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Review

Optimal timing of coronary intervention in patients resuscitated from cardiac arrest without ST-segment elevation myocardial infarction (NSTEMI): A systematic review and meta-analysis

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Abstract

Objective: Performing immediate coronary angiography (CAG) in patients with a cardiac arrest and a non-ST-elevation myocardial infarction (NSTEMI) remains a highly debated topic. We performed a meta-analysis aiming to evaluate the influence of immediate, delayed, and no CAG in patients with cardiac arrest and NSTEMI.

Methods: A comprehensive literature review of Pubmed/MEDLINE, Cochrane Library, and Embase was performed for all studies that compared immediate CAG to delayed or no CAG in the setting of cardiac arrest and NSTEMI. The primary outcome was long-term mortality and secondary outcomes included short-term mortality and a Cerebral Performance Category (CPC) score of 1–2 at the longest follow-up period. A random-effects model was used to report odds ratios (ORs) with Bayesian 95% credible intervals (CrIs), and ORs with 95% confidence intervals (CIs) for both network and direct meta-analyses, respectively.

Results: 11 studies were included in the final analysis: 8 observational, 1 post-hoc analysis and 2 randomized trials, totaling 3702 patients. The mean age was 63.8 ± 12.8 years with 78% males. We found that immediate and delayed CAG were associated with lower long-term mortality when compared to no CAG (OR 0.21; 95% CrI 0.05–0.82) and (OR 0.11; 95% CrI 0.03–0.43), as well as lower short-term mortality (OR 0.17; 95% CrI 0.04–0.64) and (OR 0.07; 95% CrI 0.01–0.29), respectively. In addition, immediate and delayed CAG were associated with a significantly higher number of patients with a CPC score of 1–2 (OR 4.15; 95% CrI 1.10–16.10) and (OR 4.67; 95% CrI 1.53–15.12), respectively. There were no significant differences between immediate or delayed CAG regarding long-term mortality, short-term mortality, or favorable CPC score.

Conclusions: Among patients who survived cardiac arrest with an NSTEMI, CAG is associated with a higher rate of survival and favorable neurological outcomes compared with no CAG. There were no differences between immediate and delayed strategies.

Keywords: Cardiac arrest, NSTEMI, Non-ST elevation, Survival, Meta-analysis

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Introduction

Despite major advancements in cardiopulmonary resuscitation, cardiac arrest remains a leading cause of mortality.[1,2] Post-resuscitation care often remains challenging as the reason behind the cardiopulmonary arrest is often not clear immediately following the arrest when treatment is most vital.[2,3]

Cardiac pathology leading to cardiac arrest, mainly coronary artery disease, is thought to be responsible for nearly 70% of cardiac arrest cases that undergo emergent coronary catheterization.[4,5] Although acute total occlusion of the culprit artery was more frequently encountered in ST-elevation myocardial infarction (STEMI) arrests, up to one-third of the cardiac arrest cases occur following non-ST-elevation myocardial infarction (NSTEMI).[6] In the case of STEMI cardiac arrest, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and the European Society of Cardiology (ESC) recommend immediate coronary angiography (CAG) with percutaneous coronary intervention (PCI), if indicated (Class 1B).[7,8] However, data regarding the urgency of coronary angiography (CAG) in patients with a high suspicion of an ongoing myocardial infarction is still limited due to lack of large randomized controlled trials (RCTs).[7–9]

Recently, many studies have demonstrated a growing interest regarding the need for immediate CAG in cardiac arrest and NSTEMI, however, these have shown conflicting results with preceding published studies.[3,10–12] Thus, we conducted our study to assess the efficacy of CAG in cardiac arrest and NSTEMI.

Methods

Literature search

This meta-analysis and systematic review was conducted according to the Cochrane Handbook for Systematic Reviews and Interventions, and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42019129828). A comprehensive literature search of Pubmed/MEDLINE, Cochrane Library, and Embase was performed for relevant studies by two authors (O.B. and Y.Z.), with the input of a third author to resolve disagreements (B.K.), from inception to March 28, 2019. The following keyword MeSH terms were searched: “cardiac arrest”; “heart arrest”; “coronary angiography”; “CAG”; “catheterization”; “catheterisation”; “revascularization”; “reperfusion”; “early”; “emergent”; “immediate”; “urgent”; “delayed”; and “late” with no language restrictions. The references of the included studies, published meta-analyses, and systematic reviews were also screened to ensure the completeness of the included studies.

Eligibility criteria

Only studies that compared immediate or early CAG with delayed or no CAG in the setting of cardiac arrest and NSTEMI were included in this study. These studies consisted of RCTs, post-hoc analyses, observational studies, and cohort studies. Studies that reported outcomes for acute coronary syndrome (both STEMI and NSTEMI) without distinguishing the NSTEMI patients’ outcomes were excluded.

Data extraction

Two independent authors (A.A. & H.D.) extracted relevant data into a predesigned standardized data collection table. Any discrepancies between authors were resolved by an independent third investigator (O.B.).

Quality assessment

Quality assessment of the observational trials was conducted by utilizing the Newcastle Ottawa Scale, whereas the quality assessment for RCTs was conducted using the Jadad scale (eTables 1–2, Supplement 1).

Outcomes of interest

Our analysis focused closely on three outcomes. First, long-term mortality was defined as the reported mortality at the longest reported follow-up period. Second, short-term mortality was defined as the reported mortality $\leq$30 days of admission. Finally, neurological outcome was defined as the number of patients with a Cerebral Performance Category (CPC) score of 1 (Normal) or 2 (mild or moderate functional impairment, but independent) at the end of the follow-up period. The 5-item scale of the CPC was implemented according to the Utstein guidelines: CPC 3 indicates conscious with severe neurological disability and dependent, CPC 4 indicates coma or vegetative state, and CPC 5 indicates deceased.[14]

Statistical analysis

In performing our network analysis, we used the Markov Chain Monte Carlo (MCMC) simulation, with random-effects for the consistency model, to report odds ratios (ORs) and Bayesian 95% credible intervals (CrIs); this was conducted with vague prior distributions and likelihood functions to derive the posterior distribution of the parameters. Our analyses were conducted using NetMetaXL v1.6.1, and WinBUGS v1.4.3 software.

Results

After screening 1763 studies, 1698 studies were excluded and a total of 65 studies were fully assessed for inclusion (eFig. 1). 11 studies were included in the final analysis totaling 3702 patients, of whom, 1602 underwent immediate CAG, 1094 underwent delayed CAG, and 1006 received no CAG.[3,6,10,11,15–21] The mean age was 63.8 $\pm$ 12.8 years with 78% male. The longest follow-up duration was 12 months. There was mild variability in the definition of immediate CAG, but the majority defined it as less than 2 h.[3,6,10,18–21] 3 of the included trials defined the early CAG as within the first 24 h,[11,16,17] however, 2 of these trials reported the median time of early CAG as 2 h.[11,16] 8 of the included studies were observational,[6,10,11,16–20] 1 was a post-hoc analysis of the target temperature management (TTM) trial,[15] and 2 were RCTs.[3,21] Of these studies, 7 included only NSTEMI cardiac arrest,[3,10,11,15,17,20,21] and 5 studied acute coronary syndrome but reported outcomes for NSTEMI separately.[6,16,18,19] 5 trials included only patients with ventricular arrhythmias.[3,11,17,19,21] The study characteristics and demographic features are illustrated in Tables 1 and 2, respectively. Angioplasty was performed more in the immediate

Table 1 – Characteristics of the involved studies.

Author/year of publication	Number of patients	Comparative treatment	Follow-up	Study's randomization period	Countries and number of centers
Bro-jeppesen 2012	244	Early vs late CAG in NSTEMI after OHCA.	At 1 month and 1 year	June 2004 to December 2010.	Denmark (Single center)
Hollenbeck 2014	269	Early vs late/no CAG in NSTEMI who were successfully resuscitated from VF/VT arrest	At discharge from the hospital	January 2005 to November 2011	USA (Multiple centers)
Reynolds 2014	191	Early vs late/no CAG in NSTEMI who were successfully resuscitated after cardiac arrest	At discharge from the hospital	January 2005 to December 2012	USA (Single center)
Dankiewicz 2015	544	Early vs no early CAG in NSTEMI after OHCA.	At 6 months	November 2010 to January 2013	Europe and Australia (Multiple centers)
Kern 2015	548	Early vs late/no CAG in NSTEMI who were successfully resuscitated	At discharge from the hospital	February 2006 to May 2011	Europe and USA (Multiple centers)
Kleissner 2015	99	Early vs late/no CAG in NSTEMI after OHCA.	At discharge from the hospital and after 6 months	January 2007 to June 2014	Czech Republic (Single center)
Garcia 2016	203	Early vs late/no CAG in NSTEMI who were successfully resuscitated from VF/VT arrest	At discharge from the hospital	January 2013 to December 2014	USA (Multiple centers)
Patterson 2017	40	Early vs late/no CAG in NSTEMI who were successfully resuscitated from VF/VT arrest	At discharge from the hospital and after 1 month	November 2014 to April 2016	UK (Multiple centers)
Elfwen 2018	799	Early vs late/no CAG in NSTEMI who were successfully resuscitated from VF/VT arrest	At discharge, after 1 month, 1 year, and 3 years	January 2008 to December 2013	Sweden (Multiple centers)
Kim 2019	227	Early vs early CAG in OHCA survivors without STE.	At 1 month	January 2010 to December 2015	Republic of Korea (Multiple centers)
Lemkes 2019	538	Early vs late CAG in OHCA with an initial shockable rhythm survivor without signs of STEMI.	At 3 months	January 2015 to July 2018	Netherlands (Multiple centers)

CAG: coronary angiography; NSTEMI: non-ST elevation myocardial infarction; OHCA: out-of-hospital cardiac arrest; STEMI: ST elevation myocardial infarction; UK: United Kingdom; USA: United State of America; VF: ventricular fibrillation; VT: ventricular tachycardia.

Table 2 – Demographic features of the involved studies.

Author/year of publication	No. of patients		Age Mean ± SD/median (IQR)	No. of male (%)	No. of witnessed (%)	GCS on presentation, median (IQR)	No. of BLS (%)	No. of VF/VT (%)	No. of asystole/ PEA (%)	No. of TH (%)	No. of prior CABG (%)	No. of prior PCI (%)	No. of CAD (%)	No. of DM (%)	No. of HTN (%)
Bro-jeppesen	Early	82	59 ± 14	67 (82)	70 (85)	≤8	47 (57)	74 (90)	8 (10)	80 (98)	–	–	21 (26)	12 (15)	24 (30)
2012	Late or no	162	62 ± 15	127 (78)	130 (80)	≤8	91 (56)	110 (68)	52 (32)	134 (83)	–	–	42 (27)	23 (15)	32 (21)
Hollenbeck	Early	122	60.4 ± 13.7	83 (68)	104 (85.3)	16 > 3[a]	66 (54.6)	122 (100)	0 (0)	122 (100)	–	–	–	–	–
2014	Late or no	147	59.9 ± 16.8	108 (73)	125 (85.6)	38 > 3[a]	86 (59.7)	147 (100)	0 (0)	147 (100)	–	–	–	–	–
Reynolds 2014	Early	128	62.9 ± 13.4	–	–	–	–	–	–	–	–	–	–	–	–
	Late or no	63		–	–	–	–	–	–	–	–	–	–	–	–
Dankiewicz	Early	252	65 (57–71)	204 (81)	227 (90)	–	184 (73)	202 (80)	50 (20)	252 (100)	–	–	86 (34)	38 (15)	114 (46)
2015	Late or no	292	68 (59–77)	227 (78)	262 (90)	–	200 (68)	207 (71)	85 (29)	292 (100)	–	–	94 (32)	53 (18)	114 (39)
Kern 2015	Early	183	–	–	–	56 > 3[a]	–	–	–	–	–	–	–	–	–
	Late or no	365	–	–	–		–	–	–	–	–	–	–	–	–
Kleissner 2015	Early	25	59 ± 11	23 (92)	12 (48)	–	13 (52)	22 (88)	–	25 (100)	–	–	10 (40)	–	–
	Late or no	74	58 ± 18	55 (74)	30 (41)	–	31 (42)	51 (69)	–	74 (100)	–	–	24 (39)	–	–
Garcia 2016	Early	130	55.6 ± 10.8	177(77)	152 (66)	–	100 (43)	130 (100)	0(0)	–	9 (4)	28 (12)	–	–	–
	Late or no	73	54.5 ± 1.93	65 (77)	53 (53)	–	37 (44)	73 (100)	0(0)	–	9 (11)	10 (12)	–	–	–
Patterson 2017	Early	20	60 ± 17	15 (83)	18 (100)	3 (3–14)	10 (56)	18 (100)	0 (0)	–	2 (11)	2 (11)	6 (33)	4 (22)	8 (44)
	Late or no	20	61 ± 14	16 (89)	18 (100)	4 (3–10)	12 (67)	18 (100)	0 (0)	–	1 (6)	3 (17)	5 (28)	2 (11)	7 (39)
Elfwen 2018	Early	275	64 (57-70)	227 (82)	275 (100)	≤8	199 (73)	275 (100)	0 (0)	–	–	5 (2)	31 (11)	27 (10)	66 (24)
	Late or no	524	67 (58-74)	402 (76)	524 (100)	≤8	379 (73)	524 (100)	0 (0)	–	–	20 (4)	136 (26)	85 (16)	140 (27)
Kim 2019	Early	112	57.25 ± 13.31	85 (76)	84 (75)	–	57 (51)	49 (44)	63 (56)	112 (100)	–	–	12 (11)	33 (30)	44 (39)
	Late	115	57.23 ± 13.43	85 (74)	72 (62)	–	58 (50)	55 (48)	60 (52)	115 (100)	–	–	12 (10)	21 (18)	45 (39)
Lemkes 2019	Early	273	65.7 ± 12.7	223 (81.7)	218 (80)	3 (3–3)	–	273 (100)	0 (0)	257 (94)	43 (16)	46 (17)	99 (36)	55 (20)	131 (49)
	Late or no	265	64.9 ± 12.5	202 (76.2)	203 (77)	3 (3–3)	–	265 (100)	0 (0)	247 (93)	24 (9)	60 (23)	96 (36)	44 (17)	126 (47.5)

BLS: basic life support; CABG: coronary artery bypass graft; CAD: coronary artery disease; DM: diabetes mellitus; GCS: glasgow coma scale; HTN: hypertension; IQR: interquartile range; PCI: percutaneous coronary intervention; PEA: pulseless electrical activity; SD: standard deviation; TH: therapeutic hypothermia; VF: ventricular fibrillation; VT: ventricular tachycardia.

[a] Number of patients with GCS > 3.

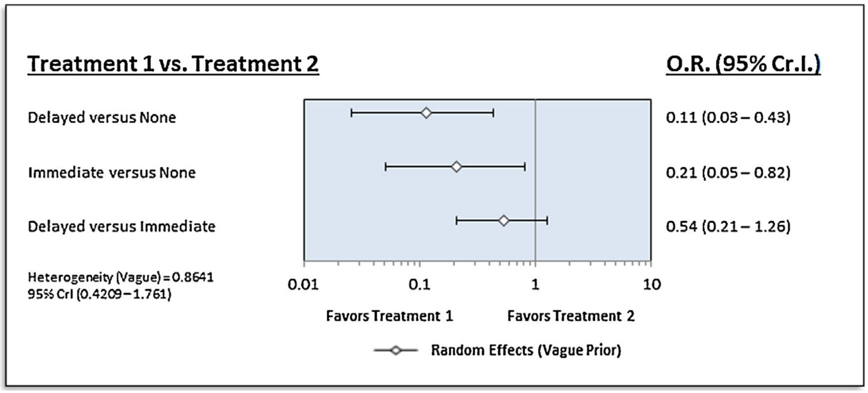

Fig. 1 – The network analysis demonstrating the results of the long-term mortality in patients with immediate, delayed, and no CAG.

CAG group (38%) compared to delayed CAG (24%) ($P < 0.001$). The angiographic findings of each study is illustrated in eTable 3.

Clinical outcomes

Performing CAG, either immediate or delayed, was associated with a significantly lower long-term mortality when compared to no CAG (OR 0.21; 95% CrI 0.05–0.82) and (OR 0.11; 95% CrI 0.03–0.43), respectively (Fig. 1). Furthermore, patients who underwent either immediate or delayed CAG were associated with a significantly lower short-term mortality (OR 0.17; 95% CrI 0.04–0.64) and (OR 0.07; 95% CrI 0.01–0.29), respectively, and these groups had more patients with CPC scores of 1–2 when compared with no CAG (OR 4.15; 95% CrI 1.10–16.10) and (OR 4.67; 95% CrI 1.53–15.12), respectively (Figs. 2 and 3). There were no significant differences between immediate and delayed CAG with regard to long-term mortality, short-term mortality, and favorable neurological outcomes (OR 0.54; 95% CrI 0.21–1.26), (OR 0.44; 95% CrI 0.13–1.25) and (OR 1.12; 95% CrI 0.43–3.05), respectively (Figs. 1–3).

Discussion

In this network meta-analysis of 11 studies that evaluated the timing of CAG in patients with various cardiac arrest rhythms,[3,6,10,11,15–21] we found that both immediate and delayed CAG was associated with lower long-term and short-term mortality when compared with no CAG in patients who presented with cardiac arrest and NSTEMI. Furthermore, the number of patients with good neurologic outcomes (CPC score of 1–2) was significantly higher in patients treated with immediate or delayed CAG when compared to those without CAG. Finally, there was no difference between immediate and delayed CAG regarding long-term mortality, short-term mortality and good neurologic outcomes.

A previously published meta analysis by Khan et al. showed that immediate CAG had more favorable outcomes than delayed or no CAG regarding survival and neurologic outcomes.[12] By including 3 additional studies in our analysis, we have increased power and were able to study the influence of CAG time frames; we found that outcomes were comparable between the immediate and delayed CAG, while both were significantly better than no CAG in patients with cardiac arrest and NSTEMI. This was consistent with several randomized trials that revealed no mortality benefit of immediate CAG when compared with late CAG in NSTEMI but without cardiac arrest.[22,23]

The ACCF/AHA/ESC guidelines recommend emergent CAG with PCI, if needed, as a reasonable approach for select comatose patients who survive the cardiac arrest, and who have features of a high risk NSTEMI, such as electrical or hemodynamic instability (Class IIa).[24] While less common than in STEMI, a significant number of patients with NSTEMI do have an acute thrombus occluding a coronary artery that is silent on electrocardiogram (ECG).[25] Thus, if the cardiac arrest

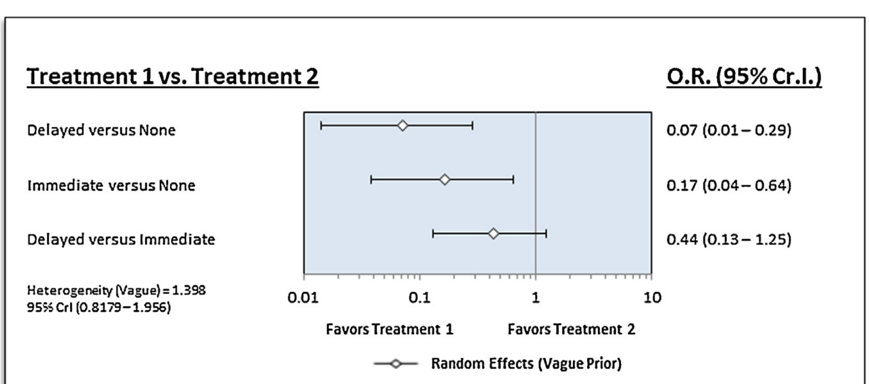

Fig. 2 – The network analysis demonstrating the results of the short-term mortality in patients with immediate, delayed, and no CAG.

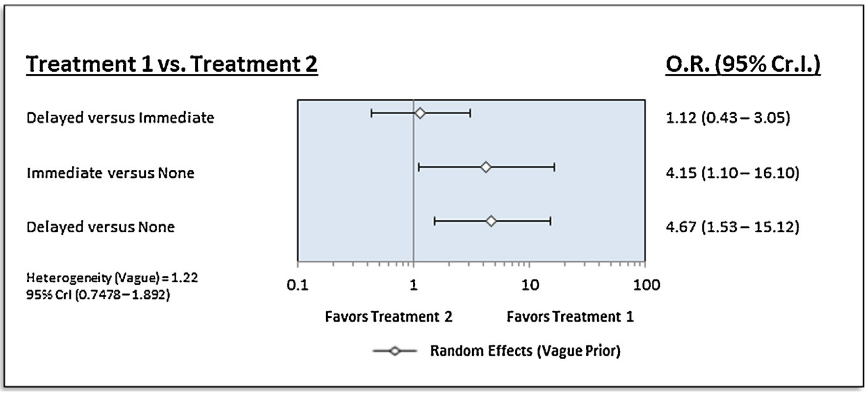

Fig. 3 – The network analysis demonstrating the results of the neurologic outcomes with a CPC score of 1–2 in patients with immediate, delayed, and no CAG.

stems from an acute thrombus, immediate CAG with PCI can save myocardium, prevent the recurrence of malignant arrhythmias, and preserves native circulation.[4] This was supported by Kern et al. and Garcia et al., who reported an acute culprit occlusion in 30% and 60% of their NSTEMI group, and perfoming an immediate CAG in this group showed better survival and more favorable neurologic outcomes.[6,19] However, the Coronary Angiography after Cardiac Arrest (COACT) trial, which is the only large RCT intended to evaluate the efficacy of immediate CAG in cardiac arrest with NSTEMI, did not provide data consistent with these observational studies regarding the survival and neurologic benefit of immediate CAG when compared with delayed CAG. This may be attributed to the paucity of acute thrombotic occlusion of the coronary artery in the immediate CAG group of the COACT trial (5%),[3] as well as the fact that PCI has no survival benefit as an initial management approach in stable coronary artery disease.[26] This discrepancy may be related to the potential risk of selection and treatment biases present in the included observational studies, which comprise over 70% of our studied patients.[6,10,11,16–20] Another explanation for the lack of survival benefit with immediate CAG in the COACT trial is that most of the non-survivors died due to brain anoxia from the cardiopulmonary arrest.[3] This is consistent with many other resuscitation studies which have reported cerebral injury as the main cause of death. Based on the fact that cerebral injury comprises nearly three times that of primary cardiac dysfunction regarding final cause of death,[27,28] it can be argued that the benefit of pursuing immediate CAG as a first line of resuscitation in patients who presented with cardiac arrest and NSTEMI is substantial.[3]

The neurological status of the surviving patients following cardiac arrest and NSTEMI who underwent immediate or delayed CAG were significantly better when compared with no CAG, while there was no difference between immediate and delayed CAG. This finding was supported by the COACT trial, which showed a comparable number of patients with a good neurologic status in both the immediate and delayed CAG group.[3] While the benefit of early targeted temperature management is still unclear,[29] in the COACT trial there was a delay in initiation and time to reach the targeted temperature during post-resuscitation care in the immediate CAG group, which may have contributed to the lack of neurological benefit in this group. On the other hand, the required time to reach the targeted temperature in the immediate CAG group was shorter than the delayed/no CAG group in the studies done by Hollenbek et al.[17] and Kleissner et al.,[20] and the immediate CAG patients were found to have significantly better neurological outcomes.

Overall, immediate or delayed CAG in patients with cardiac arrest and NSTEMI have improved survival and neurological outcomes when compared with delayed or no CAG. However, when comparing immediate CAG to delayed CAG, there is no survival or improved neurological recovery benifits. This is consistent with the management of NSTEMI in patients without cardiac arrest, and raises questions regarding the importance and benefits of immediate CAG in the delicate phase of post-resuscitation, as mobilizing the patient may affect cardiopulmonary monitoring. Moreover, introducing contrast may harm the kidneys, especially in hypotensive patients.[30] Currently, there are several RCTs (NCT02387398, NCT02309151 and NCT02750462) underway aiming to evaluate the benefit of early CAG in cardiac arrest with NSTEMI. These trials will build upon the current evidence, as most of the included trials in this analysis are observational studies.[31]

Limitations

Our study has several limitations that should be taken into consideration while interpreting the results. First, most of the included studies are retrospective observational studies associated with observational bias, which was acknowledged in these studies, such as performance of immediate CAG in young patients, CAG in witnessed arrests, CAG in patients with short time to return of spontaneous circulation, and CAG in those who have a favorable resuscitation parameter.[10,11,16–19] Second, two randomized trials were included, of which, the study conducted by Patterson et al. was underpowered. Third, there was a variability regarding the definition of immediate CAG and delayed CAG between the included studies, which may contribute to the heterogeneity of the results. Finally, all types of cardiac arrest rhythms have been included in this meta-analysis, which may be a potential confounder as patients with different cardiac rhythms have different presumed incidence of coronary occlusion as shown by previous observational studies.[18,32]

Conclusions

Among patients who survived a cardiac arrest with NSTEMI, CAG had superior survival and neurological outcomes when compared to no CAG, and there was no benefit in performing the CAG emergently. These recommendations can be confirmed or altered following publication of the RCTs in process, as this study is based largely on retrospective observational studies.

Author contributions

Mahmoud Barbarawi, Yazan Zayed, and Babikir Kheiri: Conceptualization. Mahmoud Barbarawi, Yazan Zayed, Babikir Kheiri and Owais Barbarawi: Data curation. Mahmoud Barbarawi, Yazan Zayed, Babikir Kheiri, Owais Barbarawi, Ahmad Al–Abdouh, Harsukh Dhillon, Fatima Rizk, Ghassan Bachuwa and Mohammad L. Alkotob: Formal analysis and Methodology. Mahmoud Barbarawi, Ghassan Bachuwa and Mohammad L. Alkotob: Supervision and Validation. Mahmoud Barbarawi: Writing-original draft. Mahmoud Barbarawi, Yazan Zayed, Babikir Kheiri and Mohammad L. Alkotob: Writing-review and editing.

Conflicts of interest

All authors report no relationships that could be construed as a conflict of interest.

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CRediT authorship contribution statement

Mahmoud Barbarawi: Supervision. **Ghassan Bachuwa:** Supervision. **Mohammad L. Alkotob:** Supervision.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.06.279.

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