Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Detailed Trial Characteristics

The authors responsible for writing the protocol

Jorrit Lemkes, Heleen Oudemans-van Straaten and Niels van Royen.

Steering committee

Niels van Royen (Chair), Department of Cardiology, Amsterdam University Medical Centre location VUmc, Jorrit Lemkes, Department of Cardiology, Amsterdam University Medical Centre location VUmc, Heleen Oudemans-van Straaten, Department of Intensive care medicine, Amsterdam University Medical Centre location VUmc, Lucia Jewbali, Thoraxcenter, Erasmus Medical center, Michiel Voskuil, Department of Cardiology, University Medical Centre Utrecht. Martijn Meuwissen, Department of Cardiology Amphia Hospital.

The trial statistician

Peter van de Ven

The data safety monitoring board

Freek Verheugt (Chair), OLVG, Eric Boersma (statistician), Thoraxcenter, Erasmus Medical center, Ruud Koster, Amsterdam University Medical Centre location AMC.

List of participating centers

COACT Investigators	Investigators centers	No. of patients
Current: Jorrit Lemkes Previous: Niels van Royen	Amsterdam University Medical Center, location VUmc, Amsterdam	105
Current: Lucia Jewbali Previous: Koen Nieman	Erasmus Medical Center, Rotterdam	93
Martijn Meuwissen	Amphia Hospital, Breda	48
Hans Bosker	Rijnstate Hospital, Arnhem	39
Gabe Bleeker	HAGA Hospital, Den Haag	36
George Vlachojannis	Maasstad Hospital, Rotterdam	35
Pim van der Harst	University Medical Center, Groningen	34
Michiel Voskuil	University Medical Center, Utrecht	29
Bert Beishuizen	Medisch Spectrum Twente, Enschede	28
Cyril Camaro	Radboud University Medical Center, Nijmegen	23
José Henriques	Amsterdam University Medical Center, location AMC, Amsterdam	16
Maarten Vink	OLVG, Amsterdam	14
Ton Heestermans	Noord West Ziekenhuisgroep, Alkmaar	13
Thijs Delnoij	Maastricht University Medical Center, Maastricht	12
Gillian Jessurun	Scheper Hospital, Emmen	10
Pranobe Oemrawsingh	Haaglanden Medical Center, Den Haag	7
Marcel Gosselink	Isala Hospital, Zwolle	5
Koos Plomp	Ter Gooi Hospital, Blaricum	3
Michael Magro	Elisabeth-Tweesteden Hospital, Tilburg	2

Inclusion criteria COACT Trial

- Age > 18 years
- Comatose patients (Glasgow coma score < 8) with return of spontaneous circulation after out-of-hospital cardiac arrest.
- Ventricular tachycardia or ventricular fibrillation as initial arrest rhythm. Including patients treated with an AED.

Abbreviations: AED: automatic external defibrillator.

Exclusion criteria COACT Trial

- Signs of STEMI on the ECG at the emergency department (including new LBBB or isolated ST depression in V1-V3 due to an true posterior infarct).
- Hemodynamic instability unresponsive to medical therapy. Defined as a prolonged (>30 min) systolic blood pressure <90 mmHg at the time of screening.
- An obvious or suspected non-coronary cause of the arrest.
- A known severe renal dysfunction (GFR<30 ml/min).
- Obvious or suspected pregnancy.
- Suspected or confirmed acute intracranial bleeding.
- Suspected or confirmed acute stroke.
- Known limitations in therapy or DO Not Resuscitate-order.
- Known pre-arrest Cerebral Performance Category 3 or 4.
- >4 hours (from return of spontaneous circulation to screening).
- Refractory ventricular arrhythmia.
- Known inability to complete 90-day follow-up.

ECG: electrocardiogram, GFR: glomerular filtration rate, LBBB: left bundle branch block, STEMI: ST-segment elevation myocardial infarction,

Informed consent process

Patients screened for the trial were unconscious and unable to consent at the time of screening. Legal representatives were often not present and if present frequently in no mental state to make a well-considered decision about participating in the study. The study intervention regarded an emergency intervention that had to be applied without delay and fulfilled the ethical requirements of clinical equipoise. Therefore, the patient was informed about the study intervention if and when consciousness recovered. In case the patient did not recover and remained unable to communicate, we informed the legal representative about the study. At that time, consent for use of the study data (deferred consent) was asked. If the patient had died before consent was obtained, the study data was used and no consent was obtained from the legal representatives. The rationale for the latter is that the legal representatives have no say within Dutch legislation about clinical or study data of a deceased. Furthermore, possible refusal may have caused unwanted selection bias(1).

During the first phase of the inclusion period, patients consented to a follow up period up to 90 days. As the follow up period was extended to 5 years during the inclusion period of the study, an additional consent was asked (for the group patients who had consented earlier with the 90 day follow up).

Definition of unstable coronary lesion

All coronary lesions with a stenosis severity of ≥70% and the presence of characteristics of plaque disruption including lesion irregularity, dissection, haziness or thrombus defined by coronary angiography.

Discontinuation of treatment

Patients after OHCA showing no neurological improvement after therapeutic temperature management and discontinuation of sedative medication due to postanoxic coma have a detrimental outcome. If clinical assessment, somatosensory-evoked potentials, and/or electroencephalography, performed 72 hours after the arrest and at least 24 hours after rewarming, predicts a poor outcome (defined as death or a persistent vegetative state), a multidisciplinary team may, in accordance with Dutch and European guidelines, decide to withdraw or limit life-sustaining treatment(2). If there is no consensus or uncertainty about potential recovery, the decision is postponed and the assessment is repeated at a later time.

Biomarker measurements

Venous blood samples for creatine kinase, creatine kinase-MB mass and troponin T or I determination were obtained at admission and at 3, 6, 12, 24, 36, 48 and 72 hours after admission. Creatinine and lactate were obtained at admission, at 24, 48, 72 hours, and at discharge on the ICU.

Outcome definitions

Death

Death of all cause.

Myocardial infarction:

The definition of myocardial infarction in the COACT trial is based on the universal definition of myocardial infarction(3) and is reported since the index hospitalization.

Repeat revascularization:

Any revascularization procedure (PCI or CABG) after the initial revascularization procedure during the index hospitalization.

Additional statistical analysis

Continuous variables are summarized by mean and standard deviation if data were normal and median and interquartile range (IQR) otherwise. Normality was assessed visually by means of QQ-plots. Mean differences with 95% confidence intervals are presented for normally distributed end points and ratio of geometric means with 95% confidence intervals are presented for continuous outcomes that are not normally distributed. Dichotomous outcomes are summarized by frequencies and percentage with odds ratios reported as the effect size together with a 95% confidence interval.

Time to death was visualized by means of Kaplan-Meier curves with the hazard ratio based on a Cox regression model reported as effect size.

A sensitivity analysis was performed to assess the robustness of the conclusions for the end point of survival to missingness due to drop out (lacking of informed consent). Two extreme settings were considered: a setting in which all 16 patients with missing survival data in the immediate group were assumed survivors and all 14 patients with missing survival data in the delayed group were assumed non-survivors and a setting in which all 16 patients with missing survival data in the immediate group were assumed non-survivors and all 14 patients with missing survival data in the delayed group were assumed survivors. Odds ratios with 95% confidence intervals and p-values for the chi-square test were calculated for both these extreme settings.

eFigure 1. Screening sample

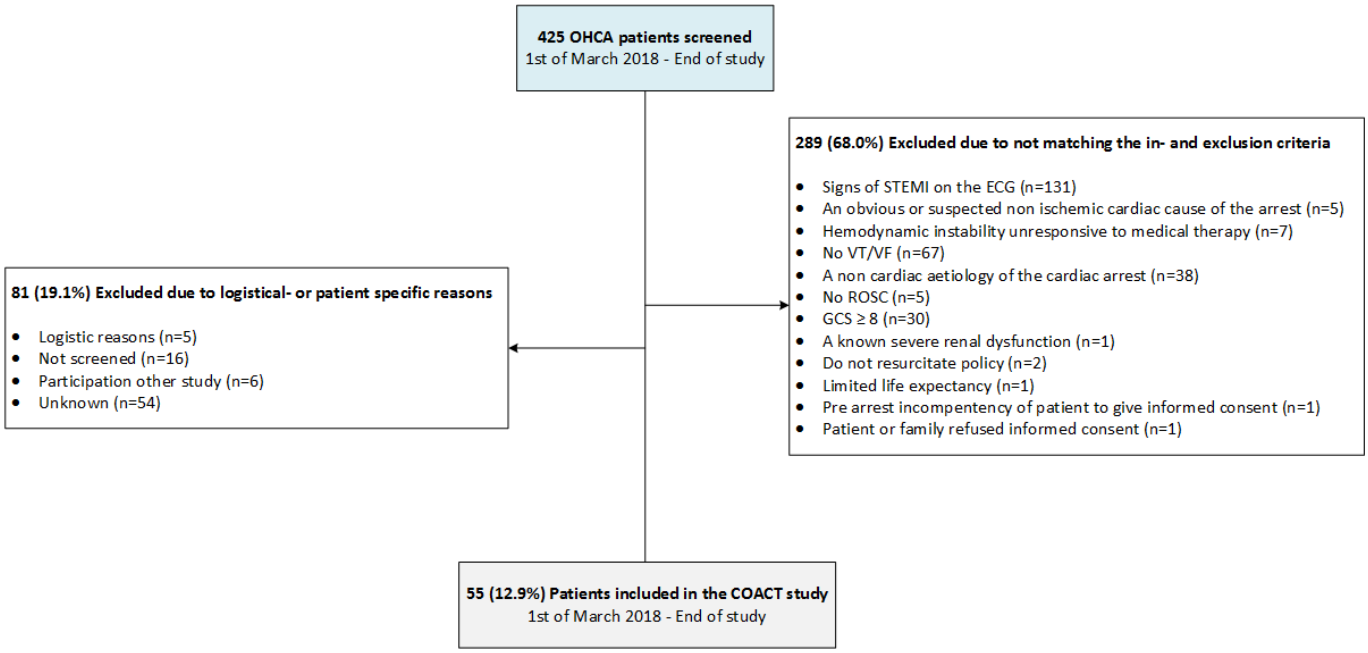


Figure legend: The screening sample comprises screened OHCA patients and their exclusion reasons from the 1st of March until the end of the study (17th of July). During this period, all participating centers were enrolling patients.

Abbreviations: COACT, coronary angiography after cardiac arrest; ECG, electro cardiogram; GCS, Glasgow coma scale; OHCA, out of hospital cardiac arrest; ROSC, return of spontaneous circulation; STEMI, ST-segment elevated myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

eTable 1. Supplementary procedural and Treatment Characteristics

Variable	Immediate Angiography group (n = 264)	Delayed Angiography group (n = 258)
CAG access site - no./total no. (%)		
Femoral	153/256 (59.8)	45/166 (27.1)
Radial	103/256 (40.2)	121/166 (72.9)
Location of acute unstable lesion - no./total no. (%)		
LM	1/33 (3.0)	1/27 (3.7)
LAD	9/33 (27.3)	10/27 (37.0)
RCX	15/33 (45.5)	11/27 (40.7)
RCA	8/33 (24.2)	5/27 (18.5)
Graft	0/33 (0.0)	0/27 (0.0)
Location acute thrombotic occlusion - no./total no. (%)		
LM	0/8 (0.0)	0/13 (0.0)
LAD	0/8 (0.0)	4/13 (30.8)
RCX	6/8 (75.0)	7/13 (53.8)
RCA	2/8 (25.0)	2/13 (15.4)
Graft	0/8 (0.0)	0/13 (0.0)
Aspiration thrombectomy - no./total no. (%)	5/256 (2.0)	1/167 (0.6)
Timing of PCI		
PCI performed during first CAG - no. (%)	61/86 (70.9)	49/63 (77.8)
Staged PCI - no. (%)	19/86 (22.1)	14/63 (22.2)
PCI both first CAG and staged - no. (%)	6/86 (7.0)	0/63 (0.0)
Treated coronary arteries by PCI - no./total no. (%)		
Left main	7/86 (8.1)	3/63 (4.8)
LAD	39/86 (45.3)	33/63 (52.4)
RCX	34/86 (39.5)	28/63 (44.4)
RCA	25/86 (29.1)	19/63 (30.2)
Graft	4/86 (4.7)	0/63 (0.0)
Median total number of stents (IQR) - no.	1 (1-2)	1 (1-2)
Stent type - no./total no. (%)		
Bare metal	1/75 (1.3)	1/57 (1.7)
Drug-eluting	70/75 (92.1)	55/57 (93.2)
Other	4/75 (5.3)	2/57 (3.4)
Median total stent length (IQR) - mm	30 (19-61)	24 (15-48)
Median time from randomization to CABG (IQR) - days	13.5 (10.5-23.4)	16.1 (14.0-19.3)
ICD implantation* - no. (%)	107 (40.5)	102 (39.5)
Intensive care support		
Noradrenaline administration - no. (%)	231 (87.5)	225 (87.2)
Dobutamine administration - no. (%)	65 (24.6)	76 (29.5)
Dopamine administration - no. (%)	11 (4.2)	17 (6.6)
Phosphodiesterase administration - no. (%)	20 (7.6)	24 (9.3)
Targeted temperature management - no. (%)	248 (93.9)	241 (93.4)
Median time to targeted temperature (IQR) - hr	5.5 (2.9-8.6)	4.7 (2.4-7.2)

Targeted temperature management goal - no./total no. (%)		
Hypothermia (30-35.9°C)	152/246 (61.8)	147/240 (61.3)
Normothermia (36-37°C)	94/246 (38.2)	93/240 (38.8)
Targeted temperature management method - no. (%)		
Surface cooling device[∞]	194/248 (78.2)	185/241 (76.8)
Intravascular cooling device[§]	54/248 (21.8)	56/241 (23.2)
Lowest temperature	33.7±1.5	33.7±1.5
Assist device used - no. (%)	9 (3.4)	6 (2.3)
Median duration of stay at ICU (IQR) - days	4 (2-6)	4 (2-6)
Medical treatment during hospitalization		
Salicylates - no. (%)	201 (76.1)	225 (87.2)
$P2Y_{12}$ inhibitor - no. (%)	152 (57.6)	184 (71.3)
Ticagrelor - no./total no. (%)	94/263 (35.7)	104/257 (40.5)
Prasugrel - no./total no. (%)	2/263 (0.8)	1/257 (0.4)
Clopidogrel - no. (%)	57/263 (21.7)	81/257 (31.5)
Unfractionated heparin/LMWH - no. (%)	238 (90.2)	229 (88.8)
Bivalirudin - no. (%)	2 (0.8)	2 (0.8)
Glycoprotein IIb/IIIa inhibitor - no. (%)	17 (6.4)	7 (2.7)
Statins - no. (%)	167 (63.3)	178 (69.0)
Betablocker - no./total no. (%)	180/263 (68.4)	181/257 (70.4)
ACE-inhibitor/angiotensin II receptor blocker -no./total no. (%)	158/263 (60.1)	164/257 (63.8)
Amiodarone - no./total no. (%)	73/263 (27.8)	81/258 (31.4)
Median duration of hospitalization (IQR) - days	11 (5-20)	14 (6-22)

Abbreviations: ACE, angiotensin-converting-enzyme; CABG, coronary artery bypass graft; CAG, coronary angiography; ICD, implantable cardioverter defibrillator; ICU, intensive care unit; IQR, interquartile range; LAD; left anterior descending artery; LMWH, low molecular weight heparin; RCA, right coronary artery; RCX, right coronary circumflex; SD, standard deviation.

[†] 35 of these patients went for urgent intervention due to cardiac deterioration.

[¥] Six of these patients went for urgent intervention due to cardiac deterioration.

***** In the immediate angiography group at least three and in the delayed angiography group at least four patients already had an ICD before inclusion.

[∞] Surface cooling devices included water circulating cooling blankets and gel-coated adhesive pads.

[§] Intravascular cooling devices are endovascular cooling catheters.

e Table 2. Reasons for crossover

Study No.	Randomized strategy	Crossover to	Comment
110098	Immediate invasive	Delayed invasive	Patient appeared to have hematoperitoneum
130021	Immediate invasive	Delayed invasive	After randomization patient appeared to have do-not-resuscitate order
140025	Immediate invasive	Delayed invasive	Patient appeared to have subarachnoidal bleeding
150024	Immediate invasive	Delayed invasive	Splenic rupture became apparent
150054	Immediate invasive	Delayed invasive	Congenital heart disease emerged as suspected cause of cardiac arrest
150062	Immediate invasive	Delayed invasive	Aorta dissection emerged as suspected cause of cardiac arrest
150093	Immediate invasive	Delayed invasive	Patient appeared to have epidural hematoma
160010	Immediate invasive	Delayed invasive	Logistical reasons
160016	Immediate invasive	Delayed invasive	Logistical reasons
230036	Immediate invasive	Delayed invasive	No significant abnormalities on recent coronary angiography
250001	Immediate invasive	Delayed invasive	High bleeding risk
250008	Immediate invasive	Delayed invasive	Logistical reasons
120005	Delayed invasive	Immediate invasive	Logistical reasons
150017	Delayed invasive	Immediate invasive	Human error
160023	Delayed invasive	Immediate invasive	Reason unknown

eTable 3. Urgent CAG in patients from the delayed invasive strategy

No. of patients	Comment
8	Recurrent ventricular arrhythmia, unresponsive to medical therapy
13	STEMI
1	Cardiogenic shock
13	Other reason

Abbreviations: STEMI, ST segment elevation myocardial infarction.

eTable 4. Reasons for withdrawal of life-sustaining treatment

Outcome	Immediate Angiography Group (N=76)	Delayed Angiography Group (N=69)	P Value
Reason withdrawal of life-sustaining treatment – no./total no. (%)			0.09
Brain death	12 (15.8)	9 (13.0)	
Neurological reasons*	44 (57.9)	40 (58.0)	
Multi organ failure	12 (15.8)	14 (20.3)	
Comorbidity	0 (0.0)	4 (5.8)	
Other reasons	8 (10.5)	2 (2.9)	

* Neurologic reasons is severe brain damage with persistent coma.

e Table 5. Sensitivity analysis of survival at 1 year

Survival at 1 year – no./total no. (%)	**Immediate Invasive Group (N=280)**	**Delayed Invasive Group (N=272)**	**Odds ratio (95% CI)**	**P Value***
Missing immediate 'yes', missing delayed 'no'	178 (63.6)	165 (61.0)	1.13 (0.79-1.60)	0.48
Missing immediate 'no', missing delayed 'yes'	162 (57.9)	179 (65.8)	0.71 (0.51-1.01)	0.055

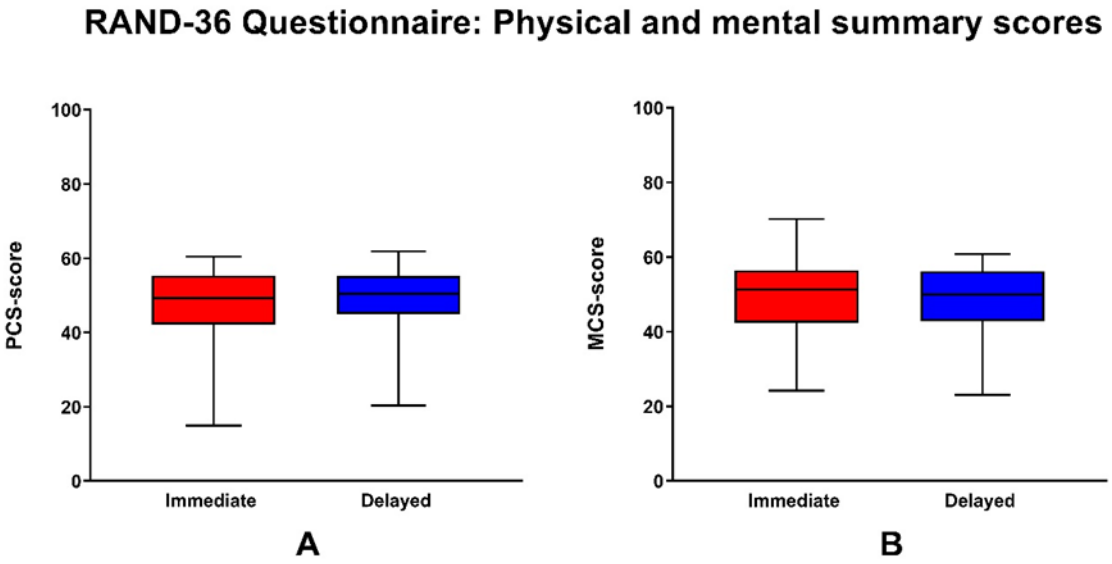
***** The delayed invasive group is used as the reference group for odds ratios and mean differences.

eTable 6 RAND-36 Questionnaire

Patient reported measures	Immediate Angiography group (n = 119)	Delayed Angiography group (n = 116)
RAND-36® PCS - Median (IQR)	49.2 (42.2-55.3)	50.4 (44.9-55.2)
RAND-36® MCS - Median (IQR)	51.3 (42.4-56.4)	50.0 (42.8-56.2)

RAND-36®, Health insurance study questionnaire. Abbreviations: PCS, Physical component summary score; MCS, Mental component summary score

eFigure 2.



RAND-36®, Health insurance study questionnaire. A: PCS, Physical component summary score B: MCS, Mental component summary score.

eReferences

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3. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012;33(20):2551-67.

