

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

IMPORTANCE: Angiotensin II (ATII) was approved for septic or other distributive shock due to its property of increasing blood pressure within 3 hours. Limited data exist regarding its effectiveness when used in real-world clinical practice.

OBJECTIVES: This study examined ATII as a third-line vasopressor based on institutional approval.

DESIGN: Retrospective observational cohort study.

SETTING AND PARTICIPANTS: Medical ICU at an academic tertiary care medical center. Adult patients requiring 3 or more vasopressor agents for septic shock or other forms of distributed shock from September 1, 2018, to January 31, 2020.

MAIN OUTCOMES AND MEASURES: Effect of ATII after norepinephrine and vasopressin on mortality and mean arterial blood pressure response after 3 hours of administration.

RESULTS: One-hundred forty-seven patients, 56 receiving ATII and 91 receiving another vasopressor (non-ATII), were enrolled. Patients in the ATII group had higher mortality compared to the non-ATII group, and more required 5 or greater vasopressor agents ($p < 0.01$). After propensity score weighting, there remains a trend in higher mortality in the ATII compared to non-ATII group, but not statistically significant (86.0% vs 71.0%, $p = 0.16$). More patients in the ATII group continued to require 5 or greater vasopressor agents compared to the non-ATII group after propensity score weighting (45.9% vs 12.5%, $p < 0.01$). SOFA score was the only variable associated with mortality (OR = 1.25, 95% CI, 1.05–1.49; $p = 0.01$). Patients were considered a “responder” if mean arterial pressure greater than 65 mm Hg at 3 hours after the third vasopressor was initiated. Among the ATII group, 37.5% patients were responders compared to 45.1% responders in the non-ATII group (relative risk = 1.07, 95% CI, 0.6–1.93; $p = 0.81$).

CONCLUSIONS AND RELEVANCE: Although previous data support the use of ATII due to its favorable hemodynamic response in patients with distributive shock, there was no observed benefit in mortality or hemodynamic response with ATII as a third-line vasopressor in our study of real-world patients.

KEY WORDS: angiotensin II; distributed shock; effectiveness; septic shock; vasopressor

Septic shock is the most common type of distributive shock and despite improvement in sepsis management, its mortality rate remains high at 40–50% (1, 2). Mortality rate increases even further when patients develop refractory shock or persistent hypotension despite high-dose vasopressor support, often greater than 0.5 µg/kg/min norepinephrine or equivalent (3, 4). Intensification of refractory shock therapy with high doses of multiple

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vasopressors has been associated with mortality of 80% or higher (5–7). Escalation of catecholamine doses to achieve hemodynamic targets in refractory shock can contribute to exacerbation of multiple organ damage. Overstimulation of the sympathetic nervous system can lead to peripheral and splanchnic ischemia, increased myocardial oxygen consumption, tachyarrhythmia, and myocardial cell damage (8, 9). Thus, a noncatecholamine vasopressor alternative for the treatment of distributive shock may mitigate the toxic effects of high-dose catecholamines.

Angiotensin II (ATII) is a naturally occurring hormone that primarily acts on angiotensin type I receptor in the renin-angiotensin system and elicits multiple effects: vasoconstriction, aldosterone and vasopressin secretion, sodium and water reabsorption, and cardiac contractility (10–12). In shock, hemodynamics are preserved primarily through the stimulation of the sympathetic nervous system, release of catecholamines and vasopressin, and vasoconstriction via the effects of ATII (13). Currently established pharmacologic therapies to supplement these responses are norepinephrine and vasopressin, which are recommended as first and second-line therapy, respectively (14). However, the role of ATII still remains controversial. The Angiotensin II for the Treatment of Vasodilatory Shock (ATHOS-3) study evaluated the role of ATII in patients with distributive shock requiring vasopressor therapy with norepinephrine (or equivalent) dose of greater than 0.2 $\mu\text{g}/\text{kg}/\text{min}$ (15). In ATHOS-3, a significantly greater number of patients who received ATII achieved mean arterial pressure (MAP) goal (defined as $\text{MAP} \geq 75 \text{ mm Hg}$ or $\text{MAP increase} \geq 10 \text{ mm Hg}$) within 3 hours and required lower catecholamine doses compared with patients who received placebo.

In December 2017, the Food and Drug Administration (FDA) approved ATII as a vasopressor to increase blood pressure in adults with septic or other distributive shock. Thereafter, ATII was added to our institution's drug formulary as a third-line vasopressor after norepinephrine and vasopressin. The most recently published Surviving Sepsis Campaign guidelines have suggested that although ATII should not be used as a first-line agent, it may have a role as an adjunctive vasopressor therapy (14).

It is evident that there is limited literature on the benefit of ATII when added to standard care. The purpose of our study was to examine the effect of ATII

on mortality in septic or distributive shock. We also examined the MAP in response to ATII after 3 hours of administration.

MATERIALS AND METHODS

Study Design and Setting

This study was a retrospective observational cohort of adult patients admitted to the medical ICU (MICU) at an academic tertiary care medical center with 507 licensed beds, including 102 ICU beds. Annually, there are over 4,500 patients admitted to the ICU at our medical center. The study was approved by the Institutional Review Board (IRB), Human Research & Compliance at Loma Linda University, approval IRB number 5200126.

Patient Population

All adult patients age 18 years and older admitted to the MICU requiring vasopressor agent(s) during September 1, 2018, to January 31, 2020, were screened from the medical records. Patients were included in the study if requiring three or more vasopressors any time during the hospital stay, with a suspected or proven infection as the primary cause of shock or not having cardiogenic, obstructive, or hypovolemic shock. Patients were excluded if they were transferred from an outside facility and already receiving three vasopressors on arrival. The indication, dosing, and titration of ATII and concomitant treatments for shock were guided by the primary treatment team and unaffected by this retrospective study. Our hospital guideline restricted ATII to be used as a third-line vasopressor therapy, after norepinephrine and vasopressin (or norepinephrine equivalent [NEE] dose $> 0.2 \mu\text{g}/\text{kg}/\text{min}$). Per our protocol, ATII was initiated at 20 $\text{ng}/\text{kg}/\text{min}$ and titrated by 5 $\text{ng}/\text{kg}/\text{min}$ every 5 minutes as needed to reach MAP greater than 65 mm Hg or a maximum dose of 40 $\text{ng}/\text{kg}/\text{min}$. The maximum dose was allowed to be increased to 80 $\text{ng}/\text{kg}/\text{min}$ with the approval of the patient's attending physician.

Data Collection

Demographic and clinical information were collected through review of the electronic medical record, including age, sex, home medications, admission diagnoses, known or suspected etiology of infection, hemodynamic variables, laboratory values, urine

output, antibiotic usage, fluids received, and use of stress-dose steroids. If a patient had more than one event of being on three or more vasopressors in one hospitalization, only the first event was used for data collection and analysis. Recent exposure to angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) was obtained from review of home medications. Immunocompromised patients were defined as those having HIV infection, neutropenia, post-transplantation, greater than or equal to 10 mg prednisone equivalent per day for at least 2 weeks, cytotoxic therapy, primary immunodeficiency, or lymphohematogenous malignancy.

We defined patients with septic shock as those who required a vasopressor to maintain a MAP of 65 mm Hg or greater. Infection was defined by the administration of antibiotics or clinician documentation of a source of infection, such as “pneumonia” or “urinary tract infection.” Time to vasopressor was defined as the amount of time from presentation of patient to the hospital and initiation of any vasopressor agent. Additionally, initial hemodynamic values (MAP, heart rate) were obtained at initiation of vasopressor agent.

Laboratory findings were obtained from the day the patient was started on three vasopressors, including the variables used to calculate the Sequential Organ Failure Assessment (SOFA) score (16). NEE dose for other catecholamine vasopressors (including epinephrine, dopamine, phenylephrine, and vasopressin) was obtained from a conversion scale developed based on the cardiovascular SOFA score (16, 17). NEE dose for vasopressin was calculated using the Vasopressin and Septic Shock Trial dataset (18). Urine output was defined as the output (in milliliters) during the 24-hour period in which the patient received the third vasopressor. Stress-dose corticosteroid was defined as a dosage equivalent to prednisone greater than or equal to 50 mg daily.

Measurable Outcomes

The primary outcome was inhospital mortality from any cause. The secondary outcomes included MAP response to ATII, ATII after 3 hours of administration, ICU length of stay, and hospital length of stay.

Statistical Analyses

Continuous variables are presented as mean \pm SD and categorical variables are presented as count (percentage).

Our primary aim was to examine the differences in patients receiving ATII versus other vasopressor (non-ATII) as the third agent (or “treatment”). Student *t* tests were used to test for pretreatment differences between these two groups on continuous variables, and chi-square tests were used to test for differences on categorical variables. A standardized mean difference of an absolute value of less than 0.1 typically indicates a negligible difference between the means between groups (19).

Given the large standardized differences on many of the pretreatment covariates, propensity score-based weighting was used to address potential confounding. Rather than the popular inverse probability of treatment weighting (IPTW), propensity overlap weighting was used in which each patient’s weight was specified as being proportional to the estimated probability of receiving the opposite treatment than what they actually received (20). Advantages of overlap weighting over IPTW include statistical precision and enhanced finite-sample balancing. Specifically, a major benefit of overlap weighting is that exact balance on the means or proportions of pretreatment covariates is guaranteed when the propensity scores are estimated using logistic regression. When overlap weights are used, the estimated treatment effect corresponds to the effect for patients who have appreciable probability of receiving either of the two treatments. To guarantee exact balance on the means and proportions of the pretreatment covariates, the propensity scores were estimated using a logistic regression model that includes all variables from the **Supplemental Table** (<http://links.lww.com/CCX/A901>). More discussions regarding the advantages of overlap weighting are provided by Thomas et al (21). The propensity score model and treatment effects were estimated using the R package “PSweight” (R Foundation, Vienna, Australia) (22, 23).

To allow propensity scores and treatment effects to be estimated using all enrolled patients, multiple imputation was performed using the predictive mean matching method within the R package “mice” (R Foundation) (24). The propensity scores were then estimated using each of 100 imputed datasets including all covariates from the Supplemental Table (<http://links.lww.com/CCX/A901>), as well as missing data indicators to account for potential differences in the rate of missingness across the two treatment groups, as described by (25). No patient was missing more than four covariates and

patients with at least one missing value were only missing a single covariate. The final propensity scores used to construct the overlap weights were then calculated by aggregating across the propensity scores estimated using each of the imputed datasets. To assess the impact of the imputation procedure on the conclusions of the analysis, the analysis was also replicated using only patients with complete data. The general conclusions remained consistent and so only the results obtained with the imputed data are presented.

By construction, the overlap weighted means or proportions of all covariates included within the propensity score model are equivalent across the two treatment groups. In addition to achieving perfect balance on the means and proportions, other summary statistics (e.g., SDs), Kolmogorov-Smirnov tests, and graphical assessments suggested that the weighted distributions of all of the covariates were adequately balanced. Further, because the missing indicators were included within the propensity score model, exact balance was also achieved on the missingness of each covariate that had at least one missing value.

Table 1 illustrates the unweighted and weighted means and proportions for the key observed variables of interest that were not included in the propensity score model. These include our primary and secondary outcomes of interest (e.g., mortality, MAP response to ATII, ICU length of stay, and hospital length of stay), as well as additional potentially post-treatment variables.

After estimating the impact of ATII on mortality using propensity weighting, multivariable logistic regression modeling was used to determine potential predictors of mortality. Age, ACE-inhibitor or ARB usage, lactate, steroid treatment, duration of mechanical ventilation, number of vasopressors, duration of vasopressors, SOFA score, and treatment with ATII were included as independent variables in the model based on their clinical likelihood of affecting outcome in our cohort of patients with septic or distributive shock.

To examine the MAP response in patients receiving ATII compared with those who did not receive ATII, mean MAP estimates and SES were obtained via a linear mixed model comparable to a repeated measures analysis of variance model. This model allows for individuals with partially missing data to be included within the analysis (26). Patients were considered a responder if MAP was greater than 65 mm Hg at 3 hours after

the third vasopressor was initiated or a nonresponder if MAP less than or equal to 65 mm Hg.

All *p* values of less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS Version 26.0 (SPSS/IBM, Chicago, IL) and R Version 3.6.1 (R Foundation, Vienna, Austria).

RESULTS

Six-hundred six patients requiring at least one vasopressor were screened, of which 147 patients, 56 receiving ATII and 91 receiving another vasopressor (non-ATII) as the third vasopressor agent, were included in the analysis (**Fig. 1** and Supplemental Table, <http://links.lww.com/CCX/A901>). Patients in the ATII group were 59.5 ± 14.9 years old compared with 62.7 ± 15.7 in the non-ATII group ($p = 0.22$). Respiratory infections were the primary source of infections in both groups (ATII 55.4% vs non-ATII 51.6%). Approximately 21.4% of the ATII patients were previously on ACE-inhibitor or ARB prior to admission compared with 24.2% of the non-ATII groups. Compared with non-ATII, patients in the ATII group had statistically significant higher BMI, lower hypertension, lower coronary artery disease, and lower heart failure. With respect to laboratory values, the ATII group had higher white blood cell count, lower glucose, and higher international normalized ratio. Patients in the ATII group received statistically significant more corticosteroid compared with the non-ATII group.

Patients in the ATII group had higher mortality compared with the non-ATII group and more required five or greater vasopressor agents ($p < 0.01$) (Table 1). After propensity score weighting, there remains a trend in higher mortality in the ATII compared with non-ATII group but not statistically significant (86.0% vs 71.0%; $p = 0.16$). More patients in the ATII group continued to require five or greater vasopressor agents compared with the non-ATII group after propensity score weighting (45.9% vs 12.5%; $p < 0.01$). There was no difference in ICU length of stay, hospital length of stay, MAP responders (see below), mechanical ventilation, time to mechanical ventilation, duration of mechanical ventilation, or total NEE dose. In the multivariable logistic regression analysis, SOFA score was the only variable associated with mortality (odds ratio, 1.25; 95% CI, 1.05–1.49; $p = 0.01$) (**Table 2**).

TABLE 1.
Outcomes and Treatments in Angiotensin II Versus Nonangiotensin II Patients, Before and After Propensity Score Weighting

Outcome/ Treatment	Unweighted				Weighted		
	ATII (n = 56)	Non-ATII (n = 91)	Standardized Mean Difference for Continuous Variable and % Difference for Categorical Variable	p	ATII	Non- ATII	Estimate (95% CI); p
Mortality, n (%)	51 (91.1)	71 (78.0)	13.1%	0.04	86.0%	71.0%	RR = 1.21 (0.93–1.57); p = 0.16
ICU LOS, mean ± SD, d	6.9 ± 6.7	9.8 ± 12.8	−0.26	0.08	6.7	9.9	MD = −3.20 (−7.02 to 0.62); p = 0.10
Hospital LOS, mean ± SD, d	11.7 ± 12.5	13.1 ± 15.1	−0.10	0.56	11.4	14.4	MD = −2.98 (−7.98 to 2.02); p = 0.24
Mean arterial pressure > 65 after 3 hr of third vasopressor initiated, n (%)	21 (37.5)	41 (45.1)	−7.6%	0.37	39.0%	36.0%	RR = 1.07 (0.60–1.93); p = 0.81
Mechanical ventilation, n (%)	51 (91.1)	87 (95.6)	−4.5%	0.27	85.0%	96.0%	RR = 0.89 (0.76–1.05); p = 0.17
Time to mechanical ventilation, mean ± SD, hr	111.3 ± 160.7	205.1 ± 945.6	−0.12	0.36	107.2	113.6	MD = −6.46 (−83.03 to 70.11); p = 0.87
Duration of mechan- ical ventilation, mean ± SD, hr	108.6 ± 128.1	126.5 ± 162.7	−0.12	0.46	99.0	131.4	MD = −32.36 (−92.93 to 28.21); p = 0.30
Total number of vaso- pressors, n (%) ^a				< 0.01			χ ² (3) = 27.92; p < 0.01
3	7 (12.5)	37 (41.1)	−28.6%		9.5%	37.1%	
4	22 (39.3)	45 (50.0)	−10.7%		44.6%	50.3%	
5	22 (39.3)	8 (8.9)	30.5%		35.9%	12.5%	
6	5 (8.9)	0 (0.0)	8.9%		10.0%	0.0%	
Other vasopressors, n (%) ^b							
Epinephrine	40 (71.4)	76 (83.5)	−12.1%	0.08	77.0%	78.6%	RR = 0.98 (0.77–1.25); p = 0.87
Dopamine	5 (8.9)	20 (22.0)	−13.1%	0.04	10.0%	28.4%	RR = 0.35 (0.12–1.08); p = 0.07
Phenylephrine	36 (64.3)	56 (61.5)	2.8%	0.64	59.4%	67.6%	RR = 0.88 (0.62–1.25); p = 0.47
Total norepinephrine equivalent, mean ± SD, µg/kg/min	1.1 ± 0.5	1.1 ± 0.4	−0.15	0.39	1.1	1.1	MD = 0.06 (−0.16 to 0.28); p = 0.60

ATII = angiotensin II, LOS = length of stay, MD = mean difference, RR = relative risk ratio.

^aTotal number of vasopressors required during the shock episode.

^bAll patients had norepinephrine and vasopressin prior to the other vasopressor agents.

Propensity scores were estimated based on baseline characteristics from Supplemental Table (<http://links.lww.com/CCX/A901>).

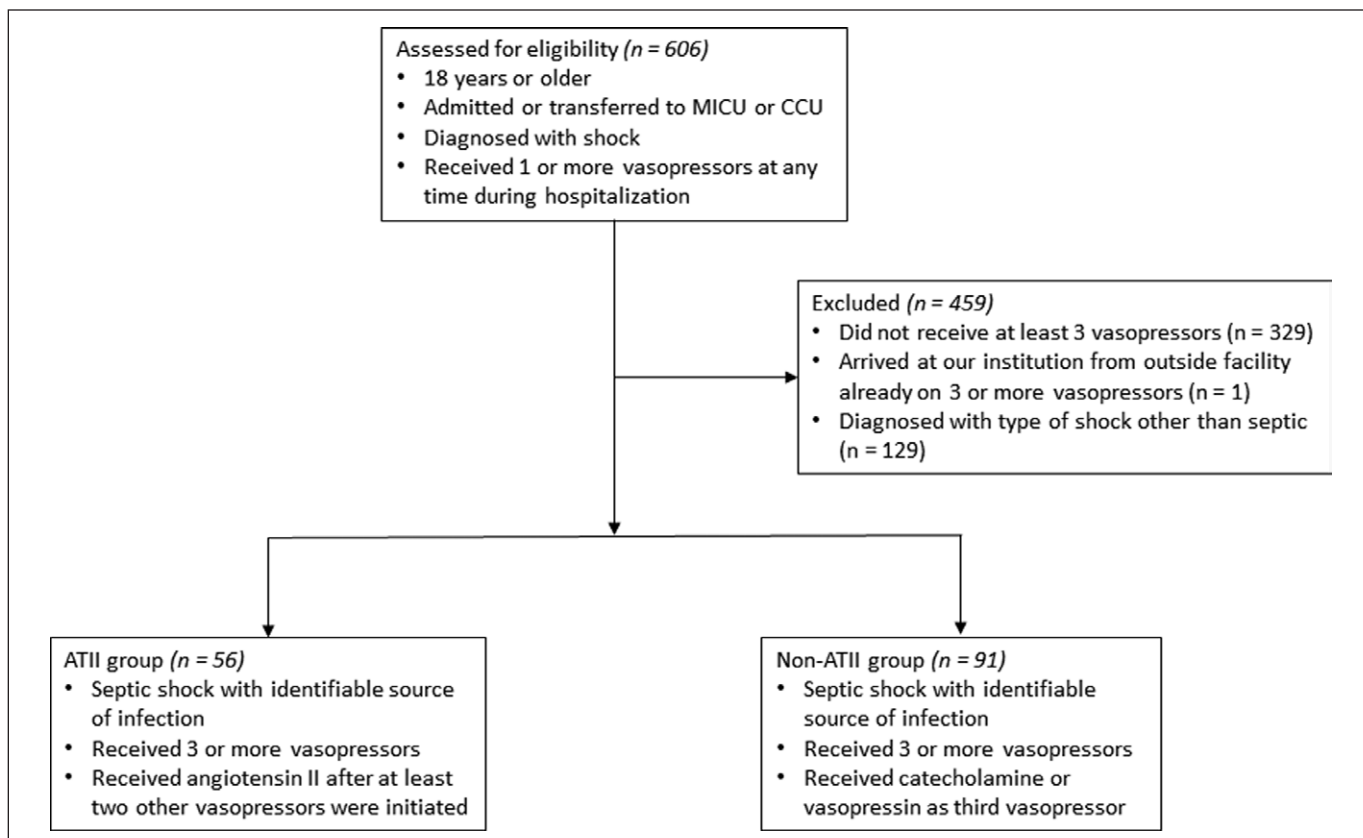


Figure 1. Study enrollment flow diagram of inclusion and exclusion criteria for angiotensin II (ATII) versus non-ATII patients. MICU = medical ICU.

The NEE dose of vasopressors at ATII initiation was 0.8 ± 0.3 $\mu\text{g}/\text{kg}/\text{min}$. Among the ATII group, 21 out of 56 patients (37.5%) were considered responders compared with 41 out of 91 responders (45.1%) in the non-ATII group (relative risk ratio, 1.07; 95% CI, 0.6–1.93; $p = 0.81$) (Fig. 2). In responders at 3 hours, MAP was 74.5 ± 2.8 mm Hg in the ATII group compared with 77.2 ± 2.0 mm Hg in the non-ATII group, with a mean difference of 2.7 mm Hg (95% CI, -3.97 to 9.41 ; $p = 0.43$). In nonresponders at 3 hours, MAP in the ATII group was 56.5 ± 2.6 mm Hg and non-ATII group 57.7 ± 2.1 mm Hg, with a mean difference of 1.2 mm Hg (95% CI, -5.36 to 7.69 ; $p = 0.73$).

DISCUSSION

In this retrospective observational cohort study, we described our real-world experience with ATII in the postmarketing setting at a single-tertiary care medical center. In patients with refractory distributive shock, there was no observed benefit in mortality, hemodynamic response, ICU length of stay, or hospital length of stay associated with ATII as a third-line vasopressor.

Current data regarding the use of ATII in distributive shock is limited. In the pivotal ATHOS-3 study leading to FDA approval, a significantly greater number of patients who received ATII demonstrated a favorable hemodynamic response in 69.9% of the treatment group compared with only 23.4% of the control group ($p < 0.001$). While it was not the primary outcome, survival benefit was not observed (15). A recent meta-analysis of randomized clinical trials examining non-catecholamine vasopressors in the treatment of septic shock identified only two studies that included ATII as the intervention, both of which were performed by the same group of investigators (15, 27, 28).

In reviewing the literature, we found two post-marketing studies examining the benefit of ATII in shock (29, 30). In a multicenter retrospective study of patients with distributive shock refractory to catecholamine vasopressors and vasopressin, Wieruszewski et al (29) showed that 67% of 270 recipients of ATII experienced a favorable hemodynamic response at 3 hours. In a severity-adjusted multivariate analysis, the authors also found a reduced likelihood of 30-day mortality in patients who had a favorable hemodynamic response

to ATII. Lower lactate concentration and the presence of vasopressin at the time of ATII initiation were associated with hemodynamic responsiveness. However, this study did not have a control group to determine the responsiveness of other catecholamine vasopressors in lieu of ATII.

In the second multicenter, retrospective observational study, Smith et al (30) examined 162 patients who received ATII for any form of shock, septic shock being the most common. Prior to initiation of ATII, 68.5% of patients were on greater than or equal to 3 vasopressors. Hemodynamic responsiveness occurred in 80.1% of patients, with significant MAP increase and NEE dose decrease at 3 hours after initiation of ATII. NEE dose decreased more in those patients on less than or equal to 3 vasopressors compared with those on greater than three vasopressors prior to ATII. Similar to the study by Wieruszewski et al (29) above, this study did not have a control group.

Additional case studies or case series performed outside the clinical trial setting also reported ATII response in distributive shock associated with cirrhosis, postcardiopulmonary bypass, liver transplant, near drowning, and COVID-19, providing further limited evidence for ATII efficacy (31–36).

In contrast to previous literature, our study showed no improvement in hemodynamic response with ATII when compared with other vasopressors. In fact, only 37.5% of patients had responded to ATII compared with 69.9%, 67%, and 80.1% responders in ATHOS-3, and the studies by Wieruszewski et al (29) and Smith et al (30), respectively (15). Interestingly, Smith et al

(30) observed a 26.3% dosing increase in norepinephrine if ATII was initiated when NEE dose was greater than 0.2 $\mu\text{g}/\text{kg}/\text{min}$, compared with a 71.5% dose reduction of norepinephrine when ATII was initiated at less than 0.2 $\mu\text{g}/\text{kg}/\text{min}$ NEE dose. These results may explain the lack of response in our study. Our institution's guideline restricted ATII to be only used as a third-line vasopressor therapy, after norepinephrine and vasopressin (or NEE dose $> 0.2 \mu\text{g}/\text{kg}/\text{min}$), while other studies have observed use of ATII even as a first-line agent (30). The data presented by Smith et al (30) would also explain our ATII patients requiring significantly higher total number of vasopressors compared with the non-ATII patients; that is, an increase in NEE dose when ATII is added to an already high dose of other vasopressors. In a review of the literature, Alam et al (37) suggested that perhaps ATII is most beneficial when used early in the course of shock, ideally before NEE dosing reaches 0.2 $\mu\text{g}/\text{kg}/\text{min}$.

Wieruszewski et al (29) showed that hemodynamic responsiveness to ATII was associated with mortality reduction. Given the low hemodynamic response rate to ATII in our study, there was no difference in mortality in patients receiving ATII compared with those not receiving ATII. Our SOFA score and mortality rate were higher compared with previous studies examining ATII in shock (15, 29, 30). Our total NEE dose was $1.1 \pm 0.5 \mu\text{g}/\text{kg}/\text{min}$ in the ATII group versus $1.1 \pm 0.4 \mu\text{g}/\text{kg}/\text{min}$ in the non-ATII group. In the ATII group, the NEE dose at initiation of ATII was $0.8 \pm 0.3 \mu\text{g}/\text{kg}/\text{min}$ in comparison to ATHOS-3 that had approximately 28.2–30.4% of its study population on higher

TABLE 2.
Predictors of Mortality (Multivariable Logistic Regression)

Predictor Variable	OR (CI)	p
Age	1.04 (1.00–1.08)	0.06
Recent angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	1.45 (0.42–5.03)	0.56
Lactate	1.12 (1.00–1.25)	0.06
Corticosteroid	0.86 (0.29–2.55)	0.79
Duration of mechanical ventilation	1.00 (0.99–1.00)	0.20
Number of vasopressors	1.73 (0.77–3.87)	0.18
Duration of vasopressors	1.00 (1.00–1.01)	0.13
Sequential Organ Failure Assessment score	1.25 (1.05–1.49)	0.01
Angiotensin II	3.10 (0.82–11.77)	0.10

OR = odds ratio.

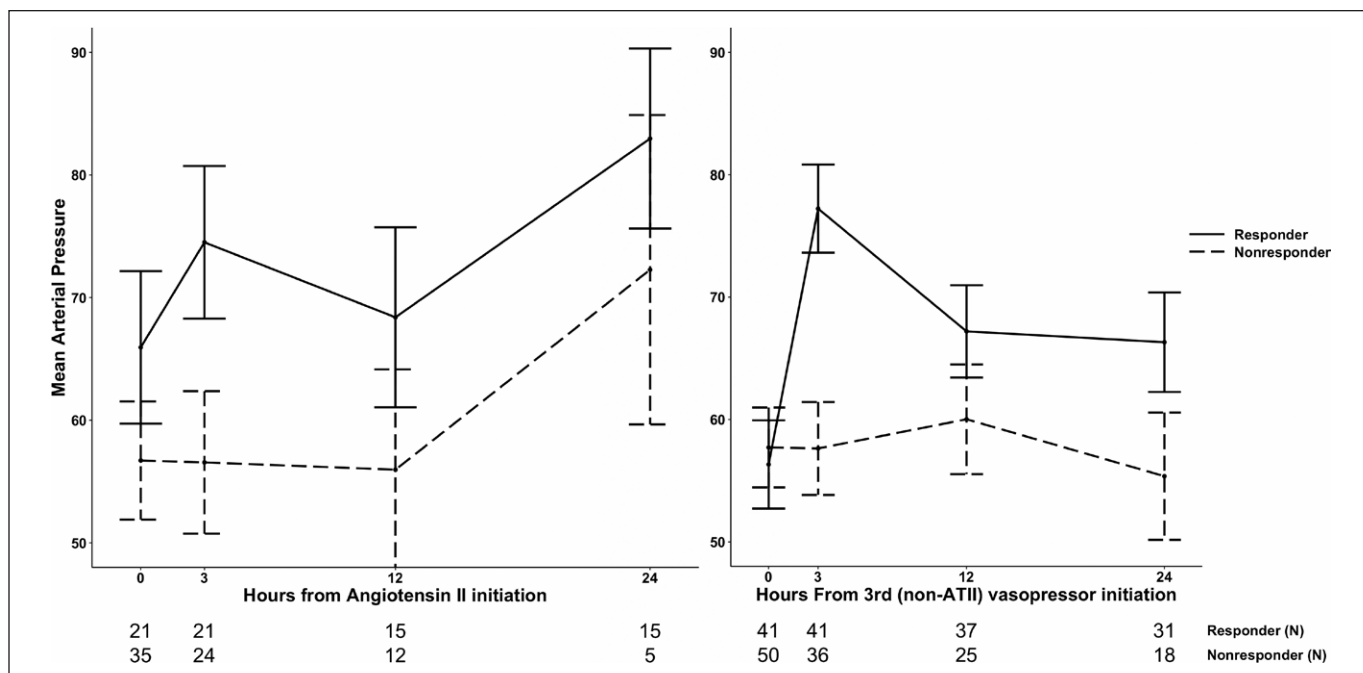


Figure 2. Hemodynamic response of angiotensin II (ATII) versus third vasopressor (non-ATII). Responder—mean arterial pressure (MAP) greater than 65 at 3 hr after third vasopressor initiation; nonresponder—MAP less than or equal to 65 at 3 hr after third vasopressor initiation. Data are mean and SE.

than 0.5 µg/kg/min at baseline (15). Patients with such high NEE dose in ATHOS-3 showed less response to ATII. Thus, our data further support the notion that ATII may not be beneficial in very sick patients with advanced refractory shock on high-dose vasopressors.

There is no clear guidance on whether increasing norepinephrine dose or adding a second vasopressor is beneficial to survival. A cost-effectiveness analysis by Lam et al (38) showed that vasopressin is most cost-effective as a second-line therapy in septic shock, compared with escalating doses of norepinephrine, or ATII as a second-line agent to norepinephrine. The use of vasopressin was associated with the highest ICU survival of 61% and the lowest cost of \$53,207. Adjunctive vasopressin resulted in the highest quality-adjusted life years (QALYs) of 4.52 compared with 3.78 and 3.95 QALY for norepinephrine monotherapy and second-line ATII, respectively. In our cost-conscious healthcare system, these results provided rationale for our institutional use of ATII only as a third-line vasopressor after norepinephrine and vasopressin.

A recent post hoc analysis of the ATHOS-3 trial may provide physiologic guidance to the administration of ATII based on serum renin level (39). As part of the renin-angiotensin-aldosterone system, renin is increased when there is insufficient production of ATII

by ACE. ACE is an endothelial membrane-bound enzyme that becomes dysfunctional with endothelial injury occurring in distributive shock. Thus, ATII and ACE levels have been shown to be decreased in sepsis and performed better than Acute Physiology and Chronic Health Evaluation II and SOFA scores in predicting outcomes (40). However, measurement of ATII and ACE is difficult. As a feedback loop, decreased ATII and ACE levels will result in increased renin, which can be easily measured by approved assays. In the ATHOS-3 trial, Bellomo et al (39) showed that baseline renin was elevated in 76% of patients. Patients who were treated with ATII had a reduction in renin of 54.3% compared with 14.1% in patients receiving placebo at 3 hours ($p < 0.01$). Importantly, in patients with elevated renin, treatment with ATII resulted in a mortality of 51.1% compared with 69.9% mortality in patients treated with placebo ($p = 0.01$). Elevated renin was independently associated with an increased risk of death (hazard ratio [HR], 2.15; 95% CI, 1.35–3.42), whereas ATII treatment in patients with elevated renin was associated with a decreased risk of mortality (HR, 0.62; 95% CI, 0.39–0.98). These results suggest that perhaps distributive shock patients with elevated renin are better candidates for the administration of ATII, resulting in improved mortality.

Our study had several limitations, including its retrospective nature and small sample size. Although our propensity-based analysis accounted for differences in our observed pretreatment covariates, there is still risk of confounding by unmeasured covariates that may have impacted both the administration of ATII and resulting mortality. Additionally, we did not evaluate safety as it would not be possible to attribute thrombosis or other adverse events to ATII given our retrospective study design. Importantly, we identified patients with distributive shock based solely on review of the medical records. We did not have complete hemodynamic profiles such as cardiac output and systematic vascular resistance to definitively select our patient population. Thus, patients may have other forms or mixed forms of shock. For example, a significant number of septic shock patients may have myocardial suppression and low cardiac output (41). It is possible that ATII would not be effective in these patients, further confounding our results. Finally, given that the majority of our patients were septic, it would have been informative to report time to appropriate antibiotics and source control.

CONCLUSIONS

In conclusion, although previous data support the use of ATII due to its favorable hemodynamic response in patients with distributive shock, there was no observed benefit in mortality, vasopressor use, or hemodynamic response with ATII in our study. It is possible that earlier initiation of ATII in the course of disease may improve hemodynamics and other patient-centered outcomes. Additionally, perhaps using ATII as a second-line vasopressor after norepinephrine may lead to a different outcome in less severe cases of distributive shock. Finally, the addition of biomarkers such as renin may better identify patients who may benefit from the addition of ATII in the management of refractory septic or distributive shock.

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