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Angiotensin II for the treatment of distributive shock in the intensive care unit: A US cost-effectiveness analysis

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Background. Patients with distributive shock who are unresponsive to traditional vasopressors are commonly considered to have severe distributive shock and are at high mortality risk. Here, we assess the cost-effectiveness of adding angiotensin II to the standard of care (SOC) for severe distributive shock in the US critical care setting from a US payer perspective.
Methods. Short-term mortality outcomes were based on 28-day survival rates from the ATHOS-3 study. Long-term outcomes were extrapolated to lifetime survival using individually estimated life expectancies for survivors. Resource use and adverse event costs were drawn from the published literature. Health outcomes evaluated were lives saved, life-years gained, and quality-adjusted life-years (QALYs) gained using utility estimates for the US adult population weighted for sepsis mortality. Deterministic and probabilistic sensitivity analyses assessed uncertainty around results. We analyzed patients with severe distributive shock from the ATHOS-3 clinical trial.
Results. The addition of angiotensin II to the SOC saved .08 lives at Day 28 compared to SOC alone. The cost per life saved was estimated to be $108,884. The addition of angiotensin II to the SOC was projected to result in a gain of .96 life-years and .66 QALYs. This resulted in an incremental cost-effectiveness ratio of $12,843 per QALY. The probability of angiotensin II being cost-effective at a threshold of $50,000 per QALY was 86 percent.
Conclusions. For treatment of severe distributive shock, angiotensin II is cost-effective at acceptable thresholds.

Assessment

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Distributive shock, defined by abnormal vasodilation, accounts for nearly two thirds of all shock cases and can result in irreversible organ failure and death if not corrected quickly (1, 2). Distributive shock is commonly considered to be severe if patients are unable to achieve or maintain target mean arterial pressure (MAP) despite fluid resuscitation and vasopressor therapy, which traditionally has been limited to catecholamines and vasopressin (1, 2). Unfortunately, high doses of vasopressors can cause various adverse events (AEs), and patients treated with high-dose vasopressor therapies have a poor prognosis (2).

Angiotensin II (Giapreza; La Jolla Pharmaceutical Company, San Diego, CA, USA) is a newly approved vasopressor shown in the double-blind, placebo-controlled, phase 3 Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) trial to increase blood pressure in adults with septic or distributive shock (3). The approval of angiotensin II provides an additional option for clinicians who treat patients with distributive shock. However, the use of angiotensin II in the clinical setting must be evaluated not only for clinical benefit but also economic benefit. Therefore, we conducted a cost-effectiveness analysis (CEA) model based on ATHOS-3 to evaluate the short-term and long-term economic benefits of angiotensin II.

Materials and Methods

Clinical Data

The design of ATHOS-3 (ClinicalTrials.gov, NCT02338843) has been summarized previously (3). Briefly, 344 adult patients with severe distributive shock were randomized 1:1 to receive either angiotensin II or placebo, in addition to standard of care (SOC) vasopressor therapy, including norepinephrine, dopamine, epinephrine, phenylephrine, and/or vasopressin. Severe distributive shock was defined as requiring a norepinephrine-equivalent catecholamine vasopressor dose of >.2 microgram/kilogram/minute for 6–48 hours to maintain a MAP between 55 and 70 mmHg. The study was conducted from May 2015 to February 2017 in seventy-five centers across nine countries in North America, Australasia, and Europe.

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Table 1. Parameter inputs

Parameters	Base value	Lower bound (DSA)	Upper bound (DSA)	Distribution (PSA)	DSA factor note/source
Clinical inputs					
Angiotensin II 28-day survival rate	54%	67%	46%	–	Upper: placebo arm (3) Lower: the highest survival rate in subgroup (20)
Postsurvival mortality, relative risk	.62	.66	.51	Uniform	High: Quartin et al. (16) Low: Shapiro et al. (17)
Cost inputs[a]					
Nonsurvivor resource inflation factor	12.4%	14.9%	9.9%	Lognormal	20%± from the base value (7)
Benefit discount rate	3%	0%	5%	Fixed	From undiscounted to 5% discount (11)
ICU daily cost	$2,687	$2,150	$3,224	Gamma	20%± in ICU cost per day (7)
Hospital ward per day cost	$2,031	$1,625	$2,437	Gamma	20%± in-hospital ward cost per day (8)
AE cost	$10,705	$8,564	$12,846	Gamma	20%± from the base value (10)
Angiotensin II drug cost (vial)	$1,500	$1,200	$1,800	Fixed	20%± of angiotensin II per vial WAC price (4)
Norepinephrine cost (μg)	$.004	$.003	$.005	Fixed	20%± among all baseline WAC prices (4)
Vasopressin cost (unit)	$8.362	$6.690	$10.034	Fixed	20%± among all baseline WAC prices (4)
Epinephrine cost (μg)	$.005	$.004	$.006	Fixed	20%± among all baseline WAC prices (4)
Dopamine cost (μg)	$.0001	$.00008	$.00012	Fixed	20%± among all baseline WAC prices (4)
Phenylephrine cost (μg)	$.001	$.0008	$.0012	Fixed	20%± among all baseline WAC prices (4)

DSA, deterministic sensitivity analysis; ICU, intensive care unit; PSA, probabilistic sensitivity analysis; WAC, wholesale acquisition cost.
[a]All vasopressor prices were obtained from Micromedex Redbook at WAC price on 2018 and weighted by market sales from January–May 2018.

Of 344 randomized patients, 321 were included in efficacy analyses (i.e., the modified intention-to-treat population). The primary end point for ATHOS-3 was a MAP response of ≥75 mmHg or an increase from baseline by ≥10 mmHg at hour 3 without an increase in SOC vasopressor doses prior to hour 3. Secondary efficacy end points included changes in the cardiovascular and total Sequential Organ Failure Assessment scores. Secondary safety end points included all-cause mortality at Day 7 and Day 28. Angiotensin II met the primary end point of increasing MAP in significantly more patients when compared to the placebo arm (69.9 percent vs. 23.4 percent; $p < .001$). Although the study was not powered to detect mortality effects, there was a nonsignificant survival difference in the angiotensin II arm at Day 28 compared to the placebo arm (hazard ratio: .78; 95 percent confidence interval: .57–1.07; $p = .12$) (3).

More than 90 percent of patients in ATHOS-3 were deemed by the investigating clinician to have a diagnosis of sepsis. For this reason, sepsis inputs were used for model parameters when literature on distributive shock was not available.

Resource Use and Costs

Drug acquisition costs and per-day hospital bed costs were included in this model. All cost parameter inputs are reported in Table 1. Angiotensin II acquisition cost was based on the listed wholesale acquisition cost (WAC) (4) and the prespecified 48-hour duration of therapy in ATHOS-3 (3). Acquisition costs for all SOC vasopressor therapies were estimated based on the listed WACs (4) and the average 48-hour dose per ATHOS-3 patient. All SOC therapy prices were weighted by each therapy's US hospital market share in 2018 Q1 from NonRetailSource (Symphony Health, Phoenix, AZ, USA) (5). No drug administration costs were included.

Intensive care unit (ICU) and hospital ward length of stay (LOS) were recorded for each ATHOS-3 trial patient. The results are reported elsewhere (6). ICU and hospital ward per-day costs were derived from the literature and applied to mean LOS in each trial arm to calculate the hospital-related utilization cost. Cost for ICU stay was sourced from Kramer et al. (7) that analyzed per-day costs across twenty-six ICUs at thirteen hospitals in the United States. We used Kramer et al.'s Day 3 costs to represent the average ICU cost because daily ICU cost stabilized after Day 2 (7). Hospital ward per-day cost was sourced using the severe sepsis diagnosis-related group (DRG 872) cost from the 2014 Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS) database (8). In comparison with the two other sepsis DRGs (870 and 871) in NIS, DRG 872 had the shortest LOS and lowest severity and was, therefore, more likely to represent a non-ICU hospital stay. Kramer et al. (7) also reported that patients who died before discharge incurred 12.4 percent greater ICU costs than survivors, even when LOS was equal. A nonsurvivor inflation factor was therefore applied to both ICU and hospital ward costs.

The costs of venous and arterial thrombotic and thromboembolic AEs were incorporated into the model as both were listed in the warnings section of the angiotensin II FDA product label (9). In ATHOS-3, 12.9 percent of the patients in the angiotensin II arm experienced venous or arterial thromboembolism compared to 5.1 percent of the patients in the placebo arm. The average cost of hospitalization for deep vein thrombosis from an analysis

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of the Premier Perspective US electronic healthcare database (10) was used to represent the thromboembolic AE treatment cost.

None of the cost inputs were discounted, as only the short-term hospitalization-related resource use was collected in ATHOS-3. All costs were adjusted to 2018 USD using the Medical Care component of the Consumer Price Index (11).

Analytic Model and Utility Estimates

A decision tree-based cost-effectiveness model was developed from the US payer perspective (12). This model evaluated the ATHOS-3 trial arms of angiotensin II plus SOC vasopressor therapy (angiotensin II arm) versus placebo plus SOC (placebo arm) for lives saved by the trial's 28-day assessment, as well as life-years gained and quality-adjusted life-years (QALYs) gained with a lifetime horizon (Supplementary Figure 1).

QALY calculations were similar to the method described by Angus et al. (13). The baseline assumption is that the quality of life (QOL) estimates of ATHOS-3 survivors were equal to the general population with the same life expectancy. First, we projected the life expectancy of each ATHOS-3 patient alive at 28 days by using the 2013 US Census life table (14), based on patients' gender and age. Second, each survivor's life expectancy estimate was discounted to reflect the increased lifetime mortality risk of distributive shock. Previous CEA studies (13, 15) adopted a postsurvival life-expectancy factor of .51 from a study of a predominantly male US Veterans Affairs cohort from 1983 to 1986 (16). The .623 factor used in this study was calculated based on more recent studies on the outcomes of sepsis patients (17, 18), with detailed methodology provided in Supplementary File 1. Third, we matched the survivor's discounted life expectancy with that of a healthy person from the general population using the 2013 US life table. Because each sepsis survivor's life expectancy was shorter than that of an age- and gender-matched healthy person (by the postsurvival life-expectancy factor of .623), we calculated the QALY for an older, healthy person assuming that the QOL estimates of an ATHOS-3 survivor were equal to a healthy person from the general population with the same life expectancy. QALYs were generated by multiplying ATHOS-3 survivors' adjusted projected life expectancy with the QOL estimates from the Quality of Well-Being (QWB) scale reported by Hanmer et al. (19).

For example, a typical 60-year-old male has a life expectancy of 22.4 years per the 2013 US Life Table. For a 60-year-old male ATHOS-3 survivor, the adjusted life expectancy is therefore $22.4 \times .623 = 14.0$ years. The 2013 US Life Table shows that a 71-year-old male has a life expectancy of 14 years. Therefore, for the 60-year-old male ATHOS-3 survivor, we applied the QWB estimate for a 71-year-old male to determine the QALY estimate. Life-years and QALYs were each discounted at 3 percent annually. Finally, we calculated an incremental cost-effectiveness ratio (ICER) in order to elucidate the cost per life-years gained and QALY gained, and compared these results to established and generally acceptable thresholds in the threshold analyses described in the sensitivity analysis.

Sensitivity Analyses

A one-way deterministic sensitivity analysis was performed to assess the robustness of the base case analysis, with parameter ranges from the literature where available (Table 1). For the angiotensin II arm survival rate, the low value was set equal to the ATHOS-3 placebo arm survival rate. For the high value, the best survival rate observed from a subgroup of angiotensin II patients was used (28-day survival of 67.1 percent) (20). We also tested whether the findings were robust to different QOL estimates, including earlier QWB (21) and EQ-5D (22) instruments. Finally, we applied low (16) and high (17) ranges for the postsurvival life-expectancy factor values that were obtained from the literature. For all other variables, each parameter was varied by ±20 percent.

A probabilistic sensitivity analysis was performed with a 10,000-iteration bootstrap resampling stratified by gender, age (below vs. above 60 years), and treatment arm. The gender, age, and treatment arm weights in the resampling process were based on ATHOS-3 data. Clinical and cost parameters were assigned appropriate statistical distributions and each jointly varied contemporaneously. For input parameters where the variance was unreported in the literature as well as the NIS-based hospital ward cost, we assumed standard errors of 20 percent of the mean (Table 1).

Table 2. Patient characteristics

Baseline patient characteristics	Angiotensin II arm $N = 163$	Placebo arm $N = 158$
Gender, male, *n* (%)	92 (56.4)	103 (65.2)
Age, yr		
Mean, yr	62.1	62.5
Age ≥60 y, *n* (%)	103 (63.2)	97 (61.4)
APACHE II score		
Median (IQR)	27 (22–33)	29 (22–34)
Mean arterial pressure		
Median (IQR), mmHg	66.3 (63.7–69.0)	66.3 (63.0–68.3)
<65 mmHg, *n* (%)	52 (31.9)	50 (31.6)
ICU LOS, mean, d		
Survivor	15.5	14.9
Nonsurvivor	6.9	6.5
Hospital ward LOS, mean, d		
Survivor	7.4	6.9
Nonsurvivor	.7	.2
AE, deep vein thrombosis, *n* (%)	21 (12.9)	8 (5.1)

ICU, intensive care unit; IQR, interquartile ratio; LOS, length of stay.

Results

Baseline Patient Characteristics

Baseline characteristics for the angiotensin II arm and the placebo arm are shown in Table 2. In the base case analysis, 163 patients were randomized to the angiotensin II arm and 158 patients to the placebo arm. Baseline patient characteristics were balanced between the angiotensin II and placebo arms.

Base Case Analysis

Each patient in the angiotensin II arm incurred a cost of $3,000 for the study drug, based on a 48-hour administration protocol. The base case analysis (Table 3) shows that using angiotensin II

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Table 3. Base case results

	Angiotensin II	Placebo
Drug cost		
Angiotensin II cost, 48 hr	$3,000	–
Baseline vasopressor cost, 48 hr	$444	$681
Hospital resource utilization		
Survivors		
ICU	$22,485	$18,503
Hospital ward	$7,527	$6,055
Nonsurvivors[a]		
ICU	$10,265	$11,239
Hospital ward	$672	$275
AE cost	$1,379	$542
Total cost	$45,772	$37,295
Short-term survival[b,c]		
Incremental live saved	.08	
Lifetime survival[b]		
Incremental life-years gained	.96	
Incremental QALY gained	.66	
Incremental cost (short-term) [b,c]	$8,477	
Incremental cost (long-term) [b,c]	$8,477	
Incremental cost per life saved[b,c]	$108,884	
ICER ($/life-years gained) [b,c]	$8,799	
ICER ($/QALY) [b,c]	$12,843	

ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; QALY, quality-adjusted life-years.
[a]Nonsurvivor ICU/hospital ward costs were inflated by 12.4% based on Kramer et al. (7) methodology.
[b]All values are reported in average.
[c]Detailed algorithms are reported in Supplementary File 2.

reduced the doses of other vasopressors relative to the placebo arm, leading to a cost savings of $212 per patient. The angiotensin II arm incurred per-patient hospital-related utilization incremental costs for both survivors and nonsurvivors of $4,787 compared to the placebo arm, in part because of the extended use of inpatient care resources due to improved survival. The angiotensin II arm also incurred an additional AE cost, $837 per patient, compared to the placebo arm.

Use of angiotensin II, on average, resulted in .08 lives saved at 28 days over the placebo arm. In the lifetime horizon, angiotensin II increased adjusted life expectancy by .96 discounted years and raised QALYs by .66 discounted years over the placebo arm. The resulting incremental cost per life saved was $108,884, the additional cost per life-year gained was $8,799, and the resulting ICER was $12,843 (Table 3). Detailed calculations of the values reported in Table 3 are listed in Supplementary File 2.

One-Way Deterministic Sensitivity Analysis and Probabilistic Sensitivity Analysis

Upon manipulation of all parameters other than angiotensin II arm survival rate, the ICER values varied only slightly, from $9,708 to $16,970 (Supplementary Table 1). When the survival rate for the angiotensin II arm was set to the upper bound (i.e., the highest survival rate in the ATHOS-3 dose-sensitive subgroup), the ICER fell to $5,027 per QALY. However, when the survival rate was set equivalent to the placebo arm, the ICER increased to $282,946 per QALY.

To further understand the impact of the angiotensin II survival rate on the ICER, we conducted a threshold analysis (Supplementary Figure 2) using cost-effectiveness benchmarks of willingness to pay (WTP) of $50,000 per QALY to $150,000 per QALY (23). All things being equal, the angiotensin II survival rate would need to decrease from 54.0 percent to 47.8 percent to have an ICER of $50,000 per QALY. The corresponding survival rates for $100,000 per QALY and $150,000 per QALY were 46.7 percent and 46.3 percent, respectively.

We also conducted an ICER threshold analysis on the cost of angiotensin II (Supplementary Figure 3). The results show that to reach an ICER of $50,000 per QALY, the price of angiotensin II would need to increase from $1,500 to $13,762 per vial. The corresponding angiotensin II cost per vial for an ICER of $100,000 per QALY was $30,262.

The results of the probabilistic sensitivity analysis are displayed in the descriptive statistics table (Supplementary Table 1), cost-effectiveness planes (Figure 1), and the cost-effectiveness acceptability curves with net monetary benefit (Supplementary Figure 4). The cost-effectiveness plane (Figure 1) showed that 92 percent of simulations were in the northeast quadrant, representing higher cost and higher effectiveness of angiotensin II versus placebo. The cost-effectiveness acceptability curves (Supplementary Figure 4) show that at a WTP threshold of $100,000, the likelihood of angiotensin II with SOC being more cost-effective than the placebo arm alone is 90 percent. The likelihood of angiotensin II being cost-effective at $50,000 per QALY is 86 percent, and the minimum threshold of WTP in which angiotensin II is more cost-effective than the placebo arm alone is $13,000.

Discussion

Comparative-effectiveness analyses are important in determining the relative value of specific ICU interventions by comparing the cost of such interventions to alternative therapies. ICER and QALY calculations can be considered to describe the "price" for improving health (23). As previously stated, the WTP per QALY in the United States has been benchmarked at a range of $50,000 to $150,000 and has been supported extensively in the literature (24).

This analysis showed that angiotensin II is among the most cost-effective of the ICU therapies with published models (24). By comparison, micafungin for ICU-acquired candidemia had an ICER of $45,967 per QALY (2018 USD) (25). The cost-effectiveness of angiotensin II is similar to that of tissue plasminogen activator for elderly stroke patients ($9,446 per QALY, 2018 USD) (26) and proportional assist ventilator mode for respiratory failure ($11,332 per QALY, 2018 USD) (27). Angiotensin II is also cost-effective compared to sepsis-related interventions in the ICU, such as drotrecogin alfa (activated) with an ICER of $90,458 per QALY (2018 USD) (13) and the integrated sepsis protocol with an ICER of $25,442 per QALY in 2018 USD (28).

Although the research method used in this study is largely consistent with previous studies on CEA in critical care, this analysis used a new postsurvival life-expectancy factor to estimate life expectancy for sepsis survivors. Using more contemporary and

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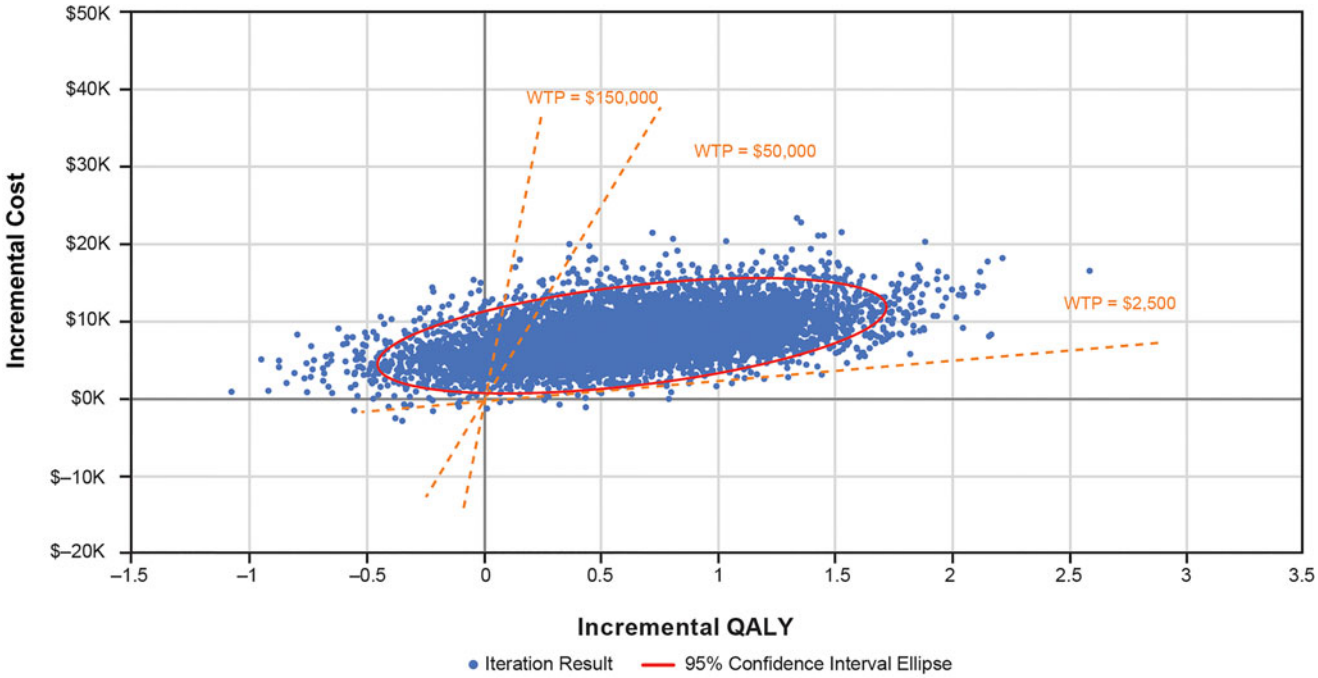

Fig. 1. Probabilistic sensitivity analysis cost-effectiveness plane (ICER, QALY). QALY, quality-adjusted life-years; WTP, willingness to pay.

relevant studies, we derived an estimated sepsis-survivor life expectancy factor that exceeded the .51 value used in prior cost-effectiveness models for sepsis patients (16), likely reflective of improved sepsis SOC. If the .51 life expectancy factor had been used in this model, the ICER for angiotensin II would have increased to $14,820 per QALY.

Our analysis has several limitations. First, it relied heavily on the observed 28-day survival rate difference from the ATHOS-3 trial to predict the lifetime effect of sepsis on QALY. However, making lifetime projections based on results from short-term clinical trials is fairly common in the medical decision-making literature (29, 30). It is impossible to run a lifetime trial, so in order to understand the lifetime impact of an intervention, we have relied on modeling to project the QOL gained. We believe analyses like ours can help the intensive care community to allocate resource use more effectively. Second, we were unable to establish an alternative survival rate estimate by linking MAP improvement (the primary outcome in ATHOS-3) with a survival rate, because the exact association between MAP improvement and distributive shock survival rate is inconclusive. None of the previous studies on vasopressors, such as the VANISH (31) and VASST (32) trials, extrapolated the survival rate by MAP improvement. Thus, the observed survival rate difference reported in ATHOS-3 remains the best data available for QALY estimates. Third, ATHOS-3 was not powered to detect mortality differences between treatment arms; however, our threshold analysis shows that as long as the survival rate difference between angiotensin II and the placebo arms was not less than 1.5 percent, the ICER per QALY results of angiotensin II were relatively robust and remained cost-effective even at the $50,000 WTP threshold. Moreover, it should be noted that many CEAs in the literature have based their conclusions on either nonstatistically significant estimates or outcomes that concluded by extrapolation. For example, a CEA of tolvaptan for the treatment of hyponatremia was based on differences in LOS derived from the SALT trials that were not statistically significant (33). In addition, a CEA comparing micafungin to fluconazole for the treatment of suspected ICU-acquired candidemia was based on a hypothetical patient population and an extrapolated attributable mortality for untreated candidemia, rather than an actual comparison of micafungin and fluconazole (25). Nonetheless, some of these uncertainties are addressed through sensitivity analysis. In our study, we performed multiple robust sensitivity analyses using multiple methodologies and based our conclusions accordingly. Fourth, the ATHOS-3 trial did not have a large sample size, rendering subgroup analysis difficult. Fifth, we used arbitrary, if conventional, ranges among some parameters in the sensitivity analyses. For parameters without literature sources of variation, we believe a ±20 percent change among parameters is sufficient to test parameter influence on cost-effectiveness and does not bias interpretation of our results. Sixth, certain model assumptions may not reflect real-life scenarios, such as the 48-hour dosing regimen for angiotensin II and other SOC vasopressors and the Day 3 cost estimate to calculate hospital costs. However, we believe our sensitivity analysis accounted for the variability expected in both of these parameters. Seventh, this analysis relied on data from a trial that did not collect QOL data. However, there are practical reasons why QOL information was not collected in ATHOS-3. Typically, most QOL instruments are designed for patients with chronic illnesses, whereas patients in ATHOS-3 were being treated for an acute illness. We believe this limitation does not negate the accepted fact that septic shock has a decremental influence on long-term QOL. In fact, we believe using studies that report 28-day mortality in modeling of long-term outcomes may underestimate the effect of septic shock on patient QOL. Each of these limitations listed may lead to underestimation or overestimation of the projected QALYs.

Finally, the current AE cost estimations for thrombotic and thromboembolic events were double-counted for LOS resources. We did not include the costs of all serious adverse events (SAEs) reported in ATHOS-3. One problem of the AE cost from the Premier data analysis is that it includes costs from

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additional LOS. Given that the model already includes LOS costs, the addition of the cost data may overestimate AE costs. Because our model already incorporated ICU and hospital ward LOS, SAE cost estimates would need to be calculated based on the increased intensity of care alone. To our knowledge, such data do not exist. Thus, by including separate and incremental thromboembolic event costs in the model (13 percent angiotensin II vs. 5 percent placebo), results are biased against angiotensin II. By comparison, if we included all SAEs reported in ATHOS-3 (60.7 percent vs. 67.1 percent for the angiotensin II group and placebo group, respectively), results would be biased in favor of angiotensin II. Both of these decisions (to add thromboembolic costs to the model and to refrain from adding other SAE costs to the model) add credence to our conclusions.

Conclusions

Given the high burden of septic shock, it is important to understand the cost and benefit of new therapeutic options for shock. As the portfolio of therapeutic options continues to expand, comparative-effectiveness analysis will be essential in identifying the most impactful therapies from a resource utilization standpoint. Such analyses will assist local pharmacy and therapeutic committees that grapple with difficult formulary choices. Our analysis showed that angiotensin II is a cost-effective therapy in severe distributive shock.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0266462320000082.

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Conflict of interest. L. W. Busse and T. E. Albertson have received research funding from and have served on the speakers bureau for La Jolla Pharmaceutical Company. G. Nicholson and R. J. Nordyke are employed by Beta6 Consulting Group and received grants from La Jolla Pharmaceutical Company during the study. C. Lee and F. Zeng were employed by La Jolla Pharmaceutical Company at the time of the study.

References

1. **Standl T, Annecke T, Cascorbi I *et al.*** (2018) The nomenclature, definition, and distinction of types of shock. *Dtsch Arztebl Int*. **115**, 757–768.
2. **Jentzer JC, Vallabhajosyula S, Khanna AK *et al.*** (2018) Management of refractory vasodilatory shock. *Chest*. **154**, 416–426.
3. **Khanna A, English SW, Wang XS *et al.*** (2017) Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med*. **377**, 419–430.
4. **Thomson Reuters** (2017) *Micromedex Clinical Evidence Solutions. RED BOOK Drug References*. New York, NY: Thomson Reuters.
5. **Symphony Health**. NonRetailSource. Visibility of the non-retail pharmaceutical market. Available at: https://symphonyhealth.com/product/nonretailsource. Accessed 2019.
6. **Khanna A, English SW, Wang XS *et al.*** (2017) Angiotensin II for the treatment of vasodilatory shock—supplementary appendix 2. *N Engl J Med*. **377**, 419–430.
7. **Kramer AA, Dasta JF, Kane-Gill SL** (2017) The impact of mortality on total costs within the ICU. *Crit Care Med*. **45**, 1457–1463.
8. **HCUP National Inpatient Sample (NIS)** (2012) *Healthcare cost and utilization project (HCUP)*. Rockville, MD: Agency for Healthcare Research and Quality. Available at: www.hcup-us.ahrq.gov/nisoverview.jsp.
9. **La Jolla Pharmaceutical Company.** (2017) Giapreza (angiotensin II): Highlights of prescribing information. San Diego, CA.
10. **Dasta JF, Pilon D, Mody SH *et al.*** (2015) Daily hospitalization costs in patients with deep vein thrombosis or pulmonary embolism treated with anticoagulant therapy. *Thromb Res*. **135**, 303–310.
11. **US Department of Labor**. Bureau of Labor Statistics. Consumer price index. Available at: https://www.bls.gov/cpi. Accessed 2019.
12. **Gray AM, Clarke PM, Wolstenholme JL *et al.*** (2010) *Applied methods of cost-effectiveness analysis in healthcare*. Oxford, UK: Oxford University Press.
13. **Angus DC, Linde-Zwirble WT, Clermont G *et al.*** (2003) Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. *Crit Care Med*. **31**, 1–11.
14. **Centers for Disease Control and Prevention. National Center for Health Statistics** (2013) Life tables. Available at: https://www.cdc.gov/nchs/products/life_tables.htm. Updated November 7, 2017. Accessed 2019.
15. **Davies A, Ridley S, Hutton J *et al.*** (2005) Cost effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in the United Kingdom. *Anaesthesia*. **60**, 155–162.
16. **Quartin AA, Schein RM, Kett DH *et al.*** (1997) Magnitude and duration of the effect of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. *JAMA*. **277**, 1058–1063.
17. **Shapiro NI, Howell MD, Talmor D *et al.*** (2007) Mortality in Emergency Department Sepsis (MEDS) score predicts 1-year mortality. *Crit Care Med*. **35**, 192–198.
18. **Linder A, Guh D, Boyd JH *et al.*** (2014) Long-term (10-year) mortality of younger previously healthy patients with severe sepsis/septic shock is worse than that of patients with nonseptic critical illness and of the general population. *Crit Care Med*. **42**, 2211–2218.
19. **Hanmer J, Kaplan RM** (2016) Update to the report of nationally representative values for the noninstitutionalized US adult population for five health-related quality-of-life scores. *Value Health*. **19**, 1059–1062.
20. **McCurdy MT, Busse LW, Gong MN *et al.*** (2018) Association of angiotensin II dose with all-cause mortality in patients with vasodilatory shock. *Crit Care*. **22(Suppl 1)**, 82. Abstract P124.
21. **Fryback DG, Dasbach EJ, Klein R *et al.*** (1993) The Beaver Dam Health Outcomes Study. *Med Decis Making*. **13**, 89–102.
22. **Sullivan PW, Ghushchyan V** (2006) Preference-based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making*. **26**, 410–420.
23. **Neumann PJ, Cohen JT** (2018) QALYs in 2018-advantages and concerns. *JAMA*. **319**, 2473–2474.
24. **Talmor D, Shapiro N, Greenberg D *et al.*** (2006) When is critical care medicine cost-effective? A systematic review of the cost-effectiveness literature. *Crit Care Med*. **34**, 2738–2747.
25. **Zilberberg MD, Kothari S, Shorr AF** (2009) Cost-effectiveness of micafungin as an alternative to fluconazole empiric treatment of suspected ICU-acquired candidemia among patients with sepsis: A model simulation. *Crit Care*. **13**, R94.
26. **Joo H, Wang G, George MG** (2017) Age-specific cost effectiveness of using intravenous recombinant tissue plasminogen activator for treating acute ischemic stroke. *Am J Prev Med*. **53**, S205–S212.
27. **Saunders R, Georgopoulos D** (2017) An analysis of cost and health outcomes related to mechanical ventilation in the United States. *Chest*. **152**, A229.
28. **Talmor D, Greenberg D, Howell MD *et al.*** (2008) The costs and cost-effectiveness of an integrated sepsis treatment protocol. *Crit Care Med*. **36**, 1168–1174.
29. **Ferket BS, Ailawadi G, Gelijns AC *et al.*** (2018) Cost-effectiveness of mitral valve repair versus replacement for severe ischemic mitral regurgitation: A randomized clinical trial from the Cardiothoracic Surgical Trials Network. *Circ Cardiovasc Qual Outcomes*. **11**, e004466.
30. **Lindemark F, Haaland ØA, Kvåle R *et al.*** (2017) Costs and expected gain in lifetime health from intensive care versus general ward care of 30,712 individual patients: A distribution-weighted cost-effectiveness analysis. *Crit Care*. **21**, 220.
31. **Gordon AC, Mason AJ, Thirunavukkarasu N *et al.*** (2016) Effect of early vasopressin vs norepinephrine on kidney failure in patients with

septic shock: The VANISH randomized clinical trial. *JAMA*. **316**, 509–518.

32. **Russell JA, Walley KR, Singer J *et al.*** (2008) Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. **358**, 877–887.
33. **Jamookeeah C, Robinson P, O'Reilly K *et al.*** (2016) Cost-effectiveness of tolvaptan for the treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion in Sweden. *BMC Endocr Disord*. **16**, 22.

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