Angiotensin II in the treatment of distributive shock: a systematic-review and meta-analysis

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Abstract

Background: While non-norepinephrine vasopressors are increasingly used as a rescue therapy in cases of norepinephrine-refractory shock, data on their efficacy are limited. This systematic review and meta-analysis aims to synthesize existing literature on the efficacy of Angiotensin II (ATII) in distributive shock.

Methods: We pre-registered our meta-analysis with PROSPERO (CRD42023456136). We searched PubMed, Scopus, and gray literature for studies presenting outcomes on ATII use in distributive shock. The primary outcome of the meta-analysis was all-cause mortality. We used a random effects model to calculate pooled risk ratio (RR) and 95% confidence intervals (CI).

Results: By incorporating data from 1555 patients included in 10 studies, we found that however all-cause mortality was similar among patients receiving ATII and controls (RR 1.02, 95% CI 0.89 to 1.16, p=0.81), the reduction in norepinephrine or norepinephrine-equivalent dose at 3h after treatment initiation was greater among patients receiving ATII (MD -0.06, 95% CI -0.11 to -0.02, p=0.008), while there were no higher rates of adverse events reported among ATII patients.

Conclusions: While ATII did not reduce mortality among distributive shock patients, it allowed for significant adjunctive vasopressor reduction at 3h without an increase in reported adverse events, deeming it a viable alternative for the increasingly adopted multimodal vasopressor for minimizing catecholamine exposure and its adverse events.

1. Introduction

Distributive or vasodilatory shock is the most common form of circulatory shock among critically ill patients. Sepsis is the most common cause with other etiologies being anaphylaxis, capillary leak syndrome, adrenal insufficiency, neurogenic vasoplegia, post-cardiopulmonary bypass vasoplegic syndrome or pharmacologic toxicity. Independent of etiology, the observed clinical syndrome consists of end-organ hypoperfusion hemodynamically characterized by normal or augmented cardiac output with low systemic vascular resistance (SVR).

While the treatment of vasodilatory shock is multimodal, the majority of patients will require vasopressor support additionally to fluid administration during the course of their illness. The choice and timing of vasopressor therapy has long been a subject of discussion among emergency and intensive care physicians, with current guidelines supporting the use of catecholamine vasopressors as first-line treatment (1). However, vascular hyporesponsiveness to catecholamines is a well-observed phenomenon in patients with distributive shock. It stems from various sources, including the excessive production of nitric oxide, increased prostacyclin expression, the heightened activity of ATP-sensitive potassium channels, and the desensitization of alpha adrenoreceptors (2).

In cases where first line treatment fails, i.e. the target mean arterial pressure of 65mmHg cannot be reached, the consensus regarding second-line vasopressor choice and drug titration strategies remains unclear and stems mostly from small studies and expert opinion on the subject (1,3). Given the above mentioned hyporesponsiveness to catecholamines due to a1 receptor saturation, the addition of alternative agents such as vasopressin or angiotensin II, instead of epinephrine, is thought to be preferrable to catecholamine escalation (1).

Additionally, it should be noted that while current evidence has suggested a possible superiority of vasopressin to norepinephrine as far as clinical outcomes are concerned, its higher costs and limited availability have lead to the strong recommendation for norepinephrine as first-line treatment. Progressive up-titration of the two commonly used vasopressor classes, i.e., catecholamines and vasopressin, often leads to a combination of significant toxicity and progressive multiorgan failure resulting from a drug-refractory state after a certain dosing threshold (3,4). Thus, drug selection, dosing and timing strategies, as well as exploring novel options for refractory cases remain pertinent questions in vasodilatory shock management.

During the last decades, both bovine and human angiotensin II (AT II) have been successfully used in addition to standard-of-care as rescue therapy for refractory shock. While a recent meta-analysis has summarized the available data on patients with cardiogenic shock, no study has as of yet synthesized clinical data on vasodilatory shock (5), where the use of ATII could be highly effective due to its physiologic properties. In order to summarize the current data and provide insight on the design of future trials, we designed and performed a systematic literature review and meta-analysis of available studies with AT II use in distributive shock.

2. Methods

2.1 Protocol and Registration

The current systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Appendix, Table S1, http://links.lww.com/SHK/B952) (6). We pre-registered the protocol with PROSPERO (CRD42023456136) and made it available online.

2.2 Inclusion and exclusion criteria

We considered for inclusion randomized controlled trials and observational cohort studies reporting data on ATII use in distributive shock and presenting outcomes on all-cause mortality and/or morbidity. We considered as eligible both peer-reviewed papers and preprints, while we excluded case reports and case series involving less than five patients. We also excluded studies when patient overlap was suspected (i.e. same hospital or medical center in the same or overlapping time periods).

2.3 Outcomes of interest

The primary outcome was to investigate the effect of ATII use on all-cause mortality in patients with distributive shock. Secondary outcomes included the effect of ATII use on intensive care unit mortality, need for continuous renal replacement therapy, change in mean arterial pressure and prevalence of thromboembolic events. A post-hoc analysis on new or worsening acute kidney injury was also done.

2.4 Search strategy

Two authors (EX and MZ) independently conducted the literature search. We systematically searched PubMed, Scopus in order to explore all available clinical studies on the topic with the search phrase: ("angiotensin" AND "shock"). We also conducted a search in the grey literature (i.e., preprint serversmedRxiv and Research Square and Google Scholar) by using the same search phrase: Another search was conducted in the reference lists of all identified reports and articles for additional studies. We retrieved all relevant articles on adult human subjects up to September 5th, 2023, with no language restrictions.

2.5 Data extraction

The titles and abstracts of studies obtained using the search strategy and those from additional sources were independently screened by 3 authors (EX, MZ and AC) to identify studies that potentially meet the inclusion criteria outlined above. The data from each study were independently extracted by two authors (EX and MZ) with a customized format. Disagreements regarding study eligibility were resolved through discussions among the authors.

A standardized proforma was used to extract data from the included studies, enabling the assessment of study quality and evidence synthesis. Extracted information included publication details (authors, year), country, type of study, number of patients receiving ATII, number of patients receiving treatment regimens not including angiotensin II, patients' clinical characteristics (comorbidities including diabetes mellitus, hypertension, ischemic cardiac disease), baseline severity of illness (as provided by either SOFA or APACHE scores), baseline norepinephrine or norepinephrine equivalent dose, baseline lactate values, baseline mean arterial pressure, baseline arterial partial pressure of oxygen (PaO2) to fraction of inspired oxygen (FiO2) ratio, and outcomes.

When not directly provided, we calculated data of interest, i.e., by transforming continuous values to the form of mean and standard deviation as described by the Cochrane Handbook version 6.3, 2022 (7). Discrepancies were resolved through discussion or with the input of the other authors if necessary. We contacted the authors of the original studies for clarifications and/or additional information.

2.6. Assessment of Methodological Quality

Articles identified for retrieval were assessed by 2 independent authors (EX, MZ) for methodological quality before inclusion in the review using a standardized critical appraisal tool. Any disagreements between the authors during the process of appraising the articles were resolved through discussion involving all the authors. The quality of the included observational studies was assessed using the modified Tool to Assess Risk of Bias in Cohort Studies, developed by the CLARITY Group at McMaster University for observational trials , while the Risk of Bias 2.0 (RoB 2.0) tool was used for randomized controlled trials (8,9). Details are provided in the Supplementary Material.

2.7 Statistical analysis and sensitivity analysis

Data synthesis for the double-arm trials was conducted using Review Manager 5.4 (RevMan 5.4.1) by the Cochrane Collaboration (10). Continuous effect measures were pooled as mean difference (MD) with 95% confidence intervals (CI). Continuous values were transformed and presented as medians to means, and interquartile range (IQR) to standard deviation (SD) as instructed by the Cochrane Handbook (7). A random effects model (der Simonian and Laird) was conservatively utilized (7). A p-value less than 0.05 was considered to denote statistical significance. The metafor package of R was used for the single-arm analysis, where a random effects model of der Simonian and Laird was applied (11). The presence of statistical heterogeneity was assessed by I^2 and interpreted according to the Cochrane Handbook recommendations; 0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: substantial heterogeneity; 75–100%: considerable heterogeneity. To explore sources of heterogeneity, a pre-specified sensitivity analysis was conducted by including only studies with low risk of bias. Data were insufficient to perform

the prespecified analysis that would have included only randomized controlled trials or studies with septic shock.

3. Results

Of the 1498 relevant citations that were identified and screened, 28 studies were selected for full review based on their abstract and were included in our final assessment for possible data extraction (Figure 1). In total, data extraction was feasible in 10 studies including patients with distributive shock who were treated with ATII (6–14, 46). **Table 1** depicts the baseline characteristics of the distributive shock patient populations in the studies included in the meta-analysis. Results regarding risk of bias assessment of included studies are summarized in the supplementary appendix (**Table S2**, http://links.lww.com/SHK/B952).

3.1 Primary outcome – All-cause mortality

Figure 2 shows that all-cause mortality was similar among patients receiving ATII and controls (RR 1.02, 95% CI 0.89 to 1.16, p=0.81; 7 studies; 1285 patients).

3.2 Secondary outcomes

Mortality in the ICU was similar among patients receiving ATII and controls (RR 1.00, 95% CI 0.86 to 1.18, p=0.81; 7 studies; 1285 patients; Figure 3). Among distributive shock patients, the reduction in norepinephrine or norepinephrine-equivalent dose at 3h after treatment initiation was greater among patients receiving ATII (MD -0.06, 95% CI -0.11 to -0.02, p=0.008; 3 studies; 445 patients; **Figure 4**). As far as adverse events are concerned, the need for continuous renal replacement therapy (RR 1.30, 95% CI 0.70 to 2.42, p=0.41; 3 studies; 166 patients; **Figure 5**) and thromboembolic events (RR 1.01, 95% CI 0.79 to 1.29,

p=0.91; 3 studies; 196 patients; **Figure 6**) were similar between the ATII and control groups. New or worsening acute kidney injury rates were also similar between the ATII and control groups (RR 1.05, 95% CI 0.72 to 1.52, p=0.81; 5 studies; 1105 patients; **Figure 7**).

3.2.1 Secondary outcome in single-arm studies: reaching mean arterial pressure target

In addition to our other analyses, we performed a non-prespecified pooling of the proportions on patients receiving ATII that reached the MAP target at 3h after treatment initiation, with data from both the ATII arm of the double-arm studies, as well as from single-arm studies. The pooled proportion was 58.5% (95% CI 29.9% to 87.1%, p<0.001, I^2 98.3%; **Figure 8**). Given the high heterogeneity of this analysis we proceeded to perform a leave-one-out analysis to identify potential outliers, in which the removal of the study of Quan et al. showed much narrower confidence intervals, thus identifying that cohort as a potential outlier (**Figure 9).**

Discussion

This systematic review and meta-analysis found that albeit ATII reduced norepinephrine or norepinephrine-equivalent doses at 3h after treatment initiation, it did not decrease all-cause and ICU mortality compared to controls. In addition, the need for continuous renal replacement therapy, new or worsening acute kidney injury and the incidence of thromboembolic events were similar between the ATII and control groups. Data from both single- and double-arm studies showed that 58.5% of the patients were able to reach the MAP target at 3h after treatment initiation with ATII, indicating that there is room for improvement in the identification of ATII-responsive patients.

Angiotensin II in distributive shock

Vasodilatory or distributive shock represents the predominant shock syndrome encountered in clinical practice and is primarily precipitated by sepsis (21). However, alternate causative factors encompass conditions such as anaphylactic reactions, spinal cord injury, and drug or toxin exposure (22).The main haemodynamic characteristics of vasodilatory shock include excessive hypovolaemia and extracellular fluid volume depletion, arterial hypotension, and decreased with disrupted oxygen extraction leading to meaningful vasodilation (21). In response to a state of shock, the organism's inherent defense physiological and adaptive mechanisms operate to maintain blood pressure levels. This involves the activation of the sympathetic nervous system, release of catecholamines and vasopressin, inhibition of cerebral and atrial natriuretic peptides, and vasoconstriction mediated by AT II (22). It should also be mentioned that hypovolemia triggers various sympathetic-adrenal and hypothalamic-pituitary-adrenal pathways, leading to the release of renin and AT II (23).

Angiotensin II demonstrates its vasopressor effects by inducing constriction in both venous and arterial blood vessels (24). It also plays a role in governing the distribution of blood flow in specific regions of the body, with a notable impact on renal circulation (25,26). Indeed, in the context of septic shock, the activation of RAAS is heightened as a reaction to reduced blood flow to the kidneys. This reduction in the stretching of the afferent arteriole and the diminished supply of chloride to the distal tubules prompt the release of renin from the juxtaglomerular apparatus (23). Moreover, experimental models of sepsis highlight that angiotensin II, while causing a reduction in renal blood flow, results in an increase in creatinine clearance and urine output(27). However, this effect has not been observed in human studies, where most investigations have reported a decrease in glomerular filtration rate (GFR), reduced plasma flow, and increased sodium retention(28).

It is firmly established that distributive shock can lead to reduced responsiveness to angiotensin II stimulation, a relative decline in plasma levels of angiotensin II, and vascular hyporesponsiveness to vasopressors as well. These phenomena, in turn, can contribute to the development of refractory shock with the potential for multiple organ failure and/or mortality (2,25). Clinical observations have substantiated the presence of vascular hypo-responsiveness in vasodilatory shock, particularly septic shock. This is evident as septic shock patients who have received volume resuscitation continue to exhibit low blood pressure even in the presence of increased levels of naturally occurring and externally administered catecholamines (29). Vascular hyporesponsiveness to endogenous and exogenous catecholamines during sepsis is probably multifactorial. It includes complex pathophysiological mechanisms, for example, excess production of NO, dysregulation of prostacyclin and COX-2 pathways, activation of ATP-sensitive potassium channels, and modifications of catecholamine signaling (2). Additional factors can have an impact on the emergence of microcirculatory dysfunction. These factors encompass low tissue oxygen pressure, the generation of hypoxia-inducible factors, changes in redox balance, and potential modifications in ATII (30). Indeed, data from animal models highlight that angiotensin II receptors become either down-regulated or less responsive to angiotensin II stimulation during sepsis (12,13,31,32). Indeed, experimental studies have demonstrated that Arap1 (AT-R1-associated protein 1) could enhance the expression of AT-R1 on the cell surface. Conversely, elevated levels of AT II could lead to a substantial reduction in Arap1, resulting in an autoregulatory process that diminishes the vasculature's sensitivity to AT II, as observed in sepsis (33). Moreover, in the context of both Gram-positive and Gram-negative sepsis, proinflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, interferon (IFN)γ, and nitric oxide (NO) are released. These substances work to decrease the expression of AT-1 receptors. Consequently, this downregulation results in systemic

hypotension and reduced aldosterone secretion, even in the presence of heightened plasma renin activity and AT II levels (31,32). These observations could be especially significant for mechanically ventilated patients, given the potential inflammatory responses associated with ventilation, particularly if lung-protective mechanical ventilation is not employed (34,35). Nevertheless, there is a shortage of available data concerning the physiology of AT II in mechanically ventilated patients. Furthermore, a relative reduction in AT II plasma levels has been documented in septic shock patients(36). This decrease is attributed to the deficiency of angiotensin-converting enzyme, which is linked to endothelial damage caused by sepsis (37,38). Finally, the decrease in adrenal AT-2 receptors observed in sepsis could hinder the release of catecholamines from the adrenal medulla. This, in turn, may have a significant role in the development of hypotension in sepsis (31)

Taking into account that imbalances of that physiologic pathway have been shown to correlate with poor prognosis on patients with distributive shock, targeted measuring of the aforementioned key components could provide insight in which patients stand to benefit most from ATII vasopressor therapy (39,40). Among the various options, quantification of Angiotensin converting enzyme (ACE)activity is not achievable by means of a simple plasma measurement and measurement of the angiotensin I/II ratio is also technically challenging and time-consuming, leaving renin as a possible surrogate biomarker for RAAS activity. To that end, in their ATHOS-3 trial post-hoc analysis, Bellomo *et al.* showed that 76% of patients had elevated baseline renin levels (41). A greater reduction in renin levels was observed in patients treated with angiotensin II than those receiving placebo at 3 hours (-54.3% vs -14.1%, respectively, $p < 0.01$). Moreover, in patients with higher baseline renin, treatment with ATII resulted in reduced mortality compared to placebo treatment (51.1% versus 69.9%, respectively, $p = 0.01$). In the multivariate logistic regression analysis, higher

serum renin was independently associated with increased mortality (HR 2.15, 95% CI, 1.35–3.42, p=0.001), while ATII administration in patients with elevated baseline renin was associated with decreased risk of mortality (HR 0.62, 95% CI, 0.39–0.98, p=0.04).

All-cause and intensive care unit mortality rates and predictors

The mortality of septic shock remains high, ranging from 38 to 46.5% despite improvements in patient diagnosis and management (42,43). Traditionally, a stepwise method is employed in resuscitation and maintaining of tissue perfusion, with fluid boluses followed by successive one-by-one vasopressor initiation and dose increase. In recent years, the switch to a multimodality approach is gaining increasing favor versus the stepwise method in an attempt to prevent prolonged hypotension and treatment delay, both factors shown to increase mortality (44).

Among the published double-arm trials, the cohort of Quan *et al.* was the first to report higher mortality among the ATII patients versus controls, a result that did not however persist after propensity score weighting (86.0% vs 71.0%, p=0.16) (15). The baseline SOFA score was the only variable associated with increased mortality (OR=1.25, 95% CI, 1.05–1.49; p=0.01). Interestingly, this cohort was also identified as an outlier in our leave-one-out analysis for achieving MAP targets at 3h, with notably lower treatment response rates than the other cohorts. The increased SOFA score of the cohort at baseline could be a possible explanation for the lower response and higher observed mortality. The prolongation of hypotension for longer periods of time could also account for the higher observed mortality (45). Therefore, refractory hypotension or the development of new hypotensive episodes while on vasopressor support should be aggressively investigated and treated to improve end-organ perfusion, as a way of improving overall mortality. In the severity-adjusted

multivariate analysis of the one-arm study of Wieruszewski et al., response to ATII (hazard ratio, HR 0.50, 95% CI, 0.35-0.71, p<0.001) and lower lactate (HR 0.94, 95% CI, 0.91-0.96, p<0.001) were associated with reduced mortality, while higher vasopressor dosage at treatment initiation was associated with increased mortality (HR 1.61, 95% CI, 1.03-2.51, p=0.037) (46).

Overall, in our meta-analysis, the mortality rates were similar between the ATII and control cohorts. Given that recent results from the MIMIC-IV database suggest that the timing of secondary vasopressors administration and noradrenaline reduction is strongly related to patient outcomes, adequately powered trials for detecting the possible true effect rather than an overall lack of a true effect of ATII and vasopressor-dose reduction on mortality are needed (44).

Factors influencing the obtainment of target mean arterial pressure and angiotensin II responsiveness

In order to maximize vasopressor therapy efficiency and minimize adverse event occurrence, drug choice, dosing and timing should be personalized for each patient based on response prognostication. To that end, researchers have attempted to identify factors relating to angiotensin II responsiveness, most commonly defined as MAP increase over the first few hours of therapy. The multivariate analysis of the ATHOS-3 cohort identified treatment with angiotensin II versus placebo (OR 12.4, 95% CI 6.72-22.8, p<0.001) and radiographic findings of Acute Respiratory Distress Syndrome (ARDS) (OR 2.03, 95% CI 1.07-3.86, p=0.03) as positive predictors for reaching target MAP at 3 hours (13). Negative predictors included a baseline albumin value of <2.5 g/dL (OR 0.40, 95% CI 0.22-0.72, p=0.002), prior exposure to ARBs (OR 0.24, 95% CI 0.07-0.79, p=0.02) and a baseline NE equivalent dose

≥0.5 µg/kg/min (OR 0.40, 95% CI 0.21-0.77, p=0.006). In the study of Smith *et al.* patients with a baseline NE dose of <0.2 µg/kg/min needed significantly less vasopressor support by hour 3 when compared to patients initially receiving higher doses (MD −97.7%, 95% CI −171.7% - −23.8%, p = 0.01). Similarly, patients initially receiving ≤3 vasopressors at the time of AT II initiation showed greater NE reduction (−28.2% vs +28.2% for patients with >3 vasopressors, p=0.04) (17). In the cohort of Wieruszewski *et al.* baseline factors associated with a favorable hemodynamic response included lower lactate concentration (OR 1.11, 95% CI, 1.05-1.17, p<0.001) and receipt of vasopressin (OR, 6.05, 95% CI, 1.98-18.6, p=0.002) (46). It is interesting to note that a favorable response in patients with lower lactate could be either due to their shock being less severe or because of an altered response to ATII in the setting of acidemia, as has been hypothesized for varying catecholamine responsiveness (47). In our analysis, the pooling of the studies reporting the obtainment of target MAP at 3h after treatment initiation indicates that more than half of patients refractory to first- and second-lines of treatment managed to achieve adequate perfusion (success rate of 61.2%).

In the leave-one-out analysis of reaching MAP targets, the study of Quan *et al.* was identified as a potential outlier with high treatment failure rates. One reason could be the inclusion of patients with partially missing and thus, inferred, data in their analysis while another possible explanation was that in this cohort ATII was used exclusively as a third-line treatment in severe shock, while some of the other cohorts it was used as a first- or second-line option.

While our pooled rates indicate an overall good response to treatment, identification of candidates that are more likely to respond to or fail with ATII is the next logical step in increasing treatment success rates and potentially decreased mortality.

Angiotensin II dosing

While institutional differences in treatment protocols are to be expected, all the included studies reported similar dosing regimens and ranges of accepted doses. In the initial ATHOS trial, Chawla *et al.* used a starting dose of 20 ng/kg/min and titrated to a maximum dose of 40 ng/kg/min with a MAP goal of 65 mmHg. Similar doses were used in the majority of cohorts, with only the study of See et al. reporting a lower starting dose of 5-10 ng/kg/min.

Catecholamine sparing

High-dose catecholamine therapy has been identified as an independent predictor of ICU (OR 5.1, p=0.001) and in-hospital mortality (OR 3.82, p=0.016) in septic shock, a fact that can be pathophysiologically explained by the phosphorylation, internalization, and desensitization of a-receptors in the setting of continually increasing doses, leading to worsening shock that is also reinforced in a positive feedback mechanism by the concurrently worsening metabolic acidosis resulting from lactate accumulation (24, 25). Due to their different target receptor, the use of alternative vasopressors such as vasopressin or ATII can be of benefit in cases of a1-receptors saturation following escalating doses of NEpi and epinephrine (50). Such patients could be clinically identified by their lack of response to increasing first-line vasopressor dose.

In addition to a lack of effectiveness for shock reversal, catecholamine high-dose monotherapy has also been shown to be associated with other cardiac adverse events such as a higher incidence of atrial fibrillation (vasopressin plus catecholamine vs catecholamine-monotherapy, 21.5% vs 29.7%, respectively, RR: 0.77, 95% CI: 0.67-0.88, p<0.001)(51). Decreasing catecholamine dose could attenuate the stimulation of arrhythmogenic myocardial

β1-receptors and associated increase in myocardial oxygen demand, that constitute the main pathophysiologic drivers for catecholamine-related cardiogenic dysfunction (51).

Adverse events

Since RAAS system activation and hypertension following AT II administration have been associated with a prothrombotic state and increased renal injury rates, several of the included studies explored the potential occurrence of thromboembolic events or renal functional decline in treated patients.

While in the initial ATHOS trial two patients in the AT II arm experienced hypertension, as a result of which drug administration was stopped, there were no reports of thromboembolic events in any of the study arms with metabolic alkalosis (p=0.09) being the only disorder occurring more often among AT II patients. Given that both patients had shock and ARDS, the authors hypothesized that individuals with severe ARDS might experience substantial damage to the pulmonary endothelium, resulting in a deficiency of ATII either absolutely or relatively due to the loss of pulmonary (ACE) (37) . Both preclinical studies and human case reports indicate that when ATII production is hindered through ACE inhibition, patients develop resistance to catecholamines (37,52). Consequently, patients with ARDS may face a heightened risk of ATII insufficiency, likely exacerbating existing hypotension. Furthermore, ATII insufficiency can contribute to acute kidney injury owing to reduced intra-glomerular pressure. They postulate that certain patients experiencing shock and ARDS may be particularly susceptible to a detrimental sequence of events associated with ATII insufficiency (37).

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Adverse event rates in the ATHOS-3 trial were similar between both study arms, with thromboembolism being reported in 1.8% of patients receiving AT II. Thrombosis was also rare (approximately 3%) in two other patient cohorts with mixed shock types, despite anticoagulation therapy at the time (46,53). Conversely, in the study of Leisman *et al.* including only COVID-19 patients, thrombosis was more commonly (16%) observed in the control group, with no events recorded among AT II patients. A similar higher thrombosis rate was observed in the cohort of Smith *et al.* without difference between study arms (29% vs 27%, angiotensin II versus controls, respectively, p=0.700), even after adjustment for baseline characteristic differences (new thrombotic events on AT II, OR, 1.02, 95% CI, 0.71–1.48, p=0.912). In patients receiving mechanical circulatory support along with AT II, mesenteric ischemia was the only thrombotic event reported in 3 patients, with only one event occurring after therapy initiation (54).

Our analysis of the pooled available data confirmed the findings of the individual studies, showing no higher thrombotic event rates, need for continuous renal replacement therapy (CRRT) or new or worsening acute kidney injury in patients being treated with angiotensin II versus standard-of-care therapy.

On the largest systematic review on the topic of adverse events incorporating data from 31.281 patients, ATII administration was generally considered safe with the most commonly reported side effects being headache, chest pressure, nausea, and dizziness (28).

Future aspects

In the currently available data, angiotensin II is mostly being administered to patients with greater baseline severity of illness and refractory shock already on high cumulative

vasopressor doses. In our analysis cumulating the data from individual studies, hemodynamic response to angiotensin II was observed in approximately two thirds of patients. Furthermore, the adverse event rates (kidney injury and thromboembolic events) of the most common side-effects associated with AT-II use did not seem to differ between the treated cohort and controls. Both the high-efficacy and the good safety profile further support that angiotensin could be further implemented in the routine shock-management both as a catecholamine-sparring agent as well as rescue therapy in cases refractory to first-line treatment. In order to also clarify the reason why approximately one third of patients did not respond to the treatment, we suggest that future trials examine factors related to the renin-angiotensin pathway on which the drug exerts its function. Biomarkers that can be easily quantified in peripheral blood such as the circulating renin levels could be the means of identifying potential treatment responders or patients that would likely benefit from a different vasoactive agent and be the defining factor in achieving personalized shock treatment in the future.

Limitations

Our meta-analysis has several limitations. Firstly, as far as our primary outcome is concerned, the majority of the individual studies mention the lack of adequate power for detecting a difference in mortality as their main limitation. Secondly, it is to be expected that institutional differences in the protocols for ATII administration could be a source of heterogeneity for our results. To address that question we summarized the different dosing regimens used in our main text. Thirdly, the main difference observed in the individual trials and confirmed in our pooling of the studies was the reduction of vasopressor-equivalent dose, that would in turn be expected to reduce vasopressor-related toxicity. Our study is limited in not being able to explore that potential effect due to the variability in reporting of treatment-

related toxicity in the individual cohorts. To address that limitation, we took care in descriptively presenting the most common ATII adverse events as summarized in the largest systematic review on the topic to date. Furthermore, while we did not detect a difference in adverse event rates between angiotensin II and controls, it should be noted that the number of studies providing data on secondary outcomes was much fewer that the primary outcome and thus our analysis may be underpowered to detect an existing difference.

Conclusion

ATII use did not reduce mortality among distributive shock patients when compared to standard of care but did allow for adjunctive vasopressor reduction at 3h without an increase in reported adverse events. While the classic approach to shock constitutes dose escalation of norepinephrine with the stepwise addition of second line vasopressors, expert opinion seems to increasingly support the adoption of a more balanced multimodal approach in order to minimize catecholamine exposure and its adverse events as well as quickly achieve satisfactory end-organ perfusion. To this end, novel vasopressor options targeting specific pathophysiologic pathways such as the RAAS system ought to be further explored as viable alternatives for shock management in both as rescue therapy and in the acute setting.

Declarations

Competing interests

The authors declare that they have no competing interests.

Ethical Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this article and its supplementary information file.

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Authors' contributions

The study was designed by EX and MZ. EX and MZ searched the articles and drafted the manuscript, to which AE and AC contributed and revised. All authors read and approved the final manuscript.

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Figure 1. Study flow chart

Figure 2. All-cause mortality of patients with distributive shock receiving ATII versus controls. Risk ratio (RR) and 95% confidence intervals (CI) were calculated using a random effects model.

Figure 3. ICU mortality of patients with distributive shock receiving ATII versus controls. Risk ratio (RR) and 95% confidence intervals (CI) were calculated using a random effects model.

Figure 4. Effect on vasopressor dose (norepinephrine or norepinephrine-equivalent dose) at 3h after treatment initiation in patients with distributive shock receiving ATII versus controls. Mean difference (MD) and 95% confidence intervals (CI) were calculated using a random effects model.

Figure 5. Need for CRRT of patients with distributive shock receiving ATII versus controls. Risk ratio (RR) and 95% confidence intervals (CI) were calculated using a random effects model.

Figure 6. Thromboembolic events of patients with distributive shock receiving ATII versus controls. Risk ratio (RR) and 95% confidence intervals (CI) were calculated using a random effects model.

Figure 7. New or worsening acute kidney injury of patients with distributive shock receiving ATII versus controls. Risk ratio (RR) and 95% confidence intervals (CI) were calculated using a random effects model.

Figure 8. Proportion of patients with distributive shock receiving ATII reaching the study-defined MAP target at 3h after therapy initiation. Proportion ratio (PR) and 95% confidence intervals (CI) were calculated using a random effects model.

Figure 9. Leave-one-out analysis on proportion of patients with distributive shock receiving ATII reaching the study-defined MAP target at 3h after therapy initiation. Proportion ratio (PR) and 95% confidence intervals (CI) were calculated using a random effects model.

Figure 1

Figure 2

Study or Subgroup	Angiotensin II Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
See et al. 2023	8	40	24	80	3.4%	0.67 [0.33, 1.35]
Chawla et al. 2014	5	10	6	10	2.6%	0.83 [0.37, 1.85]
Khanna et al. 2017	75	163	85	158	21.4%	0.86 [0.69, 1.07]
Smith et al. 2023	142	225	252	404	35.3%	1.01 [0.89, 1.15]
Quan et al. 2022	51	56	71	91	33.4%	1.17 [1.02, 1.34]
Leisman et al. 2020	6	10	9	19	3.5%	1.27 [0.63, 2.53]
Bird et al. 2023	2	7	1	12	0.4%	3.43 [0.38, 31.32]
Total (95% CI)		511		774	100.0%	1.02 [0.89, 1.16]
Total events	289		448			

Heterogeneity: Tau² = 0.01; Chi² = 9.21, df = 6 (P = 0.16); I² = 35%
Test for overall effect: Z = 0.24 (P = 0.81)

Figure 3

Study or Subgroup	Angiotensin II Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bird et al. 2023	2	7	1	12	0.5%	3.43 [0.38, 31.32]
Chawla et al. 2014	5	10	6	10	3.6%	0.83 [0.37, 1.85]
Khanna et al. 2017	75	163	85	158	23.3%	0.86 [0.69, 1.07]
Leisman et al. 2020	6	10	9	19	4.7%	1.27 [0.63, 2.53]
Quan et al. 2022	51	56	71	91	32.1%	1.17 [1.02, 1.34]
See et al. 2023	4	40	21	80	2.4%	0.38 [0.14, 1.04]
Smith et al. 2023	142	225	252	404	33.3%	1.01 [0.89, 1.15]
Total (95% CI)		511		774	100.0%	1.00 [0.86, 1.18]
Total events	285		445			

Heterogeneity: Tau² = 0.02; Chi² = 11.56, df = 6 (P = 0.07); I² = 48%
Test for overall effect: Z = 0.06 (P = 0.95)

35

Figure 4

Study or Subgroup	Angiotensin II Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Bird et al. 2023	0.3	0.17	7	0.31	0.16	12	9.0%	-0.01 [-0.17, 0.15]	
Khanna et al. 2017	0.34	0.366	155	0.38	0.41	151	28.4%	-0.04 [-0.13, 0.05]	
See et al. 2023	0.08	0.14	40	0.16	0.18	80	62.7%	-0.08 [-0.14, -0.02]	
Total (95% CI)			202			243	100.0%	-0.06 [-0.11, -0.02]	

Heterogeneity: Chi² = 1.04, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 2.63 (P = 0.008)

-0.2 -0.1 0 0.1 0.2
Angiotensin II   Control

Figure 5

Study or Subgroup	Angiotensin II Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bird et al. 2023	4	7	1	12	8.7%	6.86 [0.94, 49.82]
See et al. 2023	5	40	10	80	25.6%	1.00 [0.37, 2.73]
Smith et al. 2023	57	225	89	404	65.7%	1.15 [0.86, 1.54]
Total (95% CI)		272		496	100.0%	1.30 [0.70, 2.42]
Total events	66		100			
Heterogeneity: Tau² = 0.13; Chi² = 3.16, df = 2 (P = 0.21); I² = 37%						
Test for overall effect: Z = 0.82 (P = 0.41)						

Risk Ratio
IV, Random, 95% CI

0.1 0.2 0.5 1 2 5 10
Angiotensin II   Control

Figure 6

Study or Subgroup	Angiotensin II Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Leisman et al. 2020	0	10	3	19	0.8%	0.26 [0.01, 4.58]
See et al. 2023	6	40	5	80	4.9%	2.40 [0.78, 7.39]
Smith et al. 2023	64	225	118	404	94.3%	0.97 [0.75, 1.26]
Total (95% CI)		275		503	100.0%	1.01 [0.79, 1.29]
Total events	70		126			

Heterogeneity: Chi² = 3.21, df = 2 (P = 0.20); I² = 38%
Test for overall effect: Z = 0.06 (P = 0.95)

Figure 7

Study or Subgroup	Angiotensin II Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bird et al. 2023	4	7	1	12	3.4%	6.86 [0.94, 49.82]
Chawla et al. 2014	1	11	2	5	2.9%	0.23 [0.03, 1.96]
Khanna et al. 2017	8	163	11	158	13.8%	0.70 [0.29, 1.71]
See et al. 2023	19	40	37	80	35.6%	1.03 [0.69, 1.54]
Smith et al. 2023	57	225	89	404	44.3%	1.15 [0.86, 1.54]
Total (95% CI)		**446**		**659**	**100.0%**	**1.05 [0.72, 1.52]**
Total events	89		140			

Heterogeneity: Tau² = 0.06; Chi² = 6.48, df = 4 (P = 0.17); I² = 38%
Test for overall effect: Z = 0.24 (P = 0.81)

Figure 8

Studies	Estimate (95% C.I.)	Ev/Trt
Khanna 2017	0.699 (0.629, 0.770)	114/163
Wong 2019	0.500 (0.255, 0.745)	8/16
Konkol 2021	0.929 (0.738, 1.000)	6/6
Quan 2022	0.143 (0.086, 0.199)	21/147
Wieruszewski 2021	0.670 (0.614, 0.726)	181/270
Overall (I^2=98.32 % , P< 0.001)	0.585 (0.299, 0.871)	330/602

Figure 9

Studies	Estimate (95% C.I.)
Overall	0.585 (0.299, 0.871)
- Khanna	0.556 (0.191, 0.922)
- Wong	0.604 (0.281, 0.927)
- Konkol	0.503 (0.188, 0.818)
- Quan	0.702 (0.610, 0.794)
- Wieruszewski	0.564 (0.178, 0.950)

Study	Type of study	Setting	Total number of patients (n)	Age (years)	Sex (% male)	Disease severity	Diabetes (%)	Hypertension	Ischemic heart disease	Norepinephrine or norepinephrine-equivalent dose	Lactate	Mean arterial pressure
Chawla et al., 2014	Single-center RCT	ICU in the USA	20	68.4 (17.4) vs 57.3 (12.4)	60.0 vs 90.0	SOFA 14.9 (2.8) vs 16.9 (2.9)	40.0 vs 30.0	40.0 vs 50.0	10.0 vs 10.0	0.19 (0.11) vs 0.30 (0.20)	4.5 (3.1) vs 7.0 (5.1)	68.8 (7.0) vs 73.0 (12.6)
Khanna et al., 2017	Multicenter RCT	75 ICUs across 9 countries	321	63.0 (17.0) vs 65.0 (16.2)	56.4 vs 65.2	SOFA 11.7 (2.8) vs 12.7 (3.3)	NA	NA	NA	0.33 (0.24) vs 0.34 (0.24)	NA	66.3 (3.9) vs 66.3 (3.7)
Leisman et al. 2020	Multicenter retrospective observational	3 medical ICUs in the USA	29	56.0 (14.0) vs 57.0 (33.0)	66.0 vs 70.0	SOFA 11.3 vs 10.2	40.0 vs 53.0	40.0 vs 47.0	20.0 vs 16.0	0.48 (0.55) vs 0.09 (0.08)	NA	69.2 (15.5) vs 83.2 (27.0)
Quan et al., 2022	Single-center retrospective observational	ICU in the USA	147	59.5 (14.9) vs 62.7 (15.7)	62.5 vs 58.2	SOFA 15.8 (3.3) vs 15.3 (3.0)	37.5 vs 45.1	41.1 vs 64.8	14.3 vs 29.7	NA	9.1 (7.0) vs 7.4 (5.6)	56.1 (11.1) vs 59.7 (14.8)
See et al., 2023	Single-center prospective observational	ICU in Australia	120	62.0 (12.0) vs 63.0 (14.0)	70.0 vs 64.0	APACHE II 16.0 (5.9) vs 17.0 (7.4)	NA	NA	NA	0.15 (0.20) vs 0.18 (0.17)	2.3 (0.9) vs 2.2 (2.5)	73.0 (7.4) vs 71.5 (7.4)
Smith et al., 2023	Single-center retrospective observational	ICU in the USA	813	56.0 (16.0) vs 59.0 (16.0)	61.0 vs 64.0	SOFA 13.0 (4.0) vs 10.0 (4.0)	44.0 vs 35.0	60.0 vs 55.0	NA	0.64 (0.51) vs 0.66 (0.52)	6.2 (5.4) vs 8.3 (5.8)	67.0 (14.0) vs 71.0 (18.0)
Bird et al., 2023	Single-center retrospective observational	ICU in the USA	19	65.9 (8.0) vs 67.0 (6)	100.0 vs 100.0	STS-PROM score (%) 20.3 (23.7) vs 6.3 (11.5)	57.1 vs 33.3	85.7 vs 91.7	NA	0.49 (0.08) vs 0.30 (0.15)	NA	NA

*All values are presented as ATII vs control cohorts

n, number; SOFA, sequential organ failure assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; NA, not applicable

Supplementary Appendix

TABLE OF CONTENTS

A. METHODS

Details on our protocol are available online on PROSPERO (CRD42022299496).

i. PRISMA Cheacklist

B. Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Section 1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Section 1 last sentence
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Section 2.2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Section 2.4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Section 2.4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Section 2.5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Section 2.5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Section 2.3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Section 2.3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Section 2.6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Section 2.7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Section 2.7

B. Section and Topic	Item #	Checklist item	Location where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Section 2.7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Section 2.7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Section 2.7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Section 3
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Section 3
Study characteristics	17	Cite each included study and present its characteristics.	Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Section 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Section 3.2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Section 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Section 4
	23b	Discuss any limitations of the evidence included in the review.	Section 4

B. Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	Section 4
	23d	Discuss implications of the results for practice, policy, and future research.	Section 4
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Section 2.1
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Section 2.1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Section 2.1
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

ii.   **Risk of bias assessment**

The following questions are derived from the "Tool to assess risk of bias in cohort studies" contributed by the CLARITY Group at McMaster University:
https://www.evidencepartners.com/wp-content/uploads/2017/09/Tool-to-Assess-Risk-of-Bias-in-Cohort-Studies.pdf
The questionnaire divides the cohorts as exposed and non-exposed. The examples beneath the questions are intended to clarify the rationale behind answers in each question. The questionnaire is modified in accordance with the subject of our study.

In each question, 4 answers were possible:

1.Definitely yes (low risk of bias)

2. Probably yes

3. Probably no

4. Definitely no (high risk of bias)

Q1. Was the selection of angiotensin II and non-angiotensin II-patient cohorts drawn from the same population?
Definitely yes: Angiotensin II and/or non-angiotensin II-patient cohorts drawn from same administrative database of patients presenting at same points of care within a specified timeframe
Probably yes: Angiotensin II and/or non-angiotensin II-patients presenting to different points of care (e.g. multicenter study), in the same healthcare system
Probably no: Angiotensin II and/or non-angiotensin II-patients presenting to different points of care (e.g. multicenter study), in various healthcare systems
Definitely no: Angiotensin II and/or non-angiotensin II-patients presenting to unspecified points of care

Q2. Can we be confident in the assessment of a non-survivor status?
Due to the nature of our cohorts, **a definitely yes** was pre-specified as the appropriate answer.

Q3. Can we be confident that the outcomes of interest (i.e. survival, hospitalization length, norepinephrine equivalents) was not present at the start of the study?
Since our main outcomes of interest could either only occur after baseline or are continuous measures that were measured separately at baseline and at the specified follow-up point, a **definitely yes** was pre-specified as the appropriate answer.

Q4. Did the study match angiotensin II and/or non-angiotensin II-patient cohorts for all variables that are associated with the outcomes of interest (e.g. disease severity) or did the statistical analysis adjust for these prognostic variables?
Definitely yes: Matching or adjustment for all the prognostic variables on cohort outcomes
Probably yes: Matching or adjustment for some prognostic variables on cohort outcomes
Probably no: Matching or adjustment for one prognostic variable on cohort outcomes
Definitely no: No matching or adjustments for prognostic variables on cohort outcomes

Q5. Can we be confident in the assessment of the presence or absence of prognostic factors (e.g. disease severity)?
Definitely yes: Data collection on prognostic variables through electronic medical records
Probably yes: Data collection through database or review of charts
Probably no: Data collection without demonstration of reproducibility

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Definitely no: Data collection process not stated or no data on prognostic factors regarding survivor/non-survivor cohorts

Q6. Can we be confident in the assessment of outcomes?
Definitely yes: Data collection on outcomes through electronic medical records, outcomes objectively quantifiable
Probably yes: Data collection through database or review of charts, outcomes objectively quantifiable
Probably no: Data collection without demonstration of reproducibility or outcomes only subjectively quantifiable

Q7. Was the follow-up of cohorts adequate?
Definitely yes: Median follow-up of at least 28 days, or all patients discharged or dead
Probably yes: Median follow-up between 14-28 days
Probably no: Median follow-up between 7 and up to but not including 14 days
Definitely no: Median follow-up less than 7 days or not stated

Q8. Were co-interventions similar between cohorts?
Taking into account the fact that all patients were treated according to institutional protocols for the same disease (vasoplegic shock) along with an expected variability concerning the co-interventions between angiotensin-II and non-angiotensin II cohorts (i.e. individual differences in co-interventions as clinical, imaging and laboratory deterioration may appear during hospitalization, despite generally implementing the standard of care), **a probably yes** was pre-specified as the appropriate answer unless it was explicitly stated by the study that different co-intervention bundles were used, in which case **a definitely no** was selected.

C. RESULTS

Risk of bias assessment
Results regarding risk of bias assessment are summarized below in Table S1.

Table 2. Risk of bias assessment

Observational trials*

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Leisman et al.	light green	green	green	light green	green	green	green	light green
Quan et al.	green	green	green	green	green	green	green	light green
See et al.	green	green	green	light green	light green	light green	green	light green
Smith et al.	green	green	green	orange	green	green	green	light green
Bird et al.	green	green	green	red	light green	light green	green	light green
Wong et al.	green	green	green	gray	light green	light green	green	light green
Konkol et al.	green	green	green	gray	orange	orange	green	light green
Wieruszewski et al.	green	green	green	gray	light green	light green	green	light green

Randomized controlled trials**

Author	D1	D2	D3	D4	D5
Chawla et al.	🟢	🟢	🟢	🟢	🟢
Khanna et al.	🟢	🟢	🟢	🟢	🟢

Q=Question; 🟢= Definitely Yes; 🟢=Probably Yes; 🟡=Probably No; 🔴=Definitely No; ⚫=Not applicable

D=Domain; 🟢= Low; 🟡= Some concerns; 🔴= High

*Assessed by the modified "Tool to assess risk of bias in cohort studies" by the CLARITY Group at McMaster University (https://www.distillersr.com/resources/methodological-resources/tool-to-assess-risk-of-bias-in-cohort-studies-distillersr)
**Assessed by the RoB2: a revised tool for assessing risk of bias in randomised trials (doi: 10.1136/bmj.l4898)