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Effect of Vasopressin and Methylprednisolone vs Placebo on Return of Spontaneous Circulation in Patients With In-Hospital Cardiac Arrest
A Randomized Clinical Trial

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IMPORTANCE Previous trials have suggested that vasopressin and methylprednisolone administered during in-hospital cardiac arrest might improve outcomes.

OBJECTIVE To determine whether the combination of vasopressin and methylprednisolone administered during in-hospital cardiac arrest improves return of spontaneous circulation.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, double-blind, placebo-controlled trial conducted at 10 hospitals in Denmark. A total of 512 adult patients with in-hospital cardiac arrest were included between October 15, 2018, and January 21, 2021. The last 90-day follow-up was on April 21, 2021.

INTERVENTION Patients were randomized to receive a combination of vasopressin and methylprednisolone (n = 245) or placebo (n = 267). The first dose of vasopressin (20 IU) and methylprednisolone (40 mg), or corresponding placebo, was administered after the first dose of epinephrine. Additional doses of vasopressin or corresponding placebo were administered after each additional dose of epinephrine for a maximum of 4 doses.

MAIN OUTCOMES AND MEASURES The primary outcome was return of spontaneous circulation. Secondary outcomes included survival and favorable neurologic outcome at 30 days (Cerebral Performance Category score of 1 or 2).

RESULTS Among 512 patients who were randomized, 501 met all inclusion and no exclusion criteria and were included in the analysis (mean [SD] age, 71 [13] years; 322 men [64%]). One hundred of 237 patients (42%) in the vasopressin and methylprednisolone group and 86 of 264 patients (33%) in the placebo group achieved return of spontaneous circulation (risk ratio, 1.30 [95% CI, 1.03-1.63]; risk difference, 9.6% [95% CI, 1.1%-18.0%]; $P = .03$). At 30 days, 23 patients (9.7%) in the intervention group and 31 patients (12%) in the placebo group were alive (risk ratio, 0.83 [95% CI, 0.50-1.37]; risk difference: −2.0% [95% CI, −7.5% to 3.5%]; $P = .48$). A favorable neurologic outcome was observed in 18 patients (7.6%) in the intervention group and 20 patients (7.6%) in the placebo group at 30 days (risk ratio, 1.00 [95% CI, 0.55-1.83]; risk difference, 0.0% [95% CI, −4.7% to 4.9%]; $P > .99$). In patients with return of spontaneous circulation, hyperglycemia occurred in 77 (77%) in the intervention group and 63 (73%) in the placebo group. Hypernatremia occurred in 28 (28%) and 27 (31%), in the intervention and placebo groups, respectively.

CONCLUSIONS AND RELEVANCE Among patients with in-hospital cardiac arrest, administration of vasopressin and methylprednisolone, compared with placebo, significantly increased the likelihood of return of spontaneous circulation. However, there is uncertainty whether this treatment results in benefit or harm for long-term survival.

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In-hospital cardiac arrest occurs in approximately 2000 patients each year in Denmark and 300 000 patients each year in the United States.[1,2] Outcomes remain poor, with only approximately 25% surviving to hospital discharge in 2017 in the United States.[3] Despite this low survival, there has been limited research focused on improving outcomes for this patient population.[3]

Similar to the out-of-hospital setting, treatment of in-hospital cardiac arrest focuses on early recognition, basic life support (eg, chest compressions and ventilations), advanced life support (eg, defibrillation and drugs), and subsequent post-cardiac arrest care. Most recommendations for treatment of in-hospital cardiac arrest are extrapolated from the out-of-hospital setting. Drugs currently used during in-hospital cardiac arrest, when appropriate, includes epinephrine and amiodarone or lidocaine.[4,5]

In 2 randomized, double-blind trials, published in 2009 and 2013, Mentzelopoulos et al[6,7] compared the addition of vasopressin (20 IU for each dose of epinephrine) and 1 dose of glucocorticoids (40 mg of methylprednisolone) during cardiac arrest with placebo. Both trials, which had a combined sample size of 368 patients, showed a large improvement in outcomes.[6,7] For example, the most recent and largest of the trials found that survival with a favorable neurologic outcome occurred in 18 of 130 patients (14%) in the intervention group compared with 7 of 138 patients (5%) in the placebo group, a finding that was statistically significant.[7] Despite these findings, the current United States and European guidelines[8,9] for treatment of cardiac arrest do not recommend the use of vasopressin and glucocorticoids, reflecting lack of clinical trial data that confirmed the findings of Mentzelopoulos et al.

The Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest (VAM-IHCA) trial was designed to test whether vasopressin and glucocorticoids can improve return of spontaneous circulation for patients with in-hospital cardiac arrest.

Key Points

Question Does the combination of vasopressin and methylprednisolone administered during in-hospital cardiac arrest improve return of spontaneous circulation?

Findings In this randomized trial that included 501 patients with in-hospital cardiac arrest in Denmark, the proportion of patients who achieved return of spontaneous circulation was 42% in the vasopressin and methylprednisolone group and 33% in the placebo group, a difference that was statistically significant.

Meaning Among patients with in-hospital cardiac arrest, administration of vasopressin and methylprednisolone compared with placebo significantly increased the likelihood of return of spontaneous circulation, but it is uncertain whether there is benefit or harm for long-term survival.

Methods

Trial Design and Oversight

This trial was an investigator-initiated, multicenter, randomized, placebo-controlled, parallel group, double-blind, superiority trial of vasopressin and methylprednisolone during adult in-hospital cardiac arrest.[10] The protocol, which is provided in Supplement 1, was written by the steering committee and approved by the regional ethics committee and the Danish Medicines Agency. Minor differences between the article and the protocol are described in eAppendix 1 in Supplement 2. An independent data monitoring committee oversaw the trial. Oral and subsequent written informed consent was temporarily obtained from a physician independent of the trial until the patient regained capacity or a surrogate became available according to Danish legislation (additional details are provided in the protocol in Supplement 1). Patients or surrogates provided consent for all patients who survived.

Patients

Patients were included from 10 hospitals in Denmark, including 4 large university hospitals. Adult patients (age ≥18 years) were eligible for the trial if they had an in-hospital cardiac arrest and received at least 1 dose of epinephrine during the cardiac arrest. Patients with a cardiac arrest that started outside the hospital were not included. Exclusion criteria included a clearly documented do-not-resuscitate order prior to the cardiac arrest, prior enrollment in the trial, invasive mechanical circulatory support (extracorporeal circulation or left ventricular assist device) at the time of the cardiac arrest, and known or suspected pregnancy at the time of the cardiac arrest.

Randomization

The study kits, and therefore the patients, were randomized in a 1:1 ratio via a random number generator to either vasopressin and methylprednisolone or placebo in blocks with random sizes of 2, 4, or 6. The randomization was stratified according to site.

Intervention

The trial drugs consisted of 40 mg of methylprednisolone (Solu-Medrol, Pfizer) and 20 IU of vasopressin (Empressin, Amomed Pharma GmbH) given as soon as possible after the first dose of epinephrine. Additional doses of vasopressin (20 IU) were administered after each epinephrine dose for a maximum of 4 doses (80 IU). Placebo consisted of 9 mg/mL of sodium chloride from identical ampoules. The trial drugs were placed in a blinded study kit, which was brought to the cardiac arrest by a dedicated member of the clinical cardiac arrest team. The trial was double-blind, with patients, investigators, clinicians, and outcome assessors unaware of the allocated treatment.

Outcomes

The primary outcome was return of spontaneous circulation, which was defined as spontaneous circulation with no further need for chest compressions sustained for at least 20 minutes.[11]

Key secondary outcomes included survival at 30 days and survival at 30 days with a favorable neurologic outcome, which was defined as a Cerebral Performance Category score of 1 or 2. The Cerebral Performance Category score is a 5-point scale assessing neurologic outcomes after brain damage, with higher scores indicating worse outcomes.[12] Additional outcomes, as described below, were considered tertiary outcomes.

Neurologic outcome was also assessed using the modified Rankin Scale, which is a 7-point scale, with higher scores indicating worse outcomes.[13] A score of 0 to 3 was considered a favorable outcome. At 30 days, health-related quality of life was assessed using the EuroQol 5 Dimension 5 Level (EQ-5D-5L) and indexed based on Danish data.[14,15] The results from the EQ-5D-5L are reported both as the numeric value directly assessed by the patient and as the indexed value. The numeric value is reported on a scale from 0 to 100, with higher scores indicating a better health-related quality of life, while the indexed value can also be negative. Outcomes were assessed in person if the patient was still in the hospital and otherwise by a telephone interview. If the patient was not able to participate, a relative or clinical personnel provided the assessment. Similar outcomes were assessed at 90 days, 180 days, and 1 year. Results for the 30- and 90-day follow-up are provided here, while data on longer-term outcomes are still being collected.

As a measure of organ dysfunction after return of spontaneous circulation, we collected data on the Sequential Organ Failure Assessment (SOFA) score at 24, 48, and 72 hours after the cardiac arrest as well as vasopressor- and ventilator-free days within the first 14 days. The SOFA score ranges from 0 to 24, with higher scores indicating worse organ dysfunction.[16] Predefined potential adverse events, including hyperglycemia, hypernatremia, infections, gastrointestinal bleeding, and mesenteric and peripheral ischemia, were also collected, with a full list and definitions provided in the protocol in Supplement 1.

Sample Size Calculation

The sample size was based on the primary outcome of return of spontaneous circulation. Based on unpublished preliminary data from the participating hospitals, we assumed that 45% of patients in the placebo group would achieve return of spontaneous circulation. We assumed an absolute difference of 13% between the placebo and intervention group, corresponding to 58% of patients achieving return of spontaneous circulation in the intervention group. This effect estimate is consistent with the Mentzelopoulos et al[6,7] trials. With these estimates, an α of .05, and the use of the χ^2 test, a total of 492 patients were required to have 80% power to detect a statistically significant difference between groups.

Statistical Analysis

Patients were analyzed according to their randomized assignment. The analyses only included patients receiving the first dose of either of the trial drugs and meeting all inclusion criteria and no exclusion criteria.[17]

Binary data are presented as counts and percentages, and differences between groups are presented as both risk differences and risk ratios with 95% CIs. CIs were estimated using the method described by Miettinen and Nurmimen.[18] Continuous data are presented as means with SDs or medians with first and third quartiles, depending on the distribution of the data. Differences between groups in continuous outcomes are presented as mean differences with 95% CIs obtained from generalized linear models with robust errors. As a sensitivity analysis, the risk ratio for the primary outcome was estimated while adjusting for site and strong prognostic factors, specifically age, whether the cardiac arrest was witnessed, and the initial rhythm, as covariates.[19,20] Modified Poisson regression was used for this analysis.[21]

Two-sided *P* values, obtained from Fisher exact test, are reported for the primary and key secondary outcomes. A *P* value of less than .05 was considered significant. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary outcomes should be interpreted as exploratory. Five subgroup analyses, all prespecified in the protocol, were performed according to the first documented rhythm, witnessed status, patient age, time from cardiac arrest to trial drug administration, and time from epinephrine administration to administration of the trial drug.

All analyses were performed in SAS version 9.4 (SAS Institute).

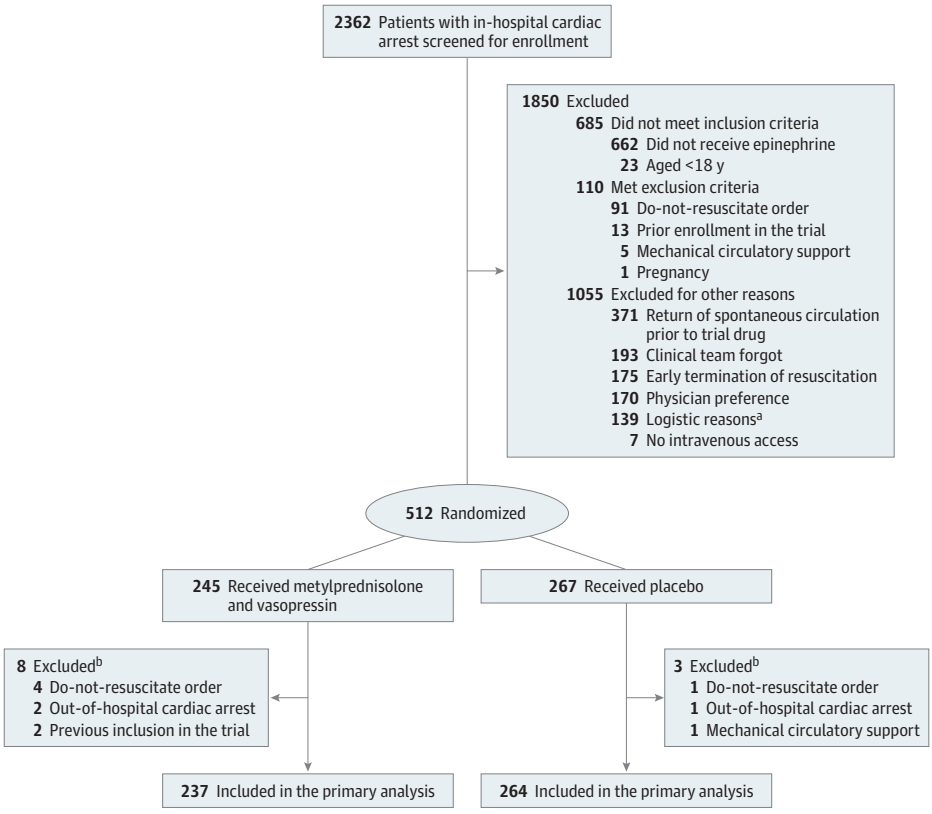
Results

Patient Characteristics

From October 15, 2018, to January 21, 2021, 512 patients were randomized and received the trial drugs (**Figure 1**; eTable 1 in Supplement 2), with the last 90-day follow-up occurring on April 21, 2021. Eleven patients were excluded because they did not meet all inclusion criteria or met at least 1 exclusion criterion, leaving 501 patients for the analysis (237 in the intervention group and 264 in the placebo group). There was no loss to follow-up.

Baseline characteristics were similar between the 2 groups (**Table 1**; eTable 2 in Supplement 2). The mean (SD) age was 71 (13) years and 322 (64%) were men. Most of the cardiac arrests (66%) occurred among patients who were receiving care in standard medical or surgical units and presented with an initial nonshockable rhythm (90%). The median time from the cardiac arrest to epinephrine and trial drug administration was 5 minutes (first and third quartiles: 3, 8) and 8 minutes (first and third quartiles: 6, 12), respectively. Non-trial-related interventions during and after the cardiac arrest were generally similar between groups (eTables 3 and 4 in Supplement 2). There were 14 patients (3%) who did not receive the methylprednisolone/placebo trial drug but received vasopressin/placebo and 8 patients (2%) who did not receive the vasopressin/placebo trial drug but received methylprednisolone/placebo (eTable 5 in Supplement 2). Of those receiving vasopressin/placebo, 139

Figure 1. Screening and Randomization in the VAM-IHCA Trial of Methylprednisolone and Vasopressin for In-Hospital Cardiac Arrest



[a] Logistic reasons included not enough personnel (n = 61), no study drug available (n = 45), inability to obtain surrogate consent (n = 1), and other (n = 32), which included patients isolated with COVID-19.

[b] Patients who were excluded after receiving the trial drugs had inclusion/exclusion criteria not known at the time of the cardiac arrest.

(28%), 145 (29%), 81 (16%), and 128 (26%) received 1, 2, 3, and 4 doses, respectively (eTable 5 in Supplement 2).

Primary Outcome

There were 100 patients (42%) in the intervention group and 86 patients (33%) in the placebo group who achieved return of spontaneous circulation, corresponding to a risk ratio of 1.30 (95% CI, 1.03-1.63; risk difference, 9.6% [95% CI, 1.1%-18.0%]; P = .03; **Table 2**). The risk ratio was slightly higher when adjusting for site and prognostic factors (risk ratio, 1.38 [95% CI, 1.10-1.72]). Results were generally consistent across predefined subgroups (**Figure 2**). The median time to return of spontaneous circulation was 16 minutes (first and third quartiles: 12, 25) in the intervention group and 18 minutes (first and third quartiles: 11, 31) in the placebo group.

Secondary Outcomes

At 30 days, 23 patients (9.7%) in the intervention group and 31 patients (12%) in the placebo group were alive (risk ratio, 0.83 [95% CI, 0.50-1.37]; risk difference, −2.0% [95% CI, −7.5% to 3.5%]; P = .48). A favorable neurologic outcome, based on the Cerebral Performance Category score, was observed in 18 patients (7.6%) in the intervention group and 20 patients (7.6%) in the placebo group at 30 days (risk ratio, 1.00 [95% CI, 0.55-1.83]; risk difference, 0.0% [95% CI, −4.7% to 4.9%]; P > .99). Results for survival and favorable neurologic outcome were generally consistent across predefined subgroups (eFigures 1 and 2 in Supplement 2).

Tertiary Outcomes

A favorable neurologic outcome at 30 days, based on the modified Rankin Scale score, was observed in 11 patients (4.6%) in the intervention group and 19 patients (7.2%) in the placebo group (risk ratio, 0.64 [95% CI, 0.32-1.31]; risk difference, −2.6% [95% CI, −6.9% to 1.7%]). Health-related quality of life did not differ between groups at 30 days (Table 2).

Outcomes at 90 days are presented in Table 2 and eFigure 3 in Supplement 2 and showed no statistically significant difference between groups.

Post-cardiac arrest organ dysfunction, as assessed by the SOFA score, were not statistically significantly different between groups, as were the number of vasopressor- and ventilator-free days (eTable 6 in Supplement 2). Additional details about the outcomes are reported in eTables 7, 8, and 9 in Supplement 2.

Adverse Events

Predefined potential adverse events are reported in eTable 10 in Supplement 2. In patients with return of spontaneous

Table 1. Baseline Characteristics According to Treatment Assignment[a]

Characteristic	No. (%)	
	Vasopressin and methylprednisolone (n = 237)	Placebo (n = 264)
Patient characteristics		
Age, y	71 (13)	70 (12)
Sex		
Male	148 (62)	174 (66)
Female	89 (38)	90 (34)
BMI[b]	26 (23-31)	26 (23-31)
Medical history[c]		
Arterial hypertension	148 (62)	167 (63)
Coronary artery disease	76 (32)	92 (35)
Atrial fibrillation	69 (29)	66 (25)
Diabetes	69 (29)	78 (30)
Pulmonary disease	67 (28)	82 (31)
Cancer	55 (23)	49 (19)
Kidney disease	54 (23)	49 (19)
Chronic heart failure	47 (20)	56 (21)
Stroke	46 (19)	40 (15)
Venous thromboembolism	15 (6)	14 (5)
Liver disease	8 (3)	11 (4)
Dementia	5 (2)	3 (1)
Any glucocorticoids prior to hospital admission	34 (14)	30 (11)
Interventions prior to cardiac arrest		
Kidney replacement therapy	25 (11)	20 (8)
Invasive mechanical ventilation	20 (8)	30 (11)
Vasopressor infusion	13 (5)	23 (9)
Cardiac arrest characteristics		
Location		
Hospital ward	163 (69)	168 (64)
Intensive care unit	23 (10)	18 (7)
Emergency department	19 (8)	38 (14)
Cardiac catherization laboratory	12 (5)	23 (9)
Operating room	4 (2)	3 (1)
Other[d]	16 (7)	14 (5)
Monitored	87 (37)	121 (46)
Witnessed	168 (71)	202 (77)
Initial rhythm		
Pulseless electrical activity	134 (57)	138 (52)
Asystole	82 (35)	95 (36)
Ventricular fibrillation	17 (7)	22 (8)
Ventricular tachycardia	4 (2)	9 (3)
Time from cardiac arrest recognition to		
Epinephrine administration, min	5 (3-7)	5 (3-8)
Drug administration, min	8 (6-12)	9 (6-12)

Abbreviation: BMI, body mass index.

[a] Continuous variables are presented as means with SDs or medians with first and third quartiles and categorical variables as counts and percentages.

[b] Data not available on 13 patients in the intervention group and 10 patients in the placebo group. Calculated as weight in kilograms divided by height in meters squared.

[c] Definitions are provided in eAppendix 2 in Supplement 2. Medical history was based on review of the electronical medical record.

[d] Other includes multiple different locations including the radiology department, the dialysis department, the psychiatric department, and outside departments (eg, hospital entrance).

circulation, hyperglycemia occurred in 77 (77%) in the intervention group and 63 (73%) in the placebo group. Hypernatremia occurred in 28 (28%) and 27 (31%) in the intervention and placebo groups, respectively.

Table 2. Outcomes According to Treatment Assignment[a]

	Vasopressin and methylprednisolone (n = 237)	Placebo (n = 264)	Difference, % (95% CI)[b]	Risk ratio (95% CI)	*P* value
Primary outcome					
Return of spontaneous circulation	100 (42)	86 (33)	9.6 (1.1 to 18.0)	1.30 (1.03 to 1.63)	.03
Secondary outcomes					
30-d Outcomes					
Survival	23 (9.7)	31 (12)	−2.0 (−7.5 to 3.5)	0.83 (0.50 to 1.37)	.48
Favorable neurologic outcome (CPC 1-2)[c]	18 (7.6)	20 (7.6)	0.0 (−4.7 to 4.9)	1.00 (0.55 to 1.83)	>.99
Favorable neurologic outcome (mRS 0-3)[d]	11 (4.6)	19 (7.2)	−2.6 (−6.9 to 1.7)	0.64 (0.32 to 1.31)	
EQ-5D-5L[e]	62 (15)	56 (23)	6 (−4 to 17)		
EQ-5D-5L-Index[e]	45 (37)	40 (33)	5 (−14 to 24)		
90-d Outcomes					
Survival	20 (8.4)	24 (9.1)	−0.7 (−5.7 to 4.5)	0.93 (0.53 to 1.62)	
Favorable neurologic outcome (CPC 1-2)[c]	18 (7.6)	20 (7.6)	0.0 (−4.7 to 4.9)	1.00 (0.55 to 1.83)	
Favorable neurologic outcome (mRS 0-3)[d]	15 (6.3)	20 (7.6)	−1.3 (−5.8 to 3.4)	0.84 (0.44 to 1.58)	
EQ-5D-5L[e]	70 (18)	69 (18)	1 (−9 to 11)		
EQ-5D-5L-index[e]	69 (32)	72 (26)	−3 (−20 to 14)		

Abbreviations: CPC, Cerebral Performance Category; EQ-5D-5L, EuroQol 5 Dimension 5 Level; mRS, modified Rankin Scale.

[a] Continuous variables are presented as means with SDs and categorical variables as counts and percentages.

[b] Risk difference for binary outcomes and mean difference for continuous outcomes.

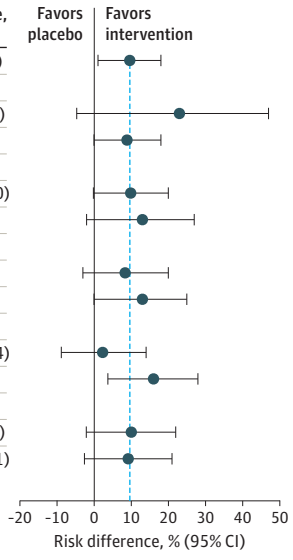
[c] Cerebral Performance Category is a 5-point scale assessing neurologic outcomes after brain damage, with higher scores indicating worse outcomes. A score of 1 or 2 is considered a favorable outcome.

[d] The mRS is a 7-point scale with higher scores indicating worse outcomes. A score of 0 to 3 is considered a favorable outcome.

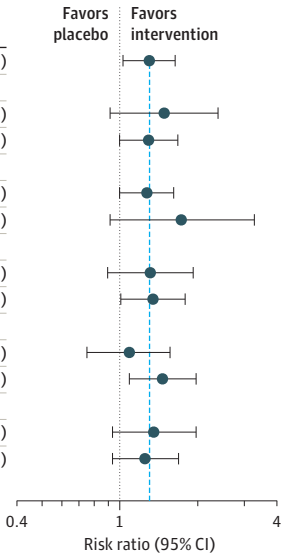
[e] The results from the EQ-5D-5L are reported both as the numeric value directly assessed by the patient and as the indexed value. The numeric value is reported on a scale from 0 to 100, with higher scores indicating a better health-related quality of life, while the indexed value can also be negative.

Figure 2. Subgroups Results for Return of Spontaneous Circulation

	No./total (%)		
	Vasopressin and methylprednisolone	Placebo	Risk difference, % (95% CI)
Overall	100/237 (42)	86/264 (33)	9.6 (1.1 to 18)
Initial rhythm			
Shockable	15/21 (71)	15/31 (48)	23 (-4.7 to 47)
Nonshockable	85/216 (39)	71/233 (30)	8.9 (0 to 18)
Witnessed			
Yes	79/168 (47)	75/202 (37)	9.9 (-0.2 to 20)
No	21/69 (30)	11/62 (18)	13 (-2 to 27)
Age, y			
>72	45/127 (35)	33/122 (27)	8.4 (-3 to 20)
≤72	55/110 (50)	53/142 (37)	13 (0.3 to 25)
Time from arrest to trial drug, min			
>8	38/115 (33)	41/135 (30)	2.7 (-8.8 to 14)
≤8	62/122 (51)	45/129 (35)	16 (3.7 to 28)
Time from epinephrine to trial drug, min			
>2	42/110 (38)	35/124 (28)	10 (-2.1 to 22)
≤2	58/127 (46)	51/140 (36)	9.2 (-2.6 to 21)



Risk ratio (95% CI)



Subgroup results are presented for 5 predefined subgroups. Continuous variables were dichotomized at the median. The time of the cardiac arrest corresponds to the recognition of the cardiac arrest. The blue dashed lines indicate overall effect.

Discussion

In this trial, the combination of vasopressin and methylprednisolone compared with placebo administered during in-hospital cardiac arrest resulted in a statistically significant improvement in the primary outcome of return of spontaneous circulation. There were no differences in the secondary outcomes including survival and favorable neurologic outcome at 30 and 90 days.

The administration of vasopressin, which is also known as antidiuretic hormone, results in vasoconstriction. Because of this effect, vasopressin has been recommended as a second-line vasoactive agent in the setting of septic shock.[22] Vasoconstriction is also of interest in relation to cardiac arrest, because an increase in arterial blood pressure may increase the coronary perfusion pressure and thereby the chance of return of spontaneous circulation,[23,24] a prerequisite for longer-term survival. Despite these potential beneficial effects, trials of vasopressin in primarily out-of-hospital cardiac arrest have failed to show an improvement in outcomes, perhaps partly due to the late administration of drugs in this setting.[25] Corticosteroids, another drug often used in the setting of septic shock due to a reduction in vasopressor requirements,[26] exerts a wide range of functions in the body, including regulation of metabolism, inflammation, and cell proliferation. Studies in patients with cardiac arrest have demonstrated that levels of cortisol are higher in patients who have been resuscitated when compared with patients who have not been resuscitated,[27] which may illustrate an impaired endocrine response in nonsurvivors. This is supported by animal studies where the administration of hydrocortisone during cardiac arrest increased return of spontaneous circulation.[28] Data on glucocorticoid administration during human cardiac arrest are limited, and small studies have shown conflicting results.[29]

In the 2 trials by Mentzelopoulos et al,[6,7] the investigators found improvements in return of spontaneous circulation as well as an improvement in survival to hospital discharge. The current trial found an improvement in return of spontaneous circulation with a risk ratio of 1.30, which is consistent with the previous trials' findings.[6,7] However, contrary to the previous trials, there was no improvement in survival. In the current trial, the point estimate for survival suggested harm, while the confidence included both clinically relevant harm and benefit. There are a number of possible explanations for the difference in results between the current and the previous trials. First, the previous trials included the administration of post-cardiac arrest hydrocortisone to patients with circulatory shock in the intervention group.[6,7] Second, in the previous trials, research personnel administered the trial interventions, whereas it was administered by the clinical personnel in the current trial. Thus, while the current approach is more consistent with clinical practice, it might have resulted in a delay in the administration of the trial drugs compared with the previous trials. Third, there are important differences in patient characteristics. Patients in the previous trials were younger and more often had a cardiac arrest that was witnessed, occurring in the intensive care unit, and with an initial rhythm of asystole.[6,7] Survival in the control group was higher in the current trial despite a lower proportion of patients with return of spontaneous circulation.[6,7]

Trials within cardiac arrest have found that intracardiac arrest pharmacological interventions can increase return of spontaneous circulation with little or no clear improvement in long-term outcomes.[4,5] In the current trial, there was an absolute increase of 9.6% in return of spontaneous circulation. Other than epinephrine, this effect is larger than what previously has been shown for any other pharmacological intracardiac arrest intervention. Return of spontaneous circulation is the principal goal of cardiopulmonary resuscitation and a prerequisite for longer-term survival. The mechanistic goal of vasopressin and methylprednisolone is to increase return of spontaneous circulation and it is possible that other interventions, including post–cardiac arrest interventions, are needed to translate this effect into improvements in longer-term outcomes.

The current trial has strengths. Within the context of in-hospital cardiac arrest,[3] the trial was large and included more patients than the 2 previous trials combined. The trial was multicenter and included hospitals of various sizes. Long-term outcomes, including quality of life, were obtained from all patients with no loss to follow-up.

Limitations

The trial has several limitations. First, a large proportion of patients, who were potentially eligible, were not included (Figure 1). While this has no influence on the trial's internal validity, it could affect generalizability.

Second, while the median time to drug delivery was only 8 minutes, the drug was delivered relatively late in some patients. This could influence the results but is likely a reflection of clinical practice.

Third, the trial was powered to the primary outcome of return of spontaneous circulation. Given the much lower proportion of patients with survival and favorable neurologic outcome, the trial was not powered for these outcomes. The results cannot exclude potential benefit or harm of the intervention on these outcomes.

Fourth, while overall survival might appear low in the current trial (8%-9%), this is likely a reflection of the inclusion criteria, which required administration of at least 1 dose of epinephrine. Outcomes for cardiac arrest in Denmark are generally favorable compared with other countries.[2,3]

Conclusions

Among patients with in-hospital cardiac arrest, administration of vasopressin and methylprednisolone, compared with placebo, significantly increased the likelihood of return of spontaneous circulation. However, there is uncertainty whether this treatment results in benefit or harm for long-term survival.

ARTICLE INFORMATION

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Author Contributions: Dr Andersen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Andersen and Granfeldt.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Andersen and Granfeldt.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Andersen and Holmberg.
Obtained funding: Andersen.
Administrative, technical, or material support: All authors.

Conflict of Interest Disclosures: Dr Andersen reported receiving grants from Aarhus University Research Foundation, the Department of Clinical Medicine at Aarhus University, and Independent Research Fund Denmark, and nonfinancial support from Amomed Pharma GmbH, which provided trial drug during the conduct of the study. Dr J. Kjærgaard reported receiving grants from the Novo Nordisk Foundation (NNF17OC0028706) outside the submitted work. Dr Lauridsen reported receiving grants from Independent Research Fund Denmark during the conduct of the study. Dr Kurth reported receiving personal fees from Teva, TotalEnergies, Eli Lilly & Company, and *The BMJ* outside the submitted work. Dr Granfeldt reported receiving personal fees from Noorik Biopharmaceuticals outside the submitted work. No other disclosures were reported.

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Meeting Presentation: Presented via livestream for Critical Care Reviews; September 29, 2021.

Data Sharing Statement: See Supplement 3.

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Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest – A Randomized, Double-Blind, Placebo-Controlled Trial

Acronym: VAM-IHCA

TRIAL PROTOCOL

Version 1.8

Oct 30, 2020

EudraCT number: 2017-004773-13

ClinicalTrials.gov number: NCT03640949

Principal investigator and sponsor:

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Content

Preface

The "Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest – A Randomized, Double-Blind, Placebo-Controlled Trial" (VAM-IHCA) will be conducted according to this protocol. The trial will be conducted in accordance with all applicable national and international laws, regulations, and guidelines including the revised version of the Declaration of Helsinki[1], European regulations[2], and the international Good Clinical Practice guidelines[3]. The trial and this protocol is developed in accordance with the International Conference on Harmonization (ICH) guidelines[3-5] and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement[6,7]. The principal investigator wrote the protocol with input from the steering committee. Any substantial changes or amendments to the protocol will be clearly documented and communicated to all relevant parties.

30/10 - 2020

Lars W. Andersen, M.D., M.P.H., Ph.D., D.M.Sc. Date

List of abbreviations

CPC: Cerebral performance category

CPR: Cardiopulmonary resuscitation

ICH: International Conference on Harmonization

IDMC: Independent data-monitoring committee

IHCA: In-hospital cardiac arrest

ILCOR: International Liaison Committee on Resuscitation

mRS: Modified Rankin scale

OHCA: Out-of-hospital cardiac arrest

ROSC: Return of spontaneous circulation

SOFA: Sequential organ failure assessment

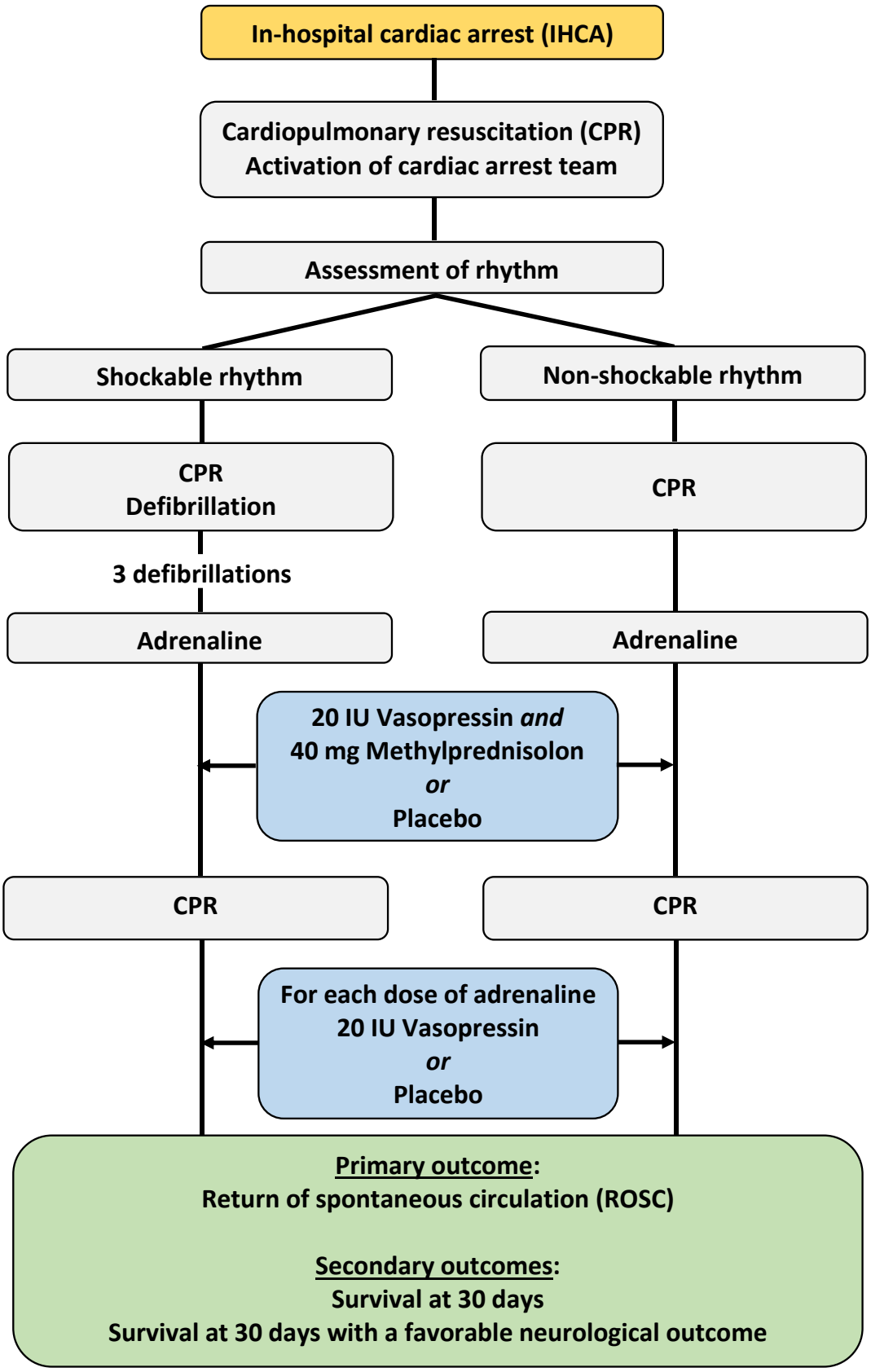
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

VSE: Vasopressin, steroids, and epinephrine

Overview

Registry and trial number	EudraCT number: 2017-004773-13, ClinicalTrials.gov number: NCT03640949
Date of registration	EudraCT: 25/1-2018, ClinicalTrials.gov: 21/8-2018
Sources of monetary or material support	Aarhus University Research Foundation Department of Clinical Medicine, Aarhus University Independent Research Fund Denmark Amomed Pharma GmbH (only vasopressin)
Primary sponsor	Lars W. Andersen, Aarhus University
Contact	Lars W. Andersen, lwandersen@clin.au.dk
Title	Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest – A Randomized, Double-Blind, Placebo-Controlled Trial
Country of recruitment	Denmark
Condition studied	In-hospital cardiac arrest
Interventions	Methylprednisolone (40 mg) *combined with* Vasopressin (20 IU per adrenaline dose, maximum 80 IU)
Comparator	Placebo (for both methylprednisolone and vasopressin)
Inclusion criteria	1) In-hospital cardiac arrest 2) Age ≥ 18 years 3) Received at least one dose of adrenaline during CPR
Exclusion criteria	1) Clearly documented "do-not-resuscitate" order prior to the cardiac arrest 2) Prior enrollment in the trial 3) Invasive mechanical circulatory support at the time of the cardiac arrest 4) Known or suspected pregnancy at the time of the cardiac arrest
Study type	Interventional — Allocation: Randomized (1:1) Intervention model: Parallel group — Masking: Double-blind
Date of first screening	Sept. 17, 2018
Target sample size	492
Recruitment status	Recruiting
Primary outcomes	Return of spontaneous circulation
Key secondary outcomes	Survival at 30 days Survival at 30 days with a favorable neurological outcome (cerebral performance category 1 or 2)

Trial flow chart



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Conflicts of interest

The members of the steering committee have no conflicts of interest related to the current trial. A list of all conflict of interests is provided in Appendix 1.

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Amendments

Version 1.7 (May 14, 2020) to 1.8 (Oct. 30, 2020)

- Corrections of minor typos and grammatical issues as well as minor clarifications
- Minor change to the publication plan (section 12)
- Removal of three sites including site investigators (multiple sections)
- Multiple changes to the statistical analyses plan including (section 6):
    - Change of the primary analysis
    - Addition of a sensitivity analysis for the primary outcome
    - Subgroup analyses on both the relative and absolute scale
    - Only reporting P values for certain key outcomes
    - Removal of two subgroup analyses and addition of two
    - Analysis of survival to 90 days as a binary outcome

Version 1.6 (Nov. 11, 2019) to 1.7 (May 14, 2020)

- Addition of four new sites (multiple sections)
- Change of site investigator in Viborg from Therese Straarup to Kim B. Pælestik (multiple sections)
- Addition of Mathias Holmberg to the steering committee (multiple sections)
- Corrections of minor typos and grammatical issues

Version 1.5 (Apr. 4, 2019) to 1.6 (Nov. 11, 2019)

- Change of site investigator in Aalborg from Signe Juul Riddersholm to Jacob Moesgaard Larsen (multiple sections)
- Addition of a subgroup analysis based on time from adrenaline administration to first study drug and removal of the site subgroup analysis (section 6.2.3)
- Addition of funding (section 14)

Version 1.4 (Sep. 12, 2018) to 1.5 (Apr. 4, 2019)

- Addition of four sites + site investigators (multiple sections)

Version 1.3 (Mar. 19, 2018) to 1.4 (Sep. 12, 2018)

- Corrections of minor typos and grammatical issues
- Change of address for the principal investigator (title page)

- Addition of EudraCT and ClinicalTrials.gov numbers (title page)
- Update of the overview table
- Addition of Kasper Glerup Lauridsen as a site investigator in Randers (multiple sections)
- Change of site investigator in Aalborg from Jacob Moesgaard Larsen to Signe Juul Riddersholm (multiple sections)
- Reference to Appendix 2 in section 3.3.3
- Clarification that the study kits will be created at Skanderborg Pharmacy (section 3.3.3 + 3.3.4)
- Clarification that the site investigator and the research nurse will also be responsible for study kits at each site (section 3.3.4)
- Change in exclusion criteria from "Extracorporeal circulation at the time of the cardiac arrest" to "Invasive mechanical circulatory support at the time of the cardiac arrest" (section 4.3)
- Minor change in the definition of hospital disposition (section 5.3)
- Addition of a reference to COSCA (section 5.3)
- Change in definition of vasopressor-free days (section 5.3)
- Addition of invasive ventilation-free days as a tertiary outcome (section 5.3)
- Change in the timepoints of SOFA score calculation from 4 and 24 hours to 24, 48, and 72 hours (section 5.3 + 7.2.4)
- Change in the definition of hyperglycemia (section 5.4.3)
- Change in definition of prior use of glucocorticoids from 5 days to 14 days (section 6.2.3)
- Addition of a subgroup analysis related to time from cardiac arrest to first study drug (section 6.2.3)
- Clarification that multiple imputation will only be performed if missing data is substantial (< 10%) (section 6.2.5)
- Clarification that data collection will not include the timing of the methylprednisolone dose (section 7.1)
- Removal of ethnicity as a variable (section 7.2.2)
- Removal of the reference to the updated IHCA Ustein guidelines (section 7.2.1)
- Addition of the Glasgow Outcome Scale Extended (section 7.2.4)
- Change in terminology from "legally authorized surrogate" and "next of kin" to "surrogate" (section 9.2.2 + 9.3.2)
- Clarification that the legal guardian cannot be related to trial procedures for the specific patient but can be involved in trial procedures for other unrelated patients (section 9.2.3 + 9.3.2)
- Update indicating approval by the regional ethics committee (section 9.3)

- Removal of sentence stating that data on non-enrollled patients can be obtained from DANARREST (section 11.3)
- Addition of Appendix 2
- Minor updates to Appendix 3
- Addition of Appendix 4
- Removal of Appendix 6 and 7
- Appendix 8 renumbered as Appendix 6 and updated

Version 1.2 (Jan. 24, 2018) to 1.3 (Mar. 19, 2018)

- Change of the primary pharmacy to Skanderborg Pharmacy
- Addition details provided on the follow-up telephone interview (section 5.3)
- Clarification that the trial has been reported to the Danish Data Protection Agency (section 7.4)
- Clarification that consent after the cardiac arrest will be obtained by a physician (section 9.3.2)
- Addition of feasibility data from Odense (section 11.2)
- Clarification that shared data will be completely anonymized according to Danish law (section 13)

Version 1.1 (Jan. 24, 2018) to 1.2 (Jan. 24, 2018)

- Change of the primary pharmacy to Pharma Skan ApS
- Addition of Odense University Hospital as a site (multiple sections)

Version 1.0 (Aug. 31, 2017) to 1.1 (Jan. 24, 2018)

- Corrections of minor typos and grammatical issues
- Clarification of the intervention being the combination of methylprednisolone and vasopressin (Overview, Trial flow chart)
- Clarification that the vasopressin placebo ampules and vasopressin ampules are identical (section 3.3.2)
- Production and labelling of the study kits at Pharma Skan ApS instead of the university pharmacy (section 3.3.3 and 3.3.4)
- Clarification that that the unblinded pharmacy staff will not be involved in outcome evaluation (section 3.4)
- Storage of medicine at room temperature as oppose to 2°C to 8°C (section 3.3.3)
- Clarification that the site investigator will keep track of study kits at each site (section 3.3.4)

- Clarification that data will also be obtained from the case report forms (section 3.5.1)
- Removal of E-Learning as a modality for education of study personnel (section 3.5.2)
- Clarification that patients who re-arrest in the emergency department can be included if they had sustained ROSC prior to the cardiac arrest (section 4.2)
- Definition of ROSC when patients are put on extracorporeal circulation redefined (section 5.1.1)
- Addition of the Glasgow Outcome Scale Extended for neurological outcome (section 5.3)
- Addition of a section of reporting of adverse events (section 5.4.6)
- Clarification of the follow-up after 90 days (section 5.5)
- Addition of a draft of the CONSORT flow diagram (section 6.2.1 + Appendix 3)
- Addition of two subgroup analyses according to the location of the cardiac arrest and the prior use of glucocorticoids (section 6.2.3)
- Addition of ordinal logistic regression (section 6.2.4)
- Various additions to the data collection (section 7.2)
- Clarification that the IDMC, the Good Clinical Practice unit, and regulatory agencies will have access to all relevant trial data (section 7.5)
- Clarification of the “legal guardian” (section 9)
- Clarification that consent for future data collection will be obtained from the legal guardian and the patient’s next of kin if the patient is not able to provide consent (section 9.3.2)
- Clarification that the study results will be published irrespective of the results (section 12)
- Funding updates (overview and section 14)
- Removal of the section on potential expansion of the trial (section 15)
- Addition of Appendix 8: Charter for the independent data-monitoring committee (IDMC)

1. BACKGROUND

1.1 In-hospital cardiac arrest

1.1.1 Incidence and mortality

In-hospital cardiac arrest (IHCA) is relatively common with an estimated 200,000 treated cases in the United States each year.[8] Although no published data is currently available on the incidence of IHCA in Denmark, we estimate that approximately 2500-3000 IHCA occur each year. Unfortunately, outcomes remain poor with approximately 60% achieving return of spontaneous circulation (ROSC) and only 20-30% surviving to hospital discharge.[9-11] Furthermore, in initial survivors, there are substantial post-discharge morbidity and early mortality.[10,12-14]

1.1.2 An understudied entity

Clinical trials are sparse in cardiac arrest[15,16], and especially in IHCA[17], relative to the burden of the condition. In a systematic review of all randomized clinical trials involving cardiac arrest from 1995 to 2014, Sinha et al. found that 81 (88%) were exclusively in out of hospital cardiac arrest (OHCA), 7 (8%) involved OHCA and IHCA, and only 4 (4%) involved exclusively IHCA. The total number of included patients were 83 times higher in OHCA studies as compared to IHCA studies.[18]

Currently, there is a scarcity of evidence-based pharmacological interventions for IHCA.[19-21] The evidence for adrenaline (epinephrine) and amiodarone, the only two drugs currently recommended, is limited and based on extrapolation from OHCA.[19-23] There is therefore an, currently unmet, need for additional randomized clinical trials in IHCA in order to advance the science and improve patient outcomes.

1.1.3 Pathophysiology

In broad terms, cardiac arrest can be divided into three phases: pre-cardiac arrest, intra-cardiac arrest, and post-cardiac arrest, where intra-cardiac arrest can be further divided into a no-flow (no circulation) and a low-flow (circulation induced by chest compressions) phase. One of the main drivers of poor outcomes after cardiac arrest is the duration of the cardiac arrest (i.e. no-flow and low-flow time); for each minute increase in the length of the cardiac arrest, mortality substantially increases.[24,25] Because of this, and since ROSC is a prerequisite for more long-term survival, the main goal of intra-cardiac arrest interventions is to establish ROSC and limit the duration of the cardiac arrest.

The pathophysiology of cardiac arrest and the post-cardiac arrest syndrome is complex and has been described in extensive details elsewhere.[26-28] Ischemia during the cardiac arrest and subsequent ischemia-reperfusion injury activates multiple harmful pathways including systemic inflammation, endothelial

activation, activation of immunological and coagulation pathways, adrenal insufficiency, mitochondrial damage, and microvascular dysfunction.[26] Consequently this leads to a clinical state (the post-cardiac arrest syndrome) with global brain injury, impaired myocardial function, macrocirculatory failure, and increased susceptibility to infections.[26] Patient are often hemodynamically unstable following a cardiac arrest and early post-cardiac arrest hypotension is strongly associated with poor outcomes.[29]

1.2 Vasopressin

1.2.1 Pharmacology

Vasopressin (also known as antidiuretic hormone or arginine vasopressin) is a nonapeptide produced in the hypothalamus and secreted into the circulation through the posterior pituitary gland. Vasopressin exerts its effects through binding to one of its three receptor subtypes V1-V3. The V1 receptor mediates vasoconstriction, while binding to V2 mediates the antidiuretic effects in the kidney and activation of the V3 receptor in the pituitary gland stimulates the secretion of hormones. During states of shock, levels of vasopressin are low and exogenously administered vasopressin exerts profound vasoconstrictive effects. Where the vasoconstrictive effects of other vasopressors are reduced in conditions of hypoxia and acidosis the vasoconstrictive effects of vasopressin are maintained.[30] When administered intravenously, vasopressin has a half-life of approximately 10 to 35 minutes[31,32]

1.2.2 Use outside cardiac arrest

Vasopressin is licensed in several countries, including the United States, Sweden, Germany, and the United Kingdom, to treat refractory shock in patient with sepsis. The 2016 Surviving Sepsis Guidelines recommends vasopressin as the second-line vasopressor after noradrenaline.[33] Vasopressin might also be beneficial in other forms of shock.[34] Terlipressin and desmopressin, synthetic vasopressin analogs with slower onset but longer duration[35,36], are licensed in Denmark for the treatment of esophageal varices bleeding and diabetes insipidus, respectively.

1.2.3 Use in cardiac arrest

The rationale for the use of vasopressin during cardiac arrest is based on studies demonstrating that plasma levels of vasopressin are lower in non-survivors compared to survivors[37], and that vasopressin, through its potent vasoconstrictive properties, increases the coronary perfusion pressure and thereby the chance of ROSC.[38,39] These properties lead to clinical trials where vasopressin was compared to standard treatment.[40-43] Only one relatively small trial included IHCA patients.[44] In a meta-analysis of six randomized clinical trials,

there was no overall benefit of vasopressin administration during cardiac arrest.[41] However, there were a potential benefit in subgroups according to a first rhythm of asystole and early (< 20 minutes) drug administration.[41] In addition, a recent meta-analysis demonstrated that the administration of vasopressin increases the rate of ROSC and survival in patients with in-hospital arrest.[43] These latest findings are largely based on studies by Mentzelopoulos et al.[45,46] as described in more detail in section 1.4.

1.3 Methylprednisolone

1.3.1 Pharmacology

Methylprednisolone is a synthetic glucocorticoid which is a class of corticosteroids that is part of the larger group of steroid hormones. Glucocorticoids are produced in the adrenal cortex and exerts a wide range of functions in the body including regulation of metabolism, inflammation, and cell proliferation.[47] During situations with stress, glucocorticoids are secreted as a defense mechanism exerting widespread physiological functions.[48] The primary effect of glucocorticoids is exerted through binding to the glucocorticoid receptor followed by translocation to the nucleus where it modulates gene transcription through binding to glucocorticoid-responsive elements.[49] This is termed the genomic effects of glucocorticoids and it takes hours for a response to fully develop.[50] However, glucocorticoids also possess rapid (within minutes) non-genomic effects through interaction with cellular membranes and receptors, which are relevant in the setting of cardiac arrest.[49-51] Methylprednisolone is administered intravenously and has a biological half-life of approximately 12 to 36 hours.[52]

1.3.2 Use outside cardiac arrest

Methylprednisolone is primarily licensed in Denmark as Solu-medrol® (Pfizer). Clinically, glucocorticoids have been used for decades in the treatment of various diseases due to its anti-inflammatory effects[53] and methylprednisolone is on the World Health Organization's list of essential medicines[54]. Glucocorticoids are used in several acute and critical conditions including bacterial meningitis, anaphylactic shock, and severe asthma or chronic obstructive pulmonary disease exacerbations. Glucocorticoids have been especially well-studied in the setting of septic shock where treatment with glucocorticoids increases shock reversal (i.e. weaning for vasopressor support) and may lower mortality.[55]

1.3.3 Use in cardiac arrest

Studies in patients with cardiac arrest have demonstrated that levels of cortisol are higher in patients that are resuscitated when compared to patients that are not resuscitated[56] which may illustrate an impaired

endocrine response in non-survivors. This is supported by animal studies where the administration of hydrocortisone during cardiac arrest increases ROSC rates.[57] This may relate to the cardiovascular effects of glucocorticoids which include increases in enzymes involved in adrenaline synthesis, inhibition of catecholamine re-uptake and breakdown, and by enhancement of cardiovascular sensitivity to catecholamines by increasing the binding capacity and affinity.[48,58] Data on glucocorticoid administration during human cardiac arrest is limited and small studies have shown conflicting results.[59]

1.4 The vasopressin, steroids, and epinephrine (VSE) trials

In two trials, published in 2009 and 2013, Mentzelopoulos et al. examined the effect of adding vasopressin and glucocorticoids to standard treatment in IHCA.[45,46] In these two Greek, randomized, double-blind trials, the authors compared the addition of vasopressin (20 IU for each dose of adrenaline) and glucocorticoids (40 mg methylprednisolone) during cardiac arrest to placebo. After the cardiac arrest, patients in the intervention arm furthermore received glucocorticoids (300 mg hydrocortisone) if they had vasopressor-dependent shock. The results, which were published in the *Archives of Internal Medicine* (now *JAMA Internal Medicine*) and the *Journal of the American Medical Association (JAMA)*, were remarkable. The combined rate of ROSC was 148/178 (83%) in the intervention group vs. 118/190 (62%) in the control arm ($p < 0.001$). In the first trial, survival to hospital discharge was higher in the intervention group as compared to the placebo group (9/48 [19%] vs. 2/52 [4%], $p = 0.02$).[45] In the second trial, the primary outcome of survival to hospital discharge with a favorable neurological outcome (cerebral performance category [CPC] score of 1 or 2) was higher in the intervention group as compared to the placebo group (18/130 [14%] vs. 7/138 [5%], $p = 0.02$).[46] The authors also showed beneficial effects on post-cardiac arrest hemodynamics, organ failure, and inflammation.[45,46]

1.5 Guidelines regarding vasopressin and glucocorticoids

The VSE trials have received a great deal of attention in the literature with most commentaries arguing for external validation studies before clinical implementation.[60-63] The International Liaison Committee on Resuscitation (ILCOR) reached the same conclusion: "Confidence in the treatment effects from bundled treatments [i.e. vasopressin and glucocorticoids] will increase if confirmed in further studies".[19] The current American and European guidelines from 2015 do not recommend the routine use of vasopressin and glucocorticoids in IHCA primarily due to lack of trials externally validating the findings from the VSE trials.[20,21] The American guidelines recognized the importance of this as a potential therapeutic option but specifically state "… further studies are needed before recommending the routine use of this therapeutic strategy".[21]

1.6 Standard of care

The standard of care during cardiac arrest is described by guidelines from the European Resuscitation Council and the American Heart Association.[20,21] Pharmacological treatment is generally limited to amiodarone/lidocaine and adrenaline for patients with a refractory shockable rhythm and adrenaline for patients with a non-shockable rhythm.[20,21] Although the evidence for amiodarone/lidocaine and adrenaline is limited and controversial[22,23], these drugs are currently recommended and are given, when applicable, to most patients with cardiac arrest. The interventions of the current trial (vasopressin and methylprednisolone) will therefore be compared to placebo and both groups will receive the established standard of care consistent with the two VSE trials.[45,46]

1.7 Post-cardiac arrest glucocorticoids

The intervention in the VSE trials included hydrocortisone for patients with vasopressor dependent shock 4 hours after the cardiac arrest. 300 mg of hydrocortisone was administered per day until shock reversal or for a maximum of 7 days.[45,46] For several reasons, this part of the intervention is not included in the current trial. First, considerable beneficial effects were seen in the original trials before the hydrocortisone was administered. This includes a substantial increase in ROSC as noted above, improvements in early hemodynamics, and an increase in 4-hour survival (intervention: 111/194 [57%] vs. placebo: 96/206 [47%], p = 0.01).[45,46] Second, a separate randomized clinical trial by members of our study team, not including the intra-cardiac arrest interventions, found no benefit of hydrocortisone for post-cardiac arrest patients with vasopressor dependent shock.[64] Third, assessing both intra- and post-cardiac arrest interventions combined does not allow for assessment of the individual effects of each intervention. If the current trial is positive, future trials are needed to then assess the post-cardiac arrest aspect of the VSE trials. Lastly, the primary outcome of the current trial is ROSC which will not be influenced by post-cardiac arrest treatment.

2. TRIAL OBJECTIVES AND HYPOTHESES

Primary objective: To determine whether the combination of vasopressin and methylprednisolone, as compared to placebo, when administered during IHCA, will increase ROSC

Hypothesis: The combination of vasopressin and methylprednisolone administered during IHCA will increase ROSC

Secondary objective: To determine whether the combination of vasopressin and methylprednisolone, as compared to placebo, administered during IHCA will increase survival at 30 days and survival at 30 days with a favorable neurological outcome (CPC score 1 or 2)

Hypothesis: The combination of vasopressin and methylprednisolone administered during IHCA will increase survival at 30 days and survival at 30 days with a favorable neurological outcome (CPC score 1 or 2)

3. TRIAL DESIGN

3.1 Overview

This is an investigator-initiated, multicenter, randomized, placebo-controlled, parallel group, double-blind, superiority trial of vasopressin and methylprednisolone during adult IHCA. There will be 10 enrolling sites in Denmark. 492 adult patients with IHCA receiving at least one dose of adrenaline will be enrolled. The primary outcome is ROSC and key secondary outcomes include survival at 30 days and survival at 30 days with a favorable neurological outcome.

3.2 Allocation

Patients will be randomized in a 1:1 ratio to either vasopressin and methylprednisolone or placebo in blocks with random sizes of 2, 4, or 6. The randomization will be stratified according to site.[65] An independent statistician will create the randomized allocation list using a random number generator. The list will only be shared with the pharmacy, which will not be involved in clinical care. The pharmacy and the independent statistician will both store the randomization list. As described in section 3.3 and section 3.4, sites will be provided with numbered blinded kits including either vasopressin and methylprednisolone or placebo ensuring allocation concealment.

3.3 Interventions

3.3.1 Methylprednisolone and vasopressin

The study drugs will consist of 40 mg methylprednisolone (Solu-medrol®, Pfizer) and 20 IU of vasopressin (Empressin®, Amomed Pharma GmbH) given as soon as possible after the first dose of adrenaline. Additional doses of vasopressin (20 IU) will be administered after each adrenaline dose for a maximum of four doses (80 IU). The drugs will be produced, managed, and stored according to all relevant guidelines and regulations.

These drugs and doses are similar to the original VSE trial.[45,46] However, for practical reasons (i.e. that one ampule of vasopressin contain two doses) this trial will include a maximum of four doses of vasopressin as compared to a maximum of five doses in the original trials.[45,46]

3.3.2 Placebo

The placebo for vasopressin will consist of 1 mL of 9 mg/mL NaCl (“normal saline”) from 2 mL ampules identical to the vasopressin ampules. The placebo for methylprednisolone will also consist of 1 mL of 9

mg/mL NaCl. Normal saline is often administered to critically ill patients and have no effects or side-effects with these very small volumes.

3.3.3 Procedures

The study drugs will be placed in a blinded study kit (a small box, see Appendix 2) containing one 40 mg dose of methylprednisolone (or placebo) and two 40 IU ampules (i.e. four 20 IU doses) of vasopressin (or placebo). The study kits will be prepared at Skanderborg Pharmacy, a company that specializes in the production of medicine and is approved by the Danish Health authorities, and shipped to the participating sites regularly. The study kit will be stored at room temperature and protected from light according to the manufacturers' instructions and brought to the IHCA by a designated member of the cardiac arrest team. Once it is anticipated that the patient will receive at least one dose of adrenaline, the kit will be opened, and the patient will be considered randomized. A designated member of the cardiac arrest team will then prepare the study drugs. Preparation of methylprednisolone will include mixing of the methylprednisolone powder (or placebo) with the solvent in a blinded manner (see section 3.4). The vasopressin (or placebo) will require no mixing. A visual guide showing the procedures will be placed in the kit and cardiac arrest team members will have training in the procedures (see section 3.5.2). We expect that these procedures will take approximately 1 minute and that they will not interfere with the clinical management of the patient. Once prepared, the drugs will be administered as soon as possible after the first dose of adrenaline; first the 20 IU (1 mL) vasopressin and then the 40 mg (1 mL) methylprednisolone (or their respective placebos). Additional doses of 20 IU vasopressin (or placebo) will be administered with each dose of adrenaline which is given every 3-5 minutes irrespective of the underlying rhythm.[20] A maximum of 4 doses of vasopressin (80 IU) will be administered. Only one dose of methylprednisolone will be administered.

3.3.4 Overview of study medication

Study kits will be produced and labelled centrally (Skanderborg Pharmacy). Study kits will be labelled with a unique ID consecutively according to site (e.g. 1XXX for site 1, 2XXX for site 2, etc.). The study kits and drugs will be clearly labelled according to standard practices for clinical trials (see Appendix 2). Study kits will be prepared and shipped to the participating sites on a regular basis. Once a study kit is opened, the site investigator, the research nurse, and the principal investigator will be informed. The central pharmacy will keep a tally of all study kits and make sure, along with the site investigator and the research nurse, that sites are always equipped with enough kits. The site investigator at each site will keep track of all delivered and used study kits. Data on actual drug administration (see section 3.3.3) will be entered in real-time on the

case report form and subsequently into the online database (see section 7). This will ensure optimal tracking of study drug delivery.

3.4 Blinding

The trial will be double-blind; patients, investigators, and the clinical team will be blinded to the allocation. Only the pharmacy providing the blinded, numbered kits will be aware of the allocation. The pharmacy will not be involved with clinical care or outcome evaluation.

Vasopressin placebo will consist of normal saline which, like vasopressin, is colorless and without any identifying features. The normal saline will be stored in 2 mL ampules that are identical to the vasopressin ampules. Furthermore, vasopressin has no distinctive rapid effects (except those related to the trial) resulting in possible identification. We therefore do not anticipate any risk of unblinding.

Methylprednisolone placebo will consist of an empty vial completely covered such that the clinical team cannot distinguish whether the vial is empty or contains the methylprednisolone powder. The methylprednisolone solvent or the NaCl placebo, which are identical in appearance, will be injected into the vial and the vial will be shaken to immediately dissolve the powder. The mixed solution will then be aspirated from the vial and administered to the patient. Since the mixed solution is colorless and without any identifying features, the clinical team will remain blinded to the treatment arm. A similar approach is being used in the ongoing SUP-ICU trial which is a multicenter, double-blind, randomized trial.[66]

In the blinded intervention kit, a sealed opaque envelope will contain the allocation assignment which will allow for emergency unblinding. The decision to unblind will be at the complete discretion of the treating physician and clinical team. However, we do not expect scenarios where emergency unblinding will be necessary. In case unblinding occurs, the reason(s) will be clearly documented in the case report form. The patient will remain in the trial.

3.5 Trial procedures

3.5.1 Patients

The trial procedures will be limited to the interventions given during the cardiac arrest (see section 3.3) and the telephone interviews for long-term follow-up. (see section 5.3 and 5.5). There will be no planned blood draws, other interventions, or additional procedures. Data will be obtained from the study specific case report form, the electronic medical records, and the national Danish IHCA registry (DANARREST) (see section 7).

3.5.2 Clinical personnel

Prior to the beginning of patient enrollment and continuously throughout the enrollment period, the clinical teams involved in IHCA resuscitation at the participating hospitals will be informed about the trial. Clinical personnel will be informed about the background and objectives of the trial, the inclusion/exclusion criteria, the interventions, and the trial procedures they are involved in (see section 3.3.3 and 9.3.2). A demonstration of correct procedures using the study kits will be included. We anticipate formal, in-person didactics quarterly with informal sessions and emails as applicable in between.

4. SETTING AND PATIENT POPULATION

4.1 Setting

The trial will be conducted at 10 hospitals in Denmark. All participating sites have clinical experience and expertise in treating IHCA patients.

4.2 Inclusion criteria

Inclusion criteria:

1) IHCA

2) Age ≥ 18 years

3) Received at least one dose of adrenaline during CPR

Cardiac arrest is defined as unconsciousness, abnormal breathing, and a loss of pulses requiring chest compressions and/or defibrillation. IHCA is defined as any individual with a cardiac arrest on hospital grounds where the IHCA team is activated. This will include patients who re-arrest in the emergency department or elsewhere after an OHCA if they, prior to the re-arrest, had sustained ROSC (i.e. spontaneous circulation for at least 20 minutes).

These broad inclusion criteria were chosen to reflect the inclusion criteria in the two original VSE trials.[45,46] The original trials included primarily patients with a non-shockable rhythm (84%). However, the results were consistent and significant in both those with shockable and non-shockable initial rhythms and there was no subgroup difference (p = 0.90, S. Mentzelopoulos, M.D., Ph.D., written communication, July 2017). We will therefore include IHCA patients with both shockable and non-shockable rhythms.

4.3 Exclusion criteria

Exclusion criteria:

1) Clearly documented "do-not-resuscitate" order prior to the cardiac arrest

2) Prior enrollment in the trial

3) Invasive mechanical circulatory support at the time of the cardiac arrest

4) Known or suspected pregnancy at the time of the cardiac arrest

Occasionally CPR is inadvertently started in patients with a pre-existing "do-not-resuscitate" order. If a "do-not-resuscitate" order is clearly documented in the electronical medical record prior to the cardiac arrest, the patient will be excluded. Patients previously included in the trial will be excluded to avoid statistical complexity related to correlated data. Since information on "do-not-resuscitate" orders and prior enrollment in the trial is documented (but might not be known by the cardiac arrest team) prior to the cardiac arrest and the intervention, any post-randomization exclusions will not lead to bias.[67] Mechanical circulatory support includes extracorporeal circulation and left ventricular assist devises. Patients having an IHCA while on mechanical circulatory support constitutes a very specific patient population with different characteristics and outcomes. They will therefore be excluded. Given that vasopressin and methylprednisolone are generally not recommended in pregnancy, patients with known or suspected pregnancy will be excluded. Cardiac arrest during pregnancy is exceedingly rare[68] and we expect that this exclusion criterion will lead to only few, if any, exclusions. If pregnant patients are included (i.e. if the pregnancy is not known and not obvious), we do not expect any harm to the patient or fetus. Guidelines recommend that cardiac arrest in pregnancy is treated according to usual guidelines including intra-cardiac arrest medications.[69]

4.4 Co-enrollment

There will be no general restrictions on entry into other (post-cardiac arrest) clinical trials although this will be evaluated on a case-by-case basis.[70] We are not aware of any ongoing or planned trials in this patient population in Denmark.

5. OUTCOMES

5.1 Primary outcome

5.1.1 Definition

The primary outcome will be ROSC. ROSC will be defined as spontaneous circulation with no further need for chest compressions sustained for at least 20 minutes. This definition is consistent with the second VSE trial[46], the *Get With the Guidelines® – Resuscitation* registry[11], the Danish registry for IHCA (DANARREST)[71], and the Utstein guidelines[72]. If a patient is placed on extracorporeal circulation during the cardiac arrest, the patient

will only be considered to have ROSC if they are able to be successfully weaned from the extracorporeal circulation with spontaneous circulation for at least 20 minutes.[73]

5.1.2 Rationale

The rationale for any intra-cardiac arrest intervention is primarily to increase the rate of ROSC to subsequently improve the rate of meaningful survival. Since ROSC is a prerequisite for more long-term survival and since the focus of this investigation is intra-cardiac arrest interventions, ROSC is a logical and meaningful primary outcome. ROSC is a core outcome measure in both the IHCA[72] and OHCA[73] Utstein guidelines and is suggested as a potential primary outcome measure by the American Heart Association[74].

5.2 Secondary outcomes

5.2.1 Definitions

The key secondary outcomes will be survival at 30 days and survival at 30 days with a favorable neurological outcome. A favorable neurological outcome will be defined as a CPC score of 1 or 2. The CPC score is a 5-point scale assessing neurological/functional outcomes after brain damage (Table 1).[75] Patients not alive at 30 days will be categorized as a poor neurological outcome.

Table 1. Cerebral performance category (CPC) score

Score	Definition
1	Good cerebral performance Conscious, alert, able to work, might have mild neurologic or psychologic deficit.
2	Moderate cerebral disability Conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
3	Severe cerebral disability Conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
4	Coma or vegetative state Any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
5	Brain death Apnea, areflexia, electroencephalogram silence, etc.

5.2.2 Rationale

Survival at 30 days and survival at 30 days with a favorable neurological outcome are considered key outcome measures in cardiac arrest research.[72-74] The use of 30-day outcomes as compared to outcomes at hospital discharge avoids limitations related to potential difference in discharge practices.[76-78] The use of the CPC score is consistent with the second VSE trial[46], the *Get With the Guidelines® – Resuscitation* registry[11], and recommend by the Utstein guidelines[72,73] and the American Heart Association[74].

5.3 Tertiary outcomes

Tertiary outcomes will include:

1) Vasopressor-free days
2) Invasive ventilation-free days
3) Sequential organ failure assessment (SOFA) score at 24, 48 and 72 hours
4) Hospital disposition
5) Modified Rankin scale (mRS) and Glasgow Outcome Scale Extended (GOSE) at 30 days
6) Health-related quality of life (EQ-5D-5L) at 30 days
7) 90-day outcomes:
   Survival
   Neurological outcome (CPC, mRS, GOSE)
   Health-related quality of life (EQ-5D-5L)

The trial will include additional outcomes focused on hemodynamics, organ failure, additional measures of neurological outcome, and long-term outcomes.

To assess the potential beneficial effects of the intervention on hemodynamics, we will measure vasopressor-free days. A vasopressor will be defined as any continuous infusion of noradrenaline, dopamine, dobutamine, terlipressin, vasopressin, phenylephrine, and/or adrenaline. Vasopressor-free days will be defined as the number of days within the first 7 days after the cardiac arrest where the patient is not receiving vasopressors and is alive. Receiving vasopressors for at least 6 hours on a given day is defined as receiving vasopressors for that day. Contrary to other vasopressor outcomes, such as time to weaning from vasopressors, this outcome accounts for both vasopressor use and mortality.[79] Invasive ventilation-free days will be defined in a similar manner. Invasive ventilation is defined as mechanical ventilation through an endotracheal or tracheostomy tube.

To assess hemodynamics and organ failure, we will calculate SOFA score[80] at 24, 48 and 72 hours after the cardiac arrest in those alive. The SOFA score is a validated and widely used measure of organ failure assessing the respiratory, nervous, cardiovascular, hepatic, coagulation, and renal systems.[80] We will assess both the cardiovascular sub score as well as the overall SOFA score. The calculation of the SOFA score will be based on available clinical and laboratory data. Laboratory and clinical data closest to the given time point will be used. If a given component (e.g. bilirubin) is not available, it will be assumed to be within normal ranges. If PaO_2 values are not available, they will be imputed using imputations based on SpO_2 values.[81,82]

To further characterize neurological outcome and to allow for comparison with other trials and meta-analyses, the mRS[83] and GOSE[84] at 30 days and hospital disposition (e.g. home, rehabilitation, nursing home, hospice) will be collected. Hospital disposition will be defined at the time of discharge from the initial acute care hospital.

We will include 90-day survival as a measure of long-term survival. 90 days were chosen since it is unlikely that later mortality will be directly linked to the cardiac arrest or the trial interventions. 90 days is also consistent with recommendations from the American Heart Association.[74]

Both 30-day and 90-day survival will be obtained from the follow-up phone interview or the Danish Civil Personal Register which allows for accurate and virtually complete follow-up.[85] Neurological outcome (CPC, mRS and GOSE) and health-related quality of life (EQ-5D-5L[86]) at 30 and 90 days will be assessed via telephone communication with the patient or a surrogate. The telephone interview will be semi-structured and based on the GOSE and the EQ-5D-5L questionnaires. The interview will be conducted by a centrally located and trained member of the research team according to detailed standard operating procedures. In case the patient is still in the hospital, this interview will be face-to-face. In addition to CPC, both the mRS and health-related quality of life are recommended as outcome measures by the AHA.[74] Assessment of neurological outcome and health-related quality of life per telephone is valid and reliable.[87,88] A structured interview will be used to determine CPC, mRS, and GOSE.[84]

The mRS is a 7-point scale, ranging from 0 (no symptoms) to 6 (dead), assessing the degree of disability and dependence after a neurological injury such as stroke or cardiac arrest. A good outcome will be defined as a mRS of 0 to 3 and a poor outcome as 4 to 6. The GOSE is a 8-point scale that is an extension of the Glasgow Outcomes Scale (which is identical to the CPC, only with inverse scores) where the scores 1, 2 and 3 from the CPC score is divided into two.[84] The EQ-5D-5L is a well-established measure of health-related quality of life that is quantified as a utility (i.e. a measure of quality of life between 0 and 1). In addition to being a relevant outcome in itself, this will also allow for potential future cost-effectiveness analyses and comparison to the background population.

All outcomes recommended by the recent COSCA initiative (Core Outcome Set for Cardiac Arrest) are included in the current study.[89]

5.4 Harm

5.4.1 General consideration

Patients with IHCA have an in-hospital mortality of 70 to 80% and many patients experience post-cardiac arrest complications such as global brain injury, impaired myocardial function, macrocirculatory failure, and increased susceptibility to infections.[26] Furthermore, patients suffering from IHCA often have multiple underlying conditions including heart failure, myocardial infarction, respiratory insufficiency, diabetes, infections, and/or renal insufficiency.[90] The immediately preceding cause might be related to circulatory failure (e.g. cardiogenic shock, sepsis), respiratory failure (e.g. pneumonia, chronic obstructive pulmonary disease), arrhythmias (e.g. primary arrhythmias, myocardial infarction), or rarely neurological disorders.[91-94] Given this, it is difficult, if not impossible, to comprehensively report all adverse events and assess their possible relationship with the intervention in this patient population. Both vasopressin and methylprednisolone are considered safe and are commonly used in clinical practice. The overall benefit and potential harm of the interventions will be captured in our primary and secondary outcomes. Any specific adverse events suspected by the clinical team to be related to the intervention will be documented.

5.4.2 Definitions

The following definitions will be used[2]:

Adverse event: any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment

Serious adverse event: any untoward medical occurrence that at any dose requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death

Unexpected serious adverse reaction: a serious adverse reaction, the nature, severity, or outcome of which is not consistent with the reference safety information

5.4.3 Specific adverse events

To assess specific adverse and potentially serious adverse events (primarily related to methylprednisolone), we will collect data on the following:

1) Hyperglycemia (> 180 mg/dL or 10 mmol/L[95]) within the first 48 hours
2) Requirement for a continuous insulin infusion (≥ 1 hour) within the first 48 hours
3) Hypernatremia (> 145 mmol/L[96]) within the first 48 hours
4) New infections after the cardiac arrest during the hospital stay (defined below)
    4a) Bacteremia
    4b) Pneumonia
    4c) Urinary tract infections
5) New or changing antibiotics after the IHCA during the hospital stay
6) Clinical diagnosis of gastrointestinal bleeding after the IHCA requiring at least one blood transfusion during the hospital stay
7) Acute mesenteric ischemia based on a clinical diagnosis (signs and symptoms, colonoscopy and/or radiology findings) leading to surgery[97]
8) Peripheral (i.e., limps or digits) ischemia based on a clinical diagnosis (signs and symptoms and/or radiology findings) leading to surgery

Assessment of adverse events will be based on available laboratory values and clinical data. No specific procedures or blood draws will be performed.

Given the complexity of the post-cardiac arrest syndrome, it is difficult to diagnose and precisely define new infections in this patient population. For example, the new Sepsis-3 definitions[98-100] do not readably apply since many post-cardiac arrest patients will have a change in SOFA score ≥ 2 irrespective of any ongoing infection. Furthermore, fever is difficult to assess during the early post-cardiac arrest period where targeted temperature management is often utilized. Infections included here are therefore restricted to those that can be, at least partly, objectively defined and those that are the most common after cardiac arrest.[101,102] Bacteremia will be defined as a positive blood culture (not including presumed contamination or non-pathogenic bacteria not leading to antibiotics) obtained after the cardiac arrest. Pneumonia will be defined as new or progressive consolidation on a chest radiograph and at least two of the following: fever (> 38°C), leukocytosis (white blood cell count ≥ 12,000 cells/µL) or leukopenia (white blood cell count < 4,000 cells/µL), or the presence of purulent tracheobronchial secretions.[103,104] Urinary tract infection will be

defined as a positive urine culture (≥ 100,000 colony-forming units/mL from a pathogenic organism) obtained after the cardiac arrest.[105]

5.4.4 Timeline

Vasopressin has a half-life of approximately 10 to 35 minutes[31] and methylprednisolone has a biological half-life of approximately 12 to 36 hours[52]. There is therefore no anticipation of adverse events after hospital discharge as patients with IHCA have long hospital stays.[106] The above mentioned adverse events will therefore only be assessed during the hospital stay.

5.4.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reactions (SUSAR) will be reported to the independent data-monitoring committee (IDMC) (see section 10.2) and the regulatory authorities as applicable. Given the consideration outlined in section 5.4.1, most events or conditions, including but not limited to organ failure, infection, tissue ischemia, brain damage, cardiac arrest, and death, will not be considered SUSARs. This approach is compatible with an ongoing international, multicenter trial in post-cardiac arrest (ClinicalTrials.gov Identifier: NCT02908308). No events, including those outlined in section 5.4.3, will automatically lead to unblinding.

5.4.6 Reporting

Once a year the sponsor will submit a list of all registered adverse events that have occurred during the trial period as a well as a report on safety of the trial subjects to the Danish Medicines Agency. The sponsor will notify the Danish Medicines Agency when the trial has been completed (no later than 90 days thereafter) or if earlier than planned, the reasons for stopping the trial must be given. The results from the clinical trial including important adverse events will be recorded on EudraCT.

5.5 Additional follow-up

The primary trial and publication will be related to the study outcomes (section 5.1, 5.2, and 5.3). However, extended follow-up at six months and 1 year, including overall survival, neurological outcomes, and health-related quality of life, will be collected and reported. Data will be collected and analyzed like the 90-day outcomes and will be reported in a separate publication. Although the overall trial will be unblinded after the collection of the 90-day outcomes, the person assessing six months and 1-year outcomes will be blinded to treatment assignment.

6. SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS PLAN

6.1 Sample size calculation

The trial will be powered to the primary outcome of ROSC. In the original trials, the combined rate of ROSC was 148/178 (83% [95%CI: 77%, 88%]) in the intervention group and 118/190 (62% [95%CI: 55%, 69%]) in the placebo group for an absolute risk difference of 21% and a relative risk of 1.34.[45,46] For this trial, we assume a ROSC rate of 45% in the control group (based on preliminary data from some of the participating sites [see section 11.2]). We assume an absolute difference of 13% between the control and intervention group corresponding to a ROSC rate of 58% in the intervention group and a relative risk of 1.29. With these estimates, an alpha of 0.05, and the use of the chi-squared test, we will need a total of 492 patients (i.e. 246 in each group) to have 80% power to detect a statistically significant difference between groups.

With an estimated survival rate of 20% (see section 11.2), an alpha of 0.05, and the use of the chi-squared test, the power of the trial to detect a significant difference between groups is illustrated in Figure 1 according to various estimates of treatment effect (i.e. risk ratios). Of note, the risk ratio for survival to hospital discharge was 4.87 (95%CI: 1.11, 21.4) in the first VSE trial and 2.73 (95%CI: 1.18, 6.32) for survival to hospital discharge with a favorable neurological outcome in the second VSE trial.[45,46] The trial will have ≥ 98% power to detect a risk ratio of ≥ 1.80 with a survival rate of 20% or higher in the placebo group. Sample size and power was calculated with PROC POWER in SAS v. 9.4 (SAS Institute, Cary, NC, USA).

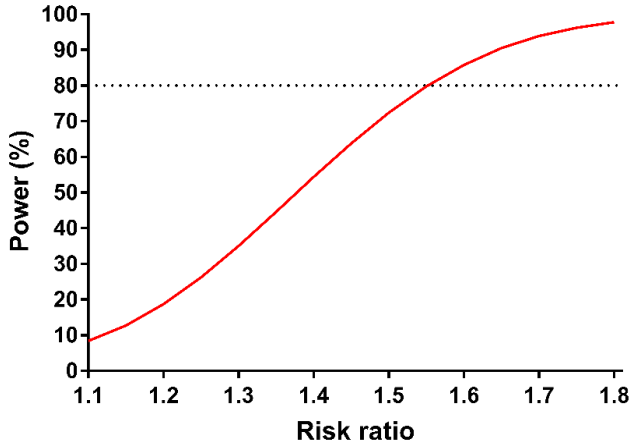


Figure 1. Relationship between treatment effect (risk ratio) for survival and trial power

6.2 Statistical analysis plan

6.2.1 General considerations

The statistical analyses and reporting will adhere to the CONSORT guidelines.[107,108] All tests will be two-sided, a P value < 0.05 will be considered significant, and all confidence intervals will have 95% coverage. P values will only be reported for the primary outcome and the two key secondary outcomes.

Patient inclusion and exclusion will be illustrated in a CONSORT flow diagram (see Appendix 3 for a draft).

All analyses will be conducted on a modified intention-to-treat basis only including patients receiving the first dose of the study drug and meeting all inclusion criteria and no exclusion criteria (except criteria #4: pregnancy). In a double-blind trial, this approach is unbiased while increasing precision.[67]

The two groups will be compared in relation to baseline patient and cardiac arrest characteristics using descriptive statistics.

The persons conducting the statistical analysis will be blinded to the randomized allocation and the statistical analysis will be performed separately by two investigators. Groups will be designated as "A" and "B" until all pre-specified analyses are performed and shared with all authors and the IDMC (see section 10.2).

6.2.2 Primary and secondary outcomes

The primary and secondary outcomes (binary variables) will be presented as counts and proportions in each group. Results will be reported as both risk ratios and risk differences. 95% confidence intervals will be obtained using methods described by Miettinen and Nurmimen.[109] In case results are significantly different between groups, the number needed to treat (with 95% confidence intervals) will also be provided. P values will be obtained from Fisher's Exact test.

As a sensitivity analysis, we will estimate the risk ratio with 95% confidence intervals for the primary outcome while adjusting for center and strong prognostic factors, specifically age, whether the cardiac arrest was witnessed, and the initial rhythm, as covariates.[110-113] Small centers (i.e. those with less than 30 patients included) will be combined. The risk ratio will be estimated from a log-binomial regression model.[114] If this model fails to converge, a modified Poisson regression model will be used instead.[114,115] Age will be included as a linear continuous variable and the initial rhythm as a binary variable (shockable or non-shockable).

6.2.3 Subgroup analyses

Subgroup analyses will be performed on both the absolute and relative scale. The analyses will include five pre-defined subgroup analyses for the primary and key secondary outcomes according to 1) first

documented rhythm, 2) whether the cardiac arrest was witnessed, 3) patient age (dichotomized by the median) , 4) time from cardiac arrest to first study drug (dichotomized by the median), and 5) time from adrenaline administration to first study drug (dichotomized by the median). First documented rhythm will be categorized as non-shockable (i.e. asystole or pulseless electrical activity) or shockable (i.e. ventricular fibrillation or pulseless ventricular tachycardia). The trial is not powered to detect subgroup differences, and these will be considered exploratory and hypothesis generating.

6.2.4 Addition analyses and outcomes

For the tertiary outcomes vasopressor-free days, SOFA scores, and health-related quality of life (continuous variables) differences between groups will be estimated using a linear regression model. SOFA scores and health-related quality of life will only be assessed in those alive at the time of measurement.

Survival until 90 days will be presented with Kaplan-Meier curves but will otherwise be analyzed as a binary outcome as described in section 6.2.2

Adverse events and other binary outcomes will be presented and analyzed like the primary and secondary outcomes.

As additional exploratory analyses, ordinal neurological outcomes (i.e. CPC, mRS, GOSE) will be analyzed using ordinal logistical regression.[124] Before these analyses, the proportional odds assumption will be tested. In case the proportional odds assumption is not met, ordinal logistical regression will not be performed, and data will be presented descriptively.

6.2.5 Missing data

Missing data will be reported in the relevant publications. We do not expect any missing data for the primary outcome or the key secondary outcomes. For mortality up to 90 days, there may be some very limited loss to follow-up. We do not expect missing data on the vasopressor-free days, SOFA scores, or adverse events. There might be some limited missing data for neurological outcomes and health-related quality of life at 90 days (and potentially at 30 days) due to loss to follow-up. Multiple imputation using known risk factors for outcomes after IHCA will be used to impute values for patients with missing data if missing data is substantial (> 10%).

6.2.6 Multiple comparisons

No adjustments will be made for multiple comparisons. The rationale for this approach is three-fold. First, the trial has a clearly defined primary outcome which will ensure that the risk of a Type I error (i.e. false positives) is equal to the set alpha (i.e. 0.05) for this outcome. Second, the simplest procedure to control the

family-wise error rate is the Bonferroni correction where the alpha is divided by the number of tests performed within the "family" of tests. However, defining the "family" is difficult and at best arbitrary.[125,126] Third, any adjustment for multiple comparisons to control the family-wise error rate increases the chance of Type II errors (i.e. false negatives).[126] Given that the risk of Type I errors is not well defined when conducting multiple secondary analyses, these specific analyses should be considered exploratory and hypothesis generating.

6.2.7 Statistical stopping criteria

Since the primary outcome is not mortality, there will be no formal stopping criteria for efficacy. There will be no predefined stopping criteria for futility since enrollment of the full cohort might allow for detection of efficacy in subgroups or in other outcomes even if the primary outcome is neutral. Furthermore, since two previous randomized clinical trials have shown efficacy[45,46], a neutral trial with an adequate sample size will be important. For potential stopping due to safety concerns, see section 10.2.

7. DATA COLLECTION AND MANAGEMENT

7.1 Data collection process

A trained research nurse, along with the site investigators, will be responsible for data collection and entry. Very limited data will be obtained from the clinical cardiac arrest team in real-time on a numbered case report form (see Appendix 4) that accompanies the study kit. This will include the patient identifier (i.e. CPR number), timing of the first adrenaline dose, timing of the first vasopressin dose, and the total doses of vasopressin administered. This, along with the telephone interviews for long-term follow-up, will be the only source data and all additional data will be obtained from the electronical medical records or DANARREST (see section 7.6) and will be based on measurements and assessments made by the clinical team. Data will be entered directly into the database software (see section 7.4).

7.2 Variables

7.2.1 Overview

All IHCA patients at the participating sites will be entered into a screening log. For those not randomized, a specific reason for non-inclusion/exclusion will be documented. All randomized patients who received the study drug will be entered into the main database.

A detailed data dictionary that clearly defines all included variables will be created prior to patient enrollment. The data dictionary will provide the name of the variable (including the code used in the

database), a detailed definition of the variable, categories for categorical variables, and units and ranges for continuous variables.

The number of collected variables will be kept relatively small to limit resource use and data entry mistakes. The included variables largely follow the IHCA Utstein guidelines from 1997.[72] Below is provided a brief overview of the included variables but details are reserved for the data dictionary.

7.2.2 Pre-cardiac arrest characteristics

Trial related variables

- Study ID
- Site
- Receipt of study medication
  - If no, reason for no study medication provided
- Doses of study medication provided
- Requirement for emergency unblinding
- Inclusion criteria
- Exclusion criteria
- Date and time consent for data collection is obtained

Patient demographics and characteristics

- Name
- Unique patient identifier (CPR number)
- Age
- Sex
- Race
- Height
- Weight

Conditions/medications prior to the cardiac arrest

- Co-morbidities (cardiac and non-cardiac)
- CPC score and mRS prior to current hospital admission
- Reason for admission
- Length of stay prior to the cardiac arrest
- Receipt of glucocorticoids within the last month

Use of oral or intravenous glucocorticoids during the current admission

Previous IHCA during this admission

7.2.3 Cardiac arrest characteristics

Location and time

Location of the cardiac arrest

Date and time of the cardiac arrest

Interventions in place

Vasopressors

Mechanical ventilation

Intravenous access

Renal replacement therapy

Cardiac arrest variables prior to the intervention

Presumed cause of the cardiac arrest

Initial rhythm

Witnessed

Time to first rhythm analysis

Cardiac arrest variables after the intervention

Date and time of the end of resuscitation (ROSC or termination without ROSC)

7.2.3 Post-cardiac arrest characteristics

Targeted temperature management

If yes, target temperature and duration

Cardiac catheterization, percutaneous coronary intervention, and coronary artery bypass grafting

Procedures related to neurological prognostication (e.g. EEG, imaging, biomarkers)

Use of intravenous glucocorticoids

Renal replacement therapy

Adverse events (see section 5.4.3)

7.2.4 Outcomes

ROSC

SOFA scores at 24, 48, and 72 hours

Vasopressor-free days

Hospital disposition

Survival at 30 and 90 days

CPC score at 30 and 90 days

mRS at 30 and 90 days

Glasgow Outcome Scale Extended at 30 and 90 days

EQ-5D-5L at 30 and 90 days

7.3 Data quality and validity

Data quality and validity will be optimized by having a single trained research nurses enter all data according to a detailed data dictionary. REDCap (see section 7.4) is designed such that data forms contain field-specific validation checks ensuring that mandatory fields are filled out and that continuous variables are within predefined ranges. Given its limited utility, double-data entry will not be performed.[127,128]

7.4 Data storage and security

The database application we will use is REDCap.[129] REDCap is a professional database that provides a user-friendly interface. The REDCap data management system is secure, fully compliant with all regulatory guidelines, and includes a complete audit-trail for data entry validation. Through these mechanisms, as well as relevant training for all involved parties, patient confidentiality will be safeguarded. REDCap is available for free at participating sites.

The short paper case report form and the consent form for each patient will initially be stored in a secure, locked place at the individual sites. Every half year these will be transported to the Research Center for Emergency Medicine in Aarhus while a copy will remain at the sites. Here they will be securely stored in locked cabinets, where only the principal investigator and the research nurse will have access. The files will be stored for 5 years after the end of the trial, where after they will be destroyed.

The trial has been reported to the Danish Data Protection Agency.

7.5 Data access

During the trial, the principal investigator and the research nurse will have access to the entire database, while site investigators will have access to data from their own sites. Once the database is locked, a deidentified version of the database will be made available to the members of the steering committee. The IDMC, the Good Clinical Practice unit, regulatory agencies, and other relevant entities will have direct access to patients' records and to all relevant trial data including the case report form as applicable.

7.6 DANARREST

For the intra-cardiac arrest characteristics, data is captured in real-time by the clinical cardiac arrest team as part of a nationwide quality improvement registry (DANARREST).[9,71] DANARREST is a quality improvement registry that aims to track the epidemiology of IHCA in Denmark. All hospitals in Denmark will participate within a few years and the clinical personnel are required to enter data. A Danish version of the DANARREST case report form is provided in Appendix 5.

8. CLINICAL TREATMENT

The clinical management of included patients will be at the complete discretion of the treating clinical team in order to test the interventions in a real-life clinical scenario. In general, management will adhere to the intra- and post-cardiac arrest guidelines provided by the European Resuscitation Council[130] and the Danish Resuscitation Council[131] but no specific treatments will be prohibited or mandated. The sites will be informed about the most recent guidelines for intra-cardiac arrest care and will be encouraged to limit premature termination of resuscitation efforts.[132] Sites will also be encouraged to follow European Resuscitation Council post-cardiac arrest guidelines[95] including appropriate neurological prognostication.

9. ETHICAL CONSIDERATIONS

9.1 Clinical equipoise

9.1.1 Potential benefits

Details about the potential benefits of the intervention are provided in the background section (section 1.2, 1.3, and 1.4). In brief, randomized controlled trials, primarily in the OHCA setting, have found no benefit or harm of sole vasopressin administration.[41] The data on steroid administration during cardiac arrest is more limited and have shown conflicting results although no study has shown harm.[59] The combination of

vasopressin and glucocorticoids has been tested in two randomized, double-blind trials finding significant and meaningful increases in ROSC, survival, and survival with a favorable neurological outcome.[45,46]

9.1.2 Potential harms

The two VSE trials found no signs of significant harm with the combination of vasopressin and glucocorticoids during cardiac arrest.[45,46] In the first VSE trial there was an increase in the number of hyperglycemic episodes on day 2 and 3 in the intervention arm.[45] In the second VSE trial, there was a small increase in the proportion of patients receiving post-cardiac arrest insulin in the intervention arm.[46] Randomized clinical trials in other intensive care unit populations such as those with sepsis have found a small increase in hyperglycemia and hypernatremia, but no increased risk of infections, gastrointestinal bleeding, or muscular weakness, with small to moderate doses of glucocorticoids.[55,133,134] The idea that glucocorticoids could impair cardiac healing after myocardial infarction is based on old case reports.[135] A meta-analysis of controlled trials of glucocorticoids in patients with acute myocardial infarction found no association with myocardial rupture and in fact noticed a decrease in mortality with the administration of glucocorticoids.[136]

9.1.3 Risk/benefit ratio

From the data provided above in section 9.1.1. and 9.1.2 and in the background section (section 1.2, 1.3, and 1.4), the current risk/benefit ratio is encouraging for vasopressin and methylprednisolone administered during IHCA. However, given the potential lack of generalizability of the two VSE trials, international guidelines are currently not recommending this treatment but instead calls for additional clinical trials.[19-21] Taken together, there is clear clinical equipoise for the combination of vasopressin and methylprednisolone during IHCA.

9.2 Research in cardiac arrest

9.2.1 General considerations

Research in cardiac arrest is ethically challenging for two reasons: 1) Patients are unconsciousness and can therefore not provide informed consent and 2) treatment must be administered within minutes limiting the possibility of obtaining informed consent from a legally authorized representative.[137,138] Despite these challenges, there is an ongoing need to conduct research in this, and similar, patient populations to improve outcomes. International guidelines, such as the revised Declaration of Helsinki[1], European regulations[2], and

the Good Clinical Practice guidelines[3], clearly supports research in such populations. For example, the revised Declaration of Helsinki states:

"Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative."[1]

The current trial will adhere to the revised Declaration of Helsinki as well as all applicable laws and regulatory guidelines.

9.2.2 Danish regulations

Danish law allows research without informed consent in situation where the following criteria are met[139,140]:

1) The research can only be conducted in the given acute situation
2) The patient is incapable of providing informed consent
3) Consent cannot be obtained from a surrogate given the urgency of the intervention
4) The research specifically involves the patient's current condition
5) There is a possibility of benefit to the patient

The current trial fulfils all the above criteria as described in section 9.2.3 for #1-4 and for #5 in section 9.1. Under these circumstances, research with pharmacological interventions is allowed if the following is obtained[139-141]:

1) Consent is obtained from a designated "legal guardian" ("forsøgsværge" in Danish)
2) Informed consent is obtained from the patient or a surrogate as soon as feasible

A “legal guardian” is a physician not involved in the research related to the specific patient and who are not in an inferior/superior position to the investigator/sponsor, who should act according to the interest of the research participant.

9.2.3 Regulations in relation to the current trial

#1. The research can only be conducted in the given acute situation
Given the high morbidity and mortality of IHCA (see section 1.1.1), clinical trials are highly needed to improve patient outcomes. Animal studies do not adequately reflect the clinical condition of cardiac arrest[142] and human trials are needed to advance the treatment of cardiac arrest patients. There is no other clinical condition that reflects cardiac arrest and any study aimed to improve outcomes for cardiac arrest patients can therefore only be conducted in this population.

#2. The patient is incapable of providing informed consent
IHCA is an unpredictable and sudden event that often occurs in patients that are already acutely sick. It is therefore impossible to obtain consent prior to the event. During the cardiac arrest, patients are unconscious and therefore not able to provide consent.

#3. Consent cannot be obtained from a surrogate given the urgency of the intervention
Cardiac arrest is an acute event that often lasts for less than 30 minutes.[106] The intervention will be administered as soon as possible after the first adrenaline dose, which is given as soon as possible in patients with a non-shockable rhythm (most often < 5 minutes from the beginning of the cardiac arrest[143]) and after the third defibrillation in patients with a shockable rhythm (approximately 6-7 minutes after the beginning of the cardiac arrest[20]). Given these time frames, it would be impossible to obtain consent from a surrogate.

#4. The research specifically involves the patient’s current condition
The interventions in this trial is specifically targeted for IHCA patients and if proven effective, will benefit this patient population.

9.3 Procedures

9.3.1 Ethical review committee

The trial has been approved by the regional ethics committee (case number: 1-10-72-42-18).

9.3.2 Trial-specific procedures

The "legal guardian" will be either a physician member of the cardiac arrest team or a physician on call and available 24/7. The physician might be involved in the clinical care of the patient but will not be involved in trial procedures related to the specific patient. The legal guardian can be involved in trial procedures for other unrelated patients. Through ongoing training and information (see section 3.5.2), the "legal guardian" will be aware of the trial including the background and significance, inclusion/exclusion criteria, and potential risks and benefits. This way, the "legal guardian" will be able to make an informed and prompt decision about patient enrollment. The specific details related to the "legal guardian" (i.e. who will be the designated "legal guardian") will be site-specific.

As soon as possible, consent for future data collection will be obtained by a physician from the patient or if the patient is not able to provide consent, then by the legal guardian and a surrogate. The consent form will be signed by the patient or a surrogate and the person obtaining the consent. If a patient dies before it is possible to obtain consent (we anticipate that approximately 50% will not survive the cardiac arrest, see section 6.1), patient data will be included in the trial.[144] If a patient denies future participation in the trial, no additional data will be collected but all data collected up until the point of withdrawal will be included consistent with Danish law.[145]

When approached, the patient or a surrogate will be informed, verbally and in writing, about the background and significance of the study, inclusion criteria, potential risks and benefits, as well as a brief description of the study protocol. They will be informed that no additional interventions or procedures, except the telephone interviews for long-term follow-up, will be performed and that future participation will only include data collection. The patient or the surrogate will then provide written informed consent utilizing the informed consent form approved by the ethical review committee. When consent is obtained from participants or a surrogate, information about potential de-identified data sharing will also be included.

9.3.3 Insurance

The patients in the study are covered by the Danish patient insurance.[146]

10. MONITORING

10.1 Good Clinical Practice monitoring

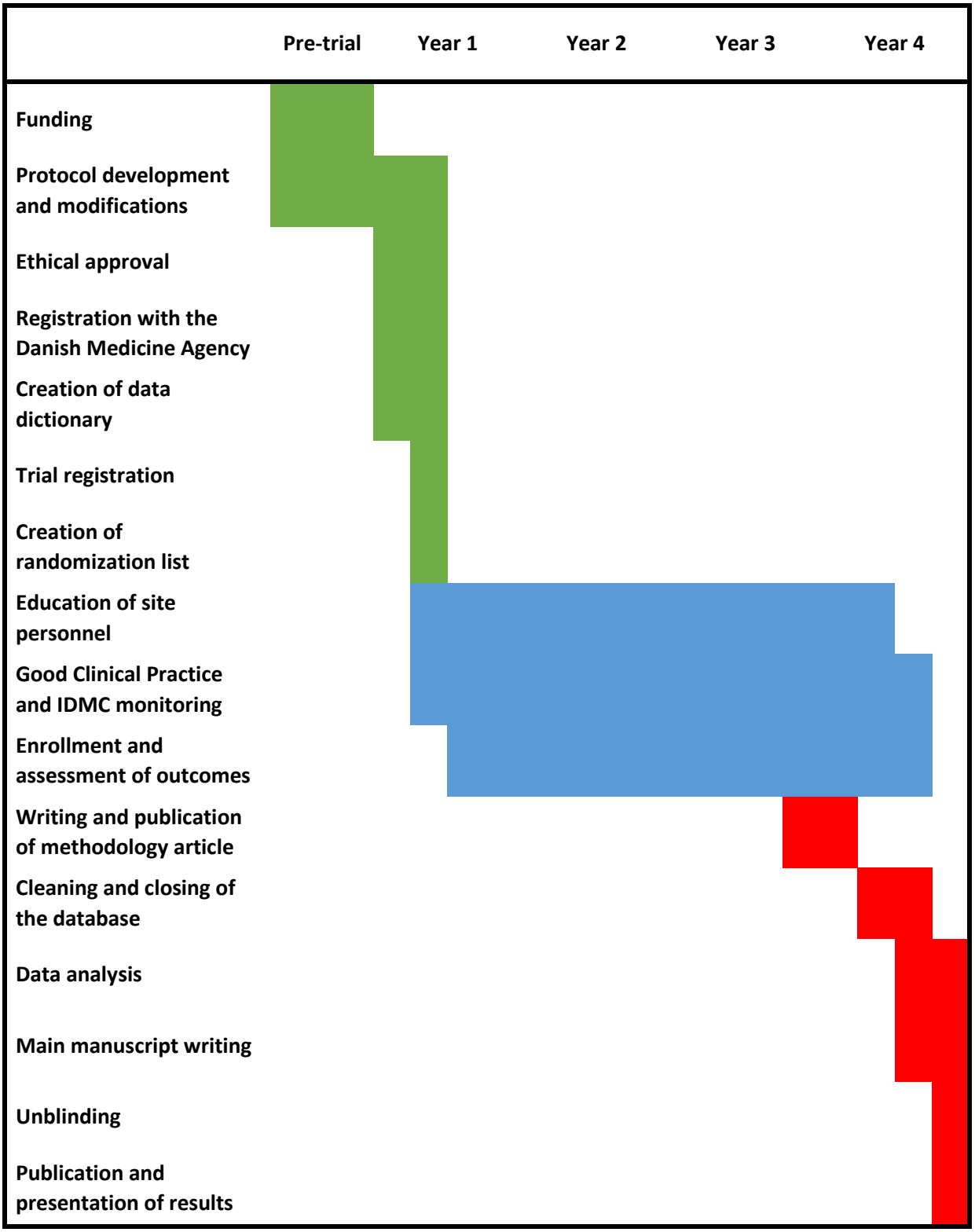
The sites will be monitored by the regional Good Clinical Practice monitoring units affiliated with the participating sites. A detailed monitoring plan will be developed prior to trial commencement.

10.2 Independent data-monitoring committee (IDMC)

The IDMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The IDMC will consist of three individuals: two clinicians/trialist with expertise in cardiac arrest/critical care research and a biostatistician/epidemiologist. The IDMC members will be chosen such to avoid any financial or intellectual conflicts of interest. The IDMC will be independent from the sponsor and the trial investigators. The IDMC will review deidentified data on a yearly basis (or more often if determined by the IDMC) for safety; unless there are group differences necessitating unblinding (as determined by the IDMC), the IDMC will be blinded to treatment groups. The trial will continue while the IDMC review data. After the yearly review, the IDMC will create a short report to the steering committee with recommendations for continuation, modifications, or termination of the trial. As noted in section 6.2.7, there will be no formal stopping criteria for efficacy or futility. Criteria for recommending termination will be at the discretion of the IDMC and there will be no formal statistical criteria for termination due to safety. The final decision regarding potential modifications or termination will rest with the steering committee and the principal investigator. A detailed charter for the IDMC is provided in Appendix 6.

11. TIMELINE AND ENROLLMENT

11.1 Timeline



11.2 Feasibility

Data from 2016 from five of the participating hospitals are provided in Table 2. As illustrated, we expect that approximately 457 patients will be eligible for enrollment each year. Given the acuity of IHCA, we do not assume that all eligible patients will be enrolled. However, given the large number of eligible patients, we will reach our target sample size over approximately 3 years of active enrollment (see section 11.1) with an enrollment rate as low as 35%. With the addition of more sites, we expect enrollment to happen faster.

Table 2. 2016 data from participating hospitals

Hospital	IHCA with indication for CPR	IHCA with ≥ 1 dose of adrenaline given (i.e. target population)	ROSC in IHCA with ≥ 1 dose of adrenaline given	30-day survival in IHCA with ≥ 1 dose of adrenaline given
Aarhus – Skejby*	100	58	21 (36%)	11 (19%)
Randers	75	56	16 (29%)	7 (13%)
Aalborg – South	208	132	60 (45%)	22 (17%)
Rigshospitalet	198	177	80 (45%)	33 (19%)**
Odense	63	34	15 (44%)	8 (24%)
Total	**644**	**457**	**192 (42%)**	**81 (18%)**

* This site is currently expanding as it is merging with two other hospitals. We therefore expect a higher number of annual IHCA at this site.

** Estimated based on the ROSC rate and data from the other sites

11.3 Enrollment

Enrollment at each site will be continuously monitored by the site investigator, the research nurse, and the principal investigator. Formal reports outlining the number of IHCA and the proportion of those enrolled at each site will be shared with the steering committee quarterly. In case multiple eligible IHCA are not enrolled, a root cause analysis will be performed, and efforts will be made to avoid such issues in the future. Given the urgency of IHCA, we do not expect 100% enrollment of eligible IHCA. However, we will aim for enrollment of > 50% of eligible IHCA. In case that a site continuously underperforms despite troubleshooting and feedback, the steering committee will evaluate whether enrollment will continue at that site.

11.4 Additional sites

In case target enrollments are not met after 6 months to 1 year of enrollment, additional sites, in Denmark or outside Denmark, will be included. The principal investigator and the steering committee have multiple national and international ongoing collaborations allowing for recruitment of new sites.

12. PUBLICATION PLAN

Three manuscripts are planned from the current trial. Prior to unblinding of the results, a methodology article will be published including a detailed description of the trial and the statistical analysis plan. The second and primary manuscript will include the main results including pre-defined primary, secondary, and tertiary outcomes. The manuscript will adhere to the CONSORT guidelines.[107,108] The principal investigator will be the first and corresponding author. Additional authorship will follow authorship guidelines from the International Committee of Medical Journal Editors[147] and will include members of the steering committee. In addition, as a guideline, sites enrolling > 50 patients will be entitled one additional author and sites enrolling > 100 patients two additional authors in addition to the site investigators and members of the steering committee. The trial results will be shared with participating sites and via press releases but not directly with the participating patients. The third manuscript will include long-term follow-up at six months and 1 year (see section 5.5). Study findings will be published irrespective of the results.

13. DATA SHARING

Six months after the publication of the last results, all de-identified individual patient data will be made available for data sharing.[148] Procedures, including re-coding of key variables, will be put in place to allow for complete de-identification of the data. Data will be completely anonymized according to Danish law.

All relevant trial-related documents, including the protocol, data dictionary, and the main statistical code, will be shared along with the data. There will be no predetermined end date for the data sharing. Data will be available for any research purpose to all interested parties who have approval from an independent review committee and who have a methodological sound proposal as determined by the steering committee of the current trial. Only the methodological qualities and not the purpose or objective of the proposal will be considered. Interested parties will be able to request the data by contacting the principal investigator. Authorship of publications emerging from the shared data will follow standard authorship guidelines from the International Committee of Medical Journal Editors[147] and might or might not include authors from the steering committee depending on the nature of their involvement.

14. FUNDING

Funding for the trial is provided by Aarhus University Research Foundation (kr. 3,000,000), the Department of Clinical Medicine, Aarhus University (kr. 950,000), the Central Denmark Region (kr. 55,751), and the Independent Research Fund Denmark (kr. 2,343,495). Empressin® and corresponding placebo ampules are provided free of charge by Amomed Pharma GmbH. The funding agencies and Amomed Pharma GmbH have no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

15. TASKS AND RESPONSIBILITIES

Principal investigator and sponsor: Overall responsibility for protocol development, funding, budget overview, data dictionary development, ethical approval, trial registration, daily management, trial oversight, contact to the pharmacy, contact to Good Clinical Practice monitoring unit and the data and safety monitoring board, assessment of overall recruitments, potential recruitment of additional sites, data analysis, and dissemination and presentation of results

Steering committee: Protocol development, funding, budget overview, data dictionary development, trial oversight, dissemination of results, responsibilities as principal investigator for short time periods

Site investigators: Responsible for site-specific enrollment, evaluation of eligible patients not included, education of personnel at participating sites, reporting of site-specific issues or challenges to the principal investigator, participant consent for data collection

Research nurse: Daily management, education of personnel at participating sites, contact to pharmacy, contact to Good Clinical Practice monitoring unit, data dictionary development, trial registration, data entry and management, patient follow-up, budget overview

Clinical team: Administration of the study drug, participant consent for data collection

Good Clinical Practice-unit: See section 10.1.

Data and safety monitoring board: See section 10.2.

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Appendices

Appendix 1: Conflict of interest disclosures for the steering committee members

Lars W. Andersen

Industry:

- None

Other:

- Member of the Advanced Life Support task force at ILCOR
- Editorial board member at *Resuscitation*
- Member of the steering committee at DANARREST
- Honorarium from *JAMA* for statistical reviews

Hans Kirkegaard

Industry:

- None

Other:

- Chairman of the steering committee for DANARREST

Michael Donnino

Industry:

- Research grants from Kaneka, General Electric, and Bristol-Myers-Squibb

Other:

- Research grants from the American Heart Association and the National Institute of Health
- Vice-chair of the Advanced Life Support task force at ILCOR

Tobias Kurth

Industry:

- Lecture fees from Novartis

Other:

- Honorarium from the *BMJ* for editorial services

Bodil S. Rasmussen

Industry:

- Research grant from Ferring

Other:

- None

Jesper Kjærgaard

Industry:

- Lecture fees from Orion Pharma, AstraZeneca, and Bayer

Other:

- None

Bo Løfgren

Industry:

- Lecture fees from Boehringer Ingelheim, AstraZeneca, and Bayer
- Recipient of a teaching award from the Danish Society of Cardiology sponsored by Merck Sharp and Dohme

Other:

- Member of The European Resuscitation Council Basic Life Support and Automated External Defibrillation International Course Committee (2010 – 2016)
- Member of the Basic Life Support task force at ILCOR (2017 – 2020)

Asger Granfeldt

Industry:

- None

Other:

- None

Jacob Moesgaard Larsen Industry:

- None

Other:

- None

Dan Isbye

Industry:

- None

Other:

- None

Stine Thorhauge Zwisler

Industry:

- None

Other:

- None

Søren Darling

Industry:

- None

Other:

- None

Kasper Glerup Lauridsen

Industry:

- None

Other:

- European Resuscitation Council Advanced Life Support (ALS) Science and Educational Committee member.

Kim B. Pælestik

Industry:

- None

Other:

- None

Christoffer Sølling

Industry:

- None

Other:

- None

Anders Kjærgaard

Industry:

- None

Other:

- None

Dorte Due-Rasmussen

Industry:

- None

Other:

- None

Kasper Iversen

Industry:

- None

Other:

- None

Martin Schultz

Industry:

- None

Other:

- None

Fredrik Folke

Industry:

- None

Other:

- None

Mette Gitz Charlot

Industry:

- None

Other:

- None

Sebastian Wiberg

Industry:

- None

Other:

- None

Rikke Malene Jepsen

Industry:

- None

Other:

- None

Mathias Holmberg

Industry:

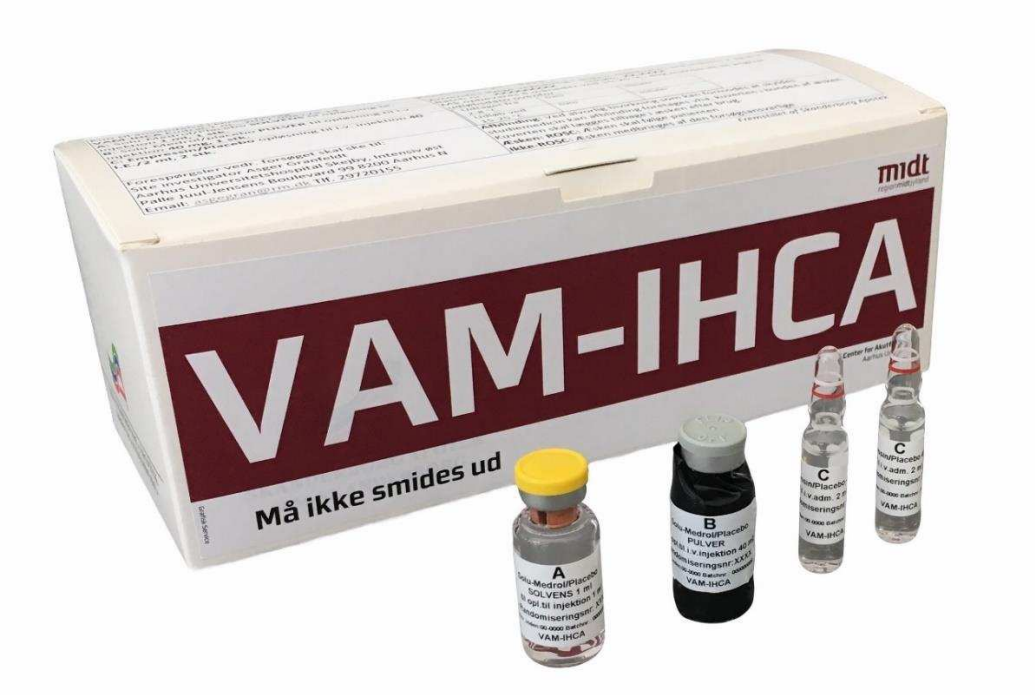
- None

Other:

- None

Appendix 2: Study kit and drug labeling (Danish)

Example from the Aarhus site.

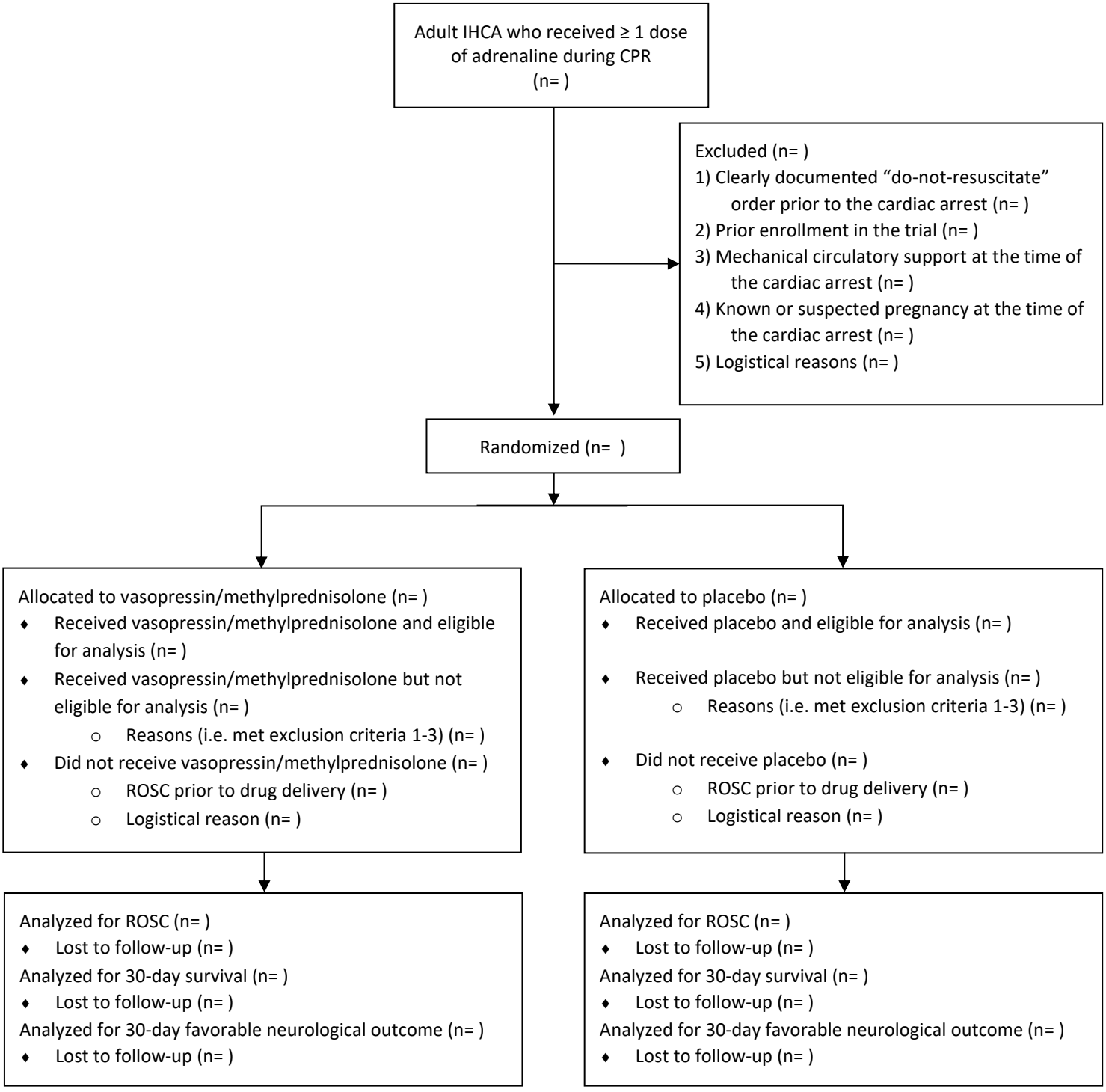


Kun til anvendelse i klinisk forsøg **VAM-IHCA** EudraCT nr.: 2017-004773-13	Randomiseringsnr: 3XXX
A: Solu-Medrol/Placebo **SOLVENS** til opløsning til injektion **1 ml, 1 stk.** **B:** Solu-Medrol/placebo **PULVER** til opløsning til i.v. injektion **40 mg, 1 stk.** **C: Empressin/Placebo** opløsning til i.v. injektion **40 I.E./2 ml, 2 stk.**	Anvendes ifølge vejledning i æsken. Opbevares ved mellem 2 og 8 °C. Udløb: Må opbevares 4 måneder ved 15-25 °C, dog maksimalt til angivet udløbsdato ovenfor. Udtaget fra 2-8 °C. Dato: Initialer: Udløb ved 15-25 °C. Dato: Initialer:
Forespørgsler vedr. forsøget skal ske til: Site investigator Asger Granfeldt Aarhus Universitetshospital Skejby, Intensiv øst Palle Juul-Jensens Boulevard 99 8200 Aarhus N email: asgegran@rm.dk Tlf. 29720155	**Afblinding:** Ved alvorlig bivirkning som kan formodes at skyldes studiemedicin kan afblinding foretages vha. kuverten i bunden af æsken. Kuverten skal lægges tilbage i æsken efter brug. **Æsken: ROSC:** Æsken skal følge patienten. **Ikke-ROSC:** Æsken medbringes af den forsøgsansvarlige.

Fremstillet af Skanderborg Apotek

A	B	C
Solu-Medrol/placebo **SOLVENS 1ml** til opl. til injektion 1ml Randomiseringsnr. XXXX Anv. Inden 00-0000 Batchnr. 0000 **VAM-IHCA**	**Solu-Medrol/placebo** **PULVER** til opl.til i.v. injektion 40mg Randomiseringsnr. XXXX Anv. Inden 00-0000 Batchnr. 0000 **VAM-IHCA**	**Empressin/placebo** til i.v. adm. 2ml Randomiseringsnr. XXXX Randomiseringsnr. XXXX Anv. Inden 00-0000 Batchnr. 0000 **VAM-IHCA**

Appendix 3: Draft of CONSORT flow diagram



Appendix 4: Case report form (Danish)

REGISTRERINGSSKEMA - VAM-IHCA

Randomiseringsnummer: _____

1) Patientnavn og CPR-nr.: Navn:_____ CPR: ☐☐☐☐☐☐ -- ☐☐☐☐	**2) Skema udfyldt af:** Navn:_____ Arbejdsmail:_____
3) Dato og tid for konstatering af hjertestoppet: D D M M Å Å Dato: ☐☐/☐☐/☐☐ T T M M Tid: ☐☐:☐☐	**4) Studiemedicin givet:** **JA** ☐ **NEJ** ☐ → **Årsag:** ↓ **Udfyld resten af skemaet** ☐ ROSC ☐ Ingen IV/IO ☐ Andet: _____
5) Tid for første adrenalin administration: T T M M Tid: ☐☐:☐☐	**6) Tid for første vasopressin/placebo (ampul C + C) administration:** T T M M Tid: ☐☐:☐☐
7) Methylprednisolon/placebo (hætteglas A + B) administreret? **JA** ☐ **NEJ** ☐	**8) Total antal vasopressin/placebo (ampul C + C) administreret:** 1 ☐ 2 ☐ 3 ☐ 4 ☐
9) ROSC (egencirkulation) opnået? **JA** ☐ **NEJ** ☐ **ECMO/CPB** ☐	ROSC: Return Of Spontaneus Circulation (egencirkulation) defineres som spontan cirkulation (dvs. en mærkbar puls eller måleligt blodtryk) uden yderligere behov for hjertemassage, der opretholdes i mindst 20 minutter.

Ved ROSC følger medicinæsken, med indhold og registreringsskema, patienten. Hvis ROSC ikke opnås, medbringes æsken af den forsøgsansvarlige.

Husk endvidere venligst at udfylde **DANARREST**.

Evt. noter eller kommentarer kan tilføjes på bagsiden.

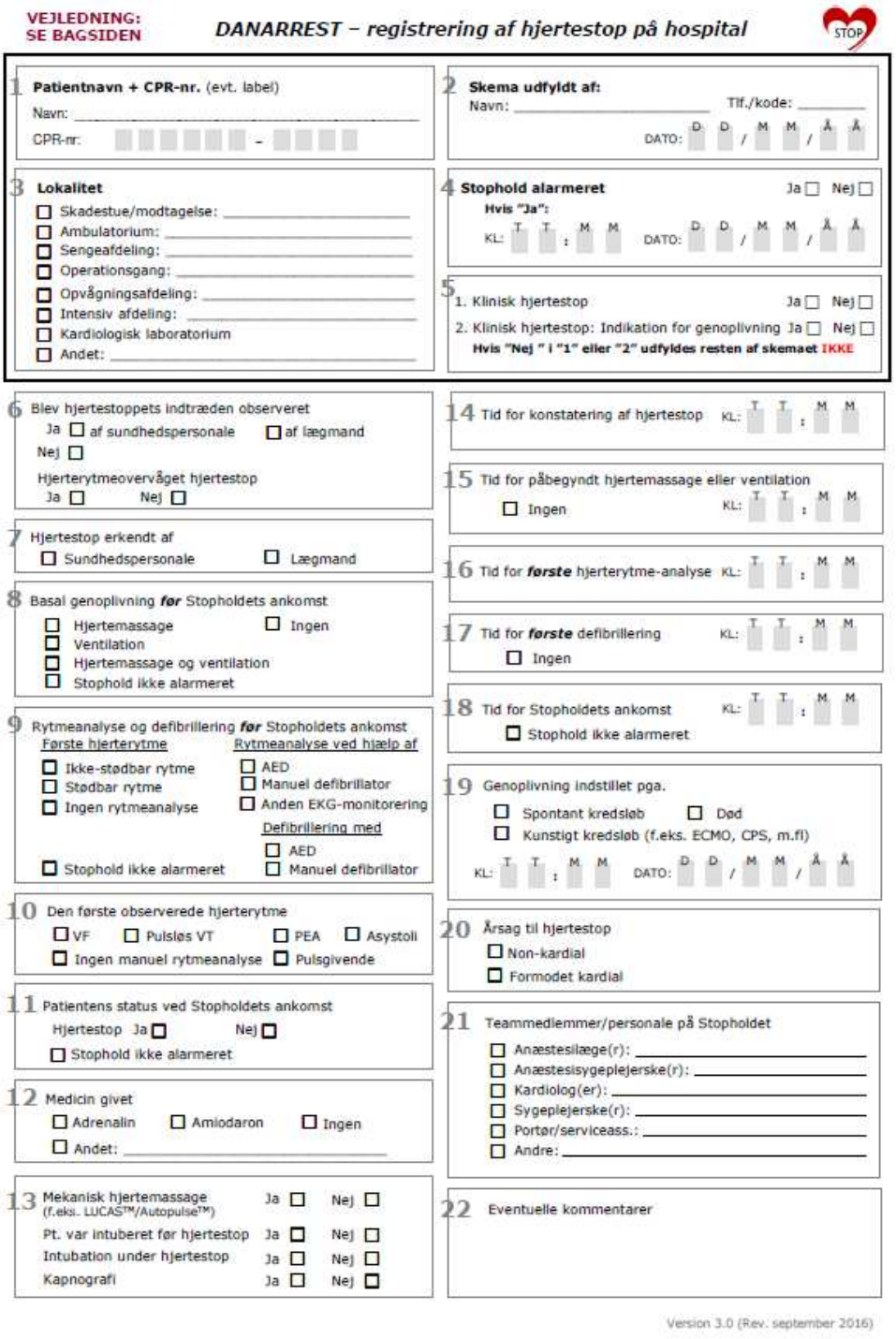
Ved spørgsmål:

Mobil nr.: 93 52 10 42 (døgnet rundt)

E-mail: hjertestop@clin.au.dk

Registreringsskema v. 1.2
VAM-IHCA

Appendix 5: DANARREST case report form (Danish)



VEJLEDNING: SE BAGSIDEN

DANARREST – registrering af hjertestop på hospital

1 Patientnavn + CPR-nr. (evt. label)
Navn: _____
CPR-nr: _____ - _____

2 Skema udfyldt af:
Navn: _____ Tlf./kode: _____
DATO: D D / M M / Å Å

3 Lokalitet
- ☐ Skadestue/modtagelse: _____
- ☐ Ambulatorium: _____
- ☐ Sengeafdeling: _____
- ☐ Operationsgang: _____
- ☐ Opvågningsafdeling: _____
- ☐ Intensiv afdeling: _____
- ☐ Kardiologisk laboratorium
- ☐ Andet: _____

4 Stophold alarmeret Ja ☐ Nej ☐
Hvis "Ja":
KL: T T : M M DATO: D D / M M / Å Å

5
1. Klinisk hjertestop Ja ☐ Nej ☐
2. Klinisk hjertestop: Indikation for genoplivning Ja ☐ Nej ☐
Hvis "Nej " i "1" eller "2" udfyldes resten af skemaet IKKE

6 Blev hjertestoppets indtræden observeret
Ja ☐ af sundhedspersonale ☐ af lægmand
Nej ☐
Hjerterytmeovervåget hjertestop
Ja ☐ Nej ☐

7 Hjertestop erkendt af
☐ Sundhedspersonale ☐ Lægmand

8 Basal genoplivning ***før*** Stopholdets ankomst
- ☐ Hjertemassage ☐ Ingen
- ☐ Ventilation
- ☐ Hjertemassage og ventilation
- ☐ Stophold ikke alarmeret

9 Rytmeanalyse og defibrillering ***før*** Stopholdets ankomst

Første hjerterytme:
- ☐ Ikke-stødbar rytme
- ☐ Stødbar rytme
- ☐ Ingen rytmeanalyse
- ☐ Stophold ikke alarmeret

Rytmeanalyse ved hjælp af:
- ☐ AED
- ☐ Manuel defibrillator
- ☐ Anden EKG-monitorering

Defibrillering med:
- ☐ AED
- ☐ Manuel defibrillator

10 Den første observerede hjerterytme
☐ VF ☐ Pulsløs VT ☐ PEA ☐ Asystoli
☐ Ingen manuel rytmeanalyse ☐ Pulsgivende

11 Patientens status ved Stopholdets ankomst
Hjertestop Ja ☐ Nej ☐
☐ Stophold ikke alarmeret

12 Medicin givet
☐ Adrenalin ☐ Amiodaron ☐ Ingen
☐ Andet: _____

13 Mekanisk hjertemassage (f.eks. LUCAS™/Autopulse™) Ja ☐ Nej ☐
Pt. var intuberet før hjertestop Ja ☐ Nej ☐
Intubation under hjertestop Ja ☐ Nej ☐
Kapnografi Ja ☐ Nej ☐

14 Tid for konstatering af hjertestop KL: T T : M M

15 Tid for påbegyndt hjertemassage eller ventilation
☐ Ingen KL: T T : M M

16 Tid for ***første*** hjerterytme-analyse KL: T T : M M

17 Tid for ***første*** defibrillering KL: T T : M M
☐ Ingen

18 Tid for Stopholdets ankomst KL: T T : M M
☐ Stophold ikke alarmeret

19 Genoplivning indstillet pga.
- ☐ Spontant kredsløb ☐ Død
- ☐ Kunstigt kredsløb (f.eks. ECMO, CPS, m.fl)

KL: T T : M M DATO: D D / M M / Å Å

20 Årsag til hjertestop
- ☐ Non-kardial
- ☐ Formodet kardial

21 Teammedlemmer/personale på Stopholdet
- ☐ Anæstesilæge(r): _____
- ☐ Anæstesisygeplejerske(r): _____
- ☐ Kardiolog(er): _____
- ☐ Sygeplejerske(r): _____
- ☐ Portør/serviceass.: _____
- ☐ Andre: _____

22 Eventuelle kommentarer

Version 3.0 (Rev. september 2016)

DANARREST – registrering af hjertestop på hospital

Vejledning til udfyldelse af registreringsskema

Registrering af hjertestop er vigtig for at dokumentere og forbedre behandlingen. Stopholdet er derfor som helhed ansvarlig for udfyldelse af skemaet. Skemaet udfyldes af lederen af Stopholdet, evt. med assistance fra et medlem af Stopholdet. Hvis Stopholdet ikke bliver tilkaldt, f.eks. på intensiv afdeling, operationsgang eller kardiologisk laboratorium, udfyldes skemaet af den for genoplivningen ansvarlige læge.

ALLE TIDSPUNKTER ANGIVES EFTER BEDSTE SKØN

1. Anfør patientnavn og CPR-nr. eller påsæt label.
2. Anfør navn og telefon/personsøger på den person der har udfyldt skemaet. Angiv endvidere tidspunkt (dag, måned, år) for udfyldelse af skemaet.
3. Afkryds lokalitet, hvor hjertestoppet er indtrådt. Herudover anføres navn på lokaliteten. Ved kryds i "Andet" anføres lokalitet.
4. Angiv tidspunkt (time, minut, dag, måned, år,) for hvornår Stopholdet alarmeres. Det tidspunkt der anføres, er det, hvor Omstillingen eller andet personale videreformidler alarmeringen til Stopholdet. Hvis Stophold ikke tilkaldes, sættes kryds i "Nej" og tidspunkt udfyldes ikke.
5. Skemaet skal udfyldes til alle patienter med hjertestop på hospital, og til alle patienter hvor Stopholdet tilkaldes. Skemaet skal således også udfyldes i fald patienten er blevet genoplivet INDEN Stopholdets ankomst. I fald patienten IKKE har eller har haft hjertestop ved Stopholdets ankomst eller der ikke er indikation for genoplivning, udfyldes kun punkt 1-5. Hvis en patient er genoplivet efter hjertestop uden for hospital (= ROSC > 20 min.), men får nyt hjertestop efter ankomst til hospital, skal skemaet ligeledes udfyldes. Der skal udfyldes et nyt skema, hvis en patient får et nyt hjertestop efter ROSC > 20 min. Hvis der forud for hjertestop foreligger en beslutning om "ingen genoplivning" afkrydses "Nej" i punkt 2. Hjertestop hos terminale patienter, hvor dødens indtræden forventes og hjertestopberedskabet ikke aktiveres, skal ikke registreres.
6. Afkryds hvorvidt hjertestop er observeret af sundhedspersonale, lægmand eller er ubevidnet. "Observeret" indebærer, at man har set eller hørt personen få hjertestop, eller identificeret ventrikelflimmer på EKG-overvågning. Afkryds hvorvidt hjertestoppet var hjerterytmeovervåget. Med hjerterytmeovervågет menes monitoreret med EKG-overvågning (telemetri eller lignende).
7. Afkryds hvorvidt hjertestoppet er erkendt af sundhedspersonale eller af lægmand. Erkendelsen af hjertestop beror på bevidstløshed og ikke normal vejrtrækning. For den trænede og erfarne behandler indgår pulsløshed ligeledes i diagnosen.
8. Afkryds hvilken form for hjertelungeredning, der er ydet før Stopholdets ankomst. Hvis Stophold ikke tilkaldes, afkryds "Stophold ikke alarmeret", og undlad at udfylde den øvrige del af punktet.
9. Hjerterytmeanalyse før Stopholdets ankomst: Afkryds hvorvidt det drejer som en stødbar rytme, en ikke-stødbar rytme eller der ingen hjerterytmeanalyse er udført. Anvendes en AED, oplyses om der er stødbar rytme eller ikke-stødbar rytme. Ved brug af manuel defibrillator aflæses rytmen på apparatets skærm. Afkryds med hvilket apparatur rytmeanalyse er foretaget. Afkryds om der er foretaget defibrillering før Stopholdets ankomst (med AED eller manuelt) eller om der ingen defibrillering er foretaget. Hvis Stophold ikke tilkaldes, afkryds "Stophold ikke alarmeret", men øvrige punkter udfyldes.
10. Afkryds den først observerede hjerterytme relateret til hjertestop, uanset om denne er observeret af afdelingens personale eller af Stopholdet. Er der ikke gjort manuel rytmeanalyse ved at vurdere hjerterytmen på EKG-overvågning eller med manuel defibrillator afkrydses" Ingen manuel rytmeanalyse".
11. Afkryds hvorvidt patienten har klinisk hjertestop ved Stopholdets ankomst. Hvis Stophold ikke tilkaldes, afkryds "Stophold ikke alarmeret", og undlad at udfylde den øvrige del af punktet.
12. Afkryds hvilken medicin der er givet (sæt om nødvendigt flere krydser). Ved kryds i "Andet" anføres de anvendte farmaka på skemaet, f.eks. calciumchlorid, magnesiumsulfat, natriumbikarbonat, lidocain, mv.
13. Afkryds om der er givet mekanisk hjertemassage (f.eks. LUCAS® eller Autopulse®), om patienten var intuberet inden hjertestoppet eller om det er sket i forbindelse med hjertestopbehandlingen, og om der er anvendt kapnografi.
14. Angiv tidspunkt for konstatering af hjertestop (time, minut).
15. Angiv tidspunkt for påbegyndt hjertemassage eller ventilation (time, minut).
16. Angiv tidspunkt for første hjerterytmeanalyse (time, minut) (hjerterytmeanalyse med AED eller manuel defibrillator).
17. Angiv tidspunkt for første defibrillering (time, minut).
18. Anfør tidspunkt for Stopholdets ankomst (time, minut). Hvis Stophold ikke tilkaldes, afkryds "Stophold ikke alarmeret", og undlad at udfylde den øvrige del af punktet. Ankomst af Stopholdet defineres ved ankomsten af lederen af Stopholdet.
19. Afkryds om genoplivningen er indstillet grundet genvundet spontant kredsløb, etablering af kunstigt kredsløb (ekstrakorporal cirkulation eller tilsvarende) eller om yderligere forsøg på genoplivning vurderes udsigtsløs ("Død"). Angiv tidspunkt (time, minut, dag, måned, år).
20. Afkryds om der er en oplagt ikke-kardial årsag til hjertestoppet (f.eks. traumatisk, hypoxisk, forgiftning, drukning/hængning), og hvis det ikke er tilfældet – er årsagen formodet kardial.
21. Personnavne eller personhenførbare data indtastes ikke i DANARREST, men anføres på papirskemaet (til opfølgning, debriefing o.lign). Den enkelte region/institution tager stilling til lokal praksis
22. Anfør eventuelle kommentarer til genoplivningsforløbet.

Definitioner	Aflevering af udfyldte skemaer
Stophold = hospitalets udrykningshold til behandling af hjertestop **Sundhedspersonale** = læge, sygeplejerske, social- og sundhedsassistent, fysio- og ergoterapeut, serviceassistent og portør **Stødbar rytme** = Ventrikelflimren og pulsløs ventrikulær takykardi **Ikke-stødbar rytme** = Asystoli og pulsløs elektrisk aktivitet **VF** = Ventrikelflimren **Pulsløs VT** = Pulsløs ventrikulær takykardi **PEA** = Pulsløs elektrisk aktivitet **AED** = Automatisk Ekstern Defibrillator ("Hjertestarter")	

Appendix 6: Charter for the independent data-monitoring committee (IDMC)

Charter for the independent data-monitoring committee (IDMC) for the VAM-IHCA trial

Trial name: Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest – A Randomized, Double-Blind, Placebo-Controlled Trial (VAM-IHCA)

Principal investigator and sponsor: Associate professor Lars W. Andersen, M.D., M.P.H., Ph.D.

EudraCT Number: 2017-004773-13

Research ethical committee no.: 1-10-72-42-18, Central Denmark Region

Introduction

This charter will define the primary responsibilities of the IDMC, its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the IDMC, and an outline of the content of the data that will be provided to the IDMC.

Responsibilities of the IDMC

The IDMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The IDMC will provide recommendations about stopping or continuing the trial to the steering committee of the VAM-IHCA trial. To contribute to enhancing the integrity of the trial, the IDMC may decide to also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control. Any such recommendations will be at the discretion of the IDMC.

The IDMC will be advisory to the steering committee. The steering committee will be responsible for promptly reviewing the IDMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The IDMC will be notified of all changes to the trial protocol or conduct. The IDMC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

The members of the IDMC will be unpaid.

Members of the IDMC

The IDMC is an independent multidisciplinary group consisting of physicians with epidemiological expertise that, collectively, has experience in the management of cardiac arrest patients and in the conduct, monitoring and analysis of randomized clinical trials.

The members of the IDMC are:

Christian Fynbo Christiansen, M.D., Ph.D. (chairman)
Clinical Associate Professor
Department of Clinical Epidemiology
Department of Clinical Medicine
Aarhus University, Aarhus, Denmark

Hans Friberg, M.D., Ph.D.
Professor
Department of Clinical Sciences
Lund University, Lund, Sweden
&
Department of Perioperative and Intensive Care
Skåne University Hospital, Lund, Sweden

Jasmeet Soar, FRCA, FFICM, FRCP
Consultant
Anaesthesia and Intensive Care Medicine
Southmead Hospital, Bristol, United Kingdom

Conflicts of interest

IDMC membership has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The IDMC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial. The IDMC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity. The IDMC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the trial. Any IDMC members who develop significant conflicts of interest during the trial should resign from the IDMC.

IDMC membership is to be for the duration of the clinical trial. If any members leave the IDMC during the trial, the steering committee will appoint the replacement(s).

Evaluations of trial data

The IDMC will review deidentified data after six months of patient enrollment and then on a yearly basis (or more often if determined by the IDMC) for safety; unless there are group differences necessitating unblinding (as determined by the IDMC), the IDMC will be blinded to treatment groups. The trial will continue while the IDMC review data. After the review, the IDMC will create a short report to the steering committee with recommendations for continuation, modifications, or termination of the trial. There will be no formal stopping criteria for efficacy or futility. Criteria for recommending termination will be at the discretion of the IDMC and there will be no formal statistical criteria for termination due to safety.

Raw data will be provided to the IDMC in Excel in the following format:

Row 1 contains the names of the variables (to be defined below)

Row 2 to N (where N-1 is the number of patients who have entered the trial) each contains the data of one patient

Column 1 to p (where p is the number of variables to be defined below) each contains in row 1 the name of a variable and in the next N-1 rows the values of this variable.

The values of the following variables will be included:
1: id: a number that uniquely identifies the patient.
2: group: The randomization code (group A or B)
3: rosc: The primary outcome return of spontaneous circulation (ROSC) (1 for ROSC, 0 for no ROSC)
4: surv_30: Survival at 30 days (1 for survival at 30 days, 0 for death prior to 30 days)
5: cpc_30: Cerebral performance category (CPC) at hospital discharge (1 to 5)

Specific adverse events (see section 5.4.3 in the protocol):
6: hyp_gly: Hyperglycemia (1 for yes, 0 for no)
7: insulin: Requirement for an insulin infusion (1 for yes, 0 for no)
8: Hyp_na: Hypernatremia (1 for yes, 0 for no)
9: infect: New infections (1 for yes, 0 for no)
10: antibio: New or changing antibiotics (1 for yes, 0 for no)

11: gas_bleed: Gastrointestinal bleeding (1 for yes, 0 for no)

12: mes_ischemia: Mesenteric ischemia (1 for yes, 0 for no)

13: per_ ischemia: Peripheral ischemia (1 for yes, 0 for no)

14: susar: Suspected Unexpected Serious Adverse Reactions (1 for yes, 0 for no)

Variables #1 and #3-14 will be provided by the steering committee and item #2 will be provided by the pharmacy.

An independent biostatistician (not a member of the IDMC) will provide aggregate data for each of the variables #3-12 stratified by treatment group (variable #2) in two-by-two tables. No statistical tests will be performed unless explicitly requested by the IDMC.

In addition to the above, the steering committee will provide the IDMC with data on the number of patients screened (i.e. all IHCA at participating sites), number of patients included in the studies, and the number of patients who have provided consent for additional data collection and long-term follow-up. Data will be provided on the specific reasons for non-inclusion and exclusion.

All data will be provided to the IDMC at least 5 days prior to their meeting.

Meeting, communication and reports

The steering committee, along with the IDMC chairman, will be responsible for scheduling and arranging the IDCM meeting. The meeting will start with a study overview provided by the principal investigator. This will include an overview of recruitment and potential problems and issues. The remainder of the meeting, which will only be attended by the IDMC members, be will be related to evaluations of trial data as described above.

The IDMC is not planned to meet physically to evaluate data. In addition to the scheduled meeting, the IDMC may whenever they decide, contact each other by telephone, videoconference, or e-mail to discuss the safety for trial participants. The recommendations of the IDMC regarding stopping, continuing or changing the design of the trial should be communicated in writing without delay to the steering committee. The steering committee has the responsibility to inform as fast as possible, and no later than 72 hours, all investigators of the trial and the sites including patients in the trial about the recommendation of the IDMC and the steering committee decision hereof.

The IDMC will prepare minutes of their meetings. The closed minutes will describe the

proceedings from all sessions of the IDMC meeting, including the listing of recommendations by the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the IDMC. The IDMC and the independent biostatistician are obligated to keep all patient-level data confidential.

Supplemental Online Content

Andersen LW, Isbye D, Kjærgaard J, et al. Effect of vasopressin and methylprednisolone vs placebo on return of spontaneous circulation in patients with in-hospital cardiac arrest: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2021.16628

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Discrepancies Between the Manuscript and the Protocol

There are a few minor discrepancies between the protocol and the manuscript. These are described here.

1) The protocol states that ventilator- and vasopressor-free days is defined as "… the number of days within the first 7 days after the cardiac arrest where the patient is not receiving vasopressors[/mechanical ventilation] and is alive" (section 5.3). 7 days were changed to 14 days before the trial started, but this was inadvertently not corrected in the protocol. The first "data dictionary", which defines all collected variables, dated Sept. 4, 2018, states "Vasopressor[/ventilation]-free days are defined as the number of days within the first 14 days after the cardiac arrest where the patient is not receiving vasopressors[/invasive mechanical ventilation] and is alive." This is consistent with the definition used in the manuscript.

2) For continuous variables, the protocol states "… differences between groups will be estimated using a linear regression model" (section 6.2.4) Upon review of blinded data, it was evident that data on sequential organ failure assessment scores and health-related quality of life were only approximately normally distributed. To better account for this, we decided to use generalized linear models with robust variance estimation.

3) Data on vasopressor- and ventilator-free days were extremely skewed and zero-inflated. Before unblinding, we therefore decided that it would be unlikely that we would be able to get a valid estimate of the mean difference between the groups using generalized linear models. This analysis was therefore not performed. We did consider other options (e.g., quantile regression, Hodges–Lehmann median difference), but given the distribution of the data, these approaches were unlikely to give meaningful and valid results.

4) The intended sample size was 492 patients. A total of 501 eligible patients were included. This small discrepancy is a result of logistical and practical issues as the trial ended. Specifically, to ensure that the sample size was reached, the trial end date was scheduled at a specific date and a relatively large number of patients were included within the last few days of the trial.

eAppendix 2. Definitions of Past Medical History

Coronary artery disease: Myocardial infarction, coronary artery bypass grafting, coronary stenting or angioplasty, or other known occlusive coronary disease including diagnosed angina pectoris.

Chronic heart failure: Chronic heart failure with or without preserved ejection fraction.

Atrial fibrillation: Paroxysmal, persistent, or chronic atrial fibrillation/flutter.

Stroke: Previous ischemic or hemorrhagic stroke or transient ischemic attack.

Venous thromboembolism: Previous deep vein thrombosis, pulmonary embolism, or another venous thromboembolism (e.g., cerebral venous sinus thrombosis).

Arterial hypertension: A diagnosis of hypertension and receiving at least one anti-hypertensive drug (e.g., angiotensin-converting-enzyme [ACE] inhibitor, angiotensin II receptor blockers [ARB], diuretic or beta-blocker).

Diabetes: A diagnosis of diabetes and receiving at least one anti-diabetic drug (e.g., metformin, insulin, biguanides, sulfonylureas, glitazones, dipeptidyl peptidase IV inhibitors, or sodium-glucose co-transporter 2 inhibitor).

Pulmonary disease: Chronic obstructive pulmonary disease or asthma requiring daily inhalation medication or other pulmonary disease e.g., emphysema, interstitial lung disease, cystic fibrosis, or idiopathic pulmonary arterial hypertension.

Renal disease: Chronic kidney disease stage 3A or higher, i.e., eGFR < 60 mL/min/1.73 m^2.

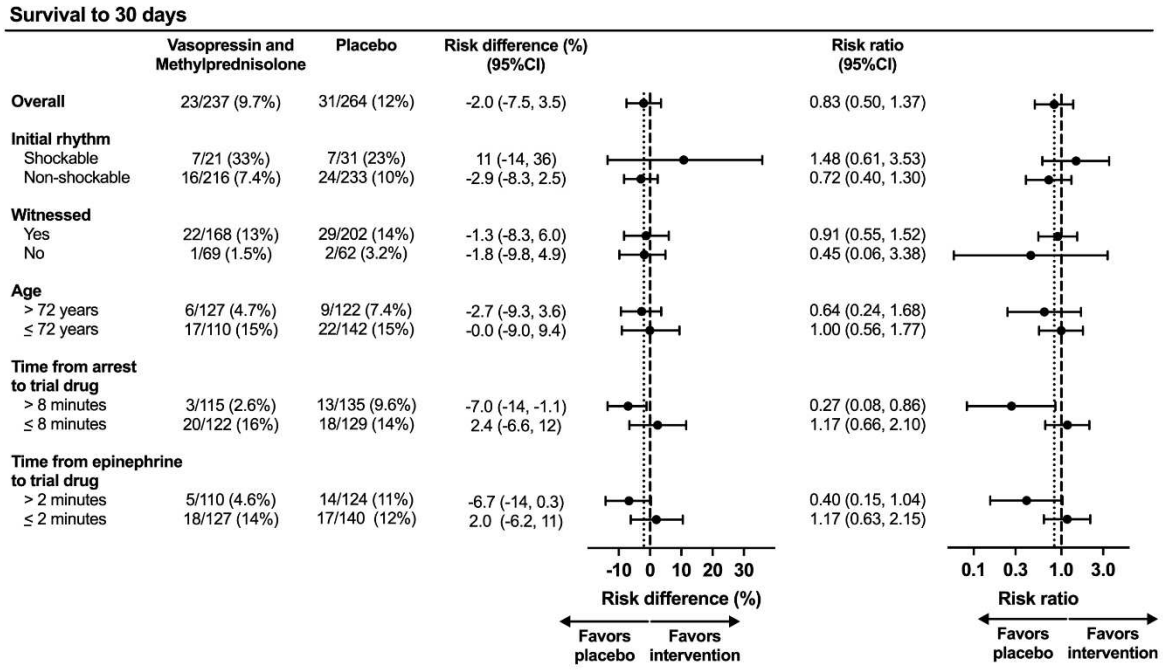
Liver disease: With or without cirrhosis. This includes chronic hepatitis B or C (not cured), non-alcoholic fatty liver disease/nonalcoholic steatohepatitis, alcoholic liver disease, autoimmune hepatitis, liver disease related to hemochromatosis, etc.

Cancer: Any active solid or hematological cancer. Non-melanoma skin cancers (basal cell or squamous cell carcinoma) are not included. Active is defined as receiving chemotherapy, radiation,

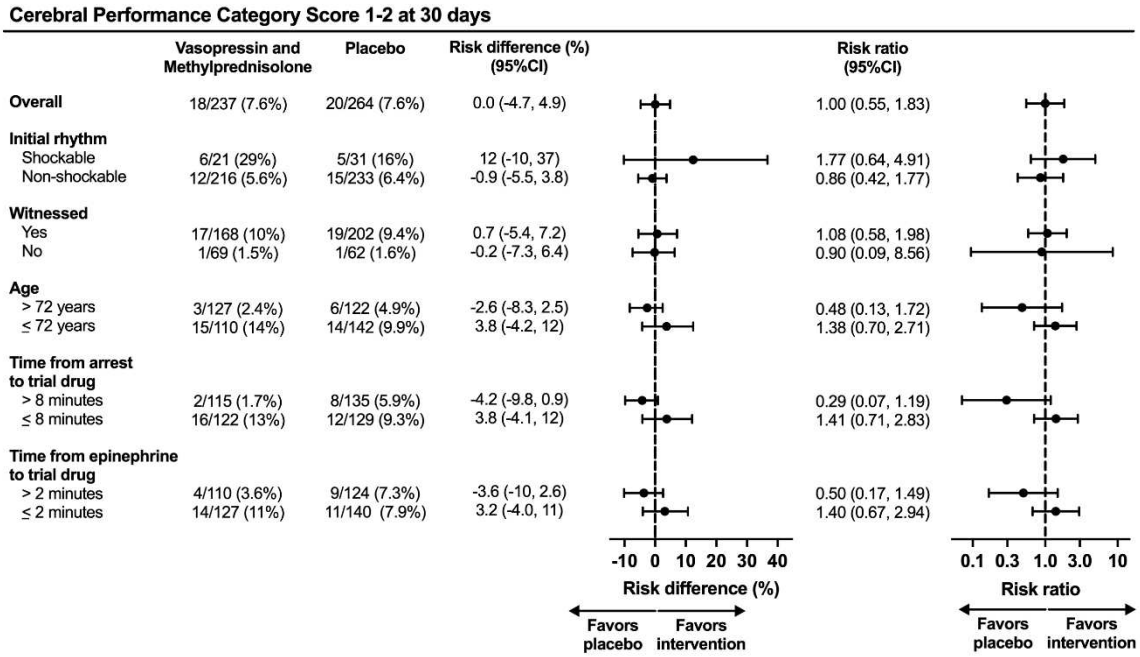
or palliative care, awaiting either of the previous, or awaiting curative or palliative surgery. Previous cancers considered cured should not be included.

Dementia: Alzheimer's disease, vascular dementia, Lewy bodies dementia, frontotemporal dementia, dementia associated with Parkinson's, etc.

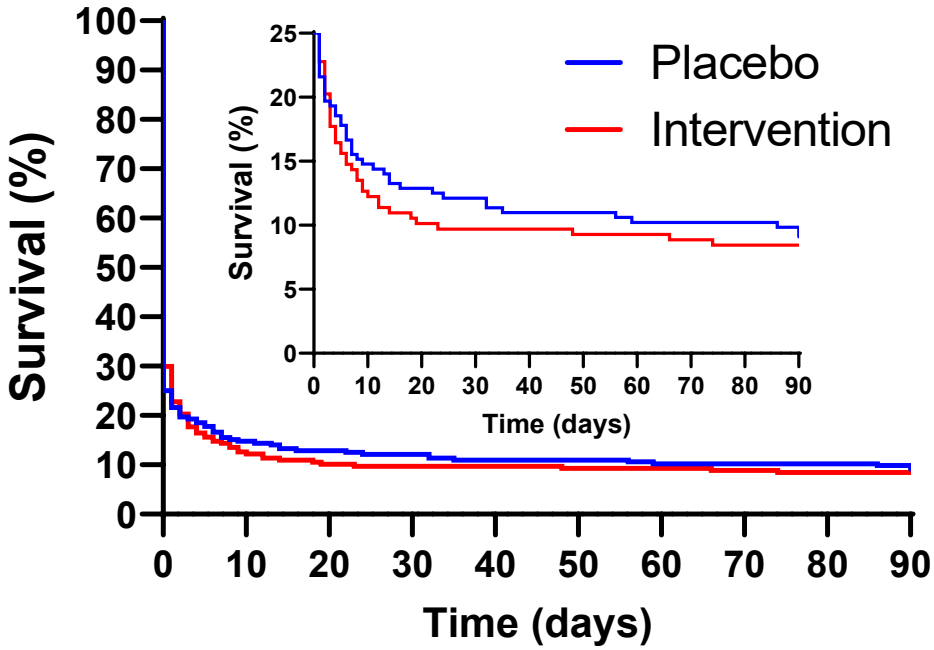
eFigure 1. Subgroup Results for 30-Day Survival



eFigure 2. Subgroup Results for 30-Day Favorable Neurologic Outcome



eFigure 3. Kaplan-Meier Curve for 90-Day Survival According to Treatment Assignment



eTable 1. Inclusions per Site				
Site	**Trial start**	**Cardiac arrests**	**Received trial drug**	**Included**
Aalborg University Hospital	15/10-18	421	54	52
Randers Regional Hospital	1/2-19	105	26	26
Aarhus University Hospital	17/9-18	456	96	93
Odense University Hospital	21/11-18	335	118	117
Copenhagen University Hospital - Rigshospitalet	1/11-18	538	123	121
Viborg Regional Hospital	1/5-19	73	20	18
Horsens Regional Hospital	8/5-19	92	17	17
Copenhagen University Hospital – Herlev	15/5-19	232	45	44
Copenhagen University Hospital – Gentofte	15/5-19	96	8	8
Zealand University Hospital - Køge	1/9-20	14	5	5
Total	-	**2362**	**512**	**501**

eTable 2. Additional Baseline Characteristics According to Treatment Assignment		
	Vasopressin and Methylprednisolone (n = 237)	**Placebo (n = 264)**
Patient Characteristics		
CPC prior to hospital admission		
CPC 1	197 (83)	232 (88)
CPC 2	36 (15)	25 (9)
CPC 3	4 (2)	7 (3)
mRS prior to hospital admission		
mRS 0	15 (6)	33 (13)
mRS 1	74 (31)	92 (35)
mRS 2	80 (34)	83 (31)
mRS 3	49 (21)	38 (14)
mRS 4	18 (8)	17 (6)
mRS 5	1 (< 1)	1 (< 1)
Frailty prior to hospital admission		
Very fit	3 (1)	0 (0)
Well	25 (11)	47 (18)
Managing well	64 (27)	94 (36)
Vulnerable	74 (31)	68 (26)
Mildly frail	34 (14)	22 (8)
Moderately frail	27 (11)	19 (7)
Severely frail	10 (4)	14 (5)
Admission Characteristics		
Type of admission		
Acute	195 (82)	221 (84)
Elective	41 (17)	43 (16)
Not admitted	1 (< 1)	0 (0)
Reason for admission[a]		
Medical - cardiac	38 (16)	66 (25)
Medical - infection	50 (21)	30 (11)
Medical – other	65 (28)	87 (33)
Surgery – cardiac	2 (1)	6 (2)
Surgery – non-cardiac	39 (17)	35 (13)
Trauma	26 (11)	28 (11)
Out-of-hospital cardiac arrest	11 (5)	7 (3)
Other	5 (2)	5 (2)
Prior in-hospital cardiac arrest	15 (6)	12 (5)
Any glucocorticoids during hospital admission	61 (26)	57 (22)
Intravenous access	229 (97)	249 (94)
Cardiac Arrest Characteristics		
Time from admission to cardiac arrest - days	2 (1, 7)	2 (0, 6)
Time of day – no. (%)		
Day (07:00 – 14:59)	89 (38)	101 (38)
Evening (15:00 – 22:59)	78 (33)	66 (25)
Night (23:00 – 06:59)	70 (30)	97 (37)
Time of week – no. (%)		
Weekday	162 (68)	201 (76)
Weekend	75 (32)	63 (24)

eTable 2. Additional Baseline Characteristics According to Treatment Assignment		
Presumed cause – no. (%)		
Cardiac	64 (27)	79 (30)
Pulmonary	86 (36)	86 (33)
Electrolyte disturbances	4 (2)	4 (2)
Hypotension/hypovolemia	30 (13)	28 (11)
Neurological	4 (2)	5 (2)
Toxicology	2 (1)	2 (1)
Unknown	47 (20)	59 (22)
Time to cardiopulmonary resuscitation - minutes	0 (0, 0)	0 (0, 0)
Time to first rhythm analysis - minutes	2 (1, 4)	2 (1, 4)
Time to arrival of the cardiac arrest team – minutes[b]	3 (2, 4)	3 (2, 4)

Continuous variables are presented as medians with first and third quartiles and categorical variables as counts and percentages

[a] One patient in the intervention group was not admitted at the time of the cardiac arrest and is therefore not included here

[b] For one patient in the intervention group, no cardiac arrest team participated in the cardiac arrest and this patient is therefore not included here

eTable 3. Cardiac Arrest Interventions		
	Vasopressin and Methylprednisolone (n = 237)	**Placebo (n = 264)**
Number of epinephrine doses[a]	3 (2, 5)	3 (2, 5)
Other drugs administered		
Amiodarone	31 (13)	34 (13)
Lidocaine	3 (1)	3 (1)
Atropine	11 (5)	15 (6)
Calcium	27 (11)	30 (11)
Magnesium	9 (4)	7 (3)
Bicarbonate	26 (11)	20 (8)
Glucose	2 (1)	3 (1)
Defibrillation	67 (28)	73 (28)
Number of defibrillations[b]	2 (1, 3)	2 (1, 3)
Intubation during cardiac arrest	175 (74)	179 (68)
Mechanical chest compression	40 (17)	41 (16)
Extracorporeal cardiopulmonary resuscitation	10 (4)	18 (7)

Continuous variables are presented as medians with first and third quartiles and categorical variables as counts and percentages

[a] Data not available on 5 patients in the intervention group and 6 patients in the placebo group

[b]Only including those with defibrillation. Data not available for 1 patient in each group

eTable 4. Post-Cardiac Arrest Characteristics in Those Surviving at Least 24 Hours		
	Vasopressin and Methylprednisolone (n = 63)	**Placebo (n = 61)**
Targeted temperature management	17 (27)	16 (26)
Temperature		
33°C	3 (18)	2 (13)
36°C	14 (82)	14 (88)
Cardiac interventions		
Coronary catherization	15 (24)	15 (25)
Percutaneous coronary intervention	6 (10)	10 (16)
Coronary artery bypass grafting	1 (2)	0 (0)
Intra-aortic balloon pump	0 (0)	0 (0)
Left ventricular assist device	2 (3)	6 (10)
Veno-arterial extracorporeal membrane oxygenation	9 (14)	18 (30)
Veno-venous extracorporeal membrane oxygenation	0 (0)	0 (0)
Renal replacement therapy	16 (25)	22 (36)
Vasopressor infusion	55 (87)	56 (92)
Any glucocorticoid administration	15 (24)	28 (46)
Neurological biomarkers/imaging		
Computed tomography	34 (54)	30 (49)
Magnetic resonance imaging	6 (10)	7 (11)
Electroencephalogram	27 (43)	21 (34)
Somatosensory evoked potential	12 (19)	7 (11)
Neuron specific enolase	12 (19)	13 (21)
s100b	3 (5)	2 (3)

Categorical variables are presented as counts and percentages

eTable 5. Trial Drug and Protocol Deviations		
	Vasopressin and Methylprednisolone (n = 237)	**Placebo (n = 264)**
Trial drug characteristics		
Methylprednisolone/placebo administration	231 (97)	256 (97)
Vasopressin/placebo administration	234 (99)	259 (98)
Vasopressin/placebo doses		
One	66 (28)	73 (28)
Two	76 (32)	69 (27)
Three	35 (15)	46 (18)
Four	57 (24)	71 (27)
Protocol deviations		
Total protocol deviations	18 (8)	19 (7)
Specific protocol deviations		
Double dose of first vasopressin/placebo dose	6 (3)	4 (2)
Double dose of two vasopressin/placebo doses	4 (2)	0 (0)
No methylprednisolone/placebo administered	6 (3)	8 (3)
No vasopressin	3 (1)	5 (2)
Other	0 (0)	2 (1)

Categorical variables are presented as counts and percentages

eTable 6. Organ Dysfunction After Return of Spontaneous Circulation			
	Vasopressin and Methylprednisolone	**Placebo**	**Mean difference (95%CI)**
SOFA score			
24 hours	10.6 (4.4) (n = 63)	10.9 (4.5) (n = 61)	-0.3 (-1.9, 1.3)
48 hours	9.6 (4.4) (n = 50)	9.7 (5.5) (n = 55)	-0.1 (-2.0, 1.8)
72 hours	8.7 (4.6) (n = 47)	9.3 (5.3) (n = 51)	-0.6 (-2.5, 1.4)
Vasopressor-free days	0 (0, 5)	0 (0, 9)	-[a]
Ventilator-free days	0 (0, 1)	0 (0, 7)	-[a]

SOFA: Sequential Organ Failure Assessment

Continuous variables are presented as means with standard deviations or medians with first and third quartiles. The SOFA score was only assessed in those alive at the given time point. If a specific SOFA score element was missing, it was assumed to be normal. Vasopressor- and ventilator-free days were defined as the number of days within the first 14 days after the cardiac arrest where the patient did not receive vasopressors or invasive mechanical ventilation, respectively, and were alive. Vasopressor- and ventilator-free days were only assessed in those with return of spontaneous circulation.

[a] Since the data was extremely skewed and zero-inflated, no effect estimate is provided.

eTable 7. Hospital Disposition and Cause of Death		
	Vasopressin and Methylprednisolone	**Placebo**
Disposition in those discharge alive	(n = 24)	(n = 32)
Home	10 (42)	10 (31)
Nursing home	0 (0)	1 (3)
Rehabilitation center	7 (29)	4 (13)
Transferred to another hospital	7 (29)	17 (53)
Cause of death[a]	(n = 76)	(n = 54)
Sudden cardiac arrest	2 (3)	4 (7)
Hemodynamic	8 (11)	17 (31)
Respiratory	2 (3)	1 (2)
Withdrawal of care due to …		
Neurological injury	25 (33)	17 (31)
Severe co-morbidity	28 (37)	13 (24)
Severe acute illness	11 (14)	2 (4)

Categorical variables are presented as counts and percentages

[a] Cause of death in those with return of spontaneous circulation who died prior to hospital discharge. The following definition were used:

Sudden cardiac arrest: Sudden cardiac arrest (with CPR) without return of spontaneous circulation not directly caused by any of the other categories. This includes both cardiac and non-cardiac causes of sudden cardiac arrest.

Hemodynamic: Progressive, refractory hemodynamic shock despite aggressive ICU care, or withdrawal of care based on the same. Hemodynamically stable patients (e.g., maintaining their mean arterial blood pressure) on aggressive ICU care (e.g., full vasopressor support) were not included in this category.

Respiratory: Respiratory failure or withdrawal of care based on the same. Respiratory failure may be related to hypoxemia, hypercapnia, or the combination thereof. Patients who are oxygenating sufficiently on highest ventilator settings were not included in this category.

Neurological withdrawal of care: Withdrawal of care based on expectations of a poor neurological recovery based on brain imaging, a neurologic exam, or a formal opinion of a neurologist stating that the prognosis for neurologic recovery is very poor. If an assessment off sedation is not done, there must be other evidence of severe neurologic injury (e.g., severe cerebral edema or herniation).

Co-morbidity withdrawal of care: Withdrawal of care or refusal of life-sustaining therapy based on the expectation of a poor quality of life. This may be related to a preexisting or newly discovered terminal illness or other serious medical condition (e.g., dementia or cancer).

Severe acute illness withdrawal of care: Withdrawal of care or refusal of life-sustaining therapy based on an acute illness that is not amenable to treatment. This could be a ruptured aortic aneurism, severe bowel ischemia, multiorgan failure, etc. This category was only used if none of the others applied.

eTable 8. Neurologic Outcomes				
	30 DAYS		90 DAYS	
	Vasopressin and Methylprednisolone (n = 237)	Placebo (n = 264)	Vasopressin and Methylprednisolone (n = 237)	Placebo (n = 264)
Cerebral Performance Category				
CPC 1	11 (5)	18 (7)	15 (6)	18 (7)
CPC 2	7 (3)	2 (1)	3 (1)	2 (2)
CPC 3	5 (2)	9 (3)	2 (1)	4 (2)
CPC 4	0 (0)	2 (1)	0 (0)	0 (0)
CPC 5	214 (90)	233 (88)	217 (92)	240 (91)
Modified Rankin Scale				
mRS 0	0 (0)	0 (0)	1 (< 1)	1 (< 1)
mRS 1	3 (1)	4 (2)	7 (3)	4 (2)
mRS 2	7 (3)	7 (3)	5 (2)	10 (4)
mRS 3	1 (< 1)	8 (3)	2 (1)	5 (2)
mRS 4	7 (3)	4 (2)	3 (1)	0 (0)
mRS 5	5 (2)	8 (3)	2 (1)	4 (2)
mRS 6	214 (90)	233 (88)	217 (92)	240 (91)
Glasgow Outcome Scale Extended				
GOSE 1	214 (90)	233 (88)	217 (92)	240 (91)
GOSE 2	1 (< 1)	2 (1)	0 (0)	0 (0)
GOSE 3	9 (4)	11 (4)	3 (1)	4 (2)
GOSE 4	2 (1)	6 (2)	3 (1)	5 (2)
GOSE 5	4 (2)	5 (2)	4 (2)	5 (2)
GOSE 6	2 (1)	4 (2)	3 (1)	6 (2)
GOSE 7	3 (1)	2 (1)	2 (1)	2 (1)
GOSE 8	2 (2)	1 (< 1)	5 (2)	2 (1)

Categorical variables are presented as counts and percentages

The Glasgow Outcome Scale Extended is an 8-point scale to assess neurologic outcome after brain damage. Higher scores indicate better outcomes. It was planned to analyze these three ordinal outcomes using ordinal logistical regression. However, the proportional odds assumption was not met, and the analyses were therefore not performed consistent with the stated analysis plan in the protocol.

eTable 9. EQ-5D-5L Subcategories				
	30 DAYS		90 DAYS	
	Vasopressin and Methylprednisolone (n = 23)	Placebo (n = 31)	Vasopressin and Methylprednisolone (n = 20)	Placebo (n = 24)
Mobility				
No problems	8 (35)	4 (13)	11 (55)	10 (42)
Slight problems	1 (4)	4 (13)	2 (10)	6 (25)
Moderate problems	3 (13)	11 (35)	2 (10)	5 (21)
Severe problems	3 (13)	3 (10)	0 (0)	0 (0)
Extreme problems	8 (35)	9 (29)	5 (25)	3 (13)
Self-care				
No problems	8 (35)	8 (26)	13 (65)	15 (63)
Slight problems	2 (9)	5 (16)	3 (15)	4 (17)
Moderate problems	2 (9)	4 (13)	0 (0)	1 (4)
Severe problems	0 (0)	3 (10)	0 (0)	0 (0)
Extreme problems	11 (48)	11 (35)	4 (20)	4 (17)
Usual activities				
No problems	3 (13)	2 (6)	8 (40)	4 (17)
Slight problems	3 (13)	2 (6)	2 (10)	6 (25)
Moderate problems	2 (9)	3 (10)	3 (15)	4 (17)
Severe problems	0 (0)	5 (16)	1 (5)	0 (0)
Extreme problems	15 (65)	19 (61)	6 (30)	10 (42)
Pain/discomfort				
No problems	5 (22)	6 (19)	14 (70)	13 (54)
Slight problems	12 (52)	6 (19)	5 (15)	7 (29)
Moderate problems	4 (17)	14 (45)	1 (5)	3 (13)
Severe problems	2 (9)	5 (16)	0 (0)	1 (4)
Extreme problems	0 (0)	0 (0)	0 (0)	0 (0)
Anxiety/depression[a]				
No problems	9 (41)	8 (27)	11 (55)	15 (58)
Slight problems	5 (23)	11 (37)	5 (25)	5 (21)
Moderate problems	6 (27)	7 (23)	1 (5)	5 (21)
Severe problems	1 (5)	4 (13)	1 (5)	0 (0)
Extreme problems	1 (5)	0 (0)	2 (10)	0 (0)

Categorical variables are presented as counts and percentages

[a] For two patients, one in each group, at 30 days, it was not possible to assess for anxiety/depression due to severe neurologic compromise at the time of the assessment. When calculating the indexed value, it was assumed that these patients had “Extreme problems”.

eTable 10. Pre-defined Potential Adverse Events		
	Vasopressin and Methylprednisolone	**Placebo**
In patients with return of spontaneous circulation	**(n = 100)**	**(n = 86)**
Hyperglycemia	77 (77)	63 (73)
Insulin infusion	23 (23)	17 (20)
Hypernatremia	28 (28)	27 (31)
Infection		
Bacteremia	9 (9)	7 (8)
Pneumonia	21 (21)	15 (17)
Urinary tract infection	4 (4)	4 (5)
New or changing antibiotics	61 (61)	56 (65)
Gastrointestinal bleeding	5 (5)	3 (3)
Mesenteric ischemia	2 (2)	1 (1)
Peripheral ischemia	3 (3)	3 (3)
In those surviving at least 24 hours	**(n = 63)**	**(n = 61)**
Hyperglycemia	57 (90)	51 (84)
Insulin infusion	23 (37)	17 (28)
Hypernatremia	19 (30)	23 (38)
Infection		
Bacteremia	8 (13)	7 (11)
Pneumonia	20 (32)	15 (25)
Urinary tract infection	4 (6)	4 (7)
New or changing antibiotics	57 (90)	53 (87)
Gastrointestinal bleeding	2 (3)	2 (3)
Mesenteric ischemia	2 (3)	1 (2)
Peripheral ischemia	3 (5)	2 (3)

Categorical variables are presented as counts and percentages

Definitions for adverse events are provided in the protocol. Hyperglycemia, insulin infusion, and hypernatremia were assessed within 48 hours after return of spontaneous circulation. The remainder of the adverse events were assessed until death or hospital discharge.

Data Sharing Statement

Andersen. Effect of Vasopressin and Methylprednisolone vs Placebo on Return of Spontaneous Circulation in Patients With In-Hospital Cardiac Arrest. *JAMA*. Published September 29, 2021. doi:10.1001/jama.2021.16628

Data
Data available: Yes
Data types: Deidentified participant data, Data dictionary
How to access data: All relevant trial-related documents, including the protocol, data dictionary, and the main statistical code, will be shared along with the data. There will be no predetermined end date for the data sharing. Data will be available for any research purpose to all interested parties who have approval from an independent review committee and who have a methodological sound proposal as determined by the steering committee of the current trial. Only the methodological qualities and not the purpose or objective of the proposal will be considered. Interested parties will be able to request the data by contacting the principal investigator.
When available: Six months after the publication of the last results.

Supporting Documents
Document types: None

Additional Information
Who can access the data: As above.
Types of analyses: As above.
Mechanisms of data availability: As above.