

Effect of Vasopressin Initiation Threshold on Septic Shock Mortality

The VASSPR Cluster Crossover Randomized Strategy Trial

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IMPORTANCE The optimal vasopressor dose at which to initiate a second vasopressor in patients with septic shock is uncertain.

OBJECTIVE To compare the effects of hospital-level strategies initiating vasopressin infusion at a lower threshold vs a higher threshold on outcomes in patients with septic shock.

DESIGN, SETTING, AND PARTICIPANTS Cluster-randomized, cluster-crossover, pragmatic clinical strategy trial including adult patients receiving vasopressors for septic shock at 13 hospitals in Idaho and Utah from February 1, 2024, to July 31, 2025. The last day of follow-up for the primary outcome was February 17, 2026.

INTERVENTION Hospital-level implementation of septic shock management strategies recommending fixed-dose vasopressin initiation when the total dose of other vasopressors reached 0.1 µg/kg/min of norepinephrine or equivalent (lower-threshold strategy) or when the total dose of other vasopressors reached 0.4 µg/kg/min of norepinephrine or equivalent (higher-threshold strategy). Hospitals were randomized for the first month to an initial strategy (6 hospitals to the lower threshold vs 7 hospitals to the higher threshold) and then crossed over to the alternate strategy monthly thereafter.

MAIN OUTCOMES AND MEASURES The primary outcome of 28-day mortality and the key secondary outcome of kidney replacement therapy-free days through day 28 were analyzed using multivariable generalized linear mixed-effects models, accounting for trial site and baseline patient characteristics.

RESULTS There were 3959 unique patients with septic shock (median age, 68 [IQR, 57 to 77] years; 1903 [48%] were female). Of the patients more likely to experience differential management under the tested hospital-level vasopressin dose strategies (maximum vasopressor dose ≥ 0.07 µg/kg/min of norepinephrine or equivalent), 1034 of 1521 (68.0%) cared for under the lower-threshold strategy received vasopressin compared with 651 of 1526 (42.7%) cared for under the higher-threshold strategy. In the hospital-level strategy recommending a lower-dose threshold for vasopressin initiation, the maximum vasopressor dose received prior to vasopressin initiation was a median of 0.14 (IQR, 0.10 to 0.22) µg/kg/min of norepinephrine or equivalent vs 0.34 (IQR, 0.16 to 0.42) µg/kg/min of norepinephrine or equivalent in the hospital-level strategy recommending a higher-dose threshold for vasopressin initiation. Mortality at 28 days occurred in 628 of 1975 patients (31.8%) treated with the hospital-level strategy recommending initiation of vasopressin at a lower-dose threshold of other vasopressors vs 655 of 1984 patients (33.0%) treated with the higher-threshold strategy (adjusted marginal odds ratio, 0.98 [95% CI, 0.87 to 1.06], $P = .62$; adjusted risk difference, -0.4 [95% CI, -2.7 to 1.3] percentage points). Patients in both strategies for vasopressin initiation had a median of 29 (IQR, -1 to 29) kidney replacement therapy-free days (adjusted marginal odds ratio, 1.01 [95% CI, 0.91 to 1.14]).

CONCLUSIONS AND RELEVANCE In this large, pragmatic clinical trial comparing the effectiveness of 2 hospital-level strategies for second-line vasopressor management in septic shock, a strategy recommending initiation of vasopressin at a lower dose of other vasopressors did not reduce 28-day mortality compared with a strategy recommending vasopressin initiation at a higher dose of other vasopressors.

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Each year, nearly 49 million people worldwide experience sepsis, the syndrome of life-threatening organ dysfunction resulting from a dysregulated host response to infection.¹ Among patients who require vasopressor support for septic shock, approximately 30% to 40% die. Mortality is even higher when septic shock persists despite low doses of a first-line vasopressor.²⁻⁴

Treatment with vasopressin, an endogenous peptide hormone relatively deficient in septic shock, causes peripheral vasoconstriction via V₁ receptors and may protect kidney function, reduce fluid requirements, and help avoid putative adverse effects of catecholamine vasopressors, including arrhythmias, myocardial toxicity, and immunosuppression.⁵⁻¹³ Based on meta-analyses indicating improved mortality, international guidelines suggest initiation of vasopressin when patients with septic shock require escalating doses of first-line vasopressors.^{14,15} However, the optimal dose-based threshold for vasopressin initiation remains unclear.¹⁶ Although subgroup analyses within the Vasopressin and Septic Shock Trial (VASST) and recent observational data suggest that vasopressin initiation at lower doses yields the greatest benefit,^{17,18} concerns about potential toxic effects (including suppressed cardiac output and soft tissue and mesenteric ischemia) and cost lead some to delay initiation of vasopressin until septic shock is severe.^{5,13,19-21} The resulting clinician- and hospital-driven variation in vasopressin initiation practice is substantial.^{14,15,22} To date, no trial has directly compared vasopressin initiation thresholds.

To address this evidence gap, we conducted the Vasopressin for Septic Shock Pragmatic (VASSPR) trial. This pragmatic, cluster-randomized, cluster-crossover strategy trial compares the effects of hospital-level implementation of 2 vasopressor management strategies on 28-day mortality. The strategies recommended vasopressin initiation at a lower dose vs a higher dose of other vasopressors in patients with septic shock. We hypothesized that a hospital-level strategy recommending a lower threshold for vasopressin initiation would reduce 28-day mortality.

Methods

Trial Design

This pragmatic, multicenter, open-label, cluster-randomized, cluster-crossover, comparative effectiveness trial compared patient outcomes resulting from hospital-level implementation of 2 distinct strategies for initiating vasopressin as a secondary vasopressor for treatment of adult patients with septic shock. The Intermountain Health institutional review board approved the trial with a waiver of informed consent. Trial registration on ClinicalTrials.gov occurred prior to enrollment of the first patient. An independent data and safety monitoring board oversaw trial conduct. The trial protocol appears in [Supplement 1](#) and the statistical analysis plan appears in [Supplement 2](#); each was published²³ prior to database lock and initiation of the analyses reported herein. The trial adhered to the Consolidated Standards of Reporting Trials Extension (CONSORT Extension) reporting guideline for cluster-crossover trials.^{24,25}

Key Points

Question Does a hospital-level strategy recommending initiation of vasopressin at a lower rather than a higher dose of other vasopressors improve outcomes for patients with septic shock?

Findings In this cluster-randomized, cluster-crossover trial involving 3959 patients with septic shock from 13 hospitals, 28-day mortality was not statistically significantly different for patients assigned to a hospital-level strategy recommending initiation of vasopressin when the total dose of other vasopressors reached 0.1 µg/kg/min of norepinephrine or equivalent (628/1975; 31.8%) vs 0.4 µg/kg/min (655/1984; 33.0%).

Meaning A hospital-level vasopressor management strategy recommending a lower- vs higher-dose threshold for vasopressin initiation did not improve 28-day mortality.

Setting and Population

The trial enrolled patients at 13 hospitals in Idaho and Utah (eMethods and eTable 1 in [Supplement 3](#)). Enrollment began on February 1, 2024, and ended after 18 months on July 31, 2025 ([Figure 1](#)). The last day of follow-up for the primary outcome was February 17, 2026.

Patients were enrolled in the trial if they were aged 18 years or older, were admitted to one of the included hospitals or their emergency department, and had received vasopressor treatment for septic shock. There were no exclusion criteria. Confirmed or suspected septic shock qualifying for trial enrollment was identified pragmatically based on the indication for vasopressor treatment documented within the order for vasopressor administration entered by the clinical teams in the electronic health record. Because the vasopressin initiation strategies were implemented at the hospital level, all patients with septic shock were exposed to the assigned strategy and included in the intention-to-treat population without restriction on postrandomization factors (such as maximum vasopressor dose or strategy adherence).

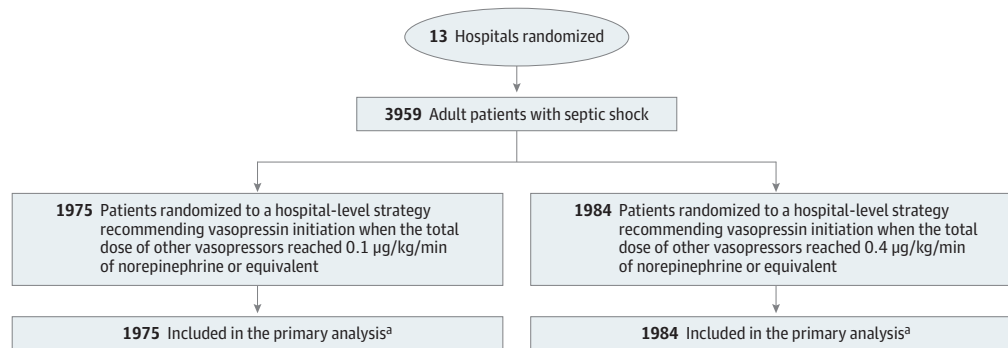
Randomization and Patient Allocation

After grouping the hospital sites into 4 strata based on historical case volumes, the vasopressin initiation strategy for the hospital during its first calendar month in the trial was assigned using block randomization via a computer-generated random sequence ([Figure 1B](#)). The strategy assignment for each hospital alternated on the first day of each subsequent calendar month with no washout period. The strategy assignment for the patients was the vasopressin initiation strategy in place at the hospital at the time each patient first met eligibility criteria. Blinding of the strategy assignment was not feasible given the nature of the intervention and its hospital-level implementation.

Interventions

The trial intervention was hospital-level implementation of 2 different strategies within the range of current usual care for initiating fixed-dose vasopressin (0.03 units/min) as a secondary vasopressor for patients with septic shock. The lower-threshold strategy recommended initiation of vasopressin when

Figure 1. Flow Diagram and Chart Depicting Hospital Cluster and Patient Enrollment

A Flow diagram for trial cluster and patient inclusion**B** Trial site randomization strategy and monthly patient enrollment^b

Vasopressin initiation strategy (randomized by hospital)																			
Lower threshold Higher threshold																			

Adapted from Peltan et al²³ under a Creative Commons CC-BY 4.0 license. Information on patient flow accounting for all patient encounters is reported in eFigure 2 in Supplement 3.

^aPatients were analyzed at the level of their first eligible encounter.

^bStrategy assignment was randomized for each hospital's first calendar month of enrollment. Thereafter, each hospital crossed over to the alternate treatment assignment on the first calendar day of each subsequent month through the end of the trial. The strata are based on anticipated patient volume. Enrollment began on February 1, 2024, with a 4-month vanguard phase for optimization of

procedures for intervention implementation, support, and monitoring at trial hospital A. The remaining 12 hospitals began enrollment on June 3, 2024. Enrollment ended on July 31, 2025, at all trial sites, resulting in a total trial duration of 18 months, which included 18 months of enrollment at hospital A (9 periods assigned to each strategy) and 14 months of enrollment at all other trial sites (7 periods assigned to each strategy). The values within the cells represent the monthly count of patients enrolled during that hospital period and included in the primary analysis.

a patient's total vasopressor dose reached 0.1 µg/kg/min of norepinephrine base or equivalent.²⁶ The higher-threshold strategy recommended initiation of vasopressin when a patient's total vasopressor dose reached 0.4 µg/kg/min of norepinephrine or equivalent. Vasopressin was recommended not to be ini-

tiated in patients whose vasopressor dose never increased to 0.4 µg/kg/min of norepinephrine or equivalent.

The treating clinicians decided each individual patient's vasopressor management, including whether to implement the assigned hospital-level vasopressin initiation strategy.

We deployed numerous measures to facilitate use of and adherence to assigned hospital-level vasopressin initiation strategies for patients in whom clinicians deemed this appropriate and desirable, including (1) trial-specific orders operationalizing vasopressin initiation according to assigned thresholds and preserving that threshold across hospital strategy crossover boundaries, (2) integration of these orders as default options within sepsis order sets, and (3) decision support alerts. All other clinical care (including fluid resuscitation, corticosteroid treatment, central venous catheter placement, inotrope administration, hemodynamic assessment, and vasopressor weaning) was decided by the treating clinicians within the context of the shared sepsis care protocol at the 13 hospitals.^{14,27,28}

Data Collection

Data analysts queried the health system electronic data warehouse to extract demographic, clinical, and outcome data.²⁹ Preexisting linkages to state death records for Utah and the US Social Security Death Index captured postdischarge mortality. Self-reported race and ethnicity were collected from the electronic health records to understand the generalizability of the trial population.

Trained personnel unaware of the strategy assignments performed structured reviews of the electronic health records for vital status confirmation, verification of outlier or discrepant data points, query-assisted adjudication of safety outcomes and key comorbidities, and capture of information not available as structured data (eg, infection source identified by the care teams at trial entry).^{23,30} For patients who were enrolled at the trial site in Idaho or whose recorded home address was outside the state of Utah, we conducted a manual review of the electronic health record and of publicly available sources to confirm mortality outcomes.

Outcomes

The primary outcome was 28-day all-cause mortality. The key secondary outcome was kidney replacement therapy-free days through day 28, which was an ordinal outcome assigning a value of -1 for death on or before day 28. The exploratory outcomes were 90-day mortality, hospital mortality, vasopressor-free days, intensive care unit-free days, hospital-free days, and new kidney replacement therapy through hospital discharge. Prespecified safety outcomes measured through hospital discharge were clinically documented new-onset acute coronary syndrome, new-onset mesenteric ischemia, new-onset soft-tissue ischemia, vasopressor extravasation, clinically significant cardiac arrhythmia (new or persistent), cardiogenic shock (new or persistent), cardiac arrest, and new-onset severe hyponatremia (serum sodium level <120 mmol/L). Serum troponin level above the upper limit of normal and maximum lactate level were measured through day 7. Additional outcome definition details appear in the eMethods and in eTable 2 in Supplement 3.

Measures of after-enrollment care and cointerventions included new insertion of central venous catheters, the total volume of intravenous resuscitation fluids administered during

the 24- and 72-hour periods after enrollment, and administration of stress-dose corticosteroids.

Sample Size and Statistical Power Calculation

As prespecified in the trial protocol and statistical analysis plan,²³ to ensure between-group balance and to maximize the ability of this comparative effectiveness trial to detect small, but meaningful, outcome differences, the trial duration was fixed administratively as the shorter of 22 months or the period feasible before each hospital transitioned to a new electronic health record rather than being determined by accumulating enrollments or outcome data. Power analyses used the intention-to-treat population, including patients with a maximum vasopressor dose less than 0.1 µg/kg/min of norepinephrine or equivalent, and were based on a 16-month duration and highly conservative estimates for monthly enrollment (eMethods in Supplement 3). From statistical simulations using historical hospital data and assuming (1) 1 to 45 patients per cluster per month, (2) no strategy effect on patients with a maximum vasopressor dose less than 0.1 µg/kg/min of norepinephrine or equivalent, (3) a within-cluster outcome correlation of 0.003, (4) cluster autocorrelation of 1.0, and (5) 28-day mortality of 33.0% in the higher-threshold strategy, we estimated that enrollment of 2050 patients over 16 months would provide 80% power at a type I error rate of 0.05 to detect a percentage-point difference of 5.4 in 28-day mortality (from 33.0% to 27.6%) for patients assigned to the lower-threshold strategy.

Statistical Analysis

As described in the statistical analysis plan published prior to trial database lock,²³ the analyses were conducted in the population defined by the first enrollment event for patients meeting eligibility criteria and performed in an intention-to-treat fashion according to assigned strategy, irrespective of maximum vasopressor dose or strategy adherence. The primary analysis reported the adjusted marginal odds ratio (OR) together with the corresponding risk difference and 95% CI for 28-day mortality associated with the lower-threshold strategy, calculated from a generalized linear mixed-effects model incorporating a random effect for trial site and fixed effects for the prespecified patient characteristics of age, sex, infection source suspected or diagnosed by the clinical care teams at the time of trial enrollment (pulmonary, urinary, gastrointestinal or abdominal, skin, other infection source, multiple infection sources, or undetermined infection source), chronic kidney disease, chronic cardiovascular disease, noncardiovascular Sequential Organ Failure Assessment score (range, 0-20; higher values indicate worse organ failure),³¹ and vasopressor initiation less than 72 hours after hospital presentation.

The key secondary outcome, exploratory outcomes, and safety outcomes derived effect estimates using parallel models substituting mixed-effects ordinal regression for outcomes of support-free days and mixed-effects linear regression for the outcome of maximum lactate level. The analyses were restricted to the first eligible encounter for each patient to ensure independence of observations.

Assessment of experimental separation between strategies focused on patients with a maximum vasopressor dose after enrollment in the range of 0.07 µg/kg/min of norepinephrine or equivalent or greater for whom we expected clinicians might anticipate continued increases in the vasopressor dose and begin differential management (eg, start vasopressin; administer intravenous fluids) for patients assigned to the hospital-level strategy recommending vasopressin initiation at a lower dose of other vasopressors. Principal measures for strategy adherence were the proportion of patients receiving vasopressin after trial entry and the maximum vasopressor dose after enrollment without vasopressin initiation (eMethods and eFigure 1 in [Supplement 3](#)).

Exploratory analyses investigated heterogeneity of the treatment effect for prespecified candidate effect modifiers. Prespecified sensitivity analyses for the primary and key secondary outcomes evaluated strategy eligibility, strategy intent, treatment crossover, encounter eligibility, time effects, and statistical modeling methods (eTable 3 in [Supplement 3](#)). Post hoc sensitivity analyses excluded the hospital with the highest enrollment and examined treatment effect heterogeneity based on hospital-level experimental separation.

The analyses were performed using R version 4.5.1 (R Foundation for Statistical Computing). A 2-sided *P* value ≤ .05 was considered statistically significant. Because the analyses were not adjusted for multiple comparisons, the results for the exploratory outcomes and analyses should be considered hypothesis-generating. The single interim analysis for efficacy applied Haybittle-Peto stopping criteria to data on patients enrolled during the first 8 months (50% of the conservative trial duration).³²⁻³⁴

Results

Patient Characteristics

The primary analysis included the first eligible encounter with septic shock for 1975 patients assigned to the hospital-level strategy recommending vasopressin initiation at a lower threshold of other vasopressors vs 1984 patients assigned to a higher threshold at 13 hospitals from February 1, 2024, to July 31, 2025 (Figure 1 and eFigure 2 in [Supplement 3](#)). Overall, 1903 patients (48.1%) were female and the median age was 68 years (IQR, 57-77 years) (Table 1 and eTable 4 in [Supplement 3](#)). Individual hospitals enrolled between 31 and 1429 unique patients (eTable 5 in [Supplement 3](#)).

Assessment of Vasopressin Exposure by Strategy Assignment

Of patients with a maximum vasopressor dose of 0.07 µg/kg/min of norepinephrine or equivalent or greater, which is in the range expected to result in differential management under the studied hospital-level strategies, there were 1521 (77.0%) assigned to the lower-threshold strategy and 1526 (76.9%) assigned to the higher-threshold strategy. Vasopressin was administered to 1034 (68.0%) of these patients managed under the lower-threshold strategy and to 651 (42.7%) of these patients managed under the higher-threshold strat-

egy (between-group difference, 25.3% [95% CI, 21.7% to 28.4%]). For these patients who received 0.07 µg/kg/min of norepinephrine or equivalent or greater, the maximum dose of vasopressors administered without initiation of vasopressin was lower for those assigned to the lower threshold (median, 0.12 [IQR, 0.10 to 0.20] µg/kg/min of norepinephrine or equivalent) compared with the higher threshold (median, 0.20 [IQR, 0.10 to 0.36] µg/kg/min of norepinephrine or equivalent) (between-group difference in medians, -0.08 [95% CI, -0.08 to -0.06] µg/kg/min of norepinephrine or equivalent) (eFigure 3 in [Supplement 3](#)).

Among patients who received vasopressin, those who were assigned to the hospital-level strategy recommending a lower threshold for vasopressin initiation had a lower maximum dose of vasopressors administered prior to vasopressin initiation (median, 0.14 [IQR, 0.10 to 0.22] µg/kg/min of norepinephrine or equivalent compared with 0.34 [IQR, 0.16 to 0.42] µg/kg/min of norepinephrine or equivalent for the higher threshold; between-group difference in medians, -0.20 [95% CI, -0.22 to -0.16] µg/kg/min of norepinephrine or equivalent) and started vasopressin earlier after enrollment (median, 1.4 hours [IQR, 0.4 to 4.3 hours] vs 2.2 hours [IQR, 0.5 to 7.3 hours], respectively; between-group difference in medians, -0.8 hours [95% CI, -1.4 to -0.4 hours]). Use of trial-specific vasopressin orders was similar across strategies (Table 2).

Primary Outcome

Through day 28, 628 patients (31.8%) died among those assigned to the hospital-level strategy recommending vasopressin initiation at a lower-dose threshold of other vasopressors compared with 655 patients (33.0%) among those assigned to the higher-dose threshold (Table 3 and eFigure 4 in [Supplement 3](#)). There was no difference in 28-day mortality between hospital-level vasopressin initiation strategies in the primary analysis (adjusted marginal OR, 0.98 [95% CI, 0.87 to 1.06], *P* = .62; adjusted risk difference, -0.4 percentage points [95% CI, -2.7 to 1.3 percentage points]; Table 3). The results were similar in the sensitivity analyses evaluating alternative analysis populations (eTables 6-12 in [Supplement 3](#)); conditional effects (eTable 13 in [Supplement 3](#)); alternative statistical methods; and potential effects of cluster-level carryover, temporal trends, and patient-level strategy crossover, contamination, and dilution, including the analysis restricted to patients with a maximum vasopressor dose of 0.07 µg/kg/min of norepinephrine or equivalent or greater (eTable 14 in [Supplement 3](#)).

Exploratory analyses did not suggest treatment effect heterogeneity for prespecified subgroups (Figure 2 and eTable 15 in [Supplement 3](#)) or according to hospital-level experimental separation (eFigure 5 in [Supplement 3](#)). Within-hospital outcome correlation for 28-day mortality was 0.021; cluster autocorrelation was 0.998.

Secondary, Exploratory, and Safety Outcomes

Kidney replacement therapy-free days did not differ between hospital-level vasopressin initiation strategies (adjusted marginal OR, 1.01 [95% CI, 0.91-1.14]; eFigure 6 in

Table 1. Patient Demographics and Baseline Clinical Characteristics

Characteristic	Vasopressin initiation strategy, No. (%) ^a	
	Lower threshold (n = 1975)	Higher threshold (n = 1984)
Demographics		
Age, median (IQR), y	67 (56-77)	68 (57-77)
Sex		
Female	959 (48.6)	944 (47.6)
Male	1016 (51.4)	1040 (52.4)
Race and ethnicity, No./total (%) ^b		
Hispanic or Latino	170/1732 (9.8)	201/1761 (11.4)
Non-Hispanic and race other than White ^c	136/1732 (7.9)	130/1761 (7.4)
Non-Hispanic White	1426/1732 (82.3)	1430/1761 (81.2)
Clinical factors		
Chronic kidney disease ^d	569 (28.8)	594 (29.9)
Chronic cardiovascular disease ^e	1048 (53.1)	1032 (52.0)
Weighted Elixhauser comorbidity score, median (IQR) ^f	16 (5-26)	16 (5-28)
Live in a long-term care facility	240 (12.2)	245 (12.3)
Noncardiovascular SOFA score, median (IQR) ^g	5 (3-7)	5 (3-7)
Temperature, median (IQR), °C	36.9 (36.3-37.2) [n = 1958]	36.9 (36.2-37.2) [n = 1969]
Heart rate, median (IQR), beats/min	91 (77-107) [n = 1974]	92 (76-108) [n = 1984]
Glasgow Coma Scale score, median (IQR) ^h	14 (10-15) [n = 1973]	14 (10-15) [n = 1982]
Laboratory parameters		
Lactate		
>2 mmol/L, No./total (%)	1167/1915 (60.9)	1123/1925 (58.3)
Median (IQR), mmol/L	2.5 (1.6-4.4) [n = 1915]	2.5 (1.5-4.6) [n = 1925]
White blood cell count, median (IQR), in 1000s/ μ L	12.6 (8.1-18.4) [n = 1967]	12.6 (8.1-18.9) [n = 1977]
Sodium, median (IQR), mmol/L	136 (133-139) [n = 1888]	136 (133-140) [n = 1905]
Type of treatment		
Kidney replacement therapy at enrollment	141 (7.1)	157 (7.9)
Chronic kidney replacement therapy	99 (5.0)	115 (5.8)
Acute kidney replacement therapy	42 (2.1)	42 (2.1)
Invasive mechanical ventilation	504 (25.5)	506 (25.5)
Initiation of vasopressors within 72 h of hospital arrival	1759 (89.1)	1748 (88.1)
Source of infection (suspected or diagnosed at enrollment)		
Pneumonia or pulmonary	574 (29.1)	553 (27.9)
Abdominal or gastrointestinal	311 (15.8)	309 (15.6)
Urinary tract	308 (15.6)	306 (15.4)
Skin or soft tissue	121 (6.1)	107 (5.4)
Other source, multiple sources, or undetermined source	661 (33.5)	709 (35.7)

Abbreviation: SOFA, Sequential Organ Failure Assessment.

^a Some data are expressed as median (IQR) or No./total (%) as indicated in the rows.^b Self-reported as recorded in the electronic health record.^c Race other than White includes American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and other or multiple races.^d Defined by end-stage kidney disease managed with chronic hemodialysis, a baseline glomerular filtration rate less than 60 mL/min/1.73 m², or clinical diagnosis of chronic kidney disease without contradictory laboratory data.^e Defined by a documented clinical history of myocardial infarction, coronary artery disease, congestive heart failure, or peripheral vascular disease.^f Scores range from -19 to 89; higher scores indicate increased chronic comorbid disease burden.³⁵ Values greater than 11 represent the top tertile of comorbidity burden when considering all adult hospital admissions to the study health system.³⁶^g Scores range from 0 to 20; higher scores indicate worse noncardiovascular organ failure. Values near the median represent substantial organ failure.^h Scores range from 3 to 15; lower values indicate a worse level of consciousness. Values at the median indicate mildly impaired consciousness.

Supplement 3). The sensitivity analyses yielded similar results (eTable 16 in Supplement 3). The exploratory outcomes were not different between strategies (Table 3 and eFigure 6 in Supplement 3). The only between-strategy difference in safety outcomes was for persistent or new-onset cardiogenic shock, for which 95% CIs (not adjusted for multiple testing)

excluded 1.0 from the exploratory adjusted marginal OR but not the conditional OR (Table 3). The mean arterial blood pressure trajectory through 72 hours of the trial and the trajectories of vasopressor dose, lactate level, and sodium level through day 7 were similar between vasopressin initiation strategies (eFigures 7-10 in Supplement 3). Intraclass correlations for

Table 2. Measures of Vasopressin Exposure

	Vasopressin initiation strategy, No. (%) ^a		Between-strategy difference (95% CI) ^b
	Lower threshold (n = 1975)	Higher threshold (n = 1984)	
All enrolled patients			
Threshold-based vasopressin initiation order entered by clinical team	1644 (83.2)	1661 (83.7)	−0.5 (−2.8 to 1.9)
Vasopressin administered after enrollment	1034 (52.4)	653 (32.9)	19.5 (16.4 to 22.2)
Maximum vasopressor dose, median (IQR), µg/kg/min of norepinephrine or equivalent			
After enrollment without vasopressin initiation	0.10 (0.06 to 0.17) [n = 1910]	0.14 (0.06 to 0.30) [n = 1949]	−0.04 (−0.04 to −0.02)
After enrollment	0.20 (0.08 to 0.50) [n = 1973]	0.19 (0.08 to 0.50) [n = 1978]	0.01 (0 to 0.04)
Strict adherence to assigned hospital-level vasopressin initiation strategy ^c	1135 (57.5)	1452 (73.2)	−15.7 (−18.7 to −12.9)
Patients with a maximum vasopressor dose ≥0.07 µg/kg/min of norepinephrine or equivalent			
No. of patients	1521	1526	
Threshold-based vasopressin initiation order entered by clinical team	1269 (83.4)	1272 (83.4)	0 (−2.6 to 2.7)
Vasopressin administered after enrollment	1034 (68.0)	651 (42.7)	25.3 (21.7 to 28.4)
Maximum vasopressor dose after enrollment prior to vasopressin initiation, median (IQR), µg/kg/min of norepinephrine or equivalent	0.14 (0.10 to 0.22) [n = 1459]	0.34 (0.16 to 0.42) [n = 1498]	−0.20 (−0.22 to −0.16)
Time from enrollment to vasopressin initiation, median (IQR), h	1.4 (0.4 to 4.3)	2.2 (0.5 to 7.3)	−0.8 (−1.4 to −0.4)
Maximum vasopressor dose, median (IQR), µg/kg/min of norepinephrine or equivalent			
After enrollment without vasopressin initiation	0.12 (0.10 to 0.20) [n = 1458]	0.20 (0.10 to 0.36) [n = 1497]	−0.08 (−0.08 to −0.06)
After enrollment	0.30 (0.15 to 0.66)	0.29 (0.14 to 0.67)	0.01 (−0.02 to 0.04)
Strict adherence to assigned hospital-level vasopressin initiation strategy ^c	686 (45.1)	1000 (65.6)	−20.5 (−23.8 to −16.8)

^a Some data are expressed as median (IQR) as indicated in the rows.

^b Data are expressed as percentage (95% CI) or median (95% CI).

^c Strict adherence was determined as shown in eFigure 1 in Supplement 3.

secondary, exploratory, and safety outcomes appear in eTable 17 in Supplement 3.

Cointerventions

Slightly more patients assigned to the hospital-level strategy recommending a lower vasopressin initiation threshold started or continued stress-dose corticosteroids within 7 days of enrollment (eTable 18 in Supplement 3). Other cointerventions were similar between hospital-level vasopressin initiation strategies.

Discussion

In this pragmatic, cluster-randomized strategy trial enrolling more than 3900 patients with septic shock across 13 US hospitals, a hospital-level strategy recommending vasopressin at a lower dose of other vasopressors did not improve mortality compared with a strategy using a higher threshold. Kidney replacement therapy-free days also did not differ.

International guidelines suggest vasopressin initiation for adults with septic shock receiving escalating doses of norepinephrine. However, the guideline panelists themselves reported substantially varying dose-based vasopressin initiation thresholds.¹⁵ Hospital-level practice also varies substantially²² in the context of potential risks,^{37,38} cost considerations,^{5,19} and limited availability in some resource-

constrained settings.^{39,40} Meanwhile, building on the VASST trial's subgroup analysis suggesting that adding vasopressin to norepinephrine improved outcomes only for patients receiving a norepinephrine dose of less than 15 µg/min at randomization,^{17,41} recent observational studies applying innovative machine learning and causal inference methods have increased interest in the potential for benefit from vasopressin initiation at lower doses of other vasopressors and earlier in the temporal course of septic shock.^{18,42-44} However, the present large, randomized clinical trial did not find benefit from hospital-level deployment of a septic shock management strategy recommending vasopressin initiation at a lower dose of other vasopressors vs a strategy deferring vasopressin until more severe shock developed.

This randomized trial investigated the real-world comparative effectiveness of vasopressin initiation strategies in septic shock via an intervention that simulated adoption of 2 alternative hospital-level guidelines incorporating explicit recommendations for dose-based vasopressin initiation thresholds while still allowing clinician discretion for individual patients. As intended for this effectiveness trial, vasopressin treatment reflected the desired application of clinical judgement to nominal hemodynamic thresholds implemented within hospital-level vasopressor strategies for septic shock, with strategies providing reference points but not rules for management of this dynamic condition. Nevertheless, the trial achieved substantial experimental separation.

Table 3. Primary, Secondary, Exploratory, and Safety Outcomes

	Vasopressin initiation strategy, No. (%) ^a		Adjusted marginal OR (95% CI) ^b	Adjusted risk difference (95% CI) ^c
	Lower threshold (n = 1975)	Higher threshold (n = 1984)		
Primary outcome				
All-cause mortality at 28 d	628 (31.8)	655 (33.0)	0.98 (0.87 to 1.06) ^d	-0.4 (-2.7 to 1.3)
Secondary outcome				
Kidney replacement therapy-free days to 28 d, median (IQR)	29 (-1 to 29)	29 (-1 to 29)	1.01 (0.91 to 1.14)	
Exploratory outcomes				
All-cause mortality at 90 d	748 (37.9)	762 (38.4)	1.01 (0.93 to 1.11)	0.3 (-1.6 to 2.2)
All-cause in-hospital mortality	514 (26.0)	526 (26.5)	1.00 (0.91 to 1.15)	0.1 (-1.5 to 2.0)
New kidney replacement therapy, No./total (%) ^e	149/1834 (8.1)	151/1827 (8.3)	0.98 (0.78 to 1.18)	-0.1 (-1.7 to 1.1)
Hospital-free days to 28 d, median (IQR)	17 (-1 to 23)	17 (-1 to 23)	1.03 (0.94 to 1.11)	
ICU-free days to 28 d, median (IQR)	22 (-1 to 26)	22 (-1 to 26)	1.04 (0.95 to 1.11)	
Vasopressor-free days to 28 d, median (IQR)	26 (-1 to 27)	26 (-1 to 27)	1.05 (0.96 to 1.21)	
Safety outcomes				
Clinically significant arrhythmia	363 (18.4)	359 (18.1)	1.03 (0.89 to 1.42)	0.5 (-1.7 to 5.4)
Cardiogenic shock	146 (7.4)	124 (6.3)	1.19 (1.01 to 1.42)	0.8 (0 to 1.5)
Cardiac arrest	91 (4.6)	88 (4.4)	1.05 (0.74 to 1.31)	0.2 (-1.3 to 1.2)
Ischemia, No./total (%)				
Mesenteric ^f	21/1909 (1.1)	21/1916 (1.1)	1.00 (0.50 to 1.51)	0 (-0.6 to 0.4)
Soft tissue ^f	16/1952 (0.8)	14/1970 (0.7)	1.12 (0.70 to 2.61)	0.1 (-0.3 to 0.5)
Acute coronary syndrome, No./total (%) ^g	14/1923 (0.7)	11/1937 (0.6)	1.32 (0.17 to 2.10)	0.2 (-0.6 to 0.5)
Abnormal troponin	812 (41.1)	769 (38.8)	1.10 (0.81 to 1.33)	0.8 (-1.9 to 2.2)
Vasopressor extravasation	42 (2.1)	35 (1.8)	1.21 (0.66 to 2.00)	0.3 (-0.6 to 1.0)
Severe hyponatremia, No./total (%), mmol/L ^h	8/1946 (0.4)	8/1965 (0.4)	1.03 (0.37 to 4.68)	0 (-0.4 to 0.5)
Maximum lactate level, median (IQR), mmol/L ^g	2.9 (1.7 to 5.9) [n = 1660]	2.8 (1.7 to 5.9) [n = 1665]	0.10 (-0.14 to 0.34) ^h	

Abbreviations: ICU, intensive care unit; OR, odds ratio.

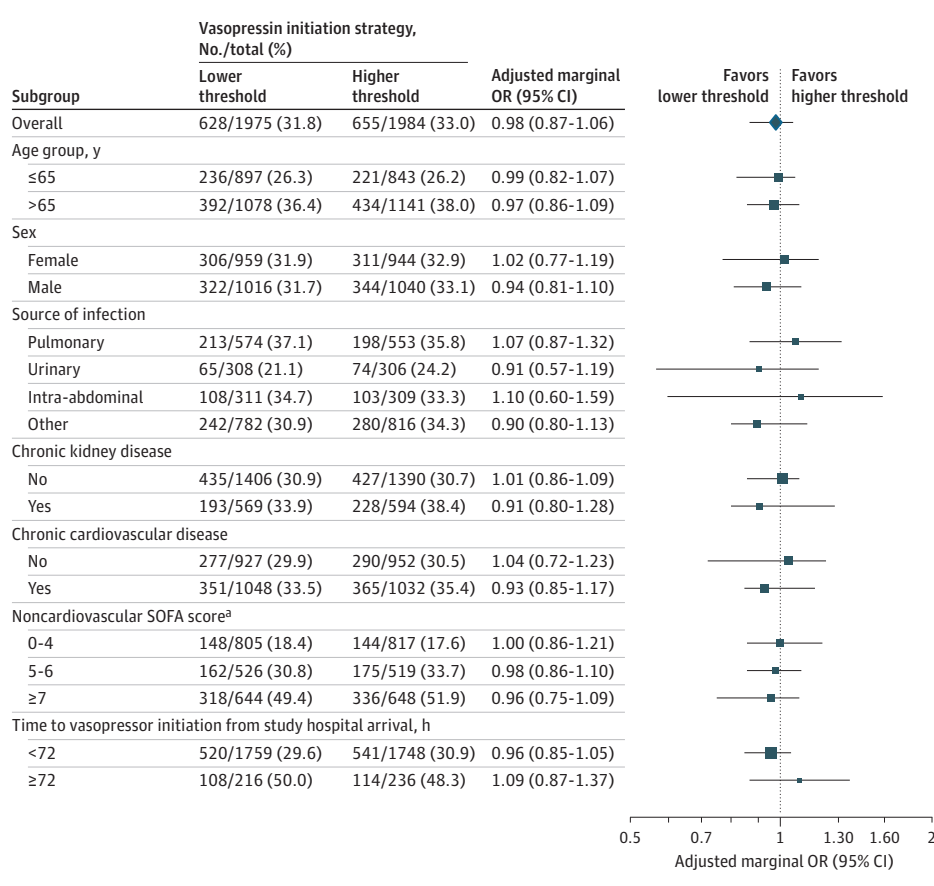
^a Some data are expressed as median (IQR) or No./total (%) as indicated in the rows.^b For most of the outcomes (except kidney replacement therapy-, hospital-, ICU-, and vasopressor-free days), an improved outcome in the lower-threshold group is reflected by an OR less than 1. For kidney replacement therapy-, hospital-, ICU-, and vasopressor-free days, an improved outcome in the lower-threshold group is reflected by an OR greater than 1.^c Data are expressed as percentage (95% CI) or median (95% CI).^d $P = .62$ for comparison between strategies.^e Patients receiving kidney replacement therapy prior to trial enrollment were excluded.^f Patients with onset of this outcome before enrollment were excluded.^g Patients without a measurement between enrollment and trial day 7 were excluded.^h Adjusted change in the outcome resulting from assignment to the lower threshold vs the higher threshold.

Of the patients with a maximum vasopressor dose of 0.07 $\mu\text{g/kg/min}$ of norepinephrine or equivalent or greater and who were, therefore, more likely to experience differential management under the tested hospital-level strategies, 68% assigned to the strategy recommending a lower vasopressin initiation threshold received vasopressin compared with 43% assigned to the higher threshold. Median vasopressor exposure without vasopressin initiation was also lower for patients with a maximum vasopressor dose of 0.07 $\mu\text{g/kg/min}$ of norepinephrine or equivalent or greater assigned to the lower threshold (0.12 $\mu\text{g/kg/min}$ of norepinephrine or equivalent vs 0.20 $\mu\text{g/kg/min}$ of norepinephrine or equivalent for the higher threshold) and, if vasopressin was started, the duration of septic shock without vasopressin initiation was shorter (1.4 hours vs 2.2 hours, respectively).

The observed results, therefore, describe the real-world effectiveness of implementing hospital-level recommendations for vasopressin initiation thresholds under the degree of adherence achieved in the trial. Nevertheless, even though the 95% CIs from the current analysis do not include a mortality benefit of the magnitude suggested for lower-threshold vasopressin initiation by the VASST trial subgroup analysis (absolute 28-day mortality risk reduction of 9 percentage points) or a recent observational analysis (adjusted OR of 0.81 for in-hospital mortality risk),^{17,18} the 95% CI of -2.7 to 1.3 percentage points for the adjusted risk difference does not exclude a small difference in 28-day mortality between the tested hospital-level strategies.

Persistent or new-onset cardiogenic shock was possibly more common with the hospital-level strategy recommending

Figure 2. Dot-and-Whisker Plot Displaying 28-Day All-Cause Mortality in Prespecified Subgroups



the lower threshold for vasopressin initiation. Although biologically plausible and concordant with increased inotrope treatment in the vasopressin group in the VASST trial,^{13,21} the analysis was exploratory and the 95% CIs were not adjusted for the concurrent evaluation of 16 other secondary or exploratory outcomes. Interpretation of this finding, therefore, requires caution, particularly given that the 95% CIs crossed null in the sensitivity analysis of this outcome.

Limitations

This trial had limitations. First, this comparative effectiveness trial evaluated the effectiveness of hospital-level guidelines for vasopressin initiation under real-world conditions that allowed clinician discretion, crossover, and imperfect adherence. Whether an efficacy trial that strictly enforced vasopressin initiation thresholds would have observed different results is unknown. However, our findings suggest it is unlikely that a modest effect in a subsequent efficacy trial would translate to patient benefit in real-world application. Our trial design also preserved the randomized comparison in this open-label trial by enrolling and analyzing all patients with septic shock exposed to these strategies (ie, all patients with septic shock), including patients with mild shock not expected to experience differential management or differential outcomes under the 2 tested strategies. Inclusion of these patients could dilute an effect confined to patients with more

severe shock. However, the power calculations accounted for this effect, enrollment substantially exceeded the minimum planned sample, and analyses yielded similar results when restricted to patients whose maximum vasopressor dose was 0.07 µg/kg/min of norepinephrine or equivalent or greater and who, therefore, had increased likelihood of differential management under the tested hospital-level strategies. Nevertheless, a trial restricted to patients with doses of other vasopressors in the range intended to trigger differential vasopressin management might have yielded different results.

Second, the knowledge by the clinical teams of hospital-level vasopressin management strategy could have influenced some treatment decisions for the patients. The patients assigned to the lower threshold received stress-dose steroids slightly more often, but other key cointerventions were similar between strategies, including postenrollment fluid resuscitation, which is an essential therapy that influences and may be influenced by vasopressor management.^{45,46} Even though we believe it is unlikely that changes in sepsis cointerventions abrogated clinically important outcome differences between hospital-level vasopressin initiation strategies, we also note that any such management changes are integral to the real-world effect of hospital-level treatment strategy implementation rather than a source of bias to be eliminated.

Third, the primary mechanisms of strategy delivery ensured stable patient-level implementation of already-assigned strategies when hospital-level strategies changed across period boundaries, but various mechanisms for patient-level crossover (including carryover of clinical behaviors across period boundaries) could have diminished separation between groups and biased results toward the null. Prespecified sensitivity analyses addressing this issue were reassuring.

Fourth, inclusion of both community hospitals and referral hospitals was a trial strength, but results may not be generalizable to less integrated health systems, to resource-limited care environments, or to contexts in which typical practice involves starting vasopressin at a substantially higher dose of other vasopressors than recommended for the higher-threshold strategy.

Fifth, it is unknown whether results would have been different if the trial's strategies had been more strongly enforced, recommended different dose-based thresholds, applied time-based thresholds,¹⁸ or integrated more information into the vasopressin initiation decision, including predicted individual-

ized treatment effect,¹⁸ shock cadence and trajectory,⁴⁷ measures of cardiac function or end-organ perfusion,^{48,49} or clinical or molecular phenotypes.^{50,51}

Sixth, trial design and power estimates accounted for cluster size imbalance, but varying enrollment combined with higher than planned within-site outcome correlation could have affected statistical power.⁵² In addition, new kidney replacement therapy was rare compared with 28-day mortality, potentially obscuring intervention effects on the secondary outcome of kidney replacement therapy-free days.

Conclusion

In this large, pragmatic clinical trial comparing the effectiveness of 2 hospital-level strategies for second-line vasopressor management in septic shock, a strategy recommending initiation of vasopressin at a lower dose of other vasopressors did not reduce 28-day mortality compared with a strategy recommending vasopressin initiation at a higher dose of other vasopressors.

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