After Eighty Study

Non ST-Elevation Myocardial Infarction (NSTEMI) and Unstable Angina Pectoris (UAP) in patients over 80 years.

A randomised prospective study of an invasive strategy versus medical therapy.

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1. Introduction

During the last two decades, both early and late mortality of acute coronary syndrome (ACS) has declined due to prompt reperfusion therapy and use of aspirin, thienopyridines, beta-blockers, statins, angiotensin-converting enzyme inhibitors, and risk factor reduction in the post discharge management. However, introduction of new diagnostic criteria for ACS in year 2000 has created a need for new studies of the three categories of ACS: ST-Elevation Myocardial Infarction (STEMI), Non-ST Elevation Myocardial Infarction (NSTEMI) and Unstable Angina Pectoris (UAP) (1-3).

According to the guidelines, patients with NSTEMI/UAP should be stabilised medically and evaluated for invasive therapy within 72 hours (2,3). These guidelines are based on clinical studies in patients with mean age 62-66 years (4-8). However, NSTEMI/UAP is a frequent and important cause of hospital admission in the elderly, i.e. >75-80 years, but real-world studies of this population are lacking. It has been shown that older patients are at higher risk of adverse events than younger patients, but they are also less likely to receive treatment according to guidelines (9,10). Thus, further clinical research is needed to study possible benefits of a more aggressive approach in the elderly.

2. Background

The rationale of the present clinical trial is to study whether an invasive strategy in clinical stable patients over 80 years with NSTEMI/UAP may improve rates of death, reinfarction, stroke, need of urgent revascularisation, myocardial function and quality of life. The invasive approach involves coronary angiography with immediate evaluation for three different treatment options; 1. Percutaneous coronary intervention (PCI), 2. Coronary artery bypass graft (CABG) or 3. medical treatment. Clinical practice shows that older patients are commonly treated less vigorously than younger patients and the present guidelines are based on a considerably younger population. On this background, there is now sound reason for a randomised clinical study of real world patients, i.e. patients over 80 years with NSTEMI/UAP. Patient symptoms, myocardial function and quality of life will be evaluated by thorough clinical and laboratory assessments during follow up.

3. Study objectives

3.1 Primary objective

Does an invasive strategy in clinical stable patients over 80 years with NSTEMI/UAP improve rates of death, reinfarction, stroke and need of urgent revascularisation?

3.2.1 Secondary objective

Measures of quality of life (as assessed by Quality of Life questionnaire SF 36), cognitive impairment and dementia (as assessed by Informant Questionnaire on Cognitive Decline in the Elderly, IQCODE) and activities of daily living (Nottingham extended ADL score) will be performed after randomisation and during follow up. Charlsons morbidity index will also be performed.

3.2.2 Tertiary objective

Death of any cause.

3.3 Bleeding

3.3.1 Major bleeding defined as fetal bleed, and/or symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, intraarticular, pericardial, retroperitoneal, intramuscular with compartment syndrome), or/and a decrease in haemoglobin of more than 5g/dL.

3.3.2 Minor bleeding defined as a decrease in haemoglobin of more than 3g/dL(but les than 5g/dL) or spontaneous hematuria or haematemesis, or haematoma or pseudoaneurysm requiring treatment other than surgery (11).

3.4 Additional objectives

3.4.1. Does co-morbidity (previous ACS, chronic obstructive pulmonary disorder (COPD), diabetes, hypertension, renal failure, stroke) affect the results?
3.4.2 Does any biochemical markers predict the clinical endpoints?
3.4.3 Cost calculations will be performed.

4. Investigational plan

4.1 Type of study:

Randomised open label two arm-study, where one arm is randomised to coronary angiography and the other is controls.

4.2 Study design:

A randomised open labelled prospective study of an invasive strategy versus medical therapy with clinical and laboratory 12 months follow- up with main assessments of effects at 12 months.

4.2.1 Overall study schedule:

Patients over 80 years with stable NSTEMI/UAP who are eligible and who gives informed consent, are randomised to either of two equally sized groups:

A. ***Coronary angiography + PCI/ CABG/medical treatment.***
B. ***Control group, medical treatment.***
Group A is referred to Rikshospitalet University Hospital (invasive centre) 72 hours after admission.

4.2.2 Overview over protocol first phase:

	NSTEMI/UAP	Eligible/Consent/ Random	CA*	Follow up
Day:	*0*	*0*	*1-3*	

*Coronary angiography

4.2.3 Procedure of randomisation:
A patient is included in the study if eligible and after giving written informed consent. The patient will be randomised to one of two groups. Randomization will be performed by permuted block stratified by center. Two groups of sealed and opaque envelopes with consecutive inclusion numbers will be generated by the Centre for Clinical Research at Ullevål University Hospital.

4.2.4 Selection of patients:
Clinical stable patients over 80 years with NSTEMI/UAP, fulfilling the inclusion and exclusion criteria, admitted to community hospitals in Helse Sør-Øst will be invited to participate in the study on a consecutive basis. The treatment group will be transported to one centre with PCI facilities (Rikshospitalet University Hospital). A register of all patients admitted with ACS will be maintained regardless of their inclusion or exclusion from the study.

4.2.5 Number of patients (sample size):

The major end-point (EP) is a composite EP of mortality, reinfarction, stroke and need of urgent revascularisation between baseline (BL) and 12 months follow up. The outcome variable is:

$$\text{delta EP} = EP_{12\ \text{months}} - EP_{BL}$$

Considering one previous study, patients over 75 years with NSTEMI had an incidence of composite endpoints (death and myocardial infarction) of 21% at 6 months, whereas patients over age 75 years having PCI had a lower incidence of composite endpoints (10·8%).[8] This difference represents a diminution of 10% in absolute risk and 50% in relative risk. Considering a type I error of 5% and a power of 80%, we calculated a need for 2*206=412 patients (8,12). To allow for some dropouts, because of the advanced age of the patients, we decided to enroll at least 450 patients.

4.2.6 Inclusion criteria:

All criteria must be fulfilled:
*Age _ 80 years.
*Acute coronary syndrome (NSTEMI/UAP) with chest pain > 10 minutes, with or without ST-segment depression in ECG, and normal or elevated levels of troponin T or I. Elevated troponin levels are defined as values exceeding the 99 percentile of a normal population at the local laboratory at each participating site.
*Clinical stable

4.2.7 Exclusion criteria:

None criteria must be fulfilled:
*Age < 80 years.
*ST-segment elevation in ECG (STEMI)
*Clinical unstable with ongoing chest pain or other ischaemic symptoms/signs.
*Cardiogenic shock.
*Short life expectancy due to extra cardiac reason, ie. COPD, disseminated malignant disease, or other reason.
*Anamnestic indications for significant mental disorder, including dementia.
*Any condition which interferes with patients possibility to comply with protocol.

4.3 Assessments

All patients are investigated for quality of life, cognitive functioning, ADL, myocardial function and functional capacity. A brief description of the investigative methods is given below:
Quality of Life and cognitive function:
Assessment by questionnaire (SF 36).
Informant Questionnaire on Cognitive Decline in the Elderly, IQCODE
Nottingham extended ADL score
Functional capacity:
Clinical functional class assessment (NYHA/Canadian).
Blood samples:
Assessment of myocardial injury, inflammation, general clinical biochemistry.
Myocardial function:
Echocardiography:
Left ventricular function.
Heart valves
Baseline and follow up investigations are planned according to the following scheme:

Investigation: **Baseline 12 months**

Clinical status/examination
Coronary angiogr.
Echocardiography
Blood sample
SF-36
Nottingham ADL Scale
Charlsons morbidity index
IQ CODE
Baseline recordings are performed during day 1-3 after AMI.

4.4 Evaluations and patient safety

All investigations are continuously evaluated and adverse events and/or unexpected patient response in terms of cardiovascular status, biochemical status, general well being, need for rehospitalisation etc, are recorded at every follow up visit. The accumulating results are consecutively made available for the Safety and data monitoring committee. This committee has the right to advice the steering

committee to first halt inclusion and subsequently terminate the study if a significant allocation of negative patient responses in the treatment group is found. All serious adverse events and/or unexpected events will be reported to this committee.
Every patient is covered by Rikshospitalets University Hospitals membership in the patient insurance agreement (Pasientforsikringen).

4.5 Design and statistics methods

This is an explanatory trial (Zwarenstein et al) in design and analytical method. We will consider the analysis using the intention to treat strategy we analyze what we randomize it will be completed by on treatment analysis.

The major outcome is the composite endpoint. We will use censored data with a closing date. Rate ratio will be used to estimate the crude efficacy of the two strategies using a person time model. Curves showing event-free survival will use the Kaplan–Meier method. Log-rank test for equality of event free survival will be performed. Stratification analysis using the Cochran-Mantel-Haenszel method will be performed to quantify confounders and the heterogeneity test to pinpoint potential effect modifiers in important covariates chosen because of early experience in research and biological plausibility. Adjusted efficacy as hazard ratio (HR) will be estimated with the Cox regression model controlling for the confounding level of potential confounders and effect modifiers. The proportional hazard (PH) assumption will be highlighted by the Schoenfeld residuals test. A test of interaction using the log likelihood ratio test will be done when using the Cox model. A competing risk analysis for the components of our major end point will performed using the cause specific hazard function. Death from other causes is the main competing risk outcome to reinfarction, revascularisation and incidence of stroke. All p values are two-tailed (12-17).

4.6 Data management

All patient data and analysis results are managed in a database/analysis programme (EPIDATA). Patient anonymity is maintained by use of a patient number in data analysis and presentation. The formal rights behind database construction and patient data acquisition will be established by a separate application to the Norwegian Data Inspectorate (Datatilsynet).
The results of the study will be published in international referee based medical journals with high standard and impact. The publications are expected to be represented in at least one doctoral thesis works. Publication are due briefly after the last patient have completed 12 months follow-up, ie 1.5 – 2 years after first inclusion, and will prevail for the following 1 – 2 years.
We will follow the recommendations of the CONSORT statements (http://www.consort-statement.org).

4.7 Ethical considerations

The study is approved by the Regional Committee for Ethics in Medicine.

4.8 Steering committe

A steering committee is responsible for this protocol, administrates the study implementation and progression and responds to advice from the Safety and data monitoring committee.

5. Reference list

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