

TRIAL PROTOCOL

LOW-DOSE DOBUTAMINE INFUSION AND SINGLE-DOSE TOCILIZUMAB IN ACUTE MYOCARDIAL INFARCTION PATIENTS WITH HIGH RISK OF CARIOGENIC SHOCK DEVELOPMENT

– A 2X2 MULTIFACTORIAL, DOUBLE-BLINDED, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Acronym: DOBERMANN

Version: 2.7.4

Date: 9th of July 2021

Revision 09/02/2022

Sponsors protocol code no.: RH-CARD-Pharma001

EudraCT: 2021-002028-19

Health Research Ethics: H-21045751

Department of Cardiology

Rigshospitalet, University Hospital of Copenhagen

Blegdamsvej 9, 2100 Copenhagen OE, Denmark

Principal Investigator:

Helle Søholm, MD, PhD
Dept. of Cardiology, Rigshospitalet
helle.soholm@gmail.com,
tel.: +45 28770229
Registration ID: 08H8S

Co-Primary Investigator:

Martin Frydland, MD, PhD
Dept. of Cardiology, Rigshospitalet
martin.steen.frydland.01@regionh.dk,
tel.: +45 29923273
Registration ID: 0987M

Sponsor:

Christian Hassager, professor, MD, DMSc
Dept. of Cardiology, Rigshospitalet
christian.hassager@regionh.dk
tel.: +45 35450572
Registration ID: 00CFQ

GCP Monitor Representative:

Ginette Wedel
Dept. of Cardiology, Rigshospitalet
ginette.wedel@regionh.dk,
tel.: +45 35452664

TABLE OF CONTENTS

TABLE OF CONTENTS	2
STATEMENT	4
AIM	4
BACKGROUND	6
METHODS	8
SAMPLE SIZE CALCULATION	9
RECRUITING	10
INCLUSION CRITERIA	12
EXCLUSION CRITERIA	12
OUTCOMES	14
PRIMARY OUTCOME	14
SECONDARY OUTCOMES	14
LONG-TERM OUTCOMES	15
QUALITY OF LIFE, MENTAL HEALTH AND PATIENT-RELATED CLINICAL DEMOGRAPHICS	16
QUALITY OF LIFE AND MENTAL AND COGNITIVE HEALTH	16
The 5-level EuroQol-5 (EQ-5D-5L)	16
CLINICAL CHARACTERISTICS	17
SAFETY	20
TREATMENT PROCEDURES AND IMP BLINDING	21
INVESTIGATIONAL PRODUCT DOSAGE	23
TREATMENT DEESCALATION / TERMINATION	23
ADVERSE EVENT REPORTING	24
Adverse Events (AE)	24

Serious Adverse Events (SAE).....	24
Suspected Unexpected Serious Adverse Reactions (SUSARs)	25
Severity of Adverse Events	25
Relationship of AE to Trial Intervention.....	25
Reference Document	26
Procedures for Un-Blinding the Treatment Allocation	26
SAFETY MONITORING	27
INFORMED CONSENT	27
ETHICAL CONSIDERATIONS.....	29
DATA HANDLING AND RECORD KEEPING	30
DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION	30
QUALITY CONTROL AND ASSURANCE.....	30
FINANCE.....	32
TASKS AND RESPONSIBILITIES	33
REFERENCES	34

LOW-DOSE DOBUTAMINE INFUSION AND SINGLE-DOSE TOCILIZUMAB IN ACUTE MYOCARDIAL INFARCTION PATIENTS WITH HIGH RISK OF CARADIOGENIC SHOCK DEVELOPMENT

– A 2X2 MULTIFACTORIAL, DOUBLE-BLINDED, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

DANISH TITLE

LAV-DOSIS DOBUTAMIN INFUSION OG EN ENKELT DOSIS TOCILIZUMAB TIL PATIENTER MED AKUT MYOKARDIEINFARKT OG HØJ RISIKO FOR UDVIKLING AF KARDIOGENT SHOCK

– ET 2X2 MUTLIFAKTORIELT, DOBBELT-BLINDET, RANDOMISERET, PLACEBO-KONTROLLERET STUDIE.

STATEMENT

This protocol including amendments, as well as written information and consent forms will be submitted to the regional ethics committee for review and approval prior to initiation of the trial. The trial will be executed in accordance with this protocol and its amendments, compliant to regulatory demands and applicable law.

AIM

In the present study, we aim to investigate the effects of dobutamine infusion and/or a single intravenous (IV) dose of the IL-6 antagonist Tocilizumab administered after percutaneous coronary intervention (PCI) to patients with acute myocardial infarction (AMI) presenting < 24 hours from onset of chest pain and an intermediate to high risk of cardiogenic shock (CS) by assessment with the ORBI risk score (≥ 11 – *not* in overt shock at hospital admission), Table 1. Plasma concentrations of N-terminal pro-B-type natriuretic peptide (NTproBNP) as a proxy for development of cardiogenic shock (CS) and hemodynamic instability will be sampled for primary endpoint analysis. Effects on clinical parameters, mortality, morbidity as well

as specific indicators of inflammation, cardiac function, and infarct size will secondarily be assessed noninvasively.

The rationale behind the current study is that inflammatory and neurohormonal responses are associated with subclinical hemodynamic instability in patients with AMI with high risk of CS have worse outcomes. The potentially unstable condition may be targeted pharmacologically as an add-on to existing therapy. This is investigated in patients at elevated risk of CS by sampling biomarkers reflecting the inflammatory and neurohormonal responses, as well as determining effects on patient outcomes and infarct size.

TABLE 1. VARIABLES COMPRISING THE *ORBI RISK SCORE*

Variable	Points
Age>70 years old	2
Previous stroke/TIA	2
Presentation as cardiac arrest	3
Anterior myocardial infarction	1
First medical contact-to-PCI>90 min	2
Killip class II on admission	2
Killip class III on admission	6
Heart rate >90/min on admission	3
sBP <125 mmHg and PP <45 mmHg on admission	4
Glycemia >10 mmol/L on admission	3
Culprit lesion of the left main	5
Post-PCI TIMI flow <3	5

First medical contact is defined as time from first ECG confirming the AMI-diagnosis to first balloon (PCI).

Abbreviations: TIA (transient ischemic attack), PCI (percutaneous coronary intervention), sBP (systolic blood pressure), PP (pulse

pressure), TIMI (thrombolysis in myocardial infarction), ECG (electrocardiogram), AMI (acute myocardial infarction).

BACKGROUND

Despite an overall reduction in mortality in patients with ST-elevation myocardial infarction (STEMI), patients developing CS have a high short-term mortality of up to 50%.¹⁻³ A systemic inflammatory response is often seen in patients with CS thereby complicating the intensive care (ICU) treatment.¹

Approximately 1/3 of STEMI-patients developing CS are not in overt shock at time of hospital admission, but will develop hemodynamical instability within the following hours to days.^{2,3} Patients at risk for CS development may be clinically stable or relative hypotensive or tachycardic but with e.g. normal lactate (Society for Cardiovascular Angiography and Interventions (SCAI) classification A and B).⁴ Irrespective of when CS occurs, mortality has been shown to remain high.²

NTproBNP is a biomarker reflecting neurohormonal activation released from the myocardium in response to cardiomyocyte stretch⁵ and myocardial ischemia.⁶⁻⁸ It is inversely correlated with hemodynamic measurements (including cardiac output)⁹ and associated with mortality in patients with STEMI.¹⁰ Previous studies suggest that the plasma concentration of biomarkers reflecting neurohormonal activation is higher in patients developing CS after hospitalization compared to hemodynamically stable STEMI-patients.¹¹⁻¹³

Dobutamine is a sympathomimetic drug with an agonistic effect primarily on the beta1-receptor and some beta2- and minimal alpha-receptor activation. In patients with myocardial infarction dobutamine induces significant positive inotropic- and dose-dependent

chronotropic effects and decreases afterload by peripheral vasodilatation. The combination of the inotropic effect and the afterload reduction significantly increases cardiac output.¹⁴

In ischemic heart disease (IHD), a range of studies from the pre-primary PCI era to modern day treatment suggest that modulation of the inflammatory response may prove beneficial – both in the acute and chronic phase.¹⁵⁻²⁰ Interestingly, the humanized anti-interleukin (IL) 6 anti-body Tocilizumab targeting the IL-6 receptor (IL6RA) has recently been shown to reduce troponin leakage and increase salvage index suggesting reducing final infarct size when administered to patients with acute myocardial infarction (MI).^{21 22} Furthermore, a recently published trial showed reduced troponin / creatin-kinase-MB (CKMB) levels in patients with out-of-hospital cardiac arrest (OHCA) of cardiac etiology indicating a reduction in infarct size and a temporal reduction in NTproBNP in the Tocilizumab group compared to the placebo group.²³

A recent study has established and validated a new score for prediction of the development of in-hospital CS - the Observatoire Régional Breton sur l'Infarctus (ORBI) risk score (Table 1) in two French STEMI-cohorts.²⁴ The risk score showed a high predictive value for development of in-hospital CS with an area under the receiver operating characteristics (AUC_{ROC}) curve of 0.84 (95% confidence interval (CI) = 0.81-0.87) vs. 0.83 (0.80-0.87) in the derivation vs. the validation cohort, respectively.²⁴ The ORBI Risk Score was validated in a Danish cohort of 2,247 patients with suspected STEMI in two tertiary heart centers and found a comparable predictive value with an AUC_{ROC} of 0.84 (0.78 – 0.89).^{2 11 25}

METHODS

The planned study is an investigator-initiated, randomized, double blinded clinical trial.

Consecutive patients at Copenhagen University Hospital, Rigshospitalet admitted with AMI < 24 hours from chest pain will be screened.

Patients eligible for trial inclusion will be randomized 2:2 to receive a continuous IV dobutamine infusion of 5 mcg/kg/minute versus placebo for 24 hours and to receive a single IV dose of tocilizumab (1-hour infusion) versus placebo administered after PCI.^{21 22}

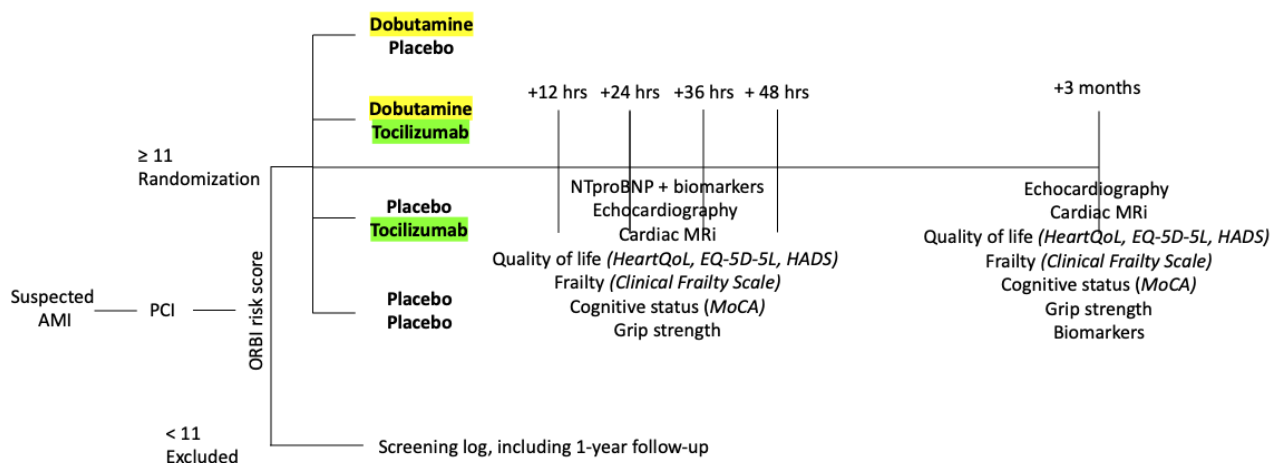
Treatment with the investigational drug will be initiated as soon as possible but no later than 2 hours after transfer to the coronary care unit (CCU) and after informed consent. All included patients will follow usual treatment according to current guidelines.²⁶

The biomarker NTproBNP will be measured in blood samples drawn upon hospital admission in patients with ORBI risk score ≥ 11 , and after 3, 12, 24, 36 and 48 hours from admission (Figure 1). After treatment termination, 2D-echocardiography will be performed acutely and within 2 days to evaluate left ventricular ejection fraction (LVEF), and cardiac magnetic resonance imaging (cMRI) with late gadolinium enhancement technique prior to hospital discharge as close to 48 hours post-MI and after 3 months after discharge will be performed to calculate area at risk and salvage index after AMI.

Blood samples (40 mL) will be obtained and stored in a biobank for subsequent measurement of biomarkers reflecting inflammation, neurohormonal activation, neuronal injury, connective tissue function and other relevant pathophysiological processes. These biomarkers will solely have research interest and no clinical implications. Furthermore, no genetic biomarkers and markers associated with malignancy development will be measured. Any leftover blood from the research biobank will be transferred to a biobank for future

research and stored for up to 10 years solely for research purposes. After this period blood samples will be destroyed.

FIGURE 1: Stratification and randomization



Abbreviations: AMI (Acute Myocardial Infarction), PCI (percutaneous coronary intervention), ORBI (Observatoire Régional Breton sur l’Infarctus), NTproBNP (N-terminal proB-type natriuretic peptide), HeartQoL (*European Quality of life survey*), EQ-5D-5L (*The 5-level EuroQol-5, Health-Related Quality of Life*), HADS (Hospital Anxiety and Depression Scale), MoCA (*Montreal Cognitive Assessment*).

A research fellow will validate and register data on all screened patients in a REDCap database including ORBI risk score, biomarkers, angiographic findings, and PCI (when performed), chest pain after the procedure and ST-segment elevation resolution, age, gender, demography, clinical characteristics, and events during index admission will be recorded.

Data will be coupled to the national patient registry, which holds information on all Danish citizens with regards to ICD-10 codes from all hospital admission and outcome measures, and the Danish National Database of Reimbursed Prescriptions.

SAMPLE SIZE CALCULATION

Based on recent data from our institution (yet unpublished), atrial natriuretic peptide (ANP) levels measured 12 hours after admission were assumed to be distributed in a log-normal fashion with a variation coefficient of 0.59. Assuming a minimal clinically relevant difference of 30% between treatment strata, the trial would achieve a power of 0.86 at a significance level of 0.05 if 88 patients were included. To correct for dropouts and missing data, we chose to include 100 patients in the trial. Assuming that ANP and BNP/NTproBNP have similar distributions, we expect a reduction in NTproBNP from 1338 ng/L to 937 ng/L in the intervention group based on previous data.²⁷

RECRUITING

When the AMI-patient is treated acutely in the catheterization laboratory (cath. lab.) the staff will evaluate the ORBI Risk Score in all patients for initial risk stratification. If the patient is eligible for inclusion in the study with an ORBI risk score ≥ 11 and not fulfilling any exclusion criteria the treating physician will ask the patient for permission to notify the research fellow on call with the purpose of obtaining informed consent for randomization in the study. At the CCU written study material is handed to the patient. The patient will be offered to involve an impartial witness when receiving information regarding the study, as in the case when he/she is unable to read. Verbal information will be given by a sub investigator (medical doctors only) whom has been delegated this role and who is GCP certified. The patient will, to the best of the department's ability, be placed in a quiet, uninterrupted area in order to preserve privacy and a freely given consent. The patient will be given a minimum of 30 minutes to consider the material, with the opportunity to ask questions before and during this time. The time frame for consent has been determined based on the pathophysiology

for which intervention is sought in this trial, as a longer delay to treatment implies a risk of patients entering the condition of cardiogenic shock before the treatment is initiated.

All registrations concerning screening and informed consent will be stored in a RedCap database.

RANDOMIZATION

Randomization will be performed utilizing a module integrated with the eCRF in accordance with the institution Standard Operating Procedure (SOP-RED.007.01- Randomization i REDCap). It follows that the sponsor nominates an entity to perform the technical task of setting up and generating an allocation table in accordance with the protocol, as described in the referenced SOP section concerning blinded allocation. The investigator or assigned co-investigator will enter the eCRF module patient identification data and parameters determining in- and exclusion and stratification by STEMI/NSTEMI. The computerized module will assign the treatment arms corresponding to a label “A” or “B” and “C” or “D”.

PARTICIPANTS

INCLUSION CRITERIA

- Acute myocardial infarction ²⁸
- Revascularization with PCI
- Presentation within 24 hours of chest pain
- ORBI risk score ≥ 11 ²⁴
- Age ≥ 18

EXCLUSION CRITERIA

- Unwilling to give informed consent to study participation
- Unable to give consent due to language barrier
- Comatose after cardiac arrest
- Cardiogenic shock with systolic blood pressure < 100 mmHg for more than 30 minutes or need for vasopressor to maintain blood pressure and arterial lactate $> 2,5$ (2,0) mmol/L developed before leaving the cath. lab.
- Other major clinical non-coronary condition (stroke, sepsis etc.), which can explain a high ORBI risk score
- Referral for acute coronary artery bypass grafting (CABG) (< 24 hours) after the CAG, whereas subacute (>24 hours) will be included)
- Contraindications against dobutamine infusion (sustained ventricular tachycardia prior to admission or noted in the cath.lab., known pheochromocytoma, idiopathic hypertrophic subaortic stenosis)
- Tocilizumab allergy
- Pregnant- or breastfeeding women

- Known liver disease/dysfunction
- Ongoing uncontrollable infection
- Immune deficiency/treatment with immunosuppressants
- Known, uncontrolled gastrointestinal (GI) disease predisposing to GI perforation

In patients with coronary biomarkers without dynamic elevation ('rise-and-fall') reflecting other condition than AMI, treatment with the assigned study drug(s) will be completed and the patient will be included in sensitivity analyses but will not have cMRi performed. Inclusion in other studies/trials will *not* automatically lead to exclusion.

OUTCOMES

PRIMARY OUTCOME

NT-proBNP plasma concentration being assessed at multiple time points (including the primary endpoint) will be analyzed by application of a linear mixed model of covariance. As the biomarker will be measured prior to initiation of the study drug, the models will be baseline corrected (i.e., constrained linear mixed models, CLMM). The main result of these analyses will be the treatment-by-time interaction as a marker of whether the NTproBNP levels change differently over time in the treatment versus the placebo arm.

We will conduct analyses for the two interventions (dobutamine and Tocilizumab) separately. For the analysis, we will include the dobutamine-Tocilizumab interaction in order to analyze co-linearity in possible treatment effects. Logarithmic transformation will be applied to approximate normal distribution as appropriate. Analyses will be adjusted for pre-admission use of betablockers. Stratification in non-STEMI (NSTEMI) vs. STEMI will be included in the randomization algorithm to ensure an equal distribution of the two patient categories. Patients dying prior to intervention but after obtaining biomarkers a modified intention to treat analyses will be applied with sensitivity analyses of the third quartile of the biomarker in the living patients.

SECONDARY OUTCOMES

- Development of in-hospital CS and/or in-hospital cardiac arrest
- Infarct size and salvage index measured by cMRi
- Long-term all-cause mortality

- Biomarkers reflecting neurohormonal activation, endothelial function/damage, inflammation (pro- and anti-inflammatory processes – including IL-6 and C-reactive peptide (CRP)), connective tissue damage, organ dysfunction, and other relevant processes
- PCI operator's post-procedure clinical assessment of the patient (survives to discharge 'yes/no')
- Development of non-cardiac arrest arrhythmia (sustained ventricular tachycardia, atrial fibrillation with a frequency above 120 for more than 30 minutes) during index admission (safety)
- 2D echocardiographic measurements of hemodynamics (VTI) and left ventricular function including strain measurements according to protocol
- Re-admission (all cause and cardiovascular) during the first year after index hospitalization
- Re-admission with heart failure and re-infarction
- SOFA score^{29 30} (PaO₂, FiO₂, on medical ventilation, Platelets, GCS, Bilirubin, mean arterial pressure OR administration of vasoactive agents required, Creatinine, Is this a COVID-19 patient?)
- Quality of Life and mental and cognitive health at baseline and after three months

LONG-TERM OUTCOMES

If a significant reduction in the primary endpoints is observed, we will continue inclusion to assess mortality in more centers aiming at a national level.

QUALITY OF LIFE, MENTAL HEALTH AND PATIENT-RELATED CLINICAL DEMOGRAPHICS

QUALITY OF LIFE AND MENTAL AND COGNITIVE HEALTH

European Quality of life survey (HeartQoL)

To measure disease-specific health-related quality of life the HeartQoL is chosen. The development of the instrument was supported by the European Society of Cardiology and the European Association of Preventive Cardiology.³¹ The 14 items patient reported outcome has been cross-culturally translated into Danish and showed acceptable psychometric properties in cardiac patients following heart valve surgery, ischemic heart disease and recipients of implantable cardioverter defibrillator.³²⁻³⁴ Moreover, the outcome measure have shown a significant linear association between all-cause mortality and both lower global HRQoL (HR = 1.67, 95% CI: 1.26-2.23) and physical HRQoL scores (HR=1.71, 1.33-2.21) and between readmission and both lower HRQoL global (HR=1.73, 1.41-2.12) and physical HRQoL scores (HR = 1.63, 1.35-1.96) in patients with ischemic heart disease.³³

The 5-level EuroQol-5 (EQ-5D-5L)

The EQ-5D-5L is a generic Health-Related Quality of Life (HRQoL) measurement tool developed as a generic instrument for HRQoL.³⁵ EQ-5D-5L consists of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which has five levels (no problems, slight problems, moderate problems, severe problems or unable to), and a visual analogue scale (EQ VAS). The EQ VAS records the patient's self-rated health on a visual analogue scale (0-100), where the endpoints are labelled 'The best health

you can imagine' and 'The worst health you can imagine'. The EQ-5D-5L is translated to Danish but no psychometric evaluation of the Danish version has been published. However, several studies have evaluated the English version and found acceptable psychometric properties for convergent validity and test-retest reliability. An overall Cronbach's α of 0.73 has been found in a population of coronary heart disease patients.³⁶

Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS), a 14-item questionnaire is designed to detect the presence of mild degrees of mood disorders in non-psychiatric hospital outpatients.³⁷ The HADS consists of 2 sub-scales: depression and anxiety. Higher scores represent more emotional problems. The scale has a concurrent validity of 0.73 compared with the Beck Depression Inventory and alpha is 0.83 (anxiety subscale) and 0.82 (depression subscale). The HADS is a valid and internally consistent measure, with a mean Cronbach's α of 0.83 and 0.82 for the HADS-A and HADS-D, respectively. Scores of 0–7 for either subscale are regarded as normal and scores of 8–10 suggest the presence of a mood disorder.³⁸ Scores of 11 and above indicate the probable presence of a mood disorder.³⁹

Questionnaires will be administered at baseline and after three months. The questionnaires in the trial will be completed electronically in the questionnaire system Redcap with 'single user', which meets the data legislation for logging. If patients do not complete the questionnaire electronically, the material can be administered in paper form and independent trial personnel then enters the responses into the database.

CLINICAL CHARACTERISTICS

Cognitive status

Montreal Cognitive Assessment (MoCA)

To evaluate the patient's cognitive status the Montreal Cognitive Assessment tool (MoCA) will be used.⁴⁰ The MoCA is a one-page 30-point brief stand-alone cognitive six-dimensional screening test administered in approximately 10 minutes. The MoCA evaluates six cognitive domains for detecting even mild cognitive impairment: Attention, visuospatial, construction, executive functioning, memory, language and orientation. MoCA is validated in a Danish cohort age above 65. The maximum score is 30 points. A summary score of $\geq 26-30$ is considered normal.

Frailty

Frailty is measured by the Clinical Frailty Scale developed by Rockwood and colleagues.⁴¹ It is a cumulative deficit model consisting of a 9-point scale where patients' frailty is measured based on clinical judgement – clinical signs, symptoms, diseases and disabilities. A frailty index (FI) score is calculated as a proportion of the number of deficits present. Each 1-category increment of the scale significantly increased the risk of death. It is recommended for use in AMI populations.⁴²

The Clinical Frailty Scale is supplemented by the Study of Osteoporotic Fractures of Frailty (SOF index).⁴³ It comprises three items and assesses weight loss, inability to rise from a chair five times without using the arms and self-reported poor energy. Frailty defined by the SOF index is identified by the presence of 2 or more of the following 3 components: (1) weight loss (irrespective of intent to lose weight) of 5% or more between (2) the subject's

inability to rise from a chair 5 times without using her arms; and (3) reduced energy level, as identified by an answer of “no” to the question “Do you feel full of energy?”. Patients with none of these components are considered to be robust, and those having 1 component are considered to be in an intermediate of pre-frail stage.

Grip strength

Is measured by the SAEHAN Digital Hand Dynamometer. The SAEHAN Digital Hand Dynamometer is a Highly accurate grip strength measurement. It measures from 0-200 pounds (lbs.) or from 0-90 kilograms (kg).

SAFETY

Patients included in the present study are as indicated by the ORBI risk score high-risk AMI patients, but not in overt shock when included. Therapeutic agents aiming to reduce the risk of cardiogenic shock and thereby a high risk of death are needed, but at the same time without compromising the safety of the patient. The present study investigates the effect of anti-inflammatory treatment prior to PCI with a single IV dose of 280 mg Tocilizumab vs placebo and the vasoactive and inotropic agent dobutamine vs. placebo for hemodynamic support following PCI.

Tocilizumab is a humanized monoclonal antibody targeting the IL-6 receptor. It is approved for treatment of rheumatoid arthritis but has shown promising results when administered to patients with AMI.^{21 22} In addition, a previous small trial on Tocilizumab vs. placebo administered to AMI-patients revealed no safety concerns.⁴⁴ Furthermore, in rheumatoid arthritis patients, Tocilizumab was evaluated in a systematic review of 19 studies (11 RCTs) and appeared safe compared to other treatments with regards to risk of AMI, stroke and major adverse cardiac events (MACE)⁴⁵, and Tocilizumab was not seen causing QTc-prolongation.⁴⁶ A recent randomized pilot trial from our group in 80 comatose patients resuscitated from OHCA with Tocilizumab vs. placebo for modulation of the systemic inflammatory response (SIRS) showed no increased occurrence of adverse- or serious adverse events.²³ ⁴⁷ Especially no increased frequency of infections using the same dosage of Tocilizumab as planned for the present study were found.²³ Tocilizumab has also been tested as a potential treatment for the ongoing Covid19-pandemic, and a review of its efficacy and safety likewise found no increased risk of infections and adverse events.⁴⁸

With regards to hemodynamic support in high-risk AMI patients dobutamine was chosen for its inotropic properties with increased cardiac contractility and reduction of systemic

vascular resistance and thereby unloading of the left ventricle.⁴⁹ Concerns regarding the use of classic inotropic agents stimulating the beta-receptor–cAMP pathway for patients not experiencing acute heart failure with hypoperfusion have been raised, due to a possible increased risk of arrhythmia, progression of myocardial ischemia and potentially increased mortality.⁵⁰ Dobutamine is contraindicated in patients with hypertrophic obstructive cardiomyopathy and may be less effective in patients receiving betablockers, which we will investigate as a supplementary interaction analysis. The adverse effects of dobutamine are dose-related, facilitating atrioventricular conduction, with possible rapid ventricular response in patients developing atrial fibrillation.

Clinical parameters including blood pressure will be measured every hour during the first three hours and if stable every three hours during the first 24 hours of admission or according to Early Warning Score (EWS) algorithm. Patients will be monitored by telemetry during admission and during dobutamine infusion additional continuous cardiac monitoring will be performed. From this device, mean, maximum and minimum heart rate frequency will be recorded. This will give us the opportunity for registration of detailed ectopic activity including supraventricular and ventricular ectopic beats, runs and sustained arrhythmias.

TREATMENT PROCEDURES AND IMP BLINDING

The IL-6 receptor antagonist tocilizumab and placebo will both be administered intravenously over a period of one hour starting as soon as possible after admission. Prepared study drug must be kept refrigerated until used and must be administered within 8 hours of production. The study drug administration schedule will be identical for subjects receiving tocilizumab and placebo. Qualified healthcare personnel will perform all infusions of the study drug, and subject self-administration will not occur.

The site will establish a formal, documented collaboration with a near-by ward with 24/7 service for preparation of the study drug. The attending nurse at the preparation ward will be notified to prepare a set of study drug and placebo. Identification, mixing, dilution and labeling of the investigational products will be cross-checked within the collaborating ward according to an agreed, documented, two-person workflow under the sponsor's responsibility to assure that safety, registration and blinding criteria are met, and unintentional unblinding is avoided.

The prepared drug kits will be delivered to the investigation ward with the study labels as sole means of reference.

Personnel will be specifically trained prior to and have access to written, printed instructions concerning all details regarding preparation, administration, and monitoring procedures available with the kits of study drugs. All personnel will be qualified and trained in accordance with GCP, and the sponsor will maintain documentation pertaining to everyone's qualifications and consent to registration. IMP storage, handling and any discarding will be subject to mandatory record keeping in agreement with the institution GCP unit's standard operating procedure guidelines.

Record keeping will include timed interval temperature measurements of storage as well as inventory management with the purpose of obtaining full traceability of batch identification and amount dispensed. Inventory will also be kept at a center-level, comprising name, strength and packaging size of the medication, the amount received, date of receipt, batch number, date of expiry, amount available on location, date and initials of the record-keeping individual.

INVESTIGATIONAL PRODUCT DOSAGE

The single dose Tocilizumab (RoActemra®, Roche) of 280 mg will be added isotonic (9%) normal saline to a total volume of 100 ml. This treatment regimen is similar to the regimen used for rheumatoid arthritis and recently used in a clinical trial in STEMI patients.²² The placebo kit will contain 100 mL of isotonic (0.9% normal saline). Tocilizumab infusion is administered within one hour. The infusion can be administered in a central or peripheral intravenous line. The study drug label ('A' or 'B') is documented along with time of study drug infusion start, time of study drug infusion completion.

Standard dosage of Dobutamine is initially 2-3 yg/kg/min, which in a daily clinical setting can be increased up to 20 yg/kg/min. Due to the possible adverse effects of tachyarrhythmia, a low maintenance dose in the current study of 5 yg/kg/min of Dobutamine is chosen. The study drug label ('C' or 'D') is documented along with time of study drug infusion start, time of study drug infusion completion.

The manufacturing nurse will use RedCap confirming his/her identity as investigational drug manufacturer and will through the website obtain information as to whether kit 'A' or 'B' will contain Tocilizumab and / or saline and 'C' or 'D' will contain Dobutamine and/or saline.

TREATMENT DEESCALATION / TERMINATION

In case of persistent supraventricular tachy-arrhythmia > 130 BPM for > 30 minutes Dobutamine infusion will be diminished to 2.5 yg/kg/min. Hereafter in case of further tachy-arrhythmia dobutamine will be discontinued at the discretion of the treating physician.

The dose of the Tocilizumab will be fixed. If clinical signs of an allergic reaction or other severe side effects are suspected, the infusion will be terminated immediately. No dosage

adjustments are intended. A standard operating procedures (SOP) manual will be made available to all clinicians involved in the study.

ADVERSE EVENT REPORTING

Adverse events will be recorded daily for the first 7 days in a pre-specified form in the eCRF. Adverse events occurring after day 7 will be evaluated at 30- and 180-day follow-up. At each assessment of all adverse events, serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR) must be recorded by the investigator and evaluated. Each SAE and SUSAR requires the sponsor to fill in the AE form, including the following variables: description of event, onset and end of event, severity, relation to the intervention, action taken, and outcome. Any adverse events occurring during the study will be treated according to established standards, and the subject will be followed until the event has disappeared or stabilized. On a yearly basis, a safety rapport containing information on serious adverse events/reactions will be submitted to the Danish Health and Medicines Authority.

Adverse Events (AE)

Events are defined as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Adverse events will be reported daily, within 24 hours from awareness, through the eCRF.

Serious Adverse Events (SAE)

For each AE reporting, there will be an additional question, as to whether there has been a serious adverse event. A SAE is an AE that results in death, is life threatening, requires hospitalization or prolongation of hospitalization, or results in significant disability, including

congenital anomaly or birth defect. Any SAE must be reported to the sponsor within 24 hours of awareness.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SUSAR is an unexpected and serious reaction to the investigational drug. The investigator assesses potential causality between investigational product, and whether the reaction is suspected will be assessed by the sponsor. The Summary of Product Characteristics for RoActemra and Dobutrex will be used for this assessment. The sponsor will be responsible to report all life-threatening or lethal SUSARS to the Danish Health and Medicines Authority as soon as possible and no later than 7 days after being aware of such an event. Non-life threatening SUSARs will be reported as soon as possible and no later than 15 days after the event.

Severity of Adverse Events

For each AE, severity will be graded accordingly:

- Mild: Transient symptoms, no interference with subject's daily activities
- Moderate: Marked symptoms, moderate interference with subject's daily activities
- Severe: Considerable interference with subject's daily activities

Relationship of AE to Trial Intervention

For each AE, relationship to trial intervention will be rated accordingly:

- Probable: Good reason and sufficient documentation to assume a causal relationship
- Possible: A causal relationship is likely and cannot be excluded
- Unlikely: The event is most likely related to an etiology other than the intervention

- Unknown: Causality is not assessable

For the conditions bleeding, infection and arrhythmia, the following definitions will apply in reporting:

Major bleeding: Uncontrolled bleeding (>1 unit of blood/10kg/hour), or any bleeding causing fatality or critical organ affection, (e.g. intracranial, intraocular, intraarticular, pericardial), or any other bleeding requiring > 2 units of transfused blood or volume replacement.

Infection: Upper airway infection, pneumonia, sepsis, pyelonephritis, diverticulitis.

Arrhythmia: Ventricular fibrillation (VF), sustained ventricular tachycardia (VT), new-onset atrial fibrillation/flutter, persistent supraventricular tachy-arrhythmia (> 130 BPM > 30 minutes).

Reference Document

Relationship to trial intervention will be determined according to the manufacturer 'summary of product characteristics (Appendix D, E).

Procedures for Un-Blinding the Treatment Allocation

The identification of treatment allocation will be maintained at a computer located at Rigshospitalet but protected from participants of the study. Authorized site staff will be provided with a unique Personal Identification Number (PIN) to obtain unblinding information. This PIN is unique to the individual and must not be shared.

A subject's treatment assignment should only be unblinded by a study site when knowledge of the treatment is essential for the further management of the subject or if needed for safety

reporting to regulatory authorities. Unblinding at the study site for any other reason will be considered a protocol deviation.

For unblinding at the site, the Principal Investigator should if possible be contacted before unblinding any subject's treatment assignment. At the latest, the principal investigator must be notified within 1 working day after the event, and the unblinding must be documented in the subject's case report form.

SAFETY MONITORING

The trial will be conducted according to the Act No. 593 of 14 June 2011 on Act on Research Ethics. Review of Health Research Projects. The investigators will immediately notify the regional ethics committee and Danish Medicines Agency in case of occurrence of unexpected serious adverse reactions within the interventions period. The report will be accompanied by comments on possible implications for the trial, and notification will be made within seven days after the investigators have obtained knowledge of the event. Please see the supplementary material.

INFORMED CONSENT

The study will be conducted in adherence to national and international standards of GCP. A subject has the right to withdraw from the study at any time, for any reason, without prejudice to his or her future medical care by the physician or at the institution. Any subject who withdraws consent to participate in the study will immediately be removed from further treatment and/or study observation on the date of request. In addition, the investigator and the sponsor have the right to withdraw a subject from the study if any of the following occurs:

1. Refusal by the subject to continue observations
2. Decision by the investigator that termination is in the subject's best medical interest

Should a subject request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable case report forms. A complete final evaluation and assessments according to outcome measures will be made at the time of the subject's withdrawal. The End of Study case report form will be completed with an explanation for the withdrawal. If the withdrawal of a subject is due to an adverse event, follow-up visits should be scheduled until the adverse event has resolved or stabilized. Unless consent has been withdrawn, follow-up data on deaths and hospitalizations will be collected until study termination or a maximum of 48 months since enrolment of the subject. Unless specifically requested by the patient, the patient will be followed for the primary endpoint until end of study.

ETHICAL CONSIDERATIONS

All patients will be included after informed (written and oral) consent in accordance with the Danish Data Protection Act and the General Data Protection Regulation with electronic signature in via RedCap. Neither participation in the trial nor administration of study drug will interfere with or delay diagnostic or therapeutic procedures. The trial will investigate the beneficial effects of the IL-6RA Tocilizumab and / or dobutamine administered as soon as possible after PCI in AMI-patients presenting < 24 hours from chest pain and ORBI risk score ≥ 11 .

The ethical justifications for acute administration of Tocilizumab and dobutamine in AMI-patients are that knowledge of the inflammation reducing effects of IL-6RA in AMI-patients cannot be gained outside of the acute setting as proposed. Similar research in a non-acute setting is not possible, as we aim to investigate the development of cardiogenic shock after hospital admission, which often occurs during the first couple of hours after AMI. The aim of the study is to assess the benefit of reducing inflammation in AMI-patients – a response that has been proposed associated with poor outcome. Infusion of dobutamine will need to be initiated as soon as possible after PCI to alleviate the progressive ischemia-reperfusion injury following AMI and early revascularization.

Study drug infusion is approved for other medical conditions and is expected to be of minimal risk to the subjects. Increased knowledge on the therapeutic potential of Tocilizumab would increase scientific knowledge of AMI-patients in general, and the SIRS-like response in particular, without exposing the patients to high risk. Inclusion in the study may benefit the individual participant as we hypothesize that development of CS and infarct size will be diminished, and therefore will be valuable to the group of high-risk AMI-patients, since further knowledge is needed to continue to improve treatment in this specific patient group.

DATA HANDLING AND RECORD KEEPING

The patient's records will be reviewed by study related personnel and the endpoint committee to assess clinical endpoints. The patient is informed about this and gives informed consent to this when entering the study. The investigators are responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs. The informed consent gives the investigator and possibly control authority direct access to data from the patient's journal. These are used to view information on the participant's medical condition necessary for the conduct of the trial and for self-control, quality control and monitoring.

DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

The principal investigator will permit monitoring, audits, reviews of ethical committees and regulatory authorities' direct access to source data, blinded to treatment allocation. An independent Data Monitoring Committee consisting of members with relevant expertise will be assembled prior to study commencement. This committee will periodically review safety data and enrollment trends.

QUALITY CONTROL AND ASSURANCE

The trial will be externally monitored by the national GCP unit at the Copenhagen GCP center. A monitoring plan will be conducted prior to trial initiation. The frequency of onsite monitoring will depend on compliance with the protocol, number of enrolled patients, and quality of data handling. There will be mandatory monitoring before and after the trial and at least once during the trial. The GCP will monitor inclusion and exclusion criteria, consent

obtained in all subjects according to legislation, and data included in the eCRF. The principal investigator will be responsible for all data in the eCRFs.

PUBLICATION OF RESULTS

The results obtained in accordance with the protocol and any amendments in their approved form will be uploaded to the EudraCT portal as soon as possible within a 1-year time frame.

Data will be published to clinicaltrialsregister.eu.

FINANCE

The study is an investigator-initiated trial conceived and conducted by medical doctors from the Heart Centre at Rigshospitalet, Copenhagen University Hospital. When financial support has been obtained, the regulatory organs will be notified, and the participant information updated accordingly. The funding will cover expenses as listed in the budget overview. The financial support will be deposited to a project specific research account, which is administered by the hospital and under public revision. The study is independent of commercial interests. External sponsors will have no influence on the conduct of the study. Participants will not receive any financial compensation.

TASKS AND RESPONSIBILITIES

Joakim Kunkel, MD and Sarah Holle, MD will uptake informed consent from patients and perform inclusion in the trial.

Helle Sørholm, MD, PhD and Professor, MD, Dr. Med. Christian Hassager will take responsibility as a primary investigator and sponsor, respectively, according to current legislation and regulations.

All collaborators are GCP-certified. The sponsor holds documentation thereof.

REFERENCES

1. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. *Circulation* 2008;117(5):686-97. doi: 10.1161/CIRCULATIONAHA.106.613596
2. Obling L, Frydland M, Hansen R, et al. Risk factors of late cardiogenic shock and mortality in ST-segment elevation myocardial infarction patients. *Eur Heart J Acute Cardiovasc Care* 2018;7(1):7-15. doi: 10.1177/2048872617706503
3. De Luca L, Olivari Z, Farina A, et al. Temporal trends in the epidemiology, management, and outcome of patients with cardiogenic shock complicating acute coronary syndromes. *Eur J Heart Fail* 2015;17(11):1124-32. doi: 10.1002/ejhf.339
4. Baran DA, Grines CL, Bailey S, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. *Catheter Cardiovasc Interv* 2019;94(1):29-37. doi: 10.1002/ccd.28329 [published Online First: 2019/05/20]
5. Dietz JR. Release of natriuretic factor from rat heart-lung preparation by atrial distension. *Am J Physiol* 1984;247(6 Pt 2):R1093-6.
6. Toth M, Vuorinen KH, Vuolteenaho O, et al. Hypoxia stimulates release of ANP and BNP from perfused rat ventricular myocardium. *Am J Physiol* 1994;266(4 Pt 2):H1572-80.
7. Tateishi J, Masutani M, Ohyanagi M, et al. Transient increase in plasma brain (B-type) natriuretic peptide after percutaneous transluminal coronary angioplasty. *Clin Cardiol* 2000;23(10):776-80.
8. Goetze JP, Christoffersen C, Perko M, et al. Increased cardiac BNP expression associated with myocardial ischemia. *FASEB J* 2003;17(9):1105-7. doi: 10.1096/fj.02-0796fje
9. Nagaya N, Nishikimi T, Goto Y, et al. Plasma brain natriuretic peptide is a biochemical marker for the prediction of progressive ventricular remodeling after acute myocardial infarction. *Am Heart J* 1998;135(1):21-8. doi: 10.1016/s0002-8703(98)70338-2 [published Online First: 1998/02/07]
10. Jarai R, Huber K, Bogaerts K, et al. Plasma N-terminal fragment of the prohormone B-type natriuretic peptide concentrations in relation to time to treatment and Thrombolysis in Myocardial Infarction (TIMI) flow: a substudy of the Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT IV-PCI) trial. *Am Heart J* 2010;159(1):131-40. doi: 10.1016/j.ahj.2009.11.001
11. Frydland M, Moller JE, Lindholm MG, et al. Biomarkers predictive of late cardiogenic shock development in patients with suspected ST-elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2020;2048872619896063. doi: 10.1177/2048872619896063 [published Online First: 2020/01/22]
12. Katayama T, Nakashima H, Furudono S, et al. Evaluation of neurohumoral activation (adrenomedullin, BNP, catecholamines, etc.) in patients with acute myocardial infarction. *Intern Med* 2004;43(11):1015-22.
13. Jarai R, Huber K, Bogaerts K, et al. Prediction of cardiogenic shock using plasma B-type natriuretic peptide and the N-terminal fragment of its pro-hormone [corrected] concentrations in ST elevation myocardial infarction: an analysis from the ASSENT-4 Percutaneous Coronary Intervention Trial. *Crit Care Med* 2010;38(9):1793-801. doi: 10.1097/CCM.0b013e3181eaaf2a
14. Gillespie TA, Ambos HD, Sobel BE, et al. Effects of dobutamine in patients with acute myocardial infarction. *Am J Cardiol* 1977;39(4):588-94. doi: 10.1016/s0002-9149(77)80170-7 [published Online First: 1977/04/01]
15. Shah B, Pillinger M, Zhong H, et al. Effects of Acute Colchicine Administration Prior to Percutaneous Coronary Intervention: COLCHICINE-PCI Randomized Trial. *Circ Cardiovasc Interv* 2020;13(4):e008717. doi: 10.1161/CIRCINTERVENTIONS.119.008717 [published Online First: 2020/04/17]
16. Giugliano GR, Giugliano RP, Gibson CM, et al. Meta-analysis of corticosteroid treatment in acute myocardial infarction. *Am J Cardiol* 2003;91(9):1055-9. doi: 10.1016/s0002-9149(03)00148-6 [published Online First: 2003/04/26]
17. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med* 2017;377(12):1119-31. doi: 10.1056/NEJMoa1707914 [published Online First: 2017/08/29]
18. Tong DC, Quinn S, Nasis A, et al. Colchicine in Patients with Acute Coronary Syndrome: The Australian COPS Randomized Clinical Trial. *Circulation* 2020 doi: 10.1161/CIRCULATIONAHA.120.050771 [published Online First: 2020/08/31]

19. Tardif JC, Kouz S, Waters DD, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med* 2019;381(26):2497-505. doi: 10.1056/NEJMoa1912388 [published Online First: 2019/11/17]
20. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. *N Engl J Med* 2020 doi: 10.1056/NEJMoa2021372 [published Online First: 2020/09/01]
21. Kleveland O, Kunszt G, Bratlie M, et al. Effect of a single dose of the interleukin-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with non-ST-elevation myocardial infarction: a double-blind, randomized, placebo-controlled phase 2 trial. *Eur Heart J* 2016;37(30):2406-13. doi: 10.1093/eurheartj/ehw171 [published Online First: 2016/05/11]
22. Broch K, Anstensrud AK, Woxholt S, et al. Randomized Trial of Interleukin-6 Receptor Inhibition in Patients With Acute ST-Segment Elevation Myocardial Infarction. *Journal of the American College of Cardiology* 2021;77(15):1845-55. doi: 10.1016/j.jacc.2021.02.049 [published Online First: 2021/04/17]
23. Meyer MAS, Wiberg S, Grand J, et al. Treatment Effects of Interleukin-6 Receptor Antibodies for Modulating the Systemic Inflammatory Response After Out-of-Hospital Cardiac Arrest (The IMICA Trial): A Double-Blinded, Placebo-Controlled, Single-Center, Randomized, Clinical Trial. *Circulation* 2021;143(19):1841-51. doi: 10.1161/CIRCULATIONAHA.120.053318 [published Online First: 2021/03/23]
24. Auffret V, Cottin Y, Leurent G, et al. Predicting the development of in-hospital cardiogenic shock in patients with ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention: the ORBI risk score. *Eur Heart J* 2018 doi: 10.1093/eurheartj/ehy127
25. Frederiksen KP, Soeholm H, Hassager C, et al. Biomarkers reflecting neurohormonal activation and inflammation are correlated with the ORBI Risk Score and predictive of in-hospital cardiogenic shock development in STEMI-patients. *SESSION ACVC Essentials 4 You - ePublications* 2020
26. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017 doi: 10.1093/eurheartj/ehx393
27. Buchner S, Debl K, Barlage S, et al. Dynamic changes in N-terminal pro-brain natriuretic peptide in acute coronary syndromes treated with percutaneous coronary intervention: a marker of ischemic burden, reperfusion and outcome. *Clin Chem Lab Med* 2010;48(6):875-81. doi: 10.1515/CCLM.2010.164 [published Online First: 2010/05/06]
28. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation* 2018;138(20):e618-e51. doi: 10.1161/CIR.0000000000000617 [published Online First: 2018/12/21]
29. Trzeciak S, McCoy JV, Phillip Dellinger R, et al. Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. *Intensive Care Med* 2008;34(12):2210-7. doi: 10.1007/s00134-008-1193-6 [published Online First: 2008/07/03]
30. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22(7):707-10.
31. Oldridge N, Saner H, McGee HM, et al. The Euro Cardio-QoL Project. An international study to develop a core heart disease health-related quality of life questionnaire, the HeartQoL. *Eur J Cardiovasc Prev Rehabil* 2005;12(2):87-94. doi: 10.1097/01.hjr.0000159408.05180.0e [published Online First: 2005/03/24]
32. Zangger G, Zwisler AD, Kikkenborg Berg S, et al. Psychometric properties of HeartQoL, a core heart disease-specific health-related quality of life questionnaire, in Danish implantable cardioverter defibrillator recipients. *Eur J Prev Cardiol* 2018;25(2):142-49. doi: 10.1177/2047487317733074 [published Online First: 2017/09/28]
33. Hansen TB, Thygesen LC, Zwisler AD, et al. Self-reported health-related quality of life predicts 5-year mortality and hospital readmissions in patients with ischaemic heart disease. *Eur J Prev Cardiol* 2015;22(7):882-9. doi: 10.1177/2047487314535682 [published Online First: 2014/05/14]
34. Gronset CN, Thygesen LC, Berg SK, et al. Measuring HRQoL following heart valve surgery: the HeartQoL questionnaire is a valid and reliable core heart disease instrument. *Qual Life Res* 2019;28(5):1245-53. doi: 10.1007/s11136-018-02098-1 [published Online First: 2019/01/06]
35. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33(5):337-43. doi: 10.3109/07853890109002087 [published Online First: 2001/08/09]
36. De Smedt D, Clays E, Doyle F, et al. Validity and reliability of three commonly used quality of life measures in a large European population of coronary heart disease patients. *Int J Cardiol* 2013;167(5):2294-9. doi: 10.1016/j.ijcard.2012.06.025 [published Online First: 2012/07/04]

37. Snaith RP, Zigmond AS. The hospital anxiety and depression scale. *Br Med J (Clin Res Ed)* 1986;292(6516):344. doi: 10.1136/bmj.292.6516.344 [published Online First: 1986/02/01]
38. Bjelland I, Dahl AA, Haug TT, et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;52(2):69-77. doi: 10.1016/s0022-3999(01)00296-3 [published Online First: 2002/02/08]
39. Snaith RP. The Hospital Anxiety And Depression Scale. *Health Qual Life Outcomes* 2003;1:29. doi: 10.1186/1477-7525-1-29 [published Online First: 2003/08/14]
40. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x [published Online First: 2005/04/09]
41. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173(5):489-95. doi: 10.1503/cmaj.050051 [published Online First: 2005/09/01]
42. Bebb O, Smith FG, Clegg A, et al. Frailty and acute coronary syndrome: A structured literature review. *Eur Heart J Acute Cardiovasc Care* 2018;7(2):166-75. doi: 10.1177/2048872617700873 [published Online First: 2017/10/25]
43. Ensrud KE, Ewing SK, Taylor BC, et al. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *J Gerontol A Biol Sci Med Sci* 2007;62(7):744-51. doi: 10.1093/gerona/62.7.744 [published Online First: 2007/07/20]
44. Carroll MB, Haller C, Smith C. Short-term application of tocilizumab during myocardial infarction (STAT-MI). *Rheumatol Int* 2018;38(1):59-66. doi: 10.1007/s00296-017-3842-y [published Online First: 2017/10/27]
45. Castagne B, Viprey M, Martin J, et al. Cardiovascular safety of tocilizumab: A systematic review and network meta-analysis. *PLoS One* 2019;14(8):e0220178. doi: 10.1371/journal.pone.0220178 [published Online First: 2019/08/02]
46. Kobayashi H, Kobayashi Y, Yokoe I, et al. Heart Rate-corrected QT Interval Duration in Rheumatoid Arthritis and Its Reduction with Treatment with the Interleukin 6 Inhibitor Tocilizumab. *J Rheumatol* 2018;45(12):1620-27. doi: 10.3899/jrheum.180065 [published Online First: 2018/09/03]
47. Meyer MAS, Wiberg S, Grand J, et al. Interleukin-6 Receptor Antibodies for Modulating the Systemic Inflammatory Response after Out-of-Hospital Cardiac Arrest (IMICA): study protocol for a double-blinded, placebo-controlled, single-center, randomized clinical trial. *Trials* 2020;21(1):868. doi: 10.1186/s13063-020-04783-4 [published Online First: 2020/10/22]
48. Tleyjeh IM, Kashour Z, Damlaj M, et al. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. *Clin Microbiol Infect* 2020 doi: 10.1016/j.cmi.2020.10.036 [published Online First: 2020/11/09]
49. Schumann J, Henrich EC, Strobl H, et al. Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome. *Cochrane Database Syst Rev* 2018;1:CD009669. doi: 10.1002/14651858.CD009669.pub3 [published Online First: 2018/01/30]
50. Landmesser U, Drexler H. Update on inotropic therapy in the management of acute heart failure. *Curr Treat Options Cardiovasc Med* 2007;9(6):443-9. doi: 10.1007/s11936-007-0039-9 [published Online First: 2008/01/29]