Angiotensin II for the Treatment of Refractory Shock: A Matched Analysis*

Lane M. Smith, MD, PhD[1]
Graciela B. Mentz, PhD[2]
Milo C. Engoren, MD[1]

OBJECTIVES: To determine if angiotensin II is associated with improved outcomes as measured by 30- and 90-day mortality as well as other secondary outcomes such as organ dysfunction and adverse events.

DESIGN: Retrospective, matched analysis of patients receiving angiotensin II compared with both historical and concurrent controls receiving equivalent doses of nonangiotensin II vasopressors.

SETTING: Multiple ICUs in a large, university-based hospital.

PATIENTS: Eight hundred thirteen adult patients with shock admitted to an ICU and requiring vasopressor support.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Angiotensin II use had no association with the primary outcome of 30-day mortality (60% vs 56%; $p = 0.292$). The secondary outcome of 90-day mortality was also similar (65% vs 63%; $p = 0.440$) as were changes in Sequential Organ Failure Assessment scores over a 5-day monitoring period after enrollment. Angiotensin II was not associated with increased rates of kidney replacement therapy (odds ratio [OR], 1.39; 95% CI, 0.88–2.19; $p = 0.158$) or receipt of mechanical ventilation (OR, 1.50; 95% CI, 0.41–5.51; $p = 0.539$) after enrollment, and the rate of thrombotic events was similar between angiotensin II and control patients (OR, 1.02; 95% CI, 0.71–1.48; $p = 0.912$).

CONCLUSIONS: In patients with severe shock, angiotensin II was not associated with improved mortality or organ dysfunction and was not associated with an increased rate of adverse events.

KEY WORDS: angiotensin; kidney replacement therapy; mortality; shock; vasopressor agents

Distributive shock is a life-threatening condition characterized by peripheral vasodilatation and impaired tissue perfusion (1, 2). It accounts for more than 270,000 deaths and 1.7 million hospitalizations annually in the United States (3). Treatment of distributive shock involves restoration of tissue perfusion with IV fluids and vasopressors while correcting underlying causes (4–6).

Approved by the Food and Drug Administration (FDA) in 2017, angiotensin II (AT2) is an endogenous vasoconstrictor that acts via the renin-angiotensin-aldosterone system (RAAS) to increase blood pressure through direct vasoconstriction, augmenting sympathetic activity, and promoting fluid retention (7). AT2 was shown to improve blood pressure in catecholamine-resistant distributive shock among patients receiving high doses of norepinephrine equivalents (NEs) in the Angiotensin II for the Treatment of Vasodilatory Shock (ATHOS-3) trial (8). However, this trial required invasive testing for inclusion that is rarely performed outside of a clinical trial and was designed to determine if AT2 could improve

*See also p. 1821.

DOI: 10.1097/CCM.0000000000005975

KEY POINTS

Question: Does the addition of angiotensin II improve 30-day mortality in patients with severe, refractory shock requiring high doses of vasopressors.

Findings: In this retrospective, matched analysis of patients with refractory shock receiving angiotensin II compared with both historical and concurrent controls, the addition of angiotensin II was not associated with a statistically significant improvement in 30-day mortality.

Meaning: Angiotensin II was not associated with improved outcomes in refractory shock when used as a salvage therapy but further studies are needed to determine if it improves outcomes as a first- or second-line vasopressor.

blood pressure as the primary outcome. Importantly, it did not find a difference in mortality. These limitations in the ATHOS-3 trial resulted in AT2 often being used as a form of salvage therapy in refractory shock and in a manner different than the parent trial (9–13).

Subgroup analysis of the ATHOS-3 data suggest improvements in mortality from AT2 use in patients receiving kidney replacement therapy (KRT), with severe shock, with elevated plasma renin levels, and those having nondistributive shock (14–16). Recently, Quan et al (13) retrospectively studied 56 patients who received AT2 as a third-line vasopressor and 91 similar patients in shock treated without AT2 and found no difference in mortality (86% vs 71%; $p = 0.16$).

Given that both the prospective ATHOS-3 trial and the retrospective trial by Quan et al (13) were underpowered to find clinically significant differences in mortality, we undertook a retrospective analysis with sufficient power to determine if AT2 use in shock was associated with a difference in mortality. We hypothesized that there were no differences in the primary outcome of 30-day mortality or secondary outcomes between patients receiving AT2 or other vasopressors.

MATERIALS AND METHODS

Study Design and Setting

This is a retrospective matched cohort study of adult patients with shock admitted to an ICU at a large, university-based health system between 2016 and 2022. The system admits 48,000 patients and performs more than 50,000 surgeries each year. Typically, norepinephrine is used as the first-line vasopressor for distributive shock. Norepinephrine is usually titrated up to 0.20 μg/kg/min at which time vasopressin is added. Attempts to order vasopressin at norepinephrine doses less than 0.15 μg/kg/min result in a "best practices advisory" in the medical record that must be answered to complete the order. Vasopressin is typically started at 0.03 U/min and may be increased up to 0.083 U/min. Epinephrine is typically initiated for inotropy but is sometimes added when other vasopressors are inadequate. Phenylephrine and dopamine are used less commonly. The hospital has no restrictions on the use of AT2, leaving it to the physicians' discretion but it was typically started after vasopressin for refractory shock. Venous thromboembolism prophylaxis at our institution followed published guidelines (17). The study was approved by our Institutional Review Board (IRB) with a waiver of informed consent (University of Michigan IRB No. HUM005206; reapproval date: December 6, 2021). The study procedures were followed in accordance with the IRBs ethical standards on human experimentation and the Helsinki Declaration of 1975.

Data Extraction

We used DataDirect (University of Michigan, Ann Arbor, MI) to extract relevant information from the health system's electronic data warehouse (Epic, Verona, WI). Adult patients (≥ 18 yr old) were included if they received an IV infusion of norepinephrine, epinephrine, phenylephrine, vasopressin, dopamine, or AT2 in the ICU between January 1, 2016, and February 28, 2022, for treatment of shock. We excluded patients if AT2 was initiated in the operating room. Two control populations were identified, one historical and the other concurrent, to account for possible changes in practice once AT2 became available. We defined historical controls as patients who received vasopressors before AT2 was available between January 1, 2016, and March 14, 2018. Patients who received vasoconstrictors other than AT2 after March 14, 2018 (when AT2 first became available in our hospital) were defined as concurrent controls.

Doses of epinephrine, phenylephrine, vasopressin, and dopamine were converted to NEs (**Table S1**, http://links.lww.com/CCM/H368) and summed at each time

to determine the total NE dose as μg/kg/min (8, 18, 19). For patients who received AT2, the NE dose at AT2 initiation was recorded and the patients were then matched to both a concurrent and an historical control patient with the same NE dose ± 0.005 μg/kg/min. If there was more than one concurrent or one historical potential match, one was selected at random.

We extracted demographics, vital signs, and laboratory values, receipt of KRT, and receipt of mechanical ventilation from the data warehouse. Baseline values were collected within 24 hours of enrollment. Mean arterial pressure (MAP) and Sequential Organ Failure Assessment (SOFA) score values were calculated for a 5-day monitoring period after enrollment in all three cohorts (20). Culture and antibiotic use were extracted to determine a diagnosis of septic shock according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (21). Hemorrhagic shock was defined as shock associated with acute blood loss and activation of a massive transfusion protocol. Vasoplegic shock was defined at MAP less than 65 mm Hg with central or mixed venous oxygen saturation greater than 70% or cardiac index greater than or equal to 2.3 L/min/BSA m^2 or central venous pressure less than 8 mm Hg prior to enrollment without criteria for sepsis (8). Other shock was defined as MAP less than 65 mm Hg with central or mixed venous saturation less than 70% or cardiac index less than 2.3 L/min/BSA m^2 or central venous pressure greater than or equal to 8 mm Hg without criteria for sepsis. *International Statistical Classification of Diseases*, 10th Revision codes (**Table S2**, http://links.lww.com/CCM/H368) and data from the Michigan Death Index were used to determine complications and determine mortality.

Outcomes

The primary outcome was 30-day mortality from all causes. Secondary outcomes were 90-day mortality and receipt of new onset KRT and mechanical ventilation in patients not receiving KRT or mechanical ventilation prior to study enrollment. Tertiary outcomes were the mortality-adjusted SOFA (MA-SOFA) scores; major thrombotic events occurring within 30 days of enrollment consisting of venous thromboembolism, acute coronary syndrome, mesenteric ischemia, and stroke; and ventilator-free days. MA-SOFA score was calculated so that patients who expired during the 5-day monitoring of SOFA scores were assigned the maximum score of 24 for the remaining days. Ventilator-free days were calculated as days alive and free from ventilation to day 30. Patients not surviving to day 30 were assigned zero ventilator-free days. We then performed a subgroup analysis evaluating patients with septic shock to control for confounding from nondistributive shock. We also performed a sensitivity analysis using only concurrent controls. In these two sets of analyses, we determined the association of AT2 use with 30-day and 90-day mortality as well as receipt of new onset KRT and mechanical ventilation prior to study enrollment.

Statistical Analysis

The historical and concurrent cohorts of non-AT2 patients were combined into one control group. Standard exploratory data analysis techniques such as frequency distribution were used to assess the distribution of outcome measures (primary and secondary), identification of extreme values. Analysis of missing patterns and rates was conducted. Missing rates were less than 5% and complete case analysis was deemed to provide unbiased estimates. Univariate comparisons were made with standardized differences (SDiffs) and with chi-square test for categorical variables and independent *t* test for continuous variables. To test our hypothesis of no difference in 30-day mortality of patients receiving AT2 versus other vasoconstrictors, we used the Generalized Estimating Equation (GEE) approach adjusting for basic demographics, NE equivalent dose, time to study enrollment (AT2 initiation or time to the same NE equivalent dose in the non-AT2 patients), number of vasopressors, comorbidities, laboratory values, SOFA score calculated at study enrollment, cultures, type of sepsis, and processes of care. An unstructured working correlation matrix with logit link was used. Similarly, GEE models were constructed for the other outcomes. Where the number of patients in the analysis was decreased (analyses of subgroups and of secondary or tertiary outcomes), to prevent overfitting of the models, we reduced the number of variables in the model using SDiffs and clinical relevance to inform the choice. SDiffs greater than 0.10 or less than −0.10 were deemed clinically significant and *p* value of less than 0.05 denoted statistical significance. SAS (SAS Institute, Cary, NC) was used for all analyses.

Power Calculation

Based on the ATHOS-3 trial, which found an absolute difference in mortality of 8% between the AT2 patients and controls at 7 days, we estimated that 198 AT2 patients and 396 control patients (1:2 ratio) would provide us with 90% power to detect the same 8% difference in mortality using the equivalence test for difference between two correlated proportions (PASS Software, NCSS Statistical Software, Kaysville, UT) (8).

RESULTS

Demographics and Clinical Characteristics

We identified 21,011 unique ICU patient visits requiring vasopressor support between January 1, 2016, and February 28, 2022. Patients were more commonly male (n = 11,672, 60%) and White (n = 15,718, 81%) with mean age was 61 ± 16 years. In this cohort, 271 patients received AT2, and we identified an equal number of NE-matched concurrent and historical controls for a total of 542 control patients (**Fig. S1**, http://links.lww.com/CCM/H368).

Pre-enrollment NE equivalent dosing was well-balanced (SDiff = 0.004; p = 0.956) between the AT2 and controls (**Table 1**). **Figure S2*A–C*** (http://links.lww.com/CCM/H368) illustrates the distribution of NE equivalent dosing in the study cohorts. **Figure S3**, ***A*** and ***B*** (http://links.lww.com/CCM/H368) illustrate the initial and maximum doses of AT2. Patients receiving AT2 had a higher SOFA score (12 ± 3 vs 10 ± 4; SDiff = 0.614; p < 0.001), lower MAP (69 ± 15 vs 73 ± 18 mm Hg; SDiff = –0.221; p = 0.004), and were more likely to be diagnosed with septic shock (69 ± 15 vs 73 ± 18 mm Hg; SDiff = –0.221; p = 0.004) (**Table S3**, http://links.lww.com/CCM/H368). They also had higher rates of chronic illnesses, higher lactate (8.5 ± 5.9 vs 5.9 ± 5.3 mg/dL; SDiff = 0.45; p < 0.001) and creatinine (2.2 ± 1.6 vs 2.0 ± 1.4 mg/dL; SDiff = 0.16; p = 0.012) values and were more likely to have received mechanical ventilation (92% vs 71%; SDiff = 0.557; p < 0.001) or KRT (33% vs 17%; SDiff = 0.371; p < 0.001) at enrollment (Table S3, http://links.lww.com/CCM/H368). Patients treated with AT2 received the drug for a median of 0.7 days (interquartile range, 0.2–1.9 d) (**Fig. S2*D***, http://links.lww.com/CCM/H368).

Outcomes in Matched Cohorts

Mortality at 30 days (60% vs 56%; SDiff = 0.079; p = 0.292) and 90 days (65% vs 63%; SDiff = 0.058; p = 0.440) was similar in the AT2 and control groups (**Table S4**, http://links.lww.com/CCM/H368). Organ dysfunction, quantified by MA-SOFA score, was more severe in patients receiving AT2 compared with controls for the entire 5-day monitoring period after enrollment (day 1: 12 ± 4 vs 10 ± 4; p < 0.001 and day 5: 16 ± 5 vs 14 ± 5; p < 0.001) (Table S4, http://links.lww.com/CCM/H368). However, changes in daily SOFA score from pre-enrollment values were similar in the AT2 and control cohorts during the next 5 days (**Fig. 1*A***). The overall thrombotic rate was similar between AT2 treated patients and controls (29% vs 27%; SDiff = 0.029; p = 0.700) as were the individual types of thrombotic events.

Although pre-enrollment MAP was lower in patients receiving AT2, both study populations experienced an increase in MAP during the 5-day observation period. By the fifth day, there was no significant difference in MAP between the AT2 patients or controls (**Fig. 1*B***).

Multivariant Analysis

After adjustment for differences in baseline characteristics, we found no association between AT2 and the primary outcome of mortality at 30 days (odds ratio [OR], 0.95 d; 95% CI, 0.61–1.48 d; p = 0.827) (**Table 2**). We found that mortality at 30 days was associated with multiple disease-oriented factors such as older age (OR, 1.03; 95% CI, 1.02–1.05; p < 0.001), higher lactate (OR, 1.11; 95% CI, 1.06–1.16; p < 0.001), prior need for KRT (OR, 2.32; 95% CI, 1.35–3.97; p = 0.002), and higher NE equivalent doses (OR, 4.31; 95% CI, 2.59–7.16; p < 0.001) at enrollment. Protective features against 30-day mortality included postoperative state (OR, 0.48; 95% CI, 0.32–0.73; p = 0.001) and higher MAP (OR, 0.99; 95% CI, 0.97–1.00; p = 0.013) at enrollment. Mortality at 30 days was not associated with other shock therapies such as glucocorticoids, anticoagulation, vitamin C, methylene blue, or vitamin B12 (**Table S5**, http://links.lww.com/CCM/H368).

We found after adjustment that AT2 was not associated with the secondary outcomes of 90-day mortality (OR, 0.91; 95% CI, 0.58–1.44; p = 0.689) (Table 2), new KRT (OR, 1.39; 95% CI, 0.88–2.19; p = 0.158), or new receipt of mechanical ventilation (OR, 1.50; 95% CI,

TABLE 1.
Patient Characteristics

Characteristic	Total Control ($n = 542$)	Angiotensin II ($n = 271$)	Standardized Difference Comparing the Angiotensin II Patients to the Combined Total Control Cohort	p
Male sex, *n* (%)	331 (61)	175 (65)	0.25	0.331
Race, *n* (%)				
White	417 (77)	192 (71)	0.27	0.570
African American	75 (14)	53 (20)	0.27	0.931
Other	50 (9)	26 (10)	−0.01	0.898
Etiology of shock, *n* (%)				
Septic[a]	404 (75)	225 (83)	0.21	**0.008**
Hemorrhagic/trauma	39 (7)	11 (4)	−0.14	0.089
Vasoplegic[b]	23 (4)	17 (6)	0.09	0.229
Other	76 (14)	18 (7)	−0.24	**0.002**
NE equivalent dose (µg/kg/min), median (IQR)	0.43 (0.26,0.84)	0.43 (0.26,0.85)	0.004	0.973
NE equivalent dose (µg/kg/min), median (SD)	0.62 (0.51)	0.62 (0.52)	0.004	0.956
Age, yr, *n* (%)	59 (16)	57 (16)	−0.32	0.069
Weight, kg, *n* (%)	89 (29)	88 (28)	−0.02	0.774
Mean arterial pressure, mm Hg, *n* (%)	73 (18)	69 (15)	−0.22	**0.004**
Number of vasopressors, *n* (%)	2.6 (0.9)	2.8 (0.8)	0.28	**< 0.001**
Sequential Organ Failure Assessment score, *n* (%)	10 (4)	12 (4)	0.61	**< 0.001**
Time to enrollment, hr, *n* (%)	29 (251)	5 (11)	−0.14	**0.024**

IQR = interquartile range, NE = norepinephrine.

[a]Sepsis was defined using the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (18).

[b]Vasoplegic shock defined as mean arterial pressure < 65 mm Hg with central or mixed venous oxygen saturation > 70% or cardiac index ≥ 2.3 L/min/BSA m^2 or central venous pressure < 8 mm Hg prior to enrollment without criteria for sepsis.

Total control includes both historical ($n = 271$) and concurrent ($n = 271$) control cohorts. Detailed analysis of concurrent and historical control cohorts found in Table S3 (http://links.lww.com/CCM/H368).

Boldface values indicate statistical significance ($p < 0.05$).

0.41–5.51; $p = 0.539$) (**Table 3**). There was also no association between AT2 use and the tertiary outcomes of thrombotic events (OR, 1.02; 95% CI, 0.71–1.48; $p = 0.912$) (**Table 4**) or ventilator-free days (B = 0.39; 95% CI, −1.20 to 2.08; $p = 0.827$) (**Table S6**, http://links.lww.com/CCM/H368).

Sensitivity Analysis: Angiotensin II Patients Versus Concurrent Controls

Similar to the main analysis, in this sensitivity analysis AT2 patients and concurrent controls received similar NE equivalents, but AT2 patients had lower MAP and higher SOFA scores (**Tables S7** and **S8**, http://links.lww.com/CCM/H368). In adjusted outcomes, receipt of AT2 was not associated with any differences in mortality, new KRT, or new mechanical ventilation (**Tables S9–S12**, http://links.lww.com/CCM/H368).

Patients With Septic Shock

Characteristics of only septic shock patients who received AT2 and the control groups are described in **Table S13** (http://links.lww.com/CCM/H368).

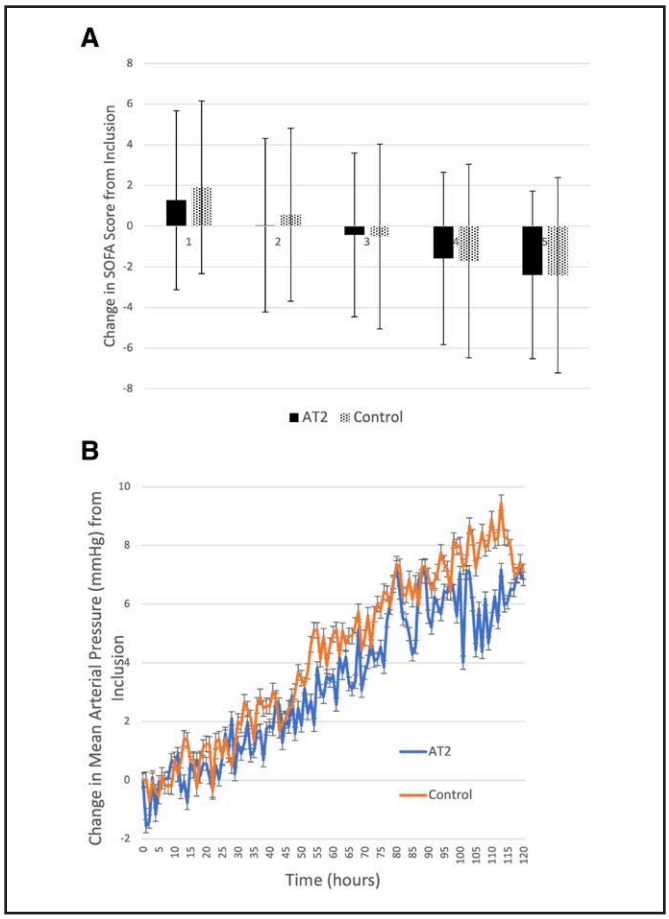

Figure 1. Change in organ failure and blood pressure. **A**, Plot showing the mean with one SD in daily change in Sequential Organ Failure Assessment (SOFA) score from pre-inclusion values in daily survivors who received angiotensin II (AT2) (*solid*) or did not (*halftone*). *p* values between the groups are 0.318, 0.364, 0.207, 0.424, and 0.435 for days 1–5, respectively. **B**, Plot showing the mean with one SD change in mean arterial blood pressure (mm Hg) from pre-inclusion values during the 5-d monitoring period in patients receiving AT2 and controls.

Pre-enrollment NE equivalent dosing was well-balanced (SDiff = –0.04; $p = 0.956$) between the AT2 and controls in this subgroup. Similar to the main analysis, AT2 was not associated with mortality, KRT, or receipt of new mechanical ventilation (**Tables S14–S18**, http://links.lww.com/CCM/H368).

DISCUSSION

In this single-center, cohort study of 813 patients with severe shock matched on NE dose, AT2 use was not associated with improved 30-day mortality. We also found no association between AT2 receipt and the other outcomes such as 90-day mortality, new onset KRT, thrombotic complications, receipt of mechanical ventilation, and ventilator-free days. Furthermore, AT2 use did not improve hypotension or SOFA scores. Instead, outcomes from shock were associated with pre-enrollment organ dysfunction such as prior need for KRT, higher NE equivalent doses, and higher lactate values. We present the first adequately powered study of patients receiving AT2 to detect differences mortality and other important outcomes and found no difference with standard care.

The rationale behind AT2's use as a vasopressor in distributive shock is supported by decades of animal and human evidence that RAAS prevents hypotension in hypovolemic conditions (22, 23). Largely mediated by the angiotensin-1 receptor, AT2 causes vasoconstriction, sodium and water reabsorption, and aldosterone secretion that restore intravascular volume and increase blood pressure (23). The early evidence behind exogenous AT2 used as a vasopressor in distributive shock suggests that AT2 is effective at restoring blood pressure but may impair regional blood flow to organs such as the kidney (24).

Increased rate of KRT was seen in a small, retrospective study of vasoplegic shock in post-cardiac surgery patients who received AT2 (66.7% vs 9.1%; $p = 0.03$), although confounding from higher baseline NE equivalents in the AT2 group was likely (11). We noted no association between AT2 use and the need for post-enrollment KRT after adjustment for other factors including preexisting hypotension and organ dysfunction. Our findings are consistent with a post hoc analysis of the ATHOS-3 trial that found AT2 use in patients requiring new KRT was associated with enhanced liberation from KRT at 7 days (38% vs 15%; $p = 0.007$) (15). A possible mechanism for kidney injury caused by AT2 is that AT2-induced vasoconstriction disproportionally affects the efferent arterioles and causes increased glomerular filtration pressure and decreased renal blood flow (24). Animal models examining the renal effects of AT2 are conflicting as to whether the reductions in renal blood flow result in kidney injury suggesting that dose and duration of AT2 exposure as well as other patient factors may impact the development of acute kidney injury and the need for KRT after AT2 exposure (24, 25). Analysis of renin levels from patients in ATHOS-3 suggests that high plasma levels may identify patients more likely to benefit from AT2 (16). However, none of our patients had renin measurements, which may limit the usefulness

TABLE 2.
Factors Associated With Mortality

Variable	30-d Mortality		90-d Mortality	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Received angiotensin II	0.95 (0.61–1.48)	0.827	0.91 (0.58–1.44)	0.689
Time to enrollment (d)	1.00 (1.00–1.00)	0.891	1.00 (1.00–1.00)	0.889
Norepinephrine equivalents (μg/kg/min)	4.31 (2.59–7.16)	**< 0.001**	4.32 (2.50–7.45)	**< 0.001**
Age	1.03 (1.02–1.05)	**< 0.001**	1.04 (1.02–1.05)	**< 0.001**
Weight	1.01 (1.00–1.02)	**0.004**	1.01 (1.00–1.01)	0.155
Female	1.59 (1.06–2.39)	**0.025**	1.74 (1.14–2.65)	**0.010**
White race	0.83 (0.53–1.30)	0.422	0.80 (0.51–1.27)	0.347
Previous kidney replacement therapy[a]	2.32 (1.35–3.97)	**0.002**	2.85 (1.59–5.12)	**< 0.001**
Mechanical ventilation[b]	0.77 (0.48–1.24)	0.281	0.75 (0.46–1.24)	0.262
Anticoagulation	1.35 (0.86–2.12)	0.197	1.23 (0.77–1.95)	0.392
Postoperative	0.48 (0.32–0.73)	**0.001**	0.48 (0.31–0.75)	**0.001**
Lactate (mmol/L)	1.11 (1.06–1.16)	**< 0.001**	1.09 (1.04–1.15)	**< 0.001**
Mean arterial pressure (mm Hg)	0.99 (0.97–1.00)	**0.013**	0.98 (0.97–1.00)	**0.009**
Sequential Organ Failure Assessment score	1.06 (1.00–1.13)	0.069	1.02 (0.96–1.09)	0.480
Number of vasopressors	1.09 (0.86–1.38)	0.468	1.45 (1.13–1.85)	**0.003**
Glucocorticoid therapy	0.59 (0.31–1.10)	0.094	0.49 (0.25–0.97)	**0.040**
Shock type[c]				
Hemorrhagic/traumatic	0.68 (0.30–1.53)	0.352	0.50 (0.22–1.14)	0.100
Vasoplegic[d]	0.36 (0.13–0.97)	**0.044**	0.27 (0.10–0.71)	**0.008**
Other/multiple[e]	0.82 (0.45–1.48)	0.509	0.74 (0.40–1.34)	0.314

OR = odds ratio.

[a]Previous kidney replacement therapy defined as kidney replacement therapy required within 7 d before inclusion.

[b]Previous mechanical ventilation defined as mechanical ventilation required within 7 d before inclusion.

[c]References types of shock against septic shock defined using the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (18).

[d]Vasoplegic shock defined as mean arterial pressure (MAP) < 65 mm Hg with central or mixed venous oxygen saturation > 70% or cardiac index ≥ 2.3 L/min/BSA m^2 or central venous pressure < 8 mm Hg prior to enrollment without criteria for sepsis.

[e]Other shock was defined as MAP < 65 mm Hg with central or mixed venous saturation < 70% or cardiac index < 2.3 L/min/m^2 or central venous pressure ≥ 8 mm Hg without criteria for sepsis.

Boldface values indicate statistical significance ($p < 0.05$).

of our study at hospitals that routinely measure renin. Additional prospective studies in patients with shock and renal dysfunction are needed to determine if AT2 has a protective or deleterious effect on the need for KRT, and whether plasma renin measurement can guide AT2 use.

While we similarly found no difference in mortality between the AT2 and non-AT2 groups, the use of AT2 differed between our study and ATHOS-3. The ATHOS-3 trial maintained AT2 dose while down titrating the other vasopressors (8). AT2 was used at our institution as a salvage therapy for refractory shock where it was the last medication started and tended to be the first removed. Our practice mirrors much of the post-marketing experience with AT2, which has yielded conflicting results when AT2 was used as a last-line or salvage vasopressor (9–16). However, these studies, which found no improvement in mortality, are limited by small size or lack of a control group. While consistent with our findings that AT2 was not associated with improved mortality, these studies lacked the power to analyze other patient-centered outcomes

TABLE 3.
Factors Associated With New Kidney Replacement Therapy or New Mechanical Ventilation

Variable	Kidney Replacement Therapy		Mechanical Ventilation	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Received angiotensin II	1.39 (0.88–2.19)	0.158	1.50 (0.41–5.51)	0.539
Time to enrollment (d)	1.00 (1.00–1.00)	0.248	1.00 (0.99–1.01)	0.848
Norepinephrine equivalents (μg/kg/min)	0.99 (0.97–1.00)	**0.037**	1.02 (0.99–1.04)	0.143
Age	0.58 (0.36–0.93)	**0.024**	1.63 (0.68–3.94)	0.275
Weight	1.00 (0.99–1.01)	0.658	1.01 (0.99–1.02)	0.358
Female	0.99 (0.64–1.55)	0.972	0.42 (0.19–0.95)	**0.037**
White race	1.50 (0.89–2.53)	0.127	1.44 (0.54–3.81)	0.466
Pre-enrollment care				
Postoperative	0.88 (0.55–1.41)	0.605	1.05 (0.46–2.40)	0.900
Enrollment values				
Hemoglobin (g/dL)	1.05 (0.96–1.15)	0.313	1.07 (0.92–1.24)	0.416
Creatinine (mg/dL)	1.74 (1.44–2.10)	**< 0.001**	0.93 (0.74–1.16)	0.505
Lactate (mmol/L)	1.09 (1.05–1.14)	**< 0.001**	1.09 (0.98–1.20)	0.117
Mean arterial pressure (mm Hg)	1.00 (0.99–1.01)	0.970	1.02 (1.00–1.05)	0.093
Sequential Organ Failure Assessment score	1.07 (1.01–1.14)	**0.028**	0.87 (0.75–1.01)	0.062
Number of vasopressors	1.65 (1.27–2.13)	**< 0.001**	1.34 (0.83–2.15)	0.229
Shock type[a]				
Hemorrhagic or traumatic	0.82 (0.35–1.97)	0.660	0.34 (0.06–2.08)	0.244
Vasoplegic[b]	0.34 (0.12–0.97)	**0.044**	0.08 (0.01–0.63)	**0.017**
Other/multiple[c]	0.18 (0.07–0.49)	**0.001**	0.05 (0.01–0.21)	**< 0.001**
Other shock therapy				
Glucocorticoids	0.98 (0.46–2.06)	0.949	1.03 (0.34–3.12)	0.962

OR = odds ratio.

[a]References types of shock against septic shock.

[b]Vasoplegic shock defined as hypotension with central/mixed venous oxygen saturation > 70% or cardiac index > 2.2 L/min/m^2 prior to enrollment without criteria for sepsis.

[c]Other defined as shock with central/mixed venous saturation < 70% or cardiac index < 2.2 L/min/m^2 or features of mixed shock prior to enrollment.

C-statistic for receipt of kidney replacement therapy = 0.804, 95% CI (0.756–0.852); *C*-statistic for mechanical ventilation = 0.786, 95% CI (0.717–0.855).

Boldface values indicate statistical significance ($p < 0.05$).

found in our study such as organ dysfunction, need for KRT, and duration of mechanical ventilation.

Because we mostly used AT2 as a salvage vasopressor, we cannot comment on whether different regimens would produce better outcomes. Thus, prospective studies are needed to determine if AT2 is a suitable first- or second-line vasopressor.

AT2 impairs thrombolysis and increases thrombin formation, and the FDA package insert reports increased rates of combined venous and arterial thrombotic events (13% vs 5%; $p = 0.02$) with AT2 use (26–28). Rates of thrombotic events were high in our study but similar in AT2 treated and control cohorts. Given that studies to find thrombotic events were ordered based on clinical changes and not prospectively, the actual rates of thromboses in our study are probably higher.

Our study has several limitations. First, our findings were derived from data obtained at a single, large health system that may not be generalizable to

TABLE 4.
Factors Associated With Thromboembolic Events

Variable	Thrombotic Events	
	OR (95% CI)	*p*
Received angiotensin II	1.02 (0.71–1.48)	0.912
Time to enrollment (d)	1.00 (1.00–1.00)	0.761
Norepinephrine equivalents (per 0.1 µg/kg/min)	0.91 (0.62–1.32)	0.612
Age	1.01 (1.00–1.02)	0.242
Female	0.90 (0.64–1.28)	0.565
White race	1.08 (0.72–1.6)	0.722
Comorbidities		
Pulmonary disease	0.67 (0.47–0.95)	**0.023**
Congestive heart failure	1.22 (0.84–1.77)	0.290
Diabetes mellitus	0.95 (0.68–1.34)	0.769
Hypertension	1.12 (0.71–1.76)	0.621
Lymphoma	0.85 (0.43–1.68)	0.638
Metastatic cancer	1.12 (0.69–1.82)	0.635
Pre-enrollment care		
Kidney replacement therapy[a]	0.72 (0.46–1.13)	0.157
Mechanical ventilation[b]	1.11 (0.71–1.74)	0.654
Anticoagulation	0.73 (0.48–1.11)	0.143
Postoperative	1.27 (0.88–1.83)	0.203
Enrollment values		
Platelet count (k/µL)	1.00 (1.00–1.00)	0.449
Creatinine (mg/dL)	1.10 (0.97–1.26)	0.137
White cell count (k/µL)	1.01 (1.00–1.02)	0.167
Urea nitrogen (mg/dL)	1.00 (0.99–1.01)	0.582
Lactate (mmol/L)	1.00 (0.97–1.03)	0.996
Mean arterial pressure (mm Hg)	1.01 (1.00–1.02)	0.094
Sequential Organ Failure Assessment score	1.02 (0.96–1.07)	0.520
Number of vasopressors	1.06 (0.87–1.30)	0.555
Shock type[c]		
Hemorrhagic or traumatic	0.70 (0.34–1.44)	0.334
Vasoplegic[d]	0.64 (0.29–1.39)	0.258
Other/multiple[e]	0.68 (0.39–1.20)	0.181

OR = odds ratio.

[a]Previous kidney replacement therapy (KRT) defined as KRT required within 7 d before inclusion.

[b]Previous mechanical ventilation defined as mechanical ventilation required within 7 d before inclusion.

[c]References types of shock against septic shock.

[d]Vasoplegic shock defined as hypotension with central/mixed venous oxygen saturation > 70% or cardiac index > 2.2 L/min/m^2 prior to enrollment without criteria for sepsis.

[e]Other defined as shock with central/mixed venous saturation < 70% or cardiac index < 2.2 L/min/m^2 or features of mixed shock prior to enrollment.

C-statistic for thrombotic events = 0.642, 95% CI (0.592–0.693).

Boldface value indicates statistical significance ($p < 0.05$).

other settings. Second, we did not consistently and uniformly measure cardiac outputs or mixed venous oxygen saturation to confirm that patients had distribution shock. While some patients may have had other forms of shock, 75% of our patients had septic shock suggesting a predominance of distributive physiology in our population. There were also some imbalances in the degree of hypotension and organ dysfunction between the AT2 cohort and controls suggesting that despite the same NE dose, AT2 was being reserved for higher acuity patients which might blunt its effectiveness. Despite multivariant adjustment for these imbalances, residual confounders may exist and bias the study in unknown ways.

The strengths of our study include that we were adequately powered to detect an 8% absolute difference in mortality. Furthermore, our findings of no difference in outcomes with AT2 use were consistent across the main analysis and two sets of subgroup analyses.

CONCLUSIONS

In conclusion, our single-center study failed to show an association with AT2 and improved outcomes in severe shock when used as a salvage therapy. Therefore, we do not recommend that AT2 be added as a third- or fourth-line vasopressor in patients with shock that is refractory to high doses of first- and second-line medications such as norepinephrine or vasopressin. Further studies are needed to determine a possible role for AT2 as a first- or second-line vasopressor.

1 *Department of Anesthesiology, Section of Critical Care, University of Michigan, Ann Arbor, MI.*

2 *Department of Anesthesiology, University of Michigan, Ann Arbor, MI.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Dr. Smith involved in study design, data analysis, and article development and editing. Dr. Mentz involved in statistical analysis, data analysis, and article editing. Dr. Engoren involved in study design, data extraction and analysis, and article development and editing

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: Lane.Smith@Atriumhealth.org

REFERENCES

1. Vincent JL, De Backer D: Circulatory shock. *N Engl J Med* 2013; 369:1726–1734
2. De Backer D, Biston P, Devriendt J, et al; SOAP II Investigators: Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; 362:779–789
3. Rhee C, Dantes R, Epstein L, et al; CDC Prevention Epicenter Program: Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. *JAMA* 2017; 318:1241–1249
4. Rhodes A, Evans L, Alhazzani W, et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017; 43:304–377
5. Asfar P, Meziani F, Hamel JF, et al; SEPSISPAM Investigators: High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 2014; 370:1583–1593
6. Andreis DT, Singer M: Catecholamines for inflammatory shock: A Jekyll-and-Hyde conundrum. *Intensive Care Med* 2016; 42:1387–1397
7. Corrêa TD, Takala J, Jakob SM: Angiotensin II in septic shock. *Crit Care* 2015; 19:98
8. Khanna A, English SW, Wang XS, et al; ATHOS-3 Investigators: Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med* 2017; 377:419–430
9. Chow JH, Galvagno SM Jr, Tanaka KA, et al: When all else fails: Novel use of angiotensin II for vasodilatory shock – a case report. *A A Pract* 2018; 11:175–180
10. Evans A, McCurdy MT, Weiner M, et al: Use of angiotensin II for post cardiopulmonary bypass vasoplegic syndrome. *Ann Thorac Surg* 2019; 108:e5–e7
11. Bird S, Chand M, Tran TL, et al: Evaluation of the addition of angiotensin II in patients with shock after cardiac surgery at a Veterans Affairs medical center. *Ann Pharmacother* 2023; 57:141–147
12. Lam SW, Barreto EF, Scott R, et al: Cost-effectiveness of second-line vasopressors for the treatment of septic shock. *J Crit Care* 2020; 55:48–55
13. Quan M, Cho N, Bushell T, et al: Effectiveness of angiotensin II for catecholamine refractory septic or distributive shock on mortality: A propensity score weighted analysis of real-world experience in the medical ICU. *Crit Care Explor* 2022; 4:e0623
14. Szerlip H, Bihorac A, Chang S, et al: Effect of disease severity on survival in patients receiving angiotensin II for vasodilatory shock. *Crit Care Med* 2018; 46:3
15. Tumlin JA, Murugan R, Deane AM, et al; Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3) Investigators: Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. *Crit Care Med* 2018; 46:949–957
16. Bellomo R, Forni LG, Busse LW, et al: Renin and survival in patients given angiotensin II for catecholamine-resistant vasodilatory shock. *Am J Respir Crit Care Med* 2020; 202:1253–1261
17. Schünemann HJ, Cushman M, Burnett AE, et al: American Society of Hematology 2018 guidelines for management of venous thromboembolism: Prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv* 2018; 2:3198–3225

18. Chawla LS, Russell JA, Bagshaw SM, et al: Angiotensin II for the treatment of high-output shock 3 (ATHOS3): Protocol for a phase III, double-blind, randomized controlled trial. *Crit Care Resusc* 2017; 19:43–49
19. Russell JA, Walley KR, Singer J, et al; VASST Investigators: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–887
20. Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22:707–710
21. Singer M, Deutschman CS, Seymour CW, et al: The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; 315:801–810
22. Fyhrquist F, Saijonmaa O: Renin-angiotensin system revisited. *J Intern Med* 2008; 264:224–236
23. Paul M, Poyan MA, Kreutz R: Physiology of local renin-angiotensin systems. *Physiol Rev* 2006; 86:747–803
24. Wan L, Langenberg C, Bellomo R, et al: Angiotensin II in experimental hyperdynamic sepsis. *Crit Care* 2009; 13:R190
25. Corrêa TD, Jeger V, Pereira AJ, et al: Angiotensin II in septic shock: Effects on tissue perfusion, organ function, and mitochondrial respiration in a porcine model of fecal peritonitis. *Crit Care Med* 2014; 42:e550–e559
26. Kaminska M, Mogielnicki A, Stankiewicz A, et al: Angiotensin II via AT1 receptor accelerates arterial thrombosis in renovascular hypertensive rats. *J Physiol Pharmacol* 2005; 56:571–585
27. Celi A, Cianchetti S, Dell'Omo G, et al: Angiotensin II, tissue factor and the thrombotic paradox of hypertension. *Expert Rev Cardiovasc Ther* 2010; 8:1723–1729
28. Giapreza (Angiotensin II) Injection for Intravenous Infusion [package insert]. San Diego, CA, La Jolla Pharmaceutical Company, 2021