Coronary angiography after cardiac arrest: Rationale and design of the COACT trial

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Background Ischemic heart disease is a major cause of out-of-hospital cardiac arrest. The role of immediate coronary angiography (CAG) and percutaneous coronary intervention (PCI) after restoration of spontaneous circulation following cardiac arrest in the absence of ST-segment elevation myocardial infarction (STEMI) remains debated.

Hypothesis We hypothesize that immediate CAG and PCI, if indicated, will improve 90-day survival in post–cardiac arrest patients without signs of STEMI.

Design In a prospective, multicenter, randomized controlled clinical trial, 552 post–cardiac arrest patients with restoration of spontaneous circulation and without signs of STEMI will be randomized in a 1:1 fashion to immediate CAG and PCI (within 2 hours) versus initial deferral with CAG and PCI after neurological recovery. The primary end point of the study is 90-day survival. The secondary end points will include 90-day survival with good cerebral performance or minor/moderate disability, myocardial injury, duration of inotropic support, occurrence of acute kidney injury, need for renal replacement therapy, time to targeted temperature control, neurological status at intensive care unit discharge, markers of shock, recurrence of ventricular tachycardia, duration of mechanical ventilation, and reasons for discontinuation of treatment.

Summary The COACT trial is a multicenter, randomized, controlled clinical study that will evaluate the effect of an immediate invasive coronary strategy in post–cardiac arrest patients without STEMI on 90-day survival. (Am Heart J 2016;180:39-45.)

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death in Europe and the United States. Despite advances in the field of resuscitation and intensive care management, the outcome of these patients remains poor. A recent large trial reported a mortality of 50% in patients successfully resuscitated from OHCA admitted to the intensive care unit (ICU) for targeted temperature management (TTM). This high mortality rate is the result of post–cardiac arrest syndrome, a condition that includes anoxic brain injury, myocardial dysfunction, and systemic ischemic reperfusion injury due to hypoperfusion during the cardiac arrest.
The etiology of OHCA itself is diverse and consists of both cardiac and noncardiac causes. The most frequent cardiac cause is ischemic heart disease, and coronary artery disease has been reported in up to 70% of resuscitated patients referred for immediate coronary angiography (CAG).3

Directly after the arrest, the exact diagnosis and prognosis are often unclear and can lead to uncertainty on the optimal hospital management. In patients presenting with a ST-segment elevation myocardial infarction (STEMI) and cardiac arrest, the preferred treatment is an acute CAG with percutaneous coronary intervention (PCI) because this can salvage myocardium and may improve outcome.4,5

In cardiac arrest patients without signs of STEMI, the etiology of the arrest is heterogeneous and includes noncardiac causes, nonschemic cardiac causes, and chronic coronary artery disease. Nevertheless, an acute thrombotic coronary occlusion was reported during early angiography in up to 26.6% of postresuscitation patients without signs of STEMI on the electrocardiogram (ECG).6 It might therefore be insufficient to select patients eligible for an immediate invasive strategy solely on the ECG findings. Moreover, postresuscitation ECGs often tend to be difficult to interpret. Furthermore, information normally used when choosing an invasive strategy in patients suspected of an acute coronary syndrome who are not resuscitated, such as medical history and symptoms, is often lacking in OHCA patients who are unresponsive on admission.

This is why it has been suggested that an immediate CAG should be considered in OHCA patients without an obvious noncoronary cause, regardless of ECG patterns.7

However, no randomized controlled trials have been published aiming to determine the effectiveness of an immediate CAG in reducing mortality in OHCA patients. Several nonrandomized studies have reported on patients resuscitated from cardiac arrest where immediate CAG was only performed in selected cases.6,8-18

A number of these studies showed a survival benefit for patients who underwent an acute CAG. However, these studies included patients with cardiac arrest of mixed etiology and contained both patients with STEMI and those with non-STEMI (NSTEMI). Furthermore, these results should be interpreted with caution because of potential selection bias by choosing patients with a presumed better prognosis for an immediate invasive strategy.20

The here outlined CoroNary Angiography after Cardiac arresT (COACT) study is a randomized controlled trial investigating the effects of immediate CAG (and PCI as needed) in patients after OHCA without signs of STEMI or an obvious noncoronary cause of the arrest.

Methods
Study design
COACT is a prospective, multicenter, randomized, controlled clinical study evaluating the effect of an immediate CAG in patients after OHCA on 90-day survival. A total of 14 centers in the Netherlands will enroll patients. These centers are all high-volume PCI centers with 24/7 STEMI service and extensive experience treating OHCA patients. Patients are eligible for the study if they have ventricular tachycardia or fibrillation during the arrest, have restoration of spontaneous circulation (ROSC), and are without ECG signs of STEMI or an obvious noncoronary cause of the arrest.

Further inclusion and exclusion criteria are listed in Tables I and II. A total of 552 eligible patients will be randomized to either immediate CAG (and PCI as indicated) or delayed CAG (and PCI as indicated) after neurological recovery. The study flowchart is depicted in the Figure.

The trial is conducted with a research grant of the Netherlands Heart Institute and an unrestricted grant of Astra-Zeneca.

The authors are solely responsible for the design and conduct of the study, all study analyses, the drafting and editing of the paper, and its final contents.

Study protocol
Patients with OHCA and ROSC will be screened at the emergency department. Eligible patients will be randomized to either an immediate or delayed invasive strategy using a Web-based system (Castor EDC). If the patient is allocated to the immediate invasive group, the CAG will be performed as soon as possible and should be initiated within 2 hours after randomization. In the delayed invasive group, the CAG will be done after neurological recovery and generally after discharge from the ICU. In all patients, targeted temperature control will be initiated as soon as possible and should be maintained for at least 24 hours. Life-supporting therapy, including antiarrhythmic and antithrombotic agents, electrolyte supplementation, and sedation, is delivered according to local practice.

Venous blood samples for creatine kinase (CK), CK-MB mass, and troponin T determination will be obtained at admission and at 3, 6, 12, 24, 36, 48, and 72 hours after admission. Creatinine, lactate, and central venous oxygen saturation will be obtained at admission and every 24 hours on the ICU. Glasgow Coma Score and Cerebral Performance Category (CPC) score will be determined routinely at ICU discharge and 90-day follow-up by trained personnel.

CAG and revascularization strategy
Coronary angiography will be performed in accordance with local protocol. The access site and anticoagulant strategy are left to the treating physician.
Table I. Inclusion criteria COACT trial

- Age > 18
- Comatose patients (Glasgow coma score < 8) with ROSC after OHCA
- Ventricular tachycardia or ventricular fibrillation during the arrest. Including patients treated with an AED.

AED, Automatic external defibrillator.

The angiographic findings in patients after OHCA without STEMI can differ greatly. They include normal coronary arteries, angiographic stable coronary artery disease, or the presence of a typical unstable coronary lesion (Thrombolysis in Myocardial Infarction [TIMI] 0-1 flow with an abrupt occlusion or TIMI 2-3 flow with angiographic findings suggesting thrombus or ulcerated plaques). There is a lack of studies addressing the optimal revascularization strategy in patients after OHCA. European experts in the field of intervention cardiology have suggested to treat only the culprit lesion during an acute coronary intervention in hemodynamically stable patients. In the COACT trial, the revascularization strategy is left up to the discretion of the treating physician but should include all suspected unstable coronary lesions. In case of multivessel disease, the strategy should be based on the Syntax score and local Heart team protocol. If coronary artery bypass grafting is the treatment of choice for a patient in the immediate invasive group, this procedure can be deferred until after neurological recovery.

In case patients initially allocated to the delayed invasive group show signs of cardiogenic shock, recurrent life-threatening arrhythmias, or recurrent ischemia during their hospitalization, they will undergo urgent CAG.

End points

The primary end point of the trial is survival at 90 days. Secondary end points include 90-day survival with good cerebral performance or moderate disability, myocardial injury measured by troponin and CK-MB as area under the curve, acute kidney injury according to Acute Kidney Injury Network criteria, need for renal replacement therapy, time to target temperature, duration of inotropic support, neurological status at ICU discharge, markers of shock, recurrence of ventricular tachycardia requiring defibrillation or electrical cardioversion, duration of mechanical ventilation, TIMI major bleeding, and rate and reason for discontinuation of life-sustaining treatment (Table III).

Neurological outcome will be scored according to the CPC scale (CPC 1: good cerebral performance, may have mild deficits; 2: moderate cerebral disability, sufficient for independent activities of daily life; 3: severe cerebral disability; 4: coma or vegetative state; 5: dead).

Table II. 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 a true posterior infarct)
- Hemodynamic instability unresponsive to medical therapy. Defined as a prolonged (>30 min) systolic blood pressure < 90 mm Hg at the time of screening
- An obvious or suspected noncoronary 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 prearrest CPC 3 or 4
- > 4 h (from ROSC to screening)
- Refractory ventricular arrhythmia
- Known inability to complete 90-d follow-up

LBBB, Left bundle-branch block; GFR, glomerular filtration rate.

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 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. If there is no consensus or uncertainty about potential recovery, the decision is postponed and the assessment is repeated at a later time.

Statistical considerations

Sample size. The study is powered for the primary end point of 90-day survival. The survival rates between the 2 treatment groups are compared with a 2-sided χ² test at a significance level of 5%. A previous meta-analysis of 10 nonrandomized studies showed improved survival for immediate angiography relative to conventional treatment: 56% versus 32%, with an odds ratio of 2.78 and a 95% CI between 1.89 and 4.10. We therefore hypothesize that an immediate angiography will improve survival.

With 2 × 251 patients, the study will have 85% power to detect an increase of the survival rate from 32% to 45% (ie, a proportional increase of the survival rate with 40%). To allow for a loss to follow-up of 10%, 552 patients will be included in total.

Furthermore, the study has an adaptive design allowing for an increase of sample size if the survival benefit is substantial but smaller than the 40% increase mentioned above. The Data Safety Monitoring Board of the study is
entitled to recommend an increase of the sample size on the basis of the outcomes of the first 400 patients.

**Statistical analysis.** Outcome measures will be analyzed for all randomized patients in an intention-to-treat analysis. Values are reported as mean ± SD or median (25th-75th percentile) for continuous variables and as frequency with percentage for categorical variables. For the analysis of binary end points, treatment comparisons will be performed using Fisher exact probability test. For continuous outcomes, independent-samples t tests are used. All calculations are generated by Statistical Package for Social Sciences software (SPSS, Chicago, IL).

**Ethical considerations**

The study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act and the statements of the Dutch Central Committee on Research Involving Human Subject addressing deferred consent in unresponsive patients.27

The study has been approved by the Ethics Committees of the participating hospitals.

Patients screened for the trial are unconscious and unable to consent at the time of screening. Legal representatives are often not present and if present are frequently in no mental state to make a well-considered
decision about participating in the study. The study intervention regards an emergency intervention that has to be applied without delay and fulfills the ethical requirement of clinical equipoise. This is why the patient will be informed about the study intervention if and when his consciousness recovers or the legal representative if the patient remains unable to communicate. Consent for use of the study data (deferred consent) will be asked at that time. If the patient has died before consent can be obtained, the study data will be used and no consent will be asked 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 cause unwanted selection bias.27

Data collection and follow-up

The following variables from the patients’ records will be collected: age, gender, smoking history, hypertension, diabetes, hypercholesterolemia, previous myocardial infarction, previous PCI, previous coronary artery bypass grafting, previous cerebrovascular accident, ECG data, resuscitation data, angiographic data, and laboratory results. Follow-up data will be obtained by a telephone interview with the patient or family members by a blinded research nurse or from information acquired from the patient’s general physician. All data will be stored in a Web-based database (Castor EDC).

Prespecified subgroups

The following subgroups are prespecified for analysis of the primary end point: male versus female, patients >70 years versus patients <70 years, patients with previous coronary artery disease versus patients without previous coronary artery disease, patients with a pH >7.2 on admission versus patients with pH <7.2 on admission, witnessed arrest versus nonwitnessed arrest, bystander cardiopulmonary resuscitation versus no bystander cardiopulmonary resuscitation, and ROSC >30 minutes versus ROSC <30 minutes.

Duration of the study

The COACT trial started including patients in January 2015. We expect that recruitment will be completed within 36 months. Therefore, it is expected that the patient inclusion will be finished in January 2018. The 90-day follow-up data will be completed in April 2018.

Expected results

The COACT trial is being conducted to determine whether an immediate invasive strategy in patients after OHCA and without STEMI or an obvious noncoronary cause of the arrest will improve survival. Currently, a randomized controlled trial addressing this topic has not been published. The results of this trial will impact the future treatment of this patient group and will influence future treatment guidelines.

Discussion

The effect of an immediate invasive strategy in patients after OHCA and without ECG signs of STEMI has been debated for some time. Several observational studies have reported on the effect of immediate CAG in OHCA patients on survival.6,8-18 However, only a few have done so in the specific group of patients without signs of STEMI. Bro-Jeppesen et al15 found that immediate CAG was not associated with a reduction in mortality (HR adjusted = 0.69, 95% CI 0.4-1.2, \( P = .18 \)). Moreover, Dankiewicz et al20 reported no benefit of early CAG in patients without ST-segment elevation in their post hoc analysis from the TTM trial (HR adjusted = 1.03, 95% CI 0.80-1.32, \( P = .82 \)). A study by Hollenbeck et al6 did show a significant increase in survival in OHCA patients with a shockable arrest rhythm and the absence of STEMI, selected for an early CAG (65.6% vs 48.6%; \( P = .017 \)). They found an acute coronary occlusion in 26.6% of patients treated with early CAG. Noteworthy is the observation in this study that the outcomes in patients with early PCI were not significantly better compared with those who received early CAG but no PCI, leaving the question of how early CAG can improve outcome for other reasons than PCI. The authors suggest that early CAG may be associated with a greater “intensity of care” in the early phase of hospitalization. They observed that patients treated with early CAG were more likely to receive mechanical support and aggressive anticoagulation. It is also possible that other diagnostic and therapeutic measures associated with early CAG, such as the timely establishment of central venous access, invasive

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<th>Table III. Secondary end points</th>
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<td>• 90-d survival with good cerebral performance or minor/moderate disability. Defined as a CPC of 1 or 2</td>
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<td>• Occurrence of acute kidney injury according to AKIN criteria22</td>
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AKIN, Acute Kidney Injury Network.
hemodynamic monitoring, and the rapid titration of vasoactive medications, may play a role in the improved outcomes.\textsuperscript{6}

Both before and after the introduction of TTM for the treatment of patients resuscitated from OHCA, the main cause of death in this patient group is neurologic injury. Laver et al\textsuperscript{28} found neurologic injury as cause of death in 67.7\% and a cardiac cause in 23.1\% of cases in patients admitted after OHCA. The recent TTM trial reported neurologic injury as cause of death in 58\% and a cardiac cause in 24\% of all deaths.\textsuperscript{4} If only a minority of patients admitted to the ICU after OHCA die from a cardiac cause, it might be difficult to improve survival with cardiac angiography and revascularization, especially as several randomized trials addressing the role of an immediate versus delayed CAG in patients with myocardial infarction without \textit{ST} segment elevation (NSTEMI) who were not resuscitated have failed to show a benefit of immediate intervention.\textsuperscript{29-31} The mortality in these trials (1%-6\%) however differs greatly with that of the resuscitated population, and the results of these trials can therefore not be extrapolated to the OHCA patient group. The TIMACS trial did show that NSTEMI patients with higher risk (Global Registry of Acute Coronary Events score $>140$) benefited from a CAG within the first 24 hours after admission in reducing the composite end point of death, myocardial infarct, or stroke compared with a delayed strategy ($>36$ hours).\textsuperscript{32} Although post-resuscitation patients were not included in the TIMACS trial, this very high risk group may also benefit from an early invasive strategy.

It has been suggested that immediate CAG may delay cooling and increase risk of bleeding complications and stent thrombosis augmented by hypothermia. Several studies\textsuperscript{6,33} however have shown that immediate CAG does not delay time to therapeutic hypothermia or time to target temperature, and therapeutic hypothermia has been demonstrated to improve outcome when combined with PCI.\textsuperscript{5,10,34,35} Furthermore, the optimal temperature management after cardiac arrest has not been settled yet. No difference was found in clinical outcomes between hypothermia targeting at a temperature of $33^\circ$C as compared with a temperature of $36^\circ$C.\textsuperscript{1}

Dankiewicz et al\textsuperscript{20} found bleeding complications to be rare but somewhat more common among patients who received early CAG. This difference was driven by minor bleeds from access sites and was thought to be clinically insignificant.

The results on the occurrence of stent thrombosis in post–cardiac arrest patients after stenting for acute myocardial infarction differ. Joffre et al\textsuperscript{36} reported a higher risk of stent thrombosis in cardiac arrest patients treated with PCI and hypothermia. Rosillo et al\textsuperscript{37} found no such increased risk in their analysis of post–cardiac arrest patients treated with PCI and hypothermia. Both studies were relatively small in size.

Although both European and American guidelines\textsuperscript{4,5} for the management of STEMI have a Class I recommendation for performing immediate CAG and PCI in comatose patients with STEMI and OHCA, the guidelines are less clear for comatose cardiac arrest patients without STEMI. The European guidelines state that immediate angiography with an option for primary PCI should be considered in survivors of cardiac arrest without diagnostic ECG ST-segment elevation but with a high suspicion of ongoing infarction (Class IIa).\textsuperscript{4} However, identifying ongoing infarction in comatose patients is cumbersome.

Recently, the European Association for Percutaneous Cardiovascular Interventions/Stent for Life groups and the American Interventional Council of the American College of Cardiology have addressed the topic of invasive coronary strategies after OHCA in a consensus statement and a treatment algorithm to supplement current guidelines. They state that an immediate invasive strategy should be considered in selected post–cardiac arrest patients without STEMI. Both publications furthermore conclude that there is a great need for randomized controlled trials of early PCI in post cardiac-arrest patients without \textit{ST}-segment elevation on the ECG.\textsuperscript{7,38} The COACT trial will be such a trial.

References