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Clinical paper

Early coronary angiography in patients resuscitated from out of hospital cardiac arrest without ST-segment elevation: A systematic review and meta-analysis

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A R T I C L E I N F O

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Objective: A meta-analysis of published studies was performed to determine the impact of performing early versus delayed or no coronary angiography in patients without ST-segment elevation myocardial infarction following out of hospital cardiac arrest.
Methods: A structured search was conducted using Medline, Embase and Ovid by two independent investigators using a variety of keywords. The primary outcome was short term (at discharge) and long term (at 6–14 months follow-up) mortality whereas the secondary end-point was good neurological outcome (defined as a Cerebral Performance Category Score of 1 or 2), at discharge and follow up. Random-effects model was utilized to pool the data, whilst publication bias was assessed using funnel plot.
Results: A total of 8 studies (7 observational studies and 1 randomized control trial) were identified and incorporated into the meta-analysis. The use of early angiography was associated with decreased short term (OR = 0.46, 95% CI = 0.36–0.56, $P < 0.001$) and long term (OR = 0.59, 95%CI = 0.44–0.74, $P < 0.001$) mortality. Early angiography was also shown to be associated with improved neurological outcomes on discharge (OR = 2.00, 95% CI = 1.50–2.49, $P < 0.001$) as well as on follow-up (OR = 1.48, 95% CI = 1.06–1.90, $P < 0.001$).
Conclusion: The results of our meta-analysis support the use of early coronary angiography in out of hospital cardiac-arrest patients presenting without ST-segment elevation on the post-resuscitation electrocardiogram. However, given the low level of evidence of available studies, future guideline changes should be directed by the results of large-scale randomized clinical trials on the subject matter.

Introduction

Out of Hospital Cardiac Arrest (OHCA) is a major healthcare concern worldwide with more than 350,000 cases reported annually in the United States alone [1]. The management of this population of patients remains challenging with poor overall outcomes despite guideline directed measures [2], including adoption of therapeutic hypothermia (TH) [2]. Current American College of Cardiology/American Heart Association (ACC/AHA) and European Resuscitation Council (ERC)/European Society of Intensive Care Medicine (ESICM) clinical practice guidelines recommend emergent coronary angiography (CAG) and adjunctive percutaneous coronary intervention (PCI) as a Class I indication in patients with ST elevation myocardial infarction (STEMI), following OHCA [3,4]. The data is less robust in patients with OHCA presenting without ST-segment elevation myocardial infarction (NSTEMI), amongst

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Table 1
Demographic and baseline clinical variables of the included studies.

Reference	Group	Number	Age (years)	Men (%)	Witnessed (%)	GCS on presentation	BLS (%)	VF/VT (%)	Asystole/PEA (%)	PCI (%)	TH (%)
Bro-jeppesen, et al. [11]	Early/late or no CAG	82/162	59/62	82/78	85/80	≤ 8	57/56	90/68	10/32	29/15	98/83
Dankiewicz, et al. [12]	Early/late or no CAG	252/292	65/68	81/78	90/90	N/A	73/68	80/71	20/29	40/9	100/100
Garcia, et al. [16]	Early/late or no CAG	130/73	N/A	N/A	N/A	N/A	N/A	100/100	00/00	36/10	N/A
Hollenbeck, et al. [13]	Early/late or no CAG	122/147	61/63	68/73	85/85	≥ 3	54/59	100/100	00/00	33/11	100/100
Kern, et al. [5]	Early/late or no CAG	183/364	N/A	N/A	N/A	>3	N/A	N/A	N/A	N/A	N/A
Kleissner, et al. [14]	Early/late or no CAG	25/74	59/58	92/74	48/41	N/A	52/42	88/69	N/A	N/A	100/100
Patterson, et al. [15]	Early/late or no CAG	18/18	N/A	N/A	N/A	N/A	N/A	N/A	N/A	39/33	N/A
Reynolds, et al. [17]	Early/late or no CAG	128/63	63/60	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

BLS indicates By-stander basic life support; VF, Ventricular fibrillation; VT, Ventricular tachycardia; PEA, Pulseless electrical activity; PCI, Percutaneous coronary intervention and TH, Therapeutic hypothermia.

whom a quarter are noted to have acute total occlusion of the culprit vessel during coronary angiography [5]. While the current clinical guidelines by the AHA/ACC do suggest emergent angiography in a specific sub-set of NSTEMI patients who are comatose after OHCA, and are either hemodynamically or electrically unstable [6], the overall approach to OHCA patients and NSTEMI is not clear. We performed a meta-analysis of the available studies to assess the difference in outcomes between an emergent invasive approach compared with a delayed or non-invasive approach in patients with OHCA and NSTEMI.

Methods

We defined a structured study question pertaining to the Population, Intervention, Comparison and Outcomes (PICO) framework; "In patients with NSTEMI following OHCA (Population), does early CAG (Intervention), compared to late or no CAG (Comparison), improve neurologic function and mortality rate, as measured at discharge and follow up (Outcome)?"

A comprehensive literature search was performed in accordance with the principles of the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement [7]. Two independent operators (MS and AM) conducted the search using the databases PubMed, Embase, Ovid, Cochrane Central Register of Controlled Trials and Google Scholar. The search strategy employed was: "('OHCA' OR "out of hospital cardiac arrest" OR "out-of-hospital-cardiac-arrest" OR "heart arrest" OR "cardiac arrest") AND ("coronary angiography" OR "coronary angiogram" OR "CAG" OR "catheterization" OR "catheterisation" OR "PCI" OR "percutaneous coronary intervention" OR "angioplasty" OR "revascularization" OR "reperfusion") AND ("early" OR "emergent" OR "urgent" OR "immediate" OR "delayed" OR "late")". This search strategy was further adapted to maximize acquisition of all pertinent articles, per each database searched. The time-period of the search was from inception of these databases until 4th February 2017. After exhausting the above-mentioned databases, snowballing from pertinent articles was rigorously performed to ensure no relevant articles were overlooked. Lastly, Grey Literature Databases and Clinical Trials Databases were searched. All identified articles were compiled using Endnote.

Only studies that answered the specific PICO question were included, keeping relevance in mind. These consisted of randomized controlled trials (RCTs), cohort studies and observational studies. Letters to the editor, reviews, case reports, commentaries, duplicates and conference abstracts were excluded following screening of abstracts by each reviewer. Furthermore, studies which failed to quantitatively describe study outcomes, such as mortality and neurological status at discharge or follow up, were also excluded. Evaluation of full text articles for analysis was performed by both reviewers, and any conflict arising over study inclusion was resolved by mutual consensus. Data from eligible manuscripts were extracted onto a predetermined, standardized Excel spreadsheet which recorded study demographic characteristics and the baseline clinical, interventional and outcome details for the population of interest, as per Utstein data points [8]. For studies reporting outcomes in both STEMI and NSTEMI patients, following OHCA, only data pertaining to NSTEMI patients was extracted and applied in the analysis. Quality assessment was performed by two reviewers (MS and AM) for seven observational studies and one RCT. Observational studies were scored in accordance with the Newcastle Ottawa Scale (max score of 9), whereas RCTs were scored as per the Jadad Scale (max score of 5). Further evaluation of study quality was conducted in accordance with the GRADE approach, which provides a standardized and transparent tool for evaluation of risk of bias in reported outcomes across studies [9]. The same

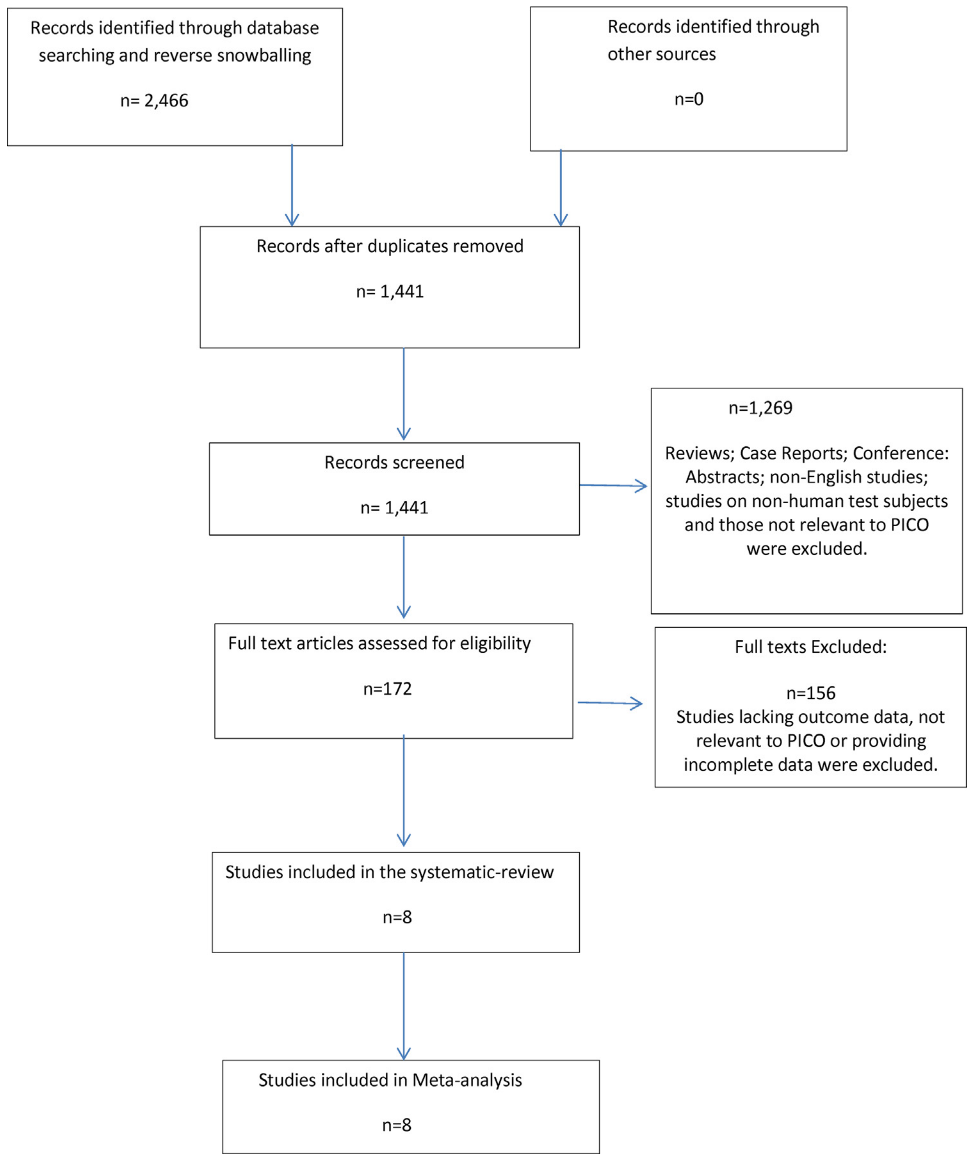

Fig. 1. Flow diagram highlighting the search strategy. PRISMA indicates Preferred Reporting Items for Systematic reviews and Meta-analyses.

has been adopted by the Cochrane collaboration for evaluation of evidence in systematic reviews [10].

Mortality and neurological outcomes were the end-points assessed in our analysis. Mortality was assessed at hospital discharge and during long-term follow up. The time to follow-up varied across the studies and ranged from 6 to 14 months. Neurological outcomes were assessed in terms of Cerebral PC (cerebral performance categories) scores. Scores of 1–2 indicating consciousness with little or no cerebral damage were considered good scores. These scores were assessed at discharge and long term; which was defined as over a period of 6–14 months. Early CAG was defined differently in every study ranging from on admission, within 2 h of admission, or between 6 and 12 h after hospital admission. The time to angiography and assessment of outcomes were accepted as defined in the included studies.

STATA14 (StataCorp) was used to pool the data using random-effects model. Statistical heterogeneity was evaluated through I^2 statistics with values of >50% representing heterogeneity. Publication bias was assessed using Funnel plot. P values less than 0.05 were taken to be significant.

Results

A total of 1441 studies were identified after removal of duplicates. After further screening, 172 articles were then assessed in full for eligibility, resulting in the inclusion of 8 studies [5,11–17] (early vs delayed or no CAG, n = 940/1193) in the *meta*-analysis. Some studies were excluded due to the inability to differentiate between STEMI and NSTEMI subgroups from the heterogeneous population of OHCA patients [18–24]. The detailed literature search is highlighted in the PRISMA flow diagram (Fig. 1). Baseline demographic and clinical characteristics of the included studies are outlined in Table 1. Out of the 8 studies included, 7 were observational in nature; 6 of which were retrospective [5,12–14,16,17]and 1 was prospective [11]. One study was an RCT [15]. Quality scores (Supplementary Tables 1–3) of the included studies showed all the studies to be of good quality with the observational studies being 6–7/9 [5,11–14,16,17] on the Newcastle Ottawa Scale and the sole RCT with a score of 4/5 on the Jadad scale [15]. Majority of the studies were conducted in the US (n = 5) [5,13,14,16,17]. Four of the studies included only reported data on NSTEMI patients [12–15]

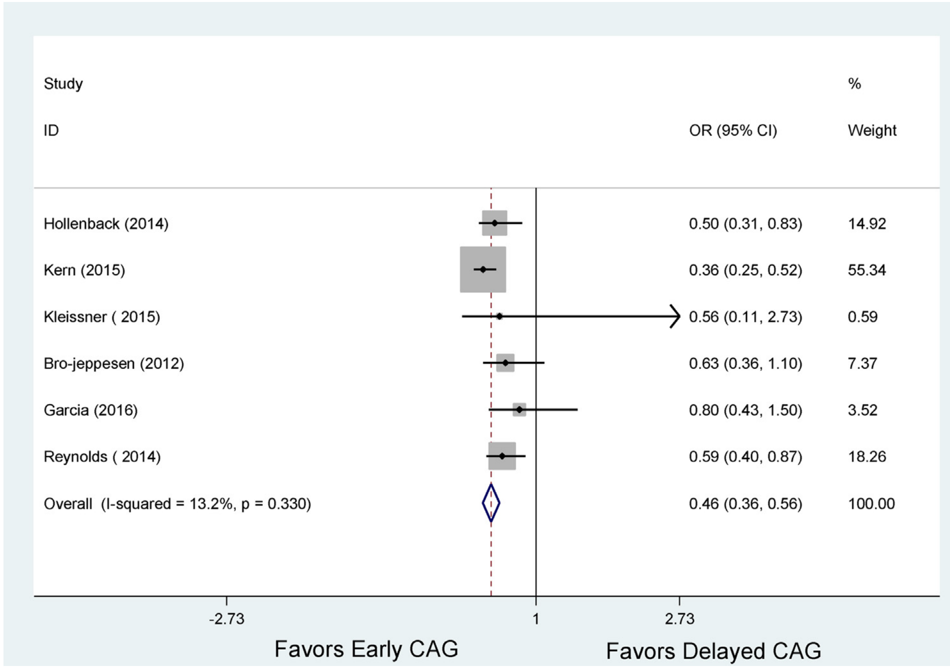

Fig. 2. Effect of early coronary angiography, versus delayed or no coronary angiography, on mortality after procedure.

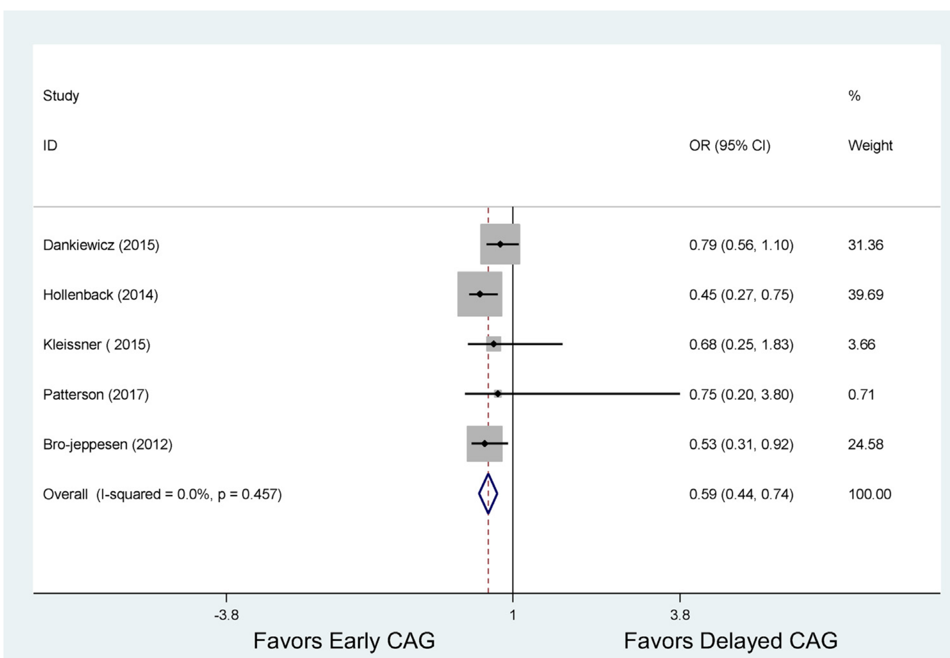

Fig. 3. Effect of early coronary angiography, versus delayed or no coronary angiography, on long-term mortality.

whereas the remaining 4 studied the outcomes of early angiography in both STEMI and NSTEMI groups [5,11,16,17]. Access to early CAG was defined differently in every study (on admission, within 2 h, or between 6 and12 h of hospital admission). Patients were followed for 6–14 months in most of the studies. The mean follow-up period was 9 months. The mean age of patients admitted was 62 years. Only 3 studies reported the Glasgow Coma Score (GCS) at the time of admission [5,11,13]. Other common characteristics, stratified by early versus late or no CAG, included male sex (81% vs 76%), witnessed cardiac arrest (77% vs 74%), by-stander BLS (59% vs 56%) and initial shock-able rhythm (92% vs 81%). Data regarding the use of TH as per standard protocol was provided by 4 studies and almost all their patients underwent it [11–14]. PCI was also attempted in most of the patients. However, it was observed that a greater number of PCI was performed in patients who underwent early CAG (35%) as opposed to those who either underwent late or no CAG (15%). Only 2 studies reported rates of bleeding [12,15]. There were 184/940(19.6%) deaths in the early CAG group and 425/1193 (35.6%) deaths in the delayed/no CAG group, at hospital discharge. Use of early CAG was shown to decrease mortality after procedure (OR = 0.46, 95%CI = 0.36–0.56; P < 0.001); (Fig. 2). Similarly, at long term follow-up, there were 223/940 (23.7%) deaths in the early CAG

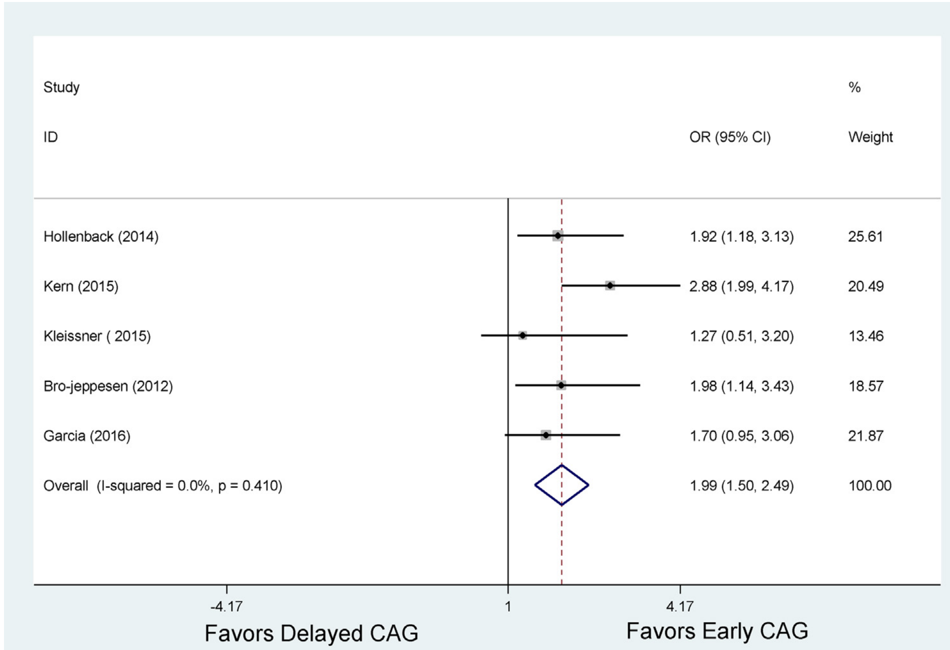

Fig. 4. Effect of early coronary angiography, versus delayed or no coronary angiography, on neurological outcome stratified by good CPC score (1–2), at discharge.

group and 358/1193 (30.0%) deaths in the delayed/no CAG group. Early CAG showed an increasing trend towards decreased long-term mortality (OR = 0.59, 95%CI = 0.44–0.74; P < 0.001); (Fig. 3).

Moreover, good neurological outcomes, as defined by CPC score of 1–2, were observed in 327/940 (34.8%) patients who underwent early CAG compared to 328/1193 (27.5%) patients who underwent delayed/no CAG. Early CAG was shown to improve neurological outcome on discharge (OR = 2.00, 95% CI = 1.50–2.49; P < 0.001); (Fig. 4). Likewise, at long-term follow up, 217/940 (23.1%) patients in the early CAG group had a good neurological outcome compared to 220/1193(18.4%) patients from the delayed/no CAG group. The pooled analysis shows increased trend towards improvement in long term neurological status with early CAG. (OR = 1.48, 95% CI = 1.06-1.90; P < 0.001); (Fig. 5).

Discussion

Acute coronary syndrome is characterized by plaque rupture, limitation of epicardial coronary flow in the culprit artery, with resultant downstream cell necrosis accompanied by ongoing ischemia and the potential for resultant electrical and hemodynamic instability. Similar to the STEMI subset, a smaller but significant proportion of patients with NSTEMI also manifest with complete occlusion of the infarct related artery that is silent on surface EKG [25]. Patients with OHCA in this setting have competing risks from both the neurological and end organs consequences of arrest, as well as the risk of recurrent electrical and hemodynamic instability. Early revascularization may benefit by preventing recurrent cardiac instability and is universally performed in the setting of manifest STEMI. Our results show that early CAG, performed as part of an emergent invasive strategy, in NSTEMI patients with OHCA is also associated with improved survival at hospital discharge and on long-term during follow-up, when compared with late or no CAG. Patients undergoing early coronary angiography in NSTEMI, following OHCA, also display favorable neurological outcomes both at discharge and follow up.

The increased use of CAG and PCI has significantly improved outcomes in OHCA patients over the past 12 years [26]. However, despite a significant prevalence of coronary artery disease in NSTEMI patients [21,27–29] the use of early CAG in this population is underutilized [26].

Our analysis supports the findings from a recent meta-analysis which showed that one in three NSTEMI patients undergoing CAG, following OHCA, presents with an acute lesion necessitating an emergent PCI [29]. The above-mentioned study reported superior survival outcomes among NSTEMI patients who were taken for an emergent PCI [29], but could not ascertain any distinguishing features of NSTEMI patients who would benefit from an early revascularization [29]. Both studies illustrate the superior outcomes achieved in patients with NSTEMI OHCA managed with an early invasive strategy; yet there is a clear distinction in the choice of intervention assessed. PCI as a comparative intervention may provide a more direct and coherent means of validating an association between a patient's revascularization status and subsequent clinical outcomes. Indeed, multiple observational studies have demonstrated the survival benefit conferred by an early and successful PCI in the setting of NSTEMI OHCA [27,29,30]. However, to date, no consensus has been reached on the appropriate identification of patients with an ishcemic cause of arrest and who would benefit from an emergent PCI. We aimed to assess the role of an early CAG as a systematic and first line post-resuscitation measure in all NSTEMI patients, following OHCA. Performance of an emergent CAG would therefore serve not only as a surrogate indicator of the beneficial outcomes achievable with early revascularization, but also as a means of assessing the feasibility, as well as validity, of a systematic and early invasive imaging modality in all NSTEMI patients, following OHCA.

According to the current 2015 AHA guidelines an "emergency coronary angiography is reasonable for *select* adult patients who are comatose after OHCA of suspected cardiac origin but without ST elevation on ECG" (Class IIa Recommendation) [6]. However, the identification of these high-risk NSTEMI patients is challenging; partly because of the lack of clinical signs of ischemia and limited diagnostic utility in this population [31,32]. An algorithm for risk stratification of NSTEMI patients likely to benefit from an early invasive strategy has been proposed by Rab et al. [33]. However, the proposed algorithm carries the risk of depriving otherwise life-saving care to patients with an assumed priori poor outcome. In a

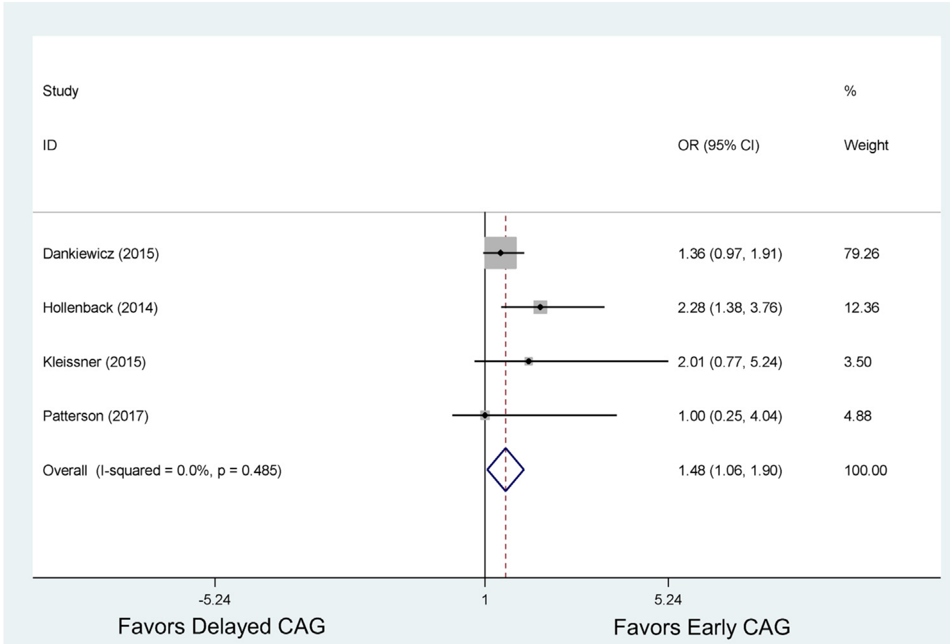

Fig. 5. Effect of early coronary angiography, versus delayed or no coronary angiography, on neurological outcome, stratified by good CPC score (1–2), on follow-up.

retrospective cohort study by Reynolds, et al, the survival benefit conferred by prompt revascularization was shown to be achievable in OHCA patients at almost every measured stratum of illness severity, excluding those with a non-cardiac cause of arrest [17].

Our results support the consideration of an early CAG as part of a standardized post-resuscitation plan in all NSTEMI patients, following OHCA, in whom a non-cardiac cause of arrest has been excluded. An emergent invasive strategy has been shown to enable prompt revascularization in these high risk patients and produce superior outcomes in varied settings; likely mediated through enhanced electrical and hemodynamic stability [11,16]. In addition, observations from the PROCAT registry have shown that in NSTEMI OHCA patients undergoing an emergent CAG, the performance of a successful PCI was independently associated with favorable outcomes at discharge [30]. However, given the preponderance of observational data accounting for our results, and corresponding low level of evidence as per the GRADE framework (Supplementary Table 3), these findings remain hypothesis generating and emphasize the need for generating more robust evidence in this setting.

Our present findings are significantly limited by the potential selection bias inherent in the observational studies we analyzed, but remain the best summative conclusions that may be garnered from the current published literature. The heterogeneity of the studies analyzed in this meta-analysis precludes to an identification of the best candidates for an early CAG. Ultimately, an accurate assessment of which subset of NSTEMI patients derive the greatest benefit from early revascularization can be best answered by a RCT. In the meanwhile, it may be reasonable to routinely employ early CAG as part of a post-resuscitation care strategy in the setting of NSTEMI OHCA, as the same has been shown to be strongly associated with superior outcomes across the heterogenous group of studies analyzed in this meta-analysis and may confer a survival benefit by means other than expedited revascularization [13].

Recently, Patterson et al. published the pilot results of a RCT investigating the outcomes of an early invasive approach in NSTEMI, following OHCA [15]. Their findings currently constitute the only randomized data, on the subject matter, in the literature and illustrate the feasibility of future RCTs in this at-risk group [15]. Accordingly, several other large scale RCTs, investigating outcomes of early CAG in NSTEMI after OHCA, are currently in the recruitment stage with study completion dates scheduled as early as 2018 [34–38].

Randomization of OHCA NSTEMI patients to an early invasive/intervention arm will have significant implications for the concomitant delivery of other goal directed therapies such as TH. Studies have shown that the combined delivery of both TH and PCI is complimentary in this setting, and may confer a greater long-term survival benefit, than is achievable with the independent use of either one intervention [39]. Likewise, the admission of NSTEMI patients, as part of randomization into an early invasive/intervention arm, to specialized centers for provision of an early CAG [15] may have the unintended effect of introducing an element of proficiency bias, as patient survival is inextricably linked to variations in hospital level care [40]. Therefore, future RCTs in this sub group should attempt to deliver standardized post resuscitation care packages which vary only in their provision of an early CAG.

Limitations

Our meta-analysis presents the favorable outcomes of 2133 NSTEMI patients undergoing early CAG, as opposed to delayed or no CAG. The treatment effect with this approach is undoubtedly magnified given the selection bias associated with these study designs. Performance of CAG in the young, or in those with favorable parameters of resuscitation, including witnessed arrest, bystander cardiopulmonary resuscitation, short time to return of spontaneous circulation (ROSC), short transfer time may result in favorable outcomes misattributed to the benefits of PCI. Unfortunately, no data was available to control for this selection bias on adjusted analysis. It is pertinent to note, however, that the association between early CAG and favorable outcomes was shown to be robust on adjusted analysis by three of the studies included [13,16,17]. Utstein parameters could not be adequately defined for the population of interest in some of the studies analyzed, (Table 1) due to incomplete reporting of the same in the studies included. The inclusion of a randomized pilot study by Patterson et al. [15] is debatable; particularly given the inherent lack of statistical power. However, the study inclusion was made based on its sound methodological design and execution; free of potential biases that are characteristic of observational studies dominating the current literature. The definitions and performance of 'early' and 'late' CAG varied across the included studies, which could have contributed to the variability in the results. Also, the revascularization rates were greater in NSTEMI patients undergoing early CAG (35%), as opposed to late or no CAG (15%) [11–13,15,16], which may have contributed to the better patient outcomes reported in the early CAG cohort. However, we can argue that this suggests that early CAG would help in identification and revascularization of these high-risk patients.

Conclusion

Our results demonstrate the consistent survival benefits conferred by an early CAG in the setting of NSTEMI OHCA. Given the lack of a clear pathway for identification and triage for NSTEMI patients with an ischemic cause of arrest, a low threshold for early CAG in a protocol based manner may be helpful. However, future guideline changes addressing the management of these patients may be shaped by the results of upcoming RCTs on the subject matter, as the current findings correspond to a low level of evidence as per GRADE framework, due to the observational nature of the studies available.

Conflicts of interest statement

None.

Funding disclosure

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2017.10.019.

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