mentioned above did not reveal a significant increase in the stroke rate with C-CABG compared with that of OPCAB. Theoretically, CPB use in ONBEAT and C-CABG would increase the incidence of postoperative stroke due to various potential mechanisms related to CPB, including embolic events, systemic inflammatory response, hypoperfusion, detachment of atherosclerotic plaques during manipulation or cross-clamping of the ascending aorta. Our present study showed a reduction of 16% in the risk of postoperative stroke for OPCAB compared with C-CABG. By ranking treatments according to their comparative effectiveness for reducing stroke rate, the model demonstrated that OPCAB was the superior surgical technique (SUCRA 82.4%), followed by ONBEAT (SUCRA 39.8%), and finally C-CABG (SUCRA 27.8%). In accordance with our results, a NMAs indicated that an aortic OPCAB was associated with a reduction of 78% in the 30-day risk of stroke compared with that of CABG; OPCAB with the clampless Heartstring device and OPCAB with a partial clamp were associated with a reduction in stroke risk of 55 and 36%, respectively, compared with those of C-CABG[28]. Another retrospective, multicenter, international study including 25 388 patients reported that the incidence of postoperative stroke was significantly lower in the OPCAB group (0.4 OPCAB versus 1.2% C-CABG, $P = 0.02$)[40]. These findings revealed the potential superiority of OPCAB in reducing the risk of postoperative stroke.

Initially, ONBEAT was conducted in high-risk patients, such as those with poor left ventricular function, progressive myocardial ischemia or infarction, or advanced age with comorbidities. A previous meta-analysis showed similar early and late mortality rates between patients who underwent ONBEAT and patients who underwent OPCAB, while ONBEAT was associated with more postoperative complications (stroke, renal failure, blood loss, and arrhythmias) and more severe myocardial injury than those of OPCAB. However, ONBEAT conferred lower rates of incomplete revascularization and greater numbers of distal anastomoses[15]. Ueki's meta-analysis compared ONBEAT and C-CABG and indicated that ONBEAT is associated with significantly lower early mortality and morbidity (including myocardial infarction, renal failure, and low output syndrome)[9], while a randomized trial revealed a higher incidence of new irreversible myocardial injury in ONBEAT than in C-CABG[41]. We found a higher incidence of myocardial injury in the ONBEAT group than in the OPCAB group and a similar risk compared with the C-CABG group. The SUCRA values showed that the OPCAB group had the highest probability of having the lowest rate of myocardial infarction (84.3%), followed by the C-CABG (63.2%) and ONBEAT groups (2.6%). This could be due to the effect of low coronary perfusion pressures in ONBEAT, especially in patients with severe proximal coronary disease.

A meta-analysis showed a decreased risk for renal dysfunction by 2.1% in the OPCAB group compared with the C-CABG group[11]. Another meta-analysis concluded that the incidence of renal failure was significantly higher in patients who underwent ONBEAT than in patients who underwent OPCAB[15]. Renal impairment occurs more frequently after the use of CPB.

Notwithstanding, the present study found no significant difference in the incidence of renal impairment, and the SUCRA values indicated that OPCAB had the highest probability of reducing postoperative renal impairment (70.1%), followed by that of C-CABG (52.7%) and then that of ONBEAT (27.2%). Thus, patients with preoperative renal dysfunction might benefit from OPCAB, but evidence from high-quality randomized trials is still needed.

In general, the RCT presents the highest level of evidence; however, it shows an idealized outcome, because of the excluding of some 'special' patients sometimes. In real-world practice, patients are usually complex and with multiple comorbidities, so surgical revascularization strategies still need to be individualized. For instance, in patients with significant calcification of the aorta or with significant pulmonary disease, the OPCAB is reasonable when performed by experienced surgeons. C-CABG is more suitable for low-risk patients without contraindications of CPB and inexperienced surgeons in OPCAB. And in high-risk patients with cardiac dysfunction, which cannot tolerate position shifts and prolonged surgical procedures, ONBEAT seems to be an effective protective surgical strategy. It would always be a matter needs comprehensive consideration, with a fundamental tenet of maximizing the patient benefits.

Several limitations exist in the present study. First, we only included RCTs to eliminate potential selection bias, and thus, there were only five trials enrolled concerning the ONBEAT group. The results may be influenced by publication bias on this occasion, although the statistical tests for publication bias showed no significant evidence of this. Second, we merely compared the early results between the ONBEAT group and the other two groups due to the lack of long-term follow-up in the ONBEAT trials, and consequently, we examined the occurrence of early (d ≤ 30) and long-term (d > 30) mortality separately in subgroup analyses. Third, studies spanning two decades were included in the present meta-analysis, of which the results would be influenced by the improvements in surgical techniques over that period.

Finally, as a statistical approach, NMA also has some limitations. NMA is limited to analyze the results of RCTs and is for direct and indirect comparisons in a set of interventions[42]. In addition, the conclusions of NMA are affected by some other factors of the included RCT studies: researchers, funding agencies, and the research ethics committees guidelines, etc., which could affect the issues and results of RCTs[43]. In fact, the publication bias of small-scale studies should be considered[44]. Studies with a small number of patients actually cause publication bias and may generate a large treatment effect[45]. In this study, we evaluated publication bias by performing sensitivity analysis and funnel plots. Although NMA has some limitations, it is still the most powerful analysis with respect to scientific persuasion[46].

Conclusion

This NMAs of all available studies found that OPCAB was associated with higher all-cause mortality but lower postoperative stroke than that of C-CABG. OPCAB was associated with a lower postoperative myocardial infarction than that of ONBEAT. The occurrence of early mortality was comparable among OPCAB, ONBEAT, and C-CABG. Overall, the optimal surgical strategy should still be individualized for better outcomes in patients, which depends on the complexity of the lesions, comorbidities, and experience of the surgeons. In addition, further work is required to verify these findings.

Ethical approval

This manuscript was not given ethical approval, cause ethics clearance was not necessary in this manuscript. In this study, we were presenting the analyzing and processing data from random controlled trials. This study did not include any animal experiments or human trials, thus we could not give the ethical approval.

Patient consent

Not applicable.

Sources of funding

This work was supported by the Beijing Advanced Innovation Center for Food Nutrition and Human Health, the National Natural Science Foundation of China (31970717, 82170429, 82170487), National Foreign Expert Program of Ministry of Science and Technology (G2022001039L), the Chinese Universities Scientific Fund (2020TC015), the Beijing Municipal Natural Science Foundation (7222111), the National High Level Hospital Clinical Research Funding (bj-2023-72).

Author contribution

Y.L. and H.Z.: contributed to the quality checks; L.Z. and D.L.: contributed to the reference screening, data extraction, data quality checks, risk of bias assessments, supervision of data collection and interpretation of results; X.Z. and S.W.: contributed to the data extraction and data quality checking; J.L., Y.L., P.A., and W.J.: contributed to the idea of the manuscript, interpretation of results, and manuscript writing.

Conflicts of interest disclosure

Lin Zhu, Dongjie Li, Xu Zhang, Sitong Wan, Yuyong Liu, HongJia Zhang, Junjie Luo, Yongting Luo, Peng An, Wenjian Jiang declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Research Registry and PROSPERO.
2. Unique identifying number or registration ID: reviewregistry1679 (Research Registry) and CRD42022351746 (PROSPERO).
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/64d05bcd48b2470028e373de/.

Guarantor

Junjie Luo, Yongting Luo, Peng An and Wenjian Jiang are guarantors.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

The datasets generated during the current study are available from the corresponding author on reasonable request.

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