Design of DISCO—Direct or Subacute Coronary Angiography in Out-of-Hospital Cardiac Arrest study

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Background Acute coronary syndrome is a common cause of out-of-hospital cardiac arrest (OHCA). In patients with OHCA presenting with ST elevation, immediate coronary angiography and potential percutaneous coronary intervention (PCI) after return of spontaneous circulation are recommended. However, the evidence for this invasive strategy in patients without ST elevation is limited. Observational studies have shown a culprit coronary artery occlusion in about 30% of these patients, indicating the electrocardiogram's (ECG's) limited sensitivity. The aim of this study is to determine whether immediate coronary angiography and subsequent PCI will provide outcome benefits in OHCA patients without ST elevation.

Methods/design We describe the design of the DIrect or Subacute Coronary angiography in Out-of-hospital cardiac arrest study (DISCO)—a pragmatic national, multicenter, randomized, clinical study. OHCA patients presenting with no ST elevation on their first recorded ECG will be randomized to a strategy of immediate coronary angiography or to standard of care with admission to intensive care and angiography after 3 days at the earliest unless the patient shows signs of acute ischemia or hemodynamic instability. Primary end point is 30-day survival. An estimated 1,006 patients give 80% power (α = .05) to detect a 20% improved 30-day survival rate from 45% to 54%. Secondary outcomes include good neurologic recovery at 30 days and 6 months, and cognitive function and cardiac function at 6 months.

Conclusion This randomized clinical study will evaluate the effect of immediate coronary angiography after OHCA on 30-day survival in patients without ST elevation on their first recorded ECG. (Am Heart J 2018;197:53-61.)

Postresuscitation care after out-of-hospital cardiac arrest (OHCA) has developed over the past decade with, for instance, implementation of target temperature protocols[1] and more active revascularization strategies.[2] Approximately two-thirds of deaths in patients admitted to the intensive care unit (ICU) after OHCA are due to brain injury.[2,3] Thus, optimal postresuscitation care should aim at both vital organ support and optimal conditions to improve recovery and prevent further injury to the vulnerable brain. Optimization of the circulation by early revascularization measures may provide better conditions also for neurologic recovery.

Acute coronary syndrome is a common cause of OHCA.[4] The use of immediate revascularization measures, thrombolysis, or coronary angiography with subsequent percutaneous coronary intervention (PCI) has gained widespread acceptance in OHCA patients with ST elevation or left bundle-branch block on first electrocardiogram (ECG) after return of spontaneous circulation (ROSC).[5] However, there is an ongoing debate regarding the timing of coronary angiography in the larger group of patients with cardiac arrest without these ECG findings. An association between early coronary angiography/PCI and improved survival in OHCA patients without ST elevation has been found in several retrospective observational studies[6-9] but to date, there are no data from prospective randomized studies specifically addressing this issue. Furthermore, in a recently published post hoc analysis from the Target Temperature Management 33°C versus 36°C after OHCA trial, no association between

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early coronary angiography and PCI and survival was seen.[10] The risk of confounding factors and selection bias due to the design of these retrospective studies limits the possibility of generalizing the results for widespread, evidence-based implementation of a more active revascularization strategy. Early revascularization may be beneficial, but many hospitals do not have access to immediate PCI, at least outside office hours. Transportation to PCI centers of a ventilated, sedated patient with recent cardiac arrest could be hazardous. The use of ECG to select patients for immediate coronary angiography after cardiac arrest appears to have poor sensitivity and has been questioned.[11,12] Therefore, it is still unclear whether an early revascularization strategy is beneficial for cardiac arrest patients without ST elevation. This uncertainty has led to a call for randomized studies.[4] The aim of this prospective randomized clinical study is to evaluate the effect on 30-day survival of immediate coronary angiography and intention for subsequent PCI in OHCA patients without ST elevation on their first recorded ECG.

Methods and design of the DISCO study

Study setting

DISCO is an open-label, prospective, randomized, national multicenter clinical study. It was designed to compare a treatment strategy including *immediate coronary angiography*, defined as within 120 minutes from first medical contact, and potential PCI versus a treatment protocol based on current clinical practice after OHCA, with patients being admitted to the ICU and provisional angiography performed at a later stage.

Ethical considerations

DISCO is conducted in accordance with regulatory requirements, with Good Clinical Practices, and the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964. The study was approved by the regional ethical review board in Stockholm, Sweden (identification number 2014/1139-31/2, 2017/990-32), and is registered at ClinicalTrials.gov (NCT02309151).

Because of the nature of the study, with randomization of comatose survivors after OHCA, informed consent cannot be obtained prior to enrolment. It is the responsibility of the investigator to provide oral and written information about the objectives and procedures of the study as early as possible to the patient's family or related persons. The study information to the next-of-kin is given as soon as the investigator can reach the relatives after enrolment and includes the possibility to withdraw from further participation in the study. This information is given as soon as possible to the surviving patients who have regained mental capacity. The information includes that their decision to participate may be reevaluated by the patient or their close relatives at any time.

Study organization

This is an academically initiated study led by researchers at Uppsala University and the Center for Resuscitation Science, Karolinska Institutet, Stockholm, Sweden. The Uppsala Clinical Research Center, Sweden, is the clinical and data coordinating center.

Funding

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Data collection and monitoring

Data on prehospital parameters such as initial rhythm, bystander CPR, number of defibrillations, drugs, and others will be collected and analyzed in a prehospital case report form (CRF). Prehospital data will be supplemented with data from the Swedish cardiopulmonary resuscitation registry, which includes prehospital parameters as well as outcomes measures.

In-hospital data from the emergency room and intensive care units are recorded in the study CRFs. Data from 30-day and 6-month follow-up are registered in test specific protocols. All data are then entered via e-CRF directly into a Web-based data capturing system.

Data from the coronary angiography will be collected from the Swedish Coronary Angiography & Angioplasty Registry which is an online, nationwide registry managed by the Uppsala Clinical Research Center. The registry covers indications, angiographic findings, procedures performed, medications used, as well as complications in conjunction with coronary angiography/PCI all over Sweden.

Each study site will be monitored by research nurses according to Good Clinical Practices standards. All patients included in the study will be monitored concerning the following variables: patient's existence, patient information and consent, inclusion/exclusion criteria, adverse and serious adverse events, Cerebral Performance Categories (CPC) scale, modified Rankin Scale (mRS), echocardiography, and ECG.

Eligibility criteria for the study

Eligible patients for the study are OHCA patients >18 years of age whose collapse was witnessed and who have achieved sustained ROSC (ie, 20 consecutive minutes with persisting signs of circulation without the need of chest compressions). Patients arriving at the hospital with ongoing CPR who achieve sustained ROSC in the emergency department (ED) may also be included. Complete inclusion/exclusion criteria are listed in Table I.

Study enrolment and randomization

OHCA patients at the participating centers who achieve ROSC are screened and logged for eligibility for the study. As soon as possible, a 12-lead ECG is obtained after ROSC and either sent from the ambulance to the hospital or, more commonly, retrieved in the ED. A cardiologist on call interprets the ECG, assesses the patient on arrival,