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CORONARY ANGIOGRAPHY IN OUT-OF- HOSPITAL CARDIAC ARREST

WHY, WHEN AND FOR WHOM?

Ludvig Elfwén



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Why, When and for Whom?

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By

Ludvig Elfwén

Principal Supervisor:

Per Nordberg, MD., PhD.
Karolinska Institutet
Department of Medicine, Solna
Division of Cardiology

Co-supervisor(s):

Leif Svensson, MD., PhD.
Karolinska Institutet
Department of Medicine, Solna
Division of Cardiology

Jacob Hollenberg, MD., PhD.
Karolinska Institutet
Department of Medicine, Solna
Division of Cardiology

Ulf Jensen, MD., PhD.
Karolinska Institutet
Department of Clinical Science and Education,
Södersjukhuset
Division of Cardiology

Opponent:

Lars Grip, MD., PhD.
University of Gothenburg
Department of Molecular and Clinical Medicine,
Sahlgrenska Academy
Division of Cardiology

Examination Board:

Malin Rundgren, MD., PhD.
Lund University
Department of Clinical Sciences
Division of Anesthesiology and Intensive Care

Hans Persson, MD., PhD.
Karolinska Institutet
Department of Clinical Sciences, Danderyd
University Hospital
Division of Cardiology

Stefan Agewall, MD., PhD.
University of Oslo
Institute of Clinical Sciences
Division of Cardiology

To my Mother, Git and my late Father, Bosse,

Both of whom have experienced cardiac arrest

ABSTRACT

Background

Among Out-of-Hospital Cardiac Arrest (OHCA) patients, where resuscitation efforts have been initiated, only about 25% are admitted alive to hospital. To optimize the chance of survival it is of great importance to identify and treat the underlying cause of the cardiac arrest. The overall aim of the current work was to study different diagnostic approaches in OHCA patients and to evaluate if early coronary angiography, with potential subsequent percutaneous coronary intervention (PCI), could improve outcome.

Methods and results

Study I. A national observational retrospective study, evaluating the effect on survival of early coronary angiography vs. no early coronary angiography in witnessed, unconscious OHCA patients with shockable rhythm and without ST-elevation on the first ECG.

Unadjusted 30-day survival in the early-angiography group was 65%, compared with 52% in the no-early-angiography group. The adjusted OR for 30-day survival was 1.42 for early angiography (95% CI 1.00-2.02, $p=0.048$). The adjusted HR for one-year survival was 1.35 for early angiography (95% CI 1.04-1.77, $p=0.03$).

Study II. An open-label, prospective, randomized, national multicenter clinical study in OHCA patients carried out to assess feasibility and safety aspects in a strategy of coronary angiography within 120 minutes from first medical contact versus coronary angiography potentially performed at a later stage. Among 79 randomized patients (from 2015 to 2017), 39 were randomized to immediate coronary angiography and 40 to standard-of-care treatment. The median time from EMS arrival to coronary angiography was 135 minutes in the immediate-angiography group. A culprit lesion was found in 14/38 (36.8 %) patients randomized to immediate coronary angiography and PCI was performed in all these patients. In patients randomized to standard of care treatment 6/40 (15%) underwent coronary angiography before the stipulated three days.

Study III. A retrospective, descriptive, single-center study, assessing the use of Focused Cardiac Ultrasound (FOCUS) in cardiac-arrest patients with ROSC and without ST-elevations on the ECG. In total, FOCUS was performed in 237 (182 OHCA and 55 in-hospital cardiac arrest) patients. FOCUS findings had an impact on management and led to further immediate diagnostic measures in 52 (21.9%) patients.

Study IV. A sub-study of Study II carried out to compare post-resuscitation myocardial function in the two randomized groups. In the immediate angiography group, median left-ventricle ejection fraction (LVEF) at 24 hours was 47% (Q1-Q3; 30-55) compared with 46% (Q1-Q3; 35-55) in the standard-of-care group. The peak Troponin-T level during the first 24 hours was 362 ng/L (Q1-Q3; 174-2020) in the immediate-angiography group compared with 377 ng/L (Q1-Q3; 205-1078) in the standard-of-care group.

Conclusions:

In a Swedish OHCA population with shockable rhythm without ST-elevation, early coronary angiography may be associated with improved short- and long-term survival.

Randomizing OHCA patients without ST-elevation to a strategy of immediate coronary angiography was feasible. No significant safety issues were observed.

No differences in post-resuscitation myocardial dysfunction parameters between the two groups were found.

Post-resuscitation assessment could include FOCUS as an adjunctive diagnostic measure shortly after ROSC.

LIST OF SCIENTIFIC PAPERS

- I. Elfwén L, Lagedal R, James S, Jonsson M, Jensen U, Ringh M, Claesson A, Oldgren J, Herlitz J, Rubertsson S, Nordberg P

Coronary angiography in out-of-hospital cardiac arrest without ST elevation on ECG—Short- and long-term survival

Am Heart J. 2018; 200:90-95

- II. Elfwén L, Lagedal R, Nordberg P, James S, Oldgren J, Böhm F, Lundgren P, Rylander C, van der Linden J, Hollenberg J, Erlinge D, Cronberg T, Jensen U, Friberg H, Lilja G, Larsson IM, Wallin E, Rubertsson S, Svensson L.

Direct or subacute coronary angiography in out-of-hospital cardiac arrest (DISCO)-An initial pilot study of a randomized clinical trial.

Resuscitation. 2019; 139:253-261

- III. Elfwén L, Hildebrand K, Schierbeck S, Sundqvist M, Ringh M, Claesson A, Olsson J, Nordberg P

Focused cardiac ultrasound after return of spontaneous circulation in cardiac-arrest patients.

Resuscitation. 2019; 142:16-22

- IV. Elfwén L, Lagedal R, Sten Rubertsson, Stefan James, Jonas Oldgren, Jens Olsson, Jacob Hollenberg, Ulf Jensen, Mattias Ringh, Leif Svensson, Per Nordberg

Post-resuscitation myocardial dysfunction in out-of-hospital cardiac arrest patients randomized to immediate coronary angiography versus standard of care

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LIST OF ABBREVIATIONS

AED	Automated external defibrillator
CAG	Coronary angiography
CI	Confidence interval
CPR	Cardiopulmonary resuscitation
CTO	Chronic total occlusion
DISCO	DIrect or Subacute Coronary angiography in Out-of-hospital cardiac arrest
ECG	Electrocardiogram
EMS	Emergency medical services
FOCUS	Focused cardiac ultrasound
HR	Hazard ratio
ICU	Intensive care unit
IQR	Interquartile range
LAD	Left anterior descending coronary artery
LBBB	Left bundle branch block
LCX	Left circumflex artery
MAP	Mean arterial pressure
NSTEMI	Non-ST-segment elevation myocardial infarction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
PCI	Percutaneous coronary intervention
PEA	Pulseless Electrical Activity
PRMD	Post-resuscitation myocardial dysfunction
RBBB	Right bundle branch block
RCA	Right coronary artery
ROSC	Return of spontaneous circulation
SCAAR	Swedish Coronary Angiography and Angioplasty Register
SRCR	Swedish register for cardiopulmonary resuscitation
STEMI	ST-segment elevation myocardial infarction

TTM	Targeted temperature management
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WLST	Withdrawal of life-sustaining treatment

1 RESEARCH QUESTION AND RATIONALE

This thesis is focused mainly on adult out-of-hospital cardiac arrest (OHCA) patients who have achieved return of spontaneous circulation (ROSC) but remain comatose at hospital arrival. Approximately 25% of patients treated by the emergency medical services (EMS) are admitted alive to hospital¹.

Management of the post-cardiac arrest patients includes determining, and if possible, treating the cause of the arrest. Even though electrocardiogram (ECG) is an important tool to identify ST-elevations, indicating acute coronary occlusion, the vast majority of cardiac-arrest patients do not have ST-elevation²⁻⁵. Furthermore, these patients are most often unconscious and unable to share their medical history. Observational studies have revealed that approximately 25 % have a coronary occlusion⁶. Thus, ECG has been shown to be insufficient in predicting an acute coronary event and currently there is a knowledge gap as to how clinicians should manage OHCA patients without ST-elevation.

Although international guidelines suggest that coronary angiography should be considered in patients with resuscitated cardiac arrest without ST-elevation on ECG and with a high suspicion of ongoing myocardial infarction⁷⁻⁹, the existing scientific evidence in favor of routine use of coronary angiography after OHCA is insufficient. To find methods to improve the identification of those patients who would benefit from early coronary angiography would be of great value for patients and care givers.

The overall aim of this work was to evaluate coronary angiography and other diagnostic approaches in out-of-hospital cardiac-arrest patients and to investigate if early coronary angiography and potential subsequent percutaneous coronary intervention (PCI) could improve outcome.

2 INTRODUCTION

2.1 OUT-OF-HOSPITAL CARDIAC ARREST

2.1.1 Definition

Out-of-hospital cardiac arrest (OHCA) is defined as the “cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation, occurring outside of a hospital setting”¹⁰.

2.1.2 Incidence

The total annual number of adult patients affected by OHCA, where resuscitation efforts have been initiated or continued by emergency medical services (EMS) has been estimated to be 275,000 in Europe¹¹ and 356,000 in the United States^{12,13}. Substantial regional variations exist in reporting systems, data collection and reporting survival¹⁴⁻¹⁶.

There is still a knowledge gap regarding the true incidence of OHCA. An effort to better understand this has been carried out by Berdowski et al., reporting the global incidence of adult EMS-treated OHCA to be 62.3 cases/100,000 person-years¹⁷. The incidence of OHCA when defined as the total number of OHCA events where resuscitation efforts have been initiated or continued by the EMS is 37.7- 49.0/100,000 person-years in Europe^{11,18} and 47.3/100,000 person-years in North America¹⁷. The number of reported EMS-treated cases in Sweden has been estimated to 52/100,000 person-years^{19,20}.

2.1.3 Overall survival and prognostic factors

The overall survival rate after resuscitation attempts by the EMS has been reported to be 10%²¹. The most important predictors of survival from OHCA are:

1. The presence of ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT) as the first recorded rhythm²², these being the strongest predictors of survival. Among patients found in VF/pVT and treated with a public automated external defibrillator (AED), survival can be as high as 70%²³. On the other hand, for each shock delivered, the chance of survival decreases, and if more than 10 defibrillations are delivered the survival rate is 5%²⁴ which underscores the fact that time to ROSC is crucial for survival.
2. Witnessed cardiac arrest²⁵, which is logical since witnessed OHCA is associated with bystander cardiopulmonary resuscitation (CPR)^{26,27} and a higher incidence of VF compared with unwitnessed OHCA²⁸.
3. Public location is associated with higher survival rates²⁹ and is associated with witnessed OHCA and VF as first rhythm. However, most cases of OHCA occur at home.
4. A relatively low age, this being associated with a higher survival rate³⁰, although it is weaker compared with other predictors.

In patients with an initial shockable rhythm and comatose on admission to hospital after ROSC, 35-50% will survive 30 days with a reasonable neurological status^{31,32}. Survival from the scene of arrest to hospital admission varies between regions and ranges from 22-57%, mostly because of regional culture, treatment differences and regional initiatives to optimize the effectiveness of the local chain of survival^{18,31,33-35}.

2.2 THE CHAIN OF SURVIVAL

With the purpose of improving survival from OHCA, the American Heart Association (AHA) presented a statement in 1991³³ called “The chain of survival”. The concept initially concerned mainly pre-hospital factors. However, during the last two decades post-resuscitation care has been more emphasized. The links in the chain of survival are:

- Early recognition of symptoms and call for help.
- Early CPR, bystander CPR most preferably.
- Early defibrillation either by using a public AED or by EMS personnel.
- Post-resuscitation care. For further treatment and prognostication.



Figure 1. Nolan et al.³⁶. Reprinted with permission from Elsevier.

The chain of survival includes the community, emergency medical dispatch, EMS and receiving hospitals. The most important links in the chain of survival are the earliest ones, early recognition of cardiac arrest, initiation of CPR and early defibrillation³⁴. For untrained witnesses or relatives, recognition of a cardiac arrest is not straightforward and in such a stressful moment call for help is difficult and requires calmness. Every minute that a patient with OHCA goes without CPR and defibrillation, the chance of survival decreases by approximately 10%³⁵. The chain of survival is essential for patients to survive to hospital admission and, subsequently, to hospital discharge.

Most patients who survive the initial resuscitation treatment are unconscious at hospital admittance, but some patients regain consciousness immediately after ROSC if early recognized as cardiac arrest and provided with treatment. The proportion of conscious

patients resuscitated from OHCA ranges from 15-36%, depending on the population studied³⁷⁻⁴⁰. Awake survivors of OHCA have limited or no brain injury and represent a less complicated group as regards post-resuscitation treatment and have a survival rate of 90-96%^{38,41}.

2.3 ETIOLOGY OF OHCA

Finding the etiology of cardiac arrest is important because it enables specific treatment of the underlying cause. Overall, the final etiology of the cardiac arrest differs between populations.

Table 1. Overview of etiologies

Ischemic heart disease	Non-ischemic heart disease	No structural heart disease	Non-cardiac disease
Acute coronary lesion	Dilated cardiomyopathy	Idiopathic ventricular fibrillation	Lung disease, COPD, pneumonia
Chronic coronary artery disease	Hypertrophic cardiomyopathy	Long QT syndrome, congenital or acquired	Intracerebral bleeding
Coronary artery dissection	Valvular heart disease	Brugada syndrome	Pulmonary embolism
Coronary artery spasm	Myocarditis	Catecholaminergic polymorphic ventricular tachycardia, CPVT	Asphyxia, drowning
Congenital coronary artery anomaly	Acute pericardial tamponade	Wolf-Parkinson White syndrome	Seizures
	Aortic dissection		Intoxication
	Arrhythmogenic right ventricular cardiomyopathy, ARVC		Hypothermia
	Acute myocardial rupture		Trauma, hypovolemia
	Congenital heart disease		Electrolyte disturbances
	Cardiac sarcoidosis		Septic shock

In early autopsy studies, ischemic heart disease was found to be the major cause of cardiac arrest, responsible for 59-61% of all deaths^{42,43}. This has been contradicted in one of the more recent autopsy studies, which revealed that only 32% of sudden cardiac deaths had stable or acute coronary heart disease as the etiology⁴⁴.

In a French publication describing patients admitted alive to an intensive care unit (ICU), and using an extensive diagnostic strategy, the arrest was attributed to a non-cardiac cause (neurological, acute respiratory failure and intoxication) in 1/3 of the patients and a cardiac cause in 2/3 of the them⁴⁵. Among the cardiac causes, acute coronary syndrome accounted for 60% (37% if including non-cardiac causes) and chronic ischemic heart disease for 20% (12% if including non-cardiac causes). Other forms of cardiomyopathy (dilated, hypertrophic, congenital, restrictive and valvular) accounted for 13% of the cardiac causes and primary electrical diseases accounted for 5%. Unexplained cardiac arrests were observed in 3% of the patients which was in accordance with older studies reporting approximately 5% of patients with normal hearts after thorough examinations⁴⁶.

In summary, ischemic heart disease, acute or chronic, is still considered as the major cause of cardiac arrest⁴⁷.

The first recorded rhythm is considered an important clue when determining the etiology and reveals substantial information about prognosis.

2.3.1 VF and pulseless VT in relation to etiology

The proportion of EMS-treated patients with VF/pVT as the presenting rhythm ranges between 22-25%^{19,48,49}. The proportion of patients with shockable rhythm has declined over the years for no clear reasons⁵⁰. Among suggested possible reasons are improved cardiac prevention care and more frequent use of implantable cardioverter defibrillators (ICDs).

If the presenting rhythm is shockable, the primary etiology is more often of ischemic heart disease origin⁵¹, either acute with coronary culprit lesions, or chronic with formation of ischemic cardiac scars. However, patients with ischemic etiology can also present with asystole and pulseless electrical activity (PEA).

The pathophysiology of VF during myocardial-cell ischemia is complex but affects the resting membrane potential and K⁺ ion concentrations, leading to alterations in conduction, refractoriness and automaticity in myocardial cells⁵².

Other causes of VF/pVT include ion-channel disorders, such as long QT-syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT)⁴⁵.

Cardiomyopathies without ischemic etiology, such as dilated cardiomyopathy, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (ARVC) may also cause VF/pVT⁵³.

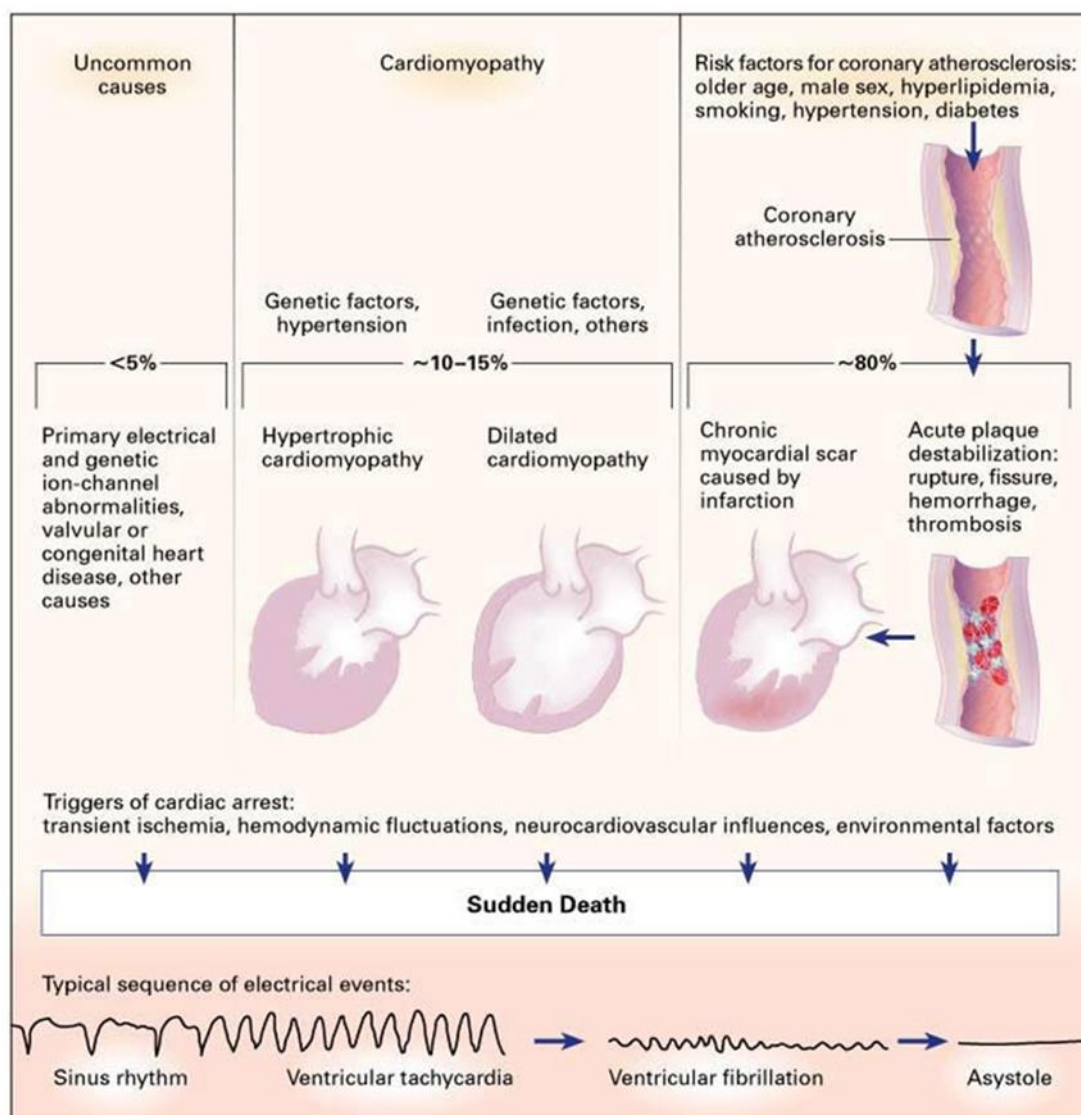


Figure 2. Mechanisms of cardiac arrest of cardiac cause. Huikuri et al.⁵⁴. Reproduced with permission from NEJM

2.3.2 Pulseless electrical activity (PEA) in relation to etiology

The general definition of PEA is the absence of signs of circulation in the presence of electrical activity. However, the definition of PEA is not totally clear. One suggestion, from Myerburg et al., is that “PEA is a syndrome characterized by the absence of a palpable pulse in an unconscious patient with organized electric activity other than ventricular tachyarrhythmia on ECG”⁵⁵. Another form of PEA is so called pseudo-PEA which can be described as a state without palpable pulse but with cardiac activity and ventricular contractions which can be detected by ultrasound⁵⁶.

A North American registry reported the proportion of cases of PEA to be 20%⁴⁹. In Sweden, the proportion of OHCA patients presenting with PEA has increased, and in 2016 it

accounted for 22%⁵⁷. PEA has been reported to be associated with older age, female gender and a history of pulmonary disease⁵⁸.

In experimental animal models asphyxia has been the model for the induction of PEA, which occurs in 3-11 minutes⁵⁹. PEA may be caused by reversible conditions and if identified correct treatment could lead to ROSC. The causes of PEA are broadly considered as the 4Hs (Hypoxia, Hypovolemia, Hyper/Hypokalemia, Hypothermia) and 4Ts (Thrombosis, Tamponade, Toxins and Tension pneumothorax), described by Kloeck et al⁶⁰ and assumed to be potentially reversible causes. Some of these are very rare causes of cardiac arrest, and according to a Swiss report the Hs&Ts represents only 55% of PEA cases⁶¹. Other causes are intracranial hemorrhage and non-ischemic cardiac causes. In the Swiss study, hypoxia and cardiac diseases were the primary etiologies of PEA.

2.3.3 Asystole in relation to etiology

Asystole is defined as the termination of electrical and mechanical activity of the heart. A large proportion of OHCA patients are found to have asystole at the scene of the arrest. If the first recorded rhythm is asystole the prognosis is poor, with a survival rate of 1-2%⁶²⁻⁶⁴.

In many cases asystole could be viewed as a surrogate marker of prolonged resuscitation efforts in cardiac arrests of all origins and all presenting rhythms, and it is unclear how often asystole is the primary rhythm. Eventually all patients will end up with asystole if not detected and treated.

Shockable rhythm conversion from initial asystole is associated with an increased rate of pre-hospital ROSC and survival^{65,66}. In a large review of patients with initial non-shockable rhythms 4.6 percent of patients had conversion to a shockable rhythm during CPR⁶⁵.

2.4 TOOLS TO DETERMINE THE ETIOLOGY OF OHCA

2.4.1 Medical history and symptoms

Comatose patients with ROSC after cardiac arrest cannot provide a medical history. Sometimes family members or the EMS can describe symptoms preceding the cardiac arrest. In one study a survey concerning warning symptoms prior to cardiac arrest was carried out. Among the deceased and survivors, 51% presented with at least one symptom within four weeks prior to their cardiac arrest. The most common symptom was chest pain, present in 46% of patients, followed by dyspnea, 18%, and palpitations or syncope present in 5%⁶⁷. In a Japanese study it was reported that the most frequent symptom preceding cardiac arrest was dyspnea (27.6%), followed by chest pain (20.7%) and syncope (12.7%)⁶⁸. Warning symptoms may activate the EMS faster, unless being ignored by the patient or family members, and this activation has been reported to be associated with improved survival^{67,69}.

Comorbidities existing prior to cardiac arrest might be of importance when assessing the cause of the arrest and, for prognosis. According to a large Swedish observational study⁷⁰, the

most common comorbidities prior to arrest were congestive heart failure (29%), a history of myocardial infarction (24%), diabetes (23%) and chronic pulmonary disease (19%). Increasing comorbidity is associated with a decreased likelihood of survival irrespective of initial rhythm⁷⁰⁻⁷².

2.4.2 ECG

In OHCA patients with ROSC and a secured airway 12-lead ECG should immediately be carried out, most preferably in the ambulance⁷³. If the ECG after ROSC indicates ST-elevation, the suspicion of a recent coronary event is high. In many observational studies it has been reported that ST-elevation has a high predictive value in diagnosing the presence of acute coronary lesions, ranging from 85% to 96%^{74,75}. In contrast, Stær-Jensen et al. found that 37% of patients with ST-elevations showed normal coronary angiography⁷⁶. For comparison, ECG in patients without cardiac arrest but with a high suspicion of acute myocardial infarction, ST-elevation has a predictive value ranging between 79-86% for an acute coronary lesion^{77,78}. Large STEMI (ST-segment elevation myocardial infarction) registers have revealed that patients with OHCA represent approximately 10% of the total STEMI population admitted to hospital⁷⁹. OHCA patients presenting with ST-elevation have a higher proportion of VF as primary rhythm compared with patients without ST-elevation⁸⁰.

Approximately 70-80% of OHCA patients present without ST-elevation on the ECG^{2,81,82}. Most OHCA studies on ECG patterns merge these cases of non-ST-elevation into one comparison group^{76,83}. Observational studies report shifting proportions of significant coronary disease in patients without ST-elevation, ranging from 46-71%^{4,82,84}.

According to ESC (European Society of Cardiology) guidelines for the management of STEMI, “left bundle branch block (LBBB) with clinical suspicion of ongoing myocardial ischemia should be managed in a similar way to STEMI patients”⁷. In the setting of cardiac arrest, LBBB has a poor predictive value as regards an acute coronary event. Staer-Jensen et al. reported that reduced coronary flow was present in only 24% of patients presenting with LBBB⁷⁶. In a study describing angiographic findings in relation to ECG, LBBB had the same proportion (40%) of normal coronary findings as normal ECG⁸⁴. Both LBBB and right bundle branch block (RBBB) are frequent on the first ECG after cardiac arrest but seems to be transient^{85,86}. In a Danish study it was observed that >90% of the LBBB’s and RBBB’s had resolved after four hours⁸⁶.

ST-depression and T-wave inversion are ECG signs suggestive of ischemia. A report from Norway presented the fact that in patients with ST-depression or T-wave inversion 24% had reduced coronary flow compared with 18% in patients with normal ECG⁷⁶.

To summarize, in observational studies it has been concluded that ECG after ROSC in OHCA patients is not a reliable method to identify acute coronary culprit lesions^{6,74,76,87}.

Other ECG abnormalities

Compared with ECG changes suggestive of coronary ischemia, ion-channel conditions such as long QT-time and Brugada syndrome can be found but are rarely seen after resuscitated cardiac arrest⁴⁵.

2.4.3 Coronary angiography

The utilization of coronary angiography after OHCA has increased during the last 20 years⁸⁸. The increased trend to perform coronary angiography after ROSC started with the landmark study by Spaulding et al. published in 1997, reporting high rates of significant coronary disease even among patients without ST-elevation⁸⁷.

European Society of Cardiology (ESC) guidelines for STEMI state that in patients with ST-elevation following cardiac arrest, primary PCI is the strategy of choice. Furthermore, “in patients without ST-elevation, but with a high suspicion of ongoing myocardial ischemia, urgent coronary angiography, and PCI if indicated, should be considered”⁷.

The latest European Resuscitation Council (ERC) guidelines, published in 2015, (post-resuscitation-care section), state that “coronary angiography, and PCI if required, should be performed in patients with ROSC and ST-elevation on the ECG”⁸. In patients without ST-elevation on the ECG, the ERC declare that it is “reasonable to discuss and consider emergent coronary angiography after ROSC in patients with the highest risk of a coronary cause for their cardiac arrest”⁸.

The availability of coronary angiography varies between countries, regions and cities⁸⁹. The decision to transfer a patient with recently ROSC to a hospital with 24/7 coronary angiography facilities may imply risks of new cardiac arrest and delays to target temperature management. However, transport distance has not been associated with lower survival rates⁹⁰⁻⁹² and it has been argued that all OHCA patients should be transported to cardiac-arrest centers with 24/7 coronary angiography facilities^{93,94}. These arguments come from observational studies, with risks of bias, and currently there is a trial randomizing OHCA patients without ST-elevation for transportation to hospitals with 24/7 angiography facilities compared with standard care at the nearest hospital⁹⁵.

Coronary angiography is also associated with potential risks. Patients are exposed to contrast medium, which may impair renal function^{96,97}, vascular risk from an invasive procedure and bleeding risk from antithrombotic medication⁹⁸.

2.4.4 Cardiac biomarkers

Cardiac troponins and high-sensitivity troponin assays are of great value for early diagnosis of acute myocardial infarction in patients without cardiac arrest⁹⁹. Elevated circulating troponin levels are specific for cardiomyocyte injury but not for myocardial infarction¹⁰⁰. In resuscitated OHCA patients troponin levels are almost always elevated as a result of myocardial damage and the levels of troponins are related to the duration of

resuscitation^{101,102}, and to prognosis¹⁰³. Geri et al.¹⁰⁴ conducted a study with the aim of determining whether or not assay of high-sensitivity cardiac troponin T was useful in diagnosis of recent coronary-artery occlusion as the cause of OHCA. Troponin T was assessed at ICU admission. They found that the optimum cut-off value of high-sensitivity troponin T was 575 ng/L with a sensitivity of 65.4% and specificity of 65.5% for recent coronary occlusion. However, the authors concluded that one blood sample of high sensitivity troponin T at the time of admission to an ICU was not enough as a diagnostic tool to select patients for coronary angiography after OHCA.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is released by myocardial cells in response to atrial and ventricular stretch. NT-proBNP is most commonly used to diagnose and assess heart failure. Elevated NT-proBNP levels have been reported to be associated with an increased risk of ventricular arrhythmias¹⁰⁵. Most comatose OHCA patients have elevated NT-proBNP levels, and increased NT-proBNP levels are associated with increased mortality^{106,107}.

2.4.5 Ultrasound

The European Resuscitation Council guidelines states that “ultrasound may be of use in assisting with diagnosis and treatment of potentially reversible causes of cardiac arrest”⁷³. Ultrasound represents a non-invasive and accessible tool to examine a cardiac-arrest patient. The challenge is to use it wisely during CPR.

Ultrasound has been reported to be associated with prolonged interruptions of chest compressions¹⁰⁸⁻¹¹⁰. The feasibility of using ultrasound during cardiac arrest depends on the image quality which has to be good enough for interpretation, and in one study it was reported that the image quality was not useful for interpretation in 40% of patients¹¹¹.

In patients with PEA there is a possibility to use ultrasound to determine the cause of the arrest¹¹². Cardiac tamponade illustrates an example where ultrasound is the best tool to provide the correct diagnosis, with a high sensitivity and specificity¹¹³. Ultrasound has also been suggested as a tool in relation to termination of resuscitation efforts in non-shockable-rhythm patients without cardiac activity^{114,115}.

The use of ultrasound after ROSC in attempts to determine the etiology of arrest has not been studied in detail, but it has the potential to facilitate further decision-making as regards whether or not to perform immediate coronary angiography.

2.4.6 Computed Tomography (CT)-thorax and head

A respiratory or neurological cause of cardiac arrest should be considered in patients without ST-elevation on the first ECG. Examples of respiratory causes of cardiac arrest include severe pneumonia and acute on chronic respiratory failure¹¹⁶.

Acute pulmonary embolism is an uncommon cause of cardiac arrest and has been reported to be responsible for 2.8-4.8% of cases¹¹⁷. Neurological causes of cardiac arrest are more or less

equal to major cerebrovascular bleeding, and in particular subarachnoid hemorrhage¹¹⁸, and they have been reported as the cause of cardiac arrest in 2.0-2.4% of patients^{116,118,119}. Aortic dissection/rupture is a rare cause of cardiac arrest, with a reported incidence of 0.1-2.3%^{116,120}, and can be identified by CT-thorax.

A report from the European association for percutaneous cardiovascular interventions (EAPCI) recommend a diagnostic work-up with CT-thorax and head in patients without ST-elevation¹²¹.

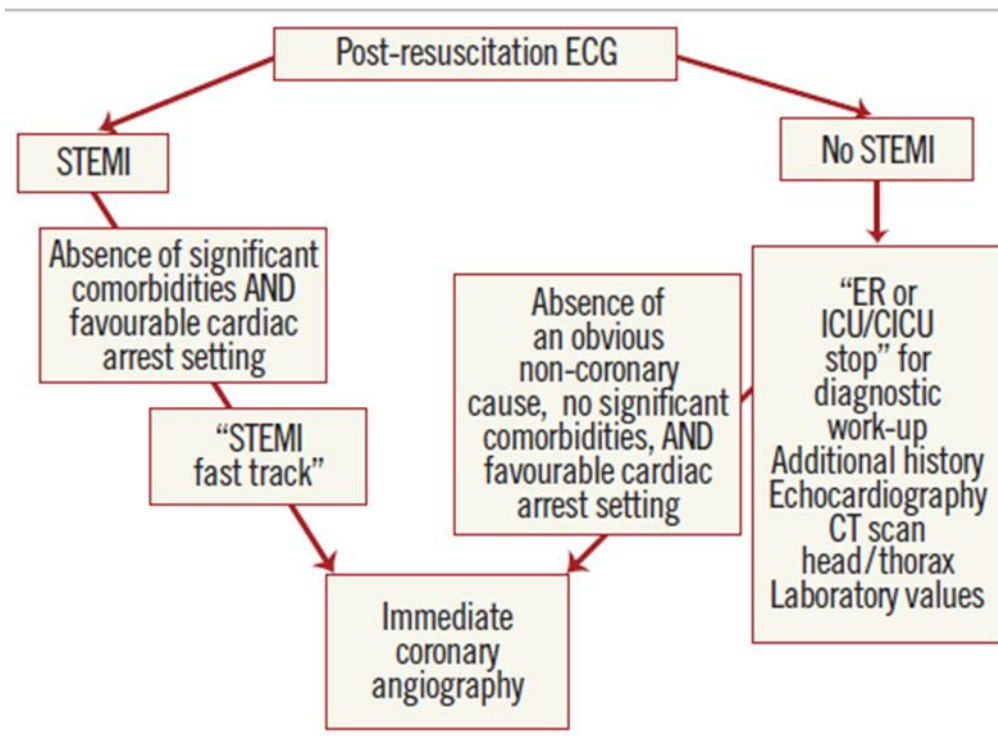


Figure 3. Proposed treatment algorithm from EAPCI. Noc et al.¹²¹. Reproduced with permission from EuroIntervention.

A French study describing OHCA of neurological causes noted that 23% of patients had ST-elevation on the admission ECG¹¹⁸. This ECG phenomenon may be caused by excessive catecholamine release with overload of the sympathetic nervous system¹²² and may inherit risk when decide on further clinical management in OHCA ST-elevation patients.

2.5 CORONARY ANGIOGRAPHIC FINDINGS AND PCI

ST-elevation after ROSC

In patients with ST-elevation on the ECG after ROSC, observational studies indicate that the left anterior descending coronary artery (LAD) is the culprit vessel in the largest proportion of cases, 49-56%, the right coronary artery (RCA) in 18-33%, the left circumflex artery (LCX) in 11-22% and the left main coronary artery in 2-3.1%^{75,123,124}. In patients presenting with ST-elevation after OHCA the rates of PCI have been reported to be between 71-89%^{3,37,123}.

European Resuscitation Council guidelines state that PCI should be performed in adult patients with ROSC and ST-elevation on the ECG⁸. There are no randomized studies supporting this recommendation, mostly because cardiac-arrest patients have been excluded from large randomized trials demonstrating the benefits of primary PCI in STEMI patients¹²⁵. However, many observational studies report an association with improved survival if early revascularization is performed after ROSC in ST-elevation patients^{126,127}.

No ST-elevation after ROSC

Patients without ST-elevation are a heterogeneous group of cardiac-arrest patients, and coronary angiographic findings and the rates of PCI are reported in different ways depending on the population studied. Most published studies report high proportions of significant coronary disease, ranging from 52-65%^{4,128-130}.

In observational studies, the finding of an occluded coronary artery, which should be of most interest, has been reported to occur in 22.9-27.0% of cases^{3,131,132}. The only randomized study published, the COACT trial, included VF patients without cardiogenic shock, acute thrombotic occlusions were reported in 3.4% of the patients randomized to immediate coronary angiography¹³⁰.

In published observational studies, a culprit lesion deemed for PCI has been found in 21-41% of patients^{2,82,133,134}, indicating that PCI was performed in some patients without coronary occlusion. In the COACT trial, PCI was performed in 33% of the patients randomized to immediate coronary angiography¹³⁰.

The distribution between coronary vessels identified as culprit-lesion locations and subsequently responsible for cardiac arrest has differed between studies. The left main coronary artery was identified as culprit in 7-13%, The LAD in 30-50%, the RCA in 23-29% and the LCX in 14-28% of cases^{3,80,131}.

In the COACT trial the proportion of cases of chronic total occlusion (CTO) was 37.7%¹³⁰. The reporting of CTO has been rare in observational studies but in one study it was reported that 8% of the patients had CTO at the time of coronary angiography after OHCA³.

Timing of coronary angiography in OHCA without ST-elevation

It is of importance to determine if immediate coronary angiography is necessary because the procedure is associated with logistical and organizational challenges. Furthermore, immediate coronary angiography may delay the time to ICU monitoring and treatment.

During the last 10 years many observational studies concerning OHCA patients without ST-elevation, have been carried out in an attempt to answer the question of whether or not early coronary angiography improves survival compared with late or no coronary angiography. The limitations in the registers regarding the exact time point of coronary angiography result in expressions such as “Immediate coronary angiography”, “Emergent coronary

angiography” and “Early coronary angiography”, meaning everything from two hours to 24 hours after cardiac arrest^{80,82,135}.

Hollenbeck et al.¹³² compared early versus late coronary angiography in patients with shockable rhythm and found that early coronary angiography was associated with a reduction in death rate. A Danish study showed that the use of emergent coronary angiography in patients without ST-elevation was not associated with reduced mortality⁸⁰. In a post-hoc analysis of the TTM (Targeted Temperature Management) trial it was concluded that early coronary angiography was not associated with improved survival¹³³.

In the COACT trial 552 patients with initial shockable rhythm were randomized to a strategy of immediate coronary angiography compared with a strategy of delayed angiography after neurologic recovery. It was concluded that there was no difference between the groups in the primary endpoint of survival at 90 days (OR 0.89; 95% CI 0.62-1.27; p=0.51)¹³⁰. The time from arrest to coronary angiography was 2.3 hours in the immediate-coronary-angiography group.

Antithrombotic treatment

Dual antiplatelet therapy is a fundamental treatment in patients undergoing PCI, carried out to prevent a new coronary event including stent thrombosis. In comatose OHCA patients intravenous administration should be considered before insertion of a nasogastric tube. There is a risk of decreased efficacy of orally administered antiplatelet therapy because of reduced absorption caused by gastroparesis and systemic inflammation after resuscitation, which may impair drug efficacy.

In one large observational study it was reported that the incidence of stent thrombosis in OHCA patients undergoing PCI was 4.7%¹³⁶. In comparison, myocardial-infarction patients without cardiac arrest and receiving a stent have a reported incidence of stent thrombosis of 0.5-1.0%^{137,138}.

Survival in relation to ECG findings

Several studies have shown that patients without ST-elevation have higher mortality rates compared with patients presenting with ST-elevation after ROSC^{3,4,80}. However, a Dutch study showed no difference in survival when comparing ST-elevation and no ST-elevation after OHCA¹³⁵.

Treatment options for non-coronary causes

Highly dependent on the presumed cause of cardiac arrest, treatment options are thrombolysis for pulmonary embolism¹¹⁷, pericardial drainage for cardiac tamponade¹³⁹, correction of electrolyte abnormalities¹³⁹ and use of antidotes in cases of suspected drug overdose¹⁴⁰.

2.6 POST-CARDIAC-ARREST CARE IN THE INTENSIVE CARE UNIT

Comatose survivors of cardiac arrest are subjects for monitoring, hemodynamic optimization, targeted temperature management and prognostication in the intensive care unit. Depending on the severity of whole-body ischemia, a great deal of patients develops post-cardiac arrest syndrome¹⁴¹, which consists of:

- Post-cardiac arrest brain injury
- Post-resuscitation myocardial dysfunction
- Systemic ischemia/reperfusion response
- Persistent precipitating pathology

Targeted temperature management (TTM) is recommended for neuroprotection⁸. In the TTM trial, 939 patients were randomly assigned to 33 °C or 36 °C for 24 hours with prevention of fever for 72 h in both groups. At 180-days follow-up there was no difference in mortality or neurologic function between the groups¹⁴². This result raises the question of whether hypothermia rather than prevention of fever improves outcome, which is the rationale for the TTM2 trial¹⁴³.

Post-resuscitation myocardial dysfunction (PRMD) is characterized by myocardial stunning and reduced myocardial contraction and is affected by the acute or chronic underlying cause of the arrest¹⁴⁴. The degree of PRMD tends to increase with longer duration of resuscitation. Hemodynamic instability after cardiac arrest may result from PRMD and/or from systemic vasodilation and often requires inotropic support and a vasopressor agent such as noradrenaline¹⁴⁵.

One randomized trial was carried out to investigate if mean arterial pressure (MAP) >85 mmHg, by optimizing cerebral perfusion, compared with MAP >65 mmHg could improve neurological outcome in cases of resuscitated OHCA. The trial failed to show any difference in neurological outcome at 180 days¹⁴⁶.

Elevated lactate levels at admission have been associated with higher mortality in OHCA patients^{147,148}, while faster lactate clearance has been shown to be protective^{149,150}.

One third of patients die from circulatory causes, mostly during the first two to three days in the ICU¹⁵¹. Two-thirds of patients dying after OHCA in the ICU die as a result of neurological injury induced by the no flow and low-flow circulation state during initial resuscitation^{151,152}. Neurological prognostication with a multimodal approach after 72 hours is recommended before deciding on withdrawal of life-sustaining treatment (WLST)¹⁵³.

2.7 FURTHER EVALUATION OF ETIOLOGY

Transthoracic echocardiography is essential after cardiac arrest for detection of abnormalities that suggest or confirm important causes of cardiac arrest.

Cardiac magnetic resonance imaging (CMR) should be performed in selected patients to detect cardiomyopathies such as ARVC (arrhythmogenic right ventricular cardiomyopathy), myocarditis, cardiac sarcoidosis and cardiac amyloidosis and should be performed before a decision on ICD implantation.

In patients resuscitated from shockable rhythm and with absence of reversible causes of cardiac arrest an ICD should be in place prior to discharge¹⁵⁴.

However, if there is clear evidence of myocardial infarction as the cause of arrest the patient could be evaluated at a later time for ICD implantation¹⁵⁴.

In cases of unexplained OHCA death (particularly in the young), obtaining a post-mortem blood sample, is recommended in the European Heart Rhythm Association guidelines¹⁵⁵ in order to perform genetic testing that may provide valuable information for the family.

2.8 NEUROLOGICAL FOLLOW-UP

Severe neurological impairment is rare among OHCA survivors and most patients are categorized as cerebral performance category (CPC) 1 and 2, considered as good neurological outcome¹⁴². However, mild to moderate cognitive impairment is common among survivors. The consequences of cognitive deficits may lead to impairment in quality of life, depression and symptoms of fatigue¹⁵⁶. A neuro-rehabilitation program focused on specific cognitive and psychological needs of patients could be beneficial¹⁵⁶.

2.9 GENDER ASPECTS

Patients suffering from OHCA are predominantly men at a proportion of 64-72%^{157,158}.

Women tend to be older, to more often present with a non-shockable rhythm and have a lower chance of receiving bystander CPR¹⁵⁷.

In a French report, men were more likely to undergo early coronary angiography (70% vs 49%). However, men had a higher prevalence of ST-elevation on the ECG (21% vs 13%). The report indicated no gender difference as regards survival¹⁵⁹.

A Swedish study, including only VF patients, was carried out to compare men and women. There was no gender difference as regards coronary angiography, but men had a higher prevalence of coronary artery disease (78 vs 54%) and more men had PCI following coronary angiography (59% vs. 42%). The study revealed no difference in survival¹⁶⁰.

3 AIMS

The overall aim of this work was to evaluate coronary angiography and other diagnostic approaches in out-of-hospital cardiac arrest patients and to investigate if early coronary angiography and potential subsequent PCI could improve outcome.

The specific aims of the studies were:

Study I:

To evaluate the association between early coronary angiography (within 24 hours of arrest) and survival in OHCA patients without ST-elevation on the ECG.

Study II:

To investigate feasibility and safety aspects of randomizing unconscious OHCA patients without ST-elevation to immediate coronary angiography compared with standard-of-care in patients admitted primarily to the intensive care unit.

Study III:

To investigate how focused cardiac ultrasound shortly after ROSC is associated with the use of further diagnostic measures and if the detection of pulmonary embolism, cardiac tamponade and acute myocardial infarction could be improved.

Study IV:

To study if immediate coronary angiography with potential PCI influenced markers of post-resuscitation myocardial dysfunction such as left-ventricular ejection fraction, biomarkers and lactate clearance in comparison with patients that were primarily admitted to the intensive care unit without immediate coronary angiography.

4 METHODS

Table 2. Overview of study design, study population and data sources.

	Study I	Study II	Study III	Study IV
Study design	Observational retrospective study	Randomized controlled trial	Descriptive study	Randomized controlled trial, Secondary analysis
Numbers	n=799	n=118	n=237	n=118
Data source	SRCR, SWEDHEART, NPR, Medical records	Study-CRF, SCAAR	Local register, medical records	Study-CRF, SCAAR
Inclusion criteria	Witnessed OHCA, VF, ECG without ST-elevation	Witnessed OHCA, ROSC	Cardiac arrest admitted to the Medical ICU, ECG without ST-elevation	Witnessed OHCA, ROSC
Years	2008–2013	2015–2017	2012–2017	2015–2017
Statistical method	Descriptive statistics, logistic regression, Cox proportional regression	Descriptive statistics	Descriptive statistics	Descriptive statistics
Outcome	30-day survival, one and three-year survival	Feasibility, logistics and safety aspects	FOCUS influence on management	LVEF, Troponin levels, lactate clearance and NTproBNP levels

SRCR, Swedish register for cardiopulmonary resuscitation; SCAAR, Swedish Coronary Angiography and Angioplasty Register; NPR, National patient register

4.1 STUDY I; OBSERVATIONAL COHORT STUDY

Study design, population and data sources

In this observational study, data from three different national registers were used. The first selection was from the Swedish register for cardiopulmonary resuscitation (SRCR) between 2008 and 2013. Patients with bystander-witnessed OHCA, first recorded rhythm of VF or VT, admitted alive to hospital and patients aged 18-79 years were included. Excluded were patients with asystole or PEA as first recorded rhythm, conscious patients with a Glasgow Coma Scale score of >8 and patients aged 80 or more.

The SRCR is a quality register for OHCA funded by the Swedish association of Local Authorities and Regions. Reports are entered in the register by all EMS organizations in Sweden if the EMS or bystanders have attempted resuscitation. Since 2010 all EMS organizations in all 21 regions in Sweden have reported to the register. The reports contain variables in accordance with the Utstein template¹⁰ for reporting cardiac arrest and cardiopulmonary resuscitation outcomes. The pre-hospital variables entered in the register are age, gender, whether the OHCA was witnessed or not, the first recorded rhythm, location of the arrest, bystander CPR, administration of drugs, defibrillation, time intervals and information on ROSC when admitted to hospital. A validation report in 2013¹⁶¹ showed that 25% of all OHCA were not reported prospectively by the EMS, but they were found after cross-checking of EMS records and entered retrospectively into the register.

The SRCR dataset was merged with data from the SWEDEHEART register, including the RIKS-HIA register, which was used for ECG information and comorbidities. The SCAAR (Swedish Coronary Angiography and Angioplasty Register) register was used for coronary angiography and PCI variables. SCAAR contains information from all 29 centers performing coronary angiography and PCI in Sweden. SCAAR coverage during the study period was almost 100%. Coronary angiographic and PCI data in SCAAR are prospectively collected, audited and monitored according to defined standards¹⁶².

Not all OHCA patients were registered in RIKS-HIA and SCAAR and therefore missing ECGs were collected from patients' medical records.

Additional data on comorbidities prior to cardiac arrest, and mortality, was collected from the National Patient Register, which is run by the Swedish National Board of Health and Welfare organization. Coverage regarding mortality is almost 100% because each Swedish citizen has a unique personal identification number¹⁶³. All hospital admissions in Sweden are reported to the registry, together with international classification of disease codes (ICD-10 codes). National coverage regarding comorbidities in the National Patient Register is almost 100% and a validation has shown that 85-95% of all diagnoses are valid¹⁶⁴.

The study cohort was classified into two groups for comparison. "Early CAG", defined as coronary angiography performed within 24 hours of the cardiac arrest, and "No Early CAG",

defined as coronary angiography performed after 24 hours or not at all. The study endpoints were 30-day survival, and one- and three-year survival.

Statistical methods

Categorical variables were presented as numbers and percentages and continuous variables as medians with interquartile ranges (IQRs). Differences between categorical data were assessed by using the Chi-Square test and differences between continuous data was assessed by using the Mann-Whitney U test. Logistic regression analysis was performed to determine the association between early CAG and 30-day survival. Backward stepwise regression was used to limit the number of variables used in multivariate analysis. To calculate long-term survival a Cox proportional regression model was used.

4.2 STUDY II AND IV; RANDOMIZED STUDY

Study design, population, treatment protocol and data sources

The DIrect or Subacute Coronary angiography in Out-of-hospital cardiac arrest study (DISCO) is an open-label, prospective, randomized, national multicenter clinical study (ClinicalTrials.gov ID: NCT02309151). The DISCO study was designed to compare a treatment strategy with immediate coronary angiography (with possible PCI), defined as angiography within 120 minutes of first medical contact, versus treatment based on current clinical practice after OHCA, with patients being admitted to an ICU and coronary angiography performed at a later stage.

Patients eligible for the study were OHCA patients over aged 18 years or more with witnessed cardiac arrest, ROSC at the latest in the emergency room and coronary angiography possible within 120 minutes of first medical contact. Excluded were patients with ST-elevation on the first ECG, obvious non-cardiac cause of cardiac arrest, terminally ill patients with a life expectancy of less than one year, patients not unconscious (defined as Glasgow coma scale >8) and patients with known pregnancy. Studies II and IV present results from the initial pilot phase of the DISCO trial.

In Study II the outcome measures were logistics, feasibility and safety aspects.

In Study IV the outcome measures were left-ventricle ejection fraction at 24 hours, peak troponin T levels, levels of NT-proBNP at 72 hours and lactate clearance at six and 24 hours.

The randomization procedure was performed through an online randomization module.

Patients randomized to immediate coronary angiography were treated by following a revascularization protocol stating that “PCI should be performed on the presumed culprit lesion and that additional significant stenoses detected should be treated in addition to the culprit lesion, i.e., PCI should be carried out on all significant stenoses that are accessible to

PCI during the acute coronary angiography”. Significant stenoses referred to stenoses of >50% as estimated by the PCI operator.

Patients randomized to standard-of-care were treated according to post-resuscitation guidelines in the ICU with potential coronary angiography performed not before three days. If circulatory instability, ventricular arrhythmias or ECG changes with ST-elevation occurred the attending physician could consider a coronary angiography before the stipulated three days.

All study data were collected in a case-report form (CRF). All data were then entered into a web-based data system at the Uppsala Clinical Research Center. Data on coronary angiography was collected from the SCAAR register. Each study site was monitored by independent research nurses according to Good Clinical Practice standards.

In the pilot phase of the study, OHCA patients with ST-elevation were also included as an observational group. This group was not randomized and was followed only for observation and for comparison regarding differences in timeframes, logistics and biomarkers.

Statistical methods

To assess feasibility and safety aspects, a sample size of 80 randomized patients was chosen. The sample size was predefined in the study protocol. The analyses included all enrolled patients, randomized patients without ST-elevation and patients with ST-elevation. Owing to the limited number of patients presented no comparative statistical measures were performed in Study II. Continuous variables were presented as medians and IQR. Categorical variables were presented as total numbers of patients and proportions (%) in each group. In Study IV differences between the groups were analyzed using the Chi-square test for categorical variables and the Mann-Whitney U test for continuous variables.

4.3 STUDY III; RETROSPECTIVE, DESCRIPTIVE STUDY

Study design, population and data sources

A retrospective, descriptive, single-center study conducted at Södersjukhuset between 2012 and 2017. The study was designed to describe how focused cardiac ultrasound (FOCUS) was used and associated with further diagnostic measures and if the detection of pulmonary embolism, cardiac tamponade and acute myocardial infarction (AMI) could be improved in the setting of post-ROSC cardiac arrest.

Patients included in the study were all adults resuscitated from cardiac arrest and admitted to the Medical ICU at Södersjukhuset. All patients identified as having successful resuscitation following OHCA or in-hospital cardiac arrest (IHCA) without any restrictions in care were included. Patients with ST-elevation on the ECG, patients admitted from other hospitals, patients without focused cardiac ultrasound examination and patients with obvious non-cardiac or respiratory causes of the cardiac arrest were excluded. The FOCUS examination was performed by the attending echocardiography-certified cardiologist.

To identify the patients, the local hospital register for cardiac arrest was used. Study variables were reviewed retrospectively from electronic medical records and organized in an anonymized local database. Interpretation of whether or not the FOCUS findings influenced further management was adjudicated from the patient's records by two cardiologists at different time points. Information on management was documented, together with the patient's final diagnosis established by clinical judgment or autopsy.

Statistical methods

Categorical variables were presented as total numbers and proportions and continuous variables were presented as medians and IQRs. Owing to the descriptive design of the study no comparative statistical tests were performed.

4.4 ETHICAL CONSIDERATIONS

The studies were approved by the regional ethics review board in Stockholm (Study I, approval number 2014/1139-31/2, Studies II and IV, approval number 2014/1170-31/1, Study III approval number 2016/1332-31).

Studies I and III were retrospective studies, and the possible harm to the participating patients was considered to be low.

Conducting research on unconscious cardiac-arrest patients requires caution. For natural reasons, unconscious OHCA patients cannot provide informed consent to participate in a randomized clinical trial.

Because of the design of the DISCO study, with enrolment as soon as possible after sustained ROSC, and the nature of the participants, comatose survivors after OHCA, informed consent could not be obtained before randomization.

When conducting a randomized trial there must be a balance of risk and benefit for the participants. When the DISCO study was designed there was (and still is) conflicting evidence concerning whether or not immediate coronary angiography could improve survival rates in OHCA patients without ST-elevation.

Potential harm to patients randomized to immediate coronary angiography could be harm attributed to the intervention and potential harm in patients randomized to standard care in the ICU could be lack of revascularization of an occluded coronary artery, with potential consequences. The DISCO study protocol states that in “patients randomized to standard care coronary angiography could be performed before three days if the patient develop circulatory instability, ST-elevation on the ECG or serious ventricular arrhythmias”¹⁶⁵.

In the DISCO study, relatives were asked for consent after randomization, most often in the ICU and in a few cases several weeks afterward. In one case the next of kin declined to give consent. All patients who survived were informed about the trial and asked for written informed consent. None of the survivors declined to give consent in the study.

During the timeline of a randomized clinical trial, new evidence could be presented which could ethically question continuation of the trial. The COACT trial¹³⁰ was presented in 2019 and the results tend to strengthen the continuation of the DISCO trial.

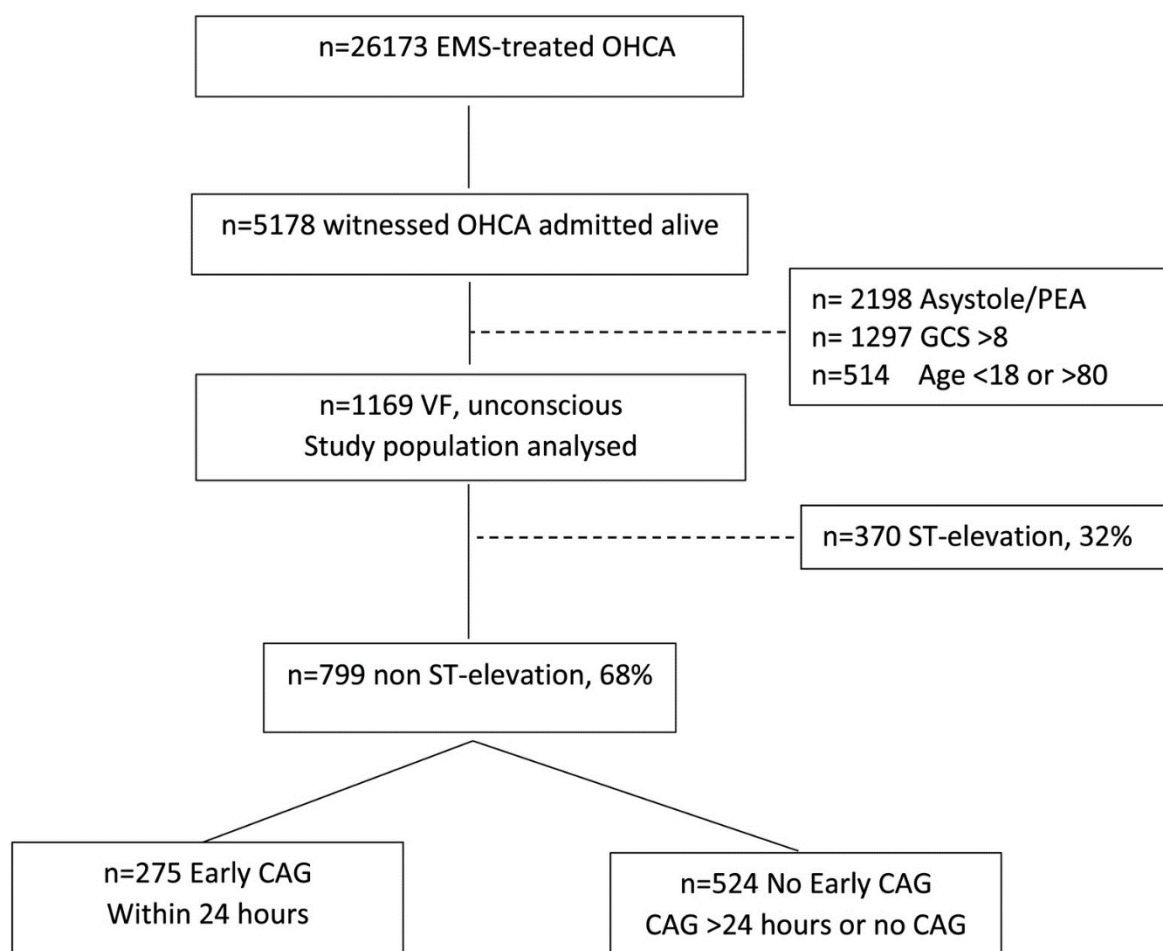
5 RESULTS

5.1 STUDY I; SURVIVAL IN OHCA-VF PATIENTS WITHOUT ST-ELEVATION

Study population

During the study period 26,173 OHCA patients were treated by the EMS and among those, 5178 were witnessed and admitted alive to hospital. Patients with asystole/PEA, awake patients, patients aged less than 18, or 80 years or more and patients with ST-elevation or presumed new LBBB on admission were excluded. A total of 799 patients were included in the final analysis. Early CAG within 24 hours was performed in 275 patients. The “no early CAG” group included 524 patients.

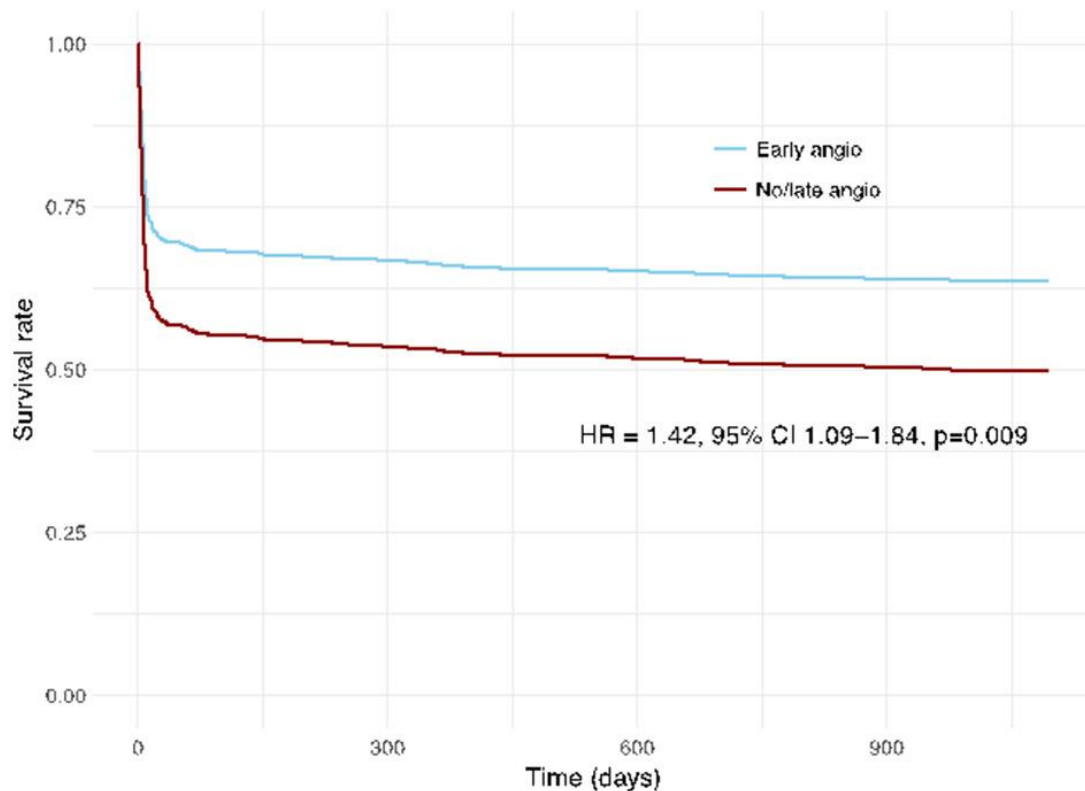
Figure 4. Study I flow chart.



Main results

Unadjusted 30-day survival in the early-CAG group was 65%, compared with 52% in the no-early-CAG group. The adjusted OR for 30-day survival was 1.42 for early CAG (95% CI 1.00-2.02, $p=0.048$). The adjusted HR for one-year survival was 1.35 (95% CI 1.04-1.77).

Figure 5. Survival using Cox proportional regression analysis, HR, adjusted hazard ratio at three years.



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Table 3. Angiographic findings

	Early CAG (%) n = 275	Late CAG (%) n = 166	P
<i>Significant coronary stenoses (>50%)</i>			
1 vessel	77 (28)	40 (24)	.37
2 vessels	49 (18)	22 (13)	.21
3 vessels	46 (17)	30 (18)	.72
Left main (LM) only	0 (0)	0 (0)	-
LM plus 1 vessel	1 (0.4)	1 (0.6)	.72
LM plus 2 vessels	7 (3)	3 (2)	.99
LM plus 3 vessels	12 (4)	10 (6)	.49
Total significant stenoses	193 (70)	106 (64)	.22
Normal/atheromatous	82 (30)	60 (36)	.24
Coronary angiography only	135 (49)	109 (66)	.002
Coronary occlusions	74 (27)	33 (20)	.03
Percutaneous Coronary Intervention (PCI)	140 (51)	57 (34)	.003

Values are numbers (%). Differences were assessed by chi-square test for categorical data. A significance level of $P < .05$ was chosen.

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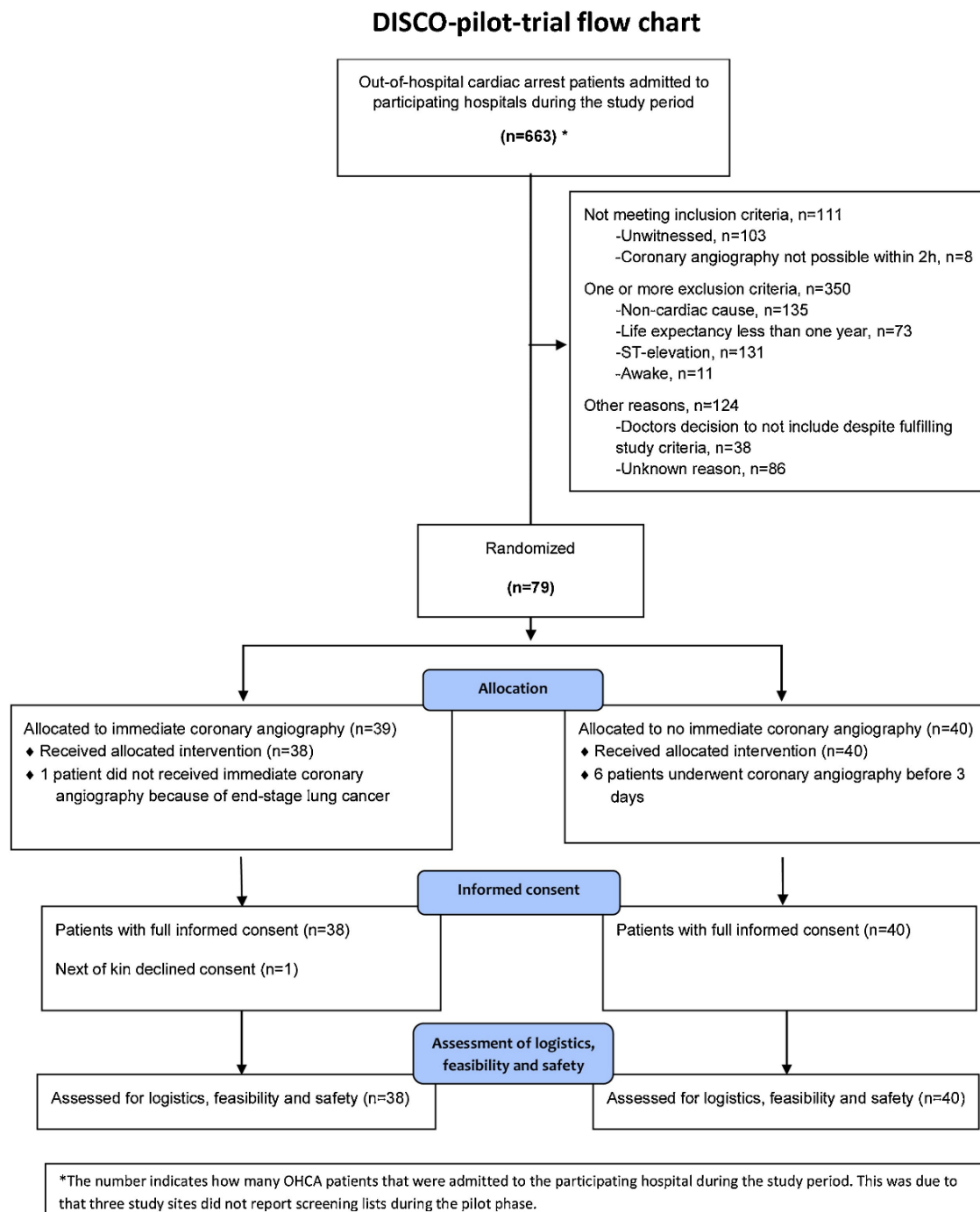
The proportion of significant stenoses was 70% in the Early-CAG group and 64% in the Late-CAG group. PCI was performed in 51% in the Early-CAG group and 34% in the Late-CAG group.

5.2 STUDY II; DISCO PILOT STUDY

Study population

In this study 79 patients were randomized from January 1st, 2015 to October 15th, 2017. There were 39 patients randomized to immediate coronary angiography and 40 patients to standard-of-care. In the observational ST-elevation group, 39 patients were included.

Figure 6.



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Feasibility

In the immediate-angiography group, the median time from EMS arrival to coronary angiography was 135 minutes (Q1-Q3: 106-178).

When reevaluating the inclusion and exclusion criteria, we found that 10 patients did not fully meet the study criteria (mainly cases of non-witnessed cardiac arrest and awake patients). However, they were included in the pilot phase of the study on a to intention-to-treat basis.

Due to the lack of 24/7 coronary angiography services in two of the participating study centers, transportation between primary and tertiary hospitals occurred in seven out of 38 cases (18.4%). No serious events occurred during the transportation from the primary hospital to the tertiary center.

Cross-over

In the standard-of-care group six patients underwent coronary angiography earlier than three days after the cardiac arrest. The reasons for earlier coronary angiography were new onset of ST-elevation, high troponin levels and echocardiography indicating ischemia.

Table 4. Time periods

	No ST elevation		ST elevation
Median times (Q1-Q3)	Immediate CAG n=38	Standard of care n=40	Observation, STEMI n=39
<i>Time from cardiac arrest to EMS arrival (min)</i>	8 (6-13)	9 (6-12)	8 (4-12)
<i>Time from cardiac arrest to ROSC (min)</i>	20 (14-35)	25 (19-34)	25 (17-30)
<i>Time from EMS arrival to vessel puncture (min)</i>	135 (106-178)	NA	NA
<i>Time from cardiac arrest to randomization (min)</i>	79 (65-96)	76 (63-92)	NA
<i>Time from randomization to angio (min)</i>	69 (42-94)	NA	NA
<i>Time from ER arrival to ICU arrival (min)</i>	155 (85-212)	104 (85-134)	176 (143-210)
<i>Time from ER arrival to vessel puncture (min)</i>	98 (68-133)	NA	NA

Times are presented as medians (Q1-Q3). Abbreviations: EMS: Emergency medical service, ROSC: Return of spontaneous circulation, CA: Cardiac arrest, ICU: Intensive care unit, ER: Emergency room, NA: Not answered

Coronary angiography and PCI findings

In the immediate-angiography group a culprit lesion was found in 14/38 patients (36.8%), PCI was performed in 15/38 patients (39.5%) and assessed as successful in 14/15 (93%) patients.

Table 5. Coronary angiography and PCI

	Immediate CAG n=38	Observation (STEMI) n=39
<i>Radial access</i>	17 (44.7%)	13 (33.3%)
<i>Femoral access</i>	18 (47.4%)	23 (59.0%)
<i>Access not answered</i>	3 (7.9%)	3 (7.7%)
<i>Culprit lesion identified</i>	14 (36.8%)	26 (66.7%)
<i>Culprit vessel, LAD</i>	5 (13.2%)	18 (46.2%)
<i>Culprit vessel, LCX</i>	3 (7.9%)	2 (5.1%)
<i>Culprit vessel, RCA</i>	4 (10.5%)	6 (15.4%)
<i>Culprit vessel, Other</i>	2 (5.3%)	0 (0%)
<i>Culprit vessel, Chronic total occlusion (CTO)</i>	2 (5.3%)	1 (2.6%)
<i>PCI of any vessel</i>	15 (39.5%)	26 (66.7%)
<i>General success</i>	14 (93%)	26 (100%)
<i>Significant stenosis outside identified culprit vessel</i>	7 (18.4%)	13 (33.3%)
<i>Complete revascularization, multi-vessel disease*</i>	2 (28.6%)	4 (30.1%)
<i>Complication related to intervention</i>		
<i>New cardiac arrest at PCI-unit</i>	3 (7.9%)	2 (5.1%)
<i>Arrhythmias (VT/VF) requiring treatment at PCI-unit</i>	2 (5.3%)	2 (5.1%)
<i>Bleeding minor</i>	0 (0%)	0 (0%)
<i>Bleeding major</i>	0 (0%)	0 (0%)
<i>Cardiac tamponade</i>	0 (0%)	0 (0%)
<i>Deceased at PCI-unit</i>	0 (0%)	0 (0%)

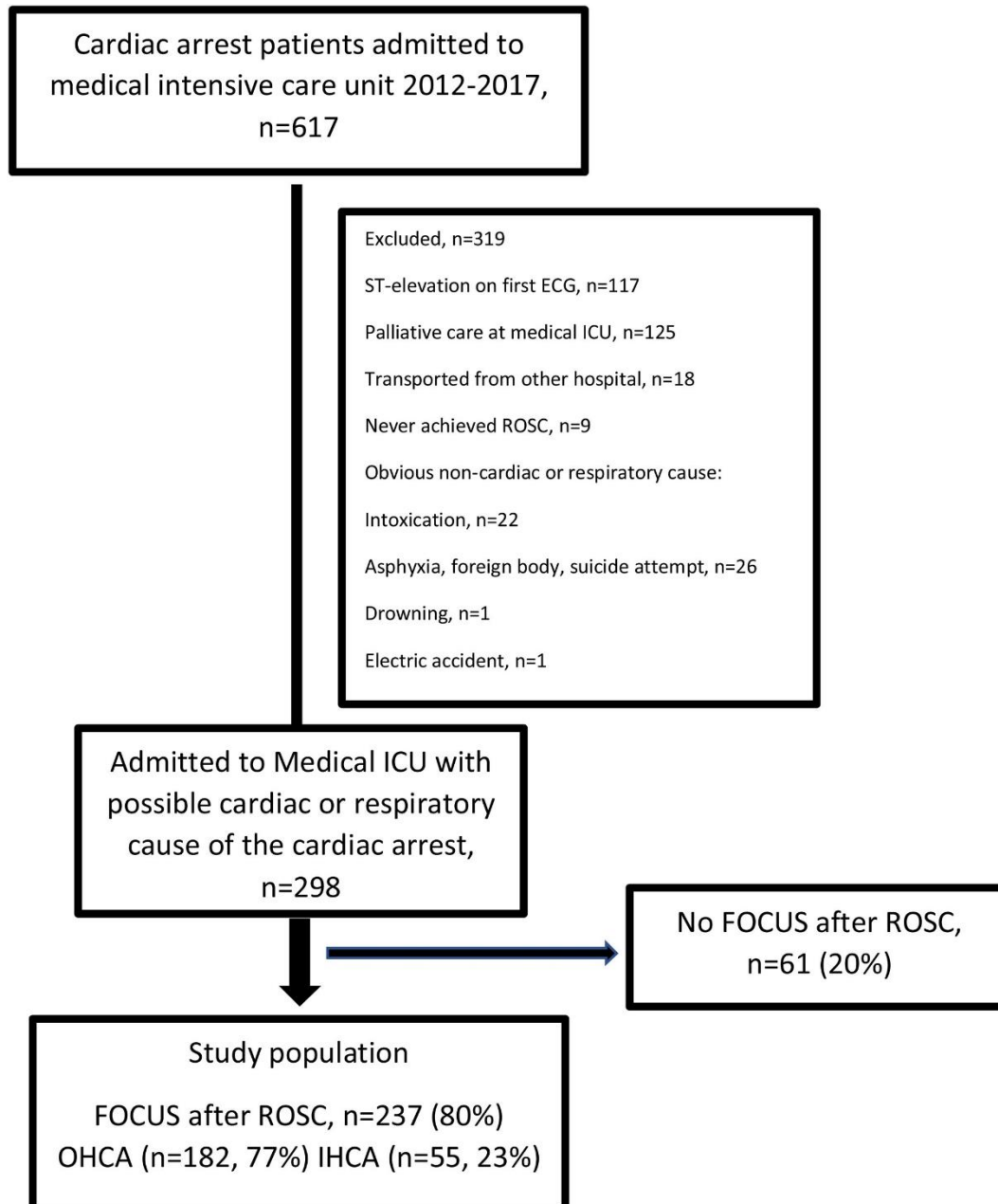
Categorical variables are presented as numbers (%). Abbreviations: LAD: Left artery descending, LCX: Left circumflex artery, RCA: Right coronary artery, PCI: Percutaneous coronary intervention, VT: Ventricular tachycardia, VF: Ventricular fibrillation *Complete revascularization of those identified as significant stenosis outside identified culprit vessel

5.3 STUDY III; FOCUSED CARDIAC ULTRASOUND AFTER ROSC

Study population

In this descriptive study, 237 patients with FOCUS examination were evaluated. The majority were included after OHCA (n=182, 77%) and a minority after IHCA (n=55, 23%).

Figure 7. Flow chart Study III



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Main results

The influence of FOCUS pathology findings in terms of leading to further diagnostic measures was detected in 21.9% of the patients. The decision to perform CT-thorax because of right ventricular dilatation and/or right ventricular pressure overload occurred in 8.9% of the patients. Left-ventricular FOCUS findings, with regional wall-motion abnormalities influenced the decision to perform emergency coronary angiography in 7.2% of the patients.

Table 6. Influence of FOCUS findings

FOCUS performed after ROSC	Total n = 237	OHCA n = 182	IHCA n = 55
FOCUS pathology influenced management (%)	52 (21.9%)	37 (20.3%)	15 (27.3%)
Normal FOCUS findings influenced management (%)	28 (11.8%)	23 (12.6%)	5 (9.1%)
Left ventricle (LV)			
FOCUS findings influenced decision to perform emergency coronary angiography (%)	20 (8.4%)	16 (8.8%)	4 (7.3%)
LVEF influenced decision to perform emergency coronary angiography (%)	9 (3.8%)	7 (3.8%)	2 (3.6%)
LV RWMA influenced decision to perform emergency coronary angiography (%)	17 (7.2%)	13 (7.1%)	4 (7.3%)
Patients with RWMA and a culprit vessel in coronary angiography (%)	9/17 (53.0%)	8/13 (61.5%)	1/4 (25%)
Patients with RWMA and PCI (%)	9/17 (53.0%)	7/13 (53.8%)	2/4 (50%)
Right ventricle (RV)			
RV abnormalities ^a influenced decision to perform CT-thorax (%)	21 (8.9%)	13 (7.1%)	8 (14.5%)
RV findings influenced decision to treat with thrombolytic agent prior to CT-thorax (%)	15 (6.3%)	9 (4.9%)	6 (10.9%)
Correlation of FOCUS findings and pulmonary embolism in CT-thorax or at autopsy (%)	11/21 (52.4%)	8/13 (61.5%)	3/8 (37.5%)
Categorical variables presented as n (%). Abbreviations: LVEF, Left ventricular ejection fraction, PCI, Percutaneous coronary intervention, RWMA, Regional wall motion abnormality.			
^a Right ventricular dilatation and/or RV pressure overload.			

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Table 7. Etiology of the cardiac arrest

Final Etiology ^a	Total n = 237 n (%)	OHCA n = 182 n (%)	IHCA n = 55 n (%)
Cardiac cause	116 (48.9)	97 (53.3)	19 (34.5)
Acute coronary syndrome	54 (22.8)	47 (25.8)	7 (12.7)
Chronic ischemic heart disease	17 (7.2)	15 (8.2)	2 (3.6)
Cardiac arrhythmia ^b	28 (11.8)	26 (14.3)	2 (3.6)
Cardiac, other ^c	17 (7.2)	9 (4.9)	8 (14.5)
Respiratory cause			
Pulmonary embolism	12 (5.1)	8 (4.4)	4 (7.3)
Hypoxia ^d	59 (24.9)	37 (20.3)	22 (40.0)
Infection ^e	9 (3.8)	5 (2.7)	4 (7.3)
Neurological ^f	14 (5.9)	13 (7.1)	1 (1.8)
Metabolic ^g	6 (2.5)	3 (1.6)	3 (5.5)
Others ^h	21 (8.9)	19 (10.4)	2 (3.6)
Final etiology judged at autopsy	50 (21.1)	42 (23.1)	8 (14.5)

^a Final etiology judged clinically or at autopsy.

^b Cardiac arrhythmia includes AV-block III, LQTS, Primary arrhythmia.

^c Cardiac other includes Chronic heart failure, Hypertrophic CM Myocarditis, Cardiac tamponade.

^d Hypoxia includes COPD, Pneumonia.

^e Infection includes Sepsis, Hypovolemia.

^f Neurological includes Cerebral bleeding, Cerebral infarction and Epileptic seizures.

^g Metabolic includes Hypokalemia, Hyperkalemia, Metabolic acidosis and Anaphylaxis.

^h Others includes unknown cause. Categorical variables presented as n (%).

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5.4 STUDY IV; POST-RESUSCITATION MYOCARDIAL DYSFUNCTION

Study population

In this secondary analysis of the DISCO pilot study 39 patients were randomized to immediate coronary angiography and 40 patients to standard-of-care. In the observational ST-elevation group, 39 patients were included.

Main results

There was no significant difference in LVEF observed at 24 hours after the cardiac arrest, with a mean LVEF of 47% (Q1-Q3; 30-55%) in the immediate-angiography group compared with 46% (Q1-Q3; 35-55) in the standard-of-care group. Peak troponin-T levels during the first 24 hours were 362 ng/L (Q1-Q3; 174-2020) in the immediate-angiography group compared with 377 ng/L (Q1-Q3; 205-1078) in the standard-of-care group. Levels of NT-proBNP at 72 hours were 931 ng/L (Q1-Q3; 396-2845) in the immediate angiography group compared with 1913 ng/L (Q1-Q3; 489-3140) in the standard-of-care group.

Table 8. Outcome measures, Study IV

	No ST elevation		
Outcome measures	Immediate CAG n=38	Standard care n=40	P-value
Ejection fraction (%), median (Q1-Q3) at 24h	47 (30-55) [n=28]	46 (35-55) [n=30]	0.74
Troponin-T (ng/L) peak value, median (Q1-Q3)	362 (174-2020) [n=31]	377 (205-1078) [n=31]	0.77
NT-proBNP (ng/L) at ICU admission, median (Q1-Q3)	749 (356-2945) [n=28]	1431 (160-2390) [n=26]	0.75
NT-proBNP (ng/L) at 72 hours, median (Q1-Q3)	931 (396-2845) [n=20]	1913 (489-3140) [n=17]	0.64
Lactate clearance at 6 hours ¹ , (%)	70.7 (56.0-79.5) [n=30]	75.2 (68.1-85.0) [n=34]	0.08
Lactate clearance at 24h ¹ , (%)	81.5 (75.0-88.0) [n=26]	79.5 (66.0-85.4) [n=32]	0.31

¹Lactate clearance at x h was calculated as 100x (Lactate at admission-Lactate at x h)/Lactate at admission

When comparing those patients who underwent PCI (n=15) vs. no PCI (n=23), the median LVEF at 24 hours was 50% in the revascularized patients compared with LVEF 45% in those with immediate angiography where PCI was not performed.

Table 9. Impact of PCI in patients undergoing immediate angiography divided into four subgroups

Outcome measures	No ST-elevation			ST-elevation		
	Immediate coronary angiography - PCI n = 15	Immediate coronary angiography - no PCI n = 23	P-value	Observation - PCI n = 26	Observation - no PCI n = 13	P-value
<i>Ejection Fraction (%) at 24 h, median, (Q1-Q3)</i>	50 (30-55) [n=11]	45 (40-55) [n=17]	0.80	45 (33-55) [n=20]	40 (34-50) [n=10]	0.72
<i>Troponin T (ng/L) at hospital admission, median (Q1-Q3)</i>	102 (29–789) [n=14]	49 (23–127) [n=17]	0.14	173 (53–903) [n=22]	93 (31–264) [n=12]	0.14
<i>Troponin T (ng/L) peak value, median (Q1-Q3)</i>	1395 (408–2500) [n=14]	227 (145–379) [n=17]	0.04	3100 (903–8650) [n=22]	854 (463–1820) [n=12]	0.03
<i>NT-proBNP (ng/L) at ICU admission, median (Q1-Q3)</i>	870 (250–3160) [n=11]	1274 (373–2945) [n=17]	0.67	380 (111–1490) [n=20]	1355 (67–3110) [n=10]	0.83
<i>NT-proBNP (ng/L) at 72h, median (Q1-Q3)</i>	1260 (773–3200) [n=7]	939 (400–4030) [n=13]	1.0	1260 (934–1953) [n=18]	975 (422–1821) [n=8]	0.33
<i>Lactate clearance at 6h^b median, (Q1-Q3)</i>	64.3 (37.8–78.5) [n=10]	71.1 (60.6–76.3) [n=20]	0.33	71.3 (54.2–79.6) [n=24]	83.9 (76.1–87.9) [n=11]	0.01
<i>Lactate clearance at 24h^b Median, (Q1-Q3)</i>	80.5 (70.4–88.8) [n=11]	83.6 (79.3–86.7) [n=15]	0.50	75.7 (66.7–86.8) [n=24]	85.1 (79.8–88.7) [n=11]	0.07

^bLactate clearance at 6h was calculated as $100 \times (\text{initial lactate} - 6\text{-hour lactate}) / \text{initial lactate}$.

6 DISCUSSION

Why does myocardial ischemia cause cardiac arrest?

Historically, acute myocardial ischemia caused by an occluded coronary artery has been considered the dominant mechanism of VF and cardiac arrest. It still plays a significant role although its dominance has been challenged by other recognized mechanisms.

Cardiac arrest associated with transient ischemia most often presents without ST-elevation on the ECG and could be related to a proximal high-grade stable coronary stenosis, and transient ischemia is initiated by the inability to meet flow requirements under a specific condition such as increased demand during physical activity, or supraventricular tachycardia. This initiates regional variations in myocardial-cell membrane electrophysiology and causes ventricular arrhythmias⁵².

Most patients with stable, unstable or acute coronary artery disease do not suffer from cardiac arrest, which implies that other factors must be present. It has been suggested that a strong genetic component exists in the risk of cardiac arrest^{166,167}, and promising genetic studies have been presented to quantify the risk of cardiac arrest¹⁶⁸. However, the underlying genetic variation remains unknown. It has been suggested that the manifestation of fatal arrhythmias is the result of an interaction between substrate, trigger, and modulating factors¹⁶⁹.

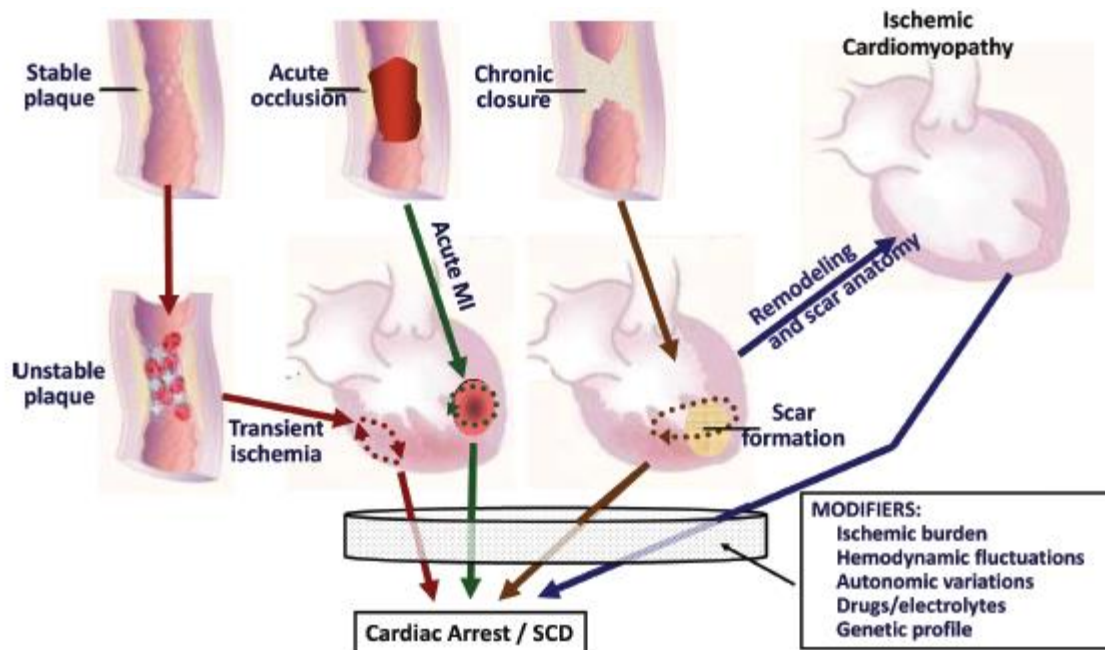


Figure 8. Mechanisms of cardiac arrest of cardiac cause. Myerburg⁵¹ et al Reproduced with permission from Circulation.

A Danish study group compared STEMI patients with and without VF before PCI and they recognized a family history of sudden death, absence of angina, high alcohol intake, younger age and history of atrial fibrillation to be independent risk factors of VF¹²⁴.

What are the potential benefits of performing immediate coronary angiography in OHCA patients without ST-elevation?

Considering the high burden of ischemic heart disease in OHCA patients, coronary angiography is a reasonable diagnostic procedure after ROSC, but there are inherent logistical and organizational challenges as a result of variable availability of coronary angiography facilities between hospitals and regions. If a culprit lesion is detected, subsequent PCI could be performed and might salvage myocardial muscle, improve ventricular function and prevent the recurrence of ventricular arrhythmias¹⁷⁰. However, the recurrence of ventricular arrhythmias is frequent during the first 24 h after ICU admission even in revascularized patients probably because of ischemia-reperfusion injuries¹⁷⁰.

In survivors, revascularization may prevent the development of ischemic heart failure. The high rates of obstructive coronary disease observed in patients presenting without ST-elevation do not *per se* explain the cardiac arrest and other causes must be considered, especially in the absence of an occluded coronary artery.

Normal coronary angiography findings provide essential diagnostic information, since the absence of an acute coronary event is an important finding, which would can speed up the search for alternative causes of the cardiac arrest. A normal coronary angiography finding will also lead to termination of antiplatelet therapy, which might decrease the risk of bleeding during post-cardiac arrest care.

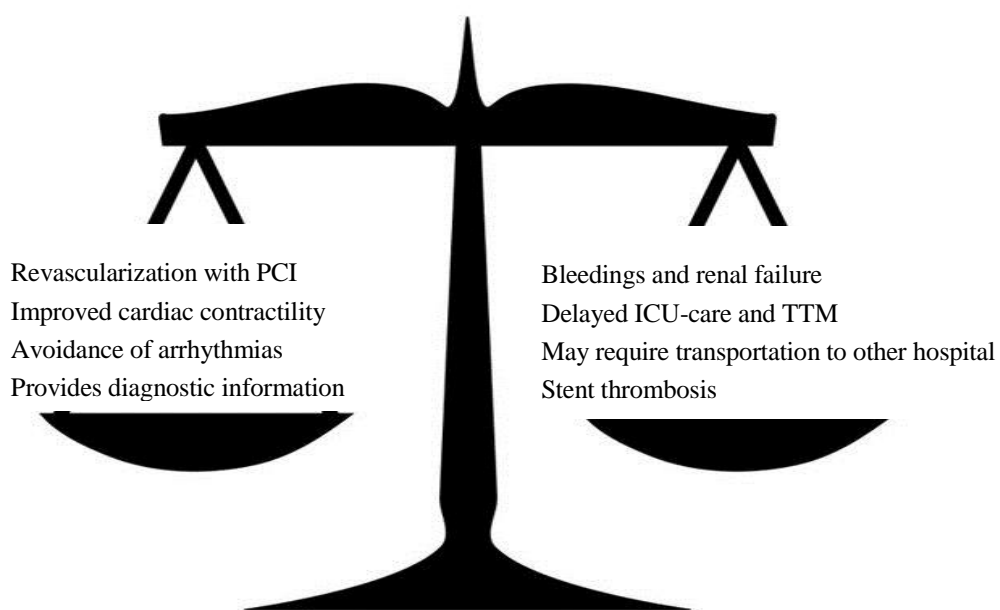


Figure 9. Benefits and risks of immediate coronary angiography.

What are the potential risks of performing immediate coronary angiography in OHCA patients without ST-elevation?

Immediate coronary angiography after ROSC is not without risk. It requires exposure to contrast agents with an increased risk of renal failure¹⁷¹, a vascular risk at the access site¹⁷², where femoral access is more common in this acute setting, and bleeding risks from antiplatelet drugs. In OHCA patients undergoing PCI there is also an increased risk of stent thrombosis¹³⁶ compared with patients without cardiac arrest.

Transferring unstable patients between hospitals in order to perform an immediate coronary angiography may be difficult, with inherent risks. Trying to cut time to the start of coronary angiography in OHCA patients could lead to insufficient clinical examination before angiography, with the risk of not detecting other potential treatable causes of the arrest, and the risk of delaying other treatment options. Other possible challenges are delays in initiating post-resuscitation measures such as target temperature management. In addition, respiratory or circulatory instability might be more difficult to handle outside the ICU. Furthermore, immediate coronary angiography is a resource-intensive and costly intervention.

However, in **Study II** the rate of bleedings and signs of renal failure were low. In the larger COACT trial¹³⁰ the rate of major bleeding complications was low and actually higher in the delayed-angiography group (4.9% vs 2.6%), probably because of lower utilization of antithrombotic medication due to the fact that normal coronary angiography without a need for PCI could exclude antithrombotic agents.

In summary, immediate coronary angiography may be considered safe in OHCA patients arriving at hospitals with angiography facilities and who do not require transfer to another hospital.

When to perform coronary angiography in OHCA without ST-elevation?

Observational studies have shown a high rate of occurrence of coronary artery disease in patients without ST-elevation on the ECG which makes immediate coronary angiography an attractive strategy.

According to the results of the COACT trial¹³⁰ it is safe to wait for neurologic recovery before performing coronary angiography which could be interpreted as keeping OHCA patients without ST-elevation at the nearest hospital without coronary angiography facilities is safe. This argument goes against the idea of centralizing all OHCA patients to cardiac arrest-centers.

The results of the COACT trial are consistent with the results of several randomized trials, concerning NSTEMI patients without cardiac arrest, which have shown no survival benefit of immediate coronary angiography compared with delayed coronary angiography^{173,174}.

How early is early?

Early is not the same as immediate when it comes to coronary angiography, and in many patients it might be favorable to wait and collect further clinical information such as Troponin changes, a more detailed medical history from next of kin, and exclusion of other causes after DT-thorax and head examinations.

In **Study II** and in the COACT trial there was a small but not negligible proportion of cross-overs in the control group. These patients showed signs of myocardial infarction such as elevated Troponins, ECG changes suggesting ongoing ischemia and echocardiographic signs of regional wall motion abnormalities.

A proposal might be to wait for up to six hours to identify those patients that might benefit from coronary angiography and possible PCI. The advantages of this concept would include avoiding unnecessary activation of the coronary angiography lab at night, avoiding transportation of a circulatory unstable patient to another hospital and increasing the likelihood of PCI.

For whom? How to select patients for immediate coronary angiography?

It is important to identify which patients will probably benefit from treatment with PCI. It is as important to identify those who will not benefit from immediate coronary angiography. It is thus essential to assess the likelihood of PCI and the likelihood of poor neurologic outcome when selecting patients for an invasive strategy. The effects of hypoxic brain injury reduce the potential value of PCI because neurologic injury remains the leading cause of death in an ICU. Accordingly, neurologic prognosis should be evaluated first before transfer for coronary angiography, especially in OHCA patients without ST-elevation.

A reliable prognostication tool could be of great value since there is no specific clinical sign to predict neurologic outcome in the first few hours after ROSC. The Cardiac Arrest Hospital Prognosis (CAHP) score is intended to stratify neurological outcome after OHCA¹⁷⁵ and consists of seven variables associated with poor prognosis: Non-shockable rhythm, age, time from collapse to basic life support (BLS), time from BLS to ROSC, location of the arrest, epinephrine dose, and arterial pH. This score was tested in an observational study and showed that only patients with low-risk scores could benefit from early coronary angiography regardless of the presence of ST-elevation¹⁷⁶.

How to predict an acute coronary culprit lesion immediately after ROSC?

The only established predictor of a coronary culprit lesion/occlusion is ST-elevation on the ECG after ROSC. However, approximately 70% of OHCA patients present without ST-elevation, which makes it more challenging to predict a culprit lesion. Suggested predictors in these patients might be:

- Preceding symptoms such as chest pain.
- Medical history of coronary artery disease or diabetes.
- Initial shockable rhythm.
- ECG with ST-depression.
- Regional left-ventricle-wall-motion abnormalities in FOCUS examination.
- Initial high-sensitivity troponin T levels of more than 150 ng/L.

This prediction model is a suggestion and comes with limitations, since in many cases information on these predictors is not available, and it has not been validated.

Does coronary angiography improve survival after OHCA?

In several observational studies, including **Study I**, higher rates of survival in patients undergoing early coronary angiography have been reported^{3,87,132}. However, is it possible that a diagnostic tool may improve survival after cardiac arrest? One can argue that the main question should be if revascularization, i.e. PCI, has the potential to improve outcomes in resuscitated OHCA patients without ST-elevation on the ECG.

The results of some observational studies suggest that PCI drives the benefit of coronary angiography^{81,177}. In one observational study, focusing on patients without ST-elevation, it was reported that successful PCI was associated with improved outcome compared with no PCI². In another study it was concluded that early coronary angiography, but not PCI, was associated with improved outcome¹³², indicating a risk of selection bias.

The largest published randomized trial, the COACT trial¹³⁰, including patients with VF and ECG without ST-elevation, revealed no difference in survival between immediate coronary angiography compared with coronary angiography after ICU-discharge. At 90 days, 64.5% in the immediate-angiography group and 67.2% in the delayed-angiography group were alive (OR, 0.89, 95% CI, 0.62-1.27; $p = 0.51$). The PCI rate was 33% in the immediate group and 24.2% in the delayed group, which indicates that the trial was underpowered to answer the question of whether or not immediate coronary angiography with revascularization could improve survival in patients without ST-elevation after OHCA.

In summary, coronary angiography *per se* does not improve survival, but revascularization of an acute occluded coronary artery should decrease the risk of dying as a result of cardiovascular conditions, although it is unlikely that revascularization could improve neurological outcome.

Why do the results differ between observational and randomized OHCA studies?

In observational studies the decision on which subjects receive coronary angiography is not entirely random and thus there is an inherent potential source of bias. Most observational studies demonstrate lower mortality rates in OHCA patients undergoing coronary angiography, even when PCI is not performed, which serves as a good example of confounding. In observational studies the early coronary angiography group may differ systematically from those that are *not* undergoing early coronary angiography. This is denoted as confounding by indication¹⁷⁸. One other potential cause of bias in observational studies on coronary angiography after OHCA is the risk of dying during the first few hours after cardiac arrest and thereby being excluded from the intervention. This type of bias is called waiting-time bias or time-dependent bias, which may exist in **Study I**.

There are various statistical methods to adjust for confounding factors, but it is impossible to correct for all variables clinicians consider when selecting patients for immediate coronary angiography or no immediate coronary angiography, this is so-called residual confounding.

Randomized controlled trials represent the gold standard for evaluating the efficacy of interventions, avoiding bias by randomly allocating participants to the treatment or control groups¹⁷⁹. In observational studies the treatment is chosen by the clinician rather than randomly assigned.

One of the major challenges in randomizing OHCA patients without ST-elevation is that clinicians may believe it is wrong to randomize patients if they are convinced that the treatment being studied is effective. When large numbers of patients are excluded from randomized trials, generalizing the results becomes more difficult. Another difficulty in performing an RCT lies in recruiting a sufficient number of patients, which has been a challenge in **Studies II** and **Study IV**.

What is the diagnostic performance of an ECG in cardiac arrest versus no cardiac arrest?

In cardiac-arrest research publications, the frequent occurrence of an occluded coronary artery in patients without ST-elevation, is often reported. However, does that differ from the situation among patients without cardiac arrest?

In patients presenting without cardiac arrest and no ST-elevation on the ECG, i.e. NSTEMI-patients, a recent published meta-analysis presented the fact that 25.5% had an occluded culprit artery¹⁸⁰, which is comparable to the figure reported in cardiac-arrest patients without ST-elevation reporting an occluded coronary vessel in 22.9-27.0% of the patients^{3,131}.

The challenge in cardiac arrest compared with NSTEMI is that the patients most often are unconscious and other diagnostic measures such as Troponins and chest pain are difficult to assess properly.

In OHCA patients ECG findings of LBBB and RBBB are more frequent than in patients with myocardial infarction without cardiac arrest⁸⁵. In **Study I** the proportion of cases of RBBB was 12.5%, consistent with figures in other studies⁸⁵. Bundle-branch block is often transient in cardiac-arrest patients which could be explained by global hypoxia during the arrest, differing from the situation in patients without cardiac arrest, where a bundle branch block should increase the suspicion of a coronary culprit lesion.

Why was the DISCO pilot study performed and what were the experiences of it?

When designing the DISCO trial, it was, to our knowledge, the first clinical trial in which it was planned to randomize unconscious OHCA patients without ST-elevation and with recent ROSC to either immediate coronary angiography or standard care. The main reasons for conducting the DISCO pilot study were to assess the feasibility of the randomization procedure, the informed-consent procedure, implementation of the intervention, evaluate adherence to protocol, the cross-over rate and assess the enrollment rate.

The pilot sample size was pragmatic and based on the necessities for examining feasibility. The pilot study result was never intended to be used for sample size calculations for the main DISCO study.

Because of the adaptive design of the DISCO study, the angiographic findings in the control group were not presented and 30-day survival was not assessed.

Experiences from the DISCO pilot study, Study II

Immediate angiography was performed at a later time point than the 120 minutes from first medical contact stipulated in the protocol and it was changed to 120 minutes *from randomization*, after evaluation of the pilot-study results.

During the timeline of the pilot study, the Culprit-Shock trial was published¹⁸¹, reporting a higher risk of immediate multi-vessel PCI in cardiogenic shock patients, and the complete revascularization strategy was changed to culprit-lesion-only PCI in the DISCO-study protocol.

Unfortunately, many eligible patients were not randomized, which may introduce a risk of selection bias in the main DISCO trial. The low enrollment rate was interpreted as a consequence of the strong belief among many clinicians that immediate coronary angiography should be carried out in all OHCA patients. The neutral results from the COACT trial may make it easier for clinicians to randomize patients in the DISCO trial since it is now more difficult to argue for immediate angiography in OHCA patients without ST-elevation.

When and how could FOCUS be used in cardiac arrest?

Ultrasound is increasingly being incorporated into cardiopulmonary resuscitation and can be performed during CPR and after ROSC. It has been suggested to be used as a prognostic and diagnostic tool during CPR, especially in PEA patients. The use of FOCUS as a diagnostic tool during CPR is very time-dependent, because high-quality CPR requires minimal interruptions in chest compression, and good FOCUS image quality is difficult to obtain.

The use of ultrasound *after* ROSC is not as time dependent as when it is performed during CPR and the opportunity to obtain good image quality for interpretation is better.

Right-ventricular echocardiographic abnormalities are common after ROSC. Acute right-ventricle dilatation occurs shortly after the cardiac arrest as blood is translocated from the systemic circulation to the right side of the heart. The results of **Study III** suggest that dilation of the right ventricle in combination with-right ventricular pressure overload should be present in order to suspect pulmonary embolism as the cause of the arrest.

Regional wall-motion abnormalities (RWMA) in ultrasound suggestive of acute myocardial infarction may be difficult to identify. In **Study III** we found that RWMA observed in FOCUS examination were not enough to predict a culprit lesion detected in coronary angiography.

The scientific evidence for using ultrasound as a diagnostic tool in cardiac arrest situations is scarce. However, its advantage is that it is non-invasive and carries no risk to the patient.

7 FUTURE PERSPECTIVES

There is still no consensus of opinion in the clinical and scientific community about the value of immediate coronary angiography in OHCA patients without ST-elevation.

The recently published COACT trial was underpowered and there was a lack of generalizability to non-shockable patients. Furthermore, definite conclusions should not be drawn from a single trial. However, there are several ongoing randomized clinical trials with very similar inclusion and exclusion criteria. The DISCO trial with a sample size of 1006 patients, the German TOMAHAWK trial¹⁸² with a sample size of 558 patients and the French EMERGE trial (ClinicalTrials.gov number, NCT02876458) are recruiting patients. The results of these trials will be important as regards providing scientific evidence and guiding clinical practice. Some of these trials will also involve assessment of left-ventricular ejection fraction at six months.

A related research question is if OHCA patients without ST-elevation should be transferred to a regional cardiac-arrest center. Those running the randomized ARREST trial⁹⁵ are currently enrolling patients to answer this question.

Since ultrasound is frequently used in conjunction with cardiac arrest, there is a need for prospective trials carried out to evaluate the usefulness of focused cardiac ultrasound after ROSC in cardiac-arrest patients.

A validated scoring model to predict a coronary cause of the cardiac arrest is also of interest for guiding clinical practice. Such a scoring model would take into account the combination of symptoms preceding the arrest, age, gender, comorbidities, primary rhythm, ECG, cardiac ultrasound and high sensitivity Troponin in order to increase the accuracy of detecting a culprit lesion in immediate coronary angiography after OHCA.

The increased implementation, knowledge and experience of coronary-CT in clinical practice for non-cardiac-arrest patients, makes this technique appealing to use in OHCA patients without ST-elevation. Either to rule in, or out, an acute coronary event responsible for the cardiac arrest. As described earlier in this work it has been suggested to perform a CT-thorax and head in OHCA patients without ST-elevation¹²¹. If adding coronary-CT to these examinations valuable information would be presented as to whether or not an invasive coronary angiography should be performed.

8 CONCLUSIONS

Study I

In this population of bystander-witnessed cases of out-of-hospital cardiac arrest with shockable rhythm and ECGs without ST-elevation, early coronary angiography may be associated with improved short- and long-term survival.

Study II

In this population of bystander witnessed out-of-hospital cardiac arrest patients without ST-elevation, a strategy to perform immediate coronary angiography was feasible, although the time-window of 120 min from EMS arrival at the scene of the arrest to the start of coronary angiography was not achieved. No significant safety issues were reported.

Study III

The retrospective data in this cardiac-arrest population supports the fact that advanced life support conformed post-resuscitation care could include FOCUS as an adjunctive diagnostic measure shortly after ROSC.

Study IV

In this secondary analysis of OHCA patients without ST-elevation on the ECG randomized to immediate coronary angiography or standard care, we found no differences in post-resuscitation myocardial dysfunction parameters between the groups.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

I Sverige inträffar varje år ca 6000 hjärtstopp utanför sjukhus där ambulans tillkallas och påbörjar behandling. Andelen som överlever till 30 dagar är 10%, dvs 600 personer överlever varje år.

Ett hjärtstopp innebär att hjärtat plötsligt slutar att pumpa blod. Efter några sekunder faller den drabbade ned medvetslös eftersom hjärnan drabbas av syrebrist. Hjärtstoppet kan utlösas av ett så kallat kammarflimmer som gör att hjärtats kammare flimrar istället för att pumpa ut blod i kroppen. Den enda behandling som kan hjälpa utanför sjukhus är hjärt-lungräddning och en tidig strömstöt från en hjärtstartare för att återställa hjärtats normala pumpfunktion.

En av de vanligaste orsakerna till hjärtstopp är hjärtinfarkt. Hjärtinfarkt orsakas av stopp eller delvis stopp i hjärtats kranskärl som försörjer hjärtat med blod och syre. Den syrebrist som uppstår i hjärtmuskeln kan leda till kammarflimmer och hjärtat stannar.

De flesta som får hjärtstopp utanför sjukhus avlider innan ambulansen kommer fram till sjukhus. En fjärdedel kommer dock in till sjukhus med pumpande hjärta. De flesta är dock medvetslösa och kan inte återberätta vad som inträffat.

En av de första åtgärder man gör på sjukhus är att kontrollera ett EKG. Om EKG visar tydliga tecken på hjärtinfarkt (ST-höjning) är den omedelbara åtgärden kranskärlsröntgen för att kontrollera hjärtats kranskärl. Om det är stopp i ett kranskärl kan man öppna kranskärllet. När hjärtat har börjat pumpa igen är det vanligt att man kontrollerar hjärtat med fokuserat ultraljud för att försöka utröna orsaken till hjärtstoppet och för att vägleda fortsatt utredning och behandling.

Om EKG inte visar tydliga tecken på hjärtinfarkt är det inte självklart att kranskärlsröntgen är den omedelbara åtgärden. Det finns en tydlig kunskapslucka om man ska utföra kranskärlsröntgen på patienter med EKG utan tydliga tecken på hjärtinfarkt och om fokuserat ultraljud av hjärtat är användbart för fortsatt handläggning.

Målsättningen med avhandlingsarbetet var att belysa några av dessa kunskapsluckor och besvara frågorna:

1. Kan tidig kranskärlsröntgen jämfört med sen eller ingen kranskärlsröntgen förbättra överlevnaden hos patienter med hjärtstopp utanför sjukhus med EKG utan tydliga tecken på hjärtinfarkt?
2. Är det praktiskt genomförbart att randomisera patienter med hjärtstopp utanför sjukhus utan tydliga tecken till hjärtinfarkt på EKG?
3. Kan fokuserat ultraljud av hjärtat vara behjälpligt för att ta reda på orsaken till hjärtstoppet och kan ultraljud av hjärtat vägleda fortsatt utredning och behandling?
4. Kan akut kranskärlsröntgen påverka hjärtfunktionen efter hjärtstopp på patienter utan säkra EKG-tecken till hjärtinfarkt?

Studie I var en observationsstudie där historiska data från svenska kvalitetsregister användes. Svenska hjärt-lungräddningsregistret användes och data kompletterades från svenska hjärtinfarkts registret och svenska registret för kranskärlsröntgen (SWEDEHEART). Mellan åren 2008–2013 registrerades 799 patienter med hjärtstopp utanför sjukhus med kammarflimmer som första rytm, medvetslösa vid ankomst till sjukhus, 18–85 år gamla samt avsaknad av ST-höjning på första EKG. Två grupper jämfördes avseende kort och långtidsöverlevnad: 1. Tidig kranskärlsröntgen 2. Sen eller ingen kranskärlsröntgen. Studie I visade att 65% av de som gjorde tidig kranskärlsröntgen överlevde till 30 dagar jämfört med 52% av de som gjorde sen eller ingen kranskärlsröntgen. Efter justering för störningsfaktorer blev slutsatsen att tidig kranskärlsröntgen är associerat med ökad 30-dagars överlevnad.

Studie II var en randomiserad kontrollerad studie där bevitnade hjärtstopp utanför sjukhus utan ST-höjning på EKG lottades till omedelbar kranskärlsröntgen eller sedvanlig vård på intensivvårdsavdelning.

Syftet med **studie II** var att utvärdera genomförbarhet, logistik och säkerhetsaspekter att randomisera dessa patienter i form av en pilotstudie eftersom en randomiserad studie aldrig genomförts på denna patientgrupp. De patienter som inkluderades var över 18 år, hade bevitnat hjärtstopp och kranskärlsröntgen bedömdes kunna genomföras inom 120 minuter från första medicinska kontakt samt medvetslösa patienter. De patienter som exkluderas var de med ST-höjning på EKG, de med uppenbar icke-kardiell orsak till hjärtstoppet (överdos, trauma eller hängning), patienter med terminal sjukdom med förväntad överlevnad mindre än ett år. Under pilotfasen följdes även de med ST-höjning på EKG som en observationsgrupp, men de randomiserades inte. Mellan 2015 och 2017 randomiserades 79 patienter och 39 patienter följdes i observationsgruppen.

Studie II visade att mediantiden från första medicinska kontakt till kranskärlsröntgen var 135 minuter. Transport mellan primärt mottagande sjukhus och sjukhus med möjlighet till kranskärlsröntgen inträffade i sju fall. Inga allvarliga händelser inträffade under transporten. Sex patienter som blev randomiserade till sedvanlig intensivvård genomförde kranskärlsröntgen tidigare än 3 dagar.

Konklusionen var att det är möjligt att randomisera denna patientgrupp. Inga allvarliga säkerhetsfrågor rapporterades. Det noterades dock att tiden från första medicinska kontakt till kranskärlsröntgen översteg 120 minuter.

Studie III var en beskrivande tillbakablickande studie med syfte att belysa hur fokuserat ultraljud på hjärtat används på hjärtstoppspatienter efter att hjärtat har börjat pumpa igen. Den hade även som syfte att beskriva hur ultraljud på hjärtat kunde vägleda till fortsatt utredning och behandling. Data inhämtades från journaler på patienter vårdade på medicinska intensivvårdsavdelningen Södersjukhuset mellan åren 2012–2017. Ca 80% av patienterna blev inlagda pga hjärtstopp *utanför sjukhus* och 20% blev inlagda på intensivvårdsavdelning efter hjärtstopp *på sjukhus*.

Studie III visade att fokuserat hjärtultraljud påverkade handläggningen i 22% av fallen. Ultraljud som visade regional rörelseinskränkning i hjärtats vänsterkammare påverkade beslutet att genomföra akut kranskärlsröntgen hos 7% av patienterna. Ultraljud som visade förändringar på hjärtats högerkammare påverkade beslutet att genomföra skiktröntgen av lungorna hos 9% av patienterna.

Studie IV var en sekundäranalys av Studie II med syfte att jämföra hjärtats vänsterkammarfunktion, nivåer av hjärtskademarkörer (Troponiner) samt metabolismen av mjölksyra mellan de två randomiserade grupperna.

Studie IV visade att det inte var någon skillnad mellan grupperna avseende vänsterkammarfunktion, hjärtskademarkörer eller metabolism av mjölksyra.

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