Early initiated vasopressor therapy vs. standard care of primarily fluid therapy in hypotensive patients in the emergency department – A pragmatic, multi-center, superiority, randomized controlled trial

Acronym: VASOSHOCK

Statistical Analysis Protocol (SAP)
Version 1.0 (15.06.2025)

EU CT identification: 2023-504584-16-00
Clinicaltrials.gov identification: NCT05931601

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Section 1: Administrative Information

This SAP follows the structure suggested by Gamble et al.[1]

Title and trial registration

1a Descriptive title that matches the protocol, with SAP either as a forerunner or subtitle, and trial acronym (if applicable):

Early initiated vasopressor therapy vs. standard care of primarily fluid therapy in hypotensive patients in the emergency department – A pragmatic, multi-center, superiority, randomized controlled trial

Acronym: VASOSHOCK

Statistical Analysis Protocol (SAP)

1b Trial registration number:
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SAP version

2 SAP version number with dates

Version 1.0 (15.06.2025)

Protocol version

3 Reference to version of protocol being used

TRIAL PROTOCOL

Version 2.1

09-12-2025

SAP revisions

4a SAP revision history

No revisions yet

4b Justification for each SAP revision

NA

4c Timing of SAP revisions in relation to interim analyses, etc

NA

Roles and responsibility

5 Names, affiliations, and roles of SAP contributors

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6a Person writing the SAP

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Section 2: Introduction

Background and rationale

From the trial protocol:

Shock is a common occurrence in Danish Emergency Departments (ED)[2] and decreases tissue perfusion while inducing cellular damage and metabolic changes, possibly leading to death[3]. Hypotension, a key component of shock, in the ED is associated with in-hospital mortality of 12% and even higher (33-52%) if identified in the pre-hospital setting.[4] Fluid resuscitation is the most widespread general use for resuscitation of patients with shock,[5,6] but can vary substantially in patients treated in Danish ED's.[7] This is problematic, as liberal fluid resuscitation, such as more than 5 litres over a short period of time, may cause harm[8-11]. When fluid therapy fails, the next step is the initiation of vasopressors such as noradrenaline[12-22]. Noradrenaline applies a primary action on α-receptors in the blood vessels and partly β-receptors in the heart muscle increasing blood pressure and organ perfusion.[23]

Initiation of peripheral noradrenaline has previously been thought harmful, but newer trials show high safety if handled correctly, while also showing positive outcomes for patients when started early. [13,14,16-22,24-29] In contrast, a delayed vasopressor initiation is associated with increased mortality, even after the first hour of resuscitation.[20] The peripheral administration of noradrenaline provides a shorter time to first infusion, with no increased mortality risk, while still showing a miniscule risk of adverse effects. [12,13,18,21,22,29-31].

This study will provide evidence if early initiated vasopressor therapy can decrease to time for achieving shock control and subsequentially improve outcomes, such as avoiding ICU admission or reduce length of stay, for some of the most critically ill patients in the Danish ED setting.

Aim:

The aim is to investigate whether the use of early initiated vasopressor therapy (i.e., noradrenaline) compared to fluid therapy alone in non-bleeding hypotensive patients presenting in the ED can improve time to shock control and by that, reduce the need for ICU admittance.

Section 3: Study Methods

Trial design

This study will be a pragmatic,[32,33] multi-center, superiority, randomized controlled trial, randomizing patients 1:1 to either the intervention group (early vasopressors in the ED) or control group (standard care in the ED).

Adult hypotensive patients who received at least 500ml crystalloid prior to screening will be assessed for eligibility.

The intervention group will receive peripheral infusion of noradrenaline with a starting dose of 0.05 mcg/kg/min and titrated up to a maximum dose of 0.15 mcg/kg/min for up to 24 hours after inclusion.

The standard care group will receive standard care according to local guidelines.

All other treatment considerations are handled at the discretion of the clinical team.

Randomization

Patients are randomized in a 1:1 ratio using block randomization by random size of 2, 4, 6 or 8, stratified by trial site. Randomization will be conducted using the web-based randomization system provided in REDCap to ensure allocation concealment.[34]

Sample size

Described in the protocol.

Framework

The trial is a superiority trial.

Statistical interim analyses and stopping guidance

13a Information on interim analyses specifying what interim analyses will be carried out and listing of time points

No interim analyses are planned

13b Any planned adjustment of the significance level due to interim analysis

No interim analyses are planned

13c Details of guidelines for stopping the trial early

No interim analyses are planned

Timing of final analysis

All analysis will be conducted for all participants when the 30-day follow-up is completed. For the long-term follow-up, this will be conducted after all participants have been assessed for 1-year follow-up and data for this is collected for patients not lost to follow-up.

Timing of outcome assessments

All data handled during the intervention period is collected at bedside by the clinical staff.

Follow-up data is collected after at least 72-hours and 30-days for the patients.

Consent for participation is collected from the participants, next of kin (of applicable) and the legal guardian as soon as possible after inclusion. In addition, the EQ-5D-5L interview is also collected at this point.

The long-term follow-up data is collected as close as possible to, and at least, 1 year after inclusion.

Outcome assessment times are presented in Table 1:

Table 1: Data collection time points during the trial

	Screening	Baseline	24-hours	72-hours	30-days
Time period	Day -2 to 0	-	1	3	30
Consent		X	X	X	X
Randomisation	X				
Fluid therapy	X		X		
Vital parameters	X	X	X		
Vasopressor therapy			X		X
SOFA-score at ED arrival		X		(X)	
Acid-base values				X	
ED LOS				X	
AE/SAE			X	X	
Acute Kidney Injury		X	X	X	
Pulmonary Oedema		X	X	X	
Infection sources		X	X	X	X
ICU admission and LOS					X
Hospital LOS					X
Dialysis					X
Non-invasive ventilation					X
Invasive ventilation					X
Mortality					X
Readmission					X

Section 4: Statistical Principles

Confidence intervals and *P* values

16 Level of statistical significance
We consider a p-value of < 0.05 statistically significant.

17 Description and rationale for any adjustment for multiplicity and, if so, detailing how the type 1 error is to be controlled
We will not perform any adjustment for multiplicity

18 Confidence intervals to be reported
We will report 95%CI for all outcomes as specified in section 6.

Adherence and protocol deviations

19a Definition of adherence to the intervention and how this is assessed including extent of exposure
Adherence to the intervention is only considered in the intervention group. Received noradrenaline from the trial during the ED admittance, or department also participating in the trial, will be considered fulfilment of the intervention. The extent of exposure is initiation of noradrenaline at any duration.

The control group receives standard care, and the trial imposes no intervention in this group.

19b Description of how adherence to the intervention will be presented
Exploratory outcomes include any vasopressor treatment at any point within 24 hours, where initiation of the intervention in the intervention group will be presented in this outcome.
The adherence will also be presented in the CONSORT diagram (See Appendix 1: CONSORT diagram draft).

19c Definition of protocol deviations for the trial
Protocol deviations are any deviation of the described trial design in the trial protocol, section 3. This can include: Using other infusion routes than mandated by the trial, not adhering to patient monitoring requirements, treating with noradrenaline past 24-hours post-inclusion and so on.

19d Description of which protocol deviations will be summarized
Protocol deviations will be presented with description of number of protocol deviations were reported, including specification of number of patients receiving noradrenaline past 24-hours or at higher doses than allowed.

Analysis populations

20 Definition of analysis populations, eg, intention to treat, per protocol, complete case, safety
The trial is analyzed as an intention-to-treat approach for all outcomes in the main analysis. Additional analysis, including safety outcomes are described in

Section 6: Analysis.

Section 5: Trial Population

Screening data

All screening data will be presented in text and a trial CONSORT flow-chart. A draft flow-chart can be seen in the appendix.

Eligibility

Inclusion criteria:

1. At least 18 years of age
2. Signs or suspicion of hypotension or shock (of any type such as septic, vasodilatory or hypovolemic not included in the exclusion criteria) defined as:
    a. SBP < 100mmHg or MAP < 65 mmHg combined with lactate > 2.0 mmol/L,
    b. Physician defined blood pressure for the individual patient combined with a lactate > 2.0 mmol/L
    c. Either SBP < 100mmHg or MAP < 65mmHg with obvious signs of shock with any lactate level evaluated by either two non-specialist physicians (e.g. registrar medical doctors) or one specialist physician.
3. Received at least 500ml of intravenous fluid before study inclusion (Including prehospital administration)
4. Clinical Frailty Score (CFS) of ≤4. If CFS is ≥5 and the treating physician find the patient suitable for ICU admittance, the participant can be enrolled, if the on-call ICU doctor would accept the patient for ICU admittance. If the treating physician is unsure of ICU eligibility, regardless of CFS score, the patient should be consulted with the ICU consultant before study inclusion.

Exclusion criteria:

1. Cardiogenic, anaphylactic, haemorrhagic, or neurogenic shock suspected by the treating physician.
2. Fertile women (<60 years of age) with positive urine human gonadotropin (hCG) or plasma-hCG or women breastfeeding
3. Patient deemed terminally ill or with a severe co-morbid status resulting in non-eligibility for ICU admittance decided by either the treating physician or ICU consultant.
4. Severe organ failure outside circulatory failure that requires immediate ICU admission.
5. Known allergy to noradrenaline.

6. Previously enrolled in the trial

Recruitment

For a draft CONSORT diagram see appendix 1.

Withdrawal/follow-up

Participants in the trial can have the intervention terminated before full conclusion of the treatment period. This can include fully termination of participation in the clinical trial including data collection and usage as defined in section 9 and 10.4.4 in the trial protocol. This is considered in the following situations:

1. The patient or their legally designated representative withdraws their consent to participate prior to completing the necessary intervention.
2. The patients next of kin, for countries where consent can be partly obtained from these, withdraws the consent for the patient to participate prior to completing the necessary intervention. This is only possible, if the patient are yet to provide consent for participation.
3. The investigator for safety reasons finds it of best interest of the patient.

In case of early termination of the trial participation and therefore treatment, the clinical staff and investigators must take appropriate steps to ensure the patients treatment and stability of their disease process during early weaning of noradrenaline. This can include quick transfer to the ICU for further treatment of their condition.

Early termination of treatment should be clearly noted, including reason for early termination, in the paper CRF for the patient.

Patients already included, and having consented, to trial participation are expected to complete follow-up, unless they die within the follow-up period.

Baseline patient characteristics

Baseline characteristics will be descriptively summarized as proportions (%), mean (SD), median (IQR). Baseline characteristics will not be statistically compared between randomization groups as recommended by CONSORT.[35]

The following baseline characteristics will be summarized:

Baseline characteristics will be presented descriptively. No statistical comparisons are carried out for these variables. Expected baseline characteristics are presented in Table 2:

Table 2: Draft of table for baseline characteristics

		Randomization	
Characteristic	**Overall** N =	**Early ED vasopressor** N =	**Standard Care** N =
Sex			
Age, years			
Height, cm			
Weight, kg			
Body Mass Index, kg/m2			
SBP at ED arrival, mmHg			
DBP at ED arrival, mmHg			
MAP at ED arrival, mmHg			
Pulse at ED arrival, /min			
SI at ED arrival			
<0.7			
0.7-0.9			
>1			
Respiratory rate at ED arrival, /min			
Oxygen saturation at ED arrival, %			
GCS at ED arrival			
Temperature at ED arrival, Celcius			
SOFA-score at ED arrival			
Fluid therapy before inclusion, mL			
Lactate at inclusion, mmol/L			
<2			
≥2 to <4			
≥4			
SBP at inclusion, mmHg			
DBP at inclusion, mmHg			
MAP at inclusion, mmHg			
Infection			
Respiratory			
Intra-abdominal			
Urinary			
Skin and soft tissue			
Blood			
Other			
Unknown Source			
Comorbidities			
0			
1-2			
3+			

Section 6: Analysis

Outcome definitions: List and describe each primary and secondary outcome including details of:

26a specification of outcomes and timings. If applicable include the order of importance of primary or key secondary end points (eg, order in which they will be tested):

Primary outcome: The primary outcome is the proportion of patients achieving either SBP >100 mmHg or MAP > 65 mmHg or a target blood pressure set by the treating physician at 90 (±15) minutes after inclusion.

Secondary outcome A: Number of ICU free days alive within 30 days

Secondary outcome B: Time without shock within 24 hours

Secondary outcome C: 30-day all-cause mortality.

Secondary outcome D: In-hospital all-cause mortality

Tertiary outcome A: Proportion of patients receiving vasopressor at any point within 24 hours.

Tertiary outcome B: Time to vasopressor initiation during hospitalization

Tertiary outcome C: Hours of vasopressor infusion during hospitalization

Tertiary outcome D: Re-admission for any reason within 30 days of inclusion

Tertiary outcome E: ED length of stay

Tertiary outcome F: Proportion of patients admitted to the ICU during hospitalization

Tertiary outcome G: ICU length of stay

Tertiary outcome H: Hospital length of stay

Tertiary outcome I: Need for mechanical ventilation (either invasive or non-invasive ventilation) within 30-days

Tertiary outcome J: Need for renal replacement therapy (continuous renal replacement therapy or dialysis) within 30-days

Tertiary Outcome K: Organ support-free days within 30 days (defined as mechanical ventilation, vasopressor or inotropic therapy, or dialysis)

Tertiary outcome L: Amount of fluid therapy received within the first 24 hours

Safety outcome A: Proportion of patients developing pulmonary oedema within 72 hours (Diagnosed by physician in accordance with local guidelines, e.g., clinical decision including evaluation with paraclinical imaging such as x-ray or lung ultrasound).

Safety outcome B: Proportion of patients developing acute kidney injury within 72 hours (Defined as an absolute increase of creatinine ≥26.5µmol/L or ≥1.5 fold from baseline)

Safety outcome C: Proportion of patients experiencing extravasation of peripheral noradrenaline

Safety outcome D: Proportion of patients having serious complications due to extravasation (Defined as a serious complication fulfilling the criteria for a serious adverse reaction, e.g. skin necrosis necessitating surgical intervention)

Safety outcome E: Proportion of patients experiencing overdosing due to noradrenaline infusion in the trial (Defined as severe hypertension, and reflex bradycardia suspected by the staff or investigators)

Safety outcome F: Proportion of patients experiencing any SAE, SAR or SUSAR related to the trial intervention or procedures registered during the trial

26b specific measurement and units (eg, glucose control, hbA$_{1c}$ [mmol/mol or %])

Measurement units are specified in the protocol available through CTIS under registration 2023-504584-16-00 and codebook (Appendix).

26c any calculation or transformation used to derive the outcome (eg, change from baseline, QoL score, time to event, logarithm, etc)

Outcomes that will assess time periods will need to be calculated. This includes, but not limited to, time without shock within 24-hours and number of ICU free days alive within 30 days.

MAP calculations will be performed in the event of missing from the dataset. MAP is not registered as standard if blood pressure targets are entered in the electronic health record. This includes calculation of MAP at ED arrival/triage, which will always be missing. If MAP is present from direct data capture in the trial, this MAP takes precedence and MAP will not be calculated for that registration. All MAP values will be calculated according to the description in section 28: Missing data.

Analysis methods

27a what analysis method will be used and how the treatment effects will be presented

Primary outcome: The primary outcome is the proportion of patients achieving either SBP >100 mmHg or MAP > 65 mmHg or a target blood pressure set by the treating physician at 90 (±15) minutes after inclusion.

The outcome will be reported as proportions with 95% confidence intervals (CIs) for both arms, and compared by estimating a relative risk (RR) with 95% CIs and p-value by logistic regression followed by prediction of risk via G-computation.

RR and associated 95%CI will be estimated using non-parametric bootstrapping.

Secondary outcome A: Number of ICU free days alive within 30 days

The outcome will be reported as means and mean difference between groups with 95% confidence intervals and compared by linear regression. To take into account the expected non-normality of data, confidence intervals and p-values will be determined by non-parametric bootstrapping.

Secondary outcome B: Time without shock within 24 hours

Secondary outcome C: 30-day all-cause mortality.

Secondary outcome D: In-hospital all-cause mortality

These outcome will be reported as proportions with 95% confidence intervals (CIs) for both arms, and compared by estimating a relative risk (RR) with 95% CIs and p-value by logistic regression followed by prediction of risk via G-computation.

RR and associated 95%CI will be estimated using non-parametric bootstrapping.

Tertiary outcome A: Proportion of patients receiving vasopressor at any point within 24 hours.

Tertiary outcome D: Re-admission for any reason within 30 days of inclusion

Tertiary outcome F: Proportion of patients admitted to the ICU during hospitalization

Tertiary outcome I: Need for mechanical ventilation (either invasive or non-invasive ventilation) within 30-days

Tertiary outcome J: Need for renal replacement therapy (continuous renal replacement therapy or dialysis) within 30-days

These outcome will be reported as proportions with 95% confidence intervals (CIs) for both arms, and compared by estimating a relative risk (RR) with 95% CIs and p-value by logistic regression followed by prediction of risk via G-computation.

RR and associated 95%CI will be estimated using non-parametric bootstrapping.

Tertiary outcome B: Time to vasopressor initiation during hospitalization

Tertiary outcome C: Hours of vasopressor infusion during hospitalization

Tertiary outcome F: Lactate level at study entry

Tertiary outcome I: ED length of stay

Tertiary outcome G: ICU length of stay

Tertiary outcome H: Hospital length of stay

Tertiary Outcome K: Organ support-free days within 30 days (defined as mechanical ventilation, vasopressor or inotropic therapy, or dialysis)

Tertiary outcome L: Amount of fluid therapy received within the first 24 hours

These outcomes will be reported as means and mean difference between groups with 95% confidence intervals and compared by linear regression. To take into account the expected non-normality of data, confidence intervals and p-values will be determined by non-parametric bootstrapping.

Safety outcome A: Proportion of patients developing pulmonary oedema within 72 hours (Diagnosed by physician in accordance with local guidelines, e.g., clinical decision including evaluation with paraclinical imaging such as x-ray or lung ultrasound).

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Safety outcome E: Proportion of patients experiencing overdosing due to noradrenaline infusion in the trial (Defined as severe hypertension, and reflex bradycardia suspected by the staff or investigators)

Safety outcome F: Proportion of patients experiencing any SAE, SAR or SUSAR related to the trial intervention or procedures registered during the trial

These outcomes will be reported as proportions with 95% confidence intervals (CIs) for both arms, and compared by estimating a relative risk (RR) with 95% CIs and p-value by logistic regression followed by prediction of risk via G-computation.

RR and associated 95%CI will be estimated using non-parametric bootstrapping.

27b any adjustment for covariates

All parameters in the main analysis will be adjusted for baseline covariates of age (divided in age groups of 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+), lactate at inclusion (<2, ≥2 - <4, ≥4) and trial site.

27c methods used for assumptions to be checked for statistical methods

Distributional assumptions on bootstraps and G-computation will be investigated by quantile-quantile plots.

27d details of alternative methods to be used if distributional assumptions do not hold, eg, normality, proportional hazards, etc

If bootstrapping of linear regression deviates markedly from distributional assumption, a quantile regression estimating the median, and median differences instead of mean and mean differences will be performed.

27e any planned sensitivity analyses for each outcome where applicable

All outcomes will be reanalyzed as a per-protocol analysis.

Due to the nature of the pragmatic trial design, only participants in the intervention group not receiving vasopressors in the ED are expected to influence the analysis groups in the per-protocol analysis. All standard care groups are expected to receive standard care.

27f any planned subgroup analyses for each outcome including how subgroups are defined

The substudies will be analysed including only those participants included in each substudy. Details on substudies are not part of this SAP.

No additional subgroup analyses are planned.

Missing data

28 Reporting and assumptions/statistical methods to handle missing data (e.g., multiple imputation)

Missing data will be reported in all relevant publications. We do not expect missing data regarding the primary outcome of the trial or key secondary outcomes. We do expect some missing data in the variables for calculating some outcomes, including the secondary outcomes, as well as missing data or loss to follow-up for the long-term outcomes in the trial. We do not expect missing data for AE or SAE.

No imputation or weighting of missing data is planned, as only a small number of missing data is expected with the following exception:

MAP values are not always registered as part of the electronic health records, as the standard is to register systolic and diastolic blood pressure, unless patients are monitored in the intensive care unit. This provides a potential substantial number of missing MAP values, especially for patients who are not receiving the intervention in the intervention group at the time of measurement, or patients who are not admitted to the ICU. For non-invasive measurements, the measured MAP values can be imprecise, especially in the event of hypotension, due to how the measurement method obtains the blood pressure values. It can therefore overestimate parameters.

We will perform imputation of missing MAP values, if the MAP is missing but systolic (SBP) and diastolic blood pressure (DBP) are present, for all timepoints during the trial. Imputation will be performed using predictive mean matching. A maximum value of each blood pressure measurement at each specific timepoint will initially be calculated using the standard formula for calculating MAP using Systolic (SBP) and Diastolic Blood Pressure (DBP):

$$MAP = \frac{2 * DBP + SBP}{3}$$

If the imputed measurement is above this calculated MAP, the calculated MAP will be used. If it is below the calculated MAP value, the imputed measurement will be used.

This data imputation is only expected to be relevant for calculating the key secondary outcome of time without shock within 24 hours. It will not apply to the primary outcome.

Additional analyses

29 Details of any additional statistical analyses required, eg, complier-average causal effect analysis

We will perform a Bayesian sensitivity analysis of the primary and secondary outcomes, following the same methodology as the main analyses. Based on this analysis we will report posterior probabilities for a range of effect sizes. The Bayesian analyses will utilize weakly informative priors, symmetric with respect to the intervention.

Harms

30 Sufficient details on summarizing safety data, e.g., information on severity, expectedness, and causality; details of how adverse events are coded or categorized; how adverse event data will be analysed, i.e., grade 3/4 only, incidence case analysis, intervention emergent analysis

Harms are presented partly as tertiary/explorative outcomes as presented in Section 6: Analysis.

Details on harms and safety are available in section 7 in the protocol.

Statistical software

31 Details of statistical packages to be used to carry out analyses

Statistical analyses will be performed using R 4.4.5 (R Core Team 2024, Vienna) or a newer version, if such is published before the analyses. The version used will be reported in the manuscript.

References

32a References to be provided for nonstandard statistical methods

G-computation: Naimi AI, Cole SR, Kennedy EH. An introduction to g methods. Int J Epidemiol. 2017;46(2):756-62.Bayesian Analysis: Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. Bayesian Data Analysis. 3rd ed2013.

32b Reference to Data Management Plan

See section 9 in the protocol.

The codebook for the REDCap database which includes definition and validation of variables collected in the trial are available as a supplementary file.

32c Reference to the Trial Master File and Statistical Master File

The Trial Master File exist partly as a physical folder in the Emergency Department at Odense University Hospital and partly as an electronic version located in a secure SharePoint server under The Region of Southern Denmark. The Trial Master File can be accessed with appropriate and necessary agreement with the Sponsor.

32d Reference to other standard operating procedures or documents to be adhered to

Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA 2017;318(23):2337-2343. DOI: 10.1001/jama.2017.18556

32e References to other litterature

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Appendix

Appendix 1: CONSORT diagram draft