

Early Versus Delayed Coronary Angiography After Out-of-Hospital Cardiac Arrest Without ST-Segment Elevation—A Systematic Review and Meta-Analysis of Randomized Controlled Trials

OBJECTIVES: The optimal timing of coronary angiography remains unclear following out-of-hospital cardiac arrest (OHCA) without ST elevation on electrocardiogram. The objective of this systematic review and meta-analysis was to evaluate the efficacy and safety of early angiography versus delayed angiography following OHCA without ST elevation.

DATA SOURCES: The databases MEDLINE, PubMed EMBASE, and CINAHL, as well as unpublished sources from inception to March 9, 2022.

STUDY SELECTION: A systematic search was performed for randomized controlled trials of adult patients after OHCA without ST elevation who were randomized to early as compared to delayed angiography.

DATA EXTRACTION: Reviewers screened and abstracted data independently and in duplicate. The certainty of evidence was assessed for each outcome using the Grading Recommendations Assessment, Development and Evaluation approach. The protocol was preregistered (CRD 42021292228).

DATA SYNTHESIS: Six trials were included ($n = 1,590$ patients). Early angiography probably has no effect on mortality (relative risk [RR] 1.04; 95% CI 0.94–1.15; moderate certainty) and may have no effect on survival with good neurologic outcome (RR 0.97; 95% CI 0.87–1.07; low certainty) or ICU length of stay (LOS) (mean difference 0.41 days fewer; 95% CI –1.3 to 0.5 d; low certainty). Early angiography has an uncertain effect on adverse events.

CONCLUSIONS: In OHCA patients without ST elevation, early angiography probably has no effect on mortality and may have no effect on survival with good neurologic outcome and ICU LOS. Early angiography has an uncertain effect on adverse events.

KEY WORDS: coronary angiography; meta-analysis; non-ST elevated myocardial infarction; out-of-hospital cardiac arrest; randomized controlled trials

Out-of-hospital cardiac arrest (OHCA) remains a leading cause of death worldwide, and survival to hospital discharge is less than 10% (1–3). Even among those with return of spontaneous circulation (ROSC) and who are admitted to hospital, survival to discharge is less than 40% (3). Among the principles of postcardiac arrest care are the identification and treatment of the underlying cause for arrest (4). However, the etiology is not always immediately clear, and this can lead to delays in cause-directed treatment.

Cardiac disease is the most common cause of OHCA in adults, of which acute coronary occlusion is a common etiology (5). Acute coronary occlusion is found

Kumait Al Lawati, MD^{1,2,3}

Ben Forestell, MD¹

Yasser Binbraik, MD^{2,4}

Sameer Sharif, MD^{1,2,5}

Craig Ainsworth, MD^{2,4}

Rebecca Mathew, MD⁶

Faizan Amin, MD^{2,4}

Mohammed Al Fawaz, MD²

Natalia Pinilla-Echeverri, MD⁴

Emilie Belley-Côté, MD, PhD^{2,4,5}

Michelle Welsford, MD¹

Bram Rochweg, MD, MSc^{2,5}

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KEY POINTS

Question: In a systematic review and meta-analysis of randomized controlled trials, what are the differences in efficacy and safety outcomes for early versus delayed coronary angiography strategies for patients without ST elevation after out-of-hospital cardiac arrest?

Findings: Five studies with 1,524 patients were included. Compared with delayed angiography, early angiography probably has no effect on mortality and may have no effect on survival with good neurologic outcome. Early angiography has an uncertain effect on most adverse events.

Meanings: There is probably no benefit to an early compared with delayed angiography strategy for patients without ST elevation after out-of-hospital cardiac arrest.

in a substantial proportion of patients post ROSC with ST-segment elevation on initial electrocardiogram (ECG), and early coronary angiography and revascularization is associated with improved survival in this population (6–8). Multiple guidelines strongly recommend early angiography after OHCA with ST elevation post ROSC (4, 9, 10). However, in patients without ST elevation post ROSC, the incidence of acute coronary occlusion is much lower, and the potential benefits of early angiography are less clear (8, 11). The proportion of patients following OHCA without ST elevation is much larger and includes noncardiac causes of cardiac arrest, such as pulmonary embolism, hypoxia, and intoxication. Despite a more heterogenous population, including patients without coronary occlusion, observational studies have suggested that patients without ST elevation post ROSC may still benefit from early angiography (6, 7, 12), although the results are based on very low certainty of evidence (13). A number of recently published randomized controlled trials (RCTs) have investigated the benefit of early coronary angiography in patients without ST elevation on ECG after ROSC (14–18), and some of these studies have been summarized in a recent systematic review (19). However, this review included both post hoc observational data and RCTs, did not include two more recent RCTs (18, 20), and did not assess the certainty of their summarized evidence (19). As such, the objective of this study was to conduct an updated systematic review

and meta-analysis of RCTs to evaluate the safety and efficacy of early versus delayed angiography in patients without ST elevation post ROSC.

METHODS

The protocol for this systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021292228) on November 19, 2021. Any deviations from the published protocol are highlighted with an accompanying explanation. The updated Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was used to guide the design and reporting of our systematic review and meta-analysis (21) (see **supplementary appendix for PRISMA Checklist, Appendix 7**, <http://links.lww.com/CCX/B149>). Given the study was a systematic review of previously published data, it was exempt from review from our Institutional Review Board.

Systematic Search

We conducted a comprehensive search of MEDLINE, PubMed EMBASE, CINHAI, and unpublished sources including World Health Organization ICTRP, ClinicalTrials.gov, and the Cochrane trial registry from inception until March 9, 2022. We searched for RCTs investigating early versus delayed coronary angiography for OHCA patients in the absence of STEMI. We did not apply language restrictions. We developed the search strategy with the assistance of an expert medical librarian and included three search terms: “Coronary angiography,” “Out of hospital cardiac arrest,” and “Non-ST-segment elevation MI” (see **supplementary appendix for search strategy, Appendices 1–5**, <http://links.lww.com/CCX/B149>). We used the Medical Subject Headings database for identification of synonyms. We examined the reference list of full-text articles for additional relevant studies. We also searched conference proceedings within the last 2 years for the Society of Critical Care Medicine, the European Society of Intensive Care and Emergency Medicine, American Heart Association, the American College of Cardiology, the European Society of Cardiology, and the Canadian Cardiovascular Society.

Study Selection

We included RCTs if they examined patients with OHCA who were randomized to early coronary

angiography as compared with delayed angiography. We included studies of adults who had been successfully resuscitated after OHCA in the absence of ST-segment elevation on post ROSC ECG. We included studies reporting on the following outcomes: mortality at longest follow-up, disability (as measured by the Cerebral Performance Category [CPC] or another validated scale as per the individual study), duration of mechanical ventilation, ICU length of stay (LOS), hospital LOS, and adverse events including ventricular arrhythmias, major bleeding (as defined by study authors), acute kidney injury (as defined by study authors), and need for renal replacement therapy. For outcomes reported at multiple timepoints, we used the longest reported follow-up.

After implementation of the search strategy, two reviewers screened potentially relevant citations independently and in duplicate. Citations deemed potentially relevant by either screener were advanced to full-text review. Full texts were subsequently reviewed for eligibility, with disagreements resolved by consensus, and third-party adjudication if required. We captured reasons for exclusion at the full-text screening stage.

Data Extraction and Quality Assessment

Reviewers extracted data independently and in duplicate using prepiloted data abstraction forms. We extracted the following information from included studies: study title, first author, demographic data, details of the intervention, control, outcome data, and risk of bias (RoB) for each study. We contacted study authors for clarification when the population characteristics, method of follow-up, or outcome data were unclear or not reported. We assessed RoB, independently and in duplicate using a modified Cochrane RoB 2 tool (22) for which each domain is rated as “low,” “probably low,” “high,” or “probably high.” We examined the following RoB domains: bias arising from the randomization process, bias due to protocol deviations, bias due to missing outcome data, bias in outcome measurement, and bias due to selective outcome reporting. We rated the overall RoB for an individual trial close to the highest risk attributed to any domain.

We assessed the overall certainty of evidence for each outcome using the Grading Recommendations Assessment, Development and Evaluation (GRADE)

approach (23). We resolved disagreements for RoB and GRADE assessment by consensus. We used the Guideline Development Tool (www.gradepro.org) to build the Summary of Findings table. For LOS outcomes, a clinically important difference was considered one day. Results were contextualized using GRADE narrative statements (24).

Statistical Analysis

We used DerSimonian and Laird random-effects models (25) to conduct the meta-analysis using RevMan 5.4 (Cochrane Collaboration, Oxford, United Kingdom) software. We generated study weights using the inverse variance method for continuous outcomes and dichotomous outcomes. We present results as relative risks (RRs) and risk difference (RD) for dichotomous outcomes and mean difference (MD) for continuous outcomes, all with 95% CIs. We calculated absolute effects using the pooled baseline prevalence from the control arm of included trials. The Hozo model was used to convert median and range to mean and variance when required (26). We assessed heterogeneity between trials using visual inspection of the forest plots, the chi-square test for homogeneity (where $p < 0.1$ indicates important heterogeneity), and the I^2 statistic (for which 50% or greater was considered reflective of potentially important heterogeneity) (27). Although planned, we did not construct funnel plots to assess for publication bias as these are inaccurate when less than 10 trials are included in the analysis (28). We planned to perform predefined subgroup analysis comparing studies of 1) high RoB compared with those at low RoB, 2) patients with initial shockable rhythm compared with nonshockable rhythm, 3) patients with known coronary artery disease compared with no known coronary artery disease, and 4) patients with duration of arrest greater than or equal to 20 minutes compared with less than 20 minutes. For subgroup findings that were significant, we planned to use the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) tool to judge subgroup credibility (29).

RESULTS

Of the 383 citations identified in the search (**Fig. 1**), we excluded 97 duplicates and a further 234 citations after

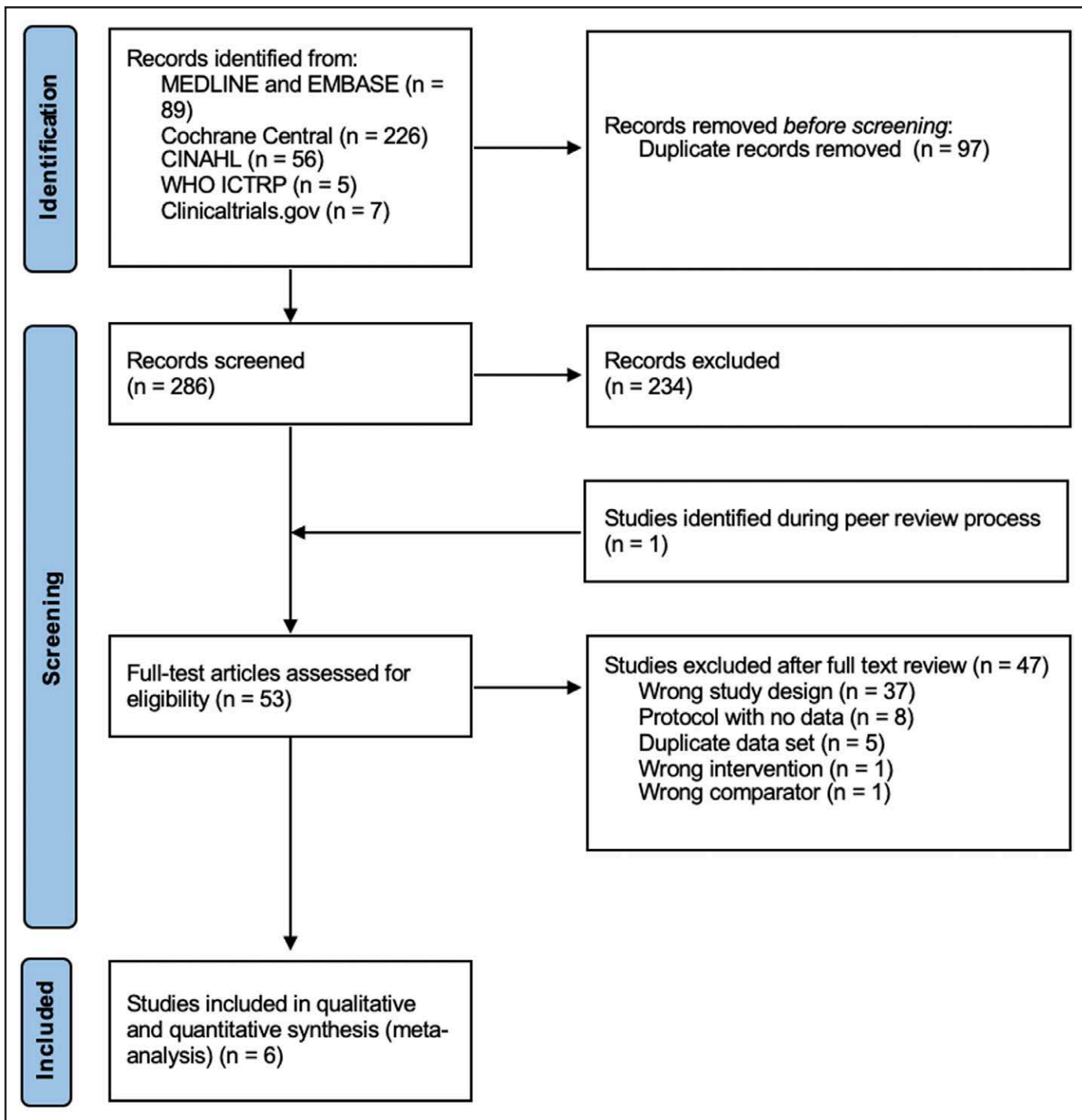


Figure 1. Study flowchart.

title and abstract screening, and we assessed 47 full texts. We included six RCTs ($n = 1,590$ patients) in the review (14–18, 20). Baseline characteristics of included trials are summarized in **Appendix 8, Supplemental Table 1** (<http://links.lww.com/CCX/B149>). One trial was originally included as an abstract; however, upon publication of the article after our search was completed, we did a full text review and included this trial

in our analysis (18). A further recent RCT was published during the peer review process and was included in our analysis (20).

Description of Included Studies

All included RCTs were multicenter studies. The mean age of participants ranged from 65 to 71 years.

Five trials included adults greater than or equal to 18 years; one trial included adults greater than or equal to 30 years (14). All trials included patients with OHCA presumed to be cardiac in origin and excluded patients who had an obvious or suspected noncardiac etiology of the cardiac arrest. One trial only included patients with initial shockable arrest rhythm (17). The timing of early angiography varied among studies: immediately after randomization in two trials (16, 18), within 1 hour of patient presentation in one trial (14), and within 2 hours of patient presentation in three trials (15, 17, 20). In the trials with early angiography immediately after presentation, one did not provide time from arrest to angiography (16), whereas the other trial had a median time from arrest to angiography of 2 hours (18). The timing of delayed angiography ranged between 6 hours and 4 days following hospital presentation. The decision to perform angiography, however, was subject to neurologic recovery or discretion of the treating physician in three trials (14, 15, 17).

Patients randomized to the delayed angiography group were initially managed with usual care in the ICU; however, all included trials provided opportunity to expedite to urgent angiography if patients deteriorated, with evidence of unstable electrical activity, concerning ECG changes, cardiogenic shock, new significant echocardiographic findings, or refractory hemodynamic instability. Across included studies, of the patients randomized to early angiography, 763 of 798 (95.6%) received angiography, whereas 473 of 792 patients (59.7%) assigned to delayed angiography received an angiogram during their index hospitalization (14–18, 20). The duration of follow-up ranged between 3 months and 1 year. Severity of coronary artery disease was reported in five trials (included in Appendix 8, Supplemental Table 1, <http://links.lww.com/CCX/B149>). Overall, an acute unstable coronary lesion was identified in 65 of 437 patients (14.9%) in one trial (17), and a culprit coronary lesion in 225 of 566 patients (39.8%) in four trials (14–16, 20). Culprit or unstable lesion was not described in one trial, but percutaneous coronary intervention was performed in 55 of 200 patients (27.5%) receiving angiography (18). Five of the included trials were judged to be at probably low RoB (14, 15, 17, 18, 20) and one trial at high RoB (16) (see **Table 1** for RoB judgments).

TABLE 1.
Risk of Bias Determination Using Modified Cochrane Risk of Bias 2 Tool

References	Bias Arising From the Randomization Process	Bias Due to Deviations From Intended Interventions	Bias Due to Missing Outcome Data	Bias in Measurement of the Outcome	Bias in Selection of the Reported Result	Overall ROB
Lemkes et al ⁽¹⁷⁾ (COACT)	Low	Probably low	Low	Low	Low	Probably low
Elfwen et al. ⁽¹⁶⁾ , (DISCO)	Low	High	Low	Low	Low	High
Kern et al ⁽¹⁵⁾ (PEARL)	Low	Probably low	Low	Low	Low	Probably low
Desch et al ⁽¹⁴⁾ (TOMAHAWK)	Low	Probably low	Low	Low	Low	Probably low
Hauw-Berlemont et al ⁽¹⁸⁾ (EMERGE)	Low	Probably low	Low	Low	Low	Probably low
Viana-Tejedor et al ⁽²⁰⁾ (COUPE)	Low	Probably low	Low	Low	Low	Probably low

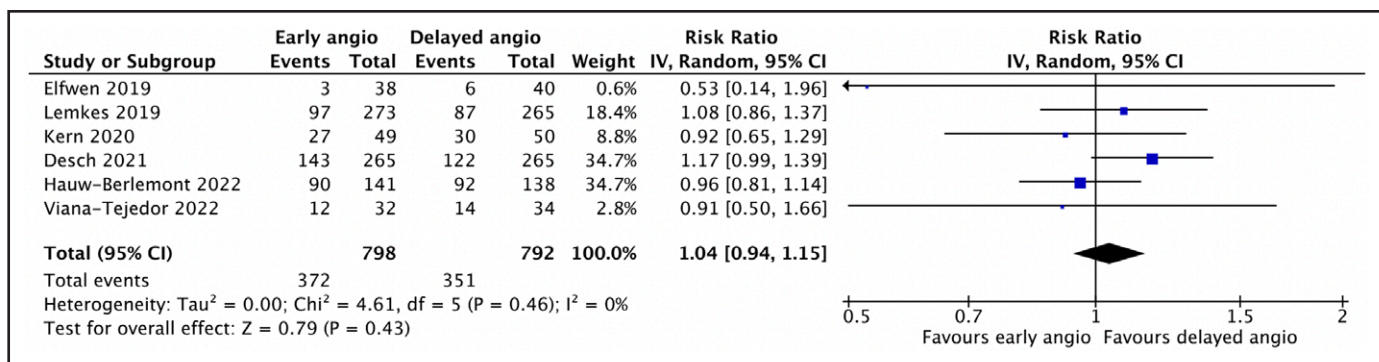


Figure 2. Forest plot comparing early versus delayed angiography after out-of-hospital cardiac arrest without ST-segment elevation for mortality at longest point of follow-up. df = degrees of freedom.

Efficacy Outcomes

Appendix 8, Supplemental Table 2 (<http://links.lww.com/CCX/B149>) shows the summary of findings for all outcomes including the certainty of evidence. Pooled analysis found that in patients with OHCA without ST elevation, early angiography probably has no effect on mortality at the longest follow-up (RR 1.04; 95% CI 0.94–1.15; RD 1.8% increase; 95% CI, 2.7% reduction to 6.6% increase; moderate certainty) (**Fig. 2**) and may have no effect on survival with good neurologic outcome as assessed with the CPC score of 2 or less (RR 0.97; 95% CI 0.87–1.07; RD 1.4% reduction; 95% CI, 6.1% reduction to 3.3% increase; low certainty) (**Fig. 3**). Early angiography may have no effect on ICU LOS (MD 0.41 d fewer; 95% CI –1.3 to 0.5 d; low certainty) (**Appendix 6, Supplemental Fig. 1**, <http://links.lww.com/CCX/B149>). Early angiography may have no effect on duration of mechanical ventilation (MD 0.29 d fewer; 95% CI –1.2 to 0.6 d; low certainty) (**Appendix 6, Supplemental Fig. 2**, <http://links.lww.com/CCX/B149>) and may have no effect on hospital LOS (MD 0.82 d fewer; 95% CI –3.9 to 2.3 d; low certainty) (**Appendix 6, Supplemental Fig. 3**, <http://links.lww.com/CCX/B149>).

Safety

Early angiography has an uncertain effect on major bleeding (RR 0.95, 95% CI 0.55–1.62; RD 0.2% decrease, 2.0% decrease to 2.7% increase; very low certainty) (**Appendix 6, Supplemental Fig. 4**, <http://links.lww.com/CCX/B149>), acute kidney injury (RR 1.18, 95% CI 0.33–4.20; RD 1.7% increase, 95% CI 6.4% decrease to 30.3% increase; very low certainty) (**Appendix 6, Supplemental Fig. 5**, <http://links.lww.com/CCX/B149>), or need for renal replacement therapy (RR 1.10, 95% CI 0.78–1.57; RD 0.9% increase, 95% CI 2.0% decrease to 5.2% increase; very low certainty) (**Appendix 6, Supplemental Fig. 6**, <http://links.lww.com/CCX/B149>). Furthermore, early angiography has an uncertain effect on the incidence of ventricular arrhythmia (RR 0.75, 95% CI 0.30–1.90; RD 2.0% decrease, 95% CI 5.6% decrease to 7.2% increase; very low certainty) (**Appendix 6, Supplemental Fig. 7**, <http://links.lww.com/CCX/B149>). The CIs for all safety outcomes were wide and did not rule out the potential for harm (**Appendix 8, Supplemental Table 3**, <http://links.lww.com/CCX/B149>).

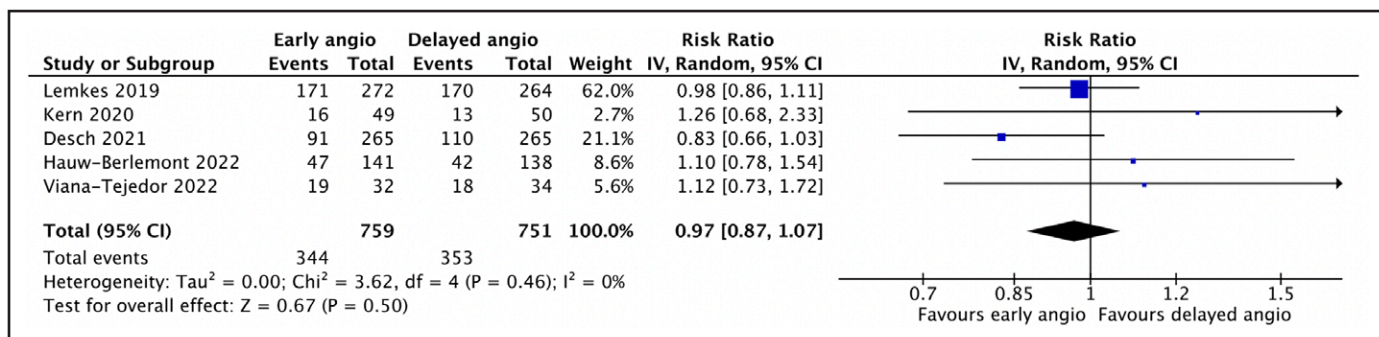


Figure 3. Forest plot comparing early versus delayed angiography after out-of-hospital cardiac arrest without ST-segment elevation for survival with good neurological outcome as defined by Cerebral Performance Score of 2 or less. df = degrees of freedom.

Sensitivity and Subgroup Analysis

Subgroup analyses comparing mortality in high RoB studies versus low RoB studies or based on initial shockable rhythm did not demonstrate effect modification for mortality at longest follow-up (p value for subgroup interaction < 0.05) (**Appendix 6, Supplemental Figs. 7 and 8**, <http://links.lww.com/CCX/B149>). Although planned, lack of data did not allow for other subgroup analyses.

DISCUSSION

This systematic review and meta-analysis of RCTs demonstrates that compared with delayed or no angiography, early angiography probably has no effect on mortality and may have no effect on survival with good neurologic outcome and ICU LOS for patients without ST elevation post OHCA. Furthermore, early angiography may have no effect on duration of mechanical ventilation and hospital LOS and has an uncertain effect on most adverse events.

The lack of benefit of early angiography post OHCA may be due to the heterogeneous population included in this group without ST elevation post ROSC. The hypothesized benefit of early angiography is the identification and subsequent revascularization of an acute coronary occlusion. However, patients without ST elevation after OHCA often do not have an acute coronary occlusion, with an incidence of only 15–40% from trials included within this review. In contrast, in patients with ST elevation after OHCA, 70–90% have an acute coronary occlusion (8). Early angiography will likely not benefit patients with other causes of cardiac arrest and may even delay identification and treatment of noncardiac causes of arrest. The trials included in this meta-analysis selected patients most likely to benefit from early angiography by excluding patients with obvious or presumed noncardiac causes of cardiac arrest (14–18). Despite this enrichment strategy, early angiography was not found to be beneficial.

The results of this analysis are consistent with a previous meta-analysis of RCTs addressing the question that did not include the most recently published RCTs (19). That being said, by including the Emergency versus Delayed Coronary Angiogram in Survivors of OHCA Without ST-Segment Elevation trial ($n = 279$) and the Coronary Angiography in Patients Without ST-segment Elevation Following OHCA trial ($n = 66$), which were

not included in the previous review (18, 20), we have achieved a higher degree of precision in findings which may provide stronger conclusions. Other incremental additions of this review compared with previous meta-analyses on the topic include using the GRADE approach to assess certainty in estimates of effect and excluding two studies which had been included in previously published meta-analysis but which were deemed ineligible for this meta-analysis (30, 31). Of these two that were excluded, one was a post hoc observational study of the targeted temperature management RCT (30), where the decision for timing of angiography was determined by the treating clinician and was not done in a randomized fashion. The second study was an RCT comparing expedited transfer to a specialized postcardiac arrest center for early angiography, versus transfer to the nearest geographical center where the decision to perform angiography in this group was left to the discretion of the treating clinician (31). Of concern, 14 of 18 patients in the control group received angiography with a median time from arrest to angiogram of 132 minutes, versus a median time of 100 minutes in early angiography group. We decided to exclude this study given this strategy does not reflect our comparator of interest but rather is comparing early angiography at a specialized cardiac arrest center versus early angiography at the geographically nearest hospital to the arrest.

It is still possible that certain subgroups of patients without ST elevation may benefit from early angiography; unfortunately, we did not have sufficient trial level data to perform many preplanned subgroup analyses. Large ongoing RCTs are comparing early angiography versus delayed or no angiography and can hopefully better delineate these subgroups of interest and provide more precision to best inform clinical decisions (32). Further consideration of clinical history of preceding chest pain, non-ST elevation ECG changes, echocardiographic findings demonstrating new regional wall motion abnormalities, and elevated troponin values could identify OHCA patients who may benefit from an early angiography strategy (33–35). Another OHCA population not captured in any of the published RCTs is noncomatose patients, a population with a better prognosis than comatose patients, and one which will be studied in the upcoming DISCO-NO-COMA trial (36–38). It is hypothesized that in the noncomatose population, early angiography may prevent progressive myocardial injury leading to re-arrest, compared with comatose patients who most

often die from neurologic injury or withdrawal of life-sustaining therapies due to anticipated poor prognosis and whose prognosis may not change with coronary revascularization (39).

Multiple international guidelines addressing cardiopulmonary resuscitation have deemphasized the role of early angiography after OHCA in patients without ST elevation post ROSC (4, 10) since the results of the Coronary Angiography after Cardiac Arrest without ST-Segment Elevation trial published in 2019 (17). However, the results of the most recent RCTs were not available during the development of those guidelines. As such, this systematic review and meta-analysis will provide further granularity and stronger conclusions for future guidelines to consider when balancing the potential benefits, harms, as well as values and preferences, and costs in developing clinical recommendations for angiography strategies for patients after OHCA without ST elevation.

This systematic review has several strengths, including adherence to a preregistered protocol, a comprehensive literature search including unpublished sources, duplicate and independent screening and data abstraction, application of the GRADE approach to assess certainty in pooled estimates of effect, and the inclusion of the most recent published RCTs. There are also limitations. First, we were unable to perform many of the preplanned subgroup analyses due to insufficient trial level data. Second, there was important heterogeneity in outcome definitions between studies, which may have contributed to serious imprecision in reporting of outcomes; however, this clinical heterogeneity did not translate into statistical heterogeneity for outcomes of interest. Third, the timing of delayed angiography varied between trials.

CONCLUSIONS

In OHCA patients without ST elevation, early angiography probably has no effect on mortality. Early angiography may have no effect on survival with good neurologic outcome, hospital LOS, and ICU LOS and has an uncertain effect on most adverse events.

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- 1 Department of Medicine, Division of Emergency Medicine, McMaster University, Hamilton, ON, Canada.
- 2 Department of Medicine, Division of Critical Care, McMaster University, Hamilton, ON, Canada.
- 3 Oman Medical Specialty Board, Muscat, Sultanate of Oman.
- 4 Department of Medicine, Division of Cardiology, McMaster University, Hamilton, ON, Canada.
- 5 Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada.
- 6 Division of Cardiology, Department of Medicine, University of Ottawa Heart Institute, Ottawa, ON, Canada.

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For information regarding this article, E-mail: ben.forestell@med-portal.ca

All data associated with this article are included in the main text and supplementary materials.

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