NORSHOCK

RESEARCH PROTOCOL

Clinical Outcome and Cost-effectiveness of Reduced Noradrenaline by Using a Lower Blood Pressure Target in Patients with Cardiogenic Shock from Acute Myocardial Infarction

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Amsterdam UMC
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PROTOCOL TITLE 'Clinical Outcome and Cost-effectiveness of Reduced Noradrenaline by Using a Lower Blood Pressure Target in Patients with Cardiogenic Shock from Acute Myocardial Infarction: A Multicenter Randomized Trial'

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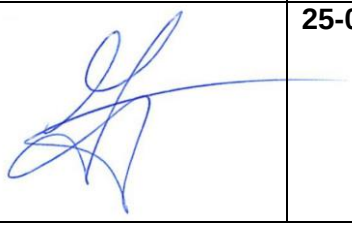
Coordinating Investigator: Prof. Dr. José P.S. Henriques, MD, PhD *Department of cardiology (Amsterdam UMC / UvA)*		**25-07-2022**

Version	**Release date**	**Summary of Changes**
1.0	03-03-2022	Initial release
2.0	19-05-2022	METC revisions
2.1	20-06-2022	METC revisions
2.2	25-07-2022	METC revisions

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
AMI	Acute Myocardial Infarction
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CCU	Coronary Care Unit
CEC	Clinical Event Committee
CS	Cardiogenic Shock
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EQ-5D-5L	5-Level EQ-5D questionnaire
EudraCT	European drug regulatory affairs Clinical Trials
ICU	Intensive Care Unit
IGJ	Inspectie Gezondheidszorg en Jeugd
iMCQ	iMTA Medical Consumption Questionnaire
iMTA	Institute for Medical Technology
iPCQ	iMTA Productivity Cost Questionnaire
LVEF	Left Ventricular Ejection Fraction
MAP	Mean Arterial Pressure
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
NSTEMI	Non ST-Elevated Myocardial infarction
QALY	Quality Adjusted Life Year
QOL	Quality Of Life
(S)AE	(Serious) Adverse Event
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
STEMI	ST-Elevated Myocardial Infarction
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Pump failure due to acute myocardial infarction (AMI) can lead to cardiogenic shock (CS): a state of low blood flow to end-organs with subsequent multi-organ failure that is associated with high mortality rates. The first line pharmacologic treatment strategy in CS is noradrenaline. This vasopressor drug is used to maintain adequate blood pressure. The current guidelines have a weak recommendation for targeting a mean arterial blood pressure (MAP) of ≥ 65 mmHg in order to improve flow and thereby tissue perfusion of the myocardium, kidneys and other organs. However, there is no evidence that an increase in MAP, if achieved by noradrenaline, leads to higher end-organ blood flow and better outcomes. As a matter of fact, the use of noradrenaline may compromise myocardial blood flow in this condition and thus lead to infarct size expansion and worse clinical outcome.

Objective: With this study we aim to investigate the (cost-)effectiveness of reduced noradrenaline in patients with CS by using a lower MAP-target of ≥ 55 mmHg, compared to standard care (target-MAP usually ≥ 65 mmHg). We hypothesize that reduced use of noradrenaline will improve overall survival and decrease renal failure requiring renal replacement therapy.

Study design: Open label, randomized controlled multicenter trial

Study population: Adults patients with CS due to AMI

Intervention: Treatment strategy of reduced noradrenaline use, by means of a lower MAP-target regimen (≥ 55 mmHg).

Main study parameters/endpoints: Primary endpoint: composite of all-cause mortality and severe renal failure leading to renal replacement therapy within 30-days after randomization.

Secondary endpoints: duration of catecholamine therapy, enzymatic infarct size, hemodynamic parameters, length of stay in hospital and Intensive Care Units (ICU), quality of life (QOL).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: In this study no new or additional medication is registered to patients when compared to routine care. This means that all potential risks originate from using a lower MAP-target and reduced use of noradrenaline. In both index and reference group, renal and cerebral functions will be closely monitored.

A potential benefit from study participation is that less exposure to noradrenaline leads to less frequent occurrence of side effects, such as (supra-)ventricular arrhythmias.

The follow-up moments are at 30-days, 3-month, 6-month and 1-year after randomization. These are all part of routine care. At follow-up information on organ function (blood test, ECG, echocardiography) will be gathered, as part of routine care. Additionally, patients will be asked to fill in a questionnaire at 30-days, 3-months, 6-months and 1-year after randomization.

1. INTRODUCTION AND RATIONALE

Yearly, around 6000 patients in the Netherlands suffer from cardiogenic shock (CS) due to acute myocardial infarction (AMI) and this number will only increase, based on demographic developments.[1] Despite efforts to improve survival mortality in CS is as high as 50% and the only evidence based therapy is early revascularization. [2-5] CS after AMI results from the loss of myocardial cells due to ischemia. The poor pumping function of the heart leads to a state with low blood flow to end-organs resulting in multi-organ failure and high mortality rates. Renal failure (and subsequent renal replacement therapy) occurs due to decreased perfusion of the kidneys and is a surrogate marker for end-organ perfusion and a strong predictor for death in CS.[6]

The first-line pharmacologic strategy in CS is noradrenaline, as recommended by current scientific statements.[2, 7] Noradrenaline is a vasopressor drug routinely used in the treatment of CS, under the assumption that a higher mean arterial blood pressure (MAP) will improve myocardial and other end-organ (e.g. renal) perfusion. However, there is no evidence that noradrenaline use and higher blood pressures improve patient outcomes. Firstly, pharmacologically induced improvement of blood pressure has not been associated with better survival. Secondly, there is no evidence that an increase in MAP, if achieved by noradrenaline, leads to greater myocardial and other end-organ blood flow. As a matter of fact, its vasoconstrictive properties reduce flow to the microcirculation of the myocardium and organs, as can be frequently seen by discolouring of skin in patients treated with noradrenaline.[8, 9] And lastly, noradrenaline is associated with adverse events such as (supra-)ventricular arrhythmias that reduce the efficacy of the myocardial pumping function and increase the myocardial oxygen demand. This can lead to expansion of infarct size and worsening of the heart muscle function.

The current, scientifically weak recommendation for noradrenaline (Class IIb) is based on one study that compared noradrenaline with dopamine in a population with all types of shock.[10] The overall trial was neutral and only in a small CS subgroup a trend was reported towards lower 28-day mortality and less arrhythmias in patients treated with noradrenaline, as compared to dopamine. However, there are serious methodological concerns as randomization was not stratified and the test for subgroup differences suggests that the effect was likely based on chance. Furthermore, the comparator group was treated with dopamine, which is known for adverse events such as arrhythmias. In light of the aforementioned limitations, the optimal first-line treatment and MAP-target in patients with CS remains unclear.

Based on the results of a recently published trial (permissive hypotension [lower MAP-target] in patients with vasodilatory hypotension), we anticipate that accepting a lower MAP will lead to a significantly reduced exposure to noradrenaline in the index group. Moreover, in this recent study, no differences were found in fluid balance or use of other vasopressor/inotropic drugs, compared to standard care (noradrenaline use and MAP-target left at discretion of treating physician).[11]

2. OBJECTIVES

Primary objective:
The primary objective of this study is to test whether a treatment strategy with reduced use of noradrenaline in patients with cardiogenic shock is superior to standard care in terms of combined all-cause mortality and renal failure at 30 days.

Secondary objective:
The secondary objectives of this study are to test the following hypotheses:

- Does a treatment strategy with reduced use of noradrenaline in patients with cardiogenic shock lead to lower all-cause mortality at 30 days?
- Does a treatment strategy with reduced use of noradrenaline in patients with cardiogenic shock lead to reduced cardiovascular death at 1 year?
- Does a treatment strategy with reduced use of noradrenaline in patients with cardiogenic shock lead to an increase of days alive and out of hospital at 30 days?

3. STUDY DESIGN

An open label, multicenter randomized controlled trial to ensure level 1 evidence for superiority of the intervention. The standardcare arm will provide a reliable basis for the cost-effectiveness analysis. Patients will be randomly assigned (1:1) to the index regimen (lower MAP-target of ≥ 55 mmHg) or reference regimen (standard MAP-target of ≥ 65 mmHg). Inclusion is estimated to take three years (36 months).

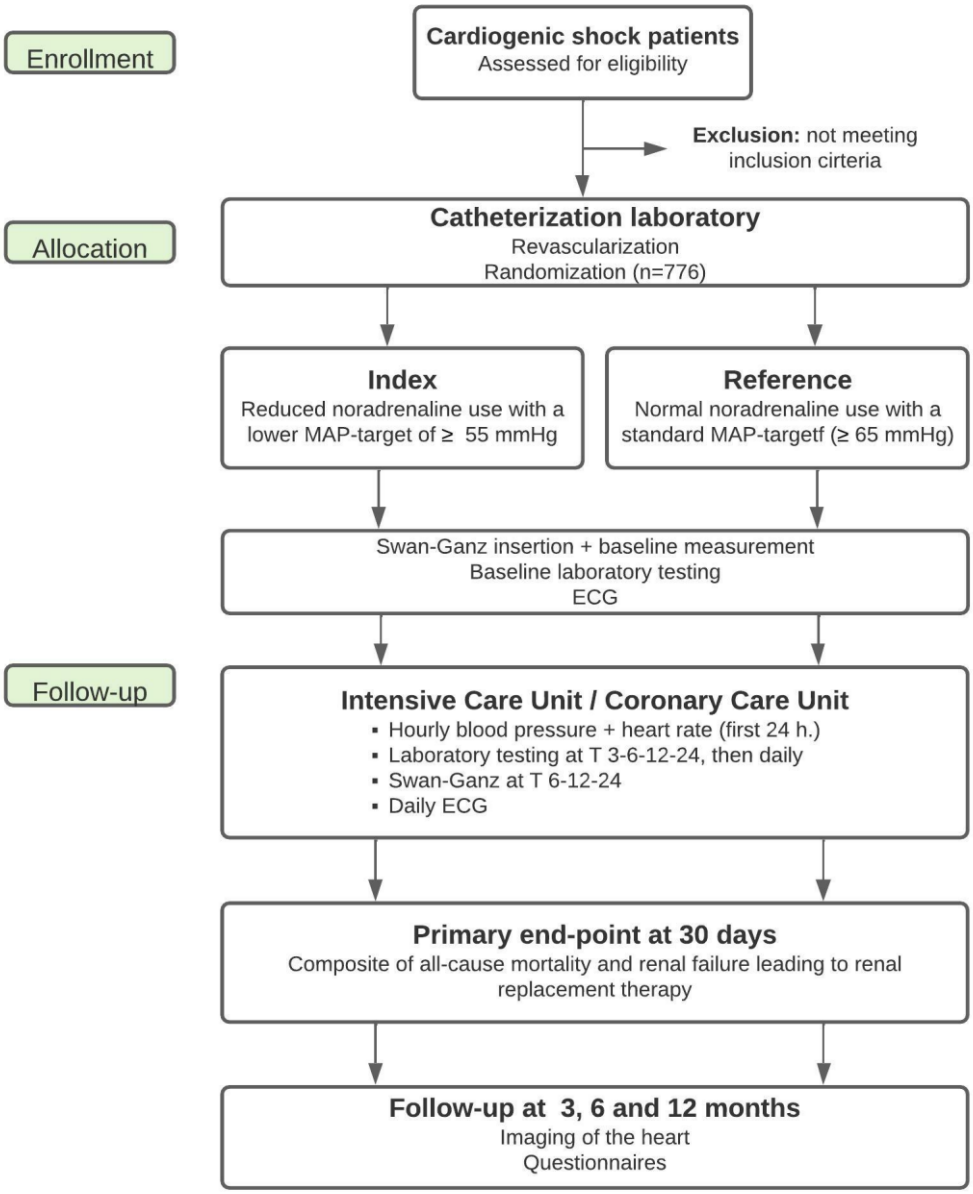

Figure 1.

4. STUDY POPULATION

4.1 Population (base)

The study consists of consecutive adult patients with acute myocardial infarction with cardiogenic shock, treated with early revascularization by PCI.

4.2 Screening

Screening for eligibility takes place at the emergency department, the catheterization laboratory or at the intensive care unit (ICU) / coronary care unit (CCU).

4.3 Inclusion criteria

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

1. Acute myocardial infarction, STEMI or NSTEMI
2. Cardiogenic shock, characterized by:
    I. Signs of impaired organ perfusion with at least one of the following criteria:
        a. Altered mental status
        b. Cold, clammy skin and extremities
        c. Oliguria with urine output < 30ml/hour
        d. Serum lactate > 2.0 mmol/L
    II. a. Systolic blood pressure (SBP) < 90 mmHg for > 30 minutes, OR
        b. Use of drugs to maintain SBP > 90 mmHg at presentation before randomization.
    III. Signs of pulmonary congestion

4.4 Exclusion criteria

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

- Resuscitation > 30 minutes
- Mechanical cause of cardiogenic shock (e.g. papillary muscle rupture, ventricular septal rupture)

- Onset of shock > 12 hours
- Imminent need for mechanical circulatory support

5. TREATMENT AND FOLLOW-UP

5.1 Randomization and treatment allocation

Patients are randomized either at the catheterization laboratory (before or after revascularization by PCI) or at the ICU / CCU up to a maximum of 2 hours after PCI, as soon as the treating physician has established the diagnosis of CS (*see criteria above*). As patients are in immediate need of treatment with noradrenaline, patients are randomized without preceding informed consent (*see section 5.6*).

Patients meeting the selection criteria are randomized in a 1:1 ratio to index regimen, with a MAP-target of ≥ 55 mmHg, or reference regimen, with a standard MAP-target. A web based randomization program with stratification per center is used. The randomized regimen is started immediately after randomization.

5.2 Index regimen with a lower MAP-target (≥ 55mmHg)

Noradrenaline therapy (dosage and duration) is given with a target MAP of ≥ 55mmHg.

- If a patient is not on vasoactive drugs at the moment of randomization, noradrenaline is only started when the MAP is < 55 mmHg. Noradrenaline is titrated in accordance with local protocols until the MAP-target of ≥ 55 mmHg has been reached.
- If a patient is on noradrenaline or other vasoactive drugs, treatment is reduced or discontinued when the MAP is consistently ≥ 55 mmHg.
- If, after an initial treatment period with noradrenaline, the target MAP of ≥ 55 mmHg is maintained without any medical intervention, no active blood pressure lowering medication is required.

Blood pressure is continuously monitored by an intra-arterial catheter which is placed according to clinical routine.

5.3 Reference regimen with a standard MAP-target (usually ≥ 65mmHg)

Noradrenaline therapy (dosage and duration) is given according to standard of care.

- If a patient is on noradrenaline or other vasoactive drugs at the moment of randomization, treatment is continued in accordance with usual care with a standard MAP-target.
- If a patient is not on noradrenaline or other vasoactive medication at the moment of randomization, noradrenaline is started in accordance with local routine.

Blood pressure is continuously monitored by an intra-arterial catheter which is placed according to clinical routine.

5.4 Use of co-interventions

The use of other vasoactive medication is allowed under strict regulations. Patients need to have some sign of clinical deterioration, e.g. a decrease in urinary output, mottling of the skin or an altered mental status. This observation should be confirmed biochemically by measurement of lactate. If lactate is ≥ 2mmol/L or higher than baseline measurement, patients are observed 2-4 hours before lactate measurement is repeated. If lactate fails to drop after this observational period, a hemodynamic profile is obtained, preferably via a pulmonary artery catheter. If invasive hemodynamic measurement indicates a poor cardiac output, physicians may consider adding inotropes. If lactate still fails to drop with this new strategy, further treatment is left at the discretion of the treating physician. This includes letting go of the MAP-target and starting any medication. The steps mentioned above are summarized in **figure 2**.

The use of mechanical circulatory support devices, such as Impella, IABP and ECMO, is allowed under strict criteria when bail-out therapy is necessary. That is when medical therapy fails (persistently high lactate, poor cardiac output) despite treatment according to the medical guidance protocol (usually on very high vasoactive treatment).

5.5 Follow-up

Patients are clinically followed until hospital discharge. Thereafter they are contacted by telephone at 30 days after randomization for assessment of neurological outcome. Questionnaires on resource utilization and on quality of life are distributed at 30 days, 3, 6 and 12 months after randomization. Information about hospital readmissions until one year is obtained. Furthermore, outcomes of diagnostic information of the routinely scheduled visit to the outpatient clinic is collected (including findings from functional imaging of the heart).

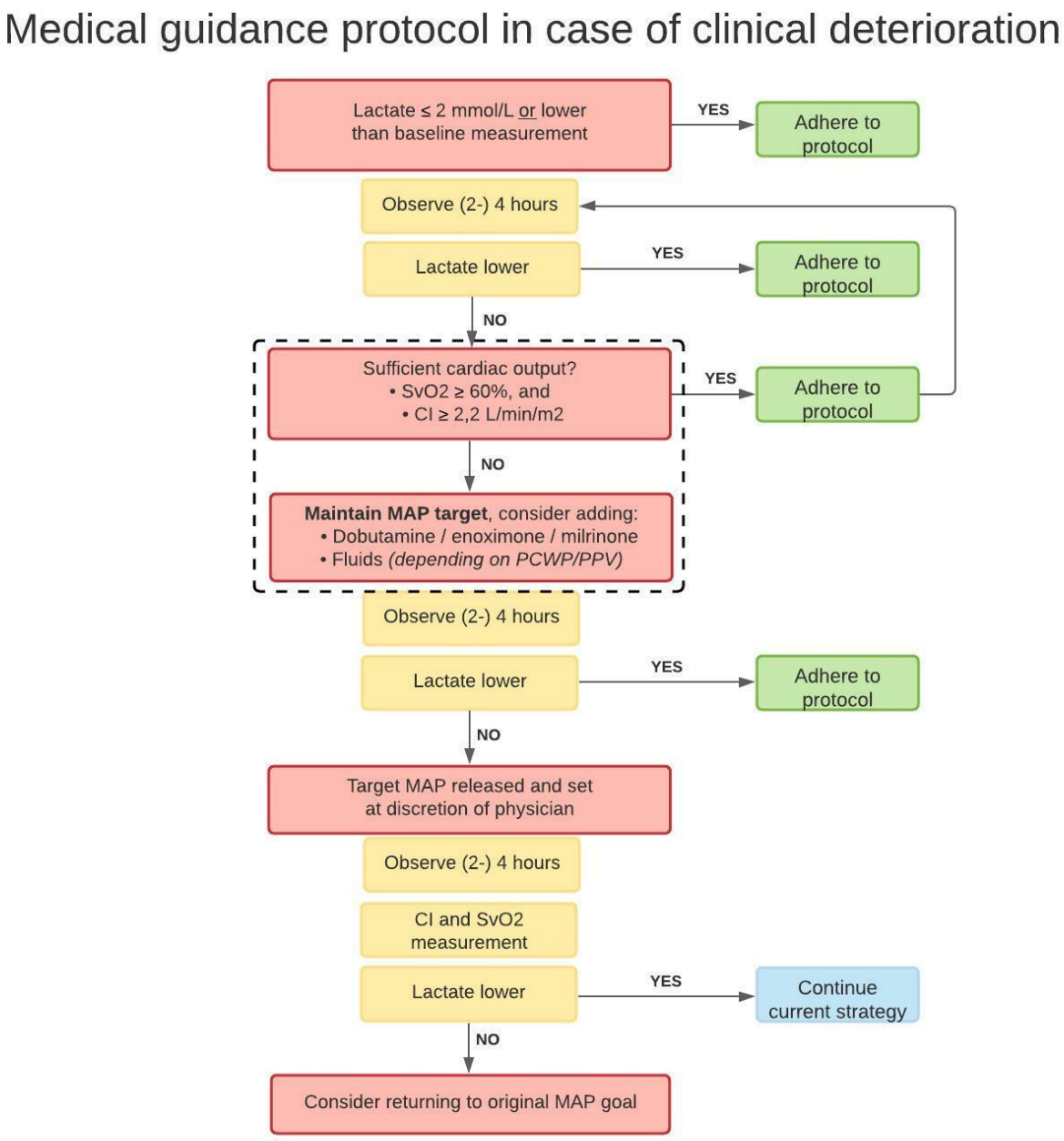
Medical guidance protocol in case of clinical deterioration
Lactate ≤ 2 mmol/L or lower than baseline measurement
YES
Adhere to protocol
Observe (2-) 4 hours
Lactate lower
YES
Adhere to protocol
NO
Sufficient cardiac output?
• SvO2 ≥ 60%, and
• CI ≥ 2,2 L/min/m2
YES
Adhere to protocol
NO
Maintain MAP target, consider adding:
• Dobutamine / enoximone / milrinone
• Fluids (depending on PCWP/PPV)
Observe (2-) 4 hours
Lactate lower
YES
Adhere to protocol
NO
Target MAP released and set at discretion of physician
Observe (2-) 4 hours
CI and SvO2 measurement
Lactate lower
YES
Continue current strategy
NO
Consider returning to original MAP goal

Figure 2.

5.6 Informed consent

5.6.1 Informed consent of a legal representative

As patients are incapacitated and legally incompetent at randomization and at the implementation of the randomized regimen assignment, legal representatives are approached to ask for consent as soon as they are available.

Legal representatives are informed of enrollment of the patient in the trial. If the legal representative(s) gives informed consent, treatment according to allocation is continued. If the legal representative(s) need more time to think, treatment according to allocation is continued until the legal representative(s) decides whether to give consent or not. The assent will be recorded in the patient notes.
If the legal representative(s) objects to treatment according to allocation and therefore does not sign the written informed consent form, patients will be treated in accordance with standard practice. This means that treatment continues in the same manner in case of allocation to reference treatment. If a patient was allocated to receive index treatment, they will be treated according to standard practice thereafter.
In case the family declines consent, but the patient survives, informed consent for further participation (questionnaires, interview by phone) and to use patient data will be asked from the patient once he or she regains consciousness. For safety reasons, if the legal representative(s) declines informed consent and the patient dies, data on the primary endpoint will still be collected (mortality, renal replacement therapy).

All information is also provided in writing.

5.6.2 Informed consent from the patient

As soon as patients have recovered, information about enrollment in the study is provided to the patient. They are explained that a legal representative has been informed about enrollment in the study.

Patients are explained that information about the clinical course until one year is needed for the study. The patients are also invited to receive a telephone call at 30 days and to fill-out questionnaires on quality of life and work resumption, via e-mail or surface mail.

Patients are asked to sign a written informed consent stating that they agree to fill out questionnaires on quality of life and work resumption (if applicable) and that clinical

information about follow-up beyond hospital discharge is gathered from hospital and general practitioners records. If the patient refuses, no further information beyond hospital discharge is collected. Patients are allowed to discontinue clinical follow-up beyond hospital discharge at any time.

Patients are also informed and asked to give consent to link patient data to existing quality registrations in the Netherlands in order to improve quality of care (the Netherlands Heart Registration (www.nederlandsehartregistratie.nl), the Dutch Hospital Data registration (www.dhd.nl), the Vektis registration (www.vektis.nl) and the NICE registration (www.stichting-nice.nl)). Also, consent to record patient data in the Netherlands Heart Registration is asked in order to answer future scientific issues considering cardiogenic shock.

6. INVESTIGATIONAL PRODUCT

6.1 Investigational product: norepinephrine

Noradrenaline is indicated for use as an emergency measure in the restoration of blood pressure in cases of acute hypotension.

Please find additional information on norepinephrine in the Summary of Product Characteristics of 'Noradrenaline (Norepinephrine) 1 mg/ml Concentrate for Solution for Infusion', that can be found on www.geneesmiddeleninformatiebank.nl.

6.2 Summary of findings from non-clinical and clinical studies

The summary of findings is not relevant for this study as the aim is not to evaluate the use or the effect of norepinephrine itself. Instead, norepinephrine is used in the same manner as is described in the authorised form of the SPC. The aim of the study is to evaluate the effect of less norepinephrine and therefore accepting a lower blood pressure.

6.3 Summary of known and potential risks and benefits

Please find a list of potential risks in paragraph 4.4 of the SPC.

6.4 Description and justification of route of administration and dosage

Please find the route of administration in paragraph 4.2 of the SPC. The noradrenaline therapy dosage is given according to standard of care.

6.5 Low intervention clinical trial

According to the definitions in the EU Clinical Trial Regulation 536/2014, this study assesses standard treatment while posing only a minimal additional risk to subject safety, and therefore should be defined as a low intervention clinical trial. Also the investigational medicinal product (noradrenaline) is already authorised and is only used in accordance with the terms of the marketing authorisation. Due to the character of low intervention studies, and the fact that this trial does not involve blinding of the label, no additional labelling of the product is required.

6.6 Drugaccountability

Patients will be prescribed noradrenaline according with routine clinical practice. Shipment, receipt and dispense of noradrenaline will be performed according to local (pharmacy) protocol. Drug accountability on individual level will be the responsibility of the study team (i.e. by recording batch numbers and expiration date). Information on drug accountability at individual level will be stored in the electronic Clinical Research Form (eCRF).

7. DATA-COLLECTION

7.1 Data collection

The NORSHOCK trial consists of information blocks containing baseline data, information about the PCI procedure, details on the clinical course during hospital admission and clinical events at 30 days. Patients are followed clinically by telephone contact at 30 days after the PCI procedure for neurological scoring. Data required for analysis is obtained as outlined in **Table 1**. For details on data collection during hospital stay, see **table 2**.

7.1.1 Baseline data

The following baseline information, collected at the moment of randomization, is entered into the electronic case report form (eCRF):

- Date of admission
- Age
- Sex
- Weight, height
- Medical history
- Cardiovascular risk factors
- Resuscitation prior to randomization
- Blood pressure, heart rate
- ECG characteristics
- Signs of impaired organ perfusion
- Timing of randomization (before or after revascularization)

7.1.2 PCI procedure

The following information about the PCI procedure is entered into the eCRF:

- The location of the culprit lesion and a complete anatomic description of coronary status (such as presence of single or multivessel disease and lesion severity)
- TIMI flow pre- and post-procedural

	Randomization	ICU stay	30 Days	3 Months	6 Months	1 Year
Eligibility criteria	X					
Demographics	X					
(sex, age, weight, height)						
Medical history	X					
(DM, HT, stroke, prior PCI/CABG, renal failure)						
OHCA prior to presentation	X					
(yes, no)						
ECG *(ST-segment elevation resolution)*	X	X				
Vitals	X					
(blood pressure and heart rate)						
CAG characteristics	X					
(LAD, RCX, RCA, Main stem, ((significant) stenosis, CTO, culprit, treated vessel))						
Hourly blood pressure and heart rate		X				
Laboratory testing	X	X				X
Hemodynamic parameters *(invasive hemodynamic measurements)*	X	X				
Use of vasoactive medication		X				
Renal replacement therapy		X				
Use of mechanical support		X				
Mechanical ventilation		X				
Protocol adherence		X				
Sedative medication		X				
Echocardiography		X				
Adverse events		X				
(arrhythmias, (suspected) infection, …)						
Neurological outcome			X			X
Resource utilization			X	X	X	X
(iMCQ+ iPCQ)						
Left ventricular ejection fraction (LVEF)		X				X
Quality of life						X
(SF-36 + EQ-5D-5L)						

Table 1.

7.1.3 Laboratory data

The following laboratory data, that are part of routine care unless stated otherwise, are entered into the eCRF(*for details, see table 2)*:

- Cardiac enzymes: serial measurements during the first 72 hours for hs-troponine T and CK-MB*.
- Lactate: will be measured at baseline, at 3 and 6 hours after randomization and with larger intervals hereafter.
- Creatinine: serial creatinine-levels during ICU / CCU stay, level at one year
- Other: C-reactive protein, glucose, hemoglobin, leukocytes, nt-proBNP* and blood urea nitrogen will be measured on admission and daily during ICU/CCU stay.

* Not part of routine care in every hospital

	T = 0 (ICU admission)	T = 3	T = 6	T = 12	T = 24	Day 2	Day 3	Day 4
Lactate	X	X	X	X	X	X	X	X
Hb	X				X	X	X	X
Leukocytes	X				X	X	X	X
CRP	X				X	X	X	X
Glucose	X							
Creatinin	X				X	X	X	X
Blood urea nitrogen	X				X	X	X	X
Liver function	X				X	X	X	X
Troponine T(hs)	X		X	X	X		X	
CK-MB	X		X	X	X		X	
Nt-proBNP	X					X		
Hourly blood pressure andheart rate for the first 24h	X	X	X	X	X			
Invasive haemodynamic measurements	X		X	X	X	X		
Urine production					X	X	X	X
Echocardiography							X	
ECG	X		X		X	X	X	X

Table 2.

7.1.4 Hemodynamic parameters

The following data on hemodynamics are entered into the eCRF

- Blood pressure and heart rate (hourly for the first 24 hours)
- Invasive hemodynamic measurements (every 8 hours during the first 48 hours)

7.1.5 Clinical data

The following information about clinical events is entered into the eCRF:

- Mortality (at 30 days, 1 year)
    - Cardiovascular
    - All-cause
- Severe renal failure requiring renal replacement therapy (at 30 days, 1 year)
- Length of ICU stay
- Length of hospital stay
- (Duration of) mechanical ventilation
- (Duration of) mechanical circulatory support
- Time to hemodynamic stabilization
- (Duration of) catecholamine therapy
- Vasoactive inotropic score
- Arrhythmias during admission
- Major vascular complication during admission (bleed or thrombo embolic event)
- Infection / sepsis during admission
- Myocardial re-infarction within 30 days
- Left ventricular ejection fraction (at 3 days, before hospital discharge and at 1 year)
- Neurological outcome (at 30 days and 1 year)
- Protocol adherence / use of bail-out therapy
- Hospital readmission for cardiac reason within 1 year

7.1.6 Cost-effectiveness

Data on quality of life is collected through questionnaires at 30 days, 3 months, 6 months and 1 year. This does not require a hospital visit.

8. STUDY ENDPOINTS

8.1 Primary endpoint

The primary endpoint of the study is the composite of all-cause mortality and severe renal failure requiring renal replacement therapy within 30 days after randomization.

8.2 Ranked secondary endpoints *(for definitions, see Appendix A)*

The ranked secondary endpoints are:

- All-cause mortality at 30 days
- Days alive and out of hospital (30 days)

8.3 Tertiary endpoints *(for definitions, see Appendix A)*

The tertiary endpoints are:

- Days alive and out of ICU (30 days)
- Cardiovascular death at 1 year
- Enzymatic infarct size
- Lactate clearance (mean + area under the curve 0-36 hours)
- Days alive and free of mechanical ventilation (30 days)
- Days alive and free of mechanical circulatory support (30 days)
- Severe renal failure requiring renal replacement therapy (at 30 days, 1 year)
- Renal function (during hospital stay and 1 year)
- Time to peak creatinine (hospital stay)
- Time to renal replacement therapy
- Days alive and free of catecholamine therapy (30 days)
- Vasoactive inotropic score (VIS) (during hospital stay)
- Time to hemodynamic stabilization (hospital stay)
- Blood pressure and heart rate during the first 24 hours
- Hemodynamic parameters (during ICU / CCU admission)
- Arrhythmias during hospital admission
- Major vascular complication during admission (bleed or thrombo embolic event)
- Infection / sepsis during hospital admission
- Myocardial re-infarction within 30 days
- Left ventricular ejection fraction (at day 3, before hospital discharge, and at 1 year)

- Neurological outcome (at 30 days and 1 year)
- Protocol adherence / use of bail-out therapy
- Hospital readmission for cardiac reason within 1 year

The cost-effectiveness endpoints are:

- Health-related quality of life based on the EQ-5D-5L questionnaire at 12 months
- Resource utilization based on iMTA Medical Consumption (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ) (at 30-day, 3-month, 6-month and 1-year follow-up)

9. STATISTICAL ANALYSIS

9.1 General methods

All descriptive statistical analyses are performed using SPSS statistical software (IBM Corp., Armonk NY, version 28.0 or higher), unless otherwise noted.
In general, continuous variables are summarized using descriptive statistics including means and standard deviations if normally distributed or median with interquartile ranges for skewed distributions. Discrete variables are summarized using absolute and relative frequencies. Demographic and baseline characteristics are summarized by randomized regimen group and for all randomized patients combined.

9.2 Main analysis of the primary endpoint and ranked secondary endpoints

The following hypotheses are tested in a hierarchical order, to preserve type I error rate:

1. A lower MAP-target regimen (≥ 55 mmHg) is non-inferior to the standard MAP-target regimen (MAP ≥ 65 mmHg) in terms of the primary endpoint of the composite of all-cause mortality and severe renal failure at 30 days.
2. A lower MAP-target regimen (≥ 55 mmHg) is superior to the standard MAP-target regimen (MAP ≥ 65 mmHg) in terms of the primary endpoint of the composite of all-cause mortality and severe renal failure at 30 days.
3. A lower MAP-target regimen (≥ 55 mmHg) is superior to the standard MAP-target regimen (MAP ≥ 65 mmHg) in terms of the first secondary endpoint of all-cause mortality at 30 days.
4. A lower MAP-target regimen (≥ 55 mmHg) is superior to the standard MAP-target regimen (MAP ≥ 65 mmHg) in terms of the second secondary endpoint of days alive and out of hospital at 30 days.

All analyses are performed on an intention-to-treat (ITT) basis. The ITT population consists of all subjects who have been randomized (i.e. when the subject number and allocated regimen are recorded in the electronic case report form (eCRF)). Patients are analysed in accordance with the randomized treatment assignment irrespective of the factual implementation of the assigned treatment regimen.

Rates of primary and first secondary endpoint are estimated as the cumulative incidence at 30 days after randomization by the Kaplan-Meier method. Rate differences are defined as the rate in the index group minus the rate in the reference group.

1. Non-inferiority of the lower MAP-target regimen in terms of combined all-cause mortality and severe renal failure at 30 days is declared if the upper limit of the 95% confidence interval (CI) of the rate difference excludes 10%. This is the equivalent of non-inferiority testing with a one-sided alpha of 0.025 with a non-inferiority limit of 10%.

2. Superiority of the lower MAP-target regimen in terms of combined all-cause mortality and severe renal failure at 30 days is declared if the 95% confidence interval (CI) of the rate difference excludes 0%. This is the equivalent of superiority testing with a 2-sided alpha of 0.05.

3. Superiority of the lower MAP-target regimen in terms of all-cause mortality at 30 days is declared if the 95% confidence interval (CI) of the rate difference excludes 0%. This is the equivalent of superiority testing with a 2-sided alpha of 0.05.

4. Superiority of the lower MAP-target regimen in terms of days alive and out of hospital at 30 days is declared if the two-sided p-value of the Mann-Whitney-U test applied to days alive and out of hospital at 30 days is lower than 0.05.

Details of the statistical analyses will be provided in the statistical analysis plan.

9.3 Determination of sample size

The rate of the primary endpoint in the reference group was estimated from the culprit-shock trial, where the event rate was 45.9%.[3] No other study ever tested the same intervention but from experimental myocardial infarction studies we have learned that the administration of noradrenaline is associated with infarct size expansion up to 22%.[12] Besides that, patients with high noradrenaline levels after myocardial infarction have a 4 times higher mortality rate compared with those without high noradrenaline levels.[13] On the basis of the much higher death rate and larger infarct size, we hypothesize that the event rate of the primary endpoint under the lower MAP-target regimen might be 10% lower than that under the standard MAP-target regimen. These assumptions form the basis for the sample size calculation for superiority testing of the primary endpoint. For non-inferiority testing we took a non-inferiority margin of 10%, equivalent to the inverse of the above mentioned treatment benefit.

We calculated that with 752 evaluable patients, the study has 80% power to show superiority of the lower MAP-target regimen (versus the standard MAP-target regimen) under the above mentioned design assumptions, with rates of the primary endpoint of 45.9% under the standard MAP-target regimen and of 35.9% under the lower MAP-target regimen.

We further calculated that with 752 evaluable patients, the study has 79% power to show non-inferiority of the lower MAP-target regimen (versus the standard MAP-target regimen) with a non-inferiority margin of 10% and event rates of the primary endpoint of 45.9% in both treatment regimens.

To allow for attrition rate of 3%, 776 (2 x 388) patients will be randomized.

Sample size calculation is made using PASS Sample Size Software, version 13.

9.4 Tertiary analyses

The statistical analyses of the tertiary endpoints will be described in the statistical analysis plan.

9.5 Subgroup analyses

Statistical analyses in subgroups are performed in line with previously stated methodology unless explicitly stated otherwise. Baseline characteristics that define subgroups of interest are:

- Sex (male, female)
- Age (<60, 60-75, >75)
- History of diabetes mellitus (yes, no)
- History of renal insufficiency (yes, no)
- History of hypertension (yes, no)
- Prior myocardial infarction (yes, no)
- Prior PCI or CABG (yes, no)
- Out of hospital cardiac arrest preceding current hospital admission (yes, no)
- Infarct related artery (left anterior descending, circumflex artery, right coronary artery)
- Multivessel disease (no, yes; 2 arteries, yes; 3 arteries)
- Initial blood pressure (per 5 mmHg MAP and 10 mmHg systolic blood pressure)
- Mechanical ventilation at randomization (yes, no)

- Timing of onset of cardiogenic shock (before PCI, after PCI)
- Type of acute myocardial infarction (NSTEMI vs STEMI)

9.6 Cost-effectiveness analyses

A separate statistical analysis plan will be created for the cost-effectiveness endpoints.

The economic evaluation is composed of both cost-effectiveness (CEA) and cost-utility (CUA) analyses from a societal perspective with a lifetime time horizon. The costs per patient alive without severe renal failure and the costs per QALY are the outcome parameters respectively. Health care costs, non-reimbursable health-related out-of-pocket expenses by patients and family members, and other costs of productivity loss due to sick leave or lower efficiency while at work due to disease are included and gathered with clinical report forms, and repetitive patient questionnaires during the first year of follow-up. The Medical Consumption Questionnaire and Productivity Costs Questionnaire will be used. EQ-5D-5L based health status scoring profiles is gathered and transposed into health utilities with existing Dutch scoring algorithms from www.eurogol.org. Incremental costs per additional patient alive without severe renal failure and per additional QALY will be quantified with uncertainty following sampling variability simulated by bias corrected and accelerated bootstrapping. Results are graphically represented by cost-effectiveness planes and cost-effectiveness acceptability curves for various willingness to pay values per extra patient alive without severe renal failure or per extra QALY. The CUA is performed in two steps. Firstly, an empirical, piggy-back CUA based on observed data during the 12 months of trial follow-up is done; secondly, a longer-term simple Markov state-transition model to project the lifetime course following CS after AMI is built and ran including successive health state reflecting progression: incident CS, stable post-CS, severe renal failure, and death. The model cycle length is set a 1 year with differential yearly discounting of costs (against 4%) and QALYs (against 1.5%) from model year 2 onwards. Yearly costs and QALY generated during successive disease stages are derived from the study itself as well as from cost analyses and health outcome data reported elsewhere.[14-19] In addition, a BIA is done, projecting the potential budgetary consequences of implementing a noradrenaline-reduced regimen by using a lower MAP-target to replace standard care pharmacologic strategy in CS for primarily the budgets of medical specialist care, rehabilitation center, and nursing homes. Scenarios for different realistic implementation rates are formulated and run in the final year of the study.

9.7 Interim analysis and safety reviews

Nor formal interim analysis for early claims of superiority of the lower MAP-target regimen over the standard MAP-target regimen will performed.

All analyses will be carried out with a view to protecting the safety of the trial participants. If the data at hand would precipitate a substantial safety concern about the lower MAP-target regimen, the DSMB will carefully balance the observed risk profile against possible signs of improved efficacy. The DSMB will seriously consider recommending early termination of the trial when the lower MAP-target regimen would show a statistically significant (two-sided p-value <0.05) increased rate of the primary endpoint or of all-cause death. The DSMB should only under exceptional circumstances recommend early termination of the trial for overwhelming evidence of efficacy of the lower MAP-target regimen over the standard MAP-target regimen, as this would compromise the scientific validity of the final analysis. The DSMB uses all available evidence and its collective judgement to base its recommendation to stop or modify the study.

Interim study reports with descriptive analysis and Kaplan-Meier curves with log-rank statistic for the primary composite endpoint are produced by an independent statistician for DSMB reports. *(Please see K5 DSMB charter.)*

10. SAFETY REPORTING

10.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study is suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

10.2 AEs and SAEs

10.2.1 Adverse events (AEs)

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

10.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

All SAE's that are part of the natural course of cardiogenic shock are not reported in *ToetsingOnline*. These expected serious adverse events are recorded in an overview list (line-listing) that will be submitted to the METC once every half year. The investigator will report all unexpected SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report unexpected SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other unexpected SAEs are reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

10.3 Follow-up of adverse events

All AEs are followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study, as defined in the protocol

11. ORGANIZATIONAL STRUCTURE

11.1 Clinical event committee

Clinical events that are part of the composite primary endpoint and the secondary endpoints are adjudicated by an independent clinical event committee (CEC). Members of the CEC are kept unaware of the regimen group assignments. If not stated otherwise, all analyses are based on findings as confirmed by the CEC.

11.2 Data Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) monitors the safety of patients throughout the study until end of trial on an ongoing basis. The composition, guiding policies, and operating procedures governing the DSMB are described in a separate DSMB charter. Based on safety data, the DSMB may recommend that the steering committee modify or stop the clinical trial. All final decisions regarding clinical trial modifications, however, rest with the steering committee.

11.3 Steering committee

The steering committee is the main policy and decision-making committee of the study and has final responsibility for the scientific conduct of the study.
The specific tasks of the steering committee are to (1) approve the study protocol; (2) approve amendments to the protocol; (3) establish the organizational structure; (4) select the members of the various committees; (5) review the activities of the study committees and change these committees if found necessary; (6) act upon recommendations of the DSMB and (7) approve study reports and papers for publication.
The steering committee meets at the request of the principal investigator and/or the DSMB. Composition of the steering committee can be found at the top of the protocol.

12. ETHICAL CONSIDERATIONS

12.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013), in accordance with the Medical Reseach Involving Human Subjects Act (WMO) and the statements of the CCMO as presented in a publication by E.J.O. Kompanje.[20]

12.2 Recruitment and consent

Due to the nature of this study population being in imminent danger for death, and the patients often being unconscious, it is not possible to ask the patient or relatives for informed consent before randomization. Therefore, as in previous studies conducted in this population, we will use a ‘’deferred consent’’ approach. Patients are randomized directly after eligibility has been confirmed. The relatives are informed of the randomization as soon as reasonably possible, by a trained intensive care doctor and/or medical researcher. Consent is asked for continuation of the treatment according to the study protocol. Patients are asked for informed consent when he/she is recovered enough to make a decision. If a patient dies before informed consent of the legal representative has been obtained, data collected during the study may be used without consent. The information and informed consent process and materials are established together with Harteraad (patient and relative association).

12.3 Benefits and risks assessment, group relatedness

The administration of noradrenaline to raise the mean arterial pressure, is part of standard care in CS patients. It has however never been established whether higher MAP levels actually lead to better end-organ perfusion whereas we do know that noradrenaline can cause side effects such as arrhythmias. By using a lower MAP-target and decreasing noradrenaline use, patients could experience less side effects. The risk and burden for the subject are therefore acceptable in light of the potential benefit.

12.4 Compensation for injury

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

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

12.5 Incentives

Participants will may receive less noradrenaline, depending on their allocated regimen, which potentially leads to better outcome. At the time of inclusion, patients are severely ill and the medical staff will decide whether the patient will be included in this study. This potential treatment benefit will thus not be an incentive for participating. Participants will not receive any incentive or benefit for participating nor will they be exposed to more follow-up visits or additional diagnostics.

13. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

13.1 Handling and storage of data and documents

To protect the privacy of all participants, all collected data are encoded and only authorized study personnel will have access to the encoding key and the acquired data. The encoding key will not be based on the patients initials and birth-date. All subject data is kept for 15 years and handling will comply with the Dutch Act on Implementation of the General Data Protection Regulation. The Dutch health inspectorate (*Inspectie Gezondheidszorg en Jeugd)* (IGJ) and monitor will have access to this data.

13.2 Monitoring and Quality Assurance

The Clinical Research Unit of the Amsterdam UMC, location AMC, is responsible for the monitoring of the trial. Trial monitors are appointed to monitor the progress of the trial on site, as frequently as seen fit. During these site visits, the eCRF and related records are checked for completeness and consistency.

13.3 Amendments

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

Non-substantial amendments are not notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

13.4 Annual progress report

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

13.5 Temporary halt and (prematurely) end of study report

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

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

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

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

13.6 Public disclosure and publication policy

The principal investigator is entitled to disseminate the findings of the trial via publications in reputable scientific journals and via presentations at seminars or scientific conferences. The principal Investigator carries final responsibility for the scientific content of the publication on the main findings of the trial. A writing group is designated to prepare a first draft, which is submitted for advice to the investigators. The principal investigator is the first or last authors of the paper on the main results of the trial. Those who have actively participated in the preparation of the manuscript are identified as such.

14. STRUCTURED RISK ANALYSIS

14.1 Potential issues of concern

The products used during the trial will be used within indication and not in combination with other products. This chapter is therefore not applicable.

14.2 Synthesis

Patients with cardiogenic shock after myocardial infarction have a poor prognosis with high mortality rates. To date, only early revascularization is of proven benefit in these patients. The first-line pharmacologic strategy in CS is noradrenaline: a vasopressor drug that increases blood pressure. It has however never been proven that medically induced increase in blood pressure leads to greater myocardial and other end-organ blood flow. As a matter of fact, its vasoconstrictive properties reduce flow to the microcirculation of organs. Besides that, noradrenaline is associated with adverse events such as (supra-) ventricular arrhythmias which also increases myocardial oxygen demand and reduces the efficacy of the myocardial pumping function. While withholding noradrenaline initially seems controversial, it may substantially increase the chances of survival and maintaining good renal function. In order to guarantee safety, a flow-chart for bail out therapy will be provided for special cases. Besides that, a DSMB will be established to periodically review and monitor study data on participant safety, study conduct, progress and efficacy. This committee will make recommendations on the continuation, modification of termination of the trial, if needed. We consider the risk and burden for the subject acceptable in light of the potential benefit.

15. REFERENCES

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Appendix A – DEFINITIONS

Medical history	
Type	Definition
Diabetes Mellitus	Diabetes mellitus diagnosed prior to intervention is characterized by chronic hyperglycemia with at least one of the following: • Fasting plasma glucose ≥ 7.0 mmol/l (≥ 126 mg/dl) • Plasma glucose ≥ 11.1 mmol/l (≥ 200 mg/dl) two hours after the intake of 75g oral glucose (glucose tolerance test) • Symptom of hyperglycaemia and casually measured plasma glucose ≥ 11.1 mmol/l (≥ 200 mg/dl) • Glycosylated hemoglobin (HbA1c) ≥ 6.5%
Hypertension	Persistent elevation of systolic or diastolic blood pressure above 140/90 mmHg or for which medication is being used.
Chronic kidney disease	Either of the following present for > 3 months: • Glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 • Markers of kidney damage (one or more of: albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, history of kidney transplantation)
Dialysis	Hemodialysis or peritoneal dialysis for renal failure on a continuous basis at the time of the admission for the current intervention.
Prior stroke	An acute symptomatic episode of neurological dysfunction, more than 24 hours in duration in the absence of therapeutic intervention or death, due to cerebral, spinal of retinal tissue injury as evidenced by neuroimaging or lumbar puncture.
Prior PCI	Patient has undergone a previous PCI or PCI combined with another procedure prior to the current intervention.
Prior CABG	Patient has undergone prior coronary artery bypass grafting (CABG) or CABG combined with other procedure prior to current intervention.

TIMI-flow	
Type	Definition
0	Complete occlusion of the infarct-related artery
1	Some penetration of the contrast material beyond the point of obstruction but without perfusion of the distal coronary bed
2	Perfusion of the entire infarct vessel into the distal bed but with delayed flow compared with a normal artery
3	Full perfusion of the infarct vessel with normal flow

ST-segment elevation resolution 1 hour after reperfusion	
Type	Definition
Normalized	No residual ST-segment elevation of 0.1 mV or more in any of the 12 leads (complete ST-segment resolution)
Improved	Residual ST-segment-elevation of less than 70% of that on the first ECG (partial ST-segment resolution);
Unchanged	Residual ST-segment elevation of 70% or more of that on the first ECG (no ST-segment elevation resolution)

Classification of death (ARC-2 definition)	
Type	Definition
Cardiovascular death	Death resulting from cardiovascular causes. The following categories may be collected: • Death caused by acute myocardial infarction • Death caused by sudden cardiac, including unwitnessed, death • Death resulting from heart failure • Death caused by stroke • Death caused by cardiovascular procedures • Death resulting from cardiovascular hemorrhage • Death resulting from other cardiovascular cause
Non-cardiovascular death	Death that is not thought to be the result of a cardiovascular cause. The following categories may be collected: • Death resulting from malignancy • Death resulting from pulmonary causes • Death caused by infection (includes sepsis) • Death resulting from gastrointestinal causes • Death resulting from accident/trauma • Death caused by other non-cardiovascular organ failure Death resulting from other non-cardiovascular cause
Undetermined	Undetermined cause of death is defined as a death not attributable to any other category because of the absence of any relevant source documents. Such deaths will be classified as cardiovascular for end point determination.

Renal failure requiring renal replacement therapy
Any indication for renal replacement therapy (both temporary and permanent) such as dialysis, hemofiltration of hemodiafiltration such as renal failure with one of the following criteria: • Otherwise untreatable volume overload • Hyperpotassemia • Severe uremia • Persistent severe metabolic acidosis

Enzymatic infarct size	
Type	Definition
Peak-value	Highest levels of hs-troponin-T (hs-cTnT) (ng/l) and creatinine-kinase myocardial band (CK-MB) (µg/L) as measured during the index admission and within 3 days after the PCI.
Area under the curve	Area under the curve until 72 hours for hs-troponin-T (hs-cTnT) (ng/l) and creatinine-kinase myocardial band (CK-MB). Missing data from patients who died before 72 hours will be imputed according to the worst case scenario (i.e., the missing value will be replaced with the highest hs-cTnT / CK-MB in the corresponding treatment group).

Lactate clearance
Mean value and area under the curve until 36 hours, in mmol/L.

Days alive and out of hospital (DAOH)
Number of days that a patient spends alive and out of hospital from randomization to 30 days. Calculated by subtracting days in hospital from 30 days for every patient that leaves the hospital alive. If a patient deceases during hospital stay, the DAOH is zero. If a patient dies after hospital discharge, the number of days from their

death to 30 days is counted.

Days alive and out of ICU
Number of days that a patient spends alive and out of the ICU from randomization to 30 days. Calculated by subtracting days in ICU from 30 days for every patient that leaves the ICU alive. If a patient deceases during ICU stay, the *days alive and out of ICU* is zero. If a patient dies after ICU discharge, the number of days from their death to 30 days is counted.

Days alive and free of mechanical ventilation
Counted as 30 days minus the amount of days that a patient was mechanically ventilated. These days are counted as the difference between start date of mechanical ventilation and the date of discontinuation. If a patient was ventilated during more than one episode, the total number of days counts. If a patient dies after discontinuation of mechanical ventilation, but before 30 days, the amount of days between their death and 30 days, are also subtracted from 30.

Days alive and free of mechanical circulatory support (MCS)
Counted as 30 days minus the amount of days that a patient received any form of MCS (IABP, Impella, ECMO, LVAD). These days are counted as the difference between start date of mechanical ventilation and the date of discontinuation. If a patient was ventilated during more than one episode, the total number of days counts. If a patient dies after discontinuation of mechanical ventilation, but before 30 days, the amount of days between their death and 30 days, are also subtracted from 30.

Renal function at during hospital stay and at 1 year
Measured by creatinine (µmol/L) and expressed as estimated glomerular filtration rate (eGFR).

Time to renal replacement therapy
Time to initiation of renal replacement therapy expressed in days from randomization.

Time to peak creatinine
Time to highest creatinine-level (µmol/L) during hospitalization expressed in days from randomization.

Days alive and free of catecholamine therapy
Counted as 30 days minus the amount of days that a patient received any type of catecholamine. These days are counted as the difference between start date of catecholamine therapy and the date of discontinuation. If a patient received catecholamine therapy during more than one episode, the total number of days counts. If a patient dies after discontinuation of catecholamine therapy, but before 30 days, the amount of days between their death and 30 days, are also subtracted from 30.

Time to hemodynamic stabilization
Earliest time by which the patient is hemodynamically stable and receives no catecholamine therapy, expressed in amount of days, counted from randomization.

Blood pressure and heart rate
As measured by (non-)invasive hemodynamic monitoring, reported hourly.

Hemodynamic parameters
Cardiac index (L/min/m^2), pulmonary capillary wedge pressure (mmHg), right atrial pressure (mmHg), pulmonary artery pressure (mmHg) and pulmonary artery pulsatility index every 8 hours during the first 48 hours of admission.

Arrhythmias during admission	
Type	Definition
Atrial	Atrial flutter, tachycardia or fibrillation
Ventricular	Monomorphic or polymorphic VT greater than 30 seconds or hemodynamically unstable ventricular arrhythmia requiring intervention, or VF.

Vasoactive inotropic score
Dopamine sode (µg/kg/min) + Dobutamine dose (µg/kg/min) + 100 x Epinephrine dose (µg/kg/min) + 10 x milrinone dose (µg/kg/min) + 10.000 x vasopressin dose (U/kg/min) + 100 x norepinephrine dose (µg/kg/min)

Ischemic complication during admission	
Type	Definition
Acute limb ischemia	
Rutherford I	Limb viable, not immediately threatened
Rutherford IIa	Limb marginally threatened, salvageable if promptly treated
Rutherford IIb	Limb immediately threatened, salvageable with immediate revascularization
Rutherford III	Limb irreversibly damaged, major tissue loss or permanent nerve damage inevitable
Mesenteric ischemia	As proven by mesenteric angiography, CT angiography, pathology or based on high clinical suspicion. (Suspicion might arise in critically ill patients with abdominal pain or distension requiring vasopressor support and evidence of multi-organ dysfunction.)

Thromboembolic event during admission
Deep venous thrombosis, pulmonary embolism, cerebrovascular event.

Major bleed during admission	
Major bleed	
BARC 2	Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone)

	that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: • requiring nonsurgical, medical intervention by a health-care professional, • leading to hospitalization or increased level of care, or prompting evaluation
BARC 3	Clinical, laboratory and/or imaging evidence of bleeding with specific healthcare provider responses as listed below:
3a	• Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL* (provided hemoglobin drop is related to bleed) • Any transfusion with overt bleeding
3b	• Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed), • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) • Bleeding requiring intravenous vasoactive agents
3c	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
BARC 4	CABG-related bleeding • Perioperative intracranial bleeding within 48 h. • Reoperation after closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period • Chest tube output more than or equal to 2L within a 24-h period
BARC 5	Fatal bleeding
5a	Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Infection / sepsis during admission
Culture proven or for which antibiotics have been started because of high suspicion.

Myocardial re-infarction within 30 days
Acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile upper reference limit and at least one of the following: • Symptoms of myocardial ischemia • New ischemic ECG changes • Development of pathological Q waves • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology Identification of a coronary thrombus by angiography or autopsy

Left ventricular ejection fraction
The fraction of chamber volume ejected in systole (stroke volume) in relation to the volume of the blood in the

ventricle at the end of diastole (end-diastolic volume), measured by echocardiography, magnetic resonance imaging (MRI) or computed tomography (CT).

Neurological outcome, measured by Modified Rankin Scale, at 30 days and 1 year	
Type	Definition
MRS 0	No symptoms
MRS 1	No significant disability. Able to carry out all usual activities, despite some symptoms
MRS 2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
MRS 3	Moderate disability. Requires some help, but able to walk unassisted.
MRS 4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
MRS 5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
MRS 6	Dead

Protocol adherence
Whether or not cross-over took place for patients who were randomized to the interventional arm.

Hospital readmission for cardiac reason within 1 year
Unscheduled hospital admission (for at least one night after discharge from the initial hospitalization) for a primary cardiac diagnosis with a length of stay that either exceeds 24 hours or crosses a calendar day after discharge from the initial hospitalization.