VAST-A

Study PROTOCOL version 9 20260522

VAsopressin and STeroids in addition to Adrenaline in cardiac arrest - a randomized clinical trial

EU CT number: 2025-521283-35-00

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1. Background

1.1 Epidemiology

The incidence of in-hospital cardiac arrest (IHCA) is rarely reported but most often ranges between 1-5/1000 hospital admissions (1, 2). In Sweden the incidence is 1.7 per 1000 hospital admissions and similar numbers are reported from Italy and the UK (3-5). The IHCA population differs from out-of-hospital cardiac arrest (OHCA) in some important aspects. IHCA patients are often older, include somewhat fewer men than OHCA, IHCA are more often witnessed and have shorter time to start of CPR (2, 6). The most common cause of IHCA is cardiac and hypoxic causes (6, 7) and the first rhythm is most often PEA unlike in OHCA where asystole is most common (2, 8). Varied survival rates have been reported worldwide, commonly around 15-30%, and 33% in Sweden last year (1, 5-7, 9).
After the introduction of cardiopulmonary resuscitation (CPR) and defibrillation survival rates have significantly increased during the last 40-50 years (10-12). There are a lot of on-going research focusing on CPR and the use of automatic external defibrillator (AED) but little is done in regards to drug therapy. Despite low survival evidence different drugs like beta-blocker, atropine, adrenaline and other inotropic have routinely been used as part of advanced life support (ALS) periodically through the years (13). The previously steady increase in survival have somewhat plateaued and the room for additional improvement is apparent (9, 10). To further increase survival rates after cardiac arrest ALS need to be further optimised, of which drug therapy is an important part. There is an urgent need to find new drugs, new combinations of old drugs and also randomly test routinely used ALS drugs.

1.2 Pathophysiology

When a sudden cardiac arrest occurs the discontinued circulation causes global ischemia and this ischemia leads to hypoxia, anaerobic metabolism, intracellular acidosis, ATP depletion, ion pump failure and finally electrolyte imbalance and cellular oedema (14). One important consequence of this reaction is a stress-induced release of catecholamine's, vasopressin, steroids and also production of inflammatory mediators as IL-1B, TNF-alpha and coagulation cascade activation (14). These reactions are also a central mechanism behind the "post cardiac arrest syndrome" (PCAS). This usually occurs after the return of spontaneous circulation (ROSC), and the phenomena can clinically cause brain injury, myocardial dysfunction and reperfusion response injury (14, 15).
Drug therapy has in this context been used to counteract or limit this physiological effect of cardiac arrest, mainly by increasing coronary and cerebral blood flow but also by membrane-stabilising drugs to potentially increase the success rate of a defibrillation. The international cardiac arrest treatment guidelines currently recommend, despite low evidence, the use of adrenaline and amiodarone in ALS (16, 17), which pharmacological effects are thought to result in increased survival. Multiple other drugs have previously been studied and used in ALS through the years with the same aim but with no shown survival benefit.

1.3 Evidence for the current used drug therapy in cardiac arrest

The evidence for the two currently recommended drug therapies is limited when it comes to

positive effects on long-term survival (13, 16). Despite this, adrenaline and amiodarone is used worldwide in today's ALS treatment.
Adrenaline is a catecholamine and increases both coronary and cerebral blood flow pressure via vasoconstrictive properties and have long been used in ALS (18).It has been associated to increased rate of ROSC and short-term survival in multiple studies but not to increased survival to hospital discharge (19-22). Some of the negative effects of adrenaline have been highlighted in recent years; adrenaline can potentially reduce microcirculation, increase oxygen demand via tachycardia and increase the risk of arrhythmias (18). In animal studies administration of adrenaline has been shown to reduce cerebral perfusion with increased short-term mortality or poor neurological outcome as a result (13, 18, 23, 24). In a recent randomised controlled study of more than 8000 patients the use of adrenaline resulted in a significantly higher rate of 30-day survival than the use of placebo, but there was no significant between-group difference in the rate of a favourable neurologic outcome because more survivors had severe neurologic impairment in the epinephrine group (19). Furthermore, when comparing adrenalin with other vasopressors, no apparent advantages have been shown (13, 25-27).
Amiodarone, is a membrane-stabilising anti-arrhythmic drug, and is recommended in shock-resistant ventricular arrhythmias as VT/VF (16). It has been shown to increase survival to hospital admission for OHCA compared to lidocain and placebo (28, 29). However, a recent published study showed no increase in survival or favourable neurological outcome at discharge when comparing amiodarone or lidocain with placebo (30).
To summarise, there are no current drug therapy with documented positive long-term survival with good neurological function.

1.4 Other potential drug therapies

Vasopressin, the vasoconstrictive hypophysal hormone, alone has not shown increased survival when compared to adrenaline (25, 31, 32). However, animal data have shown increased diastolic pressure, cerebral perfusion pressure and cerebral oxygenation in cardiac arrest treatment with vasopressin, and have when compared to adrenaline been associated with better cerebral blood flow (33-36). Vasopressin also has longer effect duration (37). In addition, animal studies have shown increased long-term survival with good neurological function with the combination of adrenaline and vasopressin (38).
Corticosteroids are currently used in septic shock treatment as a means to reduce time to shock reversal and thereby potentially improving mortality (39). Steroids have therefore also been suggested for cardiac arrest treatment. The potential role in resuscitation includes the catecholaminerg potentiation, vasoconstriction and protection from reperfusion injury (40). Several studies have demonstrated multiple similarities between the post-cardiac arrest shock state and that of septic shock (41-44), where adrenal insufficiency due to multiple pathophysiological mechanisms including ischemia/reperfusion injury of the adrenal glands and the on-going systemic inflammatory response is common and also associated with poor outcome (45-50).
In an cardiac arrest animal model steroids were administrated and increased rate of ROSC (51). In several observational studies, a higher serum cortisol concentration during resuscitation but also post ROSC, was associated with a greater likelihood of survival, these findings are shown in both animal models and humans (47-49, 52-54).

The combination of steroids and vasopressors. In two recent Greek studies rate of ROSC, survival to hospital discharge and neurologically favourable survival was improved for the combination of adrenaline, vasopressin, and methyl-prednisolone during cardiac arrest followed by daily

hydrocortisone over 7 days for patients with post-resuscitation shock compared to conventional treatment with adrenaline alone (62,63). These are the only two studies ever on drug therapy in cardiac arrest that have shown improved survival comparing one treatment to another or to placebo (13). Both studies were randomized double-blinded controlled trials altogether including 368 IHCA patients (55,56). In a recent Danish multicenter, randomized, double-blind, placebo-controlled, parallel-group superiority trial conducted across 10 hospitals in Denmark, patients were randomized to a combination of adrenaline, vasopressin, and methyl-prednisolone compared to adrenaline alone (60). In contrast to the Greek studies, the Danish research studied ROSC as the primary outcome and did not include the continuation of cortisone following ROSC. This study demonstrated increased ROSC among patients in the intervention group but without significant difference in 30 day survival or favourable neurological function.

1.5 What is the need for this trial?

Despite the very promising results from the two Greek studies, the results have not had any major impact on the 2025 guidelines recommendations (39, 40, 41). The ILCOR task force was unable to reach a consensus on recommendations for or against the use of steroids in in hospital cardiac arrest but suggest against the routine use of steroids in out of hospital cardiac arrest and they emphasise further studies (39).
The main reasons why not adapt the VSE-regime (Vasopressin, Steroids, Epinephrine/Adrenaline) into the ERC-guidelines (40) was that the population in these two studies had a very rapid ALS, a high incidence of asystolic cardiac arrest and low baseline survival compared to other in-hospital studies and therefore that the findings of these studies would not be not generalizable to all cardiac arrests and they suggested that steroids should not be used routinely for cardiac arrest. 2015 American Heart Association (AHA)) states that the combination of intra-arrest vasopressin, epinephrine, and methylprednisolone and post-arrest hydrocortisone as described (64) may be considered and that further studies are needed before recommending the routine use of this therapeutic strategy.
If VSE-regime are that effective as reported it has a considerable potential to save many lives. In Sweden about 65-70% of IHCA receive drug therapy, of which the 30-day survival is 11-19%. With an additional increase of 4-5 absolute percentage points up to 100 more lives can be saved each year. This survival increase might be similar for many western countries that have the same incidence and survival as Sweden.

Based on the plausible physiologic rationale for the potential efficacy of vasopressin and corticosteroid therapy in post-cardiac arrest patients and the promising findings in the two recent Greek studies, it is our strong believe that the value of the combination of adrenaline, vasopressin, and corticosteroids needs to be further evaluated in a large randomized trial.

2. Study design

2.1 Study summary

This is an investigator initiated randomized, open-label, superiority, multi-centre clinical trial. The estimated study project period runs over 3-4 years, including the pilot phase. Based on preliminary assumptions, to confirm or reject an increase in survival from 16% to 24%, about 784 patients will be randomized in the study. In hospital cardiac arrest patients meeting criteria(s) for adrenaline administration according to current ERC guidelines are eligible for inclusion and randomization in the study.
Patients will be randomized to, in addition to adrenaline, either treatment with vasopressin and steroids (intervention) or adrenaline only (control).
Primary outcome is survival at 30 days.
The study is divided into two phases:

1. The pilot phase. The pilot study is now finished and the results published (61). Based on the results of the pilot study changes have been made to the protocol and are described in more detail in the coming sections.

Experiences from the Swedish VASTA feasibility and safety pilot study:

In total, 183 IHCA patients were screened, of whom 39 patients (median age 77 years, 64% male) were randomized (23 control, 16 intervention). This represents 2.4 patients per month. Most cardiac arrests occurred in general wards (n=17/39, 44%), followed by cardiology wards (n=11/39, 28%). Four patients (10.3%) did not receive the study treatment according to the protocol at the scene of the arrest. In the ICU, 33.3% (3/9) of patients did not receive the study treatment according to the protocol, primarily due to a misunderstanding about the patient's inclusion status.

The time from cardiac arrest to the emergency team's arrival (2.5 minutes) was similar between the groups. In the control group (standard care), the time to adrenaline administration was five minutes, versus seven minutes in the intervention group. The time to the study drug/placebo was nine minutes versus 10:30 minutes, respectively. Three patients had a predefined treatment-specific adverse event, including infection and bleeding that required treatment. Sustained ROSC was 17.4% (4/23) in the control group and 37.5% (6/16) in the intervention group. This pilot study demonstrated that randomization to a strategy combining adrenaline, corticosteroids, and vasopressin compared to standard care can be done safely. However, some protocol refinements regarding study drug administration in the ICU and simplifying the randomization process are necessary to ensure sufficient enrollment in the VAST-A main trial, along with the recruitment of additional hospitals.

2. The main trial phase evaluating survival as primary outcome.

2.2 Objective

The primary objective of the study is to determine whether the addition of a combination of vasopressin and steroids to adrenaline will increase 30 days survival in cardiac arrest patients compared to adrenaline alone.

2.3 Hypothesis

We hypothesize that the addition of a combination of vasopressin and steroids to adrenaline will increase survival at 30 days compared to adrenaline alone.

2.4 Outcomes

Outcomes will be reported according to the Utstein Resuscitation Registry Templates for In-Hospital Cardiac Arrest (57).

2.4.1 Pilot study

During the pilot study primarily feasibility and safety endpoints are evaluated:

2.4.1.1 Primary outcome

Feasibility

Compliance to protocol for study drug administration

Safety

Adrenaline administrated prior to study drug

2.4.1.2 Secondary outcomes

ROSC

2.4.2 Main study

2.4.2.1 Primary outcome

Survival at 30 days

2.4.2 Secondary outcomes

Sustained ROSC ≥ 20 min

3-month survival

3-month Cerebral Performance Category (CPC) 1-2

2.5 Eligibility

2.5.1 Inclusion criteria

Witnessed IHCA who meet the criteria for adrenaline administration during CPR according to current ERC guidelines

Age, men ≥ 18 years and women ≥ 50 years (i. e.women not considered of childbearing potential (WOCBP).

2.5.2 Exclusion criteria

Patients with do not resuscitate (DNR) decision
Perioperative cardiac arrest
Cardiac arrest at the coronary cathetarization lab
Prehospital cardiac arrest with re-arrest at the emergency department

2.5.3. Withdrawal of subjects

A participant is free to withdraw his/her informed consent from the trial at any time and will then exit the trial. The reason for the withdrawal will be collected and reported. The participant will be asked to specify which aspects of the trial he/she is withdrawing consent and participation from; attending the follow up visits, inclusion of their data (including survival data) in the database, or publication. The participant making the withdrawal will be asked for permission to use data obtained for the primary outcome measure. If the patient declines, only data obtained before withdrawal will be retained in the database for safety reasons but not included in the statistical analysis. If the trial intervention is discontinued by the treating physician because of adverse events, or any other reason, this does not constitute subject withdrawal from the trial and the patient will not exit the trial and will be included in the statistical analysis on an intention-to-treat basis.

2.6 Study procedures

2.6.1 Consent process

The chance of surviving cardiac arrest is very low. In the IHCA setting where criteria for adrenaline administration are met, survival at 30 days is about 11-19% and in the OHCA setting even lower. In a cardiac arrest scenario treatment of CPR must be started immediately in order to increase the chance of survival.

Due to the nature of the condition of sudden cardiac arrest, informed consent for participating in the study cannot be obtained from the subject at the scene since the victim is unconscious at the time for study inclusion and the sponsor has no previous information about the patients willing to participate in the study or not. According to the EU:s Clinical Trials Regulation 536/2014 chapter 35 regarding emergency situations, informed consent is to be obtained as soon as possible. The clinical course in patients that regains circulation after a in hospital cardiac arrest shows a wide variety, from irreversible to reversible circulatory shock, irreversible brain damage and death to neurological intact survival and fast recovery in cognitive functions. Therefore, the strategy for obtaining informed consent varies dependent on patient outcome.

The strategy for obtaining informed consent is as follows according to the patient's status

1) The patient who is not regaining circulation and is declared dead at the scene of the arrest. No consent will be obtained

2) The patient who survives the initial resuscitation phase, is transferred to the ICU and is conscious. Information about the study (both oral and written) will be given. The information includes the purpose of the study, the study intervention, possible risks and benefits from participating in the study and who is legal responsible for the study. In the information it is also clarified that all participation is voluntary, the right to not participate in the study and the right to withdraw participation. The informed consent is obtained.

3) The patient who survives but is not enough conscious, GCS <14, have severe dementia, suffer from expressive and/or impressive aphasia or are unable to write his or her signature. In this case, when the patient is not able to give an informed consent by his or her own, the consent shall as soon as possible be sought after the emergency situation, circulatory shock, (defined as no need for inotropics) is resolved. This informed consent will be sought by the investigator from the patients legally designated representative without undue delay, normally after the ICU period. Among cardiac arrest patients, 96 % do not need more than 10 days of intensive care (cardiac arrest data from the Swedish intensive care registry).

If informed consent has been obtained from the legally designated representative, informed consent to continue the participation in the clinical trial shall be obtained from the patient as soon as he or she can give informed consent.
If the incapacitated patient does not have a legally designated representative the investigator has to approach the lawcourt for this purpose.

2.6.2 Randomization and allocation to study arms

Patients will be screened for study eligibility in-hospital at three levels of inclusion:

1. At the Intensive Care Unit
2. Using the Rapid Response Team on all sites at the hospital
3. At the Emergency Department

Patients found eligible will be randomised into one of the two groups (intervention or control) using an envelope containing a randomisation card. All randomisation envelopes will contain:

- **Front of envelope:** A list of inclusion and exclusion criteria
- **Front side of randomisation card:** Marked as "VASTA Main study" and a QR code.
- **Back side of randomisation card:** Initial worksheet with key variables. This information will later be transferred to RedCap.

Each patient will be assigned a unique trial and randomisation number listed on the envelope and randomisation card. Randomisation will be performed with permuted blocks of concealed size, stratified by trial site.

An overall and complete screening log will be retrospectively compiled at Södersjukhuset and will include all in-hospital cardiac arrest patients, regardless of eligibility for inclusion. This will serve as a “raw model of eligible patients” for the participating sites, together with reported in-hospital cardiac arrest in the Swedish Registry for Cardiopulmonary Resuscitation.

2.7 Intervention

All patients will receive all standard treatment according to current European Resuscitation guidelines. Standard advanced life support interventions will be provided including chest compression, defibrillation and advanced airway management as required. The exception from standard treatment is that patients in addition to adrenalin will be administered vasopressin and

methylprednisolone (intervention) for the five first cycles of drug administration and hydrocortisone in the ICU.

2.7.1 Adrenaline, vasopressin and steroids arm (intervention)

a. At randomization
   1 ml of vasopressin 20 IU/ml will be administered as soon as possible after adrenaline during the **five first** cycles of drug administration during CPR.
   1 ml metylprednisolone sodium succinate 40 mg/ml will be administered **only** during the **first** cycle of drug administration during CPR

b. In the ICU
   Hydrocortisone 3 mg/ml
   At 4 hours post ROSC, and then once daily, patients will receive an infusion, over a 24-hour period, of 100 ml (300 mg hydrocortisone/d) for 5 days or to ICU discharge if discharged earlier than 5 days after ROSC.

The company, AOP Orphan Pharmaceuticals GmbH, producing vasopressin has confirmed that the vasopressin ampoule is stable at room temperature for at least four months. This was used during the VAM-IHCA trial (60) and is further confirmed by stability data for VASOSTRICT and generic vasopressin in the USA: "Store between 2°C and 8°C (36°F and 46°F). Storage is permitted for up to 12 months at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F) within the expiry date. This, together with redesigned ampules of Vasopressin 20 IU specific for this study, further simplifies the intervention and reduces the time to drug administration, as one ampule contains only the specific dose needed and the ampules can easily be stored at the same location as the adrenaline is normally kept.

2.7.2 Adrenaline alone arm (control)

a. At randomization
   Adrenaline alone.

b. In the ICU
   Our recommendation is to consider steroid treatment only when the noradrenaline concentration exceeds 0.3 microg/kg/min.

2.8 Concomitant medication

a. All medical treatment except the study intervention will be decided by the attending physician based on the clinical assessment of the patient in accordance with current treatment guidelines. All medication will be documented in a separate part of the CRF.

b. Plasma glucose levels should be monitored in the ICU to maintain levels of 11 mmol/L or less, in accordance with current intensive care guidelines.

2.9 Prognostication

Accurate, relevant and consistent neurological prognostication is essential when conducting an RCT on a drug intervention in IHCA. Prognostication will be performed on all participants still in the ICU 72 - 96 hours after randomisation. The prognostication will be based on the ERC and European Society for Intensive Care Medicine (ESICM) recommendations and performed at approximately 72 - 96 hours after randomisation, although may be delayed due to practical reasons. In order to be consistent with other RCTs we choose a prognostication schedule according to the following:

- The physician performing the prognostication will be a neurologist, intensivist or other specialist experienced in neuroprognostication after cardiac arrest and who has not been involved in patient care.
- The prognosticator will be blinded for group allocation, but not for relevant clinical data.
- Prognostication and the potential decision to withdraw active intensive care are closely related but will be considered separate entities.
- The result of the prognostication will be categorised as "YES" or "NO", based on the answer to the question "Does this patient fulfil criteria for a likely poor neurological outcome?". This assessment will be recorded in the case report form and will be communicated to the treating clinician.
- Any decision to withdraw active life support will be made by the treating physicians, together with the patient's relatives or legal surrogates, as required by local legislation. In making this decision the treating physician may use the information from the prognostication. The blinded external physician will not make any recommendation on WLST.
- Efforts will be made to sufficiently delay prognostication to ensure that any lingering effects of sedative agents will not affect the assessment.
- Prognostication will be based on one mandatory, and five optional modalities.

2.9.1 Clinical examination - mandatory

A clinical examination including assessment of brain stem reflexes and described using the FOUR-score will be performed on all patients. The bilateral absence of pupillary and corneal reflexes at 72 - 96 hours after CA or later, is a finding indicative of a poor prognosis. A prospectively documented early status myoclonus (within 48 hours) is indicative of a poor prognosis.

2.9.2 EEG - optional

An EEG performed between 48 h and 96 h after randomisation should be considered on all participants who survive, and remain unconscious to this point, in line with standard clinical practice. An EEG with a highly malignant pattern, and without reactivity to sound and pain is indicative of a poor prognosis.

2.9.3 Brain CT – optional

If a brain-CT shows signs of global ischaemic injury, such as: generalised oedema with reduced grey/white matter differentiation and sulcal effacement, this is indicative of a poor prognosis. A CT should be considered in patients who remain unconscious to exclude other pathologies such as intracranial haemorrhage or infarction.

2.9.4 Brain MRI - optional

A brain MRI at 3 – 5 days may be incorporated into prognostication if it has been performed. Signs of global, diffuse, or bilateral multifocal ischaemic lesions is indicative of a poor prognosis.

2.9.5 Neuron specific enolase- optional

High levels of Neuron specific enolase (NSE), > 60, are indicative of a poor prognosis. NSE-sampling will not be mandatory,but may be used by sites with experience. If serial samples are available, and these are consistently higher than locally established levels associated with a poor outcome, this may be seen as indicative of a poor outcome. Samples with haemolysis should be disregarded.

2.9.6 SSEP - optional

Absent SSEP N20-responses bilaterally may be seen as indicative of a poor prognosis, if SSEP is performed more than 48h after randomisation.

2.9.7 Criteria for a likely poor neurological outcome

In the VAST-A trial the prognosis is considered likely poor if criteria A, B and C are all fulfilled.

A Confounding factors such as severe metabolic derangement and lingering sedation has been ruled out.

B The patient has no response or a stereotypic extensor response to bilateral central and peripheral painful stimulation at ≥ 72 - 96 hours after randomisation.

C At least two of the below mentioned signs of a poor prognosis are present:

C1 Bilateral absence of pupillary and corneal reflexes at 72 - 96 hours after randomisation or later

C2 A prospectively documented early status myoclonus (within 48 hours of randomisation)

C3 A highly malignant EEG-pattern without reactivity to sound and painful stimulation.

Patterns that are considered highly malignant are: (ref)

i. Suppressed background (amplitude <10mV, 100% of the recording) without discharges.
ii. ii. Suppressed background with superimposed continuous periodic discharges.
iii. iii. Burst-suppression (periods of suppression with amplitude <10mV constituting 50% of the recording) without discharges.
iv. iv. Burst-suppression with superimposed discharges.

C4 CT brain with signs of global ischaemic injury, such as: generalised oedema with reduced grey/white matter differentiation and sulcal effacement or MRI-brain with signs of global, diffuse, or bilateral multifocal ischaemic lesions

C5 Serial serum-NSE samples consistently higher than locally established levels associated with a poor outcome

C6 Bilaterally Absent SSEP N20-responses more than 48 hours after randomisation

2.10 Withdrawal of life supporting therapies (WLST)

All participants in the trial will be actively treated until 72 - 96 hours after randomisation. There will be two exemptions from this rule.

- Participants in whom further treatment is considered unethical due to irreversible organ failure, a documented medical comorbidity, or other reasons •
- Participants in whom brain death is established, however this will be defined as death and not WLST

The assumption of a poor neurological prognosis alone will not be considered sufficient to employ withdrawal of active intensive care prior to 72 - 96 hours after randomisation. After prognostication has been performed, WLST due to a presumed poor prognosis will be allowed according to current guidelines (ERC/ESICM). Participants who have an unclear prognosis at 96h after randomisation should be re-examined daily and WLST may be considered if neurological function does not improve and, metabolic and pharmacological reasons for prolonged coma are ruled out. If a decision of WLST is made, the time point and the main reasons for withdrawing life-supporting therapies will be recorded. However supporting therapy may also be continued regardless of the neurological assessment of prognosis, at the discretion of the treating physician. Participants in whom brain death due to cerebral herniation is established will be registered as dead when a conclusive assessment has been made. If death is due to brain death this will be registered.

2.11 Data collection and follow up

Data on all patients included in the study will reported according to specific e-CRFs (see Appendix).
In the study database each patient will have a unique identifier number that can be linked to all data for that patient.
Data will also be collected using the Swedish Registry for Cardiopulmonary Resuscitation, the Swedish Intensive Care Registry, the National Cause of Death Register and patient charts. Follow-up will take place at 30 days and at 3 months after the cardiac arrest.

2.12 Definitions

Postresuscitation shock was defined as sustained (>4 hours), new post arrest circulatory failure or post arrest need for 50% or greater increase in any prearrest vasopressor/ inotropic support targeted to mean arterial pressure greater than 70 mm Hg.
Circulatory failure was defined as an inability to maintain mean arterial pressure greater than 70mmHg without using vasopressors after volume loading
Respiratory failure was defined as ratio of arterial oxygen partial pressure to fraction of inspired oxygen of 200mmHg or less.
Coagulation failure was defined as a platelet count of 50×103/μL or less.
Hepatic failure was defined as a serum bilirubin concentration of 6 mg/dL or greater (to convert bilirubin to μmol/L multiply by 17.104).
Renal failure was defined as a serum creatinine level of 3.5 mg/dL or greater, requirement of renal replacement therapy or both (to convert creatinine to μmol/L multiply by 88.4)
Neurologic failure was defined asa Glasgow Coma Scale score of 9 or less.
Hyperglycemia was defined as a blood glucose level exceeding 200 mg/dL (to convert to mmol/L, multiply by 0.0555).

3. Protection of human subjects

3.1 Characteristics of human subjects involvement

The study will be a randomized controlled open-label multicentre study. The study will have an adaptive design so that the pilot study will run seamlessly into the main study. The pilot study will start in three sites for later recruitment of additional sites. The sponsor/investigators will apply for approval for the study through the new Clinical Trial Information System, CTIS. This is a new platform maintained by European Medicines Agency (EMA) and supports the flow of information between clinical trial sponsors, European Union (EU) Member States and European Commission. It supports interactions between clinical trial sponsors (researchers or companies that run a clinical trial and collect and analyse the data) and regulatory authorities in the EU Member States and EEA countries, throughout the lifecycle of a clinical trial. Instead of separate applications to the Swedish Ethical Review Authority and Swedish Medical Products Agency the CTIS coordinates accurate interactions
The study population consists of all IHCA patients, men > 18 years and women > 50 years, except those fulfilling the exclusion criteria do not resuscitate (DNR) decision where advanced life support is initiated and where ERC guidelines criteria for adrenaline administration are met

3.1.1 Informed consent

The chance of surviving cardiac arrest is very low. In the IHCA setting where criteria for adrenaline administration are met, survival at 30 days is about 11-19% and in the OHCA setting even lower. In a cardiac arrest scenario treatment of CPR must be started immediately in order to increase the chance of survival.

Informed consent for participating in the study cannot be obtained from the subject at the scene since the victim is unconscious. The cardiac arrest may be witnessed even at hospital stay by family members, but to ask for consent in such a situation is not possible for both practical and ethical reasons.
Therefore, if the patient survives the initial resuscitation phase, information about the study (both oral and written) will as soon as it is possible, i.e. when the patient is admitted to the ICU, be given to those patients who have regained consciousness and are able to understand the. A written informed consent will then be obtained from the patient. The information includes the purpose of the study, the study intervention, possible risks and benefits from participating in the study and who is legal responsible for the study. In the information it is also clarified that all participation is voluntary, the right to not participate in the study and the right to withdraw participation.
The above procedure is well established (both national and international) in cardiac arrest research where informed consent is not possible to obtain in conjunction with inclusion in the study. The investigators group have great experience from conducting research on cardiac arrest patients.

3.2 Data management procedures

Data on all patients included in the study will reported according to specific e-CRFs (see Appendix). The e-CRFs will be accessible via a separate URL and directly linked to the study database.
In the study database each patient will have a unique identifier number that can be linked to all data for that patient.

Data will also be collected using the Swedish Registry for Cardiopulmonary Resuscitation, the Swedish Intensive Care Registry, the National Cause of Death Register and patient charts. Follow-up will take place at 30 days and at 3 months after the cardiac arrest.

All personal data will be handled according to the standard procedures for the current registries and medical records and in accordance with the General Data Protection Regulation (GDPR). In the study database all personal data will be anonymized and only presented on group level. Personal numbers and all other data that can lead to identification of subjects included in the study will be coded and keys for decoding will only be accessible to key persons in the project. The database will also only be accessible to key persons in the project. Data will be stored for 10 years after termination for the study.
An independent Data and Safety Monitoring Board will be formed consisting of four independent experts with relevant clinical resuscitation research and statistical experience. The board will be responsible for the interim analysis, review adverse events and also be advisory.

3.3 Risks and benefits.

3.3.1 Potential risks

There is a time-consuming handling with 3 syringes instead of 1 in the study compared to today's guidelines. The drug batches are prepared so this time will be minimized and probably negligible.

3.3.2 Potential benefits

Vasopressin alone compered to adrenaline have shown tendency to better outcome in subgroups and physiologically vasopressin should have a favourable effect on the cardiovascular system compared to adrenaline.
Steroids alone with its favourable clinical effects have not shown increased survival but the combination of vasopressin, adrenalin and steroids compared to adrenaline alone have shown a higher rate of survival in two Greek studies (62,63) and higher rate of ROSC in a recent Danish trial (60), why this study might confirm earlier studies.

3.3.3 Anticipated risk/benefit ratio

The risks seem to be negligible so that the net benefit is likely to be determined by potential efficacy rather than safety

3.4 Legal and patient insurance aspects

In Sweden patient insurance is regulated according to the Patient Injury Act

3.5 Ethical and Medical Products Agency approval

The investigators will apply for approval for the study through the Clinical Trial Information System, CTIS, see 3.1.

4. Data management plan

4.1 Data collection

Data on all patients included in the study will reported according to specific e-CRFs (see Appendix). The e-CRFs will be accessible via a separate URL and directly linked to the study database.
In the study database each patient will have a unique identifier number that can be linked to all data for that patient.
Data will also be collected using the Swedish Registry for Cardiopulmonary Resuscitation, the Swedish Intensive Care Registry, the National Cause of Death Register and patient charts. Follow-up will take place at 30 days and at 3 months after the cardiac arrest.

4.2 Database

The database will be set up by the programming team at Karolinska Institute in agreement with the sponsor Norrtälje hospital. The template for the database and all specifications (i.e. database variables, validations checks, screens) will be agreed between the programmers, statistician and the scientific group. The database will be tested and validated in accordance with standard procedures for secure data management.

4.3 Data management, storage and archiving

All essential documentation and trial records will be stored in conformance with the applicable regulatory requirements. Access to stored information will be restricted to authorised personnel. Data will be stored in a secure area with access restricted to staff working on the trial. Any data that are transferred out of the secure environment (for example for statistical analysis) will adhere to standard procedures for secure data management.
All personal data will be handled according to the standard procedures for the current registries and medical records and in accordance with the General Data Protection Regulation (GDPR). In the study database all personal data will be pseudonymized and only handled on group level. Personal numbers and all other data that can lead to identification of subjects included in the study will be coded and keys for decoding will only be accessible to key persons in the project. The database will also only be accessible to key persons in the project.
Data will be stored for 10 years after termination for the study.

5. Adverse event management

5.1 Definitions

5.1.1 Adverse events (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical investigation participant taking part in health care research, which does not necessarily have a causal relationship with the research.

5.1.2 Adverse Reactions (AR)

An AR is defined as any untoward and unintended response to the study Investigational Medical Product (IMP), i.e. the combination of adrenaline, vasopressin and steroids (intervention). A causal relationship between the trial treatment and an adverse reaction is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

5.1.3 Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs).

An AE or AR is considered serious if it:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth-defect
- Is an important medical condition

SUSARs are SARs that are unexpected i.e their nature or severity is not consistent with the Summary of Product Characteristics.

5.1.4 Specific SAEs and SARs

The following SAEs and SARs are considered specific for the study intervention:

- Pneumonia, defined as purulent tracheal secretions, a radiographic infiltrate, i.e a pragmatic adaption of the Clinical Pulmonary Infection Score (CPIS) (58)
- Sepsis and septic shock, according to the 3rd international consensus definitions for sepsis and septic shock (59)
- Bleeding requiring transfusion
- Arrhythmias resulting haemodynamic compromise
- Heart muscle rupture

5.2 Reporting SAEs, SARs and SUSARs

Events that are related to cardiac arrest and would be expected in patients undergoing attempted resuscitation should NOT be reported. These include:

- Death
- Hospitalisation
- Persistent or significant disability or incapacity
- Organ failure

In the event that one of the specific adverse events or reactions occurs and the circumstances surrounding the event or reaction are unclear or unexpected it should be reported as an unexpected

serious adverse event or reaction. The relatedness between the trial intervention and the unexpected serious adverse event or reaction should be determined by the local investigator.
The relatedness will be categorised as:
• Not related:
The event is clearly related to other factors, such as the participant's clinical state, therapeutic interventions, or concomitant drugs administered to the participant
• Possibly related:
There is a possible temporal relationship between the intervention and the event but it could have been caused by other factors
• Probably related:
There is a plausible temporal relationship between the intervention and the event and the event is not reasonably explained by other factors.

The local investigator is required to follow each participant with an unexpected serious adverse event until resolution of symptoms. Unexpected serious adverse events or reactions must be reported to the study administration within 24 hours of becoming aware of the event.
All reports will be reviewed by the Principal Investigators and those that are considered to satisfy the criteria for being related to the IMP and unexpected will be notified to the Ethics Committee, SMPA and sponsors within 7 or 15 days of in accordance with regulatory requirements. Reports will also be reviewed by the DSMB at their regular meetings, or more frequently if requested by the DSMB Chair.

5.3 Procedures in case of pregnancy

Women considered of childbearing potential is an exclusion criterion for this trial, however, should the patient later be known to have been pregnant at the time of cardiac arrest and trial intervention then the following will apply:
Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.
All reports of congenital abnormalities/birth defects must be reported and followed up as a SAE.

5.4 Discontinuation of the Trial

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Mandated by the SMPA
- The Trial Steering Committee decides that recruitment should cease following recommendations from the DSMB
- Funding for the trial ceases

The Ethics Committee and SMPA will be notified in writing if the trial has been concluded or terminated early within 15 days.

6. Monitoring and quality assurance of study procedures

6.1 Data Quality and monitoring plan

Data entered into the trial database will be checked for accuracy in accordance with the Data Management Plan and the standard procedures of the Swedish Registry for Cardiopulmonary Resuscitation.
Quality assurance checks will be made on all participating study sites on the following parameters:

- eligibility,
- accuracy of e-CRF data in comparison with source data,
- completion of data,
- archiving of study related documents
- informed consent
- inclusion rate
- site resources for participating in the study

In the first year every participating study site will be monitored for:

- eligibility,
- accuracy of e-CRF data in comparison with source data,
- completion of data,

in one tenth of included patients and for

- informed consent in all included patients

The extent of the following monitoring on each participating study site will then be decided dependent on the results of the monitoring for the first year as a study site.

6.2 Visits to study sites

After the initial site initiation of each participating study site, the trial management group will have regular contact with all the study sites to identify any problems with compliance with the protocol, training, data collection, IMP accountability or other barriers to recruitment and progress, and to support sites with the day to day management of the trial. In addition to communication via the trial website, regular telephone and email contact, at least one site visit per year will be made to meet with the trial team to more thoroughly discuss any issues and check for consistencies.

6.3 Data and Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be formed consisting of four from the study independent experts with relevant clinical resuscitation research and statistical experience. A statistician will be included in the DSMB. The board will be responsible for the interim analysis, review adverse events and also be advisory.
During the period of recruitment into the trial, interim analyses of the accumulating data will be supplied, in strict confidence, to the DSMB, along with any other analyses that the committee may request. The frequency of these analyses will be determined by the Scientific and Steering Committee in discussion with the DSMB.
The DSMB will assess if, in their view, the randomised comparisons have provided both (i) 'proof beyond reasonable doubt' that for all, or some, the treatment is clearly indicated or clearly contraindicated. The DSMB, will then advise what actions, if any, are required. Unless the DSMB

request cessation of the trial the Primary Investigators and the collaborators will remain ignorant of the interim results.
DSMB meetings will also be attended by the Primary Investigators and the trial statistician (for nonconfidential parts of the meeting).
Any publications relating to this trial or that may have an impact on the running of the trial will be reviewed by the DSMB.
The constitution and work of the DSMB will be guided by a written charter. The DSMB charter will be approved by the DSMB before starting the trial.

6.4 Training

A training programme will be produced and provided to all participating sites. It will also be available via the open trial website. Each site will record and maintain training logs and report to the trial management group. This programme will include the following:

- trial background
- basic GCP principles
- randomisation procedures
- eligibility criteria
- ethical issues and the consent process
- data collection and documentation

All members of the trial management group, the scientific committee, the executive committee, as well as investigators at each site as administrative staff will be required to undergo GCP training and provide a CV

7. Statistical Analysis Plan (SAP)

7.1 Study population and sample size

7.1.1 Previous experience of survival rates

Data from 2016: In Sweden, using the Swedish Registry for Cardiopulmonary Resuscitation, 2,622 IHCA cases were reported in 2016 where resuscitation was initiated. In the IHCA group, adrenaline was administered to 67% of patients. Overall survival at 30 days was 32%, and by rhythm, it was 63% for VT/VF and 21% for PEA/Asystole. If adrenaline was administered at any time, survival in the IHCA group was 11%.

Data from 2021–2023: When analysing data from the Swedish registry for the years 2021, 2022, and 2023, we found that 30-day survival when adrenaline was given across all rhythms was 19%.

Data from a similar Danish study (Andersen et al., JAMA, 2021): which used a similar study design and a patient population very similar to that in Sweden, reported a survival rate of 12% in the control group (although this was not the primary endpoint). The VAST-A trial, however, will only include witnessed IHCA patients, who generally have better outcome. This contrasts with the Danish trial by Andersen et al. which included approximately 26% unwitnessed cases – patients typically associated with substantially lower survival rates.

7.1.2 Current power calculation and sample size:

Based on data from the trial by Andersen et al. (JAMA, 2021), which reported a baseline survival rate of 12% in the control group (including also unwitnessed cases), and data from the Swedish Cardiopulmonary Resuscitation Register indicating a survival rate of approximately 19% when adrenaline was given, we estimate a baseline survival rate of 16% for the study population.

Thus, the sample size calculation for the survival outcome is based on a baseline survival of 16% and an expected survival of 24% in the intervention group, with a one-sided alpha of 0.025 and a beta of 0.2. An interim analysis for efficacy will be conducted after 35% of the total sample has been enrolled. For further details, see the section on study phases below.
The final sample size for the study is 784 patients, with the interim analysis planned after 274 patients are enrolled.

7.1.3 Patients eligible for enrolment:

Based on data from the Swedish Registry for Cardiopulmonary Resuscitation, there are 1,114 cases/year of ICHA in Sweden, with adrenaline administered to men aged ≥18 years and females aged ≥50 years. The corresponding figures for the university hospitals are 312 cases/year, and for the hospitals in Stockholm, 165 cases/year.

7.2 Interim analysis

An interim analysis will be conducted after the inclusion of 274 patients to assess the likelihood of achieving a statistically significant primary endpoint at the end of the trial. Conditional power will

be calculated based on the observed data and the original effect size assumption. If the conditional power is below 20%, the interim analysis results will be considered indicative of futility. If the conditional power is moderately low, yet the interim results suggest a treatment effect in the expected direction, an adaptive sample size re-estimation may be undertaken.

Final decisions regarding continuation, modification, or early termination of the trial will rest with the steering group with advice from DSMB.

If the steering group decides to continue, the study will proceed seamlessly into a second phase. The final sample size may be re-estimated based on the interim analysis. If no changes are made, the study will conclude after enrolling 784 patients, as per the initial sample size calculation and the threshold for statistical significance set at a p-value of 0.049.

7.3 Outcome analysis

Data will primarily be analysed according to the **Intention-to-Treat (ITT) principle.** Due to the prevailing circumstances during CPR, certain information is not always available at the time of drug administration. Therefore, data will also be analysed **Per Protocol (PP)**.

a. Intention-to-Treat (primary analysis): Randomisation in the study will be made immediately at the scene of the cardiac arrest. Randomisation and the start of treatment should be performed as soon as possible by the first available, educated crew member, who may be a trained doctor or a specialised nurse, after inclusion and exclusion criteria have been evaluated. All patients randomised to the intervention/control group will be included in the Intention-to-Treat analysis.

b. Per Protocol (secondary analysis): All patients who fulfil the study criteria and receive the treatment according to the allocation (intervention/control) will be analysed using a per-protocol analysis. More specifically, patients with unwitnessed arrest or DNR order, that are identified after randomization will be excluded from the per protocol analysis.

7.3.1 Pilot study

7.3.1.1 Primary outcome

The primary feasibility endpoint will be compliance to protocol for study drug administration. It will be analysed by dichotomising drug administration to compliant or non-compliant to protocol. To be compliant all drug doses administered as described in the protocol.

The primary safety endpoint will be adrenaline administrated prior to study drug. It will be analysed by dichotomising adrenaline administration to compliant or non-compliant to protocol. To be compliant all adrenaline doses must be administered prior to corresponding study drug doses.

7.3.1.2 Secondary outcome

ROSC data will be analysed using Cox regression.

7.3.2 Main study

7.3.2.1 Primary outcome

Survival will be analysed as a binary variable at 30 days using Cox regression.

7.3.2.2 Secondary outcome

Sustained ROSC ≥20 min and 3-month Cerebral Performance Category (CPC) 1-2 will be analysed.

Survival data will be analysed using Cox regression.

8. Study organization, time schedule and funding

8.1 Principal investigators (PI):

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8.2 Sponsor

Norrtälje hospital

8.3 Head study site:

Norrtälje hospital,
Sahlgrenska university hospital and
Södersjukhuset

8.4 Pilot study sites

Norrtälje hospital,
Sahlgrenska university hospital,
Södersjukhuset

8.5 Main study sites

Norrtälje hospital,
Sahlgrenska university hospital,
Södersjukhuset,
…
…
…

8.6 Scientific Committee

Sune Forsberg, MD Associate professor, Norrtälje hospital, Karolinska Institutet
Jacob Hollenberg, MD, Associate professor, Södersjukhuset, Karolinska Institutet
Mattias Ringh, MD PhD, Södersjukhuset, Karolinska Institutet
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8.7 Steering committee

The Steering committee consist of:

Sune Forsberg, MD, Associate professor, (PI)
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Mattias Ringh, MD, Associate professor,
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8.8 Trial Management Group (TMG)

The Trial Management Group (TMG) will consist of Sune Forsberg, statistician, PhD students and research nurses.
The principal investigators (PI) from each study site will also be part of the TMG

8. 9 Data and Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be formed consisting of four independent experts with relevant clinical resuscitation research and statistical experience.

8.10 Time schedule

Planning, set-up and training	2018-01-01 – 2021-11-16
Pilot study	2021-11-17 – 2024-01-31
Recruitment main study	2026-02-01 – 2029-01-31
Analysis, dissemination and publication	2029-02-01 – 2029-06-30

8. 11 Funding

Administration of study financial means will stand under the supervision of the Steering committee.

9. Dissemination and publication

The results of the study will be published in international medical journals.

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