Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Vasopressin, Steroids, and Epinephrine and Neurologically Favorable Survival After In-Hospital Cardiac Arrest
A Randomized Clinical Trial

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IMPORTANCE Among patients with cardiac arrest, preliminary data have shown improved return of spontaneous circulation and survival to hospital discharge with the vasopressin-steroids-epinephrine (VSE) combination.

OBJECTIVE To determine whether combined vasopressin-epinephrine during cardiopulmonary resuscitation (CPR) and corticosteroid supplementation during and after CPR improve survival to hospital discharge with a Cerebral Performance Category (CPC) score of 1 or 2 in vasopressor-requiring, in-hospital cardiac arrest.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, placebo-controlled, parallel-group trial performed from September 1, 2008, to October 1, 2010, in 3 Greek tertiary care centers (2400 beds) with 268 consecutive patients with cardiac arrest requiring epinephrine according to resuscitation guidelines (from 364 patients assessed for eligibility).

INTERVENTIONS Patients received either vasopressin (20 IU/CPR cycle) plus epinephrine (1 mg/CPR cycle; cycle duration approximately 3 minutes) (VSE group, n = 130) or saline placebo plus epinephrine (1 mg/CPR cycle; cycle duration approximately 3 minutes) (control group, n = 138) for the first 5 CPR cycles after randomization, followed by additional epinephrine if needed. During the first CPR cycle after randomization, patients in the VSE group received methylprednisolone (40 mg) and patients in the control group received saline placebo. Shock after resuscitation was treated with stress-dose hydrocortisone (300 mg daily for 7 days maximum and gradual taper) (VSE group, n = 76) or saline placebo (control group, n = 73).

MAIN OUTCOMES AND MEASURES Return of spontaneous circulation (ROSC) for 20 minutes or longer and survival to hospital discharge with a CPC score of 1 or 2.

RESULTS Follow-up was completed in all resuscitated patients. Patients in the VSE group vs patients in the control group had higher probability for ROSC of 20 minutes or longer (109/130 [83.9%] vs 91/138 [65.9%]; odds ratio [OR], 2.98; 95% CI, 1.39-6.40; P = .005) and survival to hospital discharge with CPC score of 1 or 2 (18/130 [13.9%] vs 7/138 [5.1%]; OR, 3.28; 95% CI, 1.17-9.20; P = .02). Patients in the VSE group with postresuscitation shock vs corresponding patients in the control group had higher probability for survival to hospital discharge with CPC scores of 1 or 2 (16/76 [21.1%] vs 6/73 [8.2%]; OR, 3.74; 95% CI, 1.20-11.62; P = .02), improved hemodynamics and central venous oxygen saturation, and less organ dysfunction. Adverse event rates were similar in the 2 groups.

CONCLUSION AND RELEVANCE Among patients with cardiac arrest requiring vasopressors, combined vasopressin-epinephrine and methylprednisolone during CPR and stress-dose hydrocortisone in postresuscitation shock, compared with epinephrine/saline placebo, resulted in improved survival to hospital discharge with favorable neurological status.

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N eurological outcome after cardiac arrest has been the main end point of several randomized clinical trials (RCTs).[1-4] Neurologically favorable survival differs from overall survival. Among cardiac arrest survivors, the prevalence of severe cerebral disability or vegetative state ranges from 25% to 50%.[2-6]

In a previous single-center RCT,[7] combined vasopressin-epinephrine during cardiopulmonary resuscitation (CPR) and corticosteroid supplementation during and after CPR vs epinephrine alone during CPR and no steroids resulted in improved overall survival to hospital discharge. Patients in the vasopressin-steroids-epinephrine (VSE) group had more frequent return of spontaneous circulation (ROSC) and attenuated postresuscitation systemic inflammatory response[7,8] and organ dysfunction.[7] However, this preliminary study could not reliably assess VSE efficacy with respect to neurologically favorable survival to hospital discharge. We addressed this question with a 3-center RCT of vasopressor-requiring, in-hospital cardiac arrest.

ALS advanced life support

CPC Cerebral Performance Category

ROSC return of spontaneous circulation

Scvo₂ central venous oxygen saturation

VSE vasopressin-steroids-epinephrine combination

Methods

We conducted the study in the intensive and coronary care units (ICUs/CCUs), emergency departments, general wards, and operating rooms of 2 tertiary care centers in Athens, Greece (Evaggelismos General Hospital and 401 Greek Army Hospital) and 1 tertiary care center in Larissa, Greece (Larissa University Hospital). The study-protocol has been detailed elsewhere.[7] (For center-endorsed, general ICU therapeutic strategies, refer to the Supplement.)

Eligible patients had experienced in-hospital, vasopressor-requiring cardiac arrest according to guidelines for resuscitation from 2005.[9] Exclusion criteria were age younger than 18 years, terminal illness (ie, life expectancy <6 weeks) or do-not-resuscitate status, cardiac arrest due to exsanguination (eg, ruptured aortic aneurysm), cardiac arrest before hospital admission, treatment with intravenous corticosteroids before arrest, and previous enrollment in or exclusion from the current study.

Consent was not obtained for the CPR drug combination, which was based on standard guidelines for resuscitation (Supplement).[5-7] However, after CPR was performed, the patients and families were informed about the trial.[5-7] Informed, written consent from next of kin and unwritten patient consent (whenever feasible) were obtained for stress-dose hydrocortisone in postresuscitation shock.[7] The study was approved by the institutional review boards of the participating centers.

Study Design and Protocol

We conducted a 3-center, randomized, double-blind, placebo-controlled, parallel-group clinical trial. Research

Randomizer version 4 (Research Randomizer) was used by the study statistician (E.Z.) for group allocation. For each study center, random numbers (range, 1-300) were generated in sets of 4. Each random number of each set was unique and corresponded to 1 of the consecutively enrolled patients. In each set, an odd or even first number resulted in assignment of the corresponding patient to the control or VSE group, respectively. In each study center, the group allocation rule was known solely by the pharmacist, who prepared the study drugs.

Vasopressin and methylprednisolone were prepared in study center pharmacies in identical, preloaded, 5-mL syringes and placed along with epinephrine ampules in boxes bearing patient codes. At the time of patient enrollment, a box was opened and study drugs were injected intravenously according to protocol. Drug injection was followed by 10 mL of normal saline. Confirmation of ROSC at any time point preceding study drug administration resulted in patient exclusion because of "absence of vasopressor-requiring cardiac arrest."

Resuscitative interventions performed in between 2 consecutive rhythm assessments (ie, CPR cycles) lasted approximately 3 minutes. For the first 5 CPR cycles after enrollment,[7] either arginine vasopressin (20 IU/CPR cycle in VSE group; Monarch Pharmaceuticals) or normal saline placebo (control group) were added to epinephrine (1 mg/CPR cycle; Demo). Depending on CPR duration, patients in the VSE group could receive 20 to 100 IU of vasopressin. Furthermore, 40 mg of methylprednisolone sodium succinate (Pfizer) or the corresponding saline placebo was administered solely during the first CPR cycle after enrollment to VSE or control patients, respectively.[7] If ROSC was not achieved after the completion of experimental treatment, CPR was continued according to resuscitation guidelines from 2005.[7,9] Study drug stability in syringes was confirmed by high-performance liquid chromatography.[7] Advanced life support (ALS) was conducted according to contemporary standards.[7] Besides administering the experimental drug and recording data, investigators did not participate in ALS.[7]

At 4 hours after resuscitation, surviving patients in the VSE group with postresuscitation shock received stress-dose hydrocortisone (300 mg/d for ≤7 days and gradual taper; Pfizer).[7] Patients with evidence of acute myocardial infarction[7] received stress-dose hydrocortisone for 3 days or less to prevent retardation of infarct healing.[7,10]

Hydrocortisone was available in vials containing 100 mg of hydrocortisone sodium succinate powder. Daily doses were diluted in 100 mL of normal saline at study center pharmacies and administered to patients in the VSE group as continuous infusions. At the time of vasopressor cessation or on day 8 after arrest, daily hydrocortisone was consecutively reduced to 200 mg and 100 mg and then discontinued. Patients in the control group with postresuscitation shock received daily infusions of 100-mL normal saline placebo. Normal saline infusion bags were marked with patient codes. Any prescription of open-label hydrocortisone cancelled the experimental treatment.

Definitions

Circulatory failure was defined as an inability to maintain mean arterial pressure greater than 70 mm Hg without using vasopressors after volume loading.[7,11] Respiratory failure was defined as a ratio of arterial oxygen partial pressure to fraction of inspired oxygen of 200 mm Hg or less.[7] Coagulation failure was defined as a platelet count of $50 \times 10^3/\mu L$ or less.[7] Hepatic failure was defined as a serum bilirubin concentration of 6 mg/dL or greater (to convert bilirubin to μmol/L, multiply by 17.104).[7] Renal failure was defined as a serum creatinine level of 3.5 mg/dL or greater, requirement of renal replacement therapy, or both (to convert creatinine to μmol/L, multiply by 88.4).[7] Neurologic failure was defined as a Glasgow Coma Scale score of 9 or less.[7] Hyperglycemia was defined as a blood glucose level exceeding 200 mg/dL (to convert to mmol/L, multiply by 0.0555).[7]

Postresuscitation shock was defined as sustained (>4 hours), new postarrest circulatory failure or postarrest need for 50% or greater increase in any prearrest vasopressor/inotropic support targeted to mean arterial pressure greater than 70 mm Hg. Treatment-refractory shock was defined as having a mean arterial pressure less than 70 mm Hg and being unresponsive to norepinephrine infusions of 0.5 μg/kg/min or greater, while central venous pressure, pulmonary artery wedge pressure, or both exceeded 12 mm Hg.

Documentation and Patient Follow-up

Attempts at CPR were documented according to the Utstein reporting style.[7,12] Hemodynamics and gas exchange, electrolytes and glucose, lactate, and administered fluids and vasopressor/inotropic support were determined and recorded during CPR and at approximately 20 minutes and approximately 4 hours after ROSC. Investigational interventions and daily follow-up were conducted by 11 blinded investigators (7 at Evaggelismos and 2 at each collaborating center); current study personnel were not involved in our preliminary RCT.[7] At each collaborating center, 3 otherwise study-independent emergency physicians provided assistance with the resuscitation protocol.

Follow-up during days 1 through 10 after randomization included determination and recording of hemodynamics and hemodynamic support, gas exchange, fluid balance of the preceding 24 hours, and peripheral perfusion indices[7] at 9 AM and daily recording (within 8-9 AM) of laboratory data and prescribed medication. We did not measure plasma cytokine concentrations.[7] The results of 3 daily determinations (at 8 AM, 4 PM, and 12 AM) of blood glucose level were also recorded to subsequently analyze the incidence of hyperglycemia. Follow-up to day 60 after arrest included assessment of organ failure and ventilator-free days. Comorbidities and complications throughout ICU/CCU and hospital stay and times to ICU/CCU and hospital discharge were also recorded.

Outcome Measures

The primary end points were ROSC for 20 minutes or longer (adjusted to Utstein style) and survival to hospital discharge with favorable neurological recovery (ie, Glasgow-Pittsburgh Cerebral Performance Category [CPC][13] score of 1 or 2). The CPC score has 5 categories: good cerebral performance, moderate cerebral disability, severe cerebral disability, coma or vegetative state, and death. A CPC score of 1 means the patient is conscious and able to work/live normally; a CPC score of 2 means the patient is conscious and able to conduct independent daily activities but has disorders such as hemiplegia, seizures, and cognitive changes. Blinded study investigators determined the CPC score by in-person interviews and medical record review.

Secondary end points were arterial pressure during and approximately 20 minutes after CPR; arterial pressure and central venous oxygen saturation ($ScvO_2$) during days 1 through 10 after randomization; number of organ failure-free days during days 1 through 60; and potentially corticosteroid-associated complications such as hyperglycemia, infections, bleeding peptic ulcers, and paresis.[7]

Statistical Analysis

Based on prior results,[7] we predicted rates of survival with favorable neurological recovery of 15% and 4% in the VSE and control groups, respectively. For α = .05 and power = 0.80, a total sample size of 244 patients was required. A target enrollment of 300 patients would compensate for possible dropouts or incomplete data.

We analyzed data from patients with vasopressor-requiring cardiac arrest according to the intention-to-treat principle; randomized patients who did not require vasopressors were excluded. We tested for heterogeneity (I^2 statistic) among study centers with respect to primary end points (Review Manager version 5.0.1; Cochrane Collaboration). Prespecified comparisons included data from patients with postresuscitation shock and from patients who either did or did not require more than 5 mg of epinephrine during CPR. Data are reported as mean (standard deviation), median (interquartile range [IQR]), or number (percentage) unless otherwise specified. Distribution normality was tested by Kolmogorov-Smirnov test. Dichotomous and categorical variables were compared by 2-sided χ^2 or Fisher exact test. Continuous variables were compared by 2-tailed, independent samples t test or Mann-Whitney exact U test. P values of multiple t test comparisons conducted between the same subgroups and corresponding to consecutive time points of patient follow-up were multiplied by the number of comparisons (Bonferroni correction); nominal significance level was maintained unchanged.

In patients with postresuscitation shock, we used linear mixed-model analysis to determine the effects of group, time (first 10 days after randomization), group × time interaction, study center, and insulin infusion rate[14] (at 8 AM of days 1-10) on the daily recordings of mean arterial pressure, $ScvO_2$, arterial blood lactate, vasopressor infusions, fluid balance, hemoglobin concentration, arterial oxygen saturation, and $PaCO_2$.[7] We adjusted for blood glucose level while testing for dependent variables with a previously documented relationship with blood glucose.[15-17] Model

goodness-of-fit was assessed using Akaike information criteria and the likelihood ratio test. Fixed-effects significance was determined by F test. Pair-wise comparisons of estimated marginal means were adjusted for multiplicity by Bonferroni correction.

We used multivariable logistic regression to determine odds ratios (ORs) and 95% CIs for effect modifiers for achieving ROSC for 20 minutes or longer and hospital discharge with a CPC score of 1 or 2. For ROSC, the explanatory variables (effect modifiers) included in the model were study center, group,[7] cardiac arrest cause,[18] either cardiac arrest rhythm[18,19] or atropine use[19] (as rhythm determined atropine use[9]), cardiac arrest location,[18] weekday (ie, working day or holiday) and time of day,[19] and epinephrine[19] and bicarbonate dose[9] during resuscitation.

For determining the neurologically favorable survival to hospital discharge of the whole study population, we included the same effect modifiers as in ROSC analysis plus the use of therapeutic hypothermia.[1,2] In drawing inferences, we included in the models only effect modifiers with a significance level less than .05, obtaining parsimonious models. The final model for ROSC included as explanatory variables the following: group, cardiac rhythm, weekday, time of day, and epinephrine dose. The final model for neurologically favorable survival included as explanatory variables the following: group, cardiac arrest cause, atropine use, epinephrine dose, and hypothermia. Then, for a postresuscitation shock subgroup (n = 149), neurologically favorable survival was predicted using the same explanatory variables as in the whole-population model.

In addition, we used multivariable Cox regression to analyze survival data and determine hazard ratios (HRs) and their 95% CIs for predictors of poor outcome (ie, death or survival with CPC score of ≥3). Statistical significance was set at $P < .05$. Reported P values are 2-sided, and sample size was calculated by G*Power version 3.1 (Heinrich Heine University). The analysis was performed (by E.Z., A.P., and S.D.M.) using SPSS version 17.0.1 (SPSS); analyses were reviewed by E.Z. Further details about the statistical methods are provided in the online Supplement.

Results

From September 1, 2008, to October 1, 2010, 364 consecutive patients with cardiac arrest were assessed for eligibility. Advanced life support was provided to all patients by resuscitation teams.[7] Sixty-four patients were excluded and 300 patients (VSE group, n = 146; control group, n = 154) were enrolled (Figure 1). Another 32 patients (16 in each group) were excluded because ROSC was confirmed during the first postenrollment CPR cycle and before any study drug administration. Excluded patients were not followed up, but survivors' medical diagnoses at hospital discharge were recorded.[7] Discharge diagnoses did not include any neurological disorder in 44 of 96 patients (45.8%).

The data from 268 patients (VSE group, n = 130; control group, n = 138) were analyzed (Figure 1). Heterogeneity

among centers was low for ROSC (I^2 = 0.16) and neurologically favorable survival (I^2 = 0) (eFigures 1 and 2 in the Supplement).

Periarrest Data

The baseline patient characteristics and cardiac arrest causes are shown in **Table 1**. Information about cardiac arrest initial rhythms and treatment are shown in **Table 2**. There was frequent use of atropine and bicarbonate. Short CPR cycle duration resulted in relatively high vasopressor administration rate of approximately 1 dose per 3 minutes (guideline-recommended rate: 1 mg/3-5 minutes).[9] Patients in the VSE group had higher probability for ROSC for 20 minutes or longer compared with patients in the control group (109/130 [83.9%] vs 91/138 [65.9%]; OR, 2.98; 95% CI, 1.39-6.40; P = .005) (Figure 1 and eTable 2 in the Supplement). Compared with control patients, VSE patients received less epinephrine during ALS and had shorter ALS duration (Table 2) and higher mean arterial pressure during and after CPR (**Table 3**).

A periarrest (ie, within 2 hours after ROSC) percutaneous coronary intervention was performed in 7 of 130 patients in the VSE group (5.4%) and 11 of 138 control patients (7.8%; P = .47) (Supplement). Therapeutic hypothermia[1,2] was used in 32 of 130 VSE patients (24.6%) and 34 of 138 control patients (24.6%; P > .99) (Supplement). At 4 hours after resuscitation, 76 of 86 surviving VSE patients and 73 of 76 surviving controls had postresuscitation shock and were assigned to receive stress-dose hydrocortisone and saline placebo, respectively (Figure 1). Within 12 hours after arrest, all surviving patients had been admitted to the ICU or CCU.

Survival and Complications During Follow-up

Full results of multivariable analyses are presented in the online supplement (eResults in the Supplement). Study center had no significant effect on primary outcomes. Compared with patients in the control group, patients in the VSE group had lower hazard of poor outcome during follow-up (HR, 0.70; 95% CI, 0.54-0.92; P = .009) and were more likely to be alive at hospital discharge with favorable neurological recovery (18/130 [13.9%] vs 7/138 [5.1%]; OR, 3.28; 95% CI, 1.17-9.20; P = .02) (**Figure 2**A). Epinephrine, atropine, and bicarbonate doses during CPR; no use of therapeutic hypothermia; cardiac arrest rhythm (non–ventricular fibrillation/ventricular tachycardia) and cause (noncardiac); and cardiac arrest on a weekend or holiday or during the night (from 11:00 PM to 7:00 AM) were associated with increased hazard for poor outcome during follow-up, lower probability of being alive with favorable neurological recovery at hospital discharge, or both. There was no case of brain death declaration after legally specified testing or life support withdrawal.

Among survivors for 4 hours or longer (VSE group, n = 86; control group, n = 76), postarrest morbidity and complications throughout hospital stay and death causes were similar (eTable 25 in the Supplement). Regarding long-term survivors, patients in the VSE group vs control group had comparable mean (SD) ventilator-free days (43.4 days [15.2] vs 39.8

Figure 1. Study Flowchart
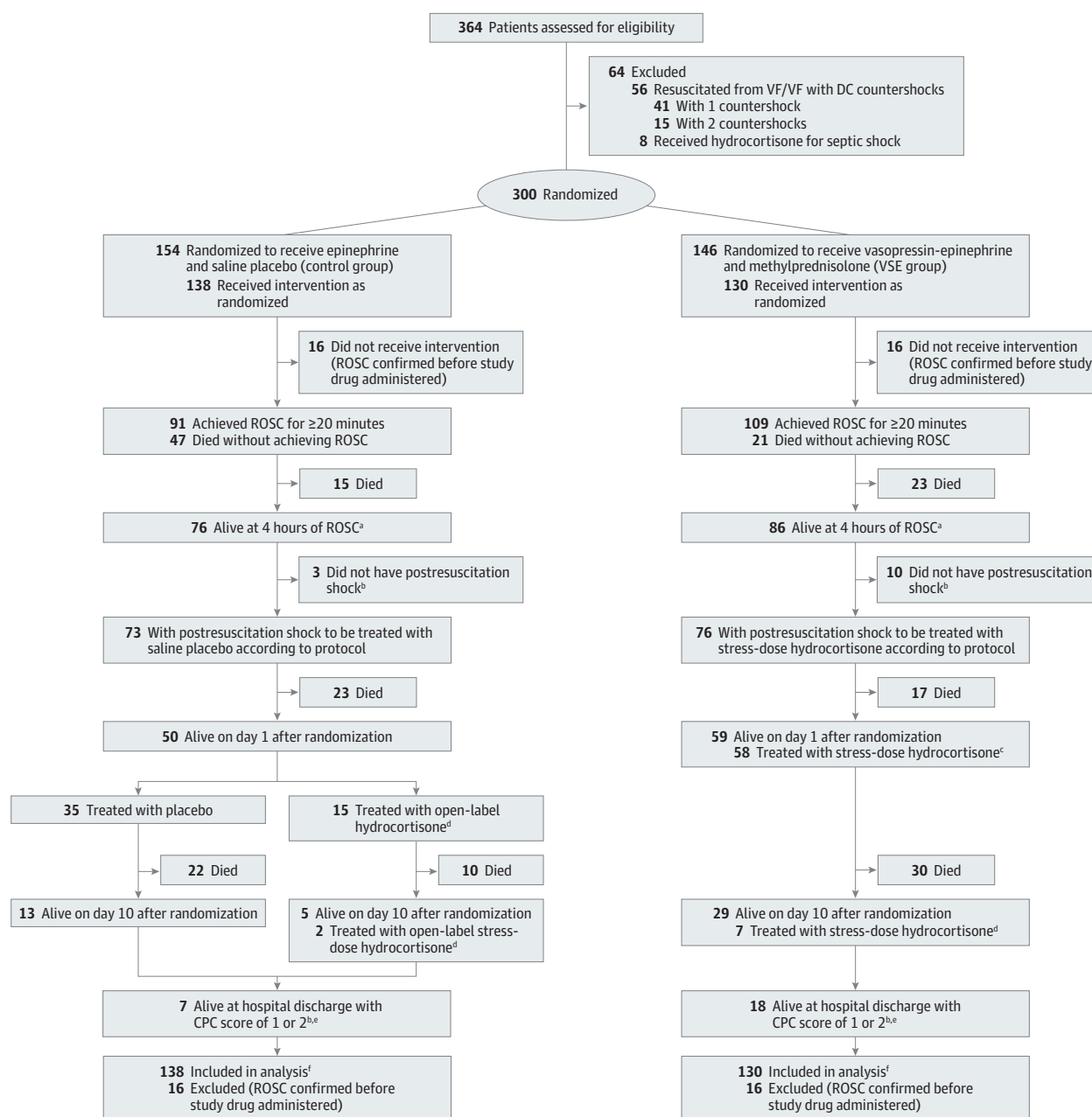
For brevity, "Died" corresponds to poor outcome as defined in the "Methods" section. VF/VT indicates ventricular fibrillation/ventricular tachycardia; DC, direct current; ROSC, return of spontaneous circulation.

[a] Within 4 hours of ROSC, 15 patients in the control group and 23 patients in the vasopressin-steroids-epinephrine (VSE) group experienced vasopressor-unresponsive hypotension (ie, treatment-refractory shock) and died.

[b] In the control group, all 3 patients were alive on days 1 and 10, and 1 patient was alive at hospital discharge with a Cerebral Performance Category (CPC) score of 1 or 2. In the VSE group, all 10 patients were alive on day 1, 6 patients were alive on day 10, and 2 patients were alive at hospital discharge with a CPC score of 1 or 2.

[c] Thirteen patients of the VSE group also received open-label hydrocortisone.

[d] This was done according to attending physician decision. According to the study protocol, control patients should receive saline placebo and VSE patients hydrocortisone; on day 10 placebo or hydrocortisone should be discontinued in both groups.

[e] In the control group, 6 survivors originated from the postresuscitation shock subgroup; in the VSE group, 16 survivors originated from the postresuscitation shock subgroup.

[f] In post hoc analysis (see also the online Supplement), 5 controls and 11 VSE patients achieved 1-year survival with a CPC score of 1 or 2.

days [19.4]; P = .57), ICU/CCU stays (23.1 days [18.9] vs 29.3 days [23.5]; P = .44), and hospital stays(48.2 days [34.9] vs 59.7 days [39.0]; P = .42). Six patients (3 in each group) had CPC scores of 3 or 4 at hospital discharge.

Follow-up in Postresuscitation Shock

Among survivors for 4 hours or longer, VSE patients with postresuscitation shock (n = 76) vs corresponding controls (n = 73) had lower hazard of poor outcome during follow-up

(HR, 0.61; 95% CI, 0.43-0.89; P = .009) and were more likely to be alive at hospital discharge with favorable neurological recovery (16/76 [21.1%] vs 6/73 [8.2%]; OR, 3.74; 95% CI, 1.20-11.62; P = .02) (Figure 2B).

Full follow-up study-data and violations of the stress-dose hydrocortisone protocol are reported in the online supplement. Compared with controls, patients in the VSE group had significantly more neurologic and renal failure–free days (eFigures 4A and 4B, respectively, in the Supplement) and more ventilator-free days (median, 0 days [IQR, 0-11] vs 0 days [IQR, 0-0]; P = .03).

During days 1 through 10 after randomization, mean arterial pressure and ScvO$_2$ were improved in the VSE group vs the control group (eFigures 5A and 5B, respectively, and 5C and 5D, respectively, in the Supplement). Patients in the VSE group vs control group had a similar frequency of hyperglycemic episodes (confirmed in 94/1269 [7.4%] vs 91/1200 [7.6%] blood glucose determinations; P = .88) but higher numbers of patient-days with insulin treatment aimed at a blood glucose level of 180 mg/dL or less (249/494 patient-days [50.4%] vs 130/361 patient-days [36.0%]; P < .001).

Additional Analyses

The eResults section in the Supplement outlines post hoc and prespecified subgroup analyses and their main results (eTable 29). Two different subgroups of patients, those treated with hydrocortisone vs those not treated, had favorable HRs for poor outcome. Also, periarrest cerebral perfusion pressure was higher in VSE patients vs controls with intracranial pressure monitoring in place.

Discussion

In this study of patients with cardiac arrest requiring vasopressors, the combination of vasopressin and epinephrine, along with methylprednisolone during CPR and hydrocortisone in postresuscitation shock, resulted in improved survival to hospital discharge with favorable neurological status, compared with epinephrine and saline placebo. These results are consistent with increased efficacy of the VSE combination vs epinephrine alone during CPR for in-hospital, vasopressor-requiring cardiac arrest.

Recently published results of out-of-hospital cardiac arrest[20-23] have cast doubt about epinephrine efficacy, even vs placebo, in achieving long-term survival with favorable neurological recovery. Furthermore, animal data suggest that epinephrine vs placebo,[24] vasopressin,[25] or combined vasopressin-epinephrine[26] reduces microcirculatory cerebral blood flow during CPR.

Cerebral microcirculatory flow is reduced by approximately 60% during chest compression–only CPR and is restored to prearrest levels in 3 minutes or longer after ROSC.[27] Periarrest cerebral ischemia depends on CPR duration.[27] The present study's experimental VSE-CPR regimen included methylprednisolone, which may enhance the vasopressor effects of vasopressin[28] and epinephrine.[29] As periarrest changes in cerebral blood flow may parallel changes in mean arterial

Table 1. Patient Characteristics Before Cardiac Arrest and Causes of Cardiac Arrest

Characteristic	Control Group (n = 138)	VSE Group (n = 130)
Age, mean (SD), y	62.8 (18.6)	63.2 (17.6)
Male sex, No. (%)	88 (63.8)	95 (73.1)
Body mass index, mean (SD)[a]	25.4 (3.8)	25.8 (4.6)
Hospital stay before arrest, median (IQR), d	2 (1-6)	5 (1-11)
Cardiovascular comorbidity, No. (%)		
Hypertension	77 (55.8)	64 (49.2)
Coronary artery disease	44 (31.9)	44 (33.8)
Diabetes	30 (21.7)	34 (26.2)
Peripheral vascular disease	24 (17.4)	34 (26.2)
Cardiac arrhythmia	27 (19.6)	25 (19.2)
Valvular heart disease	18 (13.0)	21 (16.2)
Cardiac conduction disturbances	6 (4.3)	15 (11.5)
Noncardiovascular comorbidity, No. (%)[b]	77 (55.8)	74 (56.9)
Hospital admission cause, No. (%)[c]		
Acute cardiovascular disease	36 (26.1)	39 (30.0)
Acute respiratory disease	39 (28.3)	26 (20.0)
Acute digestive disease	34 (24.6)	22 (16.9)
Acute neurologic disease	11 (8.0)	16 (12.3)
Trauma	13 (9.4)	13 (10.0)
Malignancy	11 (8.0)	11 (8.5)
Acute renal disease	9 (6.5)	8 (6.2)
Other	6 (4.4)	8 (6.2)
Cause of cardiac arrest, No.(%)[d]		
Hypotension	51 (37.0)	61 (46.9)
Respiratory depression or failure[e]	52 (37.7)	42 (32.3)
Myocardial ischemia/infarction	24 (17.4)	30 (23.1)
Metabolic	21 (15.2)	11 (8.5)
Life-threatening/lethal arrhythmia[f]	11 (8.0)	8 (6.2)
Other[g]	1 (0.7)	2 (1.5)

Abbreviations: VSE, vasopressin-steroids-epinephrine; IQR, interquartile range.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Includes chronic respiratory, neurologic, digestive, renal, endocrine, autoimmune, and musculoskeletal disease, malignancy, and immunosuppression; 16 controls (11.6%) and 10 VSE group patients (7.7%) had prior treatment with inhaled corticosteroids.

[c] Some patients had more than 1 cause of hospital admission; "other" causes included 2 cases each of urosepsis (ie, acute pyelonephritis causing septic shock), lower extremity gangrene, and scheduled resection of a benign tumor and 1 case each of thermal injury, portal vein thrombosis, visceral hemangiomatosis, diabetic ketoacidosis, cervical abscess, rheumatoid arthritis exacerbation, fistula formation between the small intestine and urinary bladder, and scheduled bone marrow transplantation.

[d] Some patients had more than 1 major disturbance precipitating the cardiac arrest.

[e] Respiratory depression occurring during spontaneous breathing; respiratory failure occurring after endotracheal intubation and initiation of mechanical ventilation.

[f] Corresponds to the presence of prearrest, electrocardiographic evidence of (1) bradycardia <40/min and complete heart block with broad (>0.12 seconds) QRS complex[9] (n = 14; control, n = 9), followed by asystole (n = 10; control, n = 8), or pulseless electrical activity (n = 4; control, n = 1); or (2) broad-complex tachycardia,[9] followed by ventricular fibrillation (n = 5; control, n = 2). The occurrence of these arrhythmias might be associated with acute intracranial or concurrent thoracic traumatic pathology (n = 11; control, n = 8) and/or myocardial ischemia (n = 10; control, n = 4). Seven of 14 patients (control, n = 3) who experienced the life-threatening bradycardia also had a history of cardiac conduction disturbances.

[g] Includes 2 cases of permanent pacemaker malfunction and 1 case of tracheal rupture during percutaneous dilatational tracheostomy.

Table 2. Advanced Life Support Data

	Control Group (n = 138)	VSE Group (n = 130)	P Value
Location of cardiac arrest, No. (%)			
Hospital ward	58 (42.0)	57 (43.8)	.81
ICU or CCU	53 (38.4)	48 (36.9)	.90
Emergency department	21 (15.2)	21 (16.2)	.87
Operating room	6 (4.3)	4 (3.1)	.75
Initial rhythm, No. (%)			
Ventricular fibrillation/tachycardia	23 (16.7)	22 (16.9)	>.99
Asystole	97 (70.3)	83 (63.8)	.30
Pulseless electrical activity	18 (13.0)	25 (19.2)	.19
Witnessed arrest, No. (%)	126 (91.3)	121 (93.1)	.65
Time to ALS initiation, median (IQR), min	2 (1-3)	2 (1-3)	.21
ALS duration, median (IQR), min	19 (9-30)	13 (6-20)	.01
Not intubated at arrest[a]	57 (41.3)	58 (44.6)	.62
No. of CPR cycles, median (IQR)	5 (3-10)	4 (2-6)	.001
CPR cycle duration, mean (SD), min	3.2 (0.4)	3.3 (0.6)	.13
No. of defibrillations, median (IQR)	0 (0-1)	0 (0-1)	.75
No. of potentially reversible causes, 4Hs and 4Ts, median (IQR)	2 (1-3)	2 (1-3)	.13
Rate of ROSC ≥20 min, after first vasopressor dose, No. (%)[b,c]	18 (13.0)	25 (19.2)	.57
Rate of ROSC ≥20 min, after second vasopressor dose, No. (%)[b,c]	28 (20.3)	44 (33.8)	.04
Overall rate of ROSC ≥20 min, No. (%)[b]	91 (65.9)	109 (83.8)	.003
Medication or treatment[c]			
Vasopressin, mean (SD), IU		70.3 (31.2)	
Epinephrine, median (IQR), mg	5 (3-9)	4 (2-5)	.002
Methylprednisolone, mean (SD), mg		40.0 (0.0)	
Atropine, mean (SD), mg[d]	2.6 (1.1)	2.7 (0.9)	.34
Amiodarone, median (IQR) [max value], mg	0 (0-0) [450]	0 (0-0) [450]	.07
Bicarbonate, median (IQR), mmol[e]	90 (0-90)	68 (0-90)	.38
Calcium, median (IQR) [max value], mmol	0 (0-0) [20]	0 (0-0) [20]	.75
Magnesium, median (IQR) [max value], mmol	0 (0-0) [16]	0 (0-0) [16]	.76
Crystalloids, median (IQR), mL	100 (0-548)	100 (0-353)	.21
Colloids, median (IQR), mL	0 (0-500)	0 (0-500)	.75
Packed red blood cells, median (IQR) [max value], units of ~300 mL	0 (0-0) [5]	0 (0-0) [4]	.37
Fresh frozen plasma, median (IQR) [max value], units of ~200 mL	0 (0-0) [6]	0 (0-0) [3]	.44
Temporary pacing, No. (%)	11 (8.0)	17 (13.1)	.23

Abbreviations: ALS, advanced life support; CCU, coronary care unit; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; IQR, interquartile range; max, maximum; ROSC, return of spontaneous circulation; VSE, vasopressin-steroids-epinephrine; 4Hs, hypoxia, hypovolemia, electrolyte disturbances such as hypo or hyperkalemia and hypocalcemia, and hypothermia[9]; 4Ts, tension pneumothorax, cardiac tamponade, toxic substances, and lethal thromboembolism (eg, massive pulmonary embolism).[9]

[a] In all cases, the trachea was successfully intubated on the first attempt and within the first 3 minutes of onset of ALS.

[b] The reporting of the original outcome measure of ROSC for ≥15 minutes was adjusted according to the Utstein style[12]; all patients who survived until 15 minutes after ROSC were also alive at 20 minutes after ROSC.

[c] All drugs were injected exclusively intravenously either via a central venous catheter (ICU or CCU patients), or via a 14-, 16-, or 18-gauge peripheral venous

catheter; a functional intravenous line was present prior to the cardiac arrest in all but 4 controls and 2 VSE patients; in all these 6 cases, an intravenous line was started within 2 minutes after the confirmation of asystole or pulseless electrical activity.

[d] Single-bolus atropine was given to 223 patients with an initial rhythm of asystole or pulseless electrical activity[9] and to 4 patients after initial cardiac rhythm conversion from ventricular fibrillation (VF) to asystole, another 8 patients with treatment-refractory VF and ALS duration of more than 30 minutes received single-bolus atropine at an instant of resuscitation team leader misdiagnosis of fine VF as asystole.

[e] Among 156 treated patients, 152 had a periarrest, arterial blood pH of ≤7.10, a potassium level of >6 mEq/L, or both and/or an ALS duration of at least 10 minutes.

pressure,[26,27] the improved periarrest hemodynamics and shorter ALS duration of VSE patients vs control patients may reflect attenuated periarrest cerebral ischemia (hypothesis supported by post hoc cerebral perfusion pressure results), possibly contributing to improved neurological recovery.

The improved early postarrest mean arterial pressure and ScvO$_2$, lower CPR dose of epinephrine,[30,31] shorter ALS duration, and use of methylprednisolone during CPR[32] are consistent with improved postarrest cardiac performance,[30-32] possibly leading to better outcomes for patients in the VSE group.[31]

Table 3. Periarrest Physiological Data and Early Postarrest Support

	Control Group	VSE Group	P Value
Physiological Data Recorded During CPR	(n = 138)	(n = 130)	
Hemodynamics, No. (%)[a,b]	77 (55.8)	53 (40.7)	
Systolic arterial pressure, mean (SD), mm Hg	76.4 (23.8)	112.3 (43.4)	<.001
Mean arterial pressure, mean (SD), mm Hg	52.2 (16.9)	75.6 (26.9)	<.001
Diastolic arterial pressure, mean (SD), mm Hg	40.1 (14.4)	57.3 (21.4)	<.001
Blood gas analysis, No.(%)[b]	82 (59.4)	69 (53.1)	
Pao_2, median (IQR), mm Hg	80 (54-121)	68 (45-112)	.31
$Paco_2$, median (IQR), mm Hg	46 (40-65)	55 (37-69)	.39
Arterial pH, mean (SD)	7.07 (0.15)	7.10 (0.17)	.16
Potassium ion, mean (SD), mEq/L	5.1 (1.4)	5.3 (1.3)	.34
Sodium ion, mean (SD), mEq/L	142.4 (7.7)	142.3 (9.1)	.90
Calcium ion, mean (SD), mEq/L	1.8 (0.4)	1.8 (0.4)	.50
Glucose, median (IQR), mg/dL	161 (123-206)	151 (107-201)	.77
Variables Recorded at Approximately 20 Minutes After ROSC	(n = 91)	(n = 109)	
Hemodynamics, No. (%)[a,b]	73 (80.2)	94 (86.2)	
Systolic arterial pressure, mean (SD), mm Hg	100.7 (29.5)	136.5 (44.1)	<.001
Mean arterial pressure, mean (SD), mm Hg	69.1 (20.4)	93.7 (31.3)	<.001
Diastolic arterial pressure, mean (SD), mm Hg	53.4 (17.1)	72.3 (26.2)	<.001
Heart rate, mean (SD), beats/min	115.0 (27.5)	110.0 (25.8)	.22
Blood gas analysis, No. (%)[b]	79 (86.8)	100 (91.7)	
Pao_2, median (IQR), mm Hg	123 (75-214)	132 (81-192)	.86
$Paco_2$, mean (SD), mm Hg	46.8 (15.4)	50.0 (16.4)	.17
Arterial pH, mean (SD)	7.18 (0.16)	7.19 (0.19)	.92
Potassium ion, mean (SD), mEq/L	4.8 (1.4)	4.7 (1.2)	.63
Sodium ion, mean (SD), mEq/L	142.1 (8.2)	144.3 (9.9)	.11
Calcium ion, mean (SD), mEq/L	1.9 (0.6)	1.8 (0.4)	.27
Glucose, mean (SD), mg/dL	179.8 (100.5)	185.1 (81.6)	.70
Hemodynamic support, No. (%)[b]	90 (98.9)	107 (98.2)	
Norepinephrine, median (IQR), μg/kg/min	0.6 (0.3-1.0)	0.5 (0.2-0.9)	.30
Dobutamine, median (IQR) [max value], μg/kg/min	0 (0-0) [24.2]	0 (0-0) [35.6]	.98
Epinephrine, median (IQR) [max value], μg/kg/min	0 (0-0) [2.4]	0 (0-0) [2.5]	.38
Dopamine, median (IQR) [max value], μg/kg/min	0 (0-0) [11.9]	0 (0-0) [13.3]	.24
Variables Determined During CPR and at Approximately 20 Minutes After ROSC	(n = 138)	(n = 130)	
Periarrest lactate, mean (SD), mmol/L[c]	9.2 (5.7)	9.3 (7.2)	.95
Cumulative intravenous fluids, median (IQR), mL[d]	525 (140-1225)	500 (130-920)	.42

Abbreviations: CPR, cardiopulmonary resuscitation; ICU, intensive care unit; max, maximum; ROSC, return of spontaneous circulation; VSE, vasopressin-steroids-epinephrine.

SI conversion factors: To convert calcium ion to mmol/L, multiply by 0.5; to convert glucose to mmol/L, multiply by 0.0555.

[a] Arterial pressure and heart rate data were obtained solely from patients with an arterial line; in 46 VSE patients and 59 controls, a radial and/or femoral arterial line was already in place before cardiac arrest; in 7 VSE patients and 18 controls, a femoral arterial line was inserted during CPR; in 48 VSE patients and 12 controls, a femoral and/or radial arterial line was inserted within the first 10 minutes after ROSC. During resuscitation, monitor-displayed intra-arterial pressure values were recorded and averaged over 1 or 2 consecutive CPR cycles during the first 5-10 minutes of CPR (arterial catheter already present before arrest) or during the first 1 or 2 consecutive CPR cycles after the establishment of an arterial line. Post-ROSC hemodynamic data were

recorded and averaged over the 15-20 minutes of sustained spontaneous circulation; subsequently, the resulting resuscitation and post-ROSC mean values were analyzed.

[b] Patients with available data.

[c] Data originate from 113 of 138 control patients (81.9%) and from 110 of 130 VSE patients (84.6%); data are arterial blood gas analysis–derived lactate concentrations during CPR approximately 20 min after ROSC; in 38 VSE patients and 34 controls, arterial blood gas analysis was performed both during and after resuscitation, and the average of the 2 lactate concentration values was used in the present analysis.
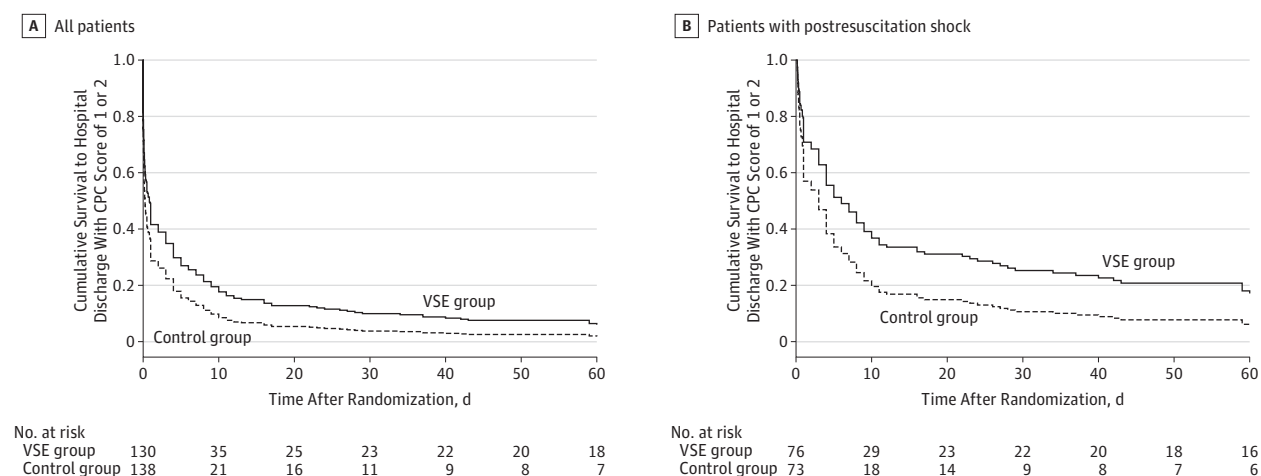
[d] Data originate from 129 of 130 VSE patients (99.2%) and 138 of 138 control patients (100.0%); values represent the total amount of intravenous fluids (ie, crystalloids, colloids, packed red blood cells, and fresh frozen plasma) administered during CPR and within the first 20 min following ROSC.

Atropine and bicarbonate use during CPR may have contributed to poor patient outcomes in both groups (eTables 4 and 7 in the Supplement).

Our study protocol precluded assessment of the effects of hydrocortisone[7,33] because of the possible additional benefit

of vasopressin[34] or steroid[35] use during CPR. The half life of vasopressin is 24 minutes,[36] and methylprednisolone may start acting within 60 minutes.[37] In the present study, methylprednisolone may have potentiated the periarrest, pressor effects of vasopressin.

Figure 2. Results on Survival Analysis

A All patients

B Patients with postresuscitation shock

No. at risk
VSE group	130	35	25	23	22	20	18
Control group	138	21	16	11	9	8	7

No. at risk
VSE group	76	29	23	22	20	18	16
Control group	73	18	14	9	8	7	6

Probability of survival with a Cerebral Performance Category (CPC) score of 1 or 2 to day 60 after randomization, which was identical to survival to hospital discharge with a CPC score of 1 or 2, in all 268 patients (A) and in the 149 patients with postresuscitation shock (B). The numbers of patients at risk were reduced according to the time points of occurrence of patient death or the

earliest follow-up neurological evaluation that was consistent with a subsequent, poor neurological outcome (ie, CPC score of ≥3) that was ultimately confirmed at the final neurological evaluation at hospital discharge. VSE indicates vasopressin-steroids-epinephrine.

There are no published data showing that postarrest glucocorticoid administration is neuroprotective.[33] Results of post hoc and sensitivity analyses support the hypothesis that postarrest hydrocortisone may be associated with reduced hazard of poor outcome (eTable 29 in the Supplement). However, this hypothesis requires further evaluation in RCTs.

Additional limitations include lack of determination of prevasopressor CPR hemodynamics, baseline stress hormone concentrations,[7] physiological variables at multiple post-ROSC time points, and postarrest myocardial function.[31] In

addition, the prespecified, limited sample size did not enable reliable assessment of 1-year outcomes.

Conclusions

Among patients with cardiac arrest requiring vasopressors, combined vasopressin-epinephrine and methylprednisolone during CPR and stress-dose hydrocortisone in postresuscitation shock, compared with epinephrine/saline placebo, resulted in improved survival to hospital discharge with favorable neurological status.

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