RESUSCITATION 160 (2021) 20 –36

Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Review

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

Patrick McFadden[a], Joshua C. Reynolds[b,*], Ryan D. Madder[c], Michael Brown[b]

[a] Spectrum Health Department of Emergency Medicine, Grand Rapids, MI, USA
[b] Michigan State University College of Human Medicine, Department of Emergency Medicine, 15 Michigan Street NE, Suite 736D, Grand Rapids, MI 49503, USA
[c] Frederik Meijer Heart and Vascular Institute, Spectrum Health, Grand Rapids, MI, USA

Abstract

Aim: Conduct a diagnostic test accuracy systematic review and meta-analysis of the post-return of spontaneous circulation (ROSC) electrocardiogram (ECG) to indicate an acute-appearing coronary lesion and revascularization.

Methods: We searched PubMed, EMBASE, CINAHL, Cochrane Library, and Web of Science through February 18, 2020. Two investigators screened titles and abstracts, extracted data, and assessed risks of bias using QUADAS-2. We estimated sensitivity (Sn), specificity (Sp), and likelihood ratios (LR) for all reported ECG features to indicate all reported reference standards. Random-effects meta-analysis pooled comparable studies without critical risk of bias. GRADE methodology evaluated the certainty of evidence.

Results: Overall, 48 studies reported 94 combinations of ECG features and reference standards with wide variation in their definitions. Most studies had risks of bias from selection for coronary angiography and blinding to the ECG and/or reference standard. Meta-analysis combined 6 studies for STE and acute coronary lesion (Sn 0.70 [95% CI 0.54-0.82]; Sp 0.85 [95% CI 0.78-0.90]; LR + 4.7 [95% CI 3.3-6.7]; LR- 0.4 [95% CI 0.2-0.6]) and 4 studies for STE and revascularization (Sn 0.53 [95% CI 0.47-0.58]; Sp 0.86 [95% CI 0.80-0.91]; LR + 3.9 [95% CI 2.8-5.5]; LR- 0.5 [95% CI 0.5-0.6]). Overall certainty of evidence was low with substantial heterogeneity.

Conclusions: Based on low certainty evidence, STE had good classification for acute coronary lesion and fair classification for revascularization. STE was more specific than sensitive for these outcomes and no single ECG feature excluded them. Uniform definitions and terminology would greatly facilitate the interpretation of subsequent studies.

Keywords: cardiac arrest, electrocardiogram, coronary angiography, revascularization, systematic review, diagnostic test accuracy

Introduction

Out-of-hospital cardiac arrest (OHCA) affects over 350,000 individuals in the United States[1] and 275,000 individuals in Europe[2,3] each year. Additionally, in-hospital cardiac arrest (IHCA) occurs in 290,000 patients per year in the United States.[4]

Acute coronary syndromes are a common etiology for cardiac arrest patients without a clear non-cardiac cause for collapse.[5] A 12-

* Corresponding author.
E-mail address: reyno406@msu.edu (J.C. Reynolds).

https://doi.org/10.1016/j.resuscitation.2020.11.039
Received 29 July 2020; Received in revised form 16 November 2020; Accepted 27 November 2020

lead electrocardiogram (ECG) should be obtained as soon as possible after return of spontaneous circulation (ROSC) to identify acute ST segment elevation (STE).[6] The European Association for Percutaneous Cardiovascular Interventions, European Resuscitation Council, and European Society of Intensive Care Medicine all recommend emergent coronary angiography (CAG) for patients with STE on ECG resuscitated from cardiac arrest of suspected cardiac etiology.[6] Although more controversial, these organizations also suggest CAG for select patients without STE on ECG without obvious non-coronary etiology or who are electrically or hemodynamically unstable.[6] These recommendations are predicated on multiple observational studies (especially in cases with shockable initial cardiac rhythms) that indicate substantial prevalence of coronary disease (CAD) (70-95%) and acute coronary lesions (70-85%) among patients with STE on ECG, as well as residual prevalence of CAD (25-50%) and acute coronary lesions (25-35%) among patients without STE on ECG.[7]

Despite these recommendations, a comprehensive assessment of ECG diagnostic test accuracy (DTA) after ROSC is lacking. Nonspecific changes and specific mimics of myocardial injury (i.e. STE, ST-segment depression, and abnormal T-wave morphology) are observed in 3-16% of newly resuscitated patients.[8] Our primary aim was to conduct a diagnostic test accuracy (DTA) systematic review on the post-ROSC ECG for a coronary lesion amenable to emergency revascularization in adult subjects with ROSC after cardiac arrest in any setting with any initial rhythm. We focused on the presence of STE but recorded all post-ROSC ECG features to estimate DTA of all reported ECG parameters in the literature. We also investigated sources of heterogeneity and explored how the DTA of ECG findings varies by study and subject characteristics.

Methods

Protocol and Registration

The study protocol was prospectively submitted to the International Prospective Register of Systematic Reviews (PROSPERO) on January 19, 2019 (CRD42019120262) and is provided in the Supplemental Materials. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] The PRISMA checklist is provided in the Supplemental Materials.

Eligibility Criteria and Definitions

The study question was framed using the PICOST (Population, Intervention, Comparator, Outcome, Study Design, Timeframe) format: Among adult patients with ROSC after cardiac arrest in any setting with any initial rhythm (P), what is the diagnostic test performance of the post-ROSC ECG (I) compared to coronary angiography (C) to detect a coronary lesion amenable to revascularization (O)? Human randomized and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-after studies, cohort studies), and diagnostic studies were eligible for inclusion so long as they contained data on both ECG findings and coronary angiography results that enabled construction of a complete 2×2 table (i.e. true positive, false positive, false negative, true negative). Studies reporting only test positive or test negative subjects were excluded since they did not provide estimates of both sensitivity and specificity. Animal studies, case series, case reports, narrative reviews, editorials, comments, letters to the editor, and unpublished studies (e.g., conference abstracts, trial protocols) were excluded. There were no limitations on publication period or manuscript language, provided there was an English abstract.

The index test was a standard 12-lead ECG, which is typically obtained as soon as possible after ROSC. We expected *a priori* that STE would be most commonly reported, but also collected data on the binary presence or absence of any reported ECG feature.

The *a priori* target condition was ‘coronary lesion amenable to revascularization’. This binary classification included coronary lesions treated by any revascularization strategy: angioplasty, stenting, or coronary artery bypass grafting (CABG) and implies that clinicians believed they were treating an acute lesion or significant occlusion associated with the cardiac arrest. We intentionally did not phrase the target condition as ‘culprit lesion’, which is difficult to adjudicate retrospectively without primary subject-level data (e.g. precise clinical history, coronary angiography images, etc.). However, upon reviewing full-text manuscripts for selection, we discovered wide variability in reporting of CAG findings and what constituted a clinically significant finding or endpoint. This included coronary artery disease (variable percentage stenosis cutoffs), angiographic evidence of an acute-appearing coronary artery lesion (variable definitions), revascularization (variable indications), and composite definitions. In order to report the complete scope of literature, we expanded the scope of our *a priori* sensitivity analyses to include these other definitions and report each of them.

Literature Search

After collaboratively developing the search strategy (Supplemental Materials) to capture each component of the PICO question, an information specialist searched the following electronic bibliographic databases through February 18, 2020: PubMed, EMBASE, CINAHL, Cochrane Library, and Web of Science. We also searched gray literature sources (Scopus, Google Scholar, and relevant professional association websites). Finally, we hand-searched references of relevant guidelines statements from the American College of Cardiology, the American Heart Association, and the International Liaison Consortium on Resuscitation, as well as those from studies included in the systematic review.

Study Selection

Two authors (PJM and JCR) used pre-defined screening criteria to independently screen all titles and abstracts retrieved by the systematic search. After resolving disagreements regarding selection of articles by discussion or adjudication with a third investigator (MDB), they independently reviewed those articles retained for full-text assessment. Disagreements regarding eligibility were resolved by discussion. We calculated Kappa statistics for inter-rater agreement during screening and final inclusion. If studies were missing key data but otherwise eligible, we contacted study authors for requisite data.

Data Collection

Two investigators (PJM and JCR) used a pre-defined and piloted standardized data collection tool to independently extract data pertinent to the PICOST question. These included study design and setting, subject selection criteria and characteristics, case features, ECG interpretation, and CAG indications and interpretation. Discrepancies in extracted data were identified and resolved via discussion.

Bias Assessment

Two investigators (JCR and PJM) independently assessed risk of bias of individual studies and disagreements were resolved via discussion, with adjudication by other study authors (MDB and RDM) when necessary. We used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist.[10] Using tailored guidelines for each domain after an initial pilot and refinement process, we assessed studies for both risk of bias and applicability to the PICOST question across the domains of subject selection, index test, reference standard, and flow and timing. The signaling questions and criteria used to rate risk of bias are the in the Supplemental Materials.

In addition to standardized risk of bias assessment, we especially considered selection bias for CAG, in which subjects selected for invasive coronary angiography are enriched with particular clinical or case features associated with a higher probability of survival and favorable neurologic outcome. Given the potential for these features to confound the true estimate of prevalence and DTA, selection bias for CAG was deemed a critical risk of bias that precluded meta-analysis. Operationally, we determined this to include studies that reported exclusion criteria for CAG other than the presence of an obvious non-cardiac etiology of cardiac arrest.

Data Analysis and Synthesis

Test positive denotes presence of the ECG finding in question (e.g. STE). Disease positive denotes presence of the reference standard in question (e.g. acute coronary lesion). We tabulated true positives, false positives, false negatives, and true negatives for each study using RevMan 5.3 (Copenhagen, Denmark). Studies were assessed for clinical, methodological, and statistical heterogeneity; a p-value <0.10 indicated statistical heterogeneity and I-squared statistic (I^2) $>$ 50% indicated substantial statistical heterogeneity. Sufficiently homogenous studies without critical risk of bias were eligible for pooling with a random effects meta-analysis using the MIDAS module for STATA 15.1 (College Station, TX) to synthesize data within the bivariate mixed-effects regression framework.[11] This model estimates mean logit sensitivity and logit specificity with respective standard errors, then back-transforms into summary estimates of sensitivity and specificity with 95% confidence

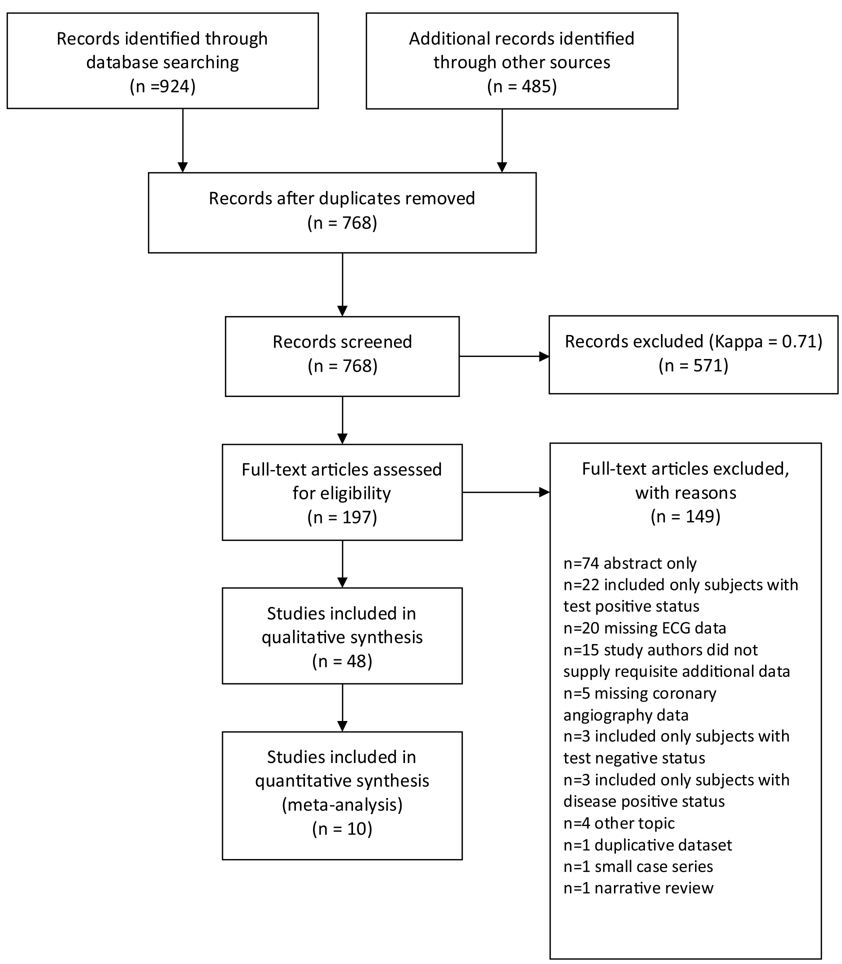

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram illustrating the selection of included studies.

Table 1 – Characteristics of included studies. CAG: coronary angiography. OHCA: out-of-hospital cardiac arrest. CAD: coronary artery disease. TH: therapeutic hypothermia. STE: ST-segment elevation. RWMA: regional wall motion abnormality. TTE: transthoracic echocardiography. VF: ventricular fibrillation. BSPM: Body surface potential mapping. ROSC: return of spontaneous circulation. cTnT: cardiac troponin T. VF: ventricular fibrillation. VT: Ventricular tachycardia. IHCA: in-hospital cardiac arrest. TTM: targeted temperature management. GCS: Glasgow coma scale. TOR: termination of resuscitation. STEMI: ST-segment elevation myocardial infarction. LBBB: left bundle branch block. WLST: withdrawal of life sustaining therapy. DNR: do not resuscitate order. ECMO: extracorporeal membrane oxygenation. AMI: acute myocardial infarction. LV: left ventricle. LVH: left ventricular hypertrophy. ECG: electrocardiogram. ACS: acute coronary syndrome.

Author / Year	Subjects / Country / Years of Enrollment	Study Design	Inclusion Criteria	Exclusion Criteria	CAG indications	Case Mix (% OHCA)	Mean/ Median Age (years)	Sex (% male)	Shockable Rhythm (%)	Known CAD (%)	CAD risk factors (%)
Abe 2015 [14]	n = 47 Japan 2006-2011	Retrospective	Adult OHCA survivors with immediate CAG	-	Probable favorable neurologic outcome; no obvious non-cardiac etiology	100%	55	89%	94%	6%	17%
Akin 2018 [15]	n = 224 Germany 2011-2015	Registry-based	Consecutive OHCA patients in HACORE registry treated per local protocol and received TH	-	No obvious non-cardiac etiology	100%	64	78%	73%	-	56%
Almalla 2019 [16]	n = 219 Germany 2011-2015	Retrospective	Adult OHCA survivors with immediate CAG	-	STE; shockable rhythm; known CAD; clinical suspicion; RWMA on TTE; rising troponin levels	100%	60	73%	70%	-	-
Anyfantakis 2009 [17]	n = 72 France 2001-2006	retrospective	adults with ROSC after OHCA; received CAG	-	No obvious non-cardiac etiology	100%	58	78%	50%	22%	62%
Aurore 2011 [18]	n = 133 France 2000-2006	Retrospective	Consecutive OHCA survivors brought to nearest coronary angiography unit	-	STE; clinical suspicion despite absent STE	100%	61	83%	68%	28%	33%
Batistia 2010 [19]	n = 90 United States 2002-2009	Retrospective	Adults with ROSC after cardiac arrest; started induced hypothermia within 6 hours; received CAG	Early cessation of induced hypothermia	STE; clinical suspicion	97%	60	70%	47%	36%	50%
Berden 2019 [20]	n = 159 Slovenia 2013-2018	Retrospective	Adults OHCA survivors; presumed cardiac etiology; received immediate CAG	-	Presumed cardiac etiology; absence of nonshockable rhythm without STE; absence of advanced age or comorbidities; absence of low probability of neurologic recovery	100%	62	85%	89%	15%	59%
Bergman 2016 [21]	n = 194 Netherlands 2003-2010	Retrospective	Consecutive adult OHCA survivors admitted to hospital	-	STE; VF; suspicious TTE; cardiologist clinical discretion	100%	61	76%	93%	25%	-
Bro-Jeppesen 2012 [22]	n = 198 Denmark 2004-2010	Prospective	Consecutive adult OHCA survivors admitted to hospital	GCS >8; Cardiogenic shock	STE; new onset LBBB	100%	60	84%	89%	14%	26%
Callaway 2014 [23]	n = 765 United States /	Prospective	Adult OHCA survivors; enrolled in PRIMED trial; survived > 60 minutes after hospital arrival	TOR prior to hospital arrival; No ROSC; prisoners; pregnant women; DNR directives; traumatic injuries; exsanguination	-	100%	62	78%	77%	-	-

(continued on next page)

Table 1 *(continued)*

Author / Year	Subjects / Country / Years of Enrollment	Study Design	Inclusion Criteria	Exclusion Criteria	CAG indications	Case Mix (% OHCA)	Mean/ Median Age (years)	Sex (% male)	Shockable Rhythm (%)	Known CAD (%)	CAD risk factors (%)
	Canada 2007-2009										
Casella 2015 [24]	n = 97 Italy 2004-2012	Prospective	Adult OHCA survivors; comatose; no obvious non-cardiac etiology	GCS >8; terminal illness	STEMI; clinical discretion	100%	67	69%	87%	32%	62%
Cronier 2011 [25]	n = 91 France 2003-2008	Prospective	Consecutive adult OHCA survivors; shockable (ventricular) rhythm; requiring mechanical ventilation	Absent data re: interval from collapse to ROSC	Age < 80 years; Hemodynamically stable	100%	58	78%	100%	24%	41%
Daly 2013 [26]	n = 35 Ireland 2003-2006	Retrospective	Adult OHCA survivors after VF; Prehospital BSPM and 12-lead EKG obtained; Post-ROSC labs sampled for cTnT; CAG < 24 hours after ROSC	-	Inclusion criteria for study	100%	69	60%	100%	57%	89%
Dumas 2010 [27]	n = 435 France 2003-2008	Registry-based	Adults OHCA survivors; no obvious non-cardiac etiology	-	No obvious non-cardiac etiology	100%	59	83%	68%	-	53%
Dumas 2012 [28]	n = 422 France 2003-2008	Registry-based	Adults with ROSC after OHCA in PROCAT registry; troponin measured on hospital admission	-	No obvious non-cardiac etiology	100%	59	83%	68%	26%	45%
Garcia 2016 [29]	n = 231 United States 2013-2014	prospective	Adult (18-75 years) OHCA survivors; shockable initial rhythm	DNR; trauma; known terminal disease; hemorrhage	Shockable initial cardiac rhythm	100%	56	77%	100%	12%	42%
Garcia-Tejada 2014 [30]	n = 84 Spain 2005-2012	retrospective	Adult OHCA survivors; Received emergency CAG	Unavailable ECG; Did not receive CAG	No obvious non-cardiac etiology; absence of significant comorbidities; perceived likelihood of neurologic recovery	100%	59	79%	79%	17%	46%
Geri 2013 [31]	n = 272 France 2006-2010	Registry-based	Adult OHCA survivors; Had CAG	-	No obvious non-cardiac etiology	100%	60	77%	67%	-	65%
Geri 2015 [32]	n = 1,094 France 2000-2013	Registry-based	Adult OHCA survivors	-	No obvious non-cardiac etiology	100%	59	78%	70%	-	41%
Jentzer 2018 [33]	n = 283 United States 2005-2013	Registry-based	Adult OHCA survivors; presumed cardiac etiology	Absence of ROSC; obvious non-cardiac etiology of OHCA	Multidisciplinary decision incorporating clinical presentation, post-arrest illness severity, and perceived likelihood of neurologic recovery	100%	61	65%	70%	25%	56%
Kearney 2018 [34]	n = 729 United States 2014-2015	Registry-based	Adult OHCA survivors	Obvious non-cardiac etiology; no prehospital resuscitation attempted; subjects presenting to hospitals without PCI capability	-	100%	64	78%	71%	34%	20%

Table 1 *(continued)*

Author / Year	Subjects / Country / Years of Enrollment	Study Design	Inclusion Criteria	Exclusion Criteria	CAG indications	Case Mix (% OHCA)	Mean/ Median Age (years)	Sex (% male)	Shockable Rhythm (%)	Known CAD (%)	CAD risk factors (%)
Kern 2015 [35]	n = 439 International 2006-2011	Retrospective	Adults with ROSC after OHCA or IHCA; comatose; within 6 hours of ROSC; receiving TTM	-	-	79%	61	71%	71%	20%	-
Lagedal 2019 [36]	n = 1,133 Sweden 2008-2013	Registry-based	Adult OHCA survivors; in SRCR database; CAG within 28 days of admission	Awake upon admission	-	100%	64	78%	79%	16%	11%
Lee 2015 [37]	n = 135 South Korea 2006-2013	retrospective	Adult OHCA survivors; received CAG or CTCA	Obvious non-cardiac etiology; no available ECG	STE or elective clinical decision	100%	54	88%	81%	19%	38%
Lee 2017 [38]	n = 82 South Korea 2010-2014	registry-based	Adult OHCA survivors	-	STE; New onset LBBB; otherwise discretion of cardiology	100%	55	48%	66%	21%	46%
Lellouche 2011 [39]	n = 225 France 2004-2007	retrospective	Adult OHCA survivors; had ECG data available	Obvious non-cardiac etiology; pregnancy; known terminal illness prior to cardiac arrest	No obvious non-cardiac etiology	100%	59	79%	68%	23%	37%
Merchant 2008 [40]	n = 30 United States 2000-2005	retrospective	Adult IHCA survivors after VF; captured from hospital billing data and ICD-9 codes	OHCA; initial rhythm other than VF; no ROSC	-	0%	67	60%	100%	50%	67%
Moutacalli 2017 [41]	n = 160 France 2006-2013	retrospective	Adult OHCA survivors; comatose; received CAG	IHCA, delayed CAG > 24 hours; obviously non-cardiac etiology	No obvious non-cardiac etiology	100%	60	85%	22%	24%	43%
Patel 2016 [42]	n = 143,830 United States 2000-2012	Registry-based	Adult OHCA survivors; shockable rhythm	DNR; missing data; pregnancy; trauma	-	100%	63	68%	100%	-	50%
Pearson 2015 [43]	n = 107 United States 2007-2012	Registry-based	TTM clinical pathway; GCS < 9, not following commands	-	Clinical discretion; STE; age <75 years; collapse-to-ROSC < 20 minutes	100%	58	71%	85%	-	-
Radsel 2011 [44]	n = 212 Slovenia 2003-2008	Retrospective	Adult OHCA survivors; received CAG	Previous CABG	Clinical decision of cardiology; no obvious non-cardiac etiology; absence of significant comorbidities; realistic hope for neurologic recovery	100%	59	85%	86%	18%	49%
Redfors 2015 [45]	n = 638 Sweden 2005-2013	Registry-based	Registry subjects receiving CAG	-	-	88%	65	76%	-	16%	43%
Reynolds 2009 [46]	n = 96 United	Retrospective	Adults with ROSC after OHCA or IHCA		-	71%	61	64%	60%	49%	-

(continued on next page)

Table 1 *(continued)*

Author / Year	Subjects / Country / Years of Enrollment	Study Design	Inclusion Criteria	Exclusion Criteria	CAG indications	Case Mix (% OHCA)	Mean/ Median Age (years)	Sex (% male)	Shockable Rhythm (%)	Known CAD (%)	CAD risk factors (%)
	States 2005-2007			Early WLST < 6 hours; unavailable first GCS; planned emergent surgical intervention; immediate re-arrest							
Reynolds 2014 [47]	n = 344 United States 2005-2012	Retrospective	Adult survivors from OHCA or IHCA	Traumatic or surgical etiology of cardiac arrest; re-arrest with failure to resuscitate; WLST < 6 hours	Clinical judgment	73%	61	65%	69%	37%	43%
Sideris 2011 [48]	n = 300 France 2002-2011	Retrospective	Adult OHCA survivors	IHCA; obvious non-cardiac etiology; GCS > 7 on admission; refractory OHCA	No obvious non-cardiac etiology	100%	56	79%	45%	18%	37%
Sideris 2014 [49]	n = 165 France 2002-2008	retrospective	Adult OHCA survivors; received CAG	No CAG; No ROSC; No initial ECG for interpretation	No obvious non-cardiac etiology	100%	56	79%	51%	18%	40%
Spaulding 1997 [50]	n = 84 France 1994-1996	prospective	Adult OHCA survivors; received CAG	-	30-75 years old; OHCA occurred within 6 hours of symptoms; patients previously living normal life; no obvious non-cardiac etiology	100%	56	70%	93%	20%	38%
Staer-Jensen 2015 [51]	n = 210 Norway 2010-2013	Prospective	Adult OHCA survivors; had CAG	pregnancy; DNR; known end-stage malignancy; unwitnessed asystole	No obvious non-cardiac etiology	100%	62	64%	76%	31%	37%
Tateishi 2018 [52]	n = 155 Japan 2011-2015	Retrospective	Adults with ROSC after OHCA; no obvious non-cardiac etiology	Prolonged asystole after ECMO; emergency surgical repair for mechanical complication of AMI (e.g. rupture of LV free wall, ventricular septum, or papillary muscle)	No obvious non-cardiac etiology	100%	61	84%	85%	-	54%
Voicu 2012 [53]	n = 163 France 2002-2008	Retrospective	Adult OHCA survivors	No ROSC; No troponin measured on admission	No obvious non-cardiac etiology	100%	56	80%	50%	18%	40%
Wester 2018 [54]	n = 4,308 Sweden 2005-2016	Registry-based	Registry subjects receiving CAG	-	-	-	65	77%	-	25%	47%
Wijesekera 2014 [55]	n = 63 Australia 2007-2009	Retrospective	Adult OHCA survivors admitted to intensive care	Non-cardiac etiology of OHCA	STE; RWMA on TTE; no severe neurologic deficit; clinician discretion	100%	62	81%	83%	26%	51%
Wilson 2017 [56]	n = 440 United States 2000-2014	Retrospective	OHCA and IHCA survivors at participating hospitals	-	STEMI; cardiogenic shock; "other"	62%	-	58%	37%	-	-
Yamamoto 2019 [57]	n = 74 Japan 2012-2017	Retrospective	Adult OHCA survivors	Non-cardiac etiology of OHCA; severe hypoxic brain injury; unfavorable comorbidities; STEMI, LBBB, or LVH	-	100%	58	85%	73%	-	-
		Retrospective		-	Clinical judgment	100%	67	79%	75%	35%	63%

Table 1 (continued)

Author / Year	Subjects / Country / Years of Enrollment	Study Design	Inclusion Criteria	Exclusion Criteria	CAG indications	Case Mix (% OHCA)	Mean/ Median Age (years)	Sex (% male)	Shockable Rhythm (%)	Known CAD (%)	CAD risk factors (%)
Zanuttini 2012 [58]	n = 66 Italy 2008-2011		Adult OHCA survivors; persistently unconscious; no obvious non-cardiac etiology								
Zanuttini 2013 [59]	n = 91 Italy 2008-2011	Retrospective	Adult OHCA survivors; no obvious non-cardiac etiology	-	STEMI; clinical judgment; absence of significant comorbidities, low probability for neurologic recovery	100%	64	76%	77%	25%	60%
Zelias 2014 [60]	n = 400 Poland 2000-2010	Retrospective	Adult OHCA survivors; likely cardiac etiology; admitted for early CAG	-	Clinical judgment; suspicion for ACS	100%	61	81%	78%	27%	56%
Zeyons 2017 [61]	n = 177 France 2009-2013	Retrospective	Adult OHCA survivors; referred for CAG	-	No obvious non-cardiac etiology; suspected of ACS (clinical history, ECG, medical history)	100%	63	74%	49%	37%	48%

intervals. The derived logit estimates additionally construct a hierarchical summary receiver operating characteristic (ROC) curve with a summary operating point and surrounding two-dimensional 95% confidence region. Finally, we performed an *a priori* subgroup analysis of shockable and nonshockable initial cardiac rhythms and a *post hoc* subgroup analysis of studies with and without selection bias for CAG.

Using guidance documents from the online Grading of Recommendations Assessment, Development, and Evaluation (GRADE) handbook,[12] we assessed the certainty of the overall evidence ranging from very low certainty to high certainty of evidence.[13] We used GRADEpro software (McMaster University, 2014) to tabulate detailed assessment of overall risk of bias, inconsistency, imprecision, and indirectness. Specific signaling questions are provided in the Supplemental Materials.

Results

Study Selection

The search identified 768 unique titles and abstracts, of which 571 were excluded after initial review (Kappa 0.71) (Fig. 1). After reviewing 197 full-text articles for eligibility, an additional 149 were excluded leaving 48 manuscripts for inclusion (Kappa 1.0). No randomized studies were identified, and all included studies were observational cohorts.

Summary of Studies

Altogether, 48 studies enrolled 160,032 subjects with CAG between 1994-2018 and were published between 1997-2020.[14–61] There were 30 studies from Europe, 11 from North America, 5 from Asia, one from Oceana, and one from a trans-continental collaboration. Twenty-eight were retrospective analyses, 13 were registry-based studies, and 7 were prospective observational studies. Most (40/48) included strictly OHCA, but one included strictly IHCA and 7 had ranges of case mixes (56-97% OHCA). The mean/median age of subjects ranged from 54-69 years, median proportion male sex was 78% (IQR 71-81%), median proportion with initial shockable rhythm was 74% (IQR 68-86%), mean proportion with known CAD was 25 (SD 11%), and mean proportion with at least one CAD risk factor was 47 (SD 14%). Two-thirds (33/48) of studies reported selection criteria for CAG that were consistent with potential selection bias, whereas 15 studies described either consecutive subject selection for CAG or only excluded those with obvious non-cardiac etiology of cardiac arrest (Table 1).

We discovered wide variability in reported ECG findings and definitions of clinically significant CAG findings (Table 2). Of the 28 variations in ECG findings described, many centered around ST segments, but we also found variable reporting of T wave changes, conduction delays, and other miscellaneous findings. CAG findings were reported in terms of coronary artery disease (with a range of 0-100% stenosis cutoff values), angiographic evidence of an acute appearing lesion (e.g. ruptured plaque, TIMI 0/1 flow, lesion easily crossed by guidewire), revascularization attempts (percutaneous intervention, systemic fibrinolysis, or surgical revascularization), or part of a composite adjudication of the etiology of cardiac arrest. Reported indications for attempted revascularization included identification of culprit lesion, acute occlusion as suspected etiology of

Table 2 – Variability in definitions and terminology of electrocardiographic (ECG) findings and coronary angiography (CAG) results. STE: ST segment elevation. STD: ST segment depression. BSPM: body surface potential mapping. LBBB: left bundle branch block. RBBB: right bundle branch block. BBB: bundle branch block. msec: milliseconds. AV: atrioventricular. FFR: fractional flow reserve. TIMI: Thrombolysis in Myocardial Infarction. PCI: percutaneous coronary intervention. CABG: coronary artery bypass grafting. TTE: transthoracic echocardiography.

	ECG Finding (Index Test)		CAG Results (Reference Standard)
ST segments	STE	Coronary artery disease	> 0% stenosis (any stenosis)
	STE with reciprocal change		> 50% stenosis
	STE without reciprocal change		> 50% stenosis or FFR < 0.8
	STE with early repolarization		> 70% stenosis
	STE without early repolarization		> 75% stenosis
	STE in aVR		> 80% stenosis
	STE or new LBBB		> 90% stenosis
	STE on BSPM		100% stenosis
	STD		Significant, stable lesion without thrombus, staining, or ruptured plaque
	STD without reciprocal change	Evidence of an acute lesion	Angiographically acute-appearing lesion
	Non-specific ST changes		TIMI grade 0/1 flow
	Any abnormal ST segment		Lesion easily crossed by guidewire
	ST or T wave abnormalities	Revascularization	Attempted PCI
T waves	T wave inversion		Attempted PCI or fibrinolysis
	Hyperacute or peaked T wave		Attempted PCI or CABG
	New LBBB	Composite adjudication	Composite adjudication of CAG, TTE, troponin
Conduction delays	Any LBBB		'CAD considered etiology of cardiac arrest'
	RBBB		Composite of acute appearing lesion plus rise in serum troponin
			Composite >70% stenosis, ruptured plaque, or angiographic staining
	Any BBB		
	QRS widening		
	QRS widening or pacemaker rhythm		
	LBBB or RBBB or QRS widening		
	Bifascicular block		
	Abnormal U wave		
Miscellaneous	Q wave		
	Early repolarization without STE		
	Other signs of ischemia [a]		
	Atrial fibrillation		

[a] horizonal/down-sloping STD with T wave inversion in contiguous leads; ventricular tachycardia with QRS duration >120 msec and AV dissociation; atypical intraventricular conduction delay with QRS > 120 msec.

cardiac arrest, hemodynamically relevant stenoses, and clinical discretion of the treating clinician. Ultimately, we made a post-hoc decision to focus on the diagnostic test accuracy of STE for angiographic evidence of an acute appearing lesion, and STE for attempted revascularization as the two most clinically relevant combinations of ECG findings and CAG results. Diagnostic test accuracy for all other combinations are reported in Supplemental Table 1.

Bias and Applicability Assessment

The majority of included studies had high risks of bias related to selection for CAG and interpretation of the reference standard (Table 3). Most studies did not specify blinding to the ECG when interpreting CAG results. Similarly, most of the retrospective studies did not specify whether investigators were blinded to CAG results while interpreting the ECG. Some studies reported mixed samples of subjects with both urgent and delayed CAG. The primary concern with applicability of studies to the PICO question was subject selection for CAG (Table 3) and the studies identified with this critical risk of bias were deemed ineligible for inclusion in meta-analysis.

Certainty of Evidence

The overall certainty of evidence was rated as low for most combinations of sensitivity, specificity, and reference standard primarily due to risk of bias and inconsistency (Supplemental Table 2). The individual studies were at risk of bias from lack of blinding both to the ECG while interpreting the reference standard, and to the reference standard while interpreting the ECG.

Main Results

In total, 17 studies (n = 2,850 subjects) reported STE for angiographic evidence of an acute lesion (Table 4).[17,18,20,26,29,31,35,49–53,55,58,59] Ultimately, 6 studies (n = 1,037 subjects) without critical risk of bias were included in meta-analyses with prevalence of an angiographically acute appearing lesion ranging from 29-77% (mean 53% [SD 17%]).[17,31,48,50–53] STE had pooled sensitivity of 0.70 (95% CI 0.54-0.82) and specificity of 0.85 (95% CI 0.78-0.90); however, substantial statistical heterogeneity was present for both sensitivity ($I^2 = 92\%$) and specificity ($I^2 = 85\%$). These estimates correspond to LR + 4.69 (95% CI 3.30-6.68) and LR- 0.35 (95% CI 0.23-0.55). Area under the ROC curve was 0.87 (95% CI 0.83-0.89) (Figs. 2 and 3).

Table 3 – Risk of bias assessment using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2). ECG: electrocardiogram.

Study (Author Year)	Risk of Bias				Applicability		
	Subject Selection	Index Test	Reference Standard	Flow and Timing	Subject selection	Index Test	Reference Test
Abe 2015 [14]	High [a]	Low	High [e]	Low	High [a]	Low	High [c]
Akin 2018 [15]	Low	Unclear [b]	High [e]	Low	Low	Low	Low
Almalla 2019 [16]	Low	Unclear [b]	High [e]	Low	Low	Low	High [c]
Anyfantakis 2009 [17]	Low	Unclear [b]	High [e]	Low	Low	Low	High [c]
Aurore 2011 [18]	High [a]	Unclear [b]	High [e]	Low	High [a]	Low	High [c]
Batista 2010 [19]	High [a]	Unclear [b]	High [e]	Low	High [a]	Low	Low
Berden 2019 [20]	High [a]	Low	Low	Low	High [a]	Low	High c[c]
Bergman 2016 [21]	High [a]	Unclear [b]	High [e]	Low	High [a]	Low	Low
Bro-Jeppesen 2012 [22]	High [a]	Unclear [b]	High [e]	Low	High [a]	Low	Low
Callaway 2014 [23]	High [a]	Unclear [b]	High [e]	Low	High [a]	Low	Low
Casella 2015 [24]	High [a]	Unclear [b]	High [e]	Low	High [a]	Low	Low
Cronier 2011 [25]	High [a]	Low	High [e]	Low	High [a]	Low	Low
Daly 2013 [26]	High [a]	Low	High [e]	Low	High [a]	Low	High [c]
Dumas 2010 [27]	Low	Unclear [b]	High [e]	Low	Low	Low	Low
Dumas 2012 [28]	Low	Unclear [b]	High [e]	Low	Low	Low	Low
Garcia 2016 [29]	High [a]	Unclear [b]	High [e]	High [d]	High [a]	Low	Low
Garicia-Tejada 2014 [30]	High [a]	Low	Low	Low	High [a]	Low	Low
Geri 2013 [31]	Low	Unclear [b]	High [e]	Low	Low	Low	High [c]
Geri 2015 [32]	Low	Unclear [b]	High [e]	Low	Low	Low	Low
Jentzer 2018 [33]	High [a]	Unclear [b]	High [e]	Low	High [a]	Low	Low
Kearney 2018 [34]	High [a]	Unclear [b]	High [e]	Low	High [a]	Low	Low
Kern 2015 [35]	High [a]	Unclear [b]	High [e]	High [d]	High [a]	Low	Low
Lagedal 2019 [36]	High [a]	Low	High [e]	High [d]	High [a]	Low	Low
Lee 2015 [37]	High [a]	Low	Low	Low	High [a]	Low	High [c]
Lee 2017 [38]	High [a]	Low	High [e]	High [d]	High [a]	Low	High [c]
Lellouche 2011 [39]	Low	Low	High [e]	Low	Low	Low	High [c]
Merchant 2008 [40]	High [a]	Unclear [b]	High [e]	Low	High [a]	Low	Low
Moutacalli 2017 [41]	Low	Unclear [b]	High [e]	Low	Low	Low	Low
Patel 2016 [42]	High [a]	Unclear [b]	High [e]	High [d]	High [a]	Low	Low
Pearson 2015 [43]	High [a]	Unclear [b]	High [e]	High [d]	High [a]	Low	Low
Radsel 2011 [44]	High [a]	Low	Low	Low	High [a]	Low	Low
Redfors 2015 [45]	High [a]	Unclear [b]	High [e]	High [d]	High [a]	Low	High [c]
Reynolds 2009 [46]	High [a]	Unclear [b]	High [e]	High [d]	High [a]	Low	High [c]
Reynolds 2014 [47]	High [a]	Unclear [b]	High [e]	High [d]	High [a]	Low	Low
Sideris 2011 [48]	Low	Unclear [b]	High [e]	Low	Low	Low	High [c]
Sideris 2014 [49]	Low	Unclear [b]	High [e]	Low	Low	Low	High [c]
Spaulding 1997 [50]	High [a]	Low	Low	Low	High [a]	Low	High [c]
Stær-Jensen 2015 [51]	Low	Low	Low	Low	Low	Low	Low
Tateishi 2018 [52]	Low	Unclear [b]	High [e]	Low	Low	Low	Low
Voicu 2012 [53]	Low	Unclear [b]	High [e]	Low	Low	Low	High [c]
Wester 2018 [54]	High [a]	Unclear [b]	High [e]	High [d]	High [a]	Low	Low
Wijesekera 2014 [55]	High [a]	Unclear [b]	High [e]	High [d]	High [a]	Low	High [c]
Wilson 2017 [56]	High [a]	Unclear [b]	High [e]	Low	High [a]	Low	Low
Yamamoto 2019 [57]	High [a]	Low	Low	High [d]	High [a]	Low	High [c]
Zanuttini 2012 [58]	High [a]	Unclear [b]	High [e]	High [d]	High [a]	Low	High [c]
Zanuttini 2013 [59]	High [a]	Low	Low	High [d]	High [a]	Low	Low
Zelias 2014 [60]	High [a]	Unclear [b]	High [e]	Low	High [a]	Low	High [c]
Zeyons 2017 [61]	Low	Unclear [b]	High [e]	Low	Low	Low	High [c]

[a] Risk of selection bias for coronary angiography.
[b] Blinding to results of coronary angiography while interpreting the ECG was not specified; however, in clinical practice the ECG is typically obtained prior to coronary angiography.
[c] Reference standard based on coronary artery disease or angiographic evidence of an acute lesion, which differed from the *a priori* reference standard but was included in *post-hoc* reporting.
[d] Case mix of urgent and delayed coronary angiography.
[e] Blinding to the ECG while interpreting coronary angiography was not specified; in clinical practice, coronary angiography is typically performed after obtaining the ECG.

Table 4 – Characteristics of studies reporting ST elevation (index test) and angiographically acute-appearing coronary lesion (reference standard). OHCA: out-of-hospital cardiac arrest. CAD: coronary artery disease. CAG: coronary angiography. TP: true positive. FP: false positive. FN: false negative. TN: true negative.

Author Year	Subjects (n) Study Design	Location (% OHCA)	Mean/Median Age (years)	Sex (% male)	Shockable Rhythm (%)	Known CAD (%)	CAG Selection Bias	Prevalence Acute Lesion (%)	TP	FP	FN	TN
Anyfantakis 2009 [17]	72 Retrospective	100	58	78%	50%	22%	No	38%	21	7	6	38
Aurore 2011 [18]	133 Retrospective	100	61	83%	68%	28%	Yes	74%	51	14	47	21
Berden 2019 [20]	159 Retrospective	100	62	85%	89%	15%	Yes	48%	49	16	27	67
Daly 2013 [26]	35 Retrospective	100	69	60%	100%	57%	Yes	74%	5	0	21	9
Garcia 2016 [29]	231 Prospective	100	56	77%	100%	12%	Yes	77%	89	12	89	41
Geri 2013 [31]	272 Retrospective	100	60	77%	67%	-	No	49%	48	8	85	131
Kern 2015 [35]	439 Retrospective	79	61	71%	71%	20%	Yes	54%	154	38	82	165
Radsel 2011 [44]	212 Retrospective	100	59	85%	86%	18%	Yes	72%	140	18	13	41
Sideris 2011 [48]	165 Retrospective	100	56	79%	51%	18%	No	36%	53	17	7	88
Sideris 2014 [49]	300 Retrospective	100	56	79%	45%	18%	Yes	31%	74	35	19	172
Spaulding 1997 [50]	84 Prospective	100	56	70%	93%	20%	Yes	38%	28	8	4	44
Staer-Jensen 2015 [51]	210 Prospective	100	62	64%	76%	31%	No	29%	42	44	18	106
Tateishi 2018 [52]	155 Retrospective	100	61	84%	-	-	No	48%	42	10	32	71
Voicu 2012 [53]	163 Retrospective	100	56	80%	50%	18%	No	37%	49	17	11	86
Wijesekera 2014 [55]	63 Retrospective	100	62	81%	83%	26%	Yes	71%	30	0	15	18
Zanuttini 2012 [58]	66 Retrospective	100	67	79%	75%	35%	Yes	58%	22	6	16	22
Zanuttini 2013 [59]	91 Retrospective	100	64	76%	77%	25%	Yes	56%	34	6	17	34

In total, 24 studies (n = 156,060 subjects) reported STE for attempted revascularization (Table 5).[15,19,21–25,27–30,32–36,42–44,47,51,54,56,59] Ultimately, 4 studies (n = 2,161 subjects) without critical risk of bias were included in meta-analyses with prevalence of attempted revascularization ranging from 28-92% (mean 54% [SD 15%]).[27,28,32,51] STE had pooled sensitivity of 0.53 (95% CI 0.47-0.58) and specificity of 0.86 (95% CI 0.80-0.91); however, substantial statistical heterogeneity was present for both sensitivity (I^2 = 60%) and specificity (I^2 = 87%). These estimates correspond to LR + 3.9 (95% CI 2.8-5.5) and LR- 0.54 (95% CI 0.49-0.60). Area under the ROC curve was 0.68 (95% CI 0.64-0.72) (Figs. 2 and 3). Exploratory meta-regression is discussed in the Supplemental Materials.

Subgroup Analysis

Two studies (n = 266 subjects) reported data on STE and acute-appearing coronary lesion for subjects with shockable rhythms.[26,29] Sensitivity ranged from 0.19 (95% CI 0.07-0.39) to 0.50 (95% CI 0.42-0.58) and specificity ranged from 0.77 (95% CI 0.64-0.88) to 1.00 (95% CI 0.66-1.00). Five studies (n = 145,348 subjects) reported data on STE and attempted revascularization for subjects with shockable rhythms.[25,29,36,42,56] Sensitivity ranged from 0.36 (95% CI 0.28-0.44) to 0.80 (95% CI 0.66-0.91) and specificity ranged from 0.73 (95% CI 0.64-0.82) to 0.91 (95% CI 0.85-0.85). No studies reported data on STE and acute-appearing coronary lesion for subjects with nonshockable rhythms. Two studies (n = 337 subjects) reported data on STE and attempted revascularization for subjects with nonshockable rhythms.[36,56] Sensitivity ranged from 0.50 (95% CI 0.40-0.59) to 0.50 (95% CI 0.35-0.65) and specificity ranged from 0.55 (95% CI 0.46-0.67) to 0.78 (95% CI 0.69-0.86).

Studies of STE with evidence of selection bias for CAG had slightly higher pooled prevalence of acute lesions (56% vs. 40%) and attempted revascularization (50% vs. 45%) compared to those without selection bias for CAG. DTA estimates were more similar. For an angiographically acute-appearing lesion, sensitivity (0.66; 95% CI 0.64-0.69) and specificity (0.81; 95% CI 0.78-0.84) of STE in studies with evidence of selection bias were similar to sensitivity (0.70; 95% CI 0.54-0.82) and specificity (0.85; 95% CI 0.78-0.90) in those without evidence of selection bias for CAG. For attempted revascularization,

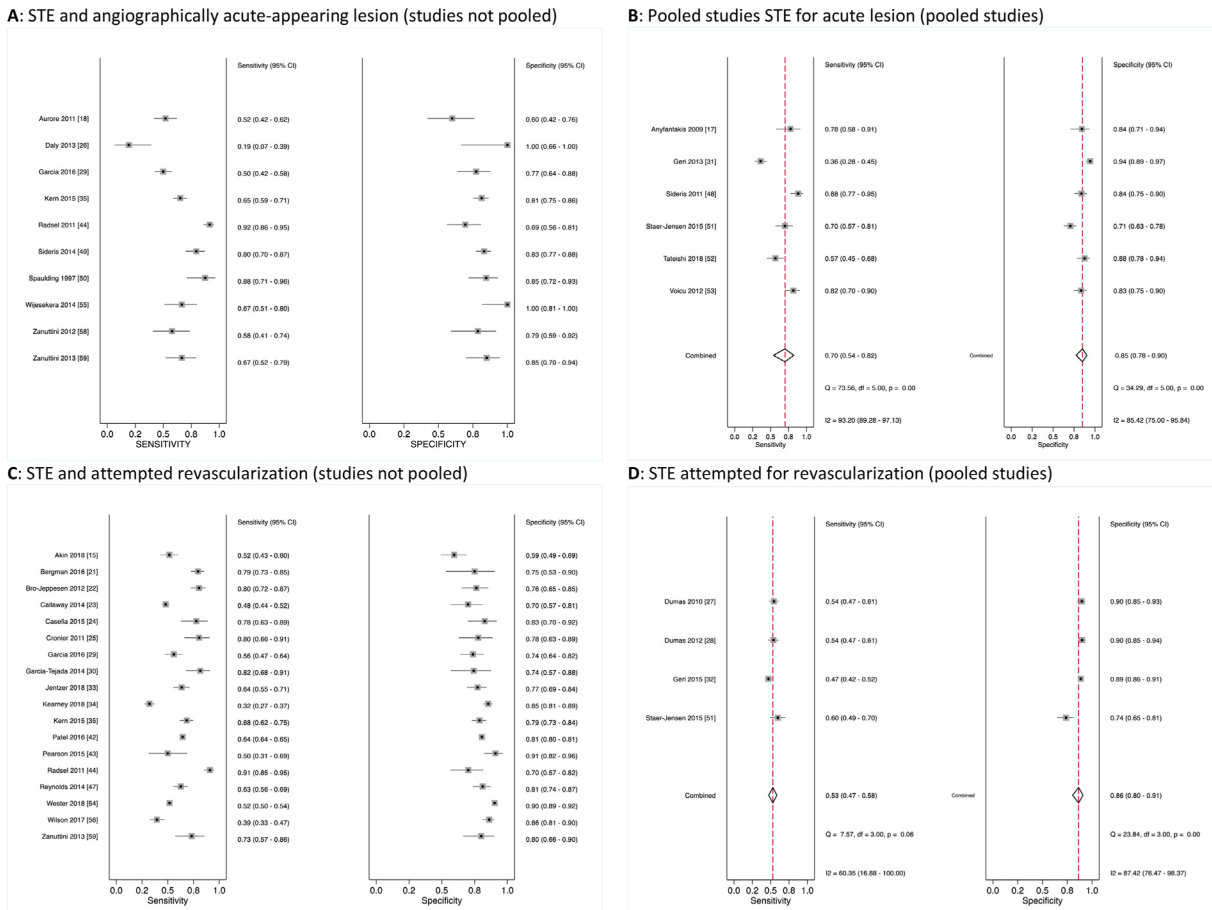

Fig. 2 – Forest Plots of sensitivity and specificity for ST segment elevation (STE) and either angiographic evidence of an acute coronary lesion (A, B) or attempted revascularization (C, D). Meta-analyses (B, D) included only those studies without critical risk of bias.
A**: STE and angiographically acute-appearing lesion (studies not pooled).** B**: Pooled studies STE for acute lesion (pooled studies).** C**: STE and attempted revascularization (studies not pooled).** D**: STE attempted for revascularization (pooled studies).**

sensitivity (0.64; 95% CI 0.63-0.64) and specificity (0.81; 95% CI 0.80-0.81) of STE in studies with evidence of selection bias were similar to estimates of sensitivity (0.53; 95% CI 0.47-0.58) and specificity (0.86; 95% CI 0.80-0.91) in those without evidence of selection bias for CAG.

Additional Findings

Sensitivity, specificity, and likelihood ratios for the other 92 combinations of ECG features and CAG findings are provided in the Supplemental Fig. 1. Overall, the specificity of most ECG features tended to be higher than its counterpart sensitivity for the reference standards of CAD, acute coronary lesions, and subsequent revascularization. Likewise, the specificity of many ECG features tended to be higher for the reference standard of CAD as opposed to an acute coronary lesion or subsequent revascularization. One study did report data on serial ECGs. Yamomoto, et al. found that among 74 subjects receiving CAG, STE in lead aVR was both more pronounced and more prevalent on repeat ECG (median 137 minutes) in those with an acute coronary lesion compared to those without an acute coronary lesion.[57] No included studies reported inter-rater reliability estimates for the interpretation of ECG or CAG.

Discussion

In this DTA systematic review and meta-analyses of electrocardiographic features in adults after resuscitation from cardiac arrest in any setting and any initial rhythm, the *a priori* target condition was a coronary lesion treated with emergency revascularization. However, given the striking variation in definitions and terminology of both ECG and CAG interpretation, we ultimately expanded this to include CAD, angiographic evidence of an acute lesion, and attempted revascularization We identified 28 discrete categories of ECG interpretation and 19 discrete definitions of a 'positive' CAG, indicating the need for professional societies to standardize terminology and reporting in this population.

Many of the identified studies contained risks of bias related to selection for CAG and lack of blinding to the index test when interpreting the reference standard. Though it would be difficult to operationalize blinding to the ECG in a prospective clinical trial of CAG, we strongly encourage subsequent observational studies to utilize methodology that minimizes this particular risk of bias. Mitigating these risks of bias would improve the certainty of evidence.

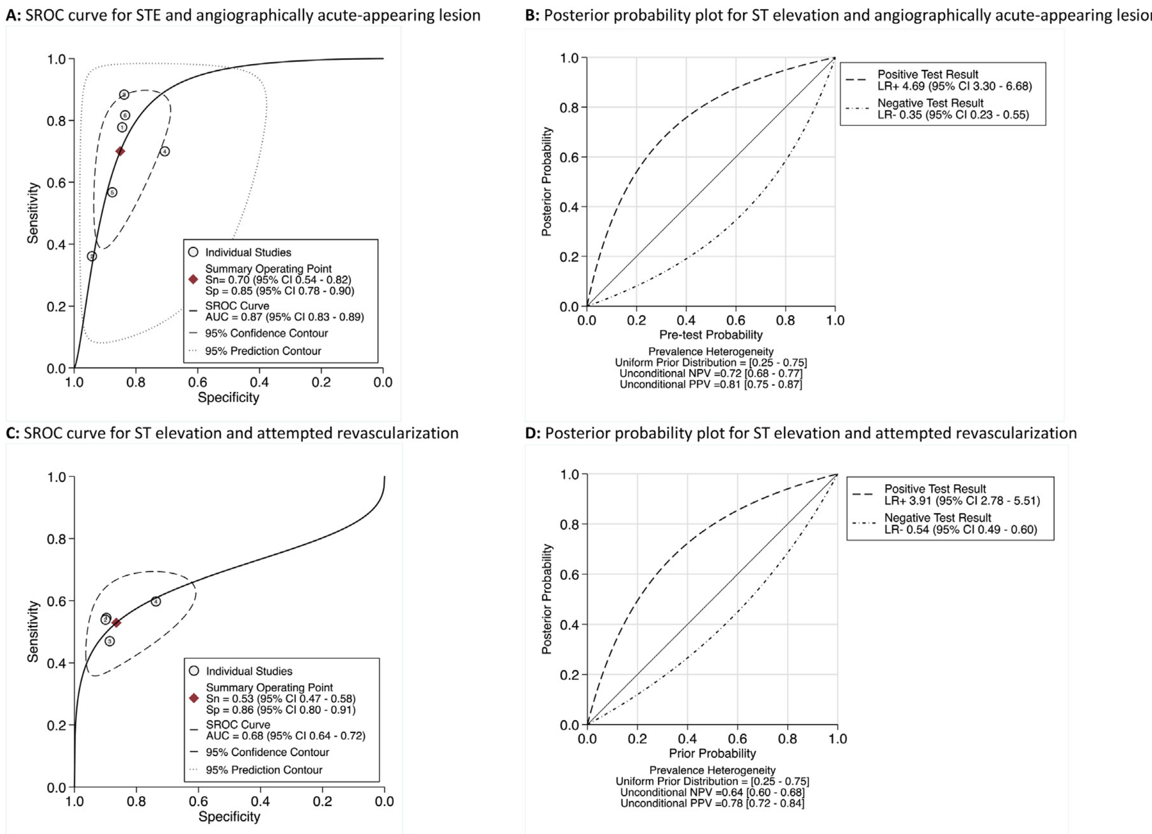

Fig. 3 – Summary receiver operating characteristic curves (SROC) (A, C) and posterior probability plots (B, D) for ST elevation and angiographically acute-appearing lesion (A, B), and ST elevation and attempted revascularization (B, D). A: **SROC curve for STE and angiographically acute-appearing lesion.** B: **Posterior probability plot for ST elevation and angiographically acute-appearing lesion.** C: **SROC curve for ST elevation and attempted revascularization.** D: **Posterior probability plot for ST elevation and attempted revascularization.**

STE tended to have higher specificity than sensitivity for acute lesions and attempted revascularization. The current practice recommendations are to perform CAG when STE is present.[6] However, best practices for subjects without STE remain uncertain, given the imperfect sensitivity of STE and residual risk of acute coronary lesions with subsequent need for revascularization. Moreover, we did not find any ECG feature with sufficient sensitivity to exclude the presence of an acute coronary lesion or subsequent need for revascularization. Overarching this issue of imperfect sensitivity are the competing risks of severe neurologic injury and/or withdrawal of life sustaining therapy due to neurologic prognosis.[62] Given these competing risks, seven additional randomized clinical trials of early vs. delayed strategies of coronary angiography will collectively enroll 5,000 subjects over the next 5 years.[7] Although our data do not directly inform the optimal timing of coronary angiography *per se*, these DTA estimates suggest prudence in pursuing additional testing in patients without STE and without a clear non-cardiac etiology of cardiac arrest. This may constitute combining specific ECG findings (Supplemental Table 1) or performing an intermediate diagnostic test such as echocardiography or computerized tomography coronary angiography. Such combination diagnostic approaches require further investigation to estimate their DTA.

When considering a delayed strategy for CAG, the false negative rate of STE (subjects without STE that actually have an acute lesion or receive attempted revascularization) is an important consideration. The COACT trial tested early and delayed strategies of coronary angiography in subjects with shockable initial cardiac rhythms, but without STE.[63] Compared to the 16% false negative rate for an acute angiographic lesion reported in the COACT trial, we tabulated higher false negative rates among two studies (both with selection bias for CAG) reporting data for 266 subjects with shockable rhythms (54%; range 50-81%).[26,29] The higher false negative rates in our data may be from more selective approach to CAG in these studies that tends to yield populations enriched with acute coronary lesions. Whereas compared to the 40% false negative rate for attempted revascularization reported in the COACT trial, we tabulated similar false negative rates among four studies (all with selection bias for CAG) reporting data for subjects for 145,117 subjects with shockable rhythms (36%; range 20-64%).[25,36,42,56] The false negative rates of STE for these outcomes will be important to note when interpreting the forthcoming trials testing early vs. delayed coronary angiography in this population.[7]

The ideal selection criteria of post-cardiac arrest patients for CAG remains an active area of clinical debate and different practice patterns emerged during this systematic review. Some studies described a more liberal approach to CAG, either including consecutive patients or only excluding those with obvious non-cardiac etiology. Most centers reported a more conservative approach

Table 5 – Characteristics of studies reporting ST elevation (index test) and attempted revascularization (reference standard). OHCA: out-of-hospital cardiac arrest. CAD: coronary artery disease. CAG: coronary angiography. TP: true positive. FP: false positive. FN: false negative. TN: true negative.

Author Year	Subjects (n) Study Design	Location (% OHCA)	Mean/ Median Age (years)	Sex (% male)	Shockable Rhythm (%)	Known CAD (%)	CAG Selection Bias	Prevalence Revascularization (%)	TP	FP	FN	TN
Akin 2018 [15]	233 Retrospective	100%	64	78%	73%	6%	Yes	57%	68	41	64	60
Batista 2010 [19]	90 Retrospective	97%	60	70%	47%	36%	Yes	22%	10	10	10	60
Bergman 2016 [21]	194 Retrospective	100%	61	76%	93%	25%	Yes	88%	135	6	35	18
Bro-Jeppesen 2012 [22]	198 Prospective	100%	60	84%	89%	14%	Yes	62%	98	18	24	58
Callaway 2014 [23]	765 Prospective	100%	62	78%	77%	-	Yes	92%	338	18	367	42
Casella 2015 [24]	97 Prospective	100%	67	69%	87%	32%	Yes	46%	35	9	10	43
Cronier 2011 [25]	91 Prospective	100%	58	78%	100%	24%	Yes	51%	37	10	9	35
Dumas 2010 [27]	435 Registry-based	100%	59	83%	68%	-	No	46%	110	24	92	209
Dumas 2012 [28]	422 Registry-based	100%	59	83%	68%	26%	No	46%	104	23	89	206
Garcia 2016 [29]	231 Prospective	100%	56	77%	100%	12%	Yes	59%	76	25	60	70
Garcia-Tejada 2014 [30]	84 Retrospective	100%	59	79%	79%	17%	Yes	58%	40	9	9	26
Geri 2015 [32]	1,094 Registry-based	100%	59	78%	70%	-	No	44%	225	70	254	545
Jentzer 2018 [33]	283 Registry-based	100%	61	65%	70%	25%	Yes	53%	96	30	55	102
Kearney 2018 [34]	729 Registry-based	100%	64	78%	71%	34%	Yes	49%	114	55	240	320
Kern 2015 [35]	439 Retrospective	79%	61	71%	71%	20%	Yes	48%	143	49	66	181
Lagedal 2020 [36]	1,133 Retrospective	100%	64	78%	79%	16%	Yes	57%	374	89	270	400
Patel 2016 [42]	143,830 Registry-based	100%	63	68%	100%	-	Yes	50%	46,083	14,077	25,436	58,234
Pearson 2015 [43]	107 Registry-based	100%	58	71%	85%	-	Yes	28%	15	7	15	70
Radsel 2011 [44]	212 Retrospective	100%	59	85%	86%	18%	Yes	73%	141	17	14	40
Reynolds 2014 [47]	344 Retrospective	73%	61	65%	69%	37%	Yes	58%	126	27	75	116
Staer-Jensen 2015 [51]	210 Prospective	100%	62	64%	76%	31%	No	44%	55	31	37	87
Wester 2018 [54]	4,308 Registry-based	-	65	77%	-	25%	Yes	55%	1,223	189	1,141	1,755
Wilson 2017 [56]	440 Retrospective	62%	-	58%	37%	-	Yes	44%	77	34	118	211
Zanuttini 2013 [59]	91 Retrospective	100%	64	76%	77%	25%	Yes	45%	30	10	11	40

in which CAG was restricted to patients with specific case features or material clinical suspicion for a cardiac etiology of cardiac arrest. Our data support the notion that selection bias for CAG yields populations enriched with angiographically acute-appearing lesions and revascularization attempts. However, despite higher prevalence of both angiographically acute appearing coronary lesions and attempted revascularization in studies with a more restrictive approach to CAG, we found fairly similar DTA estimates between studies with and without evidence of selection bias for CAG. Thus, utilizing a more liberal or restrictive approach appears to affect the post-test probability of an angiographically acute-appearing lesion or subsequent attempted revascularization by modifying pre-test probability (i.e. prevalence) as opposed to modifying the actual DTA of STE. (Fig. 3).

Applying these estimates to clinical practice depends largely on the clinical setting and selection criteria utilized for CAG. Settings with a more liberal approach to CAG will tend to have a less biased estimate of disease prevalence (i.e. pre-test probability). Based on 40% prevalence of an acute coronary lesion in studies with a liberal approach to CAG, we estimate 76% (95% CI 69-82%) post-test probability when STE is present and 21% (95% CI 12-29%) post-test probability when STE is absent. Based on 45% prevalence of subsequent revascularization in studies with a liberal approach to CAG, we estimate 76% (95% CI 70-82%) post-test probability when STE is present and 29% (95% CI 29-33%) when STE is absent. These post-test probability estimates vary somewhat depending on underlying prevalence of the target condition (Supplemental Table 3).

Additional observational studies may add to the findings of this systematic review (NCT04096079). Unfortunately, the forthcoming randomized clinical trials of CAG timing after resuscitation from cardiac arrest are unlikely to add new data to this systematic review, since they will exclusively enroll subjects without STE.[7] This will not permit completion of a 2×2 table thereby restricting DTA estimates to positive predictive value of STE. However, quantifying the variation in prevalence of acute coronary lesions and revascularization in these different settings with corresponding variation in positive predictive values of STE may prove a useful exercise.

Limitations

This systematic review had several limitations First, the reference standard ‘attempted revascularization’ potentially excludes subjects in whom a coronary lesion was not approachable with percutaneous measures but were not otherwise eligible for CABG. It also potentially excludes subjects with an acute appearing lesion that was either not treated due to mitigating clinical factors or was treated in a delayed fashion beyond the data collection of an individual study. Furthermore, advancements in interventional device technology over the 24 years of subject enrollment may have impacted which lesions were deemed amenable to revascularization. Second, we did not specifically construct the literature search to capture cases of coronary vasospasm that might have precipitated cardiac arrest but were managed medically and not necessarily revascularized. Finally, nine studies reported subject characteristics for their entire cohort, but not for the subset that received CAG (range 56-96%); in those cases, we interpolated subject characteristics from the entire cohort.

Conclusions

STE after resuscitation from cardiac arrest has good classification for acute coronary lesion, and fair classification for subsequent revascularization. However, STE is more specific than sensitive for these outcomes. The absence of STE does not exclude the presence of an acute coronary lesion and additional testing may be prudent in these patients unless a clear non-cardiac etiology of cardiac arrest is identified. This evidence is of low certainty due to inconsistency and risks of bias in measuring the index test and reference standard. The establishment of uniform definitions and terminology describing ECG and CAG findings after cardiac arrest would greatly facilitate the interpretation of subsequent studies.

Credit Author Statement

Study design: PJM, JCR, RDM, MDB

Developed methodology: PJM, JCR, MDB

Data acquisition: PJM, JCR Data analysis: PJM, JCR

Data interpretation: PJM, JCR, RDM, MDB

Drafting manuscript: PJM, JCR

Critical revision of manuscript: PJM, JCR, RDM, MDB

Sources of Funding

None

Author Disclosures

Dr. McFadden has nothing to declare.

Dr. Madder has nothing to declare.

Dr. Brown has nothing to declare.

Dr. Reynolds is an author or co-author on three studies included in this systematic review.

Acknowledgments

The authors gratefully acknowledge Iris Kovar-Gough, MA, MLIS, AHIP, for her invaluable assistance with the literature search.

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.2020.11.039.

REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019 CIR0000000000000659.

2. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. Resuscitation. 2010;81:1479−87.
3. Gräsner JT, Lefering R, Koster RW, et al. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: A prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. Resuscitation. 2016;105:188−95.
4. Holmberg M, Ross C, Fitzmaurice G, et al. Annual Incidence of Adult and Pediatric In-Hospital Cardiac Arrest in the United States. Circulation: Cardiovascular Quality and Outcomes. 2019.
5. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation. 2020;141:e139−596.
6. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation 2015;95:202−22.
7. Yannopoulos D, Bartos JA, Aufderheide TP, et al. The Evolving Role of the Cardiac Catheterization Laboratory in the Management of Patients With Out-of-Hospital Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019;139:e530−52.
8. Kim YJ, Min SY, Lee DH, et al. The Role of Post-Resuscitation Electrocardiogram in Patients With ST-Segment Changes in the Immediate Post-Cardiac Arrest Period. JACC Cardiovasc Interv. 2017;10:451−9.
9. Moher D, Liberati A, Tetzlaff J, Altman DG, PRIMSA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
10. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155:529−36.
11. Dwamena B. MIDAS: Stata module for meta-analytical integration of diagnostic test accuracy studies. Statistical Software Components. 2007. S456880, Boston College Department of Economics, revised Feb 5. 2009.
12. Schünemann H, Jan Brożek J, Guyatt G, Oxman A. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Introduction to GRADE Handbook. Updated October. 2013. . Accessed March 27, 2020 https://gdt.gradepro.org/app/handbook/handbook.html#h.f7lc8w9c3nh8.
13. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. . BMJ. 2008;336:924−6.
14. Abe T, Watanabe S, Mizuno A, Toyama M, Totten VY, Tokuda Y. A model for predicting angiographically normal coronary arteries in survivors of out-of-hospital cardiac arrest. J Intensive Care 2015;3:32.
15. Akin M, Sieweke JT, Zauner F, et al. Mortality in Patients With Out-of-Hospital Cardiac Arrest Undergoing a Standardized Protocol Including Therapeutic Hypothermia and Routine Coronary Angiography: Experience From the HACORE Registry. JACC Cardiovasc Interv 2018;11:1811−20.
16. Almalla M, Kersten A, Altiok E, Burgmaier M, Marx N, Schröder J. Outcome predictors of patients with out of hospital cardiac arrest and immediate coronary angiography [published online ahead of print, 2019 Nov 12]. Catheter Cardiovasc Interv 2019 10.1002/ccd.28582.
17. Anyfantakis ZA, Baron G, Aubry P, et al. Acute coronary angiographic findings in survivors of out-of-hospital cardiac arrest. Am Heart J 2009;157:312−8.
18. Aurore A, Jabre P, Liot P, Margenet A, Lecarpentier E, Combes X. Predictive factors for positive coronary angiography in out-of-hospital cardiac arrest patients. Eur J Emerg Med 2011;18:73−6.
19. Batista LM, Lima FO, Januzzi Jr JL, Donahue V, Snydeman C, Greer DM. Feasibility and safety of combined percutaneous coronary intervention and therapeutic hypothermia following cardiac arrest. Resuscitation 2010;81:398−403.
20. Berden J, Steblovnik K, Noc M. Mechanism and extent of myocardial injury associated with out-of-hospital cardiac arrest. Resuscitation 2019;138:1−7.
21. Bergman R, Hiemstra B, Nieuwland W, et al. Long-term outcome of patients after out-of-hospital cardiac arrest in relation to treatment: a single-centre study. Eur Heart J Acute Cardiovasc Care 2016;5:328−38.
22. Bro-Jeppesen J, Kjaergaard J, Wanscher M, et al. Emergency coronary angiography in comatose cardiac arrest patients: do real-life experiences support the guidelines? Eur Heart J Acute Cardiovasc Care 2012;1:291−301.
23. Callaway CW, Schmicker RH, Brown SP, et al. Early coronary angiography and induced hypothermia are associated with survival and functional recovery after out-of-hospital cardiac arrest. Resuscitation 2014;85:657−63.
24. Casella G, Carinci V, Cavallo P, et al. Combining therapeutic hypothermia and emergent coronary angiography in out-of-hospital cardiac arrest survivors: Optimal post-arrest care for the best patient. Eur Heart J Acute Cardiovasc Care 2015;4:579−88.
25. Cronier P, Vignon P, Bouferrache K, et al. Impact of routine percutaneous coronary intervention after out-of-hospital cardiac arrest due to ventricular fibrillation. Crit Care 2011;15:R122.
26. Daly MJ, Finlay DD, Scott PJ, Nugent CD, Adgey AA, Harbinson MT. Pre-hospital body surface potential mapping improves early diagnosis of acute coronary artery occlusion in patients with ventricular fibrillation and cardiac arrest. Resuscitation 2013;84:37−41.
27. 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;3:200−7.
28. Dumas F, Manzo-Silberman S, Fichet J, et al. Can early cardiac troponin I measurement help to predict recent coronary occlusion in out-of-hospital cardiac arrest survivors? Crit Care Med 2012;40:1777−84.
29. 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;5:e002670.
30. Garcia-Tejada J, Jurado-Román A, Rodríguez J, et al. Post-resuscitation electrocardiograms, acute coronary findings and in-hospital prognosis of survivors of out-of-hospital cardiac arrest. Resuscitation 2014;85:1245−50.
31. Geri G, Mongardon N, Dumas F, et al. Diagnosis performance of high sensitivity troponin assay in out-of-hospital cardiac arrest patients. Int J Cardiol 2013;169:449−54.
32. Geri G, Dumas F, Bougouin W, et al. Immediate Percutaneous Coronary Intervention Is Associated With Improved Short- and Long-Term Survival After Out-of-Hospital Cardiac Arrest. Circ Cardiovasc Interv 2015;8:e002303.
33. Jentzer JC, Scutella M, Pike F, et al. Early coronary angiography and percutaneous coronary intervention are associated with improved outcomes after out of hospital cardiac arrest. Resuscitation. 2018;123:15−21.
34. Kearney KE, Maynard C, Smith B, Rea TD, Beatty A, McCabe JM. Performance of coronary angiography and intervention after out of hospital cardiac arrest. Resuscitation 2018;133:141−6.
35. 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;8:1031−40.
36. Lagedal R, Elfwén L, Jonsson M, et al. Coronary angiographic findings after cardiac arrest in relation to ECG and comorbidity. Resuscitation 2020;146:213−9.
37. Lee SE, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B. Combined ECG, Echocardiographic, and Biomarker Criteria for Diagnosing Acute Myocardial Infarction in Out-of-Hospital Cardiac Arrest Patients. Yonsei Med J 2015;56:887−94.
38. Lee TR, Hwang SY, Cha WC, et al. Role of coronary angiography for out-of-hospital cardiac arrest survivors according to postreturn of

spontaneous circulation on an electrocardiogram. Medicine (Baltimore) 2017;96:e6123.
39. Lellouche N, Sacher F, Jorrot P, et al. Sudden cardiac arrest: ECG repolarization after resuscitation. J Cardiovasc Electrophysiol 2011;22:131–6.
40. Merchant RM, Abella BS, Khan M, et al. Cardiac catheterization is underutilized after in-hospital cardiac arrest. Resuscitation 2008;79:398–403.
41. Moutacalli Z, Georges JL, Ajlani B, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest without obvious extracardiac cause: Who benefits? Ann Cardiol Angeiol (Paris) 2017;66:260–8.
42. Patel N, Patel NJ, Macon CJ, et al. Trends and Outcomes of Coronary Angiography and Percutaneous Coronary Intervention After Out-of-Hospital Cardiac Arrest Associated With Ventricular Fibrillation or Pulseless Ventricular Tachycardia. JAMA Cardiol 2016;1:890–9.
43. Pearson Da, Wares Cm, Mayer Ka, et al. Troponin Marker for Acute Coronary Occlusion and Patient Outcome Following Cardiac Arrest. West J Emerg Med. 2015;16:1007–13.
44. Radsel P, Knafelj R, Kocjancic S, Noc M. Angiographic characteristics of coronary disease and postresuscitation electrocardiograms in patients with aborted cardiac arrest outside a hospital. Am J Cardiol 2011;108:634–8.
45. Redfors B, Råmunddal T, Angerås O, et al. Angiographic findings and survival in patients undergoing coronary angiography due to sudden cardiac arrest in western Sweden. Resuscitation 2015;90:13–20.
46. Reynolds JC, Callaway CW, El Khoudary SR, Moore CG, Alvarez RJ, Rittenberger JC. Coronary angiography predicts improved outcome following cardiac arrest: propensity-adjusted analysis. J Intensive Care Med 2009;24:179–86.
47. Reynolds JC, Rittenberger JC, Toma C, Callaway CW. Post Cardiac Arrest Service. Risk-adjusted outcome prediction with initial post-cardiac arrest illness severity: implications for cardiac arrest survivors being considered for early invasive strategy. Resuscitation 2014;85:1232–9.
48. Sideris G, Voicu S, Dillinger JG, et al. Value of post-resuscitation electrocardiogram in the diagnosis of acute myocardial infarction in out-of-hospital cardiac arrest patients. Resuscitation 2011;82:1148–53.
49. Sideris G, Voicu S, Yannopoulos D, et al. Favourable 5-year postdischarge survival of comatose patients resuscitated from out-of-hospital cardiac arrest, managed with immediate coronary angiogram on admission. Eur Heart J Acute Cardiovasc Care 2014;3:183–91.
50. Spaulding CM, Joly LM, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med 1997;336:1629–33.
51. Stær-Jensen H, Nakstad ER, Fossum E, et al. Post-Resuscitation ECG for Selection of Patients for Immediate Coronary Angiography in Out-of-Hospital Cardiac Arrest. Circ Cardiovasc Interv 2015;8:e002784.
52. Tateishi K, Abe D, Iwama T, Hamabe Y, Aonuma K, Sato A. Clinical value of ST-segment change after return of spontaneous cardiac arrest and emergent coronary angiography in patients with out-of-hospital cardiac arrest: Diagnostic and therapeutic importance of vasospastic angina. Eur Heart J Acute Cardiovasc Care 2018;7:405–13.
53. Voicu S, Sideris G, Deye N, et al. Role of cardiac troponin in the diagnosis of acute myocardial infarction in comatose patients resuscitated from out-of-hospital cardiac arrest. Resuscitation 2012;83:452–8.
54. Wester A, Mohammad MA, Andell P, et al. Coronary angiographic findings and outcomes in patients with sudden cardiac arrest without ST-elevation myocardial infarction: A SWEDEHEART study. Resuscitation 2018;126:172–8.
55. Wijesekera VA, Mullany DV, Tjahjadi CA, Walters DL. Routine angiography in survivors of out of hospital cardiac arrest with return of spontaneous circulation: a single site registry. BMC Cardiovasc Disord 2014;14:30.
56. Wilson M, Grossestreuer AV, Gaieski DF, Abella BS, Frohna W, Goyal M. Incidence of coronary intervention in cardiac arrest survivors with non-shockable initial rhythms and no evidence of ST-elevation MI (STEMI). Resuscitation 2017;113:83–6.
57. Yamamoto M, Witsch T, Kubota S, Hara H, Hiroi Y. Diagnostic value of lead aVR in electrocardiography for identifying acute coronary lesions in patients with out-of-hospital cardiac arrest. Resuscitation 2019;142:97–103.
58. Zanuttini D, Armellini I, Nucifora G, et al. Impact of emergency coronary angiography on in-hospital outcome of unconscious survivors after out-of-hospital cardiac arrest. Am J Cardiol 2012;110:1723–8.
59. Zanuttini D, Armellini I, Nucifora G, et al. Predictive value of electrocardiogram in diagnosing acute coronary artery lesions among patients with out-of-hospital-cardiac-arrest. Resuscitation 2013;84:1250–4.
60. Zeliaś A, Stępińska J, Andres J, Trąbka-Zawicki A, Sadowski J, Żmudka K. Ten-year experience of an invasive cardiology centre with out-of-hospital cardiac arrest patients admitted for urgent coronary angiography. Kardiol Pol 2014;72:687–99.
61. Zeyons F, Jesel L, Morel O, et al. Out-of-hospital cardiac arrest survivors sent for emergency angiography: a clinical score for predicting acute myocardial infarction. Eur Heart J Acute Cardiovasc Care 2017;6:103–11.
62. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med 2004;30:2126–8.
63. Lemkes JS, Janssens GN, van der Hoeven NW, et al. Coronary Angiography after Cardiac Arrest without ST-Segment Elevation. N Engl J Med. 2019;380:1397–407.