

The COACT trial

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Coordinating investigator/project leader	<i>Drs. J.S. Lemkes, Cardiology VUMC</i>
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder) <Multicenter research: per site>	<i>Drs. J.S. Lemkes, Cardiology VUMC</i> <i>Prof. Dr. N. van Royen, Cardiology VUMC</i> <i>Prof. Dr. H.M Oudemans- van Straaten, ICU VUMC</i> <i>Prof. Dr. A.C. van Rossum, Cardiology VUMC</i> <i>Dr. M. Voskuil, Cardiology UMCU</i> <i>Dr. L. Otterspoor, Cardiology Catharina ziekenhuis</i> <i>Dr. E.A Dubois, Cardiology Erasmus MC</i> <i>Dr. M. Meuwissen, Cardiology Amphia ziekenhuis</i> <i>Dr. G. Vlachoianis, Cardiology Maasstad ziekenhuis</i> <i>Dr. G. Bleker, Cardiology Haga ziekenhuis</i> <i>Dr. C. Camaro, Cardiology UMC Radboud</i> <i>Dr. B. Beishuizen, ICU MC Twente</i> <i>Dr. J. Henriques, Cardiology AMC</i> <i>Dr. M. Vink, Cardiology OLVG</i> <i>Prof. Dr. P. van der Harst, Cardiology, UMCG</i> <i>Dr. M. Gosselink, Cardiology, Isala klinieken</i> <i>Prof. Dr. H. Crijns, Cardiology, MUMC</i> <i>Dr. H. Bosker, Cardiology, Rijnstate.</i> <i>Dr. P.V. Oemrawsingh, Cardiology, MCH</i> <i>Drs J. Plomp, Cardiology Ter Gooi</i> <i>Dr. G. Jessurun, Cardiology Scheper Ziekenhuis</i>

	<i>Dr. Heestermans, Cardiology NWZ</i> <i>Dr. M. Magro, Cardiology ETZ</i>
Sponsor (in Dutch: verrichter/opdrachtgever)	<i>Department of cardiology VUmc</i>
Subsidising party	
Independent expert (s)	<i><please include name and contact data></i>
Laboratory sites <i><if applicable></i>	<i><please include name and contact data></i>
Pharmacy <i><if applicable></i>	<i><please include name and contact data></i>

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
<p>Sponsor or legal representative: <i><please include name and function></i></p> <p><i><For non-commercial research,></i></p> <p>Head of Department: <i><include name and function></i></p>	<p><i>Prof. Dr . H.M Oudemans- van Straaten, ICU VUMC</i></p> <p><i>Prof. Dr. A.C. van Rossum, Cardiology VUMC</i></p>	
<p>[Coordinating Investigator/Project leader/Principal Investigator]: <i><please include name and function></i></p>		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CAG	Coronary angiography
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CPC	Cerebral Performance Category score
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator’s Brochure
IC	Informed Consent
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
NSTE-ACS	Non ST segment elevation myocardial infarction
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
OHCA	Out-of-hospital cardiac arrest
PCI	Percutaneous coronary intervention
ROSC	Restore of spontaneous circulation
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not

regarded as the sponsor, but referred to as a subsidising party.

STEMI **ST segment elevation myocardial infarction**

SUSAR **Suspected Unexpected Serious Adverse Reaction**

Wbp **Personal Data Protection Act (in Dutch: Wet Bescherming
Persoonsgegevens)**

WMO **Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-
wetenschappelijk Onderzoek met Mensen)**

SUMMARY

Rationale: The clinical benefit of acute coronary angiography following return of spontaneous circulation (ROSC) in patients without an ST segment elevation myocardial infarction after out of hospital cardiac arrest (OHCA) is unclear.

Objective: Aim of this study is to compare a strategy of immediate coronary angiography followed by percutaneous coronary intervention (PCI) if indicated with delayed coronary angiography in patients presenting at the emergency department after out of hospital cardiac arrest without signs of a ST segment elevation myocardial infarction (STEMI) and no obvious non-cardiac aetiology. Primary endpoint is survival until 90 days.

Study design: The study is a prospective, randomized controlled, multi-centre study.

Study population: The research population will be recruited from the general patient population presenting with return of spontaneous circulation after out of hospital cardiac arrest without signs of a ST segment elevation myocardial infarction, at the emergency department. A total of 552 consecutive patients will be included.

Intervention (if applicable): The patients will be randomized to either the immediate or delayed coronary angiography and subsequent revascularisation group.

Main study parameters/endpoints: The primary end point of the study is 90-days survival. Secondary endpoints are 90-days survival with good, minor or moderate disability, myocardial injury measured by troponine and CK MB as area under the curve, occurrence of acute kidney injury, need for renal replacement therapy, time to target hypothermia, neurological status at ICU discharge, duration of inotropic support, markers of shock, recurrence of ventricular tachycardia, duration of mechanical ventilation and reason for discontinuation of treatment.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The risk and burden consists of early or late CAG. If PCI is indicated, early CAG will turn into a benefit by preventing further myocardial ischemia. If no indication for PCI is found, the CAG will be futile. This may be the case in both groups. During early CAG, the patient is under anaesthesia and will not be aware of the intervention. Potential medical risks of futile CAG include access site bleeding and contrast induced nephropathy. One of the treatment groups may have better outcome.

1. INTRODUCTION AND RATIONALE

Out-of-hospital sudden cardiac arrest (OHCA) is a leading cause of death in Europe and the United States. The incidence of OHCA treated by emergency medical service in Europe has been estimated to be approximately 275.000 persons per year (1). Despite advances in the field of resuscitation and critical care management, the outcome of these patients remains poor. Good outcome ranges from 2% in patients presenting asystole (2) to 40% in patients with ventricular fibrillation (3). The aetiology of OHCA is diverse and includes both cardiac and non-cardiac causes. The most frequent cardiac cause is ischemic heart disease. A diagnostic coronary angiography (CAG) is therefore a standard procedure in patients who survived OHCA. The timing of this procedure differs between institutions and operators. Sometimes logistical factors like availability of the catheterization laboratory influence the decision.

In patients presenting with a ST elevation myocardial infarction (STEMI) without cardiac arrest, the preferred treatment is an acute coronary angiography with percutaneous coronary intervention (PCI) because of a benefit in survival (4). In patients with a myocardial infarction without ST elevation (NSTEMI) who are not resuscitated, the optimal timing for CAG and subsequent PCI has been debated for years. Several randomised trials have addressed this topic. The ABOARD trial included patients with acute coronary syndromes without ST-segment elevation and compared a strategy of immediate intervention (mean, 70 min) with a strategy of intervention deferred to the next working day (mean, 21 hours) and showed no difference in myocardial infarction as defined by peak troponin level (5). In the OPTIMA trial immediate PCI was associated with an increased rate of MI in comparison with a 24-48 hours deferred strategy in patients with a NSTEMI-ACS (6). The TIMACS trial revealed a significant 38% reduction in death, MI or stroke at 6 months in high risk NSTEMI-ACS patients (GRACE score >140), with an early (≤ 24 h) compared with a delayed (≥ 36 h) strategy. No significant difference was observed in patients with a low to intermediate risk profile (GRACE score ≤ 140) (7).

In patients who survived OHCA no randomized controlled trials have been published, looking at the effectiveness of an acute CAG in reducing mortality. Several nonrandomised studies reported on patients resuscitated from cardiac arrest with acute CAG only performed in selected cases (8-13). They showed a survival benefit for patients who underwent an acute CAG. A meta-analysis of these trials performed by Larsen et al, found a significant benefit for survival in patients without an obvious non-cardiac aetiology, favouring acute CAG (14). However these studies included patients with cardiac arrest of mixed aetiology and contained both patients with STEMI and NSTEMI ACS. Furthermore these results should be interpreted

with caution because of potential selection bias. The outcome of patients after cardiac arrest primarily depends on the neurologic recovery. It is therefore difficult to understand why a acute CAG and subsequent PCI would improve survival in patients without STEMI. Especially because of the lack of survival benefit in randomised trials in patients with NSTEMI without cardiac arrest (5-7). Acute CAG could in potentially also be hazardous. One could argue that delaying optimal critical care including rapid therapeutic hypothermia by going to the catheterisation laboratory could worsen outcome. A randomised controlled trial is therefore of utmost importance in determining the role of an acute CAG in patients after OHCA without an STEMI. The COACT trial will be such a study.

2. OBJECTIVES

Primary Objective:

Can an immediate CAG and subsequent PCI in patients after OHCA without STEMI improve 90-days survival compared to a delayed CAG and subsequent PCI (after neurological recovery).

Secondary Objective(s):

- Is there a difference in 90-days survival with good, minor or moderate disability
- Is there a difference in myocardial injury measured by troponine and CK MB as area under the curve between the treatment groups.
- Is there a difference in acute kidney injury according to AKIN criteria between the treatment groups.
- Is there a difference in need for renal replacement therapy between the treatment groups.
- Is there a difference in time to target hypothermia between the treatment groups.
- Is there a difference in duration of inotropic support between the treatment groups.
- Is there a difference in neurological status at ICU discharge between the treatment groups
- Is there a difference in markers of shock: lactate and SVO₂ at day 1, 2 en 3 between the treatment groups.
- Is there a difference in the recurrence of ventricular tachycardia needing defibrillation or electrical cardioversion between the treatment groups.
- Is there a difference in the duration of mechanical ventilation between the treatment groups.
- Is there a difference in reason for discontinuation of treatment between the treatment groups.
- Is there a difference in left ventricular function between the treatment groups.

- Is there a difference in functional capacity between the treatment groups.

Is there a difference in Survival and MACE at 1 and 5 years between the treatment groups.

3. STUDY DESIGN

The study is a prospective, randomized controlled, multi-centre study. Once a patient is presented at the emergency department after OHCA with ROSC and without signs of STEMI and without obvious non-cardiac cause, randomisation to either the immediate or delayed CAG group will be performed. A deferred informed consent will be obtained. Standard intensive care support will be given in both groups. A total of 552 patients will be included.

4. STUDY POPULATION

4.1 Population (base)

The research population will be recruited from the general patient population presenting at the emergency department after OHCA, with ROSC and without STEMI or a non cardiac case of the arrest.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

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

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Signs of STEMI on the ECG at the emergency department (including new LBTB 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 mm Hg at the time of screening.
- An obvious or suspected non cardiac aetiology of the cardiac arrest.
- An obvious or suspected non ischemic cardiac cause of the arrest (such as long QT syndrome, Brugada etc)
- A known severe renal dysfunction. (GRF< 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 (240 min from ROSC to screening
- Refractory ventricular arrhythmia
- Known inability to complete 90 day follow up

4.4 Sample size calculation

The study is powered for the primary endpoint of 90 day survival. 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 10 non- randomized studies showed improved survival for immediate angiography relative to conventional treatment: 56% versus 32%, with an odds ratio of 2.78 with a 95%-confidence interval between 1.89 and 4.10.

With 2 x 251 patients, the study has 85% power to detect an increase of the survival rate from 32% to 45% (i.e. a proportional increase of the survival rate with 40%).). To allow for a loss to follow-up of 10 percent, 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 DSMB is entitled to recommend an increase of the sample size on the basis of the outcomes of the first 400 patients. An increase in sample size, will be submitted for approval to the Ethics Committee.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

For this study, patients who survive OHCA will undergo coronary angiography and PCI (if indicated) immediately after admission or after neurological recovery.

Coronary angiography and PCI will be performed according to local standard procedures and left to the discretion of the operator but should include all acute thrombotic lesions. All patients must receive a loading dose of heparin or Bivaluridine, aspirin and a P2Y12 inhibitor before PCI according to standard clinical guidelines. In case of multivessel disease the strategy should be based on the Syntax score (and local Heart team protocol). If CABG is the treatment of choice for a patient in the immediate invasive group, this procedure can be deferred until after neurological recovery.

5.2 Use of co-intervention (if applicable)

In addition to early or late CAG, all patients will be treated with therapeutic hypothermia starting directly upon hospital admission. Patients are mechanically ventilated and the circulation will be supported with fluids and vaso-active medication according to the local protocol. Other medical therapy, including anti-arrhythmics, electrolyte supplementation, anticoagulant agents and sedation, is delivered according to standard practice and at the discretion of the treating physicians. Standard blood samples will be collected during the admission to monitor myocardial markers, oxygenation and acid base and electrolyte homeostasis, haemoglobin and coagulation.

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5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT >

6.1 Name and description of investigational product(s)

Not applicable

6.2 Summary of findings from non-clinical studies

Not applicable

6.3 Summary of findings from clinical studies

Not applicable

6.4 Summary of known and potential risks and benefits

Not applicable

6.5 Description and justification of route of administration and dosage

Not applicable

6.6 Dosages, dosage modifications and method of administration

Not applicable

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

Not applicable

7.2 Summary of findings from non-clinical studies

Not applicable

7.3 Summary of findings from clinical studies

Not applicable

7.4 Summary of known and potential risks and benefits

Not applicable

7.5 Description and justification of route of administration and dosage

Not applicable

7.6 Dosages, dosage modifications and method of administration

Not applicable

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable

7.8 Drug accountability

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary end point of the study is 90-days survival.

8.1.2 Secondary study parameters/endpoints (if applicable)

- 90-days survival with good, minor or moderate disability. Defined as a Cerebral Performance Category of 1 or 2
- Myocardial injury measured by troponine and CK MB as area under the curve
- Duration of inotropic support
- Occurrence of acute kidney injury according to AKIN criteria
- Need for renal replacement therapy.
- Time to optimal hypothermia
- Neurological status at ICU discharge
- Markers of shock: lactate and SVO₂ at day 1, 2 en 3..
- Recurrence of ventricular tachycardia needing defibrillation or electrical cardioversion.
- Duration of mechanical ventilation.
- Reason for discontinuation of treatment.
- Left ventricular function on cardiac ultrasound or MRI
- Functional performance at 1 year
- MACE and survival at 1 and 5 years

8.1.3 Other study parameters (if applicable)

Not applicable

8.2 Randomisation, blinding and treatment allocation

Patients are randomised in an 1:1 ratio in either the immediate or delayed CAG group. A computer based randomization will be used.

If patients in the delayed group show signs of cardiogenic shock, recurrent life threatening arrhythmias or recurrent ischemia while waiting for their coronary angiography, they will undergo urgent intervention.

8.3 Study procedures

8.3.1 Coronary angiography

Coronary angiography is standard practice in patients surviving OHCA. The CAG is performed according to standard local procedures. The revascularisation strategy is up to the discretion of the treating physician but should include all acute thrombotic lesions. In case of multivessel disease the strategy should be based on the Syntax score (and local Heart team protocol).). If CABG is the treatment of choice for a patient in the immediate invasive group, this procedure can be deferred until after neurological recovery.

8.3.2 Percutaneous coronary intervention

Percutaneous coronary intervention (PCI) will be performed according to standard procedures and left to the discretion of the operator but should include all acute thrombotic lesions. All patients must receive a loading dose of heparin or Bivaluridine, aspirin and a P2Y12 inhibitor before PCI according to standard clinical guidelines.

8.3.3 Laboratory tests

Venous blood samples for CK, CK-MB mass and troponin T determination

will be obtained at admission and at 3, 6, 12, 24, 36, 48 and 72 h. Creatinin, lactate and SVO2 will be obtained at admission and every 24 hours on the ICU. These tests are standard care for this patient group in the ICU.

8.3.4 Neurological assessment

Glasgow coma score 6-hourly during the first 72-h

Cerebral Performance Category score (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), performed at ICU discharge and 90 days follow up.

8.3.5 Left ventricular function assessment

If cardiac ultrasound and or cardiac MRI has been performed, this will be used for assessment of the left ventricular function.

8.3.6 Functional assessment

Functional assessment will be performed at 1 year using the RAND 36 questionnaire.

8.3.7 Major Adverse Cardiac Events

Major Adverse Cardiac Event (MACE) is defined as cardiac death, myocardial infarction, coronary bypass grafting or repeat percutaneous intervention. Survival and MACE will be assessed at 1 and 5 years by telephone.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

In the case of withdrawal of subjects, new patients that meet the inclusion criteria will be included in the study.

8.6 Follow-up of subjects withdrawn from treatment

No follow up will be performed.

8.7 Premature termination of the study

Not applicable

9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

Patients after OHCA have a high risk of dying due to post-anoxic encephalopathy, as supported by SSEP and EEG, sudden cardiac arrest or myocardial failure. Furthermore, patients frequently exhibit (supra) ventricular arrhythmias. These serious adverse events are expected.

Possible serious adverse events that will be reported to toetsingonline include bleeding, and other serious complications related to the study intervention, unexpected death or unexpected complications.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Patients after OHCA have a high risk of dying due to post-anoxic encephalopathy, as supported by SSEP and EEG, sudden cardiac arrest or myocardial failure. Furthermore, patients frequently exhibit (supra) ventricular arrhythmias. These serious adverse events are expected.

Possible serious adverse events that will be reported to toetsingonline include bleeding, or other serious complications related to the study intervention, unexpected death or unexpected complications.

9.3 Annual safety report

Not applicable

9.4 Follow-up of adverse events

All patients will be followed until hospital discharge and a neurological evaluation will be done after 90-days. MACE and survival will be accessed at 1 and 5 years .

All AEs will be followed until they have abated, or until a stable situation has been reached.

Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till the end of study within the Netherlands, as defined in the protocol

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

An independent Data safety Monitoring Committee (DSMC) will be established to evaluate safety and efficacy during the trial and at 1 scheduled interim analysis . The DSMB is entitled to recommend an increase of the sample size on the basis of the outcomes of this analysis. The DSMB can also advise to continue, stop or pause the study.

10. STATISTICAL ANALYSIS

Values are reported as mean \pm SD or median (25th to 75th percentile) for continuous variables and as frequency with percentage for categorical variables. For the analysis of binary endpoints, treatment comparisons will be performed using Fisher's exact probability test. For continuous outcomes independent-samples T-tests are used. All calculations are generated by Statistical Package for Social Sciences software (SPSS).

10.1 Interim analysis (if applicable)

The DSMB will evaluate safety and efficacy during the trial and at 1 scheduled interim analysis. This analysis will take place when 400 of the patients are included.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

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 (WMO) and the statements of the CCMO as presented in the publication "Uitgestelde toestemming voor inclusie van beslissingsonbekwame patiënten in studies van spoedeisende geneeskunde" by E.J.O.Kompanje(15).

11.2 Recruitment and consent

Patients will be screened for inclusion on the emergency care department. The patients eligible for this study are unconscious. The study intervention regards an emergency intervention that has to be applied (or not) without delay and fulfils the ethical requirement of clinical equipoise. The study participant can benefit from the intervention, but up to now there is a state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment (early or late coronary angiography followed by an intervention if possible. Some centres in the Netherlands apply early angiography and others apply late

angiography. Furthermore, the eligible patients have an extremely high risk of dying (about 50%) and the legal representatives will therefore be in a disturbed mental state complicating an immediate informed decision. For the present study, the investigator or supervising doctor will inform the patient about the study intervention if and when his consciousness recovers between day three and seven or the legal representative of the patient remains unable to communicate and ask deferred proxy consent for use of the study data (deferred consent). The rationale for the deferred consent procedure is the clinical equipoise of both interventions (early versus late), the emergency of the intervention and the possible benefit for the patient with a positive benefit risk ratio. If the patient has died at that time, the study data will be used. The rationale for the latter is that the legal representatives have no independent right on inspection or say on of therapeutic or study data (CCMO: “De nabestaanden hebben geen zelfstandig recht op inzage van de tijdens de behandeling en het onderzoek verkregen gegevens en hebben daar ook geen zeggenschap over. Van toestemming voor het gebruik van de data door de nabestaanden kan daarom ook geen sprake zijn). Furthermore, possible refusal may cause selection bias and this is ethically unwanted (CCMO: het introduceren van selectiebias door het moeten vragen van toestemming aan de nabestaanden, mocht daar een grond voor zijn, ethisch niet wenselijk is) (15)

11.3 Objection by minors or incapacitated subjects

Not applicable

11.4 Benefits and risks assessment, group relatedness

Coronary angiography and revascularisation is part off the standard treatment for patients surviving OHCA. The optimal timing of coronary angiography remains a topic of discussion due to the lake of randomised data. Currently the timing of this procedure differs between institutions and operators. Sometimes logistical factors like availability of the catheterization laboratory influence the decision. The risk and burden consists of early or late CAG. If PCI is indicated, early CAG will turn into a benefit by preventing further myocardial ischemia. If no indication for PCI is found, the CAG will be futile. This may be the case in both groups. During early CAG, the patient is under anaesthesia and will not be aware of the intervention. Potential medical risks of futile CAG include access site bleeding and contrast induced nephropathy. We do not expect these risks to differ between an early or delayed procedure.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The data generated in this study will be encoded, not based on the patient initials and birth-date. The key to the code will be available to the investigators and the independent physician. Human material will be disposed after analysis. Furthermore, personal data will comply to the General Data Protection Regulation (AVG) . Encoded clinical data including ECGs, imaging (reports) and discharge letters will be collected by the trial organisation (VUmc) for core lab analysis.

12.2 Monitoring and Quality Assurance

Monitoring will be done by the cardiology research department of the VUmc

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

Not applicable

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

- a. Level of knowledge about mechanism of action

Not applicable

- b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

Not applicable

- c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Not applicable

- d. Selectivity of the mechanism to target tissue in animals and/or human beings

Not applicable

- e. Analysis of potential effect

Not applicable

- e. Pharmacokinetic considerations

Not applicable

- f. Study population

Not applicable

- g. Interaction with other products

Not applicable

- h. Predictability of effect

Not applicable

- i. Can effects be managed?

Not applicable

13.2 Synthesis

The optimal timing of coronary angiography after OHCA in patients without signs of STEMI remains unclear. These patients may benefit from immediate CAG en PCI if an acute thrombotic occlusion of one of the coronary arteries, not clearly detected by ECG, is the cause of their cardiac arrest. On the other hand delaying optimal intensive care treatment including therapeutic hypothermia by going to the catheterisation laboratory may also be hazardous. A randomised controlled trial is therefore necessary.

14. REFERENCES

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