# 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 $m^2$.

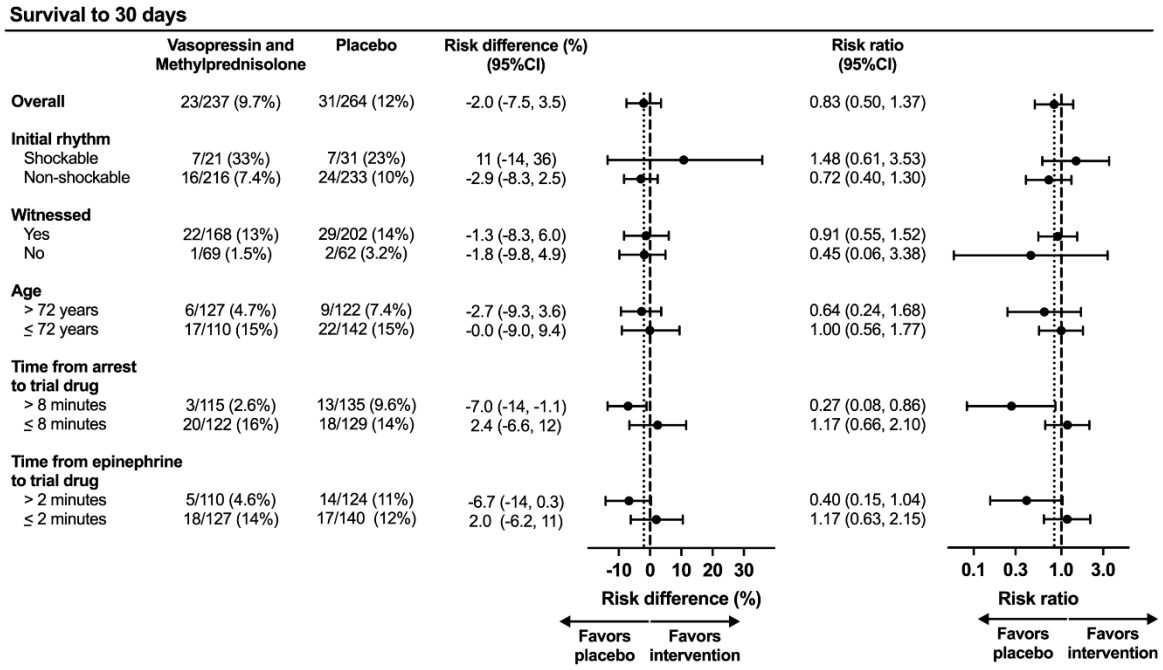
Liver disease: With or without cirrhosis. This includes chronic hepatitis B or C (not cured), non-alcoholic fatty liver disease/nonalcoholic steatohepatitis, alcoholic liver disease, autoimmune hepatitis, liver disease related to hemochromatosis, etc.

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,

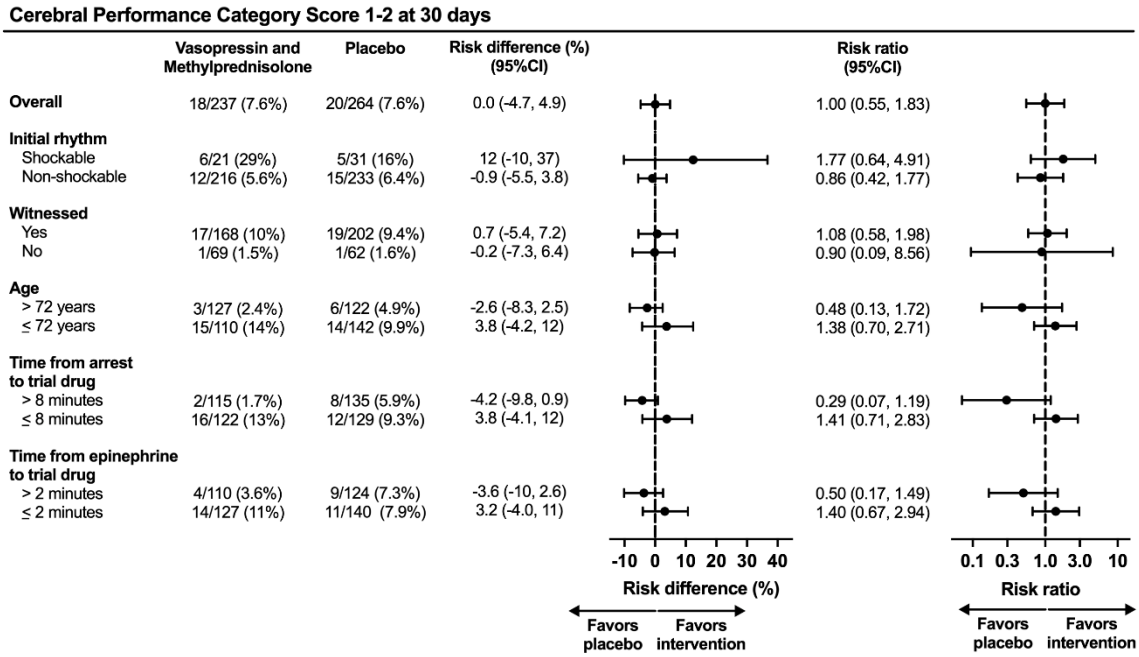
or palliative care, awaiting either of the previous, or awaiting curative or palliative surgery. Previous cancers considered cured should not be included.

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

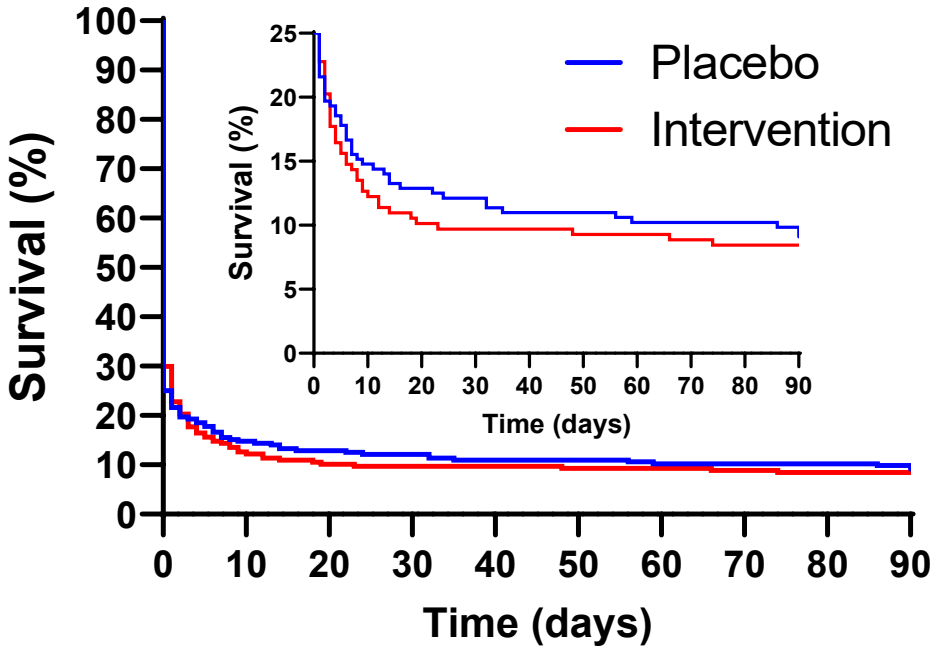
## eFigure 1. Subgroup Results for 30-Day Survival



## 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.