Angiotensin II in the Treatment of Distributive Shock, an Old Theory Revitalized

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INTRODUCTION

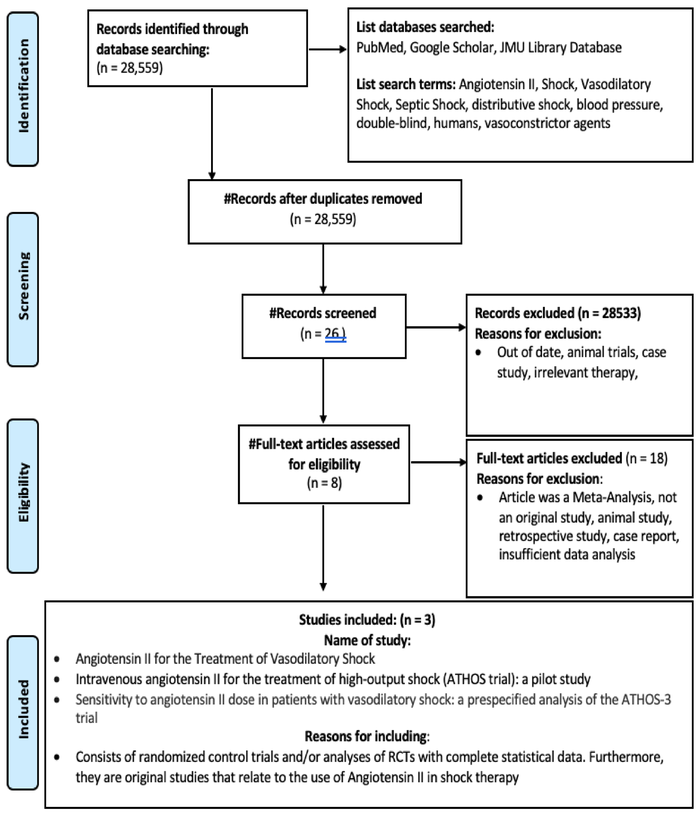
- Distributive shock is the most common category of shock and poses an extensive challenge to healthcare providers[1].
- The goal of all treatment in patients with distributive shock is to restore a mean arterial pressure (MAP) at or above 65 mmHg[2].
- Current guidelines recommend vasopressors in septic shock treatment. However, vasopressors are limited to patients in extremis (nearing death)[2] because they are found to induce immunosuppression and cause cardiac toxicity, heart failure, and mesenteric ischemia[3].
- Synthetic Angiotensin II is a newly suggested pharmacologic therapy for distributive shock due to the multiple endogenous hormonal pathways by which it elevates blood pressure and its limited side effect profile.

CLINICAL QUESTION

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

METHODS

Figure 1. *PRISMA Flow Diagram*

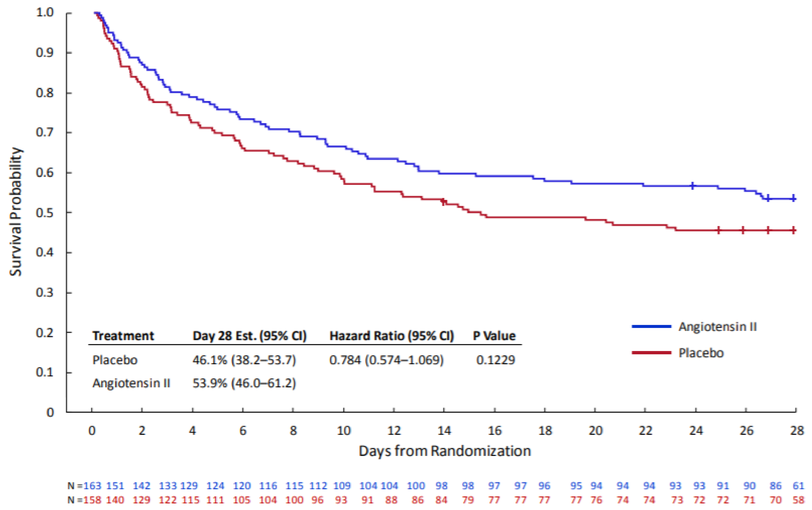


RESULTS

Table 1. *Overview of Reviewed Studies and Results*

	Study 1: Chawla LS, Busse L, Brasha-Mitchell E, et al.[4]	**Study 2: Khanna A, English S, Wang X, Ham K, et al.[5]**	**Study 3: Ham KR, Boldt DW, McCurdy MT, et al.[6]**
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
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
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
Results		Angiotensin II group achieved goal MAP after 3 hours (69.9%; P <0.001) Cardiac SOFA scores improved in the angiotensin II group (P = 0.01). Total SOFA score worsened (P = 0.49) By day 28, 46% of the angiotensin II group died (P = 0.12)	89.9% of the ≤5 ng/kg/min group achieved goal MAP response by the 3rd hour, compared to 51.2% of the >5 ng/kg/min group (P <0.001) At hour 48, 52% of the ≤5 ng/kg/min group discontinued all vasopressors versus 30% of the other group On day 28, 67% of the lower dose group remained alive and only 41% of the higher dose group remained (P <0.0007)
Strengths and/or Limitations		Strengths Double-blinded with block randomization Conducted studies internationally in 75 different ICUs Implemented an intention to treat analysis to preserve statistical power Limitations Funding by La Jolla Pharmaceutical	Strengths Strong significance with high P values Limitations Funding by La Jolla Pharmaceutical Small sample size with low power

Figure 2. *Kaplan-Meier Plot of Survival Over 28 Days*[6] – Angiotensin II shows improvement in all cause mortality on day 28.



CONCLUSIONS

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.

REFERENCES

1. David F Gaieski MD, Mark E Mikkelsen MD. Definition, classification, etiology, and pathophysiology of shock in adults. UpToDate. https://www.uptodate.com/contents/definition-classification-etiology-and-pathophysiology-of-shock-in-adults?search=vasodilatory%20shock&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H2750341. Published February 18, 2018.
2. David F Gaieski MD, Mark E Mikkelsen MD. Evaluation of and initial approach to the adult patient with undifferentiated hypotension and shock. UpToDate. https://www.uptodate.com/contents/evaluation-of-and-initial-approach-to-the-adult-patient-with-undifferentiated-hypotension-and-shock?search=vasodilatory%20shock%20treatment&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H87905499. Published September 13, 2019.
3. Paula Ferrada MD. Critical care scoring systems - critical care medicine. Merck Manuals Professional Edition. https://www.merckmanuals.com/professional/critical-care-medicine/approach-to-the-critically-ill-patient/critical-care-scoring-systems.
4. Chawla LS, Busse L, Brasha-Mitchell E, et al. Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study. Crit Care. 2014;18(5):534. doi:10.1186/s13054-014-0534-9
5. Khanna A, English S, Wang X, Ham K. Angiotensin ii for the treatment of vasodilatory shock. N Engl J Med. 2017;377(26):2601-2604. doi:10.1056/NEJMc1714511
6. Ham KR, Boldt DW, McCurdy MT, et al. Sensitivity to angiotensin II dose in patients with vasodilatory shock: a prespecified analysis of the ATHOS-3 trial. Ann Intensive Care. 2019;9(1):63. doi:10.1186/s13613-019-0536-5