JAMA | Original Investigation

Association of Vasopressin Plus Catecholamine Vasopressors vs Catecholamines Alone With Atrial Fibrillation in Patients With Distributive Shock

A Systematic Review and Meta-analysis

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IMPORTANCE Vasopressin is an alternative to catecholamine vasopressors for patients with distributive shock—a condition due to excessive vasodilation, most frequently from severe infection. Blood pressure support with a noncatecholamine vasopressor may reduce stimulation of adrenergic receptors and decrease myocardial oxygen demand. Atrial fibrillation is common with catecholamines and is associated with adverse events, including mortality and increased length of stay (LOS).

OBJECTIVES To determine whether treatment with vasopressin + catecholamine vasopressors compared with catecholamine vasopressors alone was associated with reductions in the risk of adverse events.

DATA SOURCES MEDLINE, EMBASE, and CENTRAL were searched from inception to February 2018. Experts were asked and meta-registries searched to identify ongoing trials.

STUDY SELECTION Pairs of reviewers identified randomized clinical trials comparing vasopressin in combination with catecholamine vasopressors to catecholamines alone for patients with distributive shock.

DATA EXTRACTION AND SYNTHESIS Two reviewers abstracted data independently. A random-effects model was used to combine data.

MAIN OUTCOMES AND MEASURES The primary outcome was atrial fibrillation. Other outcomes included mortality, requirement for renal replacement therapy (RRT), myocardial injury, ventricular arrhythmia, stroke, and LOS in the intensive care unit and hospital. Measures of association are reported as risk ratios (RRs) for clinical outcomes and mean differences for LOS.

RESULTS Twenty-three randomized clinical trials were identified (3088 patients; mean age, 61.1 years [14.2]; women, 45.3%). High-quality evidence supported a lower risk of atrial fibrillation associated with vasopressin treatment (RR, 0.77 [95% CI, 0.67 to 0.88]; risk difference [RD], −0.06 [95% CI, −0.13 to 0.01]). For mortality, the overall RR estimate was 0.89 (95% CI, 0.82 to 0.97; RD, −0.04 [95% CI, −0.07 to 0.00]); however, when limited to trials at low risk of bias, the RR estimate was 0.96 (95% CI, 0.84 to 1.11). The overall RR estimate for RRT was 0.74 (95% CI, 0.51 to 1.08; RD, −0.07 [95% CI, −0.12 to −0.01]). However, in an analysis limited to trials at low risk of bias, RR was 0.70 (95% CI, 0.53 to 0.92, *P* for interaction = .77). There were no significant differences in the pooled risks for other outcomes.

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis, the addition of vasopressin to catecholamine vasopressors compared with catecholamines alone was associated with a lower risk of atrial fibrillation. Findings for secondary outcomes varied.

JAMA. 2018;319(18):1889-1900. doi:10.1001/jama.2018.4528

Supplemental content

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In distributive shock, widespread vasodilation leads to decreased systemic vascular resistances and mean arterial pressure (MAP).[1] If not reversed, end-organ hypoperfusion results in significant morbidity; mortality rates reached 50% in observational studies conducted in 2013 and 2014.[2,3] Sepsis is the most common cause of distributive shock. It can also occur after cardiovascular surgery, spinal cord injury, or arise as a consequence of anaphylaxis or prolonged hypoperfusion.[1,4]

Managing distributive shock involves treating the underlying cause, volume resuscitation, and infusing vasopressors to maintain a perfusing blood pressure.[5,6] Clinicians frequently use catecholaminergic vasopressors (eg, norepinephrine, epinephrine, dopamine, dobutamine). However, catecholamines have adverse effects including myocardial ischemia and arrhythmia,[6-8] which may affect outcomes.[9]

Atrial fibrillation is a common adverse event in patients with distributive shock and is independently associated with morbidity, mortality, and increases in length of stay (LOS).[10-12]

Vasopressin, an endogenous peptide hormone, can also be used as a vasopressor. Patients with septic shock have relative vasopressin deficiency and exogenous administration of vasopressin raises blood pressure by increasing vascular tone.[13] By reducing the requirement for catecholamines, it decreases the stimulation of arrhythmogenic myocardial β_1-receptors and associated myocardial oxygen demand.[7,14] This, among other mechanisms, may translate into a reduction in adverse events, including atrial fibrillation, injury to other organs, and death.[7,15] The most recent Surviving Sepsis guidelines suggest adding vasopressin to norepinephrine to raise MAP to target, or adding vasopressin to decrease norepinephrine dosage (weak recommendations, moderate quality of evidence).[5]

The objective of this systematic review and meta-analysis was to determine the association between treatment with vasopressin in addition to catecholamine vasopressors on atrial fibrillation, morbidity, and mortality compared with catecholamines alone.

Key Points

Question In patients with distributive shock (a condition due to excessive vasodilation, most frequently from severe infection), is the addition of vasopressin to catecholamine vasopressors superior to catecholamine vasopressors alone for atrial fibrillation?

Findings In this systematic review and meta-analysis of 23 trials that included 3088 patients with distributive shock, the addition of vasopressin to catecholamine vasopressors compared with catecholamine vasopressors alone was significantly associated with a lower risk of atrial fibrillation (relative risk, 0.77).

Meaning Addition of vasopressin to catecholamines may offer a clinical advantage for prevention of atrial fibrillation.

Methods

The study protocol was registered with PROSPERO (2017: CRD42017059058). The conduct and reporting of the study follow the PRISMA guidelines.

Eligibility Criteria

Randomized clinical trials were included, irrespective of publication status, date of publication, risk of bias, outcomes published, or language. Trials were included if they enrolled adults with distributive shock, including septic shock, post-cardiovascular surgery vasoplegia, neurogenic shock, and anaphylaxis. Included studies had to compare the administration of vasopressin (or analogues [eg, terlipressin, selepressin]) with or without concomitant catecholaminergic vasopressors with the administration of catecholaminergic vasopressors alone, irrespective of dose, duration, or co-intervention.

The primary outcome was atrial fibrillation. Secondary outcomes were mortality, requirement for renal replacement therapy (RRT), myocardial injury, ventricular arrhythmia, stroke, and LOS in the intensive care unit (ICU) and hospital (eAppendices 4-5 in the Supplement). Acute kidney injury and digital ischemia were post hoc outcomes.

The outcomes were accepted as defined by study authors. For mortality, mortality at 28 to 30 days, at longest follow-up, and in-hospital were considered equivalent; ICU mortality was not pooled. Under digital ischemia, limb ischemia and peripheral ischemia or cyanosis were included. Myocardial infarction, myocardial ischemia, troponin rise, and acute coronary syndrome were pooled under myocardial injury. Ventricular tachycardia and fibrillation were pooled as ventricular arrhythmia. Cerebrovascular accident was combined with stroke.

Search Methods

MEDLINE, EMBASE, and CENTRAL were searched for keywords describing the condition, intervention, or comparator from inception to February 25, 2018 (eAppendices 1-3 in the Supplement). An information specialist reviewed the search strategies.

Trial registries were searched for ongoing and unpublished clinical trials via http://www.isrctn.com using the multiple database search option metaRegister of Controlled Trials and the World Health Organization trial registry. Authors hand-searched the conference proceedings for the scientific sessions of the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the American Thoracic Society in the last 2 years. The references of eligible papers were screened and experts were consulted to identify additional trials.

Data Collection and Analysis

Two reviewers independently screened studies' titles and abstracts for eligibility. Full papers of the potentially eligible studies were retrieved. The same 2 reviewers then independently screened full texts in duplicate and recorded the main reason for exclusion. Disagreements were resolved through discussion.

Data Extraction and Management

Independently, 2 reviewers abstracted data on intervention and outcome. They also recorded study and patient characteristics including age, sex, type of shock, and concomitant conditions (eg, cirrhosis, malignancy). They compared results and resolved disagreements by discussion with a third party. Authors were contacted to clarify ambiguities and to request data on outcomes missing in primary reports.

Assessment of Risk of Bias

In duplicate, 2 review authors assessed risk of bias.[16] In each trial, reviewers evaluated the following domains: sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessors, incomplete outcome data, and selective reporting. The results were compared and disagreements resolved by discussion. Performance and detection bias were assessed separately. All open-label studies were classified as being at high risk of performance bias. A priori, the decision was made to classify open-label designs as "likely low risk of bias" for detection bias for mortality, stroke, and LOS in the absence of other concerns, but to judge "likely high risk of bias" for detection bias for atrial fibrillation, RRT, digital ischemia, myocardial injury, and ventricular arrhythmia. For analysis and presentation purposes, risk of bias was dichotomized as high (or likely high) or low (or likely low).

For subgroup analyses, the study-level risk of bias was assessed for each outcome. If a study was at risk of selection, performance, detection, or reporting bias for that outcome, it was categorized as high risk of bias. Additionally, studies at risk of attrition bias were categorized as high risk of bias for mortality.

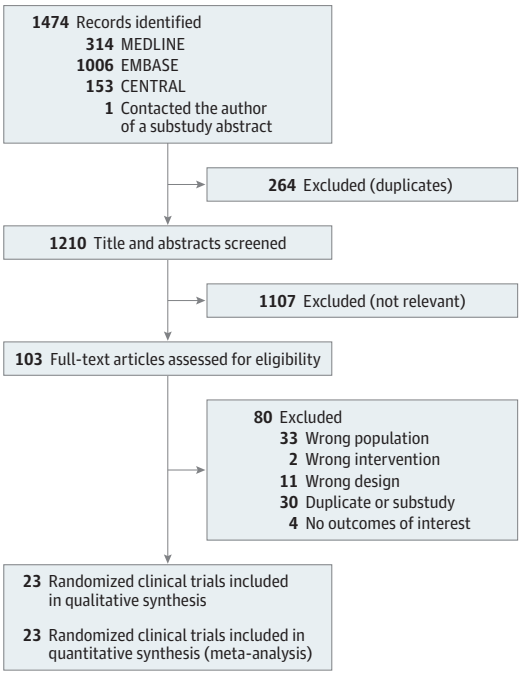
Measures of Association With Treatment

The main reported standard association measure for clinical outcomes was risk ratios (RRs) and mean differences for LOS. Risk difference and absolute risk difference were also calculated for clinical outcomes. The absolute risk difference was obtained by applying the RRs with 95% CIs to the baseline risk in the control group. To permit meta-analysis, if a study reporting on LOS provided a median and a measure of dispersion, this was converted to mean and standard deviation assuming a normal distribution.[17]

Clinical and methodological heterogeneity were assessed based on study characteristics. Statistical heterogeneity was measured with the I^2 statistic. An I^2 statistic greater than 50% was considered as showing substantial heterogeneity.[16]

RevMan (Cochrane Collaboration), version 5.3, was used to combine data quantitatively when clinical heterogeneity was nonsubstantial. A random-effects model with Mantel-Haenszel weighting was used because several comparisons were expected to show heterogeneity. After recognizing that a substantial proportion of the weight for atrial fibrillation was contributed by a single study,[18] we combined data for this outcome with a fixed-effect model in a sensitivity analysis. For trials in which patients crossed over to the other treatment, the analysis was according to their first assigned group (intention-to-treat principle). Two-sided P values less than .05 were considered statistically significant.

Figure 1. Flow of Study Selection for Trials Comparing Vasopressin + Catecholamines vs Catecholamines Alone for Patients With Distributive Shock



Subgroup and Sensitivity Analyses

Prespecified subgroup analyses were performed hypothesizing that patients with sepsis would derive greater benefit vs cardiovascular surgery. As a separate sensitivity analysis for RRT, the outcome definition was changed to acute kidney injury, as defined by study authors. P values for interaction between subgroups were tested.

Assessment of the Quality of the Evidence

The GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach[19] was used to grade the quality of evidence. GRADE appraises the confidence in estimates of effect by considering within-study risk of bias, directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias. Funnel plots of standard errors vs effect estimates were inspected for publication bias and small-study effects.

Results

Screening

The electronic search resulted in 1210 unique citations (**Figure 1**). After reference and full-text screening, 23 studies met eligibility criteria. Details on excluded and included studies and 3 potentially relevant ongoing studies are available (eAppendices 6-8 in the Supplement).

Table 1. Characteristics of Included Randomized Clinical Trials Comparing Vasopressin + Catecholamines vs Catecholamines Alone in Patients With Distributive Shock

Source	Design	Setting	No. of Patients	Condition	Treatment Group(s)	Comparison Group(s)	Planned Follow-up	Risk of Bias for Atrial Fibrillation
Abdullah et al,[20] 2012	Open label	Single center	34	Paracentesis-induced vasodilatory shock and end-stage liver disease	Terlipressin: 1 mg over 30 min, then continuous infusion of 2 µg/kg/min titrated up and weaned within 24 h	NE: 0.1 µg/kg/min titrated up and weaned within 24 h	48h	High
Acevedo et al,[21] 2009	Open label	Single center	24	Septic shock and cirrhosis	Terlipressin: 1-2 mg over 4 h	Adrenergic drugs as needed	Hospital LOS	High
Albanese et al,[22] 2005	Open label	Single center	20	Septic shock and 2 or more organ dysfunctions	Terlipressin: 1-mg bolus, then another 1-mg bolus if MAP <65 mm Hg	NE: 0.3 µg/kg, then increased by 0.3 µ/kg every 4 min until MAP between 65-75 mm Hg	Hospital LOS	High
Barzegar et al,[23] 2014	Open label	Single center	30	Septic shock	Vasopressin: 0.03 U/min	NE as needed for MAP >65 mm Hg	28d	High
Capoletto et al,[24] 2017	Double-blind	NA	107	Septic shock and cancer	Vasopressin: not described	NE: not described	90d	Low
Chen et al,[25] 2017	Open label	Single center	57	Acute respiratory distress syndrome and septic shock	Terlipressin and NE: 0.01-0.04 U/min of terlipressin and NE as needed to maintain MAP between 65-75 mm Hg	NE: >1 µg/min	28d	High
Choudhury et al,[26] 2016	Open label	Single center	84	Septic shock and cirrhosis	Terlipressin: 1.3-5.2 µg/min over 24 h	NE: 7.5-60 µg/min	28d	High
Clem et al,[27] 2016	Open label	Single center	82	Septic shock	Vasopressin and NE: 0.05-0.5 µg/kg/min of NE and 0.04 U/min of vasopressin to maintain MAP between 65-75 mm Hg	NE: 0.05-0.5 µg/kg/min to maintain MAP between 65-75 mm Hg	28d	High
Dünser et al,[28] 2003	Open label	Single center	48	Vasodilatory shock including septic shock, sepsis, and cardiotomy	Vasopressin: 4 U/h at a constant rate	NE: as needed for MAP >70 mm Hg, and additional vasopressin for NE requirements >2.26 µg/kg/min	ICU LOS	High
Fonseca Ruiz et al,[29] 2013	Open label	Single center	30	Septic shock	Vasopressin and NE: NE + vasopressin at titrated doses of 0.01 U/min, then increased by 0.01 U/min every 10 min to achieve MAP >65 mm Hg or until maximum dose of 0.04 U/min	NE	28d	High
Gordon et al,[30] 2016	Double-blind	Multicenter	421	Septic shock	Vasopressin: up to 0.06 U/min with target MAP between 65-75 mm Hg, or at physician's discretion	NE: up to 12 µg/min with target MAP between 65-75 mm Hg, or at physician's discretion	28d	Low[a]
Hajjar et al,[18] 2017	Double-blind	Single center	330	Vasoplegia after cardiac surgery	Vasopressin: 0.01-0.06 U/min with MAP >65 mm Hg	NE: 10-60 µg/min with MAP >65 mm Hg	30d	Low[a]
Han et al,[31] 2012	Open label	Single center	139	Septic shock	Pituitrin: 1.0-2.5 U/h	NE: 2-20 µg/kg/min	28d	High
Hua et al,[32] 2013	Open label	Single center	32	Septic shock and acute respiratory distress syndrome	Terlipressin: 1.3 µg/kg/h	Dopamine: 20 µg/kg/min	28d	High
Lauzier et al,[33] 2006	Open label	Multicenter	23	Septic shock	Vasopressin: 0.04-0.20 U/min	NE: 0.1-2.8 µg/kg/min	ICU LOS	High
Malay et al,[34] 1999	Double-blind	Single center	10	Septic shock	Vasopressin: 0.04 U/min	Placebo	24h	Low

(continued)

Included Studies

The 23 studies that compared vasopressin in combination with catecholamines vs catecholamines alone included 3088 patients (mean age, 61.1 years [14.2]; women, 45.3%) (**Table 1**). Five trials were multicenter.[30,33,37,39,40] Twenty-two studies included patients with septic shock.[20-41]

Table 1. Characteristics of Included Randomized Clinical Trials Comparing Vasopressin + Catecholamines vs Catecholamines Alone in Patients With Distributive Shock (continued)

Source	Design	Setting	No. of Patients	Condition	Treatment Group(s)	Comparison Group(s)	Planned Follow-up	Risk of Bias for Atrial Fibrillation
Morelli et al,[35] 2009[b]	Open label	Single center	45	Septic shock	Group 1: vasopressin: 0.03 U/min continuously over 48 h Group 2: terlipressin: 1.3 µg/kg/min continuously over 48 h	NE as needed	ICU LOS	High
Oliveira et al,[36] 2014	Double-blind	Single center	387	Septic shock	Vasopressin: 0.01-0.03 U/min	NE: 0.05-2.0 µg/kg/min	28d	High
Patel et al,[37] 2002	Double-blind	Multicenter	24	Septic shock	Vasopressin: 0.01-0.08 U/min	NE: 2-16 µg/min	4h	Low
Prakash et al,[38] 2017	Open label	NS	184	Cirrhosis and sepsis	Terlipressin and NE: 2 mg/24 h fixed dose infusion of terlipressin and 3.75-30 µg/min of NE as needed to maintain MAP >65 mm Hg	NE: 7.5-60 µg/min	30d	High
Russell et al,[39] 2008	Double-blind	Multicenter	802	Septic shock	Vasopressin: 0.01 U/min, then titrated up to 0.03 U/min with target MAP between 65-75 mm Hg, or at physician's discretion	NE: 5 µg/min to 15 µg/min with target MAP between 65-75 mm Hg, or at physician's discretion	90d	Low
Russell et al,[40] 2017	Double blind	Multicenter	53	Septic shock	Selepressin: 1.25, 2.5, or 3.75 ng/kg/min until shock resolution or a maximum of 7 d	Placebo	28d	Low[a]
Svoboda et al,[41] 2012	Open label	Single center	32	Septic shock	Terlipressin: 4 mg over 24 h for 72 h	NE as needed	28d	High

Abbreviations: ICU, intensive care unit; LOS, length of stay; MAP, mean arterial pressure; NE, norepinephrine or noradrenaline; NS, not specified.

[a] Trial judged to be at high risk of bias for mortality due to violation of the intention-to-treat principle.

[b] Morelli et al, 2009,[35] comprised 3 groups (vasopressin vs terlipressin vs norepinephrine). It was considered as 2 separate trials (vasopressin vs norepinephrine and terlipressin vs norepinephrine) in the comparison between vasopressin and vasopressin analogs. It was considered as a single trial (vasopressin or terlipressin vs norepinephrine) in all other comparisons.

Two studies evaluated patients with post-cardiac surgery vasoplegia.[18,28] Vasopressin was the intervention in 13 trials,[18,23,24,27-30,33-37,39] whereas 9 studied terlipressin,[20-22,25,26,32,35,38,41] 1 studied selepressin,[40] and 1 studied pituitrin (a mixture of vasopressin and oxytocin).[31] One 3-group study compared vasopressin vs terlipressin vs norepinephrine alone.[35] Five studies were published only as abstracts.[18,21,27,36,38]

Risk of Bias

Fifteen of 23 trials were not blinded (eAppendices 9-10 in the Supplement). Performance bias due to lack of blinding was judged to have an important effect on all outcomes; patients with distributive shock are critically ill and receiving many concomitant interventions that could be influenced by choice of concomitant vasopressor. Atrial fibrillation, myocardial injury, and digital ischemia are vulnerable to detection bias from differential capture and subjective interpretation; lack of blinding of clinicians and outcome assessors may influence these outcomes. The decision to start RRT could also be subjective. Other outcomes were judged to be at low risk of detection bias in the absence of blinding. Two studies were assessed to be at risk of selection bias due to inadequate randomization[31,36]; they did not describe their randomization process and had significant between-group imbalances. Nine studies (39%) reported the information necessary to make a definitive judgment for selection bias. Authors relied on imbalances between groups and overall methodological quality of the study to make this judgment. Attrition was found in 7 studies,[18,25,30,31,36,40,41] and judged as having an effect on mortality (**Table 2** and **Figure 2**A). Reporting bias was not detected. "Other bias" was judged to be present when studies were published as abstracts only. Prespecified sensitivity analyses were performed to assess the robustness of estimates to risk of bias if studies were dichotomized according to their risk of bias.

Primary Outcome

Atrial Fibrillation

Pooling data from 13 studies (4 studies with 0 events in either group, 1462 patients, 374 events) demonstrated a significant reduction in the risk of atrial fibrillation associated with the administration of vasopressin (RR, 0.77 [95% CI, 0.67 to 0.88], I^2 = 1%; risk difference [RD], −0.06 [95% CI, −0.13 to 0.01]) (Figure 2A). Based on the GRADE framework, this was judged to be high-quality evidence (eAppendix 13 in the

Table 2. Association of Vasopressin + Catecholamine Vasopressors vs Catecholamines Alone With Atrial Fibrillation in Patients With Distributive Shock and Sensitivity Analyses

Group	No. With Events/Total No. of Patients		Risk Difference, % (95% CI)[a]	Relative Risk[a]			Quality of Evidence
	Vasopressin + Catecholamines	Catecholamines Alone		Risk Ratio (95% CI)	*P* Value	I^2 %	
All studies[18,20,24,26-28,30,33-35,39-41]	159/739	215/723	−6 (−13 to 1)	0.77 (0.67 to 0.88)	<.001	1	High
Low risk of bias[18,24,30,34,39,40]	136/559	182/554	−7 (−20 to 5)	0.77 (0.68 to 0.88)	<.001	0	
High risk of bias[20,26-28,33,35,41]	23/180	33/169	−3 (−10 to 4)	0.73 (0.40 to 1.34)	.31	36	
Sepsis[20,24,26-28,30,33-35,39-41,b]	60/580	84/563	−3 (−7 to 1)	0.76 (0.55 to 1.05)	.09	8	
Cardiac surgery[18,28,c]	99/159	131/160	−19 (−29 to −10)	0.77 (0.67 to 0.88)	<.001	0	
Vasopressin[18,24,27,28,30,33-35,39,b,c]	151/621	201/626	−7 (−17 to 3)	0.77 (0.68 to 0.88)	<.001	0	
Vasopressin analogues[20,26,35,40,41,c]	8/118	18/112	−0.05 (−11 to 1)	0.52 (0.18 to 1.51)	.23	28	
Fixed-effect analysis[18,20,24,26-28,30,33-35,39-41,b,c]	159/739	215/723	−7 (−11 to −4)	0.75 (0.65 to 0.86)	<.001	1	

[a] Relative risk <1.0 and risk difference <0.0 favors vasopressin + catecholamines.

[b] Dünser et al, 2003,[28] included patients with both sepsis and post–cardiac surgery vasoplegia, but subgroup data were obtained for atrial fibrillation only. This study was excluded from other outcomes when sepsis and post–cardiac surgery vasoplegia were compared.

[c] Morelli et al, 2009,[35] comprised 3 groups (vasopressin vs terlipressin vs norepinephrine). It was considered as 2 separate trials (vasopressin vs norepinephrine and terlipressin vs norepinephrine) in the comparison between vasopressin and vasopressin analogs. It was considered as a single trial (vasopressin or terlipressin vs norepinephrine) in all other comparisons.

Supplement). This result was driven by the study by Hajjar et al,[18] which carried 74.8% of the weight. In absolute terms, the absolute effect is that 68 fewer people per 1000 patients (95% CI, 36 to 98) will experience atrial fibrillation when vasopressin is added to catecholaminergic vasopressors. In a sensitivity analysis excluding the 7 studies at high risk of bias for lack of blinding of outcome assessors,[20,26-28,33,35] the estimate of effect was unchanged (eAppendix 11 in the Supplement). In a second sensitivity analysis, patients with sepsis and post-cardiac surgery were considered separately. For the subgroup of post-cardiac surgery patients,[18,28] the resultant RR estimate was 0.77 (95% CI, 0.67 to 0.88), not significantly different than in patients with sepsis (RR, 0.76 [95% CI, 0.55 to 1.05], *P* for interaction = .97) (Table 2). Even though the crude rate of atrial fibrillation in this post-cardiac surgery population (73%) was considerably higher than in the sepsis studies (13%), the relative effect estimate was similar in both groups.

Secondary Outcomes

Mortality

Mortality data were available from 17 studies (2904 patients, 1123 events) (Figure 2B). When pooled, the administration of vasopressin in addition to catecholamines was associated with a reduction in mortality (RR, 0.89 [95% CI, 0.82 to 0.97], *P* = .009, I^2 = 0; RD, −0.04 [95% CI, −0.07 to 0.00]). In absolute terms, 45 lives (95% CI, 12 to 73) would be saved per 1000 patients treated with vasopressin. However, when limited to the 2 trials at low risk of bias (**Table 3**),[24,39] the RR estimate was 0.96 (95% CI, 0.84 to 1.11).

Requirement for RRT and Acute Kidney Injury

Six trials with a total of 805 patients (222 events) reported on RRT (**Figure 3**A). When combined, vasopressin was associated with a reduced risk for RRT, but the pooled estimate did not reach statistical significance and showed substantial heterogeneity (RR, 0.74 [95% CI, 0.51 to 1.08], I^2 = 70%; RD, −0.07 [95% CI, −0.12 to −0.01]; moderate-quality evidence). However, when the analysis was limited to the 2 trials at low risk of bias,[24,30] the point estimate was similar, but vasopressin was associated with a significant reduction in the risk of RRT without evidence of heterogeneity (RR, 0.70 [95% CI, 0.53 to 0.92], I^2 = 0%, *P* for interaction = .77).

Myocardial Injury

Eleven studies (1957 patients, 133 events) reported on myocardial injury; 2 trials had event rates of 0 in both groups. There was no significant difference in the risk of myocardial injury with vasopressin (RR, 0.86 [95% CI, 0.63 to 1.17], I^2 = 0%; RD, 0.00 [95% CI, −0.02 to 0.02]; low-quality evidence). After excluding studies at high risk of bias from open-label design,[20,28,33,41] the estimate did not change significantly. Because surrogates were reported for myocardial injury (eg, altered ST segments), indirectness was rated as serious.

Ventricular Arrhythmia, Stroke, and Length of Stay

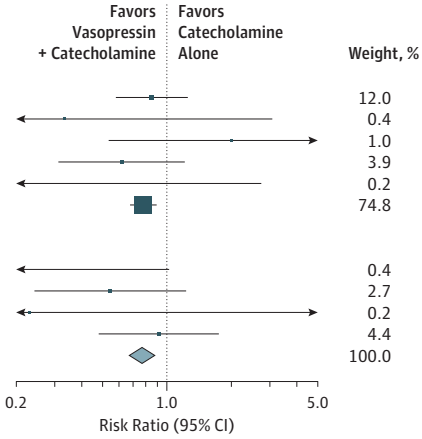
When 9 studies reporting on ventricular arrhythmia were pooled (837 patients, 87 events), the risk was not significantly different with vasopressin (RR, 0.93 [95% CI, 0.73 to 1.19], I^2 = 0%; RD, 0.00 [95% CI, −0.02 to 0.01]; low-quality evidence). There was no significant difference when pooling data from 4 studies (1358 patients, 17 events) reporting on stroke (RR, 1.61 [95% CI, 0.53 to 4.95], I^2 = 7%; RD, 0.01 [95% CI, −0.02 to 0.04]; moderate-quality evidence). LOS data were reported exclusively as medians with interquartile range and were transformed to estimate mean LOS with standard deviation. Hospital LOS was not significantly associated with vasopressin (8 studies, 1939 patients; mean difference, −1.14 days [95% CI, −3.60 to 1.32], I^2=75%; low-quality evidence) (**Table 4**). Similarly, ICU LOS was not significantly associated with vasopressin (mean difference, −0.40 days [95% CI, −1.05 to 0.25], I^2= 24%; moderate-quality evidence) when 11 studies were combined (2156 patients).

Figure 2. Relative Risks of All Trials Comparing Vasopressin + Catecholamines vs Catecholamines Alone for Patients With Distributive Shock

A Atrial fibrillation

Source	Vasopressin + Catecholamine[a] No. With Events	Vasopressin + Catecholamine[a] Total No. of Patients	Catecholamine Alone No. With Events	Catecholamine Alone Total No. of Patients	Risk Ratio (95% CI)	Weight, %
Abdullah et al,[25] 2012	0	17	0	17	Not estimable	
Capoletto et al,[38] 2017	34	125	40	125	0.85 (0.58-1.25)	12.0
Choudhury et al,[29] 2016	1	42	3	42	0.33 (0.04-3.08)	0.4
Clem et al,[30] 2016	6	41	3	41	2.00 (0.54-7.46)	1.0
Dünser et al,[39] 2003	8	24	13	24	0.62 (0.31-1.21)	3.9
Gordon et al,[20] 2016	0	205	3	204	0.14 (0.01-2.73)	0.2
Hajjar et al,[18] 2017	95	149	124	151	0.78 (0.67-0.89)	74.8
Lauzier et al,[21] 2006	0	13	0	13	Not estimable	
Malay et al,[33] 1999	0	5	0	5	Not estimable	
Morelli et al,[35] 2009	1	30	4	15	0.13 (0.02-1.02)	0.4
Russell et al,[22] 2008	7	44	14	48	0.55 (0.24-1.23)	2.7
Russell et al,[23] 2017	0	31	1	21	0.23 (0.01-5.37)	0.2
Svoboda et al,[37] 2012	7	13	10	17	0.92 (0.48-1.74)	4.4
Total events (95% CI)	159	739	215	723	0.77 (0.67-0.88)	100.0

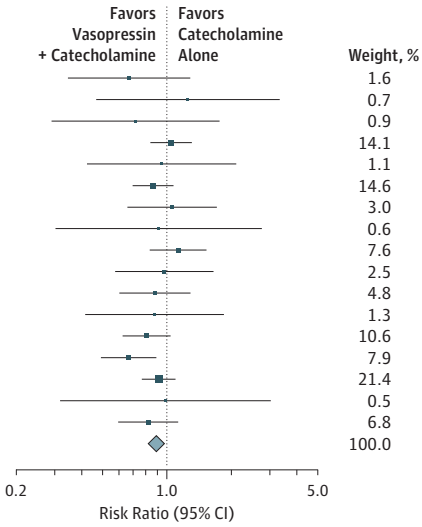
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_9 = 9.10$ ($P = .43$); $I^2 = 1\%$
Overall effect: $z = 3.79$ ($P < .001$)



B 28-d or 30-d mortality

Source	Vasopressin + Catecholamine[a] No. With Events	Vasopressin + Catecholamine[a] Total No. of Patients	Catecholamine Alone No. With Events	Catecholamine Alone Total No. of Patients	Risk Ratio (95% CI)	Weight, %
Acevedo et al,[26] 2009	6	12	9	12	0.67 (0.35-1.28)	1.6
Albanese et al,[27] 2005	5	10	4	10	1.25 (0.47-3.33)	0.7
Barzegar et al,[28] 2014	5	15	7	15	0.71 (0.29-1.75)	0.9
Capoletto et al,[38] 2017	71	125	68	125	1.04 (0.84-1.30)	14.1
Chen et al,[40] 2017	9	31	8	26	0.94 (0.43-2.09)	1.1
Choudhury et al,[29] 2016	31	42	36	42	0.86 (0.69-1.07)	14.6
Clem et al,[30] 2016	19	41	18	41	1.06 (0.65-1.70)	3.0
Fonseca Ruiz et al,[34] 2013	4	14	5	16	0.91 (0.30-2.75)	0.6
Gordon et al,[20] 2016	63	204	56	204	1.13 (0.83-1.52)	7.6
Hajjar et al,[18] 2017	23	149	24	151	0.97 (0.57-1.64)	2.5
Han et al,[31] 2012	27	66	34	73	0.88 (0.60-1.28)	4.8
Hua et al,[32] 2013	7	16	8	16	0.88 (0.42-1.84)	1.3
Oliveira et al,[36] 2014	65	191	83	196	0.80 (0.62-1.04)	10.6
Prakash et al,[41] 2017	37	91	57	93	0.66 (0.49-0.89)	7.9
Russell et al,[22] 2008	144	404	154	395	0.91 (0.76-1.09)	21.4
Russell et al,[23] 2017	6	29	4	19	0.98 (0.32-3.03)	0.5
Svoboda et al,[37] 2012	10	13	16	17	0.82 (0.59-1.13)	6.8
Total events (95% CI)	532	1453	591	1451	0.89 (0.82-0.97)	100.0

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{16} = 11.29$ ($P = .79$); $I^2 = 0\%$
Overall effect: $z = 2.62$ ($P = .009$)



The relative risks were calculated using a random-effects model with Mantel-Haenszel weighting. The size of data markers indicates the weight of the study. Error bars indicate 95% CIs.

[a] Vasopressin (or analogue [ie, terlipressin, selepressin, or pituitrin]) + catecholamine vasopressors.

Post Hoc Outcomes

Digital Ischemia

When 9 studies (1963 patients, 58 events) were pooled (Figure 3B), vasopressin in addition to catecholamines was associated with a significant increase in digital ischemia (RR, 2.38 [95% CI, 1.37 to 4.12], I^2 = 0; RD, 0.02 [95% CI, −0.01 to 0.04]; moderate-quality evidence). In absolute terms, this means 24 more occurrences (95% CI, 6 to 55) of digital ischemia per 1000 patients treated with vasopressin. When the 4 studies at high risk of bias were excluded,[23,26,29,41] the resultant estimate was not significantly different. Definitions varied for this outcome; however, when the analysis was limited to the 6 studies that specifically described "digital ischemia,"[18,23,29,30,39,40] the resultant estimate did not change significantly. Thus, evidence was not downgraded for indirectness but, because it was a post hoc outcome, it was downgraded for risk of bias.

Acute Kidney Injury

In a sensitivity analysis, the treatment effect for RRT was consistent, but not statistically significant when the definition was modified to acute kidney injury (5 trials; RR, 0.73 [95% CI, 0.46 to 1.17], I^2 = 91%).

Publication Bias

The assessment of publication bias was limited by small numbers of studies for most outcomes (eAppendix 12 in the Supplement). Visual inspection did not lead to concerns about publication bias.

Table 3. Binary Outcomes and Sensitivity Analyses for Vasopressin + Catecholamines vs Catecholamines Alone in Patients With Distributive Shock

Group	No. With Events/Total No. of Patients		Risk Difference % (95% CI)[a]	Relative Risk[a]			Quality of Evidence (Reason for Judgment)
	Vasopressin + Catecholamines	Catecholamines Alone		Risk Ratio (95% CI)	*P* Value	I^2 %	
28-d or 30-d Mortality							
All studies[18,21-27,29-32,36,38-41]	532/1453	591/1451	−4 (−7 to 0)	0.89 (0.82 to 0.97)	.009	0	Low (risk of bias)
Low risk of bias[24,39]	215/529	222/520	−2 (−8 to 4)	0.96 (0.84 to 1.11)	.6	0	
High risk of bias[18,21-23,25-27,29-32,36,38,40,41]	317/924	369/931	−4 (−8 to 0)	0.86 (0.77 to 0.95)	.004	0	
28-d or 30-d or ICU mortality[18,21-36,38-41,b,c]	567/1525	623/1505	−4 (−7 to −1)	0.89 (0.83 to 0.97)	.006	0	
Full text only[18,22,23,25,26,29-32,39-41,d]	334/993	356/984	−2 (−6 to 2)	0.91 (0.82 to 1.01)	.09	0	
Vasopressin[23,24,27,29,30,36,39,41,b]	404/1156	431/1160	−2 (−6 to 2)	0.94 (0.85 to 1.04)	.21	0	
Vasopressin analogues[21,22,25,26,31,32,38,40,41,b]	128/297	160/291	−10 (−18 to −3)	0.81 (0.70 to 0.94)	.005	0	
Sepsis[21-27,29-32,36,38-41]	509/1304	567/1300	−4 (−8 to −1)	0.89 (0.82 to 0.97)	.008	0	
Cardiac surgery[18]	23/149	24/151	−0 (−9 to 8)	0.97 (0.57 to 1.64)	.91	NA	
Requirement for Renal Replacement Therapy							
All studies[23,24,28,30,33,35,b,e]	97/412	125/393	−7 (−12 to −1)	0.74 (0.51 to 1.08)	.12	70	Moderate (imprecision)
Low risk of bias[24,30]	62/330	89/329	−7 (−13 to −2)	0.70 (0.53 to 0.92)	.01	0	
High risk of bias[23,28,33,35,b,c]	35/82	36/64	−5 (−16 to 7)	0.77 (0.42 to 1.43)	.41	67	
AKI as outcome[18,21,24,28,30,b]	154/515	204/516	−8 (−21 to 6)	0.73 (0.46 to 1.17)	.19	91	
Vasopressin[23,24,28,30,33,35,b,e]	93/397	125/393	−6 (−11 to −1)	0.76 (0.53 to 1.10)	.15	68	
Vasopressin analogues[35,b,e]	4/15	8/15	−27 (−60 to 7)	0.50 (0.19 to 1.31)	.16	NA	
Digital Ischemia							
All studies[18,23,24,26,29,30,39-41]	41/990	17/973	2 (−1 to 4)	2.38 (1.37 to 4.12)	.002	0	Moderate (post hoc outcome)
Low risk of bias[18,24,30,39,40]	23/906	9/883	1 (−1 to 3)	2.45 (1.10 to 5.43)	.03	0	
High risk of bias[23,26,29,41]	18/84	8/90	10 (0 to 19)	2.31 (1.08 to 4.94)	.03	0	
Defined as digital ischemia[18,23,29,30,33,39,40,f]	25/810	8/789	2 (0 to 3)	2.73 (1.27 to 5.87)	.01	0	
Vasopressin[18,23,24,29,30,33,39,b]	24/904	10/893	1 (−1 to 3)	2.35 (1.10 to 5.05)	.03	0	
Vasopressin analogues[26,40,41,b]	17/86	7/80	10 (−4 to 25)	2.40 (1.09 to 5.31)	.03	0	
Myocardial Injury							
All studies[18,20,24,28,30,33,34,37,39-41,b]	62/991	71/966	0 (−2 to 2)	0.86 (0.63 to 1.17)	.34	0	Low (indirectness, imprecision)
Low risk of bias[18,24,30,34,37,39,40]	61/924	66/899	1 (−1 to 3)	0.89 (0.64 to 1.25)	.52	4	
High risk of bias[20,28,33,41,b]	1/67	5/67	−5 (−12 to 3)	0.37 (0.07 to 1.95)	.24	0	
Sepsis[20,24,28,30,33,34,37,39-41,b]	51/818	51/791	1 (−1 to 2)	0.94 (0.67 to 1.32)	.71	0	
Cardiac surgery[18]	11/149	17/151	−4 (−10 to 3)	0.66 (0.32 to 1.35)	.25	NA	
Vasopressin[18,24,28,30,33,34,37,39,b]	61/930	70/912	0 (−3 to 2)	0.87 (0.61 to 1.23)	.42	6	
Vasopressin analogues[20,40,41,b]	1/61	1/54	1 (−6 to 7)	0.91 (0.10 to 8.33)	.93	0	
Ventricular Arrhythmia							
All studies[18,20,24,26,27,33,34,37,41]	39/418	48/419	0 (−2 to 1)	0.93 (0.73 to 1.19)	.55	0	Low (indirectness, imprecision)
Low risk of bias[18,34,37]	27/167	32/167	−2 (−10 to 5)	0.86 (0.54 to 1.35)	.50	NA	
High risk of bias[20,24,26,27,33,41]	12/251	16/252	0 (−1 to 1)	0.96 (0.72 to 1.28)	.78	0	
Vasopressin[18,24,27,33,34,37,b]	28/346	32/343	0 (−1 to 2)	0.88 (0.56 to 1.38)	.57	0	
Vasopressin analogues[20,26,41,b]	11/72	16/76	−2 (−7 to 3)	0.95 (0.71 to 1.27)	.73	0	
Stroke							
All studies[18,24,39,41]	11/683	6/675	1 (−2 to 4)	1.61 (0.53 to 4.95)	.40	7	Moderate (imprecision)
Low risk of bias[18,24,39]	11/670	6/658	1 (−2 to 4)	1.61 (0.53 to 4.95)	.40	7	
High risk of bias[41]	0/13	0/17	0 (−12 to 12)	NA	NA	NA	
Vasopressin[18,24,39,b]	11/670	6/658	1 (−2 to 4)	1.61 (0.53 to 4.95)	.40	7	
Vasopressin analogues[41,b]	0/13	0/17	0 (−12 to 12)	NA	NA	NA	

Abbreviation: AKI, acute kidney injury.

[a] Relative risk <1.0 and risk difference <0.0 favors vasopressin + catecholamines.

[b] Dünser et al, 2003,[28] included patients with both sepsis and post–cardiac surgery vasoplegia, but subgroup data were obtained for atrial fibrillation only. This study was excluded from other outcomes when sepsis and post–cardiac surgery vasoplegia were compared.

[c] Added 4 studies that reported on ICU mortality.

[d] "Full text only" refers to studies not published only as abstracts.

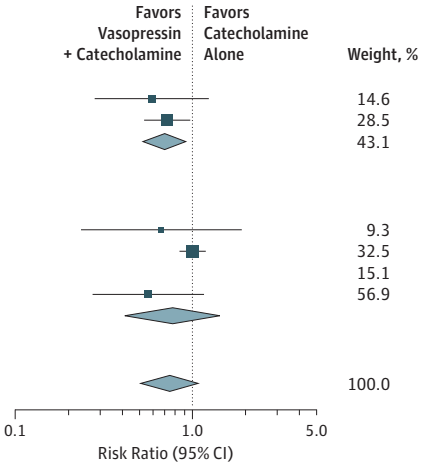
[e] Morelli et al, 2009,[35] comprised 3 groups (vasopressin vs terlipressin vs norepinephrine). It was considered as 2 separate trials (vasopressin vs norepinephrine and terlipressin vs norepinephrine) in the comparison between vasopressin and vasopressin analogs. It was considered as a single trial (vasopressin or terlipressin vs norepinephrine) in all other comparisons.

[f] Includes only studies in which the authors described the outcome as digital ischemia. Peripheral cyanosis and limb ischemia were excluded.

Figure 3. Relative Risks of All Trials Comparing Vasopressin + Catecholamines vs Catecholamines Alone for Patients With Distributive Shock

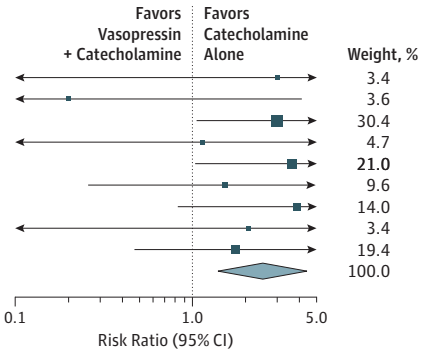
A Requirement of renal replacement therapy

Source	Vasopressin + Catecholamine[a] No. With Events	Vasopressin + Catecholamine[a] Total No. of Patients	Catecholamine Alone No. With Events	Catecholamine Alone Total No. of Patients	Risk Ratio (95% CI)
Low risk of bias[b]					
Capoletto et al,[38] 2017	10	125	17	125	0.59 (0.28-1.23)
Gordon et al,[20] 2016	52	205	72	204	0.72 (0.53-0.97)
Total events (95% CI)	62	330	89	329	0.70 (0.53-0.92)
Heterogeneity: $\tau^2=0.00$; $\chi^2_1=.24$ ($P=.62$); $I^2=0\%$					
Overall effect: $z=2.53$ ($P=.01$)					
High risk of bias[b]					
Barzegar et al,[28] 2014	4	15	6	15	0.67 (0.23-1.89)
Dünser et al,[39] 2003	22	24	22	24	1.00 (0.84-1.19)
Lauzier et al,[21] 2006	0	13	0	10	Not estimable
Morelli et al,[35] 2009	9	30	8	15	0.56 (0.27-1.16)
Total events (95% CI)	35	82	36	64	0.77 (0.42-1.43)
Heterogeneity: $\tau^2=0.19$; $\chi^2_2=5.99$ ($P=.05$); $I^2=67\%$					
Overall effect: $z=0.82$ ($P=.41$)					
Total (95% CI)	97	412	125	393	0.74 (0.51-1.08)
Heterogeneity: $\tau^2=0.10$; $\chi^2_4=13.51$ ($P=.009$); $I^2=70\%$					
Overall effect: $z=1.56$ ($P=.12$)					
Subgroup differences: $\chi^2_1=0.09$ ($P=.77$); $I^2=0\%$					



B Digital ischemia

Source	Vasopressin + Catecholamine[a] No. With Events	Vasopressin + Catecholamine[a] Total No. of Patients	Catecholamine Alone No. With Events	Catecholamine Alone Total No. of Patients	Risk Ratio (95% CI)
Barzegar et al,[28] 2014	1	15	0	15	3.00 (0.13-68.26)
Capoletto et al,[38] 2017	0	125	2	125	0.20 (0.01-4.12)
Choudhury et al,[29] 2016	12	42	4	42	3.00 (1.05-8.55)
Fonseca Ruiz et al,[34] 2013	1	14	1	16	1.14 (0.08-16.63)
Gordon et al,[20] 2016	**11**	**205**	**3**	**204**	**3.65 (1.03-12.89)**
Hajjar et al,[18] 2017	3	149	2	151	1.52 (0.26-8.97)
Russell et al,[22] 2008	8	396	2	382	3.86 (0.82-18.05)
Russell et al,[23] 2017	1	31	0	21	2.06 (0.09-48.34)
Svoboda et al,[37] 2012	4	13	3	17	1.74 (0.47-6.47)
Total events (95% CI)	41	990	17	973	2.38 (1.37-4.12)
Heterogeneity: $\tau^2=0.00$; $\chi^2_8=4.36$ ($P=.82$); $I^2=0\%$					
Overall effect: $z=3.09$ ($P=.002$)					



The relative risks were calculated using a random-effects model with Mantel-Haenszel weighting. The size of data markers indicates the weight of the study. Error bars indicate 95% CIs.

[a] Vasopressin (or analogue [ie, terlipressin, selepressin, or pituitrin]) + catecholamine vasopressors.

[b] Risk of bias categories for requirement for renal replacement therapy are the same as those for atrial fibrillation, as summarized in Table 1.

Discussion

In this systematic review and meta-analysis of randomized clinical trials, the administration of vasopressin in addition to catecholamine vasopressors in patients with distributive shock was associated with a significant reduction in the risk of atrial fibrillation when compared with catecholamines alone (high-quality evidence). Findings for other outcomes were not consistent. Although when all studies were combined the risk of mortality was lower with the addition of vasopressin, a sensitivity analysis limited to low risk of bias trials yielded a relative risk much closer to 1 and was not statistically significant.

To our knowledge, this systematic review is the first on the topic to include atrial fibrillation as an outcome. Prior reviews assessed arrhythmia,[42,43] but this outcome has limited utility due to the variety of conditions that could be found under this heading. The reduction in atrial fibrillation associated with vasopressin was consistent across 2 subtypes of distributive shock and in sensitivity analyses restricted to studies at low risk of bias.

Vasopressin may have contributed to a reduction of atrial fibrillation by sparing the adrenergic stimulation provided by catecholaminergic vasopressors.[6-8,14] This could have manifested in fewer patients developing atrial fibrillation or may have caused atrial fibrillation to be shorter in duration and lower in rate and, in consequence, less likely to be detected.

The approach to monitoring and ascertainment of atrial fibrillation in patients who are acutely ill affects the detection of this outcome.[44] This limitation would need to be addressed to more precisely estimate event rates in this population and their association with vasopressin treatment.

Table 4. Continuous Outcomes and Sensitivity Analyses for Vasopressin + Catecholamines vs Catecholamines Alone in Patients With Distributive Shock

Group	Mean Length of Stay in Days (SD)[a]		Mean Difference (95% CI), d[b]	*P* Value	I^2 %	Quality of Evidence (Reason for Judgment)
	Vasopressin + Catecholamines	Catecholamines Alone				
Hospital Length of Stay						
All studies[18,20,22,29,32,34,38,40]	21.3 (23.0)	22.6 (22.9)	−1.14 (−3.60 to 1.32)	.36	75	Low (imprecision, inconsistency)
Low risk of bias[18,24,30,39]	22.0 (24.1)	23.3 (23.8)	−1.83 (−4.47 to 0.81)	.17	69	
High risk of bias[29,32,34,40]	15.7 (8.6)	16.6 (11.1)	−0.45 (−4.40 to 3.50)	.82	62	
Vasopressin[18,24,29,30,39,c]	21.8 (24.0)	23.4 (23.7)	−2.33 (−5.05 to 0.40)	.09	67	
Vasopressin analogs[29,32,40,c]	16.1 (7.7)	14.9 (8.5)	1.03 (−1.48 to 3.53)	.42	22	
Intensive Care Unit Length of Stay						
All studies[18,20,22,28,29,31,32,35,38,39]	11.1 (12.2)	11.6 (13.4)	−0.40 (−1.05 to 0.25)	.23	24	Moderate (imprecision)
Low risk of bias[18,24,30,39]	11.2 (12.7)	12.2 (14.1)	−0.54 (−1.33 to 0.25)	.18	34	
High risk of bias[28,29,31,32,35,39,40]	10.4 (10.2)	9.4 (8.5)	−0.12 (−1.37 to 1.13)	.85	22	
Vasopressin[18,23,24,28,30,35,39,c]	11.8 (13.0)	12.4 (14.0)	−0.24 (−1.27 to 0.79)	.65	44	
Vasopressin analogues[29,31,32,35,40,c]	7.9 (7.0)	7.9 (7.0)	−0.38 (−1.33 to 0.58)	.44	0	

[a] Mean length of stay was weighted by the number of patients.

[b] Mean difference <0.0 favors vasopressin + catecholamines.

[c] Morelli et al, 2009,[35] comprised 3 groups (vasopressin vs terlipressin vs norepinephrine). It was considered as 2 separate trials (vasopressin vs norepinephrine and terlipressin vs norepinephrine) in the comparison between vasopressin and vasopressin analogs. It was considered as a single trial (vasopressin or terlipressin vs norepinephrine) in all other comparisons.

The clinical significance of atrial fibrillation in this population is not fully understood.[44] Where atrial fibrillation in patients who are critically ill has been associated with worse outcomes, including death, causality has not been proven and the consequences on long-term prognosis in survivors are unknown.[10,11,44]

This review is one of few reviews to directly compare vasopressin + catecholamines against the current standard of care—catecholamines alone. Two systematic reviews with network meta-analyses found no difference in mortality in any comparison, including between vasopressin or terlipressin and norepinephrine.[42,43] Another systematic review and meta-analysis concluded that treatment with noncatecholaminergic agents (including vasopressin and methylene blue) improved survival (RR, 0.88 [95% CI, 0.79 to 0.98]) in patients experiencing or "at risk" for distributive shock.[45] In another systematic review and meta-analysis, mortality was significantly lower in patients with septic shock treated with vasopressin or terlipressin compared with norepinephrine (RR, 0.87 [95% CI, 0.78 to 0.97]).[46] However, that review included 4 substudies of the Vasopressin and Septic Shock Trial (VASST) in the meta-analysis of mortality and did not assess evidence using GRADE.[19,39,47]

The theoretical basis for vasopressin administration stems from research identifying relative vasopressin deficiency in patients with distributive shock.[13] Vasopressin administration could lower mortality by decreasing the need for catecholaminergic drugs and reducing their adverse effects including arrhythmia, preferentially perfusing the brain and renal vascular bed—the latter leading to reductions in acute kidney injury—and decreasing activation of both the renin-aldosterone-angiotensin system and neurohormonal processes, inhibiting proinflammatory cytokines, improving calcium handling, and potentiating endogenous glucocorticoids.[47-50]

For clinicians aiming for MAP, maintaining adequate blood flow while mitigating the risk of excessive vasoconstriction (the likely mechanism of digital ischemia) is also important. An understanding of the clinical effect of these events (ie, did they simply precipitate drug discontinuation or did they lead to permanent disability?) would be needed to evaluate trade-off against a decrease in mortality.

This systematic review also evaluated requirement for RRT. The significant reduction in need for RRT with vasopressin was limited to the pooled estimate for low risk of bias studies. Renal protection related to reduced activation of the renin-aldosterone-angiotensin system is one of the hypothesized benefits of vasopressin in distributive shock; creatinine clearance has been shown to improve when vasopressin was started early after the onset of distributive shock.[33]

This review included data from the relatively large and recently published Vasopressin vs Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery (VANCS) and Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock (VANISH) trials (751 patients total).[18,30] Combining subtypes of distributive shock and considering vasopressin analogs allowed the inclusion of a larger number of studies. Bias in the review process was reduced by searching multiple databases without language restriction. Significant attempts were made to obtain clarification of published data and access to unpublished data.

Limitations

This study has several limitations. First, subgroup analyses were restricted by the study-level nature of the data. Second, the quality of reporting for many studies was not sufficient to permit definitive judgments about risk of bias in all

domains. Third, there are likely differences in the way vasopressors were initiated, titrated, and weaned between studies and approaches were infrequently described in detail. However, the general approach seemed to be to up-titrate vasopressin until the maximum dose or target MAP was reached and then to add or wean norepinephrine as needed to reach the target MAP.

Conclusions

In this meta-analysis, the addition of vasopressin to catecholamine vasopressors compared with catecholamines alone was associated with a lower risk of atrial fibrillation. However, findings for secondary outcomes varied.

ARTICLE INFORMATION

Accepted for Publication: April 5, 2018.

Author Contributions: Drs Belley-Côté and McIntyre (McMaster University) had full access to all the data in the study, conducted the analyses, and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: McIntyre, Whitlock, Belley-Côté.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: McIntyre, Belley-Côté.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: McIntyre, Um, Whitlock, Belley-Côté.
Administrative, technical, or material support: McIntyre, Um, Lengyel, Gordon, Whitlock.
Supervision: Alhazzani, Hajjar, Healey, Whitlock, Belley-Côté.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr McIntyre reported receiving grant funding from the Canadian Stroke Prevention Intervention Network and being a trainee member of the Cardiac Arrhythmia Network of Canada. Dr Gordon reported receiving grant funding from the National Institute for Health Research and Tenax Therapeutics; personal fees and nonfinancial support from Orion Pharma, Tenax Therapeutics, Ferring Pharmaceuticals, GlaxoSmithKline, and Bristol-Myers Squibb; and personal fees from Amomed Pharma. Dr Healey reported receiving grant funding from Medtronic and Bristol-Meyers Squibb/Pfizer. Dr Belley-Côté reported receiving grant funding from the Canadian Institutes of Health Research. No other disclosures were reported.

Additional Contributions: We thank the Guidelines in Intensive Care Development and Evaluation (GUIDE) Group (McMaster University) for methodological support; Neera Bhatnagar, MLIS (McMaster Health Sciences Library), for reviewing our search strategy; Yongning Ou, MSc (Population Health Research Institute), Shuhua Luo (Sick Kids Hospital), and Kevin An (McMaster University) for their assistance in assessing articles written in Chinese; the members of the McMaster Interdisciplinary Investigative Outcomes Node—Cardiac Sciences, Intensive Care and Anesthesia (McMaster University), for their methodological support; Bram Rochwerg, MD, MSc, Nancy Santesso, PhD, and Romina Brignardello-Petersen, PhD (all at McMaster University), for their tutoring and methodological support; and Kelsey McIntyre, RN (Hamilton Health Sciences), for her assistance with proofreading and data entry. They did not receive compensation for their contributions.

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