ORIGINAL ARTICLE

Angiotensin II for the Treatment of Vasodilatory Shock

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ABSTRACT

BACKGROUND

Vasodilatory shock that does not respond to high-dose vasopressors is associated with high mortality. We investigated the effectiveness of angiotensin II for the treatment of patients with this condition.

METHODS

We randomly assigned patients with vasodilatory shock who were receiving more than 0.2 μg of norepinephrine per kilogram of body weight per minute or the equivalent dose of another vasopressor to receive infusions of either angiotensin II or placebo. The primary end point was a response with respect to mean arterial pressure at hour 3 after the start of infusion, with response defined as an increase from baseline of at least 10 mm Hg or an increase to at least 75 mm Hg, without an increase in the dose of background vasopressors.

RESULTS

A total of 344 patients were assigned to one of the two regimens; 321 received a study intervention (163 received angiotensin II, and 158 received placebo) and were included in the analysis. The primary end point was reached by more patients in the angiotensin II group (114 of 163 patients, 69.9%) than in the placebo group (37 of 158 patients, 23.4%) (odds ratio, 7.95; 95% confidence interval [CI], 4.76 to 13.3; P<0.001). At 48 hours, the mean improvement in the cardiovascular Sequential Organ Failure Assessment (SOFA) score (scores range from 0 to 4, with higher scores indicating more severe dysfunction) was greater in the angiotensin II group than in the placebo group (–1.75 vs. –1.28, P=0.01). Serious adverse events were reported in 60.7% of the patients in the angiotensin II group and in 67.1% in the placebo group. Death by day 28 occurred in 75 of 163 patients (46%) in the angiotensin II group and in 85 of 158 patients (54%) in the placebo group (hazard ratio, 0.78; 95% CI, 0.57 to 1.07; P=0.12).

CONCLUSIONS

Angiotensin II effectively increased blood pressure in patients with vasodilatory shock that did not respond to high doses of conventional vasopressors. (Funded by La Jolla Pharmaceutical Company; ATHOS-3 ClinicalTrials.gov number, NCT02338843.)

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*A complete list of the Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Shock is a life-threatening syndrome characterized by decreased organ perfusion that can progress to irreversible organ failure.[1] Vasodilatory shock is the most common type of shock and is characterized by peripheral vasodilation and reduced blood pressure despite preserved cardiac output.[2] Vasodilatory shock requires immediate treatment to ensure organ perfusion through the reestablishment of adequate blood pressure while the underlying cause of shock is identified and treated.[3] Vasopressors are used when intravenous fluid resuscitation alone fails to restore blood pressure. Patients with severe vasodilation who have hypotension despite the use of high doses of vasopressors have a poor prognosis, with 30-day all-cause mortality exceeding 50%.[4,5]

Currently, only two classes of vasopressors are available: catecholamines (and other sympathomimetic amines) and vasopressin.[3] Both classes have narrow therapeutic windows owing to substantial toxic effects at high doses.[6] However, when hypotension occurs, human physiology engages a third system, which is represented by hormones in the renin–angiotensin–aldosterone system (RAAS).[7] Previously, modified bovine angiotensin II was shown to elicit consistent vasopressor effects in patients with shock.[8-10] In a recent pilot study, addition of human angiotensin II to catecholamine and vasopressin therapy increased mean arterial pressure in patients with vasodilatory shock, allowing reductions in the dose of catecholamines.[11] These findings prompted the initiation of the phase 3 Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) trial to determine whether the addition of angiotensin II to background vasopressors would improve blood pressure in patients with catecholamine-resistant vasodilatory shock.

METHODS

TRIAL DESIGN

The protocol (available with the full text of this article at NEJM.org) for this international, randomized, double-blind, placebo-controlled trial was designed by the protocol committee (see the Supplementary Appendix, available at NEJM.org) in collaboration with the sponsor, La Jolla Pharmaceutical Company, and was approved by a research ethics board at each participating institution.[12] The study was conducted in accordance with Good Clinical Practice guidelines, applicable local regulations, and the ethical principles described in the Declaration of Helsinki. The study was conducted under a special protocol assessment agreement with the U.S. Food and Drug Administration as a phase 3 registration trial[13]; the rationale for the trial design is discussed in the Supplementary Appendix.

Trial data were collected by the investigators with the assistance of a contract research organization and were analyzed by the sponsor. Study oversight was provided by an independent data and safety monitoring board. The writing committee, which included investigators and representatives of the sponsor, drafted the manuscript and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. A professional medical writer funded by the sponsor assisted with manuscript revisions. All the authors made the decision to submit the manuscript for publication.

PATIENTS

Eligible patients were 18 years of age or older and had vasodilatory shock despite intravenous volume resuscitation with at least 25 ml per kilogram of body weight over the previous 24 hours and the administration of high-dose vasopressors. We defined vasodilatory shock as a cardiac index of greater than 2.3 liters per minute per square meter or as central venous oxygen saturation of greater than 70% coupled with central venous pressure of more than 8 mm Hg, with a mean arterial pressure between 55 and 70 mm Hg. We defined high-dose vasopressors as more than 0.2 μg of norepinephrine per kilogram per minute, or the equivalent dose of another vasopressor (Table S1 in the Supplementary Appendix),[12] for at least 6 hours but no longer than 48 hours. Eligible participants also had an indwelling bladder catheter and arterial catheter. We excluded patients who had burns covering more than 20% of the total body-surface area, acute coronary syndrome, bronchospasm, liver failure, mesenteric ischemia, active bleeding, abdominal aortic aneurysm, or an absolute neutrophil count of less than 1000 per cubic millimeter or who were receiving venoarterial extracorporeal membrane oxygenation or treatment with high-dose glucocorticoids. Complete inclusion and exclusion criteria are provided in the Supplementary Appendix.[12] Written informed consent was obtained from all patients or their legal surrogates.

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TREATMENT ASSIGNMENT

We assigned patients in a 1:1 ratio to receive synthetic human angiotensin II (LJPC-501) or saline placebo administered by study personnel at participating institutions; randomization was performed in blocks through a central Web-based system. LJPC-501 and naturally occurring human angiotensin II have identical amino acid sequences. LJPC-501 is stable in refrigerated solution for at least 1 year at the recommended storage condition of 5°±3°C and is stable under the anticipated conditions of clinical use. Randomization was stratified according to mean arterial pressure at screening (<65 mm Hg or ≥65 mm Hg) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score (≤30, 31 to 40, or ≥41 on a scale of 0 to 71, with higher scores indicating greater disease severity).[14] Infusions of angiotension II and placebo were prepared locally in identical saline bags by prespecified unblinded personnel. All other investigators, research personnel, patients, families, and the sponsor were not informed of the treatment assignments at any time during the trial.

CLINICAL REGIMEN

The baseline mean arterial pressure was established as the mean of three determinations, each in triplicate, that were obtained 30, 15, and 0 minutes before treatment. Infusions were initiated at a rate equivalent to 20 ng of angiotensin II per kilogram per minute and were adjusted during the first 3 hours to increase the mean arterial pressure to at least 75 mm Hg (Table S2 in the Supplementary Appendix). During this adjustment period, doses of standard-of-care (background) vasopressors were held constant and could not be increased except for safety reasons. If these doses were increased, the patient was designated as not having had a response to the study intervention. The maximum rate of administration of the study medication or placebo allowed during the first 3 hours was equivalent to a dose of 200 ng per kilogram per minute.

After 3 hours 15 minutes, the study drug or placebo and other vasopressors were adjusted to maintain a target mean arterial pressure between 65 and 75 mm Hg. Between 3 hours 15 minutes and 48 hours, angiotensin II or placebo could be adjusted to an infusion rate in milliliters per hour that was equivalent to a dose of 1.25 to 40 ng per kilogram per minute in patients assigned to angiotensin II. The protocol included a nonbinding adjustment scheme (Table S3 in the Supplementary Appendix).

At hour 48, the study infusion was discontinued according to a protocol-specified tapering process. If the background vasopressor dose was subsequently increased to more than 0.1 μg of norepinephrine per kilogram per minute or the equivalent, or if the patient's condition became unstable, study medication or placebo could be resumed for up to 7 days. However, once the study medication or placebo was discontinued for more than 3 hours, it could not be restarted.

ASSESSMENTS AND END POINTS

The primary end point was the response with respect to mean arterial pressure at hour 3, with response defined as a mean arterial pressure of 75 mm Hg or higher or an increase in mean arterial pressure from baseline of at least 10 mm Hg, without an increase in the dose of background vasopressors. The mean values of triplicate determinations of mean arterial pressure at 2 hours 45 minutes, 3 hours, and 3 hours 15 minutes after initiation of angiotensin II or placebo were computed to assess the primary end point. Hierarchically ordered secondary efficacy end points were changes in the cardiovascular Sequential Organ Failure Assessment (SOFA) score (scores range from 0 to 4, with higher scores indicating more severe organ dysfunction) and the total SOFA score (scores range from 0 to 20, with higher scores indicating more severe organ dysfunction) between baseline measurement and hour 48 (Table S4 in the Supplementary Appendix).[15] Safety was evaluated by assessment of serious adverse events, adverse event–related drug discontinuations, all adverse events, and all-cause mortality at 7 days and 28 days.

STATISTICAL ANALYSES

We based the sample size on a hypothesized rate of achievement of the primary efficacy end point of 40% in the placebo group and 60% in the angiotensin II group. We determined that a sample size of 150 patients per treatment group would provide more than 90% power to show the superiority of angiotensin II over placebo, using a two-by-two chi-square test at a two-sided alpha level of 0.05. One interim analysis was performed, with data available only to the data and safety monitoring board, after 150 patients

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had completed the day 28 assessment. On the basis of this analysis, the data and safety monitoring board recommended that the trial continue as planned.

Safety analyses included all patients who received treatment. The primary efficacy analysis was based on the modified intention-to-treat population, which included all patients who underwent randomization and began to receive angiotensin II or placebo. Patients with missing data owing to death were considered in the assessment of efficacy end points as having treatment failure. Values missing for reasons other than death were imputed as the last observed value carried forward in modified intention-to-treat analyses; no imputations for missing data were performed in safety analyses.

Data were analyzed with the use of SAS software, version 9.4. We used descriptive statistics with 95% confidence intervals to summarize data according to treatment group. We analyzed differences between treatment groups using the Wilcoxon rank-sum test or analysis of variance for continuous or ordinal variables and the chi-square or Fisher's exact test for discrete variables. We used a two-tailed alpha level of 0.05 to test the hypothesis of treatment difference. Hierarchical testing assessed, in order, the response with respect to mean arterial pressure at hour 3, the change in cardiovascular SOFA score at hour 48, and the change in total SOFA score at hour 48.

We analyzed the primary end point using logistic regression with adjustment for dichotomized baseline mean arterial pressure, APACHE II score, vasopressin use in the 6 hours before randomization, and vasopressor dose, in norepinephrine equivalents, during the 6 hours before randomization. In addition, we used logistic-regression analysis to identify baseline factors that may have influenced the primary end point (Table S5 in the Supplementary Appendix). We conducted sensitivity analyses of the primary end point, including an unadjusted analysis with the use of a chi-square test and an analysis with stratification according to randomization variables. Time-to-event data including mortality were compared by a log-rank test and were characterized by Kaplan–Meier estimates. Hazard rates were estimated from the proportional-hazards model.

RESULTS

PATIENTS

This trial was conducted from May 2015 through January 2017 in 75 intensive care units across nine countries in North America, Australasia, and Europe (Table S6 in the Supplementary Appendix). Of 404 patients who were screened, 344 were enrolled and randomly assigned to a study group (Fig. 1). A total of 23 of the 344 patients who underwent randomization did not receive angiotensin II or placebo; the most common reasons were rapid improvement of condition (10 patients), withdrawal of consent (4), rapid decline of condition (4), and physician decision (3). Thus, the study regimen was initiated in 321 patients, of whom 163 patients received angiotensin II and 158 received placebo. The study groups were well matched with respect to baseline disease characteristics and demographics (Table 1, and Table S7 in the Supplementary Appendix). The patients in the two study groups were severely ill, as indicated by high APACHE II scores and elevated baseline vasopressor doses. Sepsis was the cause of shock in 259 of the 321 patients (80.7%).

EFFICACY OUTCOMES

All trial participants in the modified intention-to-treat population had data available for the primary end point, and no imputation was required. Significantly more patients in the angiotensin II group than in the placebo group met the criteria for the primary end point of response with respect to mean arterial pressure at hour 3 (69.9% vs. 23.4%, P<0.001; odds ratio, 7.95; 95% confidence interval [CI], 4.76 to 13.3) (Table 2). The most common reason in both groups for lack of response was failure to achieve a mean arterial pressure of at least 75 mm Hg or an increase of at least 10 mm Hg (the other reason was an increase in the dose of background vasopressors). During the first 3 hours, the angiotensin II group had a significantly greater increase in mean arterial pressure than the placebo group (12.5 mm Hg vs. 2.9 mm Hg; P<0.001) (Fig. 2A). In the angiotensin II group, the mean arterial pressure increased rapidly, allowing the angiotensin II dose to be decreased from the original 20 ng per kilogram per minute in 67% of the

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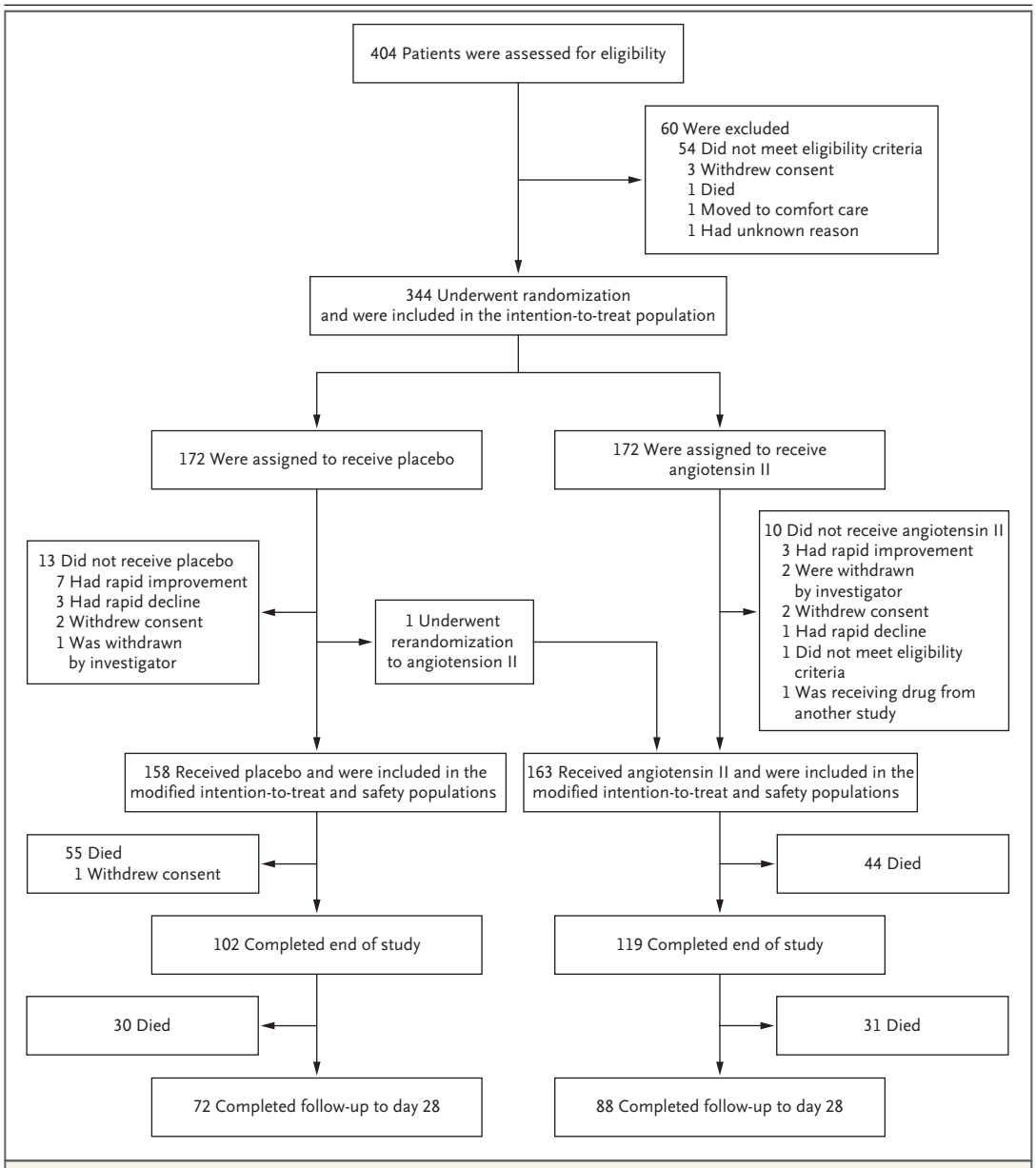

Figure 1. Screening, Randomization, and Follow-up.

Patient disposition from screening through day 28 is shown. Efficacy and safety analyses are based on the modified intention-to-treat population (all patients who underwent randomization and began to receive angiotensin II or placebo). The patient identified as undergoing rerandomization was initially assigned to the placebo group and had to be withdrawn from the study before the first dose was administered because the patient underwent an operative procedure. This patient subsequently underwent rerandomization to the angiotensin II group. In accordance with the preapproved statistical analysis plan, this patient was included in the angiotensin II group for the modified intention-to-treat (mITT) and safety analyses and in the placebo group for the intention-to-treat analyses. The end of study was day 7 or 3 days after the last administration of angiotensin II or placebo, whichever occurred later. Of the 119 patients in the angiotensin II group who completed the end of study, 3 died by day 7 but after the end-of-study assessment. The number of patients who completed follow-up to day 28 includes 2 patients who were discharged before the end-of-study visit but later completed follow-up to day 28.

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Table 1. Demographic and Baseline Disease Characteristics.*

Characteristic	Angiotensin II (N=163)	Placebo (N=158)	All Patients (N=321)
Age			
Median (IQR) — yr	63 (52–75)	65 (53–75)	64 (52–75)
≥65 yr — no. (%)	73 (44.8)	81 (51.3)	154 (48.0)
≥75 yr — no. (%)	41 (25.2)	42 (26.6)	83 (25.9)
Male sex — no. (%)	92 (56.4)	103 (65.2)	195 (60.7)
Geographic region — no. (%)			
United States or Canada	116 (71.2)	120 (75.9)	236 (73.5)
Europe	19 (11.7)	14 (8.9)	33 (10.3)
Australia or New Zealand	28 (17.2)	24 (15.2)	52 (16.2)
BMI ≥30 — no./total no. (%)†	69/161 (42.9)	71/155 (45.8)	140/316 (44.3)
Mean arterial pressure			
Median (IQR) — mm Hg	66.3 (63.7–69.0)	66.3 (63.0–68.3)	66.3 (63.7–68.7)
<65 mm Hg — no. (%)	52 (31.9)	50 (31.6)	102 (31.8)
APACHE II score‡			
Median (IQR)	27 (22–33)	29 (22–34)	28 (22–33)
Distribution — no. (%)			
≤30	105 (64.4)	93 (58.9)	198 (61.7)
31–40	50 (30.7)	54 (34.2)	104 (32.4)
≥41	8 (4.9)	11 (7.0)	19 (5.9)
Albumin			
Median (IQR) — g/dl	2.2 (1.8–2.7)	2.4 (1.9–2.8)	2.3 (1.8–2.7)
<2.5 g/dl — no./total no. (%)	103/154 (66.9)	89/156 (57.1)	192/310 (61.9)
$Scvo_2$			
Median (IQR) — %	76.9 (73.0–82.8)	77.0 (72.5–82.0)	77.0 (72.9–82.2)
Data missing — no.	43	41	84
Central venous pressure			
Median (IQR) — mm Hg	13 (10–15)	12 (10–16)	12 (10–15)
Data missing — no.	37	35	72
Cardiac index			
Median (IQR) — liters/min/m^2	3.0 (2.6–3.8)	3.2 (2.7–3.9)	3.1 (2.6–3.8)
Data missing — no.	94	85	179
Median MELD score (IQR)§	21 (15–25)	23 (17–26)	22 (16–26)
Cause of shock — no. (%)			
Sepsis	127 (77.9)	132 (83.5)	259 (80.7)
Other, potentially sepsis	20 (12.3)	11 (7.0)	31 (9.7)
Pancreatitis	0	2 (1.3)	2 (0.6)
Postoperative vasoplegia	10 (6.1)	9 (5.7)	19 (5.9)
Multifactorial	6 (3.7)	4 (2.5)	10 (3.1)
Exposure to ACE inhibitors — no. (%)	15 (9.2)	15 (9.5)	30 (9.3)
Exposure to ARBs — no. (%)	11 (6.7)	11 (7.0)	22 (6.9)

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Table 1. (Continued.)

Characteristic	Angiotensin II (N=163)	Placebo (N=158)	All Patients (N=321)
Finding of ARDS on chest radiography — no./total no. (%)	40/162 (24.7)	51/158 (32.3)	91/320 (28.4)
Vasopressin use during 6 hr before randomization — no. (%)	113 (69.3)	111 (70.3)	224 (69.8)
Vasopressor dose — μg/kg/min¶			
Median (IQR)	0.33 (0.23–0.56)	0.34 (0.23–0.56)	0.34 (0.23–0.56)
Distribution — no. (%)			
<0.35	83 (50.9)	83 (52.5)	166 (51.7)
≥0.35 to <0.50	34 (20.9)	27 (17.1)	61 (19.0)
≥0.50	46 (28.2)	48 (30.4)	94 (29.3)

* There were no significant differences between groups in any baseline characteristics. For variables with missing data, summary data are based on the adjusted number. ACE denotes angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; ARDS, acute respiratory distress syndrome; and $Scvo_2$, central venous oxygen saturation.
† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the Acute Physiology and Chronic Health Evaluation II (APACHE II) range from 0 to 71, with higher scores indicating greater disease severity.
§ Scores on the Model for End-Stage Liver Disease (MELD) range from 6 to 40, with higher scores indicating more advanced liver disease.
¶ Vasopressor doses are norepinephrine-equivalent doses.

patients within 30 minutes and permitting decreases in doses of concomitant vasopressors. During the first 48 hours, mean doses of background vasopressors were consistently less in the angiotensin II group than in the placebo group (Fig. 2B). Absolute heart rates were higher in the angiotensin II group. (Additional details can be found in Figs. S1 through S3 and Tables S8 through S10 in the Supplementary Appendix.)

At 48 hours, improvement (indicated by lower scores) in the cardiovascular SOFA score was significantly greater in the angiotensin II group than in the placebo group (–1.75 vs. –1.28, P=0.01). There were no significant differences in other SOFA score components. At 48 hours, the total SOFA score increased to a similar degree in the two groups (1.05 and 1.04, respectively; P=0.49). Efficacy was also evaluated in the intention-to-treat population, and the outcomes were similar to those in the modified intention-to-treat population. (For additional details, see Tables S11 and S12 in the Supplementary Appendix.)

In multivariate analysis, after adjustment for age, sex, and prespecified stratification variables, treatment assignment (angiotensin II vs. placebo) was the most significant positive predictor of a response with respect to mean arterial pressure (odds ratio, 12.4; 95% CI, 6.7 to 22.8; P<0.001) (Table S5 in the Supplementary Appendix). Significant negative predictors were hypoalbuminemia (odds ratio, 0.40; 95% CI, 0.22 to 0.72; P=0.002) and elevated vasopressor dose (odds ratio, 0.40; 95% CI, 0.21 to 0.77; P=0.006). A response with respect to mean arterial pressure was achieved by a greater proportion of patients in the angiotensin II group who were receiving norepinephrine-equivalent doses of less than 0.5 μg per kilogram per minute at baseline than patients who were receiving higher doses (91 of 117 patients [77.8%] vs. 23 of 46 patients [50.0%], P<0.001).

SAFETY

Adverse events of any grade were reported in 87.1% of the patients who received angiotensin II and in 91.8% of the patients who received placebo (Table 3, and Table S13 in the Supplementary Appendix). Infusion of angiotensin II or placebo was discontinued because of adverse events in 14.1% of the patients who received angiotensin II and in 21.5% of those who received placebo. The most common adverse events leading to discontinuation were similar in the two treat-

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Table 2. Primary and Secondary End Points.*

End Point	Angiotensin II (N=163)	Placebo (N=158)	Odds or Hazard Ratio (95% CI)	P Value
Primary efficacy end point: MAP response at hour 3 — no. (%)†	114 (69.9)	37 (23.4)	Odds ratio, 7.95 (4.76–13.3)	<0.001
Secondary efficacy end points				
Mean change in cardiovascular SOFA score at hour 48‡	−1.75±1.77	−1.28±1.65		0.01
Mean change in total SOFA score at hour 48§	1.05±5.50	1.04±5.34		0.49
Additional end points				
Mean change in norepinephrine-equivalent dose from baseline to hour 3¶	−0.03±0.10	0.03±0.23		<0.001
All-cause mortality at day 7 — no. (%)	47 (29)	55 (35)	Hazard ratio, 0.78 (0.53–1.16)	0.22
All-cause mortality at day 28 — no. (%)	75 (46)	85 (54)	Hazard ratio, 0.78 (0.57–1.07)	0.12

* Plus–minus values are means ±SD.
† Response with respect to mean arterial pressure (MAP) at hour 3 after the start of infusion was defined as an increase from baseline of at least 10 mm Hg or an increase to at least 75 mm Hg, without an increase in the dose of background vasopressors.
‡ Scores on the cardiovascular Sequential Organ Failure Assessment (SOFA) range from 0 to 4, with higher scores indicating more severe dysfunction.
§ The total SOFA score ranges from 0 to 20, with higher scores indicating more severe dysfunction.
¶ Data were missing for three patients in the angiotensin II group and for one patient in the placebo group.

ment groups and included septic shock, multiorgan failure, cardiogenic shock, and cardiac arrest (Table S14 in the Supplementary Appendix). Serious adverse events were reported in 60.7% of the patients who received angiotensin II and in 67.1% of the patients who received placebo (Table 3).

The rates of adverse events of special interest were similar in the angiotensin II and placebo groups. Specifically, rates of tachyarrhythmias, distal ischemia, ventricular tachycardia, and atrial fibrillation were similar in the two groups (Table S15 in the Supplementary Appendix). No patient died during the initial period of adjustment of the dose of angiotensin II or placebo. Death from any cause by day 7 occurred in 47 of 163 patients (28.8%) who received angiotensin II and in 55 of 158 patients (34.8%) who received placebo (hazard ratio, 0.78; 95% CI, 0.53 to 1.16; P=0.22) (Table 2). Death by day 28 occurred in 75 of 163 (46.0%) and 85 of 158 (53.8%) of patients in the angiotensin II and placebo groups, respectively (hazard ratio, 0.78; 95% CI, 0.57 to 1.07; P=0.12); results were similar after adjustment for age and sex (Fig. S4 in the Supplementary Appendix).

DISCUSSION

In this multinational, double-blind, randomized, controlled trial involving patients with vasodilatory shock who were receiving high doses of conventional vasopressors, the percentage of patients who met the primary end point with respect to mean arterial pressure at 3 hours was significantly greater in the angiotensin II group than in the placebo group. Patients who received angiotensin II also had lower requirements for catecholamines than patients who received placebo. In a finding consistent with this result, cardiovascular SOFA scores, which quantify catecholamine use, were significantly lower in the angiotensin group than in the placebo group at 48 hours.

The marked vasopressor effects of angiotensin were noted soon after its first isolation in the late 1930s,[16,17] and case reports have described the successful use of various bovine and human angiotensin II formulations as rescue therapy for patients with refractory shock.[18-20] The potential usefulness of angiotensin II as a vasopressor is also supported by a small pilot study.[11] In our larger trial, we evaluated a formulation of angio-

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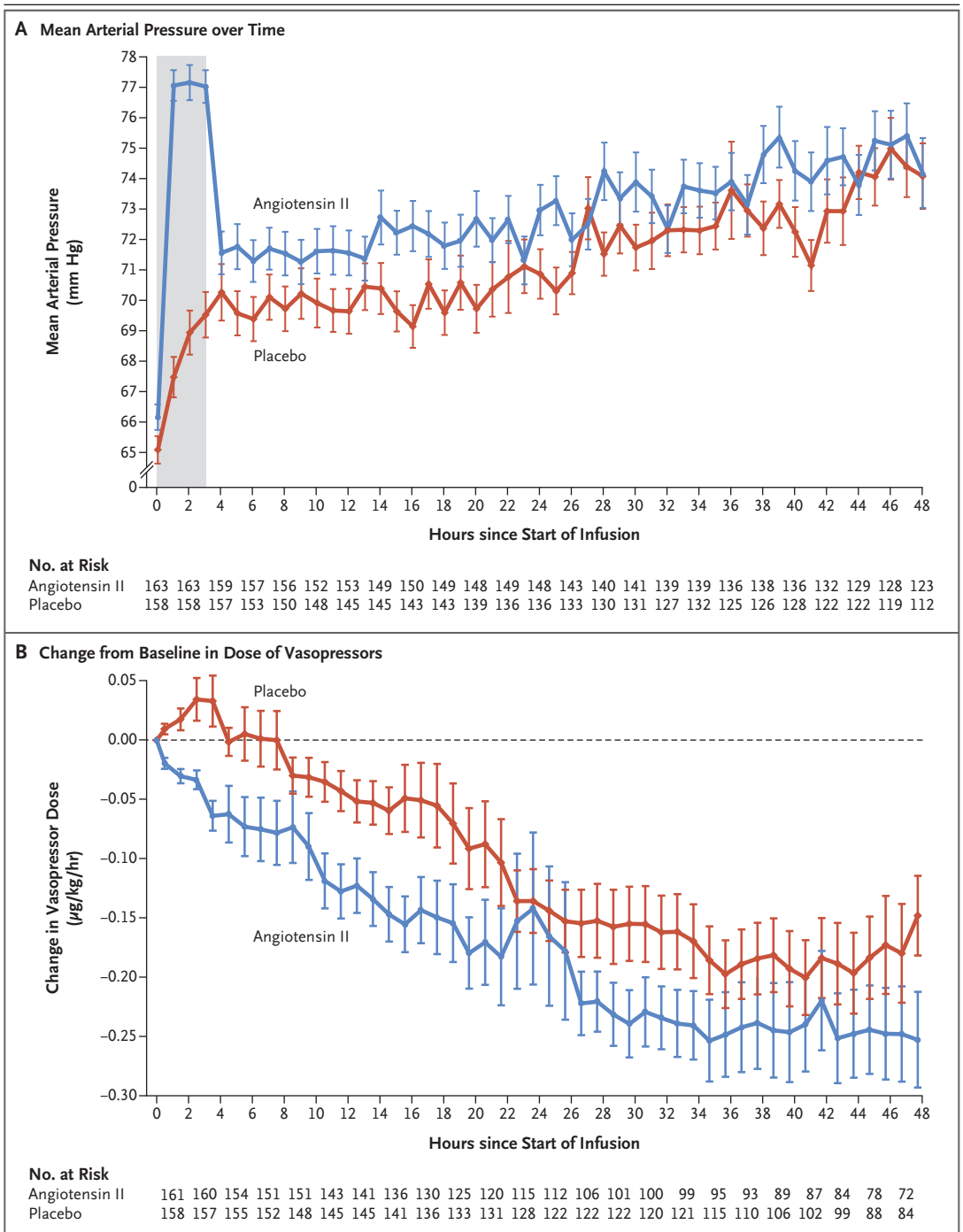

Figure 2. Treatment Responses.

Efficacy outcomes are shown according to study group. Panel A shows the mean arterial pressure from initiation of angiotensin II or placebo through 48 hours. The gray shading indicates the initial 3 hours during which the goal was to increase the mean arterial pressure to 75 mm Hg or higher; thereafter, the target mean arterial pressure was determined by the treating team. Panel B shows the changes from baseline in mean doses of vasopressors, denoted in norepinephrine-equivalents, from initiation of angiotensin II or placebo through 48 hours. In both panels, I bars indicate standard errors. At each time point, the number at risk and the mean value include only patients who were receiving at least one vasopressor.

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Table 3. Adverse Events.*

Event	Angiotensin II (N=163)	Placebo (N=158)
	no. of patients (%)	
Adverse event of any grade†	142 (87.1)	145 (91.8)
Adverse event leading to discontinuation‡	23 (14.1)	34 (21.5)
Serious adverse event with frequency ≥1% in either study group		
Any	99 (60.7)	106 (67.1)
Infection or infestation	30 (18.4)	21 (13.3)
Septic shock	18 (11.0)	10 (6.3)
Sepsis	3 (1.8)	2 (1.3)
Pneumonia	2 (1.2)	3 (1.9)
General disorder or administration-site condition		
Any	27 (16.6)	25 (15.8)
Multiorgan failure	25 (15.3)	23 (14.6)
Cardiac disorder	27 (16.6)	32 (20.3)
Cardiac arrest	7 (4.3)	9 (5.7)
Atrial fibrillation	5 (3.1)	5 (3.2)
Ventricular tachycardia	5 (3.1)	3 (1.9)
Cardiorespiratory arrest	3 (1.8)	5 (3.2)
Cardiogenic shock	2 (1.2)	4 (2.5)
Acute myocardial infarction	2 (1.2)	2 (1.3)
Tachycardia	2 (1.2)	0
Ventricular fibrillation	2 (1.2)	0
Supraventricular tachycardia	1 (0.6)	4 (2.5)
Bradycardia	1 (0.6)	2 (1.3)
Respiratory, thoracic, or mediastinal disorder	17 (10.4)	25 (15.8)
Respiratory failure	8 (4.9)	11 (7.0)
Acute respiratory failure	3 (1.8)	5 (3.2)
Pneumothorax	1 (0.6)	3 (1.9)
Acute respiratory distress syndrome	0	2 (1.3)
Respiratory distress	0	2 (1.3)
Vascular disorder	17 (10.4)	15 (9.5)
Hypotension	5 (3.1)	3 (1.9)
Peripheral ischemia	5 (3.1)	3 (1.9)
Shock	3 (1.8)	3 (1.9)
Deep-vein thrombosis	3 (1.8)	0
Distributive shock	1 (0.6)	4 (2.5)
Gastrointestinal disorder		
Any	3 (1.8)	8 (5.1)
Intestinal ischemia	1 (0.6)	3 (1.9)
Metabolic or nutrition disorder	3 (1.8)	2 (1.3)

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Table 3. (Continued.)

Event	Angiotensin II (N=163)	Placebo (N=158)
	no. of patients (%)	
Failure to thrive	2 (1.2)	1 (0.6)
Nervous system disorder	7 (4.3)	9 (5.7)
Brain injury	1 (0.6)	2 (1.3)
Brain edema	0	2 (1.3)

* For each event category, patients were counted once even if they had multiple events in that category. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*. There were no significant differences (at P<0.05) between the groups in the percentage of patients with adverse events.

† A complete listing of adverse events with frequency of 5% or more is provided in Table S13 in the Supplementary Appendix.

‡ A complete listing of adverse events leading to discontinuation of angiotensin II or placebo is provided in Table S14 in the Supplementary Appendix.

tensin II that is sufficiently stable for widespread clinical use.

Treatment options for patients with catecholamine-resistant vasodilatory shock are limited, and the treatments that are available are often associated with side effects. Specific options include glucocorticoids, vasopressins, methylene blue, and high-volume hemofiltration, all of which are used as adjunct therapies to maintain blood pressure in patients with vasodilatory shock.[21] Previously, new therapies proved to be disappointing. Notably, the nitric oxide synthase inhibitor 546C88 increased blood pressure in patients with septic shock but was associated with more frequent cardiovascular side effects and increased 28-day mortality.[22] In contrast, in our study, angiotensin II was not associated with higher mortality or a greater frequency of cardiovascular and other adverse events than was placebo.

The rationale for our study was based, in part, on the potential benefits of more closely mimicking natural physiologic responses to shock, which include increased secretion of catecholamines, vasopressin, and RAAS hormones. Preclinical and clinical data have shown that these vasoactive substances are synergistic,[23,24] and multimodal therapy may leverage this synergy to allow lower doses with potentially fewer toxic effects. The observed increases in mean arterial pressure with angiotensin II, with concomitant reductions in catecholamine requirements, support this view.

Our study has certain limitations. First, the significant blood-pressure response to angiotensin II, which permitted rapid reduction of catecholamine doses in some patients, may have allowed treating clinicians to correctly guess the treatment assignment in some cases. However, one in four placebo recipients showed a response in mean arterial pressure. Second, our study had a relatively small sample size, so the possibility of clinically important side effects attributable to angiotensin II therapy cannot be excluded. Third, because our trial was not powered to detect mortality effects, the confidence intervals around mortality point estimates are wide. Finally, because follow-up was limited to 28 days, the possibility of either beneficial or harmful long-term effects of angiotensin II therapy cannot be excluded. Larger trials with longer duration of follow-up are warranted to address these questions, as are direct comparisons of angiotensin II with other vasopressors.

In conclusion, angiotensin II administered intravenously increased blood pressure and allowed catecholamine dose reductions in patients with vasodilatory shock who were receiving high-dose vasopressors.

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APPENDIX

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