

Prehospital risk stratification in Acute Coronary Syndrome (PreACS-study)

Feasibility trial October 2017- October 2018

Project plan

Prehospital risk stratification in Acute Coronary Syndrome
(PreACS-study)

-a pilot trial (part I)

A study approved by the Norwegian regional ethics committee (REK# 2017/ 701).

1. Introduction

Acute coronary syndrome (ACS) is a common cause of death in industrialized countries and accounts for a large proportion of hospital admissions¹⁻⁶. The term ACS includes unstable angina pectoris and acute myocardial infarction (AMI). Approximately 13 000 Norwegians are diagnosed annually with acute myocardial infarction, and of these the 30-day mortality rate is 10 %⁷.

Several studies have shown that early coronary angiography and percutaneous coronary intervention (PCI) reduce the risk of death and recurrent cardiovascular events after AMI, and guidelines from the European Society of Cardiology (ESC) recommend such treatment to all patients^{8,9}. Timing of coronary angiography and revascularization are today primarily guided by electrocardiogram (ECG)^{8,10}. The benefit of urgent revascularization is well documented in ST-elevation myocardial infarction (STEMI), where most patients have an acute occlusion of a coronary artery¹¹. Because an acute coronary occlusion in most cases causes a process of irreversible myocardial damage that starts within minutes, urgent revascularization is particularly important in this subset of patients. In non-ST-elevation myocardial infarction (NSTEMI) coronary angiography is recommended within 2 or 24 hours depending on risk stratification⁸. Urgent coronary angiography is recommended for patients with very high-risk features, such as hemodynamic instability, refractory chest pain or life-threatening arrhythmias⁸. However, NSTEMI probably shares the same pathophysiology as STEMI since acute coronary occlusion is a common finding at coronary angiography also in patients with NSTEMI¹²⁻¹⁴. At coronary angiography, 25-55% of patients with NSTEMI have an occlusion of the culprit coronary artery, and ECG has limited sensitivity for identification of acute coronary occlusions^{13,15,16}. As a consequence, many patients with NSTEMI are at risk of extensive myocardial injury due to delayed revascularization^{9,17}. Only 22% of patients (<80 years of age) with NSTEMI underwent coronary angiography within 24 hours in Norway in 2014, and 24% of the patients were not offered this examination at all¹⁸.

In Norway, few hospitals offer emergency coronary angiography and PCI in suspected AMI. In order to perform earlier invasive evaluation and treatment of NSTEMI, patients with suspected AMI must be evaluated for admission directly to a hospital with PCI facilities. However, early prehospital risk stratification of patients with suspected NSTEMI is challenging because decision making based on clinical features and ECG is inadequate¹⁴. Detection of regional differences in myocardial function by means of echocardiography can help distinguishing between NSTEMI with and without coronary occlusion^{14,19}. Routine echocardiography in the emergency department is recommended in the NSTEMI-ACS ESC guidelines⁸, but has never been evaluated in the ambulance service. Telemedical digital transmission of cardiac ultrasound images from ambulances

to hospital specialists could make this feasible and may improve the diagnostic precision.

Cardiac troponin is central in defining AMI²⁰. European guidelines recommend cardiac biomarkers to be measured at presentation in all patients with suspected AMI^{8, 10}. Cardiac troponin has today the greatest sensitivity and accuracy of all biomarkers in AMI. Point-of-care test of cardiac troponin applied in the prehospital setting may also be a valuable tool for optimizing diagnosis and treatment in patients with suspected NSTEMI^{21, 22}.

2. Objectives and specific aims

The main objective of this study is in a randomized controlled trial to test the effects of prehospital risk stratification by echocardiography and Troponin T testing in patients with suspected acute coronary syndrome compared with conventional in-hospital evaluation, with time delay to coronary revascularization and AMI-size as primary outcomes (Part II – to be completed upon achievement of results from the feasibility study).

But, before being able to conduct that, a feasibility study (Part I – described in this project plan) of prehospital echocardiography examination with wireless transmission to a specialized heart Centre and point-of-care troponin testing conducted by paramedics has to be completed. The quality of echocardiographic images exploring whether semi-automatic myocardial deformation analyses (strain) conducted by paramedics in a prehospital setting can attain necessary precision, will be assessed, as well as the feasibility of prehospital troponin testing performed by paramedics.

3. Methods and study organization

3.1 Materials and Methods

3.1.1 Study design

A feasibility study of prehospital echocardiographic examination and point-of-care troponin analysis, conducted by paramedics, in patients with suspected acute coronary syndrome.

3.1.2 Study population

Inclusion criteria:

- Patients presenting to the medical dispatch center (AMK) with chest pain;

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Norwegian medical index criteria A10.2- A10.11

- Men and women
- Age \geq 18
- Informed consent for participation
- Examined by paramedics in a prehospital setting due to newly onset (<12 hours) chest pain (lasting for >20 min) and suspected AMI

Exclusion criteria:

- Any condition which interfere with the ability to cooperate
- Hemodynamic instability
- Severe mental disorder
- Pregnancy or breast-feeding
- STEMI
- Obvious non-cardiac origin of the chest pain

3.1.2 Study plan

The trial will be conducted at Sørlandet Hospital, Arendal, Norway. One acute care ambulance in Agder county will be equipped with a high-end cardiac ultrasound scanner (Vivid IQ, GE Ultrasound) with wireless communication to the cardiac centre/cardiologist, and a point-of-care troponin T quantitative analysis kit (Cobas H232, Roche Diagnostics). Four paramedics will be offered a comprehensive hands-on (5 hours) course in cardiac ultrasound image acquisition by an echo-technician and a cardiologist. Similar, a short (2 hours) course will be given in point-of-care troponin analysis.

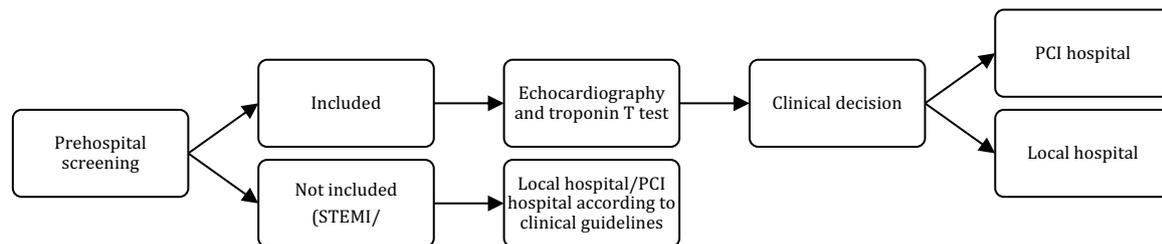
Up to 50 patients meeting the inclusion/exclusion criteria will be included consecutively. Cardiac ultrasound images over three heart cycles from five standard projections will be sampled and transferred to the hospital, and a troponin- T analysis will be done before/during transport to hospital. A cardiologist will be consulted immediately for cardiac ultrasound image interpretation, for interpretation of the troponin T value, ECG and symptoms, and for a clinical decision of further treatment.

Feasibility of the concept will be evaluated according to the following functionality criteria:

- Time intervals from patient inclusion to images achieved
- Imaging quality according to the manufacturer
- Communication between paramedic and cardiologist established
- Image transfer and interpretation by cardiologist functional
- Technical problems addressed and solved in collaboration with manufacturer

When the concept is proven fully functional on five NSTEMI patients, the evaluation board will reconsider further inclusion needs. If possible, the feasibility study is then ended and summed up.

Figure 1. Study plan



3.1.3 Outcome measures

- Feasibility of prehospital cardiac ultrasound examination and point-of-care troponin T analysis by paramedics in patients with suspected acute coronary syndrome
- Quality of prehospital echocardiography images in patients with suspected acute coronary syndrome
- Time spent on prehospital echocardiography examination and point-of-care troponin T analysis in patients with suspected acute coronary syndrome

3.1.4 Data handling and storage

The following records are collected in a secure electronic database (e-CRF) at Sørlandet Hospital, which is responsible for the data protection.

- Name, national identification number, gender and address
- Comorbidity including previous cardiovascular disorders, cardiac risk factors and medication
- Date and time of symptoms and first medical contact, and the various time delays to examination, hospitalization, treatment and discharge from hospital
- ECG findings, laboratory values and results of echocardiographic examinations
- Results of coronary angiogram
- Treatments received (PCI and medication)

- Complications, new cardiovascular events and death until discharge from hospital

The prehospital echocardiographic examination will be transferred and stored at a local image server. No personal records are stored at this server, but a unique study number is provided as a link to patient social security number.

3.1.5 Statistical analysis

Continuous variables would be presented as median (min and max value /interquartile range (IQR)), and categorical variables are presented as counts and percentages of total count. To assess the demographic differences between the groups with and without NSTEMI the Fisher exact test would be used for categorical variables, the two-sided t-test for normal distributed continuous variables, and the two sided Mann-Whitney U-test for non-normal distributed continuous variables. Shapiro-Wilk normality to be used together with qq-plot to determine normality. Further, the Levene's test to test for heteroscedastic (difference in variance) in the two groups compared. The result of this test determines if the equal variance t-test or Welsh-test will be used. A p-value < 0.05 could be considered statistically significant. Statistical analyses will be performed using R.

3.2 Organization

The trial is conducted at Sørlandet Hospital Thrust foundation in collaboration with the Norwegian Air Ambulance Foundation, Norwegian University of Science and Technology (NTNU), St. Olavs Hospital, University of Oslo and Oslo University Hospital.

The research group has considerable expertise in prehospital medicine and cardiology, and extensive research experience with risk stratification in patients with acute coronary syndromes, particularly ultrasound imaging in this population.

3.2.1 Research group

Name	Title	Institution	Study role
Jarle Jortveit	MD, PhD, HoD	Sørlandet Hospital, Arendal	Project leader & co-supervisor
Kristi Grønvold Bache	PhD, HoD	Norwegian Air Ambulance Foundation	Main supervisor
Roy Olsen	MD, PhD	Sørlandet Hospital, Arendal	Co-supervisor
Lars Jacobsen	MD, HoD	Sørlandet Hospital, Arendal	PhD candidate
Jo Røislien	Professor	Norwegian Air Ambulance Foundation & University of Stavanger	Statistician
Bjørnar Grenne	MD, PhD	NTNU & St. Olavs Hospital, Trondheim	Study participant and main supervisor candidate II (if study part II is realized)

Benthe Sjøli	MD, PhD	Sørlandet Hospital, Arendal	Study participant and future co-supervisor candidate II (if study part II is realized)
Trond Helge Lislevand	MD	Sørlandet Hospital, Arendal	Study participant and PhD candidate II (if study part II is realized)
Thor Edvardsen	Professor dr. med	Oslo University Hospital & University of Oslo, Oslo	Study participant
Tom Helge Vik Tollefsrud	Paramedic	Sørlandet Hospital HF	Study participant
Harald Brunvand	MD, PhD	Sørlandet Hospital, Arendal	Study participant
Slobodan Calic	MD	Sørlandet Hospital, Arendal	Study participant
Sunniva Bakke Archer	MD	Sørlandet Hospital, Arendal	Study participant
Thusego Motswakadikgwa	MD	Sørlandet Hospital, Arendal	Study participant
Mi Nguyen	MD	Sørlandet Hospital, Kristiansand	Study participant
Daniela Melichova	MD	Sørlandet Hospital, Arendal	Study participant
Sigve Karlsen	MD	Sørlandet Hospital, Arendal	Study participant
Thomas Dahlslett	MD	Sørlandet Hospital, Arendal	Study participant

3.3 Finance

The technical ultrasound infrastructure is supported cost-free by GE Ultrasound. The study has received an innovation grant from Helse Sør-Øst (NOK 498 000,-). PhD candidate I receives a PhD grant by Norwegian Air Ambulance Foundation, Oslo, Norway.

If study part II (the randomized controlled trial) is realized, the PhD candidate II will be funded by Centre for Innovative Ultrasound Solutions (CIUS), Norwegian University of Science and Technology, Trondheim, Norway

3.4 Progression plan

Year	Activities	Publications
2017	Establishment of study infrastructure Training of paramedics Patient inclusion	
2018	Final patient inclusion Data analysis and writing of papers	International presentation Paper 1
2019	Data analysis and writing of papers	International presentation Paper 2
2020	Writing of paper	Paper 3

	PhD dissertation	
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Planned publications:

The results of this project will be published in level 1 and 2 international peer-reviewed journals, with corresponding presentations at scientific meetings.

The following papers are planned:

1. Feasibility of echocardiographic image transfer from road ambulances in patients with acute coronary syndrome.
2. Echocardiography by paramedics in patients with acute coronary syndrome
3. Prehospital point-of-care troponin analysis in patients with acute coronary syndrome

4. User involvement

A Patient Advisory Committee consisting of three patients will be established. The committee will contribute to regular evaluation of the practical performance of the project and modifications of it within the protocol frames.

5. Ethics and legal aspects

Participation in the study will depend on informed consent by the patient. This study is an acute diagnostic- and stratification study of patients in a potentially life-threatening emergency situation, and we therefore apply for retrospective collection of written consent in hospital. The patient (or next of kin) included in the study will be informed about the study, and an oral consent in the prehospital acute phase will be obtained when possible. In the cardiac unit, before discharge, a dedicated cardiologist especially assigned, will be in charge of collecting written consent from all included patients (or next of kin). The principal investigator and the PhD-candidate will follow up obtaining consent (see attached consent text). Participation is voluntarily and the patient's decision will not influence further treatment except for the explicit tests performed as part of the study. Patients who decline participation will receive standard care.

Prehospital ECG is performed routinely in patients with chest pain and will be acquired and analysed before echocardiography and troponin to identify patients with STEMI, who need immediate revascularization and are excluded from this study. A request for approval by the Regional committee for research ethics will be sent. Data Protection official (NSD) approval will be applied too.

8. References

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