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Role of coronary angiography in patients with a non-diagnostic electrocardiogram following out of hospital cardiac arrest: Rationale and design of the multicentre randomized controlled COUPE trial

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Abstract

Background: Coronary artery disease (CAD) is a major cause of out-of-hospital cardiac arrest (OHCA). The role of emergency coronary angiography (CAG) and percutaneous coronary intervention (PCI) following cardiac arrest in patients without ST-segment elevation myocardial infarction (STEMI) remains unclear.

Aims: We aim to assess whether emergency CAG and PCI, when indicated, will improve survival with good neurological outcome in post-OHCA patients without STEMI who remain comatose.

Methods: COUPE is a prospective, multicentre and randomized controlled clinical trial. A total of 166 survivors of OHCA without STEMI will be included. Potentially non-cardiac aetiology of the cardiac arrest will be ruled out prior to

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randomization. Randomization will be 1:1 for emergency (within 2 h) or deferred (performed before discharge) CAG. Both groups will receive routine care in the intensive cardiac care unit, including therapeutic hypothermia. The primary efficacy endpoint is a composite of in-hospital survival free of severe dependence, which will be evaluated using the Cerebral Performance Category Scale. The safety endpoint will be a composite of major adverse cardiac events including death, reinfarction, bleeding and ventricular arrhythmias.

Conclusions: This study will assess the efficacy of an emergency CAG versus a deferred one in OHCA patients without STEMI in terms of survival and neurological impairment.

Keywords

Out-of-hospital cardiac arrest, coronary angiography, non-diagnostic electrocardiogram, percutaneous coronary intervention, survival, neurological outcome

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Background

Out of hospital cardiac arrest (OHCA) is a major public health problem that accounts for the majority of deaths in coronary artery disease. Despite advances in the field of resuscitation and intensive care management, the outcome of these patients remains poor and over 70% of them die or survive with severe neurological impairment.[1]

It has been reported that implementation of a standardized treatment protocol for post resuscitation care after OHCA including therapeutic hypothermia, urgent coronary intervention in appropriate patients and optimization of intensive care treatment, improved survival compared with controls before this protocol was implemented.[2]

Evidence that coronary angiography (CAG) may reduce mortality in OHCA patients was obtained from several observational studies, most of them including patients with ST-segment elevation myocardial infarction (STEMI).[3–6] Based on these studies, current guidelines and a consensus statement recommend a primary percutaneous coronary intervention (PCI) strategy in patients with resuscitated cardiac arrest and an electrocardiogram (ECG) consistent with STEMI (class of recommendation I, level of evidence B).[7–10] Current guidelines also state that an urgent CAG (and PCI if indicated) should be considered in patients with OHCA without diagnostic ST segment elevation but with a high suspicion of ongoing myocardial ischaemia (class of recommendation IIa, level of evidence C).[7,8,11] However, no randomized controlled clinical trials have been published aiming to determine the effectiveness of an immediate CAG in reducing mortality in OHCA patients without STEMI and retrospective studies do not show consistent results.[12–14] Guidelines conclude that there is a great need for randomized controlled clinical trials addressing the role of CAG in post OHCA patients without STEMI.

The Coronariography in OUt of hosPital Cardiac arrEst (COUPE) trial is a randomized controlled trial investigating the effects of an emergency CAG and angioplasty if necessary in OHCA survivors who after restoration of spontaneous circulation (ROSC) do not fulfil criteria for STEMI and do not have an obvious non-coronary cause of the arrest.

Methods

Study design

The COUPE trial is a prospective, multi-centre, randomized controlled clinical study comparing the efficacy of an emergency versus a deferred CAG in survivors from OHCA without STEMI (NCT02641626). A total of 17 centres in Spain will participate in the study (Table 4). All these hospitals are high volume PCI centres with 24/7 PCI service and with experience in treating OHCA patients in intensive cardiac care units. All of them perform therapeutic hypothermia as part of their cardiac arrest care.

Patients are eligible if they have ROSC within 60 min, remain in coma and present an ECG without STEMI or left bundle branch block. Both shockable and non-shockable rhythms can be included in the study. Obvious non-coronary aetiology of the cardiac arrest must be ruled out prior to randomization, for instance, drug overdose, pulmonary embolism, aortic dissection, acute stroke or intracranial bleeding. A cranial computed tomography (CT) and an echocardiogram will be performed for this purpose. Further inclusion and exclusion criteria are presented in Tables 1 and 2.

Eligible patients will be randomized to either immediate CAG (and PCI if needed) versus delayed CAG (and PCI if needed). Figure 1 shows the COUPE trial flowchart.

The estimated duration will be of three years, with a target follow-up of six months. Survival, neurological status and left ventricular ejection fraction (LVEF) will be evaluated on follow-up.

Data collection and follow-up

The following variables will be collected from the patients' records: age, gender, smoking history, hypertension, hypercholesterolaemia, diabetes, previous myocardial infarction,

Table 1. Inclusion criteria.

Age ⩾ 18 years.
Comatose patients after ROSC (Glasgow Coma Scale score ⩽ 8).
Prior rule out of an obvious non-cardiac cause of the cardiac arrest (head CT scan and transthoracic echocardiogram).
Absence of exclusion criteria.
Acceptance to participate in the study by the next of kin.

CT: computed tomography; ROSC: restoration of spontaneous circulation

Table 2. Exclusion criteria.

Signs of STEMI or on the ECG.
Time to ROSC > 60 minutes.
Obvious non-coronary aetiology of the comatose state: drug overdose, pulmonary embolism, aortic dissection, acute stroke or intracranial bleeding.
Hemodynamic instability (refractory cardiogenic shock despite vasoactive drugs or refractory arrhythmias).
Pregnant women or women of childbearing age unless they have a negative pregnancy test.
Known coagulopathy or bleeding.

ECG: electrocardiogram; ROSC: restoration of spontaneous circulation; STEMI: ST-segment elevation myocardial infarction

revascularization and stroke, previous medication and medication during hospitalization, ECG and resuscitation data, laboratory tests, echocardiographic and angiographic data. Survival, neurological status and LVEF will be assessed at discharge and at six months after discharge. All data will be stored in a Web-based database that will be filled in by each investigator. Confidentiality and data protection are guaranteed.

The COUPE trial started including patients in January 2017. We have already enrolled 29 patients to date. We hope that recruitment will be completed within 36 months. Therefore, it is expected that the patient inclusion will be finished in December 2019. The six-months follow-up data will be completed in July 2020.

Study protocol

Survivors of OHCA without STEMI will be screened for eligibility. The local emergency services are aware of this study and can help to identify possible candidates before arrival at the emergency department. Once there, a transthoracic echocardiogram and a cranial CT will be performed prior to randomization to rule out a potentially non-cardiac aetiology of the cardiac arrest. Afterwards, patients will be randomized in a 1:1 ratio to emergency (within 2 h from first medical contact) or deferred (performed during hospitalization) CAG. Both groups will receive routine care in the intensive cardiac care unit, including therapeutic hypothermia with a target temperature of 33ºC for 24 h. Supporting treatment, such as mechanical ventilation, sedation and any other medical therapy, will be delivered according to standard practice and at the discretion of the treating physicians. Blood and urine cultures and bronchial aspirate will be drawn at admission. After rewarming, cultures will be obtained again only if infection is suspected. Blood samples for creatine phosphokinase and troponin determination will be obtained at admission and at 6, 12, 24, 48 and 72 h after admission. Type of troponin (T, I and ultra-sensitive depending on the hospital's laboratory kits) will be recorded. Haemogram and biochemistry including magnesium, lactate, C-reactive protein, procalcitonin and neuron-specific enolase will be obtained at admission and 24, 48 and 72 h after admission. An ECG and an echocardiogram will be performed at least at admission, when the patient reaches 33°C and after rewarming.

CAG will be performed according to the local protocol. The access site, the anticoagulant therapy and the revascularization strategy are left to the discretion of the treating physicians. In cases of multivessel disease, the strategy should be discussed in the local heart team. If coronary artery bypass surgery is the treatment of choice for a patient in the immediate CAG group, this procedure can be postponed until after neurological recovery. If a patient initially randomized to the deferred CAG strategy shows signs of refractory cardiogenic shock or recurrent arrhythmias during their hospitalization, he will undergo emergency CAG (Table 2).

Endpoints

The main objective of the study is to compare the efficacy of an emergency CAG and angioplasty if necessary versus a deferred CAG in survivors from OHCA who after ROSC do not fulfil criteria for STEMI.

The primary efficacy endpoint is the composite of in-hospital survival free of severe dependence, which will be assessed with the Cerebral Performance Category (CPC) Scale,[15] good prognosis being represented by categories 1 and 2. The primary safety endpoint will be in-hospital

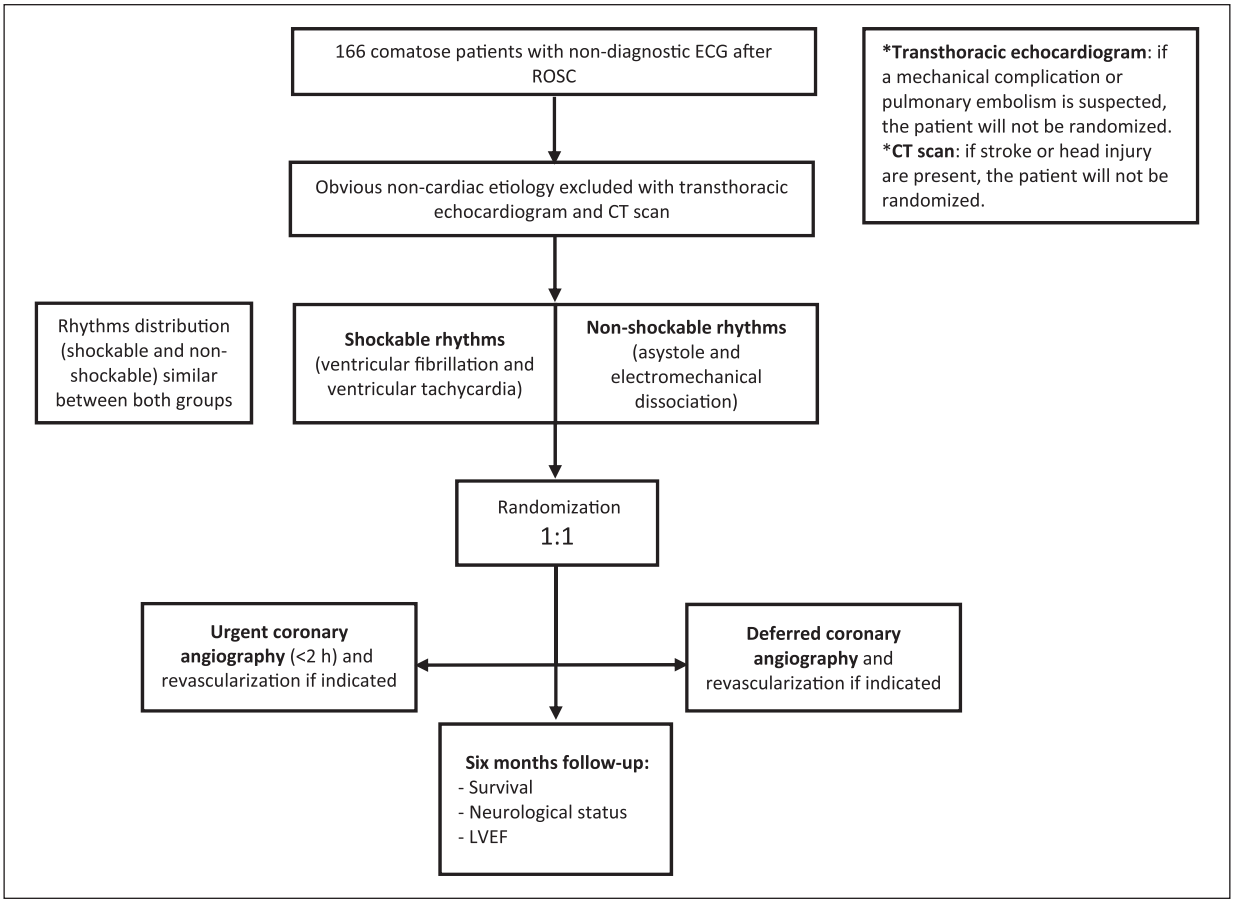

Figure 1. Flow chart of the COUPE trial.
COUPE: Coronariography in OUt of hosPital Cardiac arrEst; CT: computed tomography; ECG: electrocardiogram; LVEF: left ventricular ejection fraction; ROSC: restoration of spontaneous circulation.

major adverse cardiac events including: death, reinfarction, bleeding and ventricular arrhythmias. Secondary endpoints include in-hospital and six-month survival, in-hospital and six-month neurological prognosis assessed by the CPC Scale, in-hospital and six-month LVEF, infarction size measured with cardiac markers, vascular complications, bleeding, ventricular arrhythmias, renal failure, stent thrombosis, infections, length of intubation and length of stay (Table 3[16,17]).

Statistical considerations

Sample size. The study is powered for the primary endpoint. The survival rates between the two treatment groups are compared with a two-sided Chi-square test at a significance level of 5%. A previous meta-analysis of 55 non-randomized studies showed improved survival for immediate angiography versus conventional treatment: 58.8% *vs*. 30.9% with an odds ratio (OR) of 2.77 (95% confidence interval 2.06–3.72).[18] Based on previous studies, a sample size of 92 patients will be required to detect an absolute increase of 28% in the survival rate of the study group (emergency CAG) with 80% statistical power. Considering a 10% patient loss during the follow-up, a sample size of 102 will be needed to test the superiority hypothesis. As we also aim to test non-inferiority, this hypothesis was also included. An absolute reduction in mortality equal to or less than 15% with a deferred CAG compared with an emergency one was considered as non-inferior. A sample size of 166 patients will be necessary to test the non-inferiority hypothesis, assuming a mortality rate in the control group of 31%, with 80% of statistical power, allowing a loss to follow-up of 10% and a 5% alpha error. In summary, the final sample size was calculated to test the non-inferiority hypothesis.

Statistical analysis. Endpoints will be analysed for all recruited patients in an intention to treat analysis. Statistical analysis will be performed by an independent investigator, blinded to the study group assignment. Continuous variables will be reported as mean ± SD or median (25th to 75th percentile) for asymmetric variables. Two-tailed *t*-test will be used to compare continuous variables and the Mann–Whitney *U* test for non-normal variables. Categorical variables will be reported as frequency with percentage and comparisons will be made

Table 3. Primary and secondary outcome measures.

Primary outcome measures
In-hospital survival with good neurological outcome for activities of daily life (CPC 1–2)
In-hospital MACE: death, myocardial infarction, clinically evident bleeding (BARC[16]> 2) or ventricular arrhythmias
Secondary outcome measures
Survival (in hospital and at six months)
Neurological outcome assessed by the CPC Scale (in hospital and at six months)
Left ventricular ejection fraction (in hospital and at six months)
Infarction size defined by the maximum CK and troponin
Vascular complications (fistulae, pseudoaneurysm)
Clinically evident haemorrhage: BARC >2
Sustained ventricular arrhythmias or requirement of cardioversion
Acute renal failure: creatinine increase of > 0.5 mg/dl or > 50% baseline
Reinfarction: according to the universal definition of acute myocardial infarction
Stent thrombosis defined by the ARC[17]
Infections
Length of intubation
Length of hospital stay

ARC: Academic Research Consortium; BARC: Bleeding Academic Research Consortium; CK: creatine phosphokinase; CPC: Cerebral Performance Category; MACE: major adverse cardiac event

Table 4. Participating centres in Spain.

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with *Chi-square test* or *Fisher's exact test*. Analysis of variance test or Kruskal–Wallis test will be used for multiple comparisons. Cox regression will be used to perform a multivariable analysis that will include potential confounders.

ORs will be presented with 95% confidence intervals and a p value < 0.05 will be considered statistically significant.

Study group assignment will be performed by block randomization, in blocks of six patients. Randomization will be stratified according to the initial rhythm of the cardiac arrest (shockable and non-shockable).

Although the primary endpoint will be assessed in the whole study cohort, a stratified analysis will be performed by initial rhythm of the cardiac arrest (shockable and non-shockable).

This manuscript meets the CONSORT statement. All calculations will be generated by Statistical Package IBM SPSS Statistics V22.0.

Ethical aspects

The study will be conducted according to the principles of the Declaration of Helsinki.

The study has been approved by the ethics committees of the 17 participating hospitals (Table 4).

Patients randomized for the trial are unconscious and unable to consent at the time of screening. Therefore, informed consent will be obtained from their next of kin. The patient will be informed about the study participation if he or she recovers consciousness and will be asked for a deferred consent for use of the study data at that time. Informed consent can be withdrawn at any time and for any reason.

Discussion

Coronary artery disease (CAD) is the most common cause of OHCA, with some studies reporting an incidence of 60% to 80% of CAD as the initial aetiology of the cardiac arrest.[19,20] Immediate CAG is recommended as first-line treatment in patients with STEMI complicated with OHCA. However, it is less clear whether OHCA patients presenting with other ECG patterns may benefit from emergency CAG and subsequent revascularization. Due to the lack of randomized trials, guidelines recommendations are based on *low*-quality *evidence* derived from non-randomized studies and registries.[7,8,10,11] Therefore, there is still an ongoing debate on the use of an early invasive strategy in all survivors of OHCA with no obvious non-cardiac cause of arrest. Since Spaulding et al.[3] published their pioneer work, many observational studies have reported the feasibility and possible survival benefit from a successful immediate PCI regardless of the post-resuscitation ECG findings. On the contrary, several studies found no benefit in using such an interventional strategy and proposed to restrict its use to highly selected patients.[5,13,14,21–27]

In patients without STEMI after OHCA, the relationship between CAD and the need for revascularization is difficult to establish. Potential complications associated with emergency PCI should be considered and the benefit of revascularization should be balanced accordingly. For instance, intracranial haemorrhage is a clinical scenario associated with various non-specific ECG changes, where immediate CAG and antithrombotic treatment could even be fatal.[28] The COUPE trial will assess the efficacy and safety of an emergency CAG versus a deferred one in this population of OHCA patients without STEMI. In this respect, a cranial CT and an echocardiogram will exclude potential non-cardiac aetiologies such as an intracranial haemorrhage and mechanical complications before randomization.

Another point to consider is that among resuscitated OHCA patients, the main cause of in-hospital death is irreversible anoxic brain injury and coronary revascularization can hardly improve survival in this scenario. The TTM trial reported neurologic injury as cause of death in 58% and a cardiac cause in 24% of all deaths.[29] Therefore, in OHCA survivors, cerebral protection should be given the highest priority. In our study, we decided to include therapeutic hypothermia at a temperature target of 33°C as part of the protocol to avoid potential sources of bias due to a different temperature target. Although the optimal temperature level is not known yet, all the participating centres usually use moderate therapeutic hypothermia as part of their clinical practice. A different temperature control strategy could affect the final neurological status and therefore act as a confounding factor.

Limitations

Due to the difficulties of performing randomized studies in this particular population of comatose patients, we included 16 participating centres in order to reach the required simple size. Although all the participating hospitals will be attached to a common clinical protocol and we do not expect significant differences in the clinical management of patients, we cannot exclude the potential heterogeneity of participating centres local protocols. However, we will consider this in the multivariable analysis in order to assess whether this variable could be a potential confounder.

Conclusions

The COUPE trial will assess the efficacy of an emergency CAG versus a deferred one in OHCA patients without STEMI in terms of survival and neurological impairment. This trial will help to obtain clinical evidence to guide our strategy in this population of OHCA patients.

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Conflict of interest

The authors declare that there is no conflict of interest.

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