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Clinical paper

Early versus deferred coronary angiography following cardiac arrest. A systematic review and meta-analysis

Vishal Goel^{a,1}, Jason E Bloom^{b,c,d,e,1}, Luke Dawson^{b,c,d}, Anita Shirwaiker^c, Stephen Bernard^{b,c,e}, Ziad Nehme^{e,f}, Daniel Donner^d, Caroline Hauw-Berlemont^g, Aurélie Vilfaillot^h, William Chan^{a,c,d}, David M Kaye^{c,d}, Christian Spauldingⁱ, Dion Stub^{b,c,d,e,f,*}

Abstract

Aim: The role of early coronary angiography (CAG) in the evaluation of patients presenting with out of hospital cardiac arrest (OHCA) and no ST-elevation myocardial infarction (STE) pattern on electrocardiogram (ECG) has been subject to considerable debate. We sought to assess the impact of early versus deferred CAG on mortality and neurological outcomes in patients with OHCA and no STE.

Methods: OVID MEDLINE, EMBASE, Web of Science and Cochrane Library Register were searched according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines from inception until July 18, 2022. Randomized clinical trials (RCTs) of patients with OHCA without STE that compared early CAG with deferred CAG were included. The primary endpoint was 30-day mortality. Secondary endpoints included mortality at discharge or 30-days, favourable neurology at 30-days, major bleeding, renal failure and recurrent cardiac arrest.

Results: Of the 7,998 citations, 5 RCTs randomizing 1524 patients were included. Meta-analysis showed no difference in 30-day mortality with early versus deferred CAG (OR 1.17, CI 0.91 – 1.49, $I^2 = 27%$). There was no difference in favourable neurological outcome at 30 days (OR 0.88, CI 0.52 – 1.49, $I^2 = 63%$), major bleeding (OR 0.94, CI 0.33 – 2.68, $I^2 = 39%$), renal failure (OR 1.14, CI 0.77 – 1.69, $I^2 = 0%$), and recurrent cardiac arrest (OR 1.39, CI 0.79 – 2.43, $I^2 = 0%$).

Conclusions: Early CAG was not associated with improved survival and neurological outcomes among patients with OHCA without STE. This meta-analysis does not support routinely performing early CAG in this select patient cohort.

Keywords: Out of Hospital Cardiac Arrest, Angiography, STEMI, Mortality

Introduction

Out of hospital cardiac arrest (OHCA) is often the first manifestation of cardiovascular disease with a reported incidence of 108 per 100,000 person-years.^{1–2} In patients with OHCA who achieve initial return of spontaneous circulation (ROSC) and survive to hospital, there remains a significant risk of morbidity and mortality secondary to cerebral and cardiac dysfunction.² The role of early coronary angiography (CAG) in the management of patients presenting with OHCA and no persistent ST-elevation (STE) on electrocardiogram

(ECG), has been subject to considerable debate over the last decade. Several prior meta-analyses which have included predominantly observational studies, owing to a lack of randomized data, found that early CAG following ROSC was associated with improved survival and neurological outcomes.^{3–5} The International Liaison Committee on Resuscitation (ILCOR) have provided a weak recommendation with a low certainty of evidence, suggesting that an early or deferred approach to CAG is reasonable in comatose post-arrest patients without ST elevation on ECG.⁶ However, several randomized controlled trials (RCTs) have recently been published, assessing the role

* Corresponding author at: The Alfred Hospital & Monash University, 55 Commercial Rd, Prahran, Victoria 3004, Australia.
E-mail address: d.stub@alfred.org.au (

¹ Denotes co-first authorship.

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of early CAG in OHCA survivors without STE, and have concluded no benefits of early CAG on survival and neurological outcome.^{7–9}

This systematic review and meta-analysis reviews outcomes of RCTs with access to previously unpublished raw data to enable a comprehensive review of the impact of early versus deferred CAG on mortality and neurological outcomes in patients with OHCA and no STE.¹⁰

Methods

This article has been prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The study protocol has been lodged with the Prospective Register of Systematic Reviews (PROSPERO; CRD42021279494). As the study reviewed only previously published data and had no encounters with any human or animal subjects, it did not require Ethics Committee approval.

Search strategy

On 18th July 2022, we performed a systematic search of OVID MEDLINE, EMBASE, Web of Science, and Cochrane Library Central Register (CORE). A detailed description of the search strategy is presented in the [Supplemental Materials \(Supplementary Table 1\)](#). All studies identified were imported into an online review platform (COVIDENCE) and most duplicates were removed. Two authors (J.E.B and A.S) independently completed title and abstract screening, with the same two authors then independently assessing the full text articles which met the study's inclusion and exclusion criteria. In the case of disagreement, a third independent author (L.P.D) mediated any discordance which arose during the independent assessments.

Study population and definitions

Studies were eligible for inclusion in the primary analysis if they were RCTs, including patients with OHCA without STE on electrocardiogram and were randomized to early CAG (interventional group) or deferred CAG (control group). Early CAG and deferred CAG was defined in accordance with the definitions used in the respective studies. Neurological functional status was defined by the cerebral performance category (CPC) score.¹¹ A favourable neurological status was defined by a CPC score of 1 or 2, and scores of 3 to 5 were deemed to indicate a poor neurological recovery.

Data extraction

Selected studies were manually reviewed, and data were independently extracted by 2 authors (V.G and A.S) using a pre-piloted data extraction form based on the minimum recommended requirements in the Cochrane Handbook for Systematic Reviews. Any discrepancy on comparison was mediated by discussion with a third author (J.E.B). All data were obtained from text and figures, including Kaplan-Meier survival curves. Risk of bias assessment for all study outcomes was performed by 2 investigators (V.G and A.S) using the revised Cochrane-risk-of-bias instrument (RoB2).¹² A summary of the risk of bias assessment is presented in the [Supplemental Materials](#) in the case of missing data for assessed endpoints, attempts were made to contact the relevant corresponding author to obtain unpublished data for use in the analysis.

Endpoints

The primary endpoint assessed was 30-day mortality. Secondary endpoints included mortality at discharge or 30 days (latest reported), favourable neurological recovery (CPC score of 1 or 2) at 30 days and time of discharge to 90 days (latest reported score included), major bleeding (Bleeding Classification System Definitions (BARC)) > 2 or Thrombolysis in Myocardial Infarction (TIMI) major bleeding,¹³ requirement for renal replacement therapy, and recurrent cardiac arrest.

Statistical analysis

Meta-analysis was performed using the restricted maximum likelihood random-effects model, with the estimate of heterogeneity derived using the Mantel-Haenszel method. The presence of heterogeneity was calculated using the Cochrane Q test ($P < 0.1$ deemed significant). Effect sizes were presented as odds ratios (ORs) and 95% confidence intervals. To assess for heterogeneity, the I^2 test was used ($I^2 > 50\%$ was defined as being significant). A pre-specified subgroup analysis was performed to assess the impact of a shockable presenting rhythm on 30-day mortality. Publication bias was assessed by visual inspection of a funnel plot and quantitatively using the Begg's test. All analyses were performed with R version 4.1.1 using meta (version 5.5.0) and metafor (version 4.1.3) packages.

Results

Systematic search results and study inclusion

The systematic search yielded a total of 7,998 citations, with 1,625 duplicates removed (see [Fig. 1](#)). After screening of the initial study abstracts, a total of 34 full-text studies were assessed for eligibility out of which 5 randomized controlled trials met the study's inclusion criteria and were included in the primary analysis. A total of 1524 patients were included, with 766 patients randomized to early CAG and 758 to deferred CAG.

Study features

All studies included in the analysis randomized patients in a 1:1 fashion to receive either early or deferred CAG and were conducted between 2015 and 2020.^{10,14–17} With respect to the study interventions, there was variation in the definition and timing of both "early" and "deferred" CAG which are presented in [Table 1](#); two studies defined "early" as CAG within 2-hours of randomization^{14,16} and the remaining three did not have a defined cut-off time period,^{10,15,17} while the timing of "deferred" CAG ranged from greater than 6-hours following randomization to confirmed neurological recovery. With respect to study participant inclusion, 4 studies permitted the inclusion of both shockable and non-shockable rhythms at randomization,^{10,15–17} while Lemkes only included cases with a shockable rhythm at time of arrest.¹⁴

Patient characteristics

Patient characteristics of included studies are presented in [Table 2](#). A total of 404 (26.5%) females were included in the studies. Overall, 625 (85.9%) patients had a documented witnessed cardiac arrest in the early CAG group compared to 600 (83.6%) of patients in the delayed CAG group. There were 501 (67.8%) patients in the early CAG group that had an initial shockable rhythm compared to 510 (69.9%) patients in the delayed CAG group. There was a com-

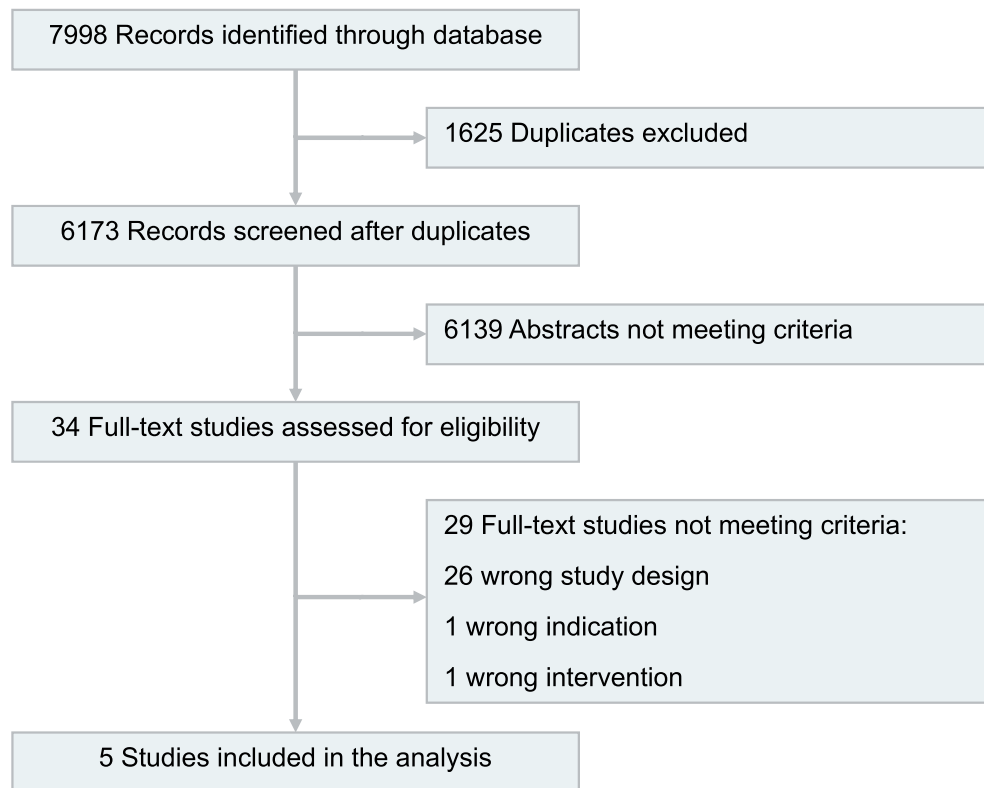


Fig. 1 – Study selection.

parable median time from initial cardiac arrest to ROSC in both the early and deferred CAG groups [17.7 minutes].

Risk of bias

Risk of bias assessment found that two studies were of moderate risk of overall risk of bias,^{10,13} while 3 studies were identified as high risk of bias^{11,13–14} (see [Supplementary Fig. 1](#) and [Supplementary Table 2](#)). The trials conducted by Lemkes¹⁴ and Desch¹⁷ were assessed as moderate risk (“some concerns”) owing to the open label designs of the studies. The studies performed by Kern¹⁶ and Hauw-Berlemont¹⁰ were assessed as high risk of bias due to its open label design and premature termination. The pilot study by Elfwen was classified as a high risk of bias due to its open label design, important deviations from the intended protocol and short follow-up time of 24 hours.¹⁵ There was no evidence of publication bias with respect to the primary outcome of 30-day mortality (Begg’s $p = 0.12$) (see [Supplementary Fig. 2](#)).

Outcomes

Primary outcome

Three studies were included in the analysis of the primary study outcome for 30-day mortality.^{10,14,17} Data was obtained for two studies from the published manuscript,^{14,17} while data from the final study by Hauw-Berlemont was provided by the authors.¹⁰ There was no difference observed in 30-day mortality with early versus deferred CAG ([Fig. 2](#), OR 1.17, CI 0.91 – 1.49, $I^2 = 27\%$).

Secondary outcome

Secondary outcomes are summarised in [Fig. 3](#). Four studies were included in the analysis for mortality at hospital discharge or 30 days^{10,14,16–17} (latest reported event included). Meta-analysis demonstrated no significant difference with early versus deferred CAG ([Fig. 3A](#), OR 1.11, CI 0.87 – 1.42, $I^2 = 22\%$). Three studies assessed 30-day survival rates in patients presenting with an initial shockable rhythm and there was overall no difference in mortality in the cohort of patients who underwent early CAG^{10,14,17} ([Fig. 3B](#), OR 1.28, OR 0.97 – 1.69, $I^2 = 0\%$).

Two studies assessed for a good neurological outcome (CPC score of 1 or 2) at 30 days and meta-analysis showed no significant difference in good neurological status in patients undergoing early versus deferred CAG^{10,17} ([Fig. 3C](#), OR 0.88, CI 0.52 – 1.49, $I^2 = 63\%$). Four studies were included in the analysis for good neurological outcome at time of discharge or 90 days (latest reported score included) and reported no significant difference in early versus deferred CAG^{10,14,16–17} ([Fig. 3D](#), OR 0.92, CI 0.70 – 1.21, $I^2 = 26\%$).

Reported complications are summarised in [Fig. 4](#) and included major bleeding, acute kidney failure leading to renal-replacement therapy, and recurrent cardiac arrest. Meta-analysis of three studies demonstrated no significant difference in major bleeding in patients undergoing early versus deferred CAG^{14,16–17} ([Fig. 4A](#), OR 0.97, CI 0.34 – 2.77, $I^2 = 46\%$). There was no difference found in an analysis of 4 studies in rates of patients developing renal failure requiring renal replacement therapy^{10,14–15,17} ([Fig. 4B](#), OR 1.14, CI 0.77 – 1.69, $I^2 = 0\%$). Analysis of four studies identified no difference in

Table 1 – Characteristics of included studies.

Trial (year)	Patients Recruited	Country	Study Period	Patient characteristics	Design	Experimental arm	Control arm	Outcomes	STEMI and No stemi	Stemi	No STEMI	All rhythms	Shockable	Non shockable	Follow up time point
Lemkes (2019)	552	Netherlands	2015–2018	Inclusion: OHCA, shockable rhythm, unconscious after ROSC. Exclusion: Signs of STEMI on ECG, Shock, obvious non coronary OHCA	RCT	Immediate CAG: CAG performed within 120 mins hours after randomization	CAG was performed after neurologic recovery. Emergency CAG performed if patient showed signs of CS, recurrent life-threatening arrhythmias, or recurrent ischemia during hospitalization.	Primary endpoint: Survival at 90 days. Secondary endpoint: FNO at 90 days, Myocardial injury, Acute renal failure, RRT, bleeding (TIMI Criteria), recurrent VT or VF requiring defibrillation, shock.	-	-	+	-	+	-	90 days
Elfwen (2019)	79	Sweden	2015–2017	Inclusion: Witnessed OHCA, Age > 18 years, ROSC and admitted alive to hospital, Absence of LBBB or STEMI. Excluded: Obvious non cardiac cause, Life expectancy < 1 year, expected time to CAG > 120 minutes, pregnancy, patient not unconscious (GCS > 8)	RCT	Immediate CAG: Urgent CAG and PCI performed on presumed culprit lesion, PCI carried out on all significant stenosis (>50% stenosis) during acute angiogram	Admit to ICU for supportive management, CAG should not be performed earlier than 3 days unless CS, ventricular arrhythmias (sustained VT or VF), STEMI	24 hour mortality, bleeding (TIMI Criteria), renal failure, RRT, subarachnoid haemorrhage, bradyarrhythmias requiring pacemaker, ventricular arrhythmias (VT or VF)	-	-	+	+	+	+	30 days
Kern (2020)	99	USA	2016–2018	Inclusion: Patients > 18 years, successful resuscitation and comatose after OHCA, all cardiac rhythms, suspected cardiac etiology for arrest, no ST elevation or new LBBB. Exclusion: Ongoing Chet compressions, pregnancy, known "do not resuscitate" order or an "opt out bracelet".	RCT	Immediate CAG: CAG performed within 120 mins after randomization	No CAG within 6 hours of hospital arrival. Urgent CAG allowed if attending cardiologist/intensivist felt it is imperative for optimal patient care	Primary endpoint: Composite end point of efficacy and safety measurements (survival to discharge and FNO at discharge, EF, wall motion score at 16–24 hours of admission, rearest, pulmonary oedema, acute renal dysfunction, bleeding (BARC classification), hypotension, pneumonia. Secondary outcomes: Prevalence of acute coronary occlusion, survival, FNO. EF and wall motion score at 180 +/- 30 days after discharge.	-	-	+	+	+	+	180 days
Desch (2021)	554	GermanyDenmark	2016–2019	Inclusion: Patients > 30 years, resuscitated OHCA of possible cardiac origin and return of spontaneous circulation, no ST elevation, all cardiac rhythms. Exclusion: ST elevation or new LBBB, severe hemodynamic or electrical instability requiring immediate CAG, obvious extra cardiac etiology, in hospital cardiac arrest, known or likely pregnancy, participation in another	RCT	Immediate CAG: Urgent CAG and revascularization of clinically relevant coronary artery disease.	Admit to ICU for further evaluation, proceed to CAG after 24 hours if suspicion of acute coronary trigger. Urgent CAG < 24 hours if substantial myocardial damage, electrical instability, CS, new ST elevation.	Primary endpoint: Death from any cause at 30 days. Secondary outcomes: Myocardial infarction at 30 days, Severe neurological deficit (CPC > 2), Composite of death from any cause of severe neurologic deficit at 30 days, length of stay in ICU, serial values for the Simplified Acute Physiology Score (SAPS II), Rehospitalization for CHF within 30 days, peak release of myocardial enzymes,	-	-	+	+	+	+	30 days

Table 1 (continued)

Trial (year)	Patients Recruited	Country	Study Period	Patient characteristics	Design	Experimental arm	Control arm	Outcomes	STEMI and No stemi	Stemi	No STEMI	All rhythms	Shockable	Non shockable	Follow up time point
Hau-Berlemont 2022	279	France	2017–2020	intervention study interfering with research question of TOMAHAWK trial Inclusion: Patients > 18 years, out of hospital cardiac arrest with ROSC, without an obvious non cardiac cause of arrest, admitted to a center with an ICU and 24/7 interventional cardiology department. Exclusion: Patients < 18 years, in hospital cardiac arrest, patients without ROSC, Presence of ST elevation on post ROSC ECG, Suspected non cardiac etiology, life expectancy < 1 year, pregnancy, adults subject to legal protection measure, participation in another interventional trial.	RCT	Immediate angiography	Admit to intensive care, coronary angiography planned 48–96 hours after admission	bleeding (BARC classification), stroke, acute kidney failure leading to RRT. Primary outcome: 180 day survival rate with no or minimal neurologic sequelae (CPC 1 or 2). Secondary endpoint: Shock, tachycardia, fibrillation episodes during the first 48 hours after hospital admission, changes in left ventricular EF between baseline and 180 days as assessed by echocardiogram, major neurologic sequelae (CPC 3 or 4 assess at ICU, 90 and 180 days), all cause death, hospital length of stay.	-	-	+	+	+	+	180 days

OHCA: Out of hospital cardiac arrest, ROSC: Return of spontaneous circulation, STEMI: ST-Elevation Myocardial Infarction, ECG: Electrocardiogram, RCT: Randomised control trial, CAG: Coronary angiography, CS: Cardiogenic Shock,

FNO: Favourable Neurological outcome, RRT: Renal Replacement Therapy, VT: Ventricular Tachycardia, VF: Ventricular Fibrillation, LBBB: Left Bundle Branch Block, GCS: Glasgow Coma Scale, PCI: Percutaneous Coronary Intervention, ICU: Intensive Care,

EF: Ejection Fraction, CPC: Cerebral Performance Scale, CHF: Congestive Heart Failure.

Table 2 – Patient Characteristics.

Trial - First author (publication year)	Treatment allocation and number of patients	Age (years)	Male (%)	HTN (%)	T2DM (%)	CHF (%)	CKD (%)	Stroke (%)	MI (%)	CAD (%)	PCI (%)	CABG (%)	Witnessed arrest(%)	Bystander CPR(%)	Shockable rhythm(%)	Time to ROSC (min)	Time from arrest to CAG (hours)	TTM (%)
Lemkes (2019)	Early CAG – 273	65.7 (12.7)	223 (81.7)	131 (48.7)	55 (20.2)	NA	NA	19 (7)	73 (26.2)	99 (36.3)	46 (16.9)	43 (15.8)	218 (79.9)	NA	273 (100)	15 (9–21)	2.3 (1.8–3.0)	257 (94.1)
	Deferred CAG – 265	64.9 (12.5)	202 (76.2)	126 (47.5)	44 (16.6)	NA	NA	15 (5.7)	76 (28.7)	96 (36.2)	60 (22.7)	24 (9.1)	203 (76.6)	NA	265 (100)	15 (8–20)	121.9 (52.0–197.3)	247 (93.2)
Elfwen (2019)	Early CAG – 38	71 (62–78)	22 (57.9)	NA	6 (15.8)	7 (18.4)	NA	6 (15.8)	6 (15.8)	9 (23.7)	4 (10.5)	3 (7.9)	NA	28 (74)	20 (52.6)	20 (14–35)	NA	NA
	Deferred CAG – 40	70 (61–77)	31 (77.5)	NA	10 (25)	6 (15)	NA	4 (10)	8 (20)	10 (25)	7 (17.5)	3 (7.5)	NA	30 (75)	22 (55)	25 (19–34)	NA	NA
Kern (2020)	Early CAG – 49	65 (57–73)	42 (85.7)	26 (53.1)	11 (22.4)	7 (14.3)	3 (6.1)	6 (12.2)	10 (20.4)	16 (32.7)	NA	NA	46 (93.9)	37 (75.5)	34 (69.4)	19 (12–24)	NA	41 (83.7)
	Deferred CAG – 50	65.5 (59–72)	36 (72)	29 (58)	16 (32)	7 (14)	7 (14)	1 (2)	7 (14)	16 (32)	NA	NA	44 (89.8)	33 (67.3)	41 (82)	20 (10–34)	NA	38 (76)
Desch (2021)	Early CAG – 265	69 (59–78)	185 (69.8)	161 (67.1)	71 (29.1)	NA	NA	24 (10.5)	44 (19.3)	79 (34.5)	40 (18.4)	19 (8.0)	236 (91.1)	142 (57.5)	126 (52.3)	15 (10–20)	2.9 (2.2–3.9)	206 (77.6)
	Deferred CAG – 265	71 (70–79)	184 (69.4)	162 (69.2)	74 (29.5)	NA	NA	20 (8.9)	45 (19.8)	93 (40.6)	58 (16.4)	25 (10.6)	226 (87.9)	152 (60.3)	142 (58.7)	15 (8–20)	46.9 (26.1–116.6)	208 (78.6)
Hauw-Berleont (2022)	Early CAG – 141	65.4 (13.8)	103 (73.1)	NA	NA	NA	NA	NA	NA	NA	NA	NA	125 (88.7)	93 (75)	48 (34.8)	27 (16.5–36.5)	2 (2–3)	NA
	Deferred CAG – 138	63.9 (15.4)	92 (66.7)	NA	NA	NA	NA	NA	NA	NA	NA	NA	127 (92.7)	98 (79.7)	40 (30.1)	25 (18–35.3)	65.5 (40.8–74.2)	NA

HTN: Hypertension, T2DM: Type 2 Diabetes Mellitus, CHF: Congestive Heart Failure, MI: Myocardial Infarction, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery Bypass Graft, CPR: Cardiopulmonary resuscitation, ROSC: Return of spontaneous circulation, CAG: Coronary angiography, TTM: Targeted temperature management, NA: Not available.

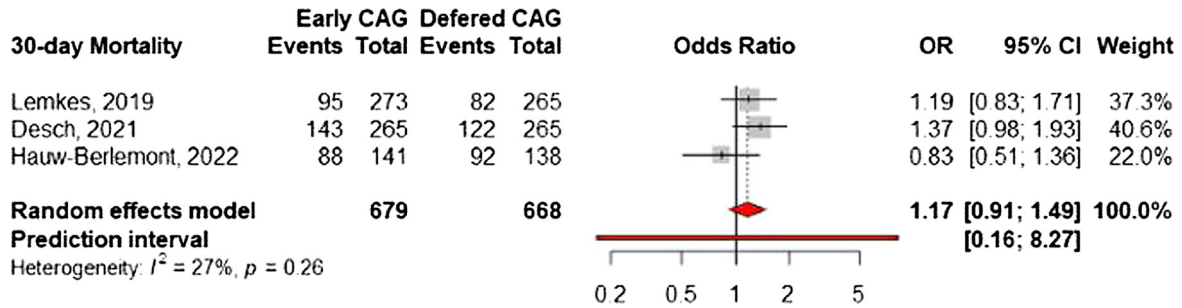


Fig. 2 – Forest plot of the primary outcome assessing individual and summary relative risks (RR) of 30-day mortality among patients with out of hospital cardiac arrest (OHCA) without ST-elevation myocardial infarction (STE) treated with early and delayed coronary angiography (CAG).

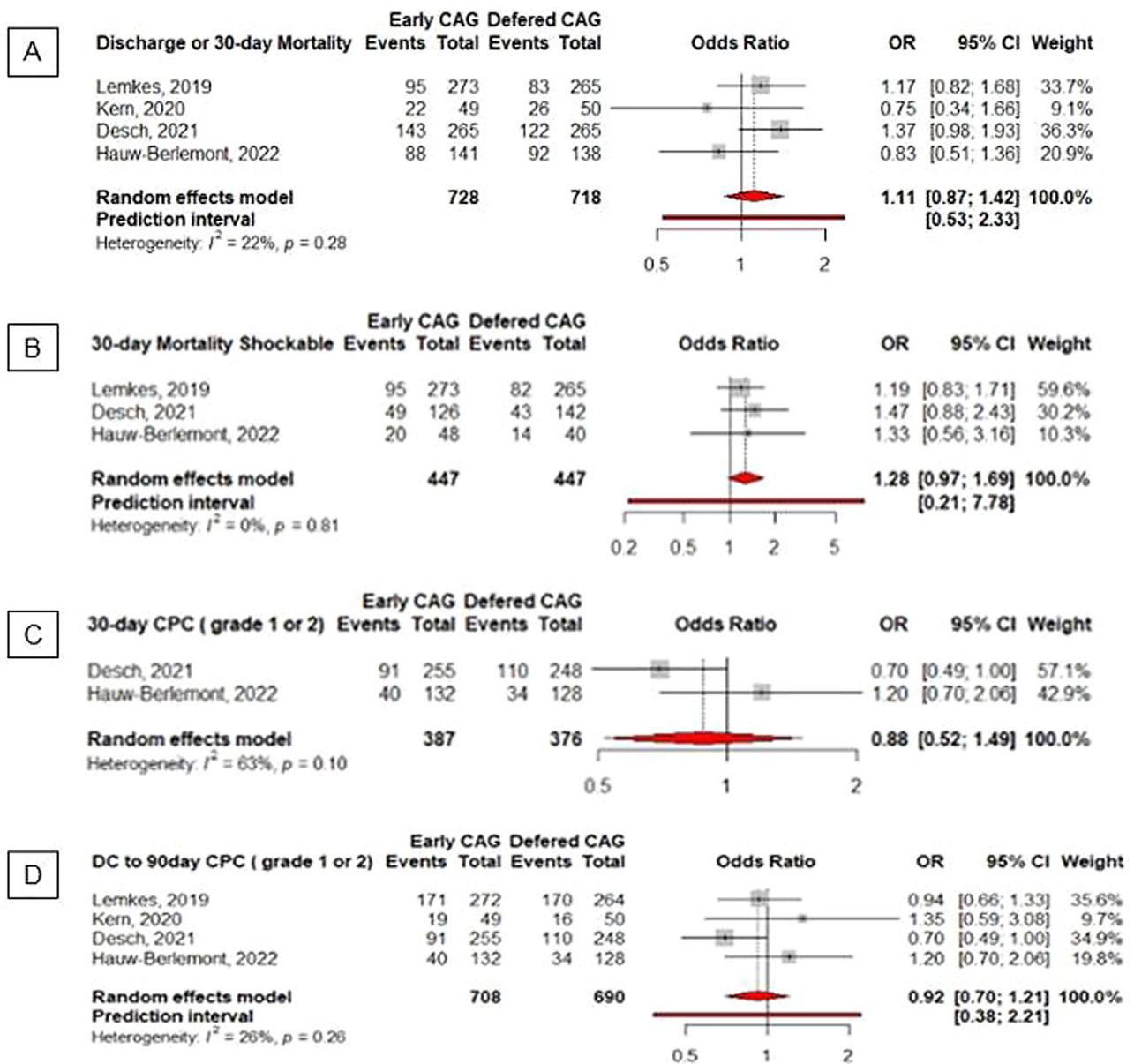


Fig. 3 – Forest plots of secondary outcomes including mortality at discharge or 30 days (latest reported), 30-day mortality in patients presenting with an initial shockable rhythm, favourable neurological recovery (Cerebral performance score (CPC) score of 1 or 2) at 30 days and favourable neurological recovery at time of discharge to 90 days (latest reported score included).

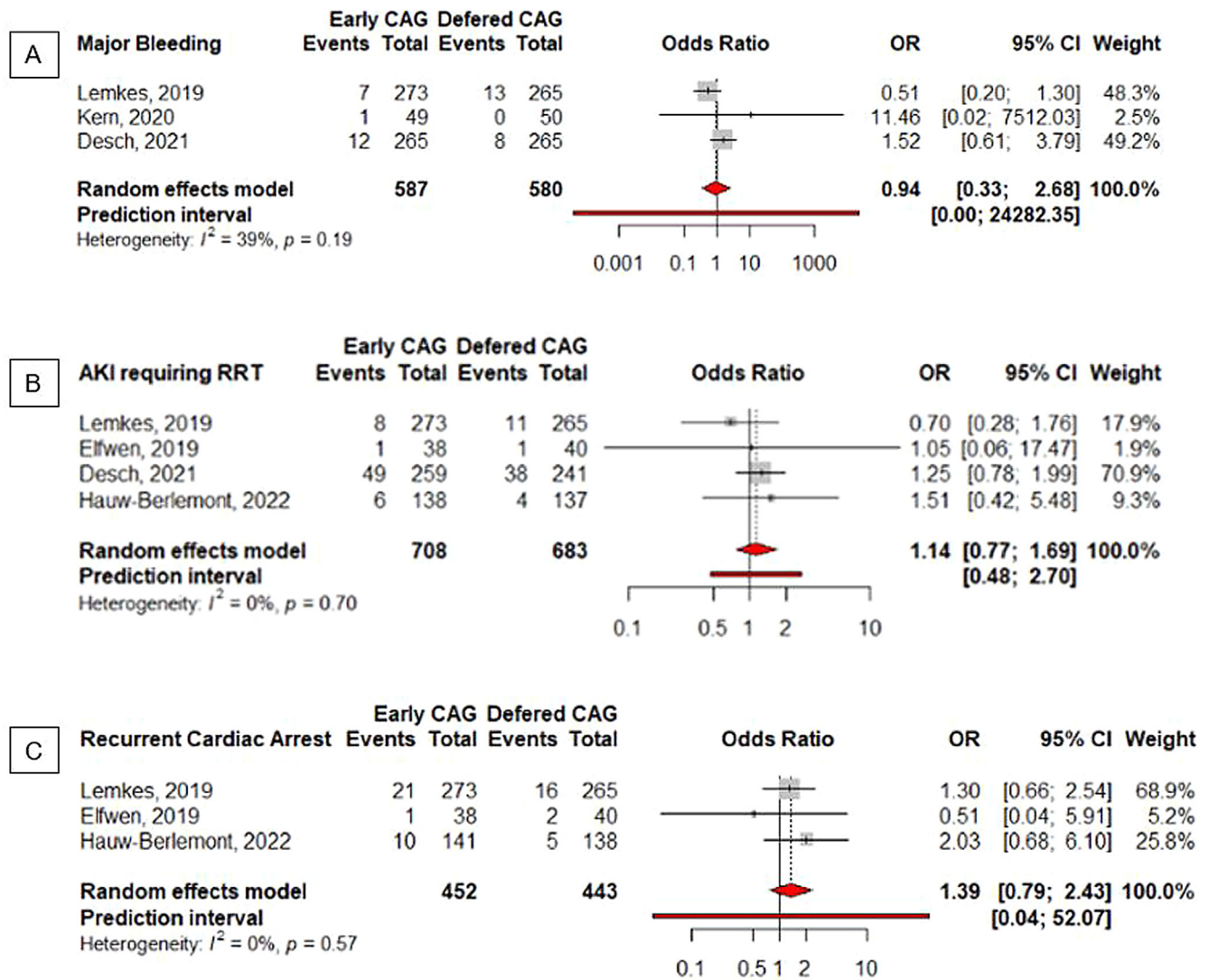


Fig. 4 – Forest plots of complications including major bleeding, acute kidney failure leading to renal-replacement therapy, and recurrent cardiac arrest.

rates of recurrent cardiac arrest in the early versus deferred CAG group^{10,14–16} (Fig. 4C, OR 1.34, CI 0.79 – 2.28, $I^2 = 0%$).

Discussion

In this meta-analysis of 5 RCTs enrolling 1524 participants, we found that in patients presenting with OHCA without STE, the strategy of performing early CAG, compared with deferred CAG, was not associated with improved 30-day survival. Furthermore, there was also no demonstrable benefit with respect to improving neurological outcomes in patients who underwent early CAG.

The findings presented in the current study differ from those of older analyses.^{3–5} The lack of benefit associated with early CAG in the current analysis, compared with studies that include older registries collected between 1990 and 2010, that show marked benefit from early CAG may be attributable to the following reasons: first, the registry data is likely to be effected by bias with selection of patients to undergo early CAG who have a favourable neurological

prognosis and; second, the underlying cause of OHCA has evolved over the last decade with a significant reduction in cardiac disease as the cause of arrest, thereby potentially diluting the effect of early CAG.¹⁸ Furthermore, while contemporary meta-analyses^{7–9} have been performed, the current study is strengthened by the inclusion of an additional, recently published, large RCT with exclusive data obtained from the trial investigators which helps further inform the study questions.¹⁰

It is noteworthy that the current findings are not applicable to patients with OHCA complicating STE, in whom early CAG has been repeatedly demonstrated to reduce mortality.^{19–20} In a *post-hoc* subgroup of the Feedback Intervention and Treatment Times in ST-elevation Myocardial Infarction trial (FITT-STEMI) of patients with STEMI complicated by OHCA, reduced time from first medical contact to reperfusion was associated with improved survival.²¹ However, in patients without STE, it may be postulated that early reperfusion is unlikely to be beneficial if the aetiology of OHCA is not related to an acute coronary event and early CAG could potentially delay treatment of the underlying cause as well as post arrest

care. This is evident with the low prevalence rates of coronary atherosclerosis and percutaneous coronary intervention amongst the patients enrolled in our studies, and highlights the importance for careful patient selection when considering early CAG. Furthermore, although there is a large body of data demonstrating the importance of emergent reperfusion in patients with acute myocardial infarction complicated by cardiogenic shock (CS),^{21–23} the impact of early CAG in patients without STE, who present with OHCA and CS is less well defined. While, three out of the five included studies permitted the inclusion of patients with CS, there was ultimately very few patients with CS at enrolment and limited outcome data available for analysis. Therefore, there remains an unmet need for further data to assess the role of early CAG in patients with CS following resuscitated OHCA who do not meet criteria for STE.

The findings of our analysis are also relevant for patients with non-shockable and shockable rhythms. Four out of the five trials included participants with either shockable or non-shockable presenting rhythms.^{10,15–17} Despite the described association between coronary ischemia and shockable rhythm at the time of cardiac arrest, the data presented in the current study do not show benefit from early CAG in this cohort.²⁴

Anoxic brain injury is the leading cause of morbidity and mortality in patients with OHCA who achieve initial ROSC.² This is consistent for the trials in our study, with anoxic brain injury the most common mode of death. Neuroprotective treatment strategies are essential in not only improving survival following OHCA, but also reducing the burden of morbidity, and improving quality of life. The current study sought to assess if early CAG improved the likelihood of achieving survival with a good neurological outcome, defined by a CPC score of 1 or 2 at 30-days post randomization. However, we found that there was no observed benefit in neurological outcomes associated with an early CAG strategy, compared with deferred CAG. The OHCA population is highly heterogenous with a complex interplay of variables impacting prognosis. The use of risk-scores to assist with neuroprognostication, such as MIRACLE2, may have utility in predicting which patients are less likely to succumb to the neurological insult from the OHCA and may therefore benefit from an early CAG strategy.¹⁹ After further validation, risk scores may inform the design of future RCTs, allowing for a nuanced approach to identify a subgroup of patients who may benefit from an early CAG strategy.

Analysis of secondary complications including major bleeding, acute kidney failure leading to renal replacement therapy, and recurrent cardiac arrest demonstrates that the overall incidence of these events was low and there was no observed difference when adopting an early versus deferred CAG approach. In the study by Desch et al, there was a higher incidence of femoral versus radial angiography performed in the immediate CAG group, however, no difference in bleeding rates were noted.¹⁷ In totality, these findings suggest that despite early CAG not conferring prognostic benefit, it appears to be safe and not associated with increased risk of major morbidity.

Limitations in study

The findings of the current study should be interpreted in the context of the following limitations. First, by including only RCTs the overall study number and number of patients are relatively small, potentially resulting in the analysis being possibly underpowered to detect benefit or harm associated with the intervention and to exclude publication bias. Second, due to the unblinded nature of the intervention, all

studies have at least a moderate risk of bias. Third, owing to a lack of standardized definitions of early and late CAG in these studies, time to immediate or deferred CAG is variable. Given our study is not a patient-level meta-analysis, the ability to directly compare treatment effects between studies may be limited. Finally, studies included patients that were predominantly male, which may limit the generalizability of these findings to female patients.

Conclusions

This meta-analysis of contemporary randomized controlled trials shows that there is no significant difference in 30-day mortality and neurological outcomes in patients with OHCA and no STE treated with an early CAG strategy compared with a deferred strategy. These findings do not support an early invasive strategy for hemodynamically stable OHCA patients without STE.

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CRedit authorship contribution statement

Vishal Goel: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Jason E Bloom:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Supervision. **Luke Dawson:** Software, Validation, Formal analysis, Writing – review & editing. **Anita Shirwaiker:** Validation, Investigation, Writing – original draft. **Stephen Bernard:** Writing – review & editing. **Ziad Nehme:** Writing – review & editing. **Daniel Donner:** Writing – review & editing. **Caroline Hauw-Berlemont:** Resources, Data curation, Writing – review & editing. **Aurélié Vilfailot:** Resources, Data curation, Writing – review & editing. **William Chan:** Writing – review & editing. **David M Kaye:** Writing – review & editing. **Christian Spaulding:** Resources, Data curation, Writing – review & editing. **Dion Stub:** Conceptualization, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Conflicts of Interest

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Appendix A. Supplementary data

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Author details

^aDepartment of Cardiology, Western Health, Melbourne, Victoria, Australia^bSchool of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia^cDepartment of Cardiology, The Alfred Hospital, Melbourne, Victoria, Australia^dThe Baker Institute, Melbourne, Victoria, Australia^eAmbulance Victoria, Australia^fDepartment of Paramedicine, Monash University, Australia^gMedical Intensive Care Unit, European Hospital Georges Pompidou, Assistance Publique–Hôpitaux de Paris, Université Paris Cité, Paris, France^hEuropean Hospital Georges Pompidou, Assistance Publique–Hôpitaux de Paris, Paris, FranceⁱDepartment of Cardiology, European Hospital Georges Pompidou, Assistance Publique–Hôpitaux de Paris, Paris Cité University, Sudden Cardiac Death Expert Center, INSERM U 971, PARCC, Paris, France

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