Iranian Heart Journal; 2024; 25 (2)

Original Article

Early vs Delayed Coronary Angiography in Out-of-Hospital Cardiac Arrest Patients Without ST-Segment Elevation: An Updated Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: The routine practice of early coronary angiography in patients who have suffered an out-of-hospital cardiac arrest without ST-segment elevation remains a subject of controversy.

Methods: We searched electronic databases for randomized controlled trials that compared early or emergency coronary angiography with delayed or no coronary angiography in patients who had an out-of-hospital cardiac arrest without ST-segment elevation. A random-effects meta-analysis was performed to estimate the odds ratio (OR) with a 95% confidence interval (CI). The outcomes of interest were mortality and neurological prognosis, based on the cerebral performance categories (CPC 1–2) scale.

Results: Seven studies involving 1623 patients (the early group [n=816] and the delayed group [n=807]) were included in the final analysis. Compared to delayed coronary angiography, early coronary angiography was associated with similar odds of mortality (OR, 1.07; 95% CI, 0.87 to 1.31; *P*=0.52) and a favorable neurological prognosis (OR, 0.97; 95% CI, 0.78 to 1.19; *P*=0.74).

Conclusions: For patients with an out-of-hospital cardiac arrest without ST-segment elevation, there was no benefit concerning mortality and neurological prognosis with early coronary angiography compared with delayed coronary angiography. ***(Iranian Heart Journal 2024; 25(2): 26-34)***

KEYWORDS: Early coronary angiography, Delayed coronary angiography, Out-of-hospital cardiac arrest, Non–ST-elevation myocardial infarction

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Received: September 30, 2023 **Accepted:** December 6, 2023

A total of 146,924 out-of-hospital cardiac arrest (OHCA) cases were reported in the Cardiac Arrest Registry to Enhance Survival (CARES) in 2021. [1] Of these, 82% were presumed to be of cardiac origin, and 16.4% of cases had an initial shockable rhythm (ventricular tachycardia or ventricular fibrillation). The majority of patients with an initial shockable rhythm were found to have severe coronary artery disease (CAD), manifesting as ST-segment-elevation myocardial infarction (STEMI). [2,3] During the immediate post-cardiac arrest care period, current guidelines advise emergent cardiac intervention in cases with STEMI due to improved survival and neurological outcomes with early coronary angiography. In patients without STEMI on the post-resuscitation ECG, earlier observational studies reported better neurological outcomes with urgent angiography. [3-5] However, multiple randomized controlled trials (RCTs) since then have shown no favorable mortality or neurological outcomes in such cases when comparing urgent/early coronary angiography to usual care or delayed angiography. [6-10] Previous meta-analyses have reported similar results. [11,12] Two recent RCTs–COUPE (coronary angiography in patients without ST-segment elevation following out-of-hospital cardiac arrest) and EMERGE (emergency vs delayed coronary angiogram in survivors of out-of-hospital cardiac arrest) also failed to show any advantage of early angiography in OHCA patients without STEMI. [13,14] Given these new data, we performed an updated meta-analysis of all the RCTs.

METHODS

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework (Fig. 1), we systematically reviewed electronic databases, including MEDLINE, EMBASE, and Cochrane. We aimed to answer our population's PICO question. (P: cardiac arrest patients without STEMI; I: intervention [early coronary angiography]; C: comparison [delayed or no coronary angiography], O: outcomes [mortality and neurological outcomes])

Our search strategy included combining MeSH terms, such as "out of hospital cardiac arrest", "non-ST elevation myocardial infarction", and "coronary angiography", in various combinations to search for RCTs from inception until September 23, 2023. Two reviewers (SD and SS) independently screened the databases, and a third reviewer (AR) resolved any conflicts. The main inclusion criteria were RCTs comparing early and delayed coronary angiography in adult OHCA patients without STEMI and reporting at least 1 clinical outcome of interest. Our exclusion criteria included 1) non-randomized design, 2) post hoc analyses of previous RCTs, and 3) studies with STEMI patients. Baseline characteristics were noted for all the RCTs, including study design, inclusion/exclusion criteria, sample size, follow-up period, mean age, and sex. Outcomes of interest were mortality and favorable neurological outcome rates. Neurological outcome was defined based on the cerebral performance categories (CPC) scale, with CPC 1–2 considered the favorable neurological outcome.

Statistical analyses were performed based on the PRISMA guidelines. [15] We used Cochrane Review Manager, version 5.4, to conduct the analysis. [16] For each clinical endpoint, a random-effects meta-analysis model with the Mantel-Haenszel method was used to calculate odds ratios (ORs) and 95% confidence intervals (CI). A P value $\leq$ 0.05 was considered significant. Heterogeneity between studies was calculated using the I^2 statistic. It was considered significant in the case of $I^2 > 50\%$. Forest plots were generated to show aggregate effect size and intervals for individual endpoints.

RESULTS

Out of the initial 135 studies found during the online search, 7 RCTs that satisfied the inclusion/exclusion criteria were included in the final analysis. [6-10,13,14] Figure 1 shows the search strategy. A total of 1623 patients were included, with 816 in the early angiography group and 807 in the delayed group. Baseline characteristics are reported for all the studies in Table 1 and Table 2. The mean follow-up period was 317 days. The mean age was 66 years and 74.6% were men. 22% of the patients had a prior history of myocardial infarction (MI), 22% had diabetes mellitus (DM), 56% had hypertension (HTN), 25% were smokers, and 9% had strokes.

From the 7 studies, event rates for mortality were 401 in the early angiography group and 384 in the delayed group (Fig. 2). Compared to delayed coronary angiography, early coronary angiography was associated with similar odds of mortality (OR, 1.07; 95% CI, 0.87 to 1.31; P=0.52). No heterogeneity was observed in the studies (I^2 = 0%).
Similarly, no significant difference was observed in favorable neurological outcomes between the early and delayed angiography groups (339 vs 339: OR, 0.97; 95% CI, 0.78 to 1.19; P=0.74) and the studies did not have any heterogeneity (I^2=0%) (Fig. 3). Sensitivity analysis performed by excluding each trial did not show any change in the outcomes (Table 3). The risk of bias assessment for the trials is shown in Figure 4.

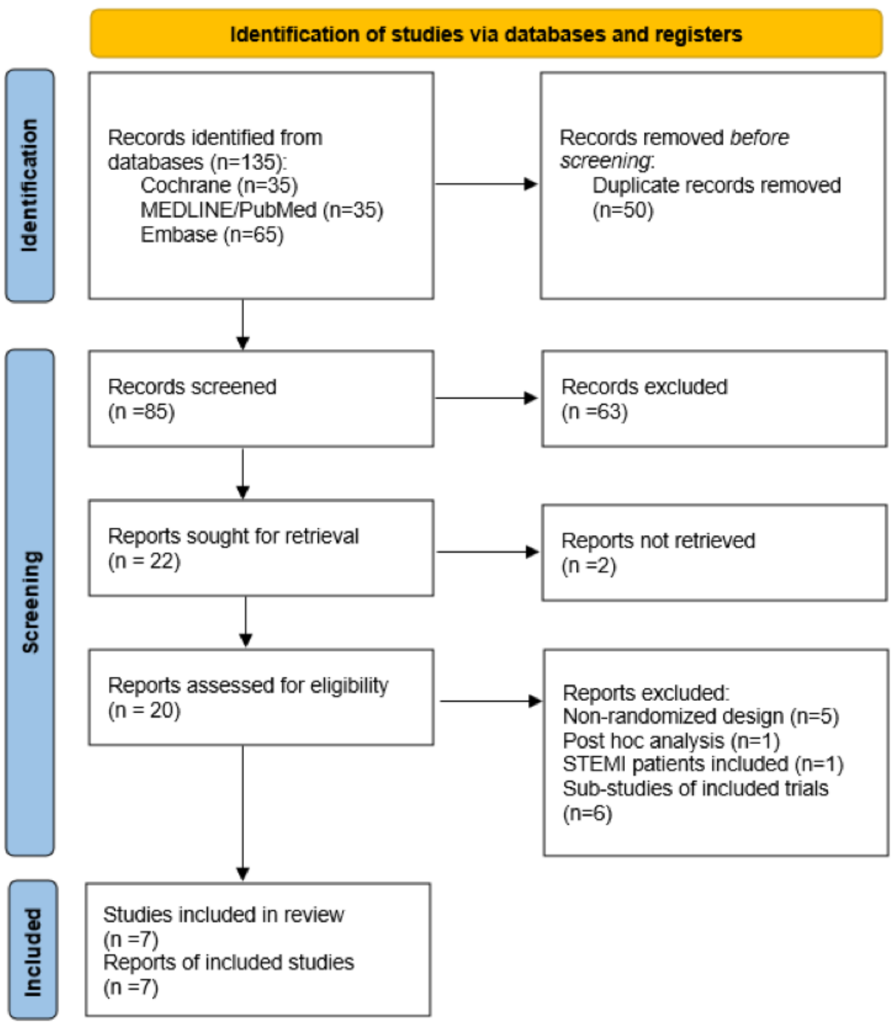

Figure 1: The image presents the PRISMA flow sheet depicting the search strategy.

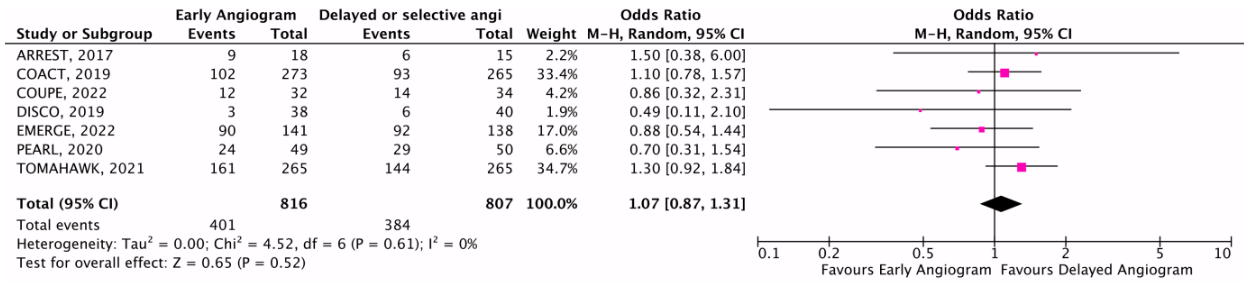

Figure 2: The image depicts the forest plot, showing mortality in the early vs delayed angiography groups.

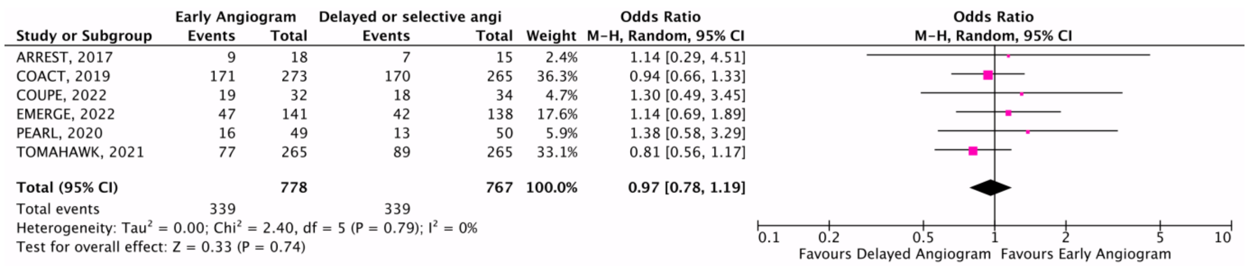

Figure 3: The image presents the forest plot showing favorable neurological outcomes in the early vs delayed angiography groups.

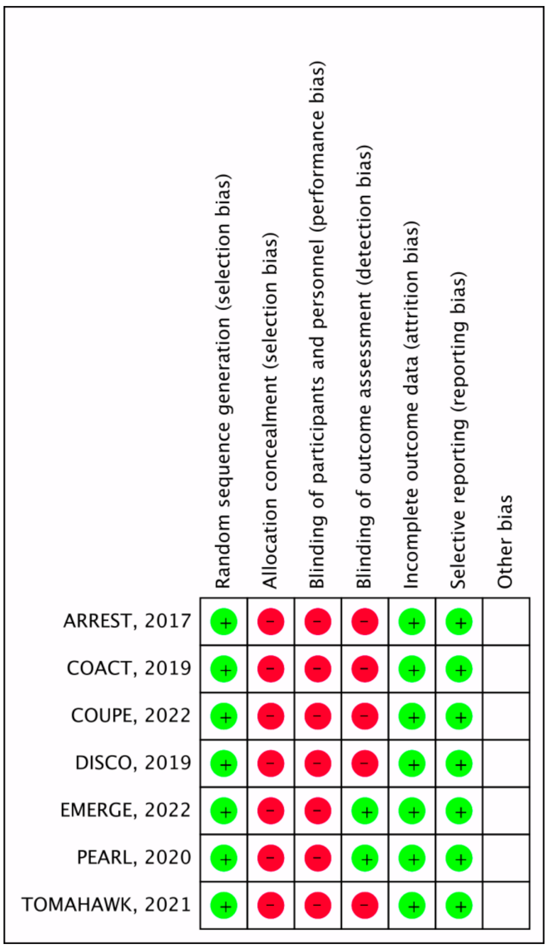

Figure 4: The image illustrates the risk of bias summary.

Table 1: Study Design of the Included Randomized Controlled Trials (RCTs)

RCT Year	Median Time to CAG post-Arrest (Range)	Inclusion Criteria	Exclusion Criteria	Initial Rhythm	Neurological Outcome
ARREST 2017	I: 100 (75-113) min C: 132 (93-187) min	OHCA	STEMI, noncardiac causes of the arrest	Shockable only	CPC
COACT 2019	I: 2.3 (1.8-3.0) h C: 121.9 (52-197.3) h	OHCA	STEMI, noncardiac causes of the arrest	Shockable only	CPC
DISCO 2019	I: 69 (42-94) min C: NA	OHCA	STEMI, noncardiac causes of arrest, New LBBB	Any	NA
PEARL 2020	I: <120 min C: >6 h	OHCA	STEMI, noncardiac causes of arrest, New LBBB	Any	CPC
TOMAHAWK 2021	I: 2.9 (2.2-3.9) h C: 46.9 (26.1-116.6) h	OHCA in >30 years old	STEMI, noncardiac causes of arrest, New LBBB	Any	CPC
COUPE 2022	I: 2.7 (1.6-3.4) C: 129 (87-186) h	OHCA, ROSC < 60 min	STEMI, noncardiac causes of arrest, New LBBB	Any	CPC
EMERGE 2022	I: 2 (2-3) h C: 65.5 (40.8-74.8) h	OHCA	STEMI, IHCA, noncardiac causes of arrest, life expectancy < 1 year	Any	CPC

CAG: coronary angiography; I: intervention group (with early angiography); C: control group (with delayed or selective angiography); OHCA: out-of-hospital cardiac arrest; STEMI: ST-elevation myocardial infarction; CPC: cerebral performance category; NA: not available; LBBB: left bundle branch block; ROSC: return of spontaneous circulation; IHCA: in-hospital cardiac arrest; ARREST: a randomized trial of expedited transfer to a cardiac arrest center for non-ST-elevation ventricular fibrillation out-of-hospital cardiac arrest; COACT: coronary angiography after cardiac arrest; DISCO: direct or subacute coronary angiography in out-of-hospital cardiac arrest; PEARL: randomized pilot clinical trial of early coronary angiography vs no early coronary angiography after cardiac arrest without ST-segment elevation; TOMAHAWK: angiography after out-of-hospital cardiac arrest without ST-segment elevation; COUPE: coronary angiography in out-of-hospital cardiac arrest; EMERGE: emergency vs delayed coronary angiogram in survivors of out-of-hospital cardiac arrest

Table 2: Patient Demographics in the Included Randomized Controlled Trials

RCT Year	I (n)	C (n)	Follow-up	Mean Age (y)	Male (%)	Prior Myocardial Infarction (I/C) (%)	Diabetes Mellitus (I/C) (%)	Hypertension (I/C) (%)	Smoking (I/C) (%)	Stroke (I/C) (%)
ARREST 2017	18	15	30 d	61.0	86	28.0/17.0	22/11	44/39	22/17	NA
COACT 2019	273	265	365 d	65.3	78.9	26.7/28.7	20.2/16.6	48.7/47.5	20.1/26.9	7.0/5.7
DISCO 2019	38	40	7 d	70.5	67.7	15.8/20.0	15.8/25.0	NA	NA	15.8/10.0
PEARL 2020	49	50	180 d	65.2	78.8	20.4/14.0	22.4/32.0	53.1/58	NA	12.2/2
TOMAHAWK 2021	265	265	365 d	70.0	69.6	19.3/19.8	29.1/29.5	67.1/69.2	29.9/34.5	10.5/8.9
COUPE 2022	32	34	3 yr.	63.5	77.4	21.9/29.4	15.6/30.3	68.8/66.7	21.9/29.4	NA
EMERGE 2022	141	138	180 d	64.6	69.9	NA	NA	NA	NA	NA

I: intervention group (with early angiography); C: control group (with delayed or selective angiography); NA: not available; ARREST: a randomized trial of expedited transfer to a cardiac arrest center for non-ST-elevation ventricular fibrillation out-of-hospital cardiac arrest; COACT: coronary angiography after cardiac arrest; DISCO: direct or subacute coronary angiography in out-of-hospital cardiac arrest; PEARL: randomized pilot clinical trial of early coronary angiography vs no early coronary angiography after cardiac arrest without ST-segment elevation; TOMAHAWK: angiography after out-of-hospital cardiac arrest without ST-segment elevation; COUPE: coronary angiography in out-of-hospital cardiac arrest; EMERGE: emergency vs delayed coronary angiogram in survivors of out-of-hospital cardiac arrest

Table 3: Sensitivity Analysis

Study	Mortality	Favorable Neurological Prognosis
Final outcome	1.07 [0.87, 1.31]	0.97 [0.78, 1.19]
Trials excluded		
ARREST 2017	1.06 [0.86, 1.30]	0.96 [0.78, 1.19]
COACT 2019	1.05 [0.82, 1.35]	0.98 [0.75, 1.28]
DISCO 2019	1.09 [0.88, 1.33]	-
PEARL 2020	1.10 [0.89, 1.36]	0.94 [0.76, 1.17]
TOMAHAWK 2021	0.96 [0.75, 1.24]	1.05 [0.81, 1.36]
COUPE 2022	1.08 [0.88, 1.33]	0.95 [0.77, 1.18]
EMERGE 2022	1.11 [0.89, 1.39]	0.93 [0.74, 1.18]

Values are presented as odds ratios [95% confidence intervals].

ARREST: a randomized trial of expedited transfer to a cardiac arrest center for non-ST-elevation ventricular fibrillation out-of-hospital cardiac arrest; COACT: coronary angiography after cardiac arrest; DISCO: direct or subacute coronary angiography in out-of-hospital cardiac arrest; PEARL: randomized pilot clinical trial of early coronary angiography vs no early coronary angiography after cardiac arrest without ST-segment elevation; TOMAHAWK: angiography after out-of-hospital cardiac arrest without ST-segment elevation; COUPE: coronary angiography in out-of-hospital cardiac arrest; EMERGE: emergency vs delayed coronary angiogram in survivors of out-of-hospital cardiac arrest

DISCUSSION

This updated meta-analysis shows no mortality or neurological outcomes benefit when early coronary angiography is performed in OHCA patients without STEMI compared with delayed angiography or usual care.

Of all the OHCA cases reported in the CARES registry in 2021, 9.1% eventually survived to hospital discharge, and 7.2% were discharged with Cerebral Performance Categories Scale (CPC) 1 or 2. [1] Better survival was noticed among patients with initial shockable rhythm compared with non-shockable rhythm (26.0% vs 5.8%; *P*<0.0001). Significant coronary artery disease is seen in patients with initial shockable rhythm and those with STEMI on the post-resuscitation ECG. [17,18] However, cardiac arrest patients without STEMI have a low incidence of acute coronary lesions (15–20%). [2] Hence, current guidelines have a class 1 recommendation of performing early angiography in cardiac arrest with STEMI patients, whereas the management of those without STEMI has been a topic of debate. [4]

In a retrospective study of cardiac arrest patients, Kern et al [3] reported that early coronary angiography has similar survival rates (54.7% vs 57.9%; *P*=0.60) but better functional outcomes regardless of the ECG finding (with or without STEMI). Similarly, as other observational studies reported better outcomes in patients without STEMI, the 2015 guidelines recommended early angiography in select cases of OHCA patients. [19] Patterson et al [6] conducted a trial of OHCA patients with non-STEMI and ventricular fibrillation randomized to either the intervention group (emergent angiography if needed) or the control (angiography in 48–72 hours if needed). No difference in mortality, neurological outcomes, or major cardiovascular events was noted between the groups. Nonetheless, the study was underpowered. This finding led to the start of multiple other randomized trials which reported similar results of no difference between early and delayed angiography in non-STEMI patients; hence, the 2020 cardiac arrest guidelines advised that these patients be managed similarly to other ACS (non-STEMI) patients where timing of angiography is based on clinical characteristics rather than routine early angiography. [4]

The recent COUPE trial (2022) found no significant difference in the in-hospital mortality between the 2 groups (HR, 0.96; 95% CI, 0.45 to 2.09; *P*=0.93), but it was limited by allocation bias and a smaller number of enrolled patients. [13] Similar outcomes were also found in the EMERGE trial in terms of mortality and neurological sequelae. [14] Our results align with those of the RCTs. In a large national inpatient registry study of 49,861 OHCA patients with non-STEMI, a decreasing trend was observed with regard to performing early angiography compared with a delayed strategy and with similar mortality in the 2 groups. [20] A recent meta-analysis by Heyne et al [21] of RCTs and non-randomized studies showed improved survival rates in patients undergoing early angiography but no difference in the sub-analysis of only RCTs. Similarly, Lawati et al [22] found no significant mortality and neurological benefits with early angiography. Our study had a similar result with a larger patient sample and the latest reported the long-term follow-up of the TOMAHAWK trial. [23]
This meta-analysis has some limitations. As a study-level analysis, differences at the patient level may be overlooked, leading to results that are subject to bias similar to those in individual trials. Further, many of the studies included were underpowered for the outcomes, which impacted the overall results. In addition, the duration of the mortality outcome varies between the studies, making it difficult to interpret for generalization. Further ongoing and future trials may provide better information as to whether such patients should receive standardized early angiography in every case. [24]

CONCLUSIONS

Early coronary angiography in OHCA patients without STEMI does not confer any benefit in terms of mortality or neurological outcomes compared with delayed or selective angiography.

Conflict of Interest
The authors declare that there are no conflicts of interest.

Funding
The authors received no financial support for their research, authorship, or publication of this article.

Ethical Approval

Not applicable

Informed Consent

Not applicable

REFERENCES

1. 2021 CARES Annual Report. https://mycares.net/sitepages/uploads/2022/2021_flipbook/index.html?page=1

2. Dumas F, Cariou A, Manzo-Silberman S, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. Circ Cardiovasc Interv. 2010 Jun 1;3(3):200-7.

3. Kern KB, Lotun K, Patel N, et al. Outcomes of Comatose Cardiac Arrest Survivors With and Without ST-Segment Elevation Myocardial Infarction: Importance of Coronary Angiography. JACC Cardiovasc Interv. 2015 Jul; 8(8):1031-1040.

4. Panchal AR, Bartos JA, Cabañas JG, et al. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020 Oct 20; 142(16_suppl_2):S366-S468.

5. Garcia S, Drexel T, Bekwelem W, et al. Early Access to the Cardiac Catheterization Laboratory for Patients Resuscitated From Cardiac Arrest Due to a Shockable Rhythm: The Minnesota Resuscitation Consortium Twin Cities Unified Protocol. J Am Heart Assoc. 2016 Jan 7;5(1):e002670.

6. Patterson T, Perkins GD, Joseph J, et al. A Randomised tRial of Expedited transfer to a cardiac arrest centre for non-ST elevation ventricular fibrillation out-of-hospital cardiac arrest: The ARREST pilot randomised trial. Resuscitation. 2017 Jun; 115:185-191.

7. Lemkes JS, Janssens GN, van der Hoeven NW, et al. Coronary Angiography after Cardiac Arrest without ST-Segment Elevation. N Engl J Med. 2019 Apr 11; 380(15):1397-1407.

8. Elfwén L, Lagedal R, Nordberg P, et al. Direct or subacute coronary angiography in out-of-hospital cardiac arrest (DISCO)-An initial pilot-study of a randomized clinical trial. Resuscitation. 2019 Jun; 139:253-261.

9. Kern KB, Radsel P, Jentzer JC, et al. Randomized Pilot Clinical Trial of Early Coronary Angiography Versus No Early Coronary Angiography After Cardiac Arrest Without ST-Segment Elevation: The PEARL Study. Circulation. 2020 Nov 24; 142(21):2002-2012.

10. Desch S, Freund A, Akin I, et al. Angiography after Out-of-Hospital Cardiac Arrest without ST-Segment Elevation. N Engl J Med. 2021 Dec 30; 385(27):2544-2553.

11. Alves N, Mota M, Cunha M, et al. Impact of emergent coronary angiography after out-of-the-hospital cardiac arrest without ST-segment elevation - A systematic review and meta-analysis. Int J Cardiol. 2022 Oct 1; 364:1-8.

12. Abusnina W, Al-Abdouh A, Latif A, et al. Timing of Coronary Angiography in Patients Following Out-of-Hospital Cardiac Arrest Without ST-Segment Elevation: A Systematic Review and Meta-Analysis of Randomized Trials. Cardiovasc Revasc Med. 2022 Jul; 40:92-98.

13. Viana-Tejedor A, Andrea-Riba R, Scardino C, et al. Coronary angiography in patients without ST-segment elevation following out-of-hospital cardiac arrest. COUPE clinical trial. Rev Esp Cardiol (Engl Ed). 2023 Feb; 76(2):94-102. English, Spanish.

14. Hauw-Berlemont C, Lamhaut L, Diehl JL, et al. Emergency vs Delayed Coronary Angiogram in Survivors of Out-of-Hospital Cardiac Arrest: Results of the Randomized, Multicentric EMERGE Trial. JAMA Cardiol. 2022 Jul 1; 7(7):700-707.

15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29; 372:n71.

16. Review Manager 5 (RevMan 5) [Computer program]. Version 5.4. Copenhagen: The Cochrane Collaboration, 2020.

17. McFadden P, Reynolds JC, Madder RD, et al. Diagnostic test accuracy of the initial electrocardiogram after resuscitation from cardiac arrest to indicate invasive coronary angiographic findings and attempted revascularization: A systematic review and meta-analysis. Resuscitation. 2021 Mar; 160:20-36.

18. Spaulding CM, Joly LM, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med. 1997 Jun 5; 336(23):1629-33.

19. Callaway CW, Donnino MW, Fink EL, et al. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015 Nov 3; 132 (18 Suppl 2):S465-82.

20. Elkaryoni A, Saad M, Elgendy IY, et al. Trends in Timing of Coronary Angiography in Patients With Out-of-Hospital Cardiac Arrest and Non-ST Elevation Myocardial Infarction: A Real-World Analysis. Am J Cardiol. 2022 Jun 15; 173:160-162.

21. Heyne S, Macherey S, Meertens MM, et al. Coronary angiography after cardiac arrest without ST-elevation myocardial infarction: a network meta-analysis. Eur Heart J. 2023 Mar 21; 44(12):1040-1054.

22. Al Lawati K, Forestell B, Binbraik Y, et al. 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. Crit Care Explor. 2023 Feb 24; 5(3):e0874.

23. Desch S, Freund A, Akin I, et al. Coronary Angiography After Out-of-Hospital Cardiac Arrest Without ST-Segment Elevation: One-Year Outcomes of a Randomized Clinical Trial. JAMA Cardiol. 2023 Sep 1; 8(9):827-834.

24. Direct or Subacute Coronary Angiography in Patients With Out of Hospital Cardiac Arrest Without Coma. (DISCO-noCOMA). https://clinicaltrials.gov/ct2/show/NCT04876222