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Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock
The VANISH Randomized Clinical Trial

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IMPORTANCE Norepinephrine is currently recommended as the first-line vasopressor in septic shock; however, early vasopressin use has been proposed as an alternative.

OBJECTIVE To compare the effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock.

DESIGN, SETTING, AND PARTICIPANTS A factorial (2×2), double-blind, randomized clinical trial conducted in 18 general adult intensive care units in the United Kingdom between February 2013 and May 2015, enrolling adult patients who had septic shock requiring vasopressors despite fluid resuscitation within a maximum of 6 hours after the onset of shock.

INTERVENTIONS Patients were randomly allocated to vasopressin (titrated up to 0.06 U/min) and hydrocortisone (n = 101), vasopressin and placebo (n = 104), norepinephrine and hydrocortisone (n = 101), or norepinephrine and placebo (n = 103).

MAIN OUTCOMES AND MEASURES The primary outcome was kidney failure–free days during the 28-day period after randomization, measured as (1) the proportion of patients who never developed kidney failure and (2) median number of days alive and free of kidney failure for patients who did not survive, who experienced kidney failure, or both. Rates of renal replacement therapy, mortality, and serious adverse events were secondary outcomes.

RESULTS A total of 409 patients (median age, 66 years; men, 58.2%) were included in the study, with a median time to study drug administration of 3.5 hours after diagnosis of shock. The number of survivors who never developed kidney failure was 94 of 165 patients (57.0%) in the vasopressin group and 93 of 157 patients (59.2%) in the norepinephrine group (difference, −2.3% [95% CI, −13.0% to 8.5%]). The median number of kidney failure–free days for patients who did not survive, who experienced kidney failure, or both was 9 days (interquartile range [IQR], 1 to −24) in the vasopressin group and 13 days (IQR, 1 to −25) in the norepinephrine group (difference, −4 days [95% CI, −11 to 5]). There was less use of renal replacement therapy in the vasopressin group than in the norepinephrine group (25.4% for vasopressin vs 35.3% for norepinephrine; difference, −9.9% [95% CI, −19.3% to −0.6%]). There was no significant difference in mortality rates between groups. In total, 22 of 205 patients (10.7%) had a serious adverse event in the vasopressin group vs 17 of 204 patients (8.3%) in the norepinephrine group (difference, 2.5% [95% CI, −3.3% to 8.2%]).

CONCLUSIONS AND RELEVANCE Among adults with septic shock, the early use of vasopressin compared with norepinephrine did not improve the number of kidney failure–free days. Although these findings do not support the use of vasopressin to replace norepinephrine as initial treatment in this situation, the confidence interval included a potential clinically important benefit for vasopressin, and larger trials may be warranted to assess this further.

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In 2015, it was estimated that there were more than 230 000 cases of septic shock with more than 40 000 deaths in the United States each year.[1] In addition to treating the underlying infection, the mainstay of cardiovascular resuscitation in septic shock is intravenous fluids and vasopressor treatment. Norepinephrine is the recommended first-line vasopressor[2] but, since a relative vasopressin deficiency in septic shock was described, there has been growing interest in the use of vasopressin as an adjunctive agent.[3] Preclinical and small clinical studies have suggested that vasopressin may be better able to maintain glomerular filtration rate and improve creatinine clearance compared with norepinephrine.[4-6]

The largest trial of vasopressin to date, the Vasopressin and Septic Shock Trial (VASST),[7] found no difference in mortality overall when vasopressin (up to 0.03 U/min) was added to existing norepinephrine treatment compared with norepinephrine alone, but there was a significantly lower mortality in the patients treated with vasopressin who had less severe shock (defined as a dose of norepinephrine <15 µg/min). Additional analyses from VASST and other investigations have suggested that early vasopressin might prevent deterioration in organ function,[5,8] particularly kidney function, and that higher doses of vasopressin (up to 0.06 U/min) may be more effective.[9] In addition, it has been proposed that there may be an interaction between vasopressin and corticosteroids when used to treat septic shock and that the combination of vasopressin and corticosteroids may improve survival[10] and reduce the duration of shock.[11]

The Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial was designed to test whether early vasopressin use, titrated up to 0.06 U/min, would improve kidney outcomes compared with norepinephrine.

Methods

Trial Design and Participants

The VANISH trial was a factorial (2×2), multicenter, double-blind, randomized clinical trial. It was conducted in 18 general adult intensive care units (ICU) in the United Kingdom between February 2013 and May 2015. The trial protocol and statistical analysis plan are available in Supplement 1.

The Oxford A research ethics committee approved the trial. In view of the emergency nature of the trial, a waiver of initial consent was granted. Patients could be enrolled into the trial without prospective consent and then written consent was obtained from the patient or a personal or professional legal representative as soon as practically possible. For cases in which a legal representative gave consent, retrospective written consent was sought once the patient regained decision-making capacity.

Adult patients (≥16 years) who had sepsis (2 of 4 systemic inflammatory response criteria due to known or suspected infection[12]) and who required vasopressors despite adequate intravenous fluid resuscitation, as assessed by clinical examination, central venous pressure, oxygen saturation, or other physiological parameters using repeated fluid challenges were eligible for the trial. Exclusion criteria were patients who had received a previous continuous infusion of vasopressors during this ICU admission, an ongoing requirement for systemic steroid treatment (ie, known adrenal insufficiency or regular systemic steroid therapy within the last 3 months), end-stage kidney failure, known mesenteric ischemia, Raynaud phenomenon, systemic sclerosis or other vasospastic disease, a medical team that was not committed to full active treatment, known pregnancy, enrollment in another interventional trial that might interact with the study drugs, or hypersensitivity to any of the study drugs.

Ethnicity was classified based on medical records, as most patients lacked capacity to provide this information at the time of their study enrollment. Documentation of ethnicity in patients' medical records is standard practice within the UK National Health Service. The main categories of ethnicity were white, black, Asian, and other. Because the vast majority of study participants were white, the descriptive statistics utilized a simplified dichotomization of white vs other.

Randomization and Masking

Enrollment, randomization, and data collection were conducted via an online system (InForm, Oracle). Patients were assigned to 1 of 4 treatment groups (vasopressin and hydrocortisone, vasopressin and placebo, norepinephrine and hydrocortisone, or norepinephrine and placebo) on a 1:1:1:1 basis with variable block size randomization (4 and 8) using computer-generated random numbers, stratified by center. The allocation sequence was prepared by an independent statistician in the Imperial Clinical Trials Unit and concealed from all investigators and treating clinicians.

Ampoules of vasopressin (Ferring), norepinephrine (Aguettant), and hydrocortisone phosphate (Amdipharm Mercury) were masked by overlabeling on the body and neck of normal drug ampoules. Matching placebo ampoules (0.9% saline) were manufactured by Sharp Clinical Services (United Kingdom) who carried out all labeling and treatment pack preparation.

Clinical Management

Patients were allocated to receive either vasopressin (titrated up to 0.06 U/min) or norepinephrine (titrated up to 12 µg/min) as the initial vasopressor infusion (study drug 1) via a central venous catheter, and titrated to maintain the target mean arterial pressure (MAP). The protocol recommended a MAP of 65 to 75 mm Hg, but this could be altered by the treating physician if clinically indicated.

Once the maximum infusion rate of study drug 1 was reached, patients received study drug 2, either 50 mg of hydrocortisone phosphate or placebo, administered as an intravenous bolus every 6 hours for 5 days, every 12 hours for 3 days, and then once daily for 3 days, as previously reported.[13] The drug could be weaned more quickly if the shock had already resolved.

If the patient was still hypotensive after the first dose of study drug 2 then additional open-label catecholamine vasopressors could be administered. As the patient recovered, open-label catecholamine vasopressors were reduced first and only once the patient was weaned off open-label vasopressors was study drug 1 then reduced. Once study drug 1 was weaned off,

if there was recurrent hypotension within 24 hours, the study drug was restarted; if hypotension recurred after 24 hours, open-label vasopressors were used at local physician discretion. All other treatment was at physician discretion, based on the Surviving Sepsis Campaign guidelines at that time.[14]

Patients could present and be recruited from any part of the hospital prior to ICU admission. Although the aim was to use study drug 1 as the initial vasopressor, study drugs could not be stored in multiple locations within the hospitals. Therefore, in an emergency when immediate treatment was required, patients could be initially resuscitated using usual (open-label) clinically prescribed vasopressors. In this situation, the patient had to be enrolled into the trial within 6 hours of commencing the open-label vasopressor infusion. As the study drug infusion was titrated up, as detailed above, the initial open-label vasopressor infusion was weaned off as quickly as possible to maximize the study drug infusion rate.

Outcome Measures

The primary outcome of the trial was kidney failure–free days (ie, the number of days alive and free of kidney failure), defined by the Acute Kidney Injury Network (AKIN) group stage 3 definition,[15] during the 28 days after randomization, with no additional penalty for death. This outcome measure was not normally distributed and had a large spike in frequency at 28 days, the point at which the measure was truncated, representing survivors who never developed kidney failure. Therefore, the prospective plan was to report the data using 2 summary measures: (1) the proportion of survivors who never developed kidney failure (the spike at 28 days) and (2) the median number of days alive and free of kidney failure for the other patients who did not survive, who experienced kidney failure, or both at any time.

Secondary outcomes included rates and duration of renal replacement therapy; length of kidney failure in survivors and nonsurvivors; 28-day, ICU, and hospital mortality rates; and organ failure–free days in the first 28 days, assessed using the Sequential Organ Failure Assessment (SOFA) score.[16]

Statistical Analysis

A sample size of 400 was chosen to provide 80% power to detect a 20% to 25% relative reduction of risk of developing kidney failure if treated with vasopressin compared with norepinephrine, assuming an overall incidence of acute kidney failure of 30% to 50%[8,11] and a significance level of .05. The calculations were based on simulation, assuming a Mann-Whitney *U* test for analysis. To allow for a 3% withdrawal of consent in line with previous critical care studies within the United Kingdom,[17] 412 patients was the recruitment target.

The primary analysis tested for a difference between the distribution of kidney failure–free days for all patients randomized to vasopressin compared with those randomized to norepinephrine using a Mann-Whitney *U* test. The main analysis was a modified intention-to-treat basis (patients who did not receive study drug because they had died or recovered or were found to be ineligible after randomization were excluded). However, because not all patients would require study drug 2, analysis was also carried out on an as-treated basis, with patients not requiring study drug 2 allocated to the placebo group, and reallocation of any crossovers. A further per-protocol analysis was carried out in which any patients not receiving the allocated study drugs or crossovers were excluded. Logistic regression models and Cox regression models were used to compare renal replacement therapy and mortality between the 4 treatment groups and test for a potential vasopressin and hydrocortisone interaction on an intention-to-treat basis accounting for study site using a hierarchical model for the logistic regression and stratification for the Cox model. All analyses were carried out using R (R Foundation), version 3.1.3, and a *P* value less than .05 was considered statistically significant using 2-sided tests.

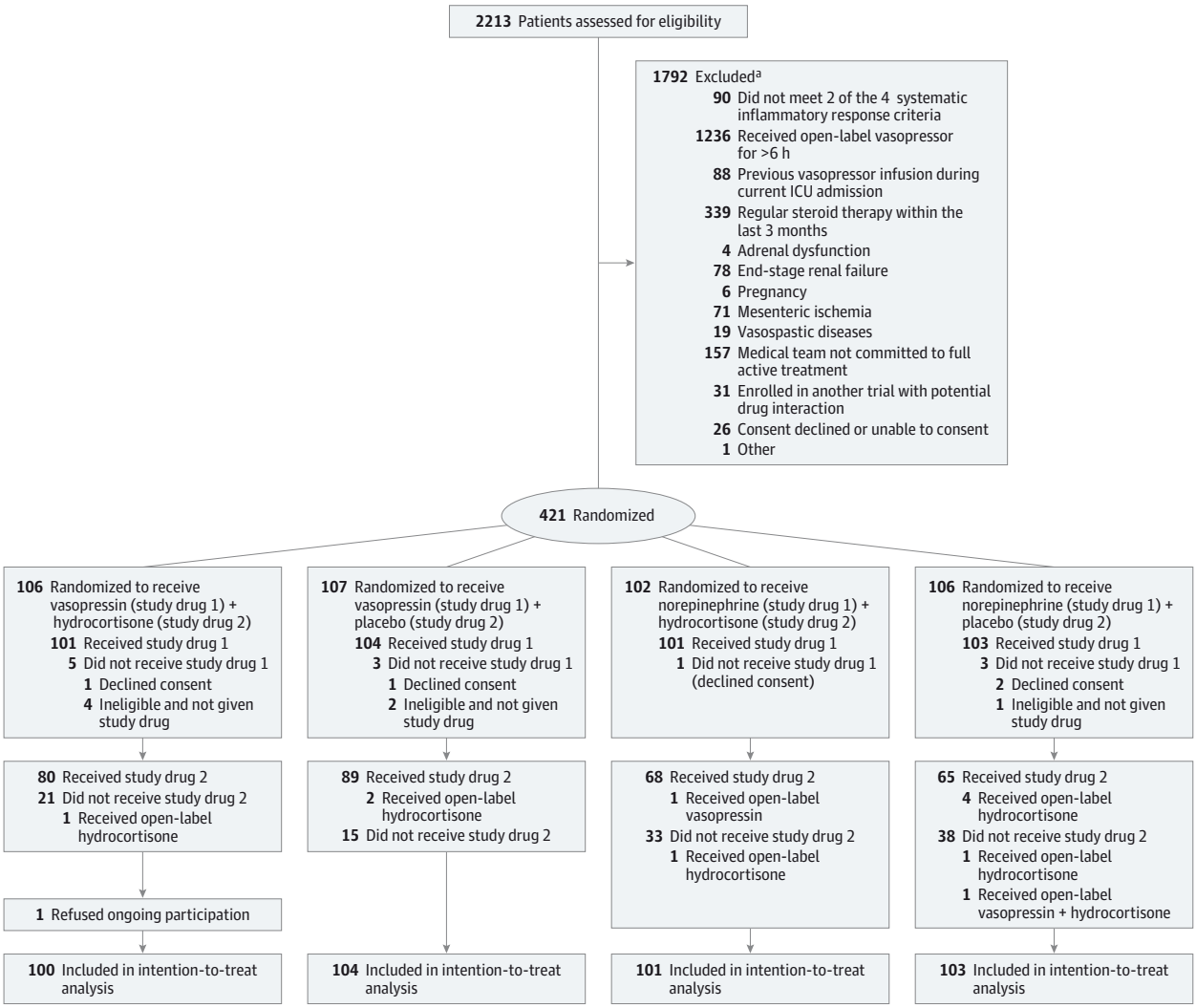
Results

Figure 1 shows the flow of patients through the trial. The most frequent reason for screening failure was exceeding the 6-hour recruitment window. A total of 421 patients were randomized. Seven patients were found to be ineligible after randomization but before receiving any study drug and 5 patients or legal representatives withheld or withdrew consent after inclusion in the trial; these patients were excluded from all analyses. One patient refused ongoing participation in the trial after inclusion, including 28-day follow-up, but allowed existing data to be included in the analyses. Therefore, 409 patients were included at baseline for safety data and some secondary outcome analyses as indicated and 408 patients were included in the primary intention-to-treat analysis. In total, 8 patients in placebo groups were given open-label hydrocortisone as "rescue" therapy or for other clinical indications and 2 patients in the norepinephrine groups were given open-label vasopressin (1 of whom was also 1 of the 8 given open-label hydrocortisone), and these patients were included as crossovers in the as-treated analysis. The patients who did not receive study drug 2 (Figure 1) were allocated to the placebo group in the as-treated analysis. All crossovers and patients not receiving the second study drug were excluded from the per-protocol analysis.

The treatment groups were well balanced at baseline (**Table 1**). The study drugs were started at a median of 3.5 hours after the diagnosis of shock. In 15% of patients, study drug 1 was the first vasopressor administered. For the 309 patients (76%) receiving norepinephrine at randomization, the median dose of open-label norepinephrine at baseline was 0.16 μg/kg/min. The MAP in all treatment groups was similar at baseline and over the first 7 days (**Figure 2**A; eFigure 1A in Supplement 2) and vasopressin spared the total dose of norepinephrine required to maintain the blood pressure (Figure 2B).

There was no significant difference in the distribution of kidney failure–free days between vasopressin and norepinephrine groups, *P* = .88 (**Figure 3**). The number of survivors who never developed kidney failure was 94 of 165 patients (57.0%) in the vasopressin group and 93 of 157 patients (59.2%) in the norepinephrine group (absolute difference, −2.3% [95% CI, −13.0% to 8.5%]) (**Table 2**). The median number of kidney

Figure 1. Recruitment, Randomization, and Patient Flow in the VANISH Trial



ICU indicates intensive care unit.

[a] Patients could meet more than 1 exclusion criteria.

failure-free days in the other patients who died, experienced kidney failure, or both at any time was 9 (interquartile range [IQR], 1 to 24) in the vasopressin group and 13 (IQR, 1 to 25) in the norepinephrine group (absolute difference, −4 days [95% CI, −11 to 5]). Similar results were obtained when using the serum creatinine values and urine output values separately to define kidney failure (eTable 2 in Supplement 2), and the as-treated and per-protocol analyses gave similar results (eTable 3 in Supplement 2).

Similar quantities of intravenous fluid were given to all groups, and total fluid balance, serum lactate levels, and heart rate were similar in all groups (eTables 4-7 in Supplement 2). Serum creatinine levels were lower and urine output slightly higher over the first 7 days in the vasopressin group compared with the norepinephrine group (**Figure 4** and eTables 8A and 9A in Supplement 2) and the rate of renal replacement therapy use was 25.4% in the vasopressin group and 35.3% in the norepinephrine group (odds ratio, 0.40 [95% CI, 0.20-0.73]) (Table 2). There was no significant difference in mortality rates between vasopressin and norepinephrine groups (28-day mortality, 30.9% in the vasopressin group vs 27.5% in the norepinephrine group; absolute difference, 3.4% [95% CI, −5.4% to 12.3%]), and hydrocortisone and placebo groups (28-day mortality, 30.8% in the hydrocortisone group vs 27.5% in the placebo group; absolute difference, 3.3% [95% CI, −5.5% to 12.1%]) (Table 2; eFigure 4A in Supplement 2), and there was no significant interaction between vasopressin and hydrocortisone (P = .98 from Cox regression model for 28-day mortality). There were no differences in rates of other new organ failures or organ failure-free days between vasopressin and norepinephrine groups (eTable 10 in Supplement 2).

In the vasopressin group 22 patients had a total of 29 serious adverse events and 17 patients in the norepinephrine group had 19 events. The breakdown of all serious adverse

Table 1. Baseline Characteristics for Patients With Septic Shock

	Vasopressin + Hydrocortisone (n = 101)	Vasopressin + Placebo (n = 104)	Norepinephrine + Hydrocortisone (n = 101)	Norepinephrine + Placebo (n = 103)	Total Trial Population (n = 409)
Age, median (IQR), y	66 (57-76)	67 (59-77)	63 (52-76)	66 (54-76)	66 (54-77)
Men, No. (%)	59 (58)	52 (50)	62 (61)	65 (63)	238 (58)
Weight, median (IQR), kg	75 (63-90)	70 (60-85)	75 (65-89)	73 (64-90)	75 (62-87)
BMI, median (IQR)	26 (23-32)	24 (22-29)	26 (23-30)	25 (23-30)	26 (22-30)
Caucasian ethnicity, No. (%)	85 (84)	89 (86)	87 (86)	88 (85)	349 (85)
Recent surgical history, No. (%)[a]	17 (17)	21 (20)	18 (18)	17 (17)	73 (18)
APACHE II score, median (IQR)	24 (19-30)	24 (19-29)	24 (20-30)	23 (18-30)	24 (19-30)
Preexisting conditions, No. (%)					
Ischemic heart disease	20 (20)	11 (11)	12 (12)	19 (18)	62 (15)
Severe COPD	2 (2)	4 (4)	6 (6)	3 (3)	15 (4)
Chronic kidney failure	9 (9)	8 (8)	5 (5)	5 (5)	27 (7)
Cirrhosis	5 (5)	3 (3)	2 (2)	5 (5)	15 (4)
Cancer	14 (14)	11 (11)	8 (8)	14 (14)	47 (11)
Immunocompromised	9 (9)	4 (4)	8 (8)	7 (7)	28 (7)
Diabetes	19 (19)	20 (19)	22 (22)	29 (28)	90 (22)
Organ failure, No. (%)[b]					
Respiratory	32 (32)	39 (38)	40 (40)	38 (38)	149 (37)
Kidney	19 (19)	19 (18)	24 (24)	23 (22)	85 (21)
Liver	4 (4)	4 (4)	6 (6)	6 (7)	20 (5)
Hematological	6 (6)	6 (6)	6 (6)	4 (4)	22 (6)
Neurological	33 (35)	33 (33)	32 (34)	30 (31)	128 (33)
Physiological variables, median (IQR)					
Mean arterial pressure, mm Hg	71 (62-80)	69 (62-75)	68 (61-75)	70 (63-78)	70 (62-77)
Heart rate, beats/min	98 (85-109)	96 (84-108)	99 (83-112)	96 (84-110)	97 (84-110)
Central venous pressure, mm Hg[c]	12 (9-17)	13 (10-16)	13 (9-17)	13 (8-17)	13 (9-17)
Lactate, mmol/L	2.1 (1.4-4.3)	2.3 (1.5-3.9)	2.6 (1.4-4.5)	2.2 (1.4-3.2)	2.3 (1.4-4)
Pao_2/FIo_2, mm Hg	190 (122-318)	189 (122-301)	171 (104-264)	195 (130-328)	188 (121-302)
Creatinine, mg/dL	1.36 (0.89-2.69)	1.26 (0.83-2.02)	1.44 (0.83-2.26)	1.5 (0.84-2.32)	1.38 (0.84-2.32)
Bilirubin, mg/dL	0.94 (0.47-1.62)	0.99 (0.53-1.67)	0.85 (0.51-1.42)	0.79 (0.45-1.45)	0.88 (0.47-1.58)
Platelets, $\times 10^3/\mu L$	194 (122-289)	176 (116-284)	182 (125-293)	198 (122-270)	188 (121-288)
GCS	14 (6-15)	14 (4-15)	14 (3-15)	14 (5-15)	14 (4-15)
Mechanical ventilation, No. (%)	55 (54)	58 (56)	62 (61)	61 (59)	236 (58)
Renal replacement therapy, No. (%)	2 (2)	4 (4)	2 (2)	3 (3)	11 (3)
Volume of IV fluid in previous 4 h, median (IQR), mL	1200 (757-2021)	1092 (725-2010)	1168 (606-2000)	1100 (613-2132)	1134 (662-2039)
Patients receiving open-label vasopressor at randomization, No. (%)	91 (90)	89 (86)	86 (85)	82 (80)	348 (85)
Time from onset of shock to receiving first study drug, median (IQR), h	3.2 (1.8-5)	3.5 (2-5.4)	3.7 (1.7-5)	3.5 (1.4-5.4)	3.5 (1.8-5.2)
Norepinephrine dose at randomization, median (IQR), µg/kg/min	0.16 (0.1-0.3) (n = 76)	0.15 (0.1-0.28) (n = 79)	0.2 (0.12-0.42) (n = 81)	0.16 (0.1-0.27) (n = 73)	0.16 (0.1-0.31) (n = 309)
Source of infection, No. (%)					
Lung	43 (44)	39 (38)	44 (45)	39 (38)	165 (41)
Abdomen	20 (20)	26 (25)	25 (26)	22 (22)	93 (23)
Soft tissue or line	5 (5)	5 (5)	3 (3)	6 (6)	19 (5)
Other	30 (31)	32 (31)	26 (27)	35 (34)	123 (31)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation (range 0-72, a higher score corresponds to more severe illness and a higher risk of death); BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Score (range 3-15, a lower score corresponds to a greater depression of consciousness); IQR, interquartile range; IV, intravenous; Pao_2/FIo_2, arterial oxygen partial pressure to fractional inspired oxygen.

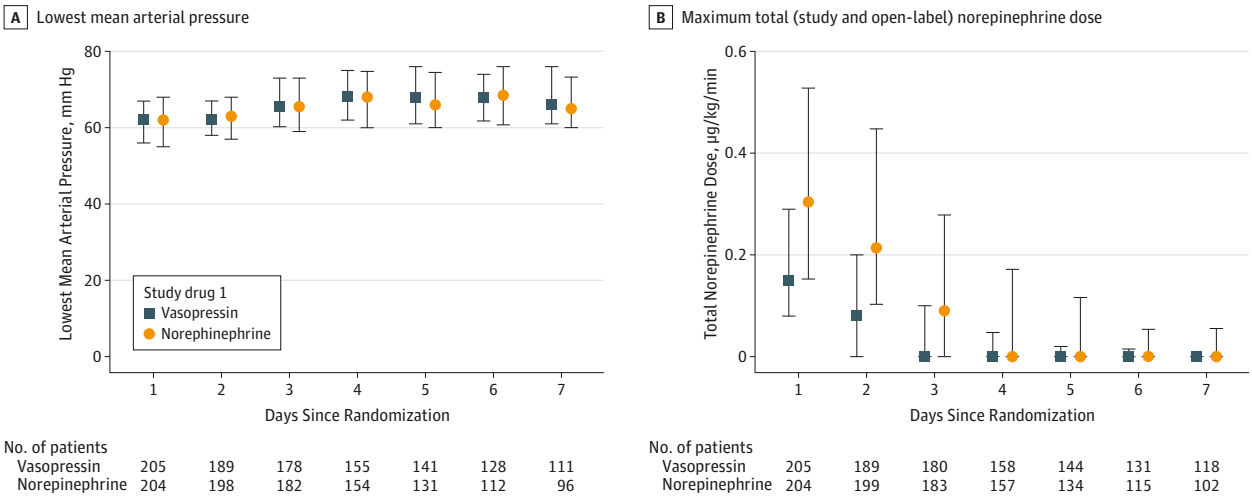
SI conversion factor: To convert creatinine to µmol/L, multiply by 88.4; bilirubin to µmol/L, multiply by 17.104.

[a] Recent surgery is defined as admitted to intensive care unit following surgery

[b] Kidney failure is defined as having acute kidney injury stage 3; other organ failures defined as having a Sequential Organ Failure Assessment score of 3 or more.

[c] Central venous pressure was only recorded in 234 patients at baseline. See eTable 1 in Supplement 2 for numbers of other missing values at baseline.

Figure 2. Mean Arterial Pressure and Maximum Total (Study and Open-Label) Norepinephrine Dose Over the First 7 Days by Study Drug 1

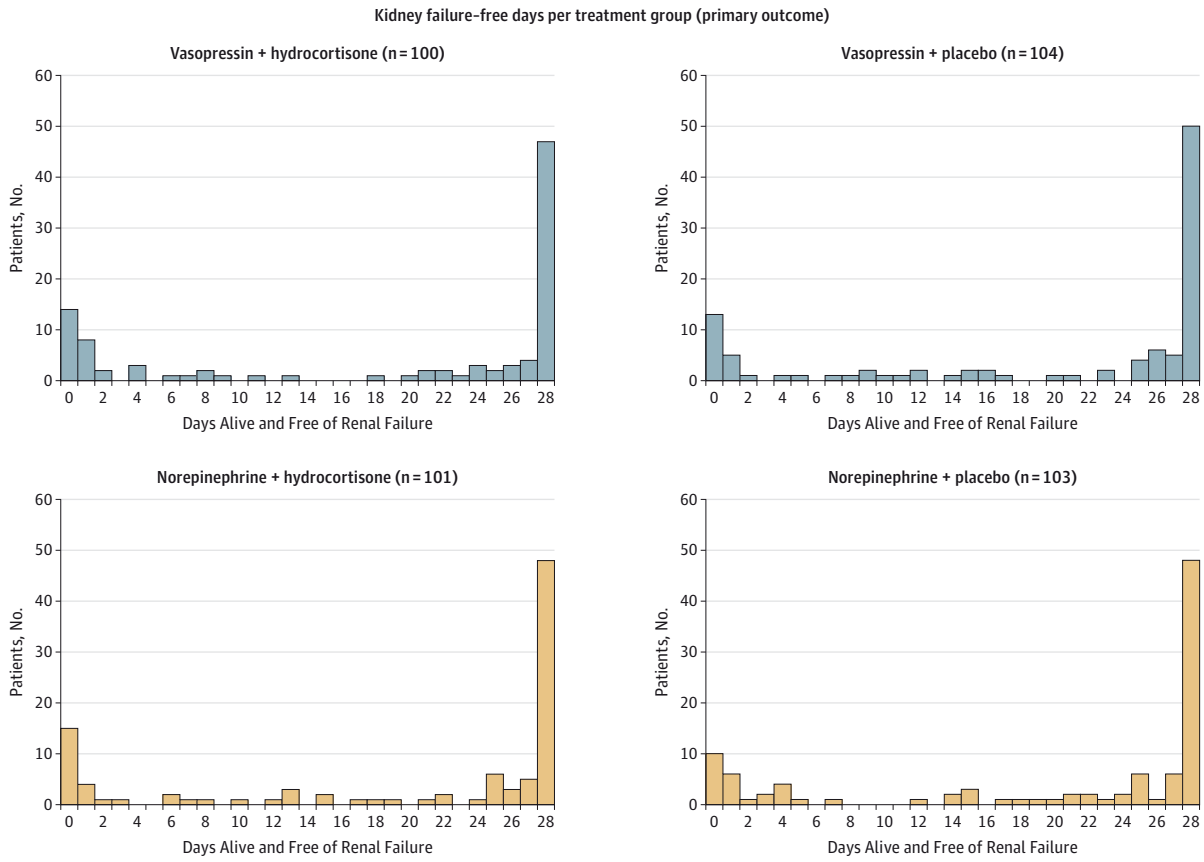


No. of patients							
Vasopressin	205	189	178	155	141	128	111
Norepinephrine	204	198	182	154	131	112	96

No. of patients							
Vasopressin	205	189	180	158	144	131	118
Norepinephrine	204	199	183	157	134	115	102

Squares and circles indicate the median. The error bars indicate the interquartile range. Day 1 runs from the time of randomization to the end of the "ICU calendar day" and is therefore less than 24 hours and varies in duration between patients.

Figure 3. Kidney Failure–Free Days by Randomized Treatment Group



The column at 28 days represents survivors who never developed kidney failure, other columns represent patients who did not survive, who experienced kidney failure, or both at any time.

events by treatment group is given in Table 2. In serious adverse events judged by the treating physician as at least "possibly related" to the study drugs, the mean dose of vasopressin on the day of the event or the day before was

Table 2. Outcome Data in the 4 Treatment Groups and Comparison of the Vasopressin Group With the Norepinephrine Group

	Vasopressin			Norepinephrine			Vasopressin vs Norepinephrine, Absolute Difference (95% CI)[b]
	Hydrocortisone[a]	Placebo	Total[a]	Hydrocortisone	Placebo	Total	
28-d Survivors who never developed kidney failure, No./total (%)[c]	46/81 (56.8)	48/84 (57.1)	94/165 (57.0)	46/77 (59.7)	47/80 (58.8)	93/157 (59.2)	−2.3 (−13.0 to 8.5)[d]
Kidney failure–free days in other patients, median (IQR), d[e]	5 (0-23)	12 (1-25)	9 (1-24)	13 (0-25)	14 (1-24)	13 (1-25)	−4 (−11 to 5)[d]
28-d Mortality, No./total (%)	33/100 (33.0)	30/104 (28.8)	63/204 (30.9)	29/101 (28.7)	27/103 (26.2)	56/204 (27.5)	3.4 (−5.4 to 12.3)
ICU mortality, No./total (%)	32/100 (32.0)	26/104 (25.0)	58/204 (28.4)	24/101 (23.8)	27/103 (26.2)	51/204 (25.0)	3.4 (−5.2 to 12.0)
Hospital mortality, No./total (%)	35/100 (35.0)	33/104 (31.7)	68/204 (33.3)	31/101 (30.7)	29/103 (28.2)	60/204 (29.4)	3.9 (−5.1 to 12.9)
Kidney failure, No./total (%)	41/101 (40.6)	46/104 (44.2)	87/205 (42.4)	46/101 (45.5)	51/103 (49.5)	97/204 (47.5)	−5.1 (−15.2 to 5.0)
Survivors	21/67 (31.3)	26/74 (35.1)	47/141 (33.3)	26/72 (36.1)	29/76 (38.2)	55/148 (37.2)	−3.8 (−15.5 to 7.9)
Nonsurvivors	20/33 (60.6)	20/30 (66.7)	40/63 (63.5)	20/29 (69)	22/27 (81.5)	42/56 (75)	−11.5 (−29.6 to 6.6)
Duration of kidney failure, median (IQR), d	4 (1 to 7)	2 (1 to 6)	3 (1 to 7)	3 (2 to 6)	4 (2 to 8)	4 (2 to 8)	−1 (2 to 0)
Survivors	4 (2 to 7)	3 (2 to 8)	4 (2 to 8)	4 (2 to 8)	4 (3 to 8)	4 (2 to 8)	0 (−3 to 2)
Nonsurvivors	2 (1 to 7)	2 (1 to 3)	2 (1 to 7)	3 (2 to 5)	2 (1 to 8)	3 (2 to 7)	−1 (−3 to 0)
Use of RRT, No./total (%)	29/101 (28.7)	23/104 (22.1)	52/205 (25.4)	32/101 (31.7)	40/103 (38.8)	72/204 (35.3)	−9.9 (−19.3 to −0.6)
Survivors	15/67 (22.4)	13/74 (17.6)	28/141 (19.9)	15/72 (20.8)	18/76 (23.7)	33/148 (22.3)	−2.4 (−12.5 to 7.7)
Nonsurvivors	14/33 (42.4)	10/30 (33.3)	24/63 (38.1)	17/29 (58.6)	22/27 (81.5)	39/56 (69.6)	−31.5 (−50.2 to −12.9)
Duration of RRT, median (IQR), d	4 (2 to 7)	3 (2 to 5)	3 (2 to 7)	3 (2 to 8)	4 (2 to 8)	3 (2 to 8)	0 (−2 to 2)
Survivors	4 (2 to 8)	3 (3 to 14)	4 (2 to 10)	4 (2 to 10)	6 (2 to 12)	5 (2 to 11)	−1 (−4 to 2)
Nonsurvivors	4 (1 to 7)	2 (1 to 4)	2 (1 to 6)	3 (2 to 4)	3 (2 to 6)	3 (2 to 6)	−1 (−2 to 2)
No. weaned from vasopressors for >24 h, No./total (%)	88/101 (87.1)	91/104 (87.5)	179/205 (87.3)	91/101 (90.1)	88/103 (85.4)	179/204 (87.7)	0.4 (−6.8 to 6.0)
Time to shock reversal, median (IQR), h	50 (28 to 92)	59 (27 to 112)	51 (28 to 99)	46 (23 to 72)	44 (23 to 90)	45 (23 to 75)	6 (−4 to 20)
Use of inotropes, No./total (%)[f]	31/101 (30.7)	24/104 (23.1)	55/205 (26.8)	24/101 (23.8)	17/103 (16.5)	41/204 (20.1)	6.7 (−1.5 to 14.9)
Duration of mechanical ventilation, median (IQR), d	5 (2 to 10)	6 (3 to 12)	5 (2 to 10)	5 (2 to 16)	5 (2 to 12)	5 (2 to 13)	0 (−2 to 2)
Mean total SOFA score, mean (SD)	6.1 (3.4)	5.8 (3.1)	6.0 (3.3)	6.1 (3.1)	6.3 (3.5)	6.2 (3.3)	−0.2 (−0.9 to 0.4)
ICU length of stay, median (IQR), d	6 (3 to 10)	7 (3 to 14)	7 (3 to 11)	5 (3 to 15)	6 (3 to 11)	5 (3 to 13)	2 (−1 to 3)
Hospital length of stay, median (IQR), d	13 (7 to 31)	17 (9 to 40)	16 (7 to 36)	16 (8 to 42)	15 (8 to 36)	16 (8 to 38)	0 (−5 to 4)
Patients who had ≥1 serious adverse events, No./total (%)	9/101 (8.9)	13/104 (12.5)	22/205 (10.7)	11/101 (10.9)	6/103 (5.8)	17/204 (8.3)	2.5 (−3.3 to 8.2)
Digital ischemia[g]	4/101 (4.0)	7/104 (6.7)	11/205 (5.4)	2/101 (2.0)	1/103 (1.0)	3/204 (1.5)	3.9 (−0.1 to 7.9)
Mesenteric ischemia[g]	2/101 (2.0)	3/104 (2.9)	5/205 (2.4)	4/101 (4.0)	1/103 (1.0)	5/204 (2.5)	0.0 (−3.0 to 3.0)
Life-threatening arrhythmia[g]	2/101 (2.0)	0/104 (0.0)	2/205 (0.98)	1/101 (1.0)	4/103 (3.9)	5/204 (2.5)	−1.5 (−4.5 to 1.5)
Acute coronary syndrome[g]	4/101 (4.0)	3/104 (2.9)	7/205 (3.4)	2/101 (2.0)	0/103 (0.0)	2/204 (1.0)	2.5 (−0.9 to 5.8)
Other[g]	2/101 (2.0)	2/104 (1.9)	4/205 (2.0)	3/101 (3.0)	1/103 (1.0)	4/204 (2.0)	0.0 (−2.7 to 2.7)

Abbreviations: IQR, interquartile range; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment (range 0-20, a higher score corresponds to more severe organ failure).

[a] One patient in the vasopressin and hydrocortisone group refused ongoing participation in the trial after inclusion, including 28-d follow-up, but allowed existing data to be included in the analyses. Their data have been used where possible, therefore the denominator varies between 104 of 105 patients or 204 of 205 patients.

[b] Absolute difference in percentage for binary variables and difference in medians for continuous variables. The 95% confidence intervals for the difference in medians were calculated using bootstrapping; values may not sum due to rounding.

[c] 28-day Survivors as a proportion of patients with no kidney failure at baseline (1 patient with no baseline kidney failure data was excluded).

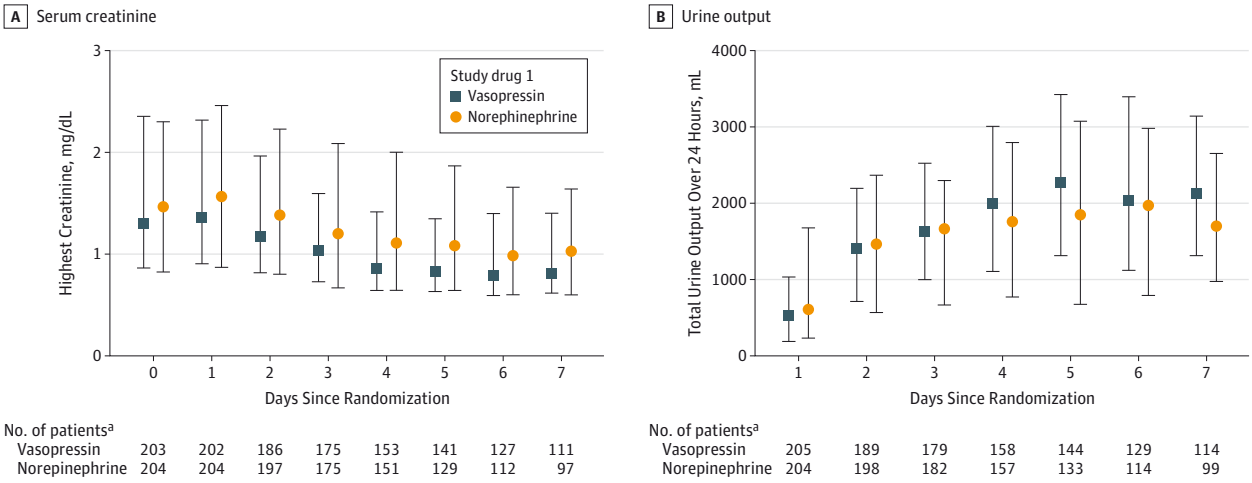
[d] Primary outcome.

[e] Other patients = those who had kidney failure, died, or both at any time.

[f] Inotropes defined as dobutamine, epinephrine, milrinone, dopamine, dopexamine.

[g] The number of serious adverse events represents the number of patients who had that subcategory of event. Patients may have had more than 1 event.

Figure 4. Serum Creatinine and Urine Output Over the First 7 Days by Study Drug 1



No. of patients[a]

Vasopressin	203	202	186	175	153	141	127	111
Norepinephrine	204	204	197	175	151	129	112	97

No. of patients[a]

Vasopressin	205	189	179	158	144	129	114	
Norepinephrine	204	198	182	157	133	114	99	

[a] No. of patients with data included.

Squares and circles indicate the median. The error bars indicate the interquartile range. Day 0 = baseline (most recent measurement prior to randomization up to a maximum of 24 hours). Day 1 runs from the time of randomization to the end of the "ICU calendar day" and is therefore less than 24 hours and varies in duration between patients.

0.06 U/min and the mean dose of norepinephrine or epinephrine was 0.55 µg/kg/min (0.33 µg/kg/min in the vasopressin group and 0.79 µg/kg/min in the norepinephrine group).

Rates of vasopressin and norepinephrine infusion are shown in eFigures 1B-D and 2 in Supplement 2. There was no difference in serum creatinine, urine output, rates of kidney failure, use of renal replacement therapy, mortality, or serious adverse events between the hydrocortisone group and the placebo group (eTables 8B, 9B, and 11 and eFigures 3A-B and 4B in Supplement 2).

Discussion

In this multicenter, factorial (2×2), double-blind, randomized clinical trial, early use of vasopressin to treat septic shock did not increase the number of kidney failure-free days compared with norepinephrine. Mortality rates were similar between all groups and there was no interaction on outcome between vasopressin and corticosteroids. Although these findings do not support the use of vasopressin to replace norepinephrine as initial treatment in this situation, the confidence interval included a potential clinically important benefit for vasopressin, and larger trials may be warranted to assess this further.

The rationale for this trial was based on the results of the previous VASST study.[7] Although there was no significant difference in mortality rates in the overall septic shock population in that trial, there was a lower mortality rate in the a priori defined subgroup of patients who had less severe shock treated with vasopressin compared with norepinephrine (28-day mortality relative risk, 0.74 [95% CI, 0.55 to 1.01], P = .05). There was no difference in mortality in those who had more severe shock (defined as norepinephrine ≥15 µg/min at baseline). Possible explanations for the VASST result might be (1) that vasopressin was more effective when used earlier before patients had become too sick (the mean time to study drug initiation was approximately 12 hours after meeting eligibility), (2) that the patients with more severe shock might have required a higher dose of vasopressin because the maximum rate of vasopressin was limited to 0.03 U/min, (3) that there was a harmful interaction between vasopressin and high-dose norepinephrine, or (4) it could have been a chance finding in a subgroup analysis, although the subgroups were large and prospectively defined, and randomization was stratified by subgroup.

Further analyses from VASST suggested that vasopressin might improve kidney function in patients at risk of kidney failure and reduce rates of progression to kidney failure and loss, but that it had no effect if acute kidney failure was already established at the time of study inclusion.[8] This was supported by evidence from a study by Lauzier and colleagues[5] that demonstrated an improvement in creatinine clearance when vasopressin was started in the first 12 hours of developing vasodilatory shock. Similarly in VASST, patients enrolled in the first 12 hours tended to have better outcomes with vasopressin treatment compared with norepinephrine, but not if enrolled after 12 hours.[7] For this reason patients in this study were randomized as early as possible, and at a maximum of 6 hours after developing hypotension. Despite this early recruitment, a number of patients already had developed acute kidney failure at the time of inclusion. However, there was no significant difference in the number of patients who had kidney failure at any time or progressed to kidney failure after randomization. Although there was no significant difference in rates of kidney failure, there was a lower rate of use of renal replacement therapy in the patients treated with vasopressin. The use of renal replacement therapy was not controlled in this trial, and it was started based on local clinical decision. It is therefore not possible to know why renal replacement therapy was or was not started. Because the trial was double-blinded, it is unlikely to be due to any obvious clinician bias. It is possible the

difference in rates of renal replacement therapy reflects the slightly lower creatinine values and higher urine outputs seen in the patients treated with vasopressin, particularly on days 3 through 6. Although use of renal replacement therapy was not the primary outcome of this trial, it is an important patient-centered outcome, and therefore this result may be important when planning patient treatment strategies.

To ensure that patients with more severe shock were treated with an adequate dose of vasopressin, the dose of vasopressin was titrated up to 0.06 U/min, double the dose used in VASST. In another randomized clinical trial, a dose of 0.067 U/min restored cardiovascular function more effectively than 0.033 U/min, without a difference in adverse events.[9] In the previous pilot trial, an infusion rate of 0.06 U/min of vasopressin led to mean plasma levels of around 300 pmol/L, well above the physiological levels seen in other shock states.[11] Although the trial by Lauzier et al,[5] which had demonstrated an improved creatinine clearance, used a vasopressin dose up to 0.2 U/min, there was concern that higher doses might lead to adverse effects, such as ischemia from excessive vasoconstriction. The mean dose of vasopressin was 0.06 U/min, and the mean dose of norepinephrine or epinephrine was 0.55 µg/kg/min, when the potentially drug-related serious adverse events occurred. In view of the uncertainty about what is the ideal blood pressure to target in septic shock,[18] clinicians need to balance the potential benefits of an increased blood pressure against the risk of vasopressor-related adverse events, particularly at high dose and should set blood pressure targets for individual patients.

The other potentially important finding from VASST that informed this trial was the potential interaction with corticosteroids. There are several possible biological interactions including that vasopressin binds to V1b receptors in the anterior pituitary that then leads to adrenocorticotropin hormone release[19] and corticosteroids have been shown to restore cytokine-mediated down-regulation of vasopressin receptors.[20] Patients in VASST who received vasopressin and corticosteroids had reduced mortality rates compared with patients who received norepinephrine and corticosteroids. In contrast with patients who did not receive corticosteroids, patients treated with norepinephrine had better outcomes.[10] Other retrospective studies also suggested that patients treated with the combination of vasopressin and corticosteroids had reduced mortality rates compared with patients receiving vasopressin alone.[21,22] In view of the Surviving Sepsis Guidelines that recommend only using hydrocortisone (200 mg/d) if hypotension is not responding to fluid and vasopressor therapy,[2] corticosteroids were only administered once study drug 1 was at its maximal infusion rate (vasopressin 0.06 U/min or norepinephrine 12 µg/min). As in the pilot study,[11] corticosteroids reduced vasopressin requirements but there was no difference in mortality rates and no evidence of an interaction between vasopressin and corticosteroids on outcome. Although not all patients required study drug 2 (hydrocortisone or placebo), the results were similar in the as-treated and the per-protocol analyses. However, because many patients did not require or receive study drug 2, the power to assess an interaction was limited and restricts the interpretation of this finding.

Limitations of this study need to be considered. The multicenter nature of the trial was designed to test the effectiveness of early vasopressin use in the treatment of septic shock in normal clinical practice. Other co-interventions, timing of initiation of renal replacement therapy, or levels of hemodynamic monitoring were not controlled, other than specifying that sites should follow the international guidelines.[14] Because the trial was blinded and randomization was stratified by center, we would expect these other factors to be balanced between groups and therefore unlikely to affect the overall result. Another important limitation is that only short time outcomes, 28-day and hospital mortality were collected, and therefore any long-term differences between treatment groups cannot be assessed. Similarly, no formal health economic analysis was originally planned, but the lower rate of renal replacement therapy in the vasopressin-treated patients means that this could be an important future assessment. Although there was no difference in the distribution or number of kidney failure–free days between vasopressin and norepinephrine groups, the 95% confidence intervals of the difference between groups has an upper limit of 5 days in favor of vasopressin, which would be clinically important. Therefore, these results are still consistent with a potentially clinically important benefit for vasopressin but a larger trial would be needed to confirm or refute this.

Conclusions

Among adults with septic shock, the early use of vasopressin compared with norepinephrine did not improve the number of kidney failure–free days. Although these findings do not support the use of vasopressin to replace norepinephrine as initial treatment in this situation, the confidence interval included a potential clinically important benefit for vasopressin, and larger trials may be warranted to assess this further.

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