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ABSTRACT:

Objective: To assess whether or not angiotensin II in combination with current treatment has a favorable outcome in the treatment of distributive shock in terms of decreasing duration of vasopressor usage, increasing mean arterial pressure (MAP) above 65 mmHg, and improving mortality.

Design: Systematic Literature Review

Methods: Searches were conducted in PubMed, Google Scholar, and the James Madison University Library Database for the key terms angiotensin II, shock, septic shock, vasodilatory shock, distributive shock, blood pressure, double-blind, humans, and vasoconstrictor agents. Search results were filtered by year, for animal trials, irrelevant therapies, meta-analysis, retrospective studies, and case studies. Only original studies published within the last ten years that used angiotensin II for human trials in the treatment of distributive shock were included in the review.

***Results*:** Two of three studies showed statistically significant data supporting the ability of angiotensin II to increase MAP above 65 mmHg; however, statistical significance was not found in the reduction of mortality.

***Conclusion*:** The addition of angiotensin II to current standard therapy for the treatment of distributive shock decreases the requirement for vasopressors and increases MAP. Further studies are needed to address the long-term effects of angiotensin II and to investigate outcomes in specific types of shock such as sepsis-induced and anaphylaxis.

INTRODUCTION:

Distributive shock, the most common type of shock, poses an extensive challenge to healthcare providers[1]. This potentially life-threatening process is the result of disease states such as anaphylaxis and sepsis due to their extreme inflammatory nature. The in vitro response to foreign antigens activates an immune response manifesting in exaggerated vasodilation with increased vascular permeability. Distributive shock's pathophysiology encompasses widespread vasodilation resulting in compromised blood flow to all vital organs, including the brain, kidneys, heart, and more. The complexity of organ system involvement and its rapid progression to multi-organ failure (MOF) makes it both demanding and multimodal in its management[2]. Other types of shock including cardiogenic, hypovolemic, and obstructive are less systemic compared to distributive shock and have better established, more effective courses of treatment[1].

While evaluating distributive shock, practitioners often enlist grading systems to determine the severity of illness as well as predict mortality. Acute Physiologic and Chronic

Health Evaluation II (APACHE II) is readily used in critical care patients, primarily looking at survivability[3]. This tool considers age, underlying health, vital signs, current diagnosis, and many other variables that together produce an illness severity score[3,4]. The higher the score, the more severe the illness[4]. Another commonly used tool is the Sequential Organ Failure Assessment (SOFA). This grading system is heavily focused on septic patients experiencing shock and determines mortality and morbidity by evaluating major organ dysfunction[4]. Again, the higher the score, the more severe the organ dysfunction[4]. Together, these assessments can assist with detecting trends in disease resolution as well as predict patient survivability.

According to current guidelines, the goal of all treatment in patients with distributive shock is to restore a mean arterial pressure (MAP) at or above 65 mmHg[5]. This recommendation is based on the desire to restore perfusion without extreme use of vasoconstrictors[6]. Best results are seen with a MAP between 60 and 65 mmHg, and the time spent below these values correlated with risk of mortality, and no additional survival benefit is found with higher MAP thresholds[6]. The first-line treatment for this syndrome involves the aggressive use of intravenous fluid boluses[5]. If the hypotension is refractory to fluid resuscitation, intravenous vasopressors such as norepinephrine and vasopressin can be given as a last resort to increase vasoconstriction and tissue perfusion[5]. However, these treatments are found to induce immunosuppression and cause cardiac toxicity, heart failure, and mesenteric ischemia[2]. For this and other reasons, the use of vasopressors is limited to patients in extremis (nearing death)[5]. These critical patients, with severe hypotension despite the use of vasopressors, still have a poor prognosis with 30-day all-cause mortality exceeding 50%[7].

A treatment regimen for distributive shock, initially studied in the 1960s, has found new vitality in recent promising studies[8]. Angiotensin II, in its synthetic form, works similarly to its endogenous cousin found within the endocrine system. It increases blood pressure through a variety of mechanisms, including sodium and water reabsorption from increased aldosterone and antidiuretic hormone (ADH) release, systemic arteriolar vasoconstriction, and sympathetic nervous system stimulation[9,10]. With its diminished side effect profile, as compared to vasopressors, this revitalized intervention may prove to benefit many patients experiencing distributive shock.

Case:

A 56-year-old male was brought to the emergency department as a high acuity trauma patient after being struck by a vehicle. He presented with hemodynamic instability with multiple injuries that later resulted in septic shock. High dose vasopressors, including norepinephrine, Vasopressin, and Epinephrine were introduced but failed to achieve a MAP of 60mmHg. Due to his rapidly deteriorating state, angiotensin II was initiated in hopes of increasing and potentially stabilizing his blood pressure. The target blood pressure was achieved within three hours, and angiotensin II was tapered down to a low dose level within 48 hours of initiating treatment. After three days of the angiotensin treatment regimen, the patient was no longer in need of vasopressors and was stabilized to the point of referral to acute rehabilitation[2,11].

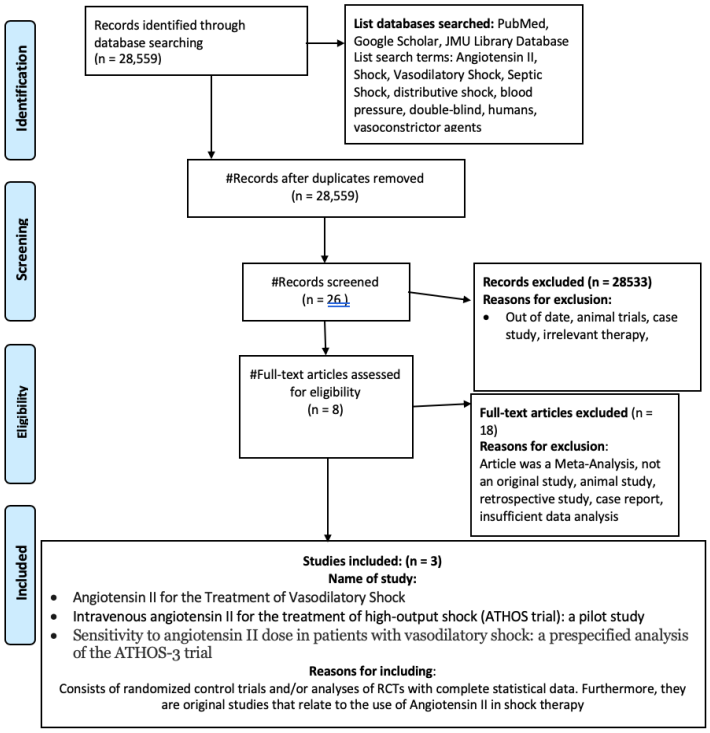
PICO:

Population: Patients experiencing distributive shock
Intervention: Angiotensin II plus Standard Therapy of IV fluids and vasopressors
Comparison: Standard Therapy alone
Outcome: Stabilized mean arterial pressure (MAP) and decreased mortality at one month

CLINICAL QUESTION:

In patients experiencing distributive shock, is the addition of angiotensin II to standard therapy of IV fluids and vasopressors, more effective at stabilizing mean arterial pressure and decreasing mortality?

Figure 1. *PRISMA diagram depicting literature review*



METHODS:

We initiated a literature review search in September of 2019 using PubMed, Google Scholar, and the James Madison University Library Database to identify reputable studies that assessed the addition of angiotensin II in the treatment of distributive shock.

The following search terms were used to filter database outputs: angiotensin II, shock, septic shock, vasodilatory shock, distributive shock, blood pressure, double-blind, humans, and vasoconstrictor agents. These keywords identified 28,559 articles after removing duplicates. Of the 28,559 articles, we excluded 28,533 from our literature review. The exclusion criteria of these 28,533 articles included: out of date articles, animal-only studies, case studies, and irrelevant therapy that is out of scope to our clinical question. Following this screening, an assessment of the remaining 26 articles found only eight articles eligible for a full-text review. The reasons for exclusion of those 18 articles were: the article was a meta-analysis, was not an original study, was an animal study, was a case report, and lastly had insufficient data analysis. Of these eight articles, three were found to be randomized control trials (RCT) or analysis of RCTs with

complete statistical data. Furthermore, these three articles are original studies directly researching the use of angiotensin II in distributive shock therapy. Table 1 provides an overview of the articles chosen for inclusion.

Table 1. *Overview of Reviewed Studies*

	Study 1: Chawla LS, Busse L, Brasha-Mitchell E, et al.	**Study 2: Khanna A, English S, Wang X, Ham K, et al.**	**Study 3: Ham KR, Boldt DW, McCurdy MT, et al.**
Year published	2014	2017	2019
Journal	*Critical Care*	*New England Journal of Medicine*	*Annals of Intensive Care*
Study design	RCT	RCT	Pre-specified analysis
Sample size	20	321 patients	163 patients
Study duration	30 days	28 days	28 days
Efficacy outcomes	Establish dosage range for angiotensin II and determine the effect of the angiotensin II infusion on the standing dose of norepinephrine required for a MAP of 65 mmHg	Primary - increase in MAP within 3 hours of initiating treatment Secondary - change in cardiac and total SOFAscore Other - all cause mortality at day 28	Increase in MAP within 3 hours of initiating treatment, change in norepinephrine dose from baseline, and mortality on day 28
Treatment groups	Study Drug, n = 10 Placebo, n = 10	Standard treatment plus angiotensin II, n = 163 Standard treatment with placebo, n = 158	≤5 ng/kg/min of angiotensin II, n = 79 >5 ng/kg/min of angiotensin II, n = 84

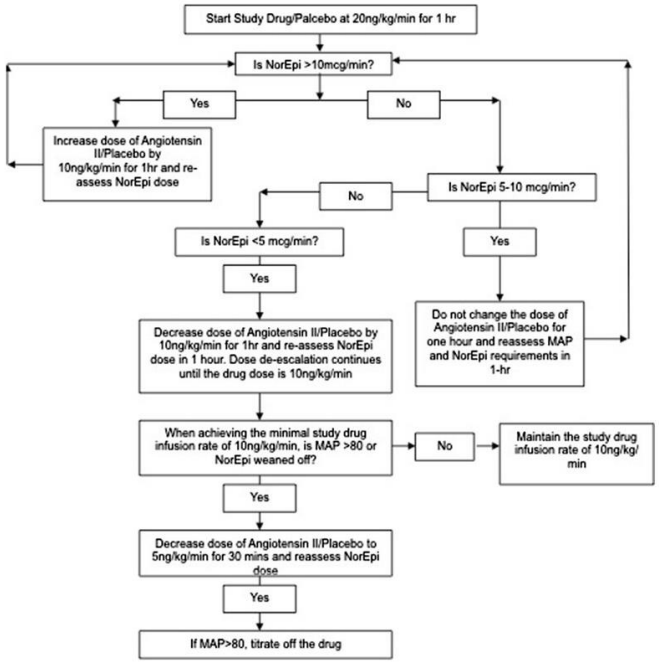
Study 1 - Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study - Chawla LS, Busse L, Brasha-Mitchell E, et al.[10]

Objective: In this study, Chawla et al. hypothesized that angiotensin II could be an effective vasopressor in the management of shock; however, the appropriate dose needed to increase blood pressure was unknown. Thus, they set an objective to determine the dosage range of angiotensin II (ATII) ideal for the control of distributive shock.

Study Design:

The investigators conducted a randomized, double-blind, placebo-controlled safety, and dose-finding feasibility study with the assistance of the Investigational Drug Services (IDS) at George Washington Hospital in Washington, D.C. The primary endpoint was the effect of the ATII infusion on the standing dose of norepinephrine that was required to maintain a MAP of 65 mmHg.

Figure 2. Study Drug Titration Protocol[10].



Twenty patients were enrolled in the study and were assigned to two cohorts using a simple computerized randomization procedure. Ten patients were assigned to receive the study drug infusion of angiotensin II acetate, and the remaining ten were assigned to receive the placebo infusion of normal saline. Both groups also received the standard-of-care treatment for high-output shock. All 20 patients who enrolled in the study were able to complete the study. The investigation was conducted for a total of 8 hours, with dose adjustments made hourly per a pre-specified protocol needed to maintain a MAP at or above 65 mmHg. The study drug titration protocol (Figure 2) was designated to elucidate the dose of angiotensin II that was required (in conjunction with a norepinephrine dose between 5 and 10mcg/min) to achieve the MAP goal of 65 mmHg. At the end of 6 hours, the study drug was down titrated and discontinued by 8 hours.

Table 2 - *Study 1 Inclusion and Exclusion Criteria*[10]

Inclusion Criteria	Exclusion Criteria
● ≥ 21 years old ● Deemed to be in high output shock (defined as a cardiovascular sequential organ function assessment (SOFA) score of 4 as well as a cardiac index >2.4 L/min/BSA 1.73 m2 ● Indwelling arterial line present ● Urinary catheter present ● Expected to be present for at least 12 hours during the study ● Deemed adequately volume-resuscitated and clinically assessed not to be volume responsive	● Acute coronary syndrome ● Hx of vasospasm or asthma ● Currently experiencing bronchospasm ● Active bleeding with an anticipated need for transfusion of: ○ >4 units of packed RBCs ○ >7 g/dL hemoglobin ○ Any condition that would contraindicate drawing serial blood samples

Study Results:

Overall, the study found that angiotensin II resulted in the reduction of norepinephrine dosing in all patients. After the first hour of treatment the required norepinephrine dose for the cohort receiving angiotensin II was 7.4 +/- 12.4 mcg/min versus 27.6 +/- 29.3 mcg/min for the placebo cohort (P=0.06). Furthermore, the investigators were able to down titrate angiotensin II levels in each study group per the titration protocol to the lowest predetermined level, and norepinephrine remained lower than those used in the placebo group. Hours 1 and 2 of the study approached statistical significance; however, throughout the entire course of the study no statistical significance could be found to show angiotensin II was better at reaching a MAP of 65 as compared to standard treatment with placebo (P = 0.13). Therefore, the investigators failed to reject the null hypothesis (ATII has no effect on distributive shock), indicating that this experiment has significant type II error and low statistical power. That said, the purpose of the study was to determine the best dosage range of angiotensin II to increase blood pressure in high output shock. Before this investigation, no established dosage range existed. This study identified both a range (5 to 40 ng/kg/min) and starting dose (2 to 10 ng/kg/min), which they believed to be best suited for follow up studies.

Study Critique:

This pilot study was remarkable in concept considering the authors recognized the need for additional therapeutic options for high output shock. They then constructed a study using an innovative, yet highly intuitive concept, involving angiotensin II, a critical blood pressure

regulating hormone. To test the concept, the authors took steps to reduce bias and error, via a double-blind, randomized control trial, and ensured safety by assigning an independent data and safety monitor. Although angiotensin II does show promise as a vasopressor in the treatment of high-output shock, this study lacked the statistical power and proper inclusion criteria needed to produce results of statistical significance. The authors noted significant heterogeneity in patients' responses to angiotensin II, which they did not expect. This could be a result of the inclusion criteria allowing critically ill patients with extremely low chance of survival to be part of the study. The variety of diseases and degrees of severity could have significantly impacted the unexpected heterogeneity. This variation likely further impeded the studies' ability to find statistical significance in the use of angiotensin II. Overall, this was a well-designed study that served as a proof of concept to prompt additional more extensive studies with more specific criteria for participation.

Study 2 - Angiotensin II for the Treatment of Vasodilatory Shock - Khanna A, English S, Wang X, Ham K, et al.[7]

Objective: The purpose of this study was to evaluate the efficacy of angiotensin II in patients experiencing distributive (vasodilatory) shock unresponsive to vasopressors.

Study Design:

The investigators conducted a randomized, double-blind, placebo-controlled trial from May 2015 through January 2017 in 75 intensive care units throughout North America, Australia, Asia, and Europe. The primary endpoint included an increase in MAP to at least 75mmHg or an increase of 10 points from baseline without increasing the vasopressor dose, all within 3 hours of initiating treatment. The secondary endpoint involved a change in cardiovascular and total SOFA scores between the baseline measurement and day two after beginning the intervention. A final endpoint, all-cause mortality at day 28, was also included. 404 patients were screened with 344 meeting inclusion criteria (table 2); however, 23 of the patients that underwent randomization did not receive a placebo or intervention. This was due to rapid improvement, rapid decline, withdrawal of consent, and physician decision. Randomization was stratified based on MAP of <65 mm Hg or ≥65 mm Hg and APACHE II score ≤30, 31-40, or ≥41. Both groups were similar

in age, gender, MAP, APACHE II score, cardiac index, vasopressor use and dose, and cause of shock. With the final total of 321, angiotensin II was given to 163 patients, and 158 received the placebo (normal saline infusion).

Table 3 - *Study 2 Inclusion and Exclusion Criteria*

Inclusion Criteria	Exclusion Criteria
● ≥ 18 years old ● Vasodilatory shock refractory to fluid resuscitation (≥25mL/kg within last 24 hours) and high dose vasopressors ○ Vasodilatory shock = cardiac index >2.3L/min/m^2 or central venous O2 saturation >70% plus central venous pressure >8mmHg, with a MAP of 55-70mmHg ○ High dose vasopressors = >0.2μg/kg/min of norepinephrine or equivalent dose of another vasopressor between 6 and 48 hours	● Burns with >20% TBSA ● Acute coronary syndrome ● Bronchospasm ● Liver failure ● Mesenteric ischemia ● Active bleeding ● Abdominal aortic aneurysm ● Absolute neutrophil count <1,000/m^3 ● Treatment involving venoarterial extracorporeal membrane oxygenation ● Treatment involving high dose glucocorticoids

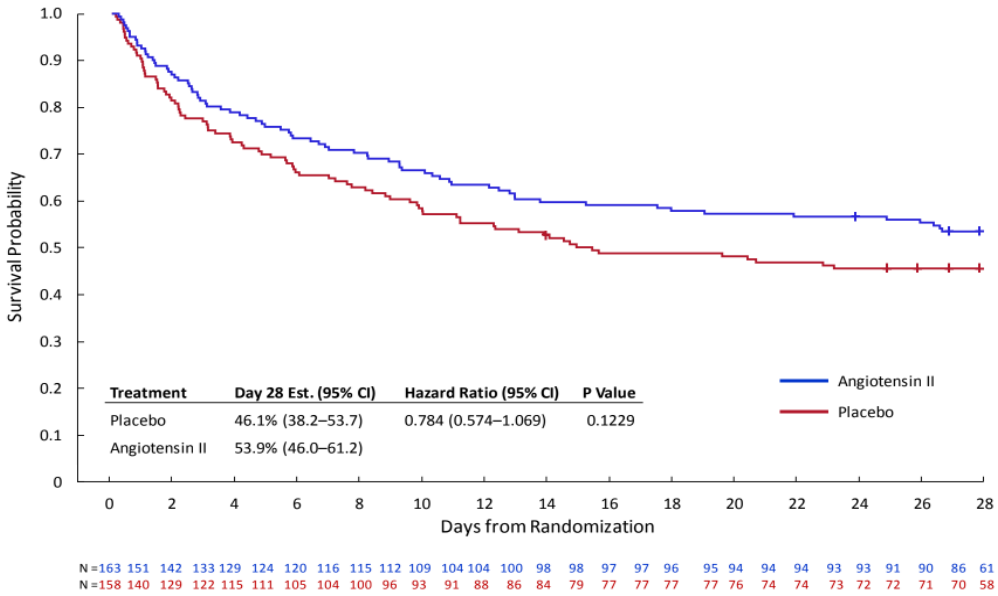
The treatment arm received 20ng/kg/min of angiotensin II and could be adjusted to reach a MAP of at least 75mmHg within the first three hours. Vasopressors were provided in conjunction but held at a constant rate during the intervention and could not be increased unless safety deemed it necessary. If vasopressors were increased, the patient was determined to be unresponsive to angiotensin II. After three hours and 15 minutes, the study drug or placebo, as well as vasopressors, were allowed to be adjusted to reach a MAP between 65 and 75mmHg. The study infusion was discontinued after 48 hours per protocol but could be continued for up to 7 days if the patient remained unstable or required increased doses of vasopressors.

Study Results:

Overall, the ATII group more readily achieved the goal MAP after three hours (69.9%) as compared to the placebo group (23.4%; P <0.001). The intervention group rapidly improved their MAPs, allowing the study drug to be decreased within the first 30 minutes in 67% of the patients, thus allowing the background vasopressors also to be lowered. The angiotensin II group also achieved a greater response if lower doses of norepinephrine were used compared to higher doses (P <0.001). Vasopressors were consistently decreased within the first 48 hours of treatment compared to the placebo group. Cardiovascular SOFA scores were more improved in the angiotensin II group (-1.75) than compared to the placebo group (-1.28) at hour 48 (P = 0.01). The total SOFA score, however, increased similarly in both groups (P = 0.49).

Discontinuation of treatment (placebo and angiotensin II) occurred in patients experiencing adverse outcomes such as septic shock, multiorgan failure, cardiogenic shock, and cardiac arrest. This occurred in 14.1% of the angiotensin II group and 21.5% of the placebo group. Other adverse events, including distal ischemia, ventricular tachycardia, and atrial fibrillation, were found to be similar among the two groups; however, the absolute heart rate was higher in the ATII group. Predictors for a negative outcome were hypoalbuminemia (P = 0.002) and the need for increased vasopressor dose (P = 0.006). The only predictor for a positive outcome was the treatment assignment (P <0.001). No deaths occurred in either group during the initial adjustment period, but death on day seven occurred in 28.8% of the experimental group and 34.8% in the control group. By day 28, 46% of the angiotensin II group died, and 53.8% of the placebo group died (P = 0.12). These results were found to be similar after adjusting for age and sex. The Kaplan-Meier survival plot seen in Figure 2 indicates that angiotensin II is associated with reduced mortality by day 28.

Figure 2. *Kaplan-Meier Survival Plot Over 28 Days After Treatment Initiation*[6]. Angiotensin II is noted to have reduced mortality as compared to placebo.



Study Critique:

This study took on the formidable task of attempting to reduce mortality in shock patients not responding to standard treatment. The investigators achieved this by demonstrating that the intervention, angiotensin II, rapidly improved patients' MAP while subsequently reducing the

need for background vasopressors, all with a strong P-value of <0.001. They also found that the intervention group experienced reduced mortality at day 28, as compared to the placebo group; however, the differences were not significant (46% vs. 53.8% mortality rate).

Overall, the study had many strengths, including that it was double-blinded with block randomization, reducing potential bias. Both angiotensin II and placebo were packaged identically to maintain blinding. It was also conducted internationally in 75 different ICUs providing diversity in the patient population; however, this could also be viewed as a weakness if there is a discrepancy in the standardization of treatment between hospitals. The investigators determined that the sample size of more than 150 patients per group provided greater than 90% power, thereby reducing the chance of type II errors. Not only this, but they also implemented an intention to treat analysis to preserve the statistical power. The investigators also determined what factors would predispose a patient to have a negative outcome, like hypoalbuminemia, for example. The unfortunate outcome is likely due to persistent hypotension as a result of reduced tonicity, causing decreased intravascular volume.

Despite these meaningful findings, the study did have its drawbacks, including sole sponsorship and funding from La Jolla Pharmaceutical Company. This conflict of interest suggests a heavy bias for the success and approval of angiotensin II in treating distributive shock. Not to mention, the blinding of investigators may have been ineffective in the angiotensin II group, who likely experienced rapid improvement in MAP, thus providing further bias. The investigators also utilized an expansive list for excluding patients (refer to table 1), but did not explain why these conditions were deemed ineligible. Another weakness was that the mortality endpoints were found to have wide confidence intervals indicating that the sample size was too small in evaluating mortality. This may also account for the poor P values associated with all-cause mortality by day 28. These wide intervals further contradict the investigator's statement of the study having appropriate statistical power. In future studies, the investigators will need to increase their study population to narrow the confidence intervals. Lastly, the investigators only followed their patients to day 28 after receiving treatment. With this short follow up period, long term effects of angiotensin II cannot be determined.

Study 3 - Sensitivity to angiotensin II dose in patients with vasodilatory shock: a prespecified analysis of the ATHOS-3 trial - Ham KR, Boldt DW, McCurdy MT, et al.[2]

Objective: To compare outcomes among shock patients requiring ≤5 ng/kg/min of angiotensin II as compared to needing >5 ng/kg/min at 30 minutes with the goal to reach a MAP ≥75 mmHg.

Study Design:

This analysis reviewed the previous study, *Angiotensin II for the Treatment of Vasodilatory Shock (ATHOS-3 trial)*, in an attempt to determine if greater benefits were observed with different dosages of ATII. The analysts utilized the same patient population as well as inclusion and exclusion criteria (refer to table 3); however, they only drew conclusions from the group receiving angiotensin II. The intervention group was further stratified in this analysis based on the dosage needed at 30 minutes to maintain a MAP ≥75mmHg or improve from baseline by 10 points. The starting dose of angiotensin II was 20 ng/kg/min; 79 out of 163 patients required ≤5 ng/kg/min at 30 minutes, and the remaining 84 required >5 ng/kg/min. Baseline endogenous angiotensin I and II levels were obtained for later data extrapolation. Background vasopressors were held constant unless an increase was needed for safety purposes. Responses to ATII were reevaluated at 3 hours, 48 hours, and lastly, at day 28.

Study Results:

At baseline, the ≤5 ng/kg/min group was more likely to have a higher MAP ($P < 0.0001$) and lower vasopressor dose needed ($P < 0.0058$) as compared to the >5 ng/kg/min group. The ≤5 ng/kg/min group was also more likely to have lower endogenous angiotensin I ($P < 0.0058$) and II ($P < 0.0009$) levels at the start of treatment. 89.9% of the lower dose group had achieved the goal MAP response by the third hour, compared to 51.2% of the higher dose group ($P < 0.001$). The lower dose group also required less background vasopressor use between three and forty-eight hours. By the 48th hour, 52% of the ≤5 ng/kg/min group had discontinued all other vasopressors versus 30% of the other group. Total SOFA and cardiovascular SOFA scores had considerably more improvement in the group with earlier angiotensin II sensitivity. Patients receiving higher doses of angiotensin, on the other hand, were more likely to experience adverse events, possibly resulting in discontinuation of the intervention. Adverse events included septic shock, atrial fibrillation, multiorgan failure, hypotension, thrombocytopenia, and hypokalemia.

On day 28, 67% of the lower dose group remained alive, whereas only 41% of the higher dose group remained as seen in figure 3 (P <0.0007). Overall, it was found that survivability was more attainable for patients needing lower doses of the intervention drug due to their low baseline endogenous levels of angiotensin II (refer to figure 4).

Figure 3. *Survival probability depending on Angiotensin II dosing*[2]. Providing a dose of ≤5 ng/kg/min is shown to provide increased survivability as compared to receiving >5 ng/kg/min.

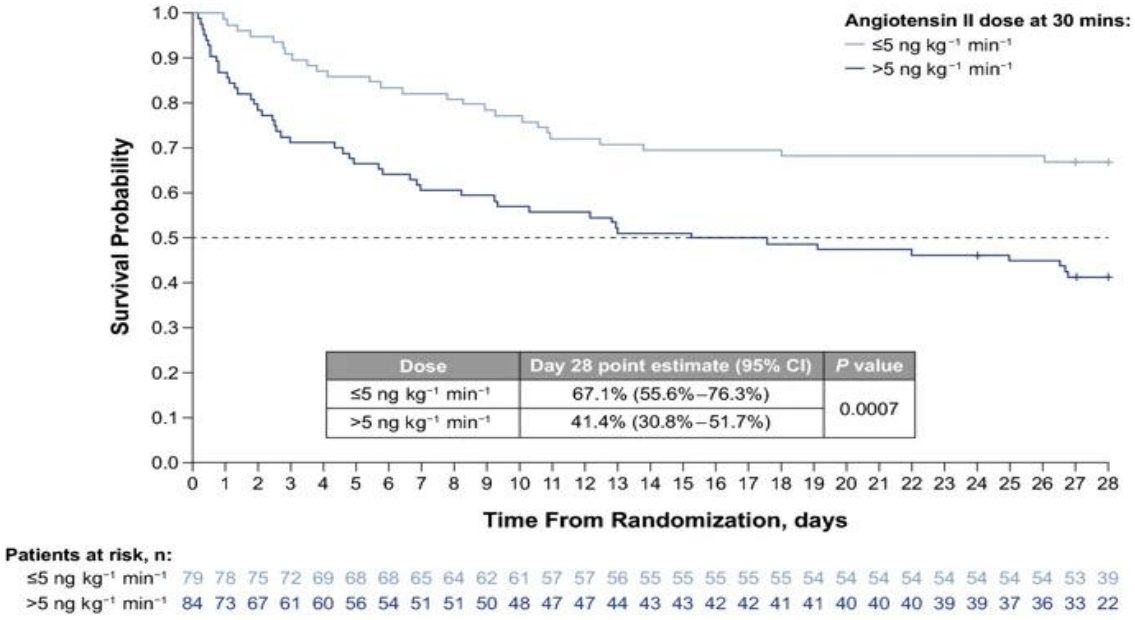
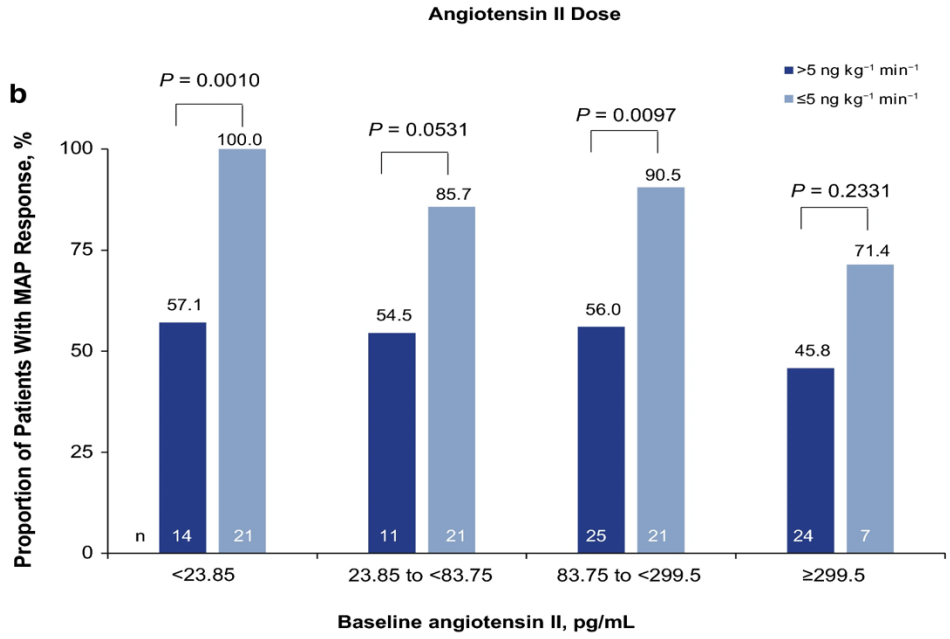


Figure 4. *Baseline Angiotensin Levels Compared to MAP Response*[2]. Patients given lower doses of angiotensin II were consistently found to have improved MAP, particularly if endogenous levels were decreased.



Study Critique:

Through the analysis of the Athos-3 trial, this study found that down titration of angiotensin II (≤5 ng/kg/min) was associated with better outcomes and reduced mortality. They presumed this was due to lower baseline levels of endogenous angiotensin II, allowing for a more exaggerated response to exogenous sources. Overall, this analysis provided data with strong significance, as indicated by their P values.

Regardless of these promising findings, this analysis holds similar flaws noted in study 2 since the same patient population and methods were utilized. The La Jolla Pharmaceutical company was again found to be the sole sponsor of this analysis, further suggesting that these experiments held biases for the success of this intervention. Also, since this analysis drew information only from the treatment group in study 2, the sample size was found to be small, indicating low power and increased risk for type II errors. Outside of study 2, this analysis was also noted to have confounding variables associated with the interpretation of survivability at day 28. The investigators stated that the reduced mortality at day 28 in the lower dose ATII group was likely related to the patients having better prognostic characteristics and therefore increased responsiveness to the intervention. This skews the data and makes it less reliable for extrapolation to the general population experiencing distributive shock.

DISCUSSION:

Distributive shock is a life-threatening condition characterized by rapid deterioration and impending multi-organ failure if left untreated. The associated inflammatory response and consequential vasodilation cause widespread hypotension resulting in critically ill patients facing morbidity and possible mortality. At present, there is little to be offered to these patients apart from the standard therapy that makes no promises of reversing this disease state. Fluid resuscitation and vasopressor therapy have been the last resort up until a new intervention was found to provide favorable outcomes. This review was aimed at evaluating the efficacy of this new treatment, angiotensin II, by analyzing three studies that targeted the elevation response of MAP as compared to standard therapy in distributive shock patients; Table 1 provides an overview of each of the studies.

The first study, although small in size and with low power, determined that ATII can reduce the need for background vasopressors (norepinephrine, specifically). Data were extrapolated using the outcomes found in the second study for percentages of patients who

achieved the desired MAP in both the study group and the placebo group. These calculations determined that the minimum sample size needed in the first study to reduce type II error below 20% and statistical power above 80% is n = 34. The study population used, however, consisted of only 20 patients. Although this analysis takes a reversed approach to determine the statistical error, it gives some clarity and causality to the statistically insignificant results in study 1. Despite the results, the clinical findings still have meaningful implications, particularly in regard to diminishing the adverse side effect profile of vasopressors such as tachycardia, severe hypertension, arrhythmias, shortness of breath, and decreased distal extremity tissue perfusion[2]. These well-known complications are extreme and have generated many necessary cautions associated with vasopressors, further limiting the utility of these drugs in treating distributive shock. The inclusion and exclusion criteria of this study allowed for a high variation in disease states, and the severity of illness in many patients may have had a limiting effect on angiotensin II responsiveness. Despite these complicating factors, in hours 1 and 2 of the study, ATII resulted in the reduction of norepinephrine vasopressors in all patients. By utilizing ATII in conjunction with vasopressors, treatment and prognosis can be more favorable. This pilot study, overall, served as an excellent step-off point for larger studies. Investigators identified multiple weaknesses that could serve as a guide for future investigations.

The larger second study supported the findings of the previous study with improved statistical significance and statistical power. Patients receiving ATII compared to placebo experienced rapid improvement in MAP, allowing not only the intervention drug to be reduced but also concurrent use of vasopressors. This bolsters the argument that ATII can be protective in avoiding the adverse effects associated with vasopressor use. Additionally, angiotensin II improved the cardiovascular SOFA score, thereby improving their prognosis; however, the total SOFA score worsened in both groups. The decline in total SOFA, which accounts for a variety of organ systems, can likely be attributed to these patients being critically ill at baseline as well as having inconsistent underlying etiologies. General side effects observed included distal ischemia, ventricular tachycardia, and atrial fibrillation, all of which were found to be similar among the two groups. These side effects cannot be extrapolated and applied to ATII only; instead, they may be consequences of the distributive shock itself since both groups were affected equally. Severe adverse outcomes resulting in discontinuation of treatment (multiorgan failure, cardiac arrest, etc.) were more common amongst the group not receiving ATII, reinforcing the statement

that ATII can improve outcomes. By the final day of the study, increased death was associated with the use of placebo, but the discrepancy between mortality rates amongst both groups was not extreme (53.8% vs. 46%). The high mortality rate in both patient groups can be attributed to the severity and poor prognosis of shock, even with appropriate interventions put in place. Distributive shock, with its differing etiologies, is a demanding, multifactorial challenge for medical providers, but with the use of angiotensin II, reduction, albeit minor, can be seen in mortality rates.

Although ATII has been proven to drastically improve MAP, it is essential to discern the optimal dosage needed. Through the analysis of the large Athos-3 trial (study 2), the final study determined that less is more when giving angiotensin II. More significant MAP improvements were observed if $\leq$5 ng/kg/min was given in conjunction with background vasopressors. Providing lower doses were also associated with the need to down-titrate the concurrent vasopressors to the point that they were discontinued. Higher doses of angiotensin II were associated with more adverse events (atrial fibrillation, hypokalemia, etc.) and increased mortality at day 28, further signifying the importance of finding an optimal dosage. Despite the lower dose group showing more promising outcomes, these patients were also found to have lower baseline endogenous angiotensin I and II levels making them more sensitive to exogenous sources. This begs the question, is this treatment able to be extrapolated to the general population, or does it have more narrow indications?

An interesting phenomenon was discovered during this review. Although there was no intention to select related studies, inadvertently, three highly interconnected investigations were found. The first study, a pilot study, provided proof of concept for the use of angiotensin II. The second reviewed study was the first major follow up on research to the pilot study. The third article identified a narrow topic from within the second study and further extrapolated data, drawing even more conclusions. Throughout our review, we identified several critiques for each investigation. However, when viewed through a more macro lens that combines all three studies, it is more clear as to why the authors made specific decisions. For example, it was noted that the first article did not provide enough inclusion and exclusion criteria to gather a sample population from which significant statistical data could be drawn. The second study was criticized for having extensive inclusion and exclusion criteria but with no explanation as to why each item was selected. From the macro perspective, we can see the progression of decisions made by

investigators who took the lessons learned of the first study in the development of the second study.

Possibly the greatest conflict of interest found repeatedly throughout this review, is the strong influence of La Jolla Pharmaceutical company, whose only current product is angiotensin II (Giaprez)[12]. The second and third studies reported sole sponsorship via this pharmaceutical company which implies strong bias and desire for positive outcomes. It is possible that unfavorable data were excluded with the intent of making this product more appealing. Further limitations include the lack of explanation for highly specific inclusion and exclusion criteria, as touched on earlier. Although the specifics of these criteria can be inferred from each study's results, explanations for excluding particular populations should be included for clarification as well as future contraindications for this drug.

The second and third studies show clear statistical significance; however, the question still exists as to the clinical relevance of angiotensin II in the treatment of distributive shock. Calculating the number needed to treat (NNT) demonstrates that thirteen patients with distributive shock must be treated with ATII for one patient to have a positive outcome. It is important to remember that this patient population is in extremis and often have a low chance of survival. In terms of MAP improvement, the NNT reveals promising data for future use considering only two patients are needed to elicit one positive outcome. Taking into consideration the low side effect profile of ATII, it is clinically appropriate to add ATII to the standard treatment for distributive shock as this course of action adds negligible chances of harm and a known benefit that may be lifesaving for that patient.

These studies were published in 2014, 2017, and 2019 respectively, and quickly gained traction in the medical community. By December 2017 the FDA expedited approval for the first synthetic angiotensin II medication, Giapreza[13]. Since its release, some unforeseen hazards have come to light such as the development of venous and arterial thrombotic and thromboembolic events. Current recommendations advise concurrent venous thromboembolism prophylaxis when using giapreza[14]. As stated earlier, each of the studies had minimal follow up (28 or 30 days) restricting their ability to evaluate for adverse side effects. Future more in depth studies will be needed to expand the understanding of ATII and its possible harmful effects.

One final important consideration is the screening angiotensin levels prior to initiating treatment. As stated earlier, worse outcomes were observed with patients needing higher level

doses of ATII with concurrent elevated endogenous levels; whereas, better outcomes were seen in patients requiring lower doses of ATII with concurrent lower endogenous levels. The pathophysiology of this finding is unclear. One plausible explanation for those patients needing lower doses of ATII is that these patients may be less critically ill. As sepsis progresses through the body, there is a broader systemic vasodilatory response. Patients with lower levels of endogenous angiotensin II may, again, be less critically ill; thus, there is less hormonal compensation from the body to help regulate/maintain a functional MAP. Furthermore, the reason patients with elevated baseline ATII levels do not respond as well could be from two plausible causes. First, they are more ill, meaning that endogenous responses with ATII are already occurring, making it more difficult for the body to respond to exogenous treatment. Second, ATII has tachyphylaxis like properties inducing a ceiling effect for the intended response. Each of the above hypotheses warrants further investigation.

CONCLUSION:

A treatment regimen for distributive shock, initially studied in the 1960s, has found new vitality in recent promising studies[8]. This research has discovered that angiotensin II used in combination with vasopressors rapidly stabilizes MAP and decreases 30-day mortality rates. While maintaining MAP, angiotensin II can also reduce the necessary doses of vasopressors, thereby minimizing their dangerous side effect profile[7,8,10]. Thrombotic events were identified following the clinical use of angiotensin II; however, this adverse side effect is well mitigated with VTE prophylaxis and continues to have a better side effect profile than that of vasopressors. Longitudinal studies are needed to assess the long-term effects of ATII as this data is currently unknown. It is worth considering if angiotensin II will have further indications pending future investigation, such as experimenting with other forms of shock or sepsis alone.

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