Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med. DOI: 10.1056/NEJMoa1704154

Angiotensin II for the Treatment of Vasodilatory Shock

Ashish Khanna, et al.

Supplementary Appendix

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Rationale for ATHOS-3 Study Design

Despite recent advancements in critical care, mortality in the ICU due to shock remains unacceptably high (>50%).[1] Substantial evidence exists that maintaining an adequate MAP is important to outcomes; even a short exposure to hypotension (defined as MAP <55 mmHg) may lead to increases in complications such as acute kidney injury and myocardial damage.[2] The human body leverages three main regulatory systems to maintain blood pressure: the sympathetic nervous system, arginine-vasopressin and the renin-angiotensin system. Clinicians currently only have two categories of therapeutic agents available for the management of hypotension, specifically catecholamines and vasopressin. Catecholamines and vasopressin are familiar and well-characterized vasopressors, but have significant side effects at high doses. Patients receiving high doses of vasopressors (>0.2ug/kg/min of norepinephrine or the equivalent) are at an increased mortality risk of >50%.[3,4] In order to defend an appropriate MAP, clinicians are often faced with the undesirable trade-off of higher toxicities due to escalating doses of catecholamines or vasopressin.

Unlike catecholamines and vasopressin, angiotensin II is not currently approved for clinical use. Angiotensin II has been studied previously in only a single randomized controlled trial of 20 patients (ATHOS-1). ATHOS-3 was designed to meet the FDA approval requirements of safety and efficacy.

A study design in which the MAP target remained 65-75 mmHg once angiotensin II was added would have necessitated a reduction in the background vasopressor dose. This reduction in background vasopressor would have offset potential toxicity and not yielded a clear examination of the safety profile of the new agent. Likewise using an active comparator would not have allowed a clear determination of the vasopressor activity nor a clear determination of the safety of angiotensin II. The placebo-controlled study design in which the MAP was allowed to rise for the first three hours was therefore chosen to clearly define the potency and safety of angiotensin II.

The study design built in two major endpoints within the first 48 hours:

1. The first three hours was a 'vasopressor' trial to test the hypothesis that angiotensin II can raise blood pressure in patients with severe vasodilatory shock already on a high dose of background vasopressors. This is important, as available data clearly show that even a short period of hypotension may lead to worse outcomes. The main utility for angiotensin II is as a vasopressor and it was essential to clearly delineate its safety and vasopressor potency.

2. The second phase of the trial was a more typical vasopressor study design wherein a new vasopressor is introduced, the clinical MAP target is maintained, and catecholamines are titrated down to estimate the effect on blood pressure. This portion of the study, which mimicked "real-world" practice, allowed the clinicians to use their clinical judgment regarding how to best leverage three different drugs in the management of hypotension.

In summary, the study design allowed for a clear assessment of safety and incorporated two key metrics of a vasopressor performance: capacity to raise blood pressure and a potency assessment as compared with catecholamine dosing.

Inclusion and Exclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Adult patients ≥18 years of age with catecholamine-resistance hypotension, defined as those who require a total sum catecholamine dose of >0.2 µg/kg/min (see Appendix D for conversion to norepinephrine equivalent) for a minimum of 6 hours and a maximum of 48 hours, to maintain mean arterial pressure (MAP) between 55–70 mm Hg.
2. Patients are required to have central venous access and an arterial line present, and these are expected to remain present for at least the initial 48 hours of study.
3. Patients are required to have an indwelling urinary catheter present, and it is expected to remain present for at least the initial 48 hours of study.
4. Patients must have received at least 25 mL/kg of crystalloid or colloid equivalent over the previous 24-hour period, and be adequately volume resuscitated in the opinion of the treating investigator.
5. Patients must have clinical features of high-output shock by meeting one of the following criteria:
    a. Central venous oxygen saturation ($ScvO_2$) >70% (either by oximetry catheter or by central venous blood gas) and central venous pressure (CVP) >8 mm Hg.

    OR

    b. Cardiac Index (CI) >2.3 L/min/m^2.

    Patient must meet 5a or 5b to be eligible.
6. Patient or legal surrogate is willing and able to provide written informed consent and comply with all protocol requirements.

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Patients who are <18 years of age.
2. Any patient with burns covering >20% of total body surface area.
3. Patients with a Cardiovascular SOFA score ≤3.
4. Patients diagnosed with acute occlusive coronary syndrome requiring intervention.
5. Patients on VA ECMO.
6. Patients who have been on ECMO for less than 12 hours.
7. Patients in liver failure with a Model for End-Stage Liver Disease (MELD) score of ≥30.
8. Patients with a history of asthma or who are currently experiencing bronchospasm requiring the use of inhaled bronchodilators, if not mechanically ventilated.
9. Patients with acute mesenteric ischemia or a history of mesenteric ischemic.
10. Patients with a history of, presence of, or highly-suspected of having an aortic dissection or abdominal aortic aneurysm.
11. Patients requiring more than 500 mg daily of hydrocortisone or equivalent glucocorticoid medication as a standing dose.
12. Patients with Raynaud's phenomenon, systemic sclerosis or vasospastic disease.
13. Patients with an expected lifespan of <12 hours.
14. Patients with active bleeding AND an anticipated need (within 48 hours of initiation of the study) for transfusion of >4 units of packed red blood cells.

15. Patients with active bleeding AND hemoglobin <7g/dL or any other condition that would contraindicate serial blood sampling.
16. Patients with an absolute neutrophil count of <1000 cells/mm^3.
17. Patients with a known allergy to mannitol.
18. Patients who are current participating in another interventional clinical trial.
19. Patients who are known to be pregnant at the time of screening.

Figure S1. Angiotensin II and Vasopressor (Norepinephrine Equivalent) Doses (mean ± SE) by Analysis Visit, Angiotensin II Group (mITT)

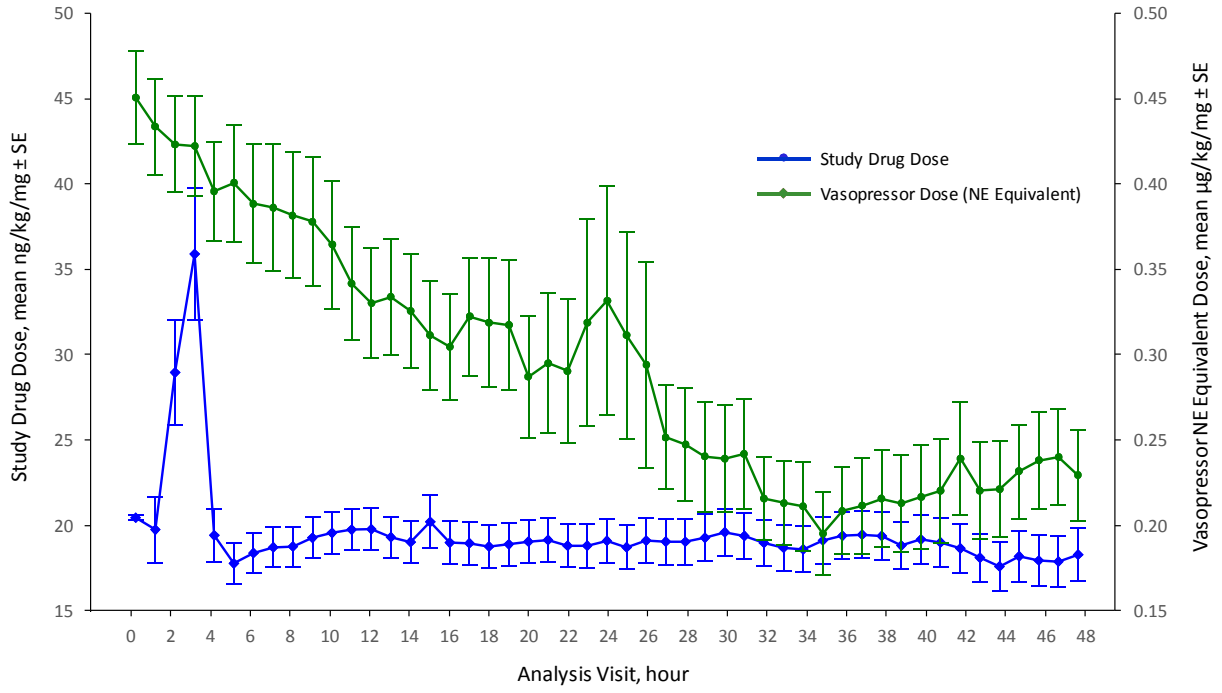

Figure S2. Doses (mean ± SE) of Study Drugs by Hour, mITT Population

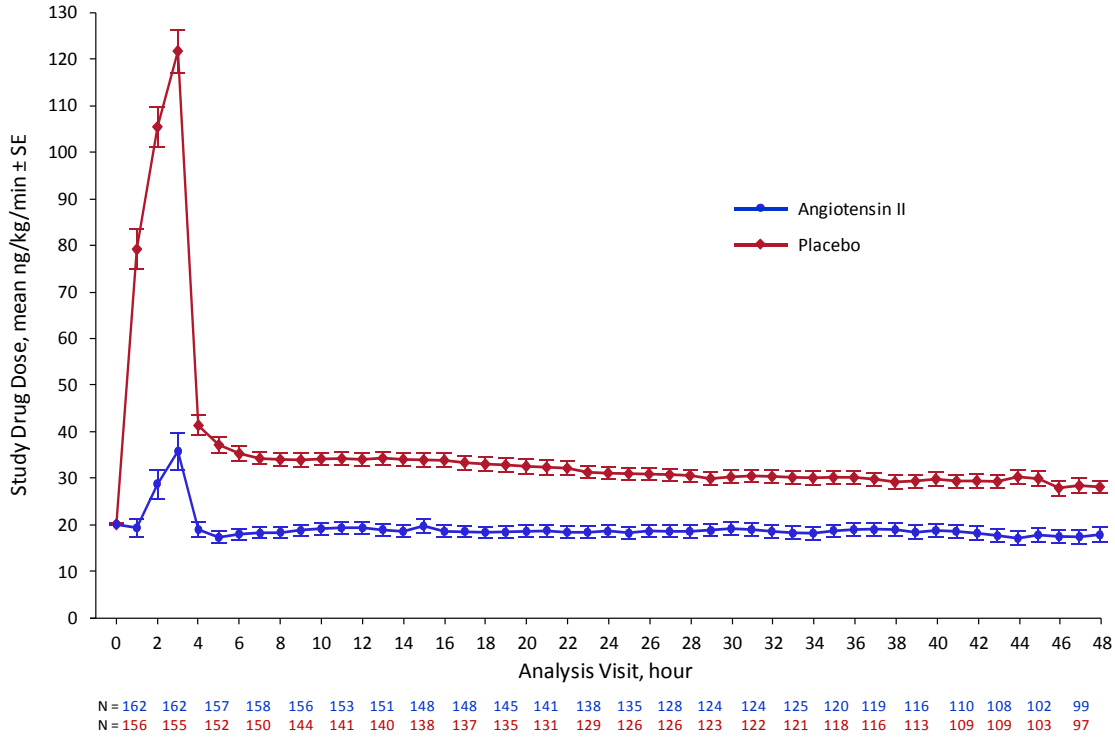

Figure S3. Absolute Heart Rate During Treatment.

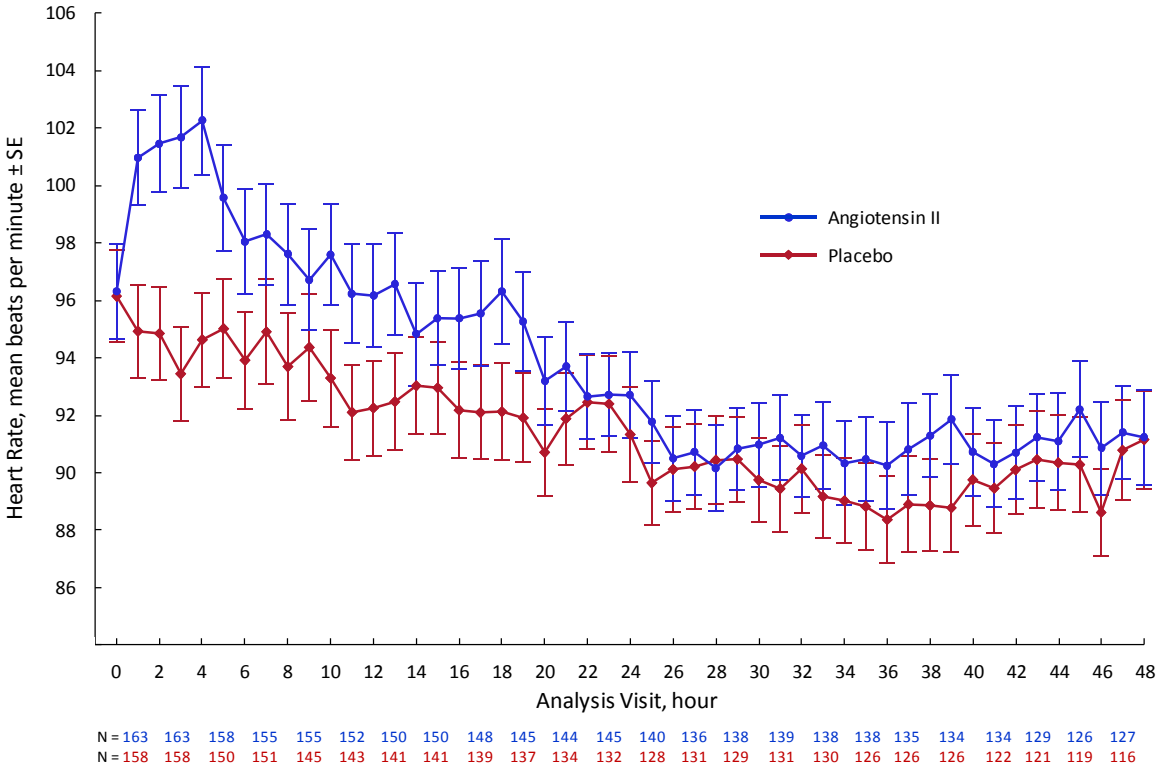

Figure S4a. Kaplan-Meier Plot of Survival Over 28 Days After Initiation of Therapy.

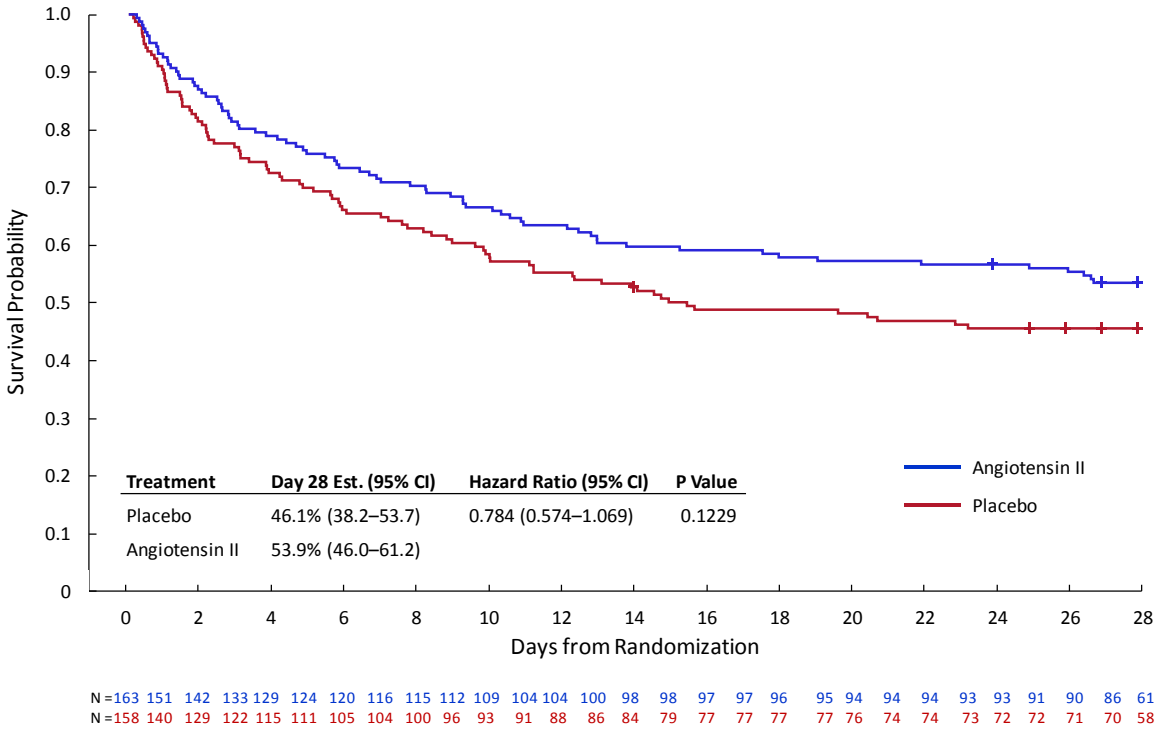

Figure S4b. Kaplan-Meier Plot of Survival Over 28 Days After Initiation of Therapy, Adjusted for Age (Continuous) and Gender.

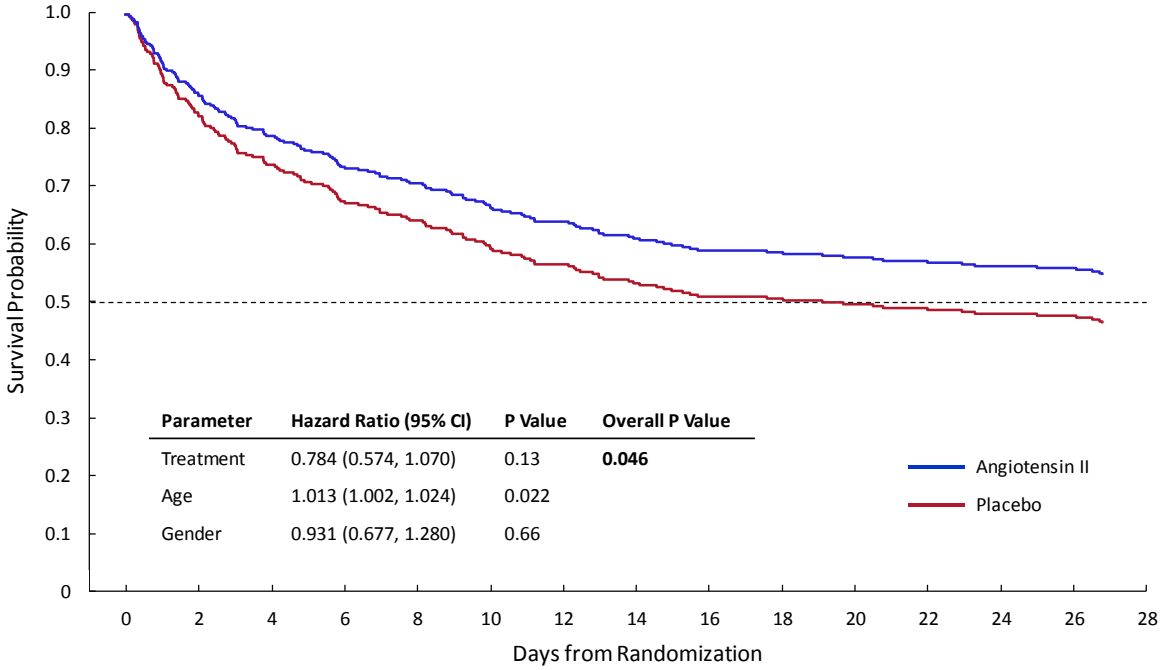

Figure S4c. Kaplan-Meier Plot of Survival Over 28 Days After Initiation of Therapy, Adjusted for Age (<65 vs ≥65 years) and Gender.

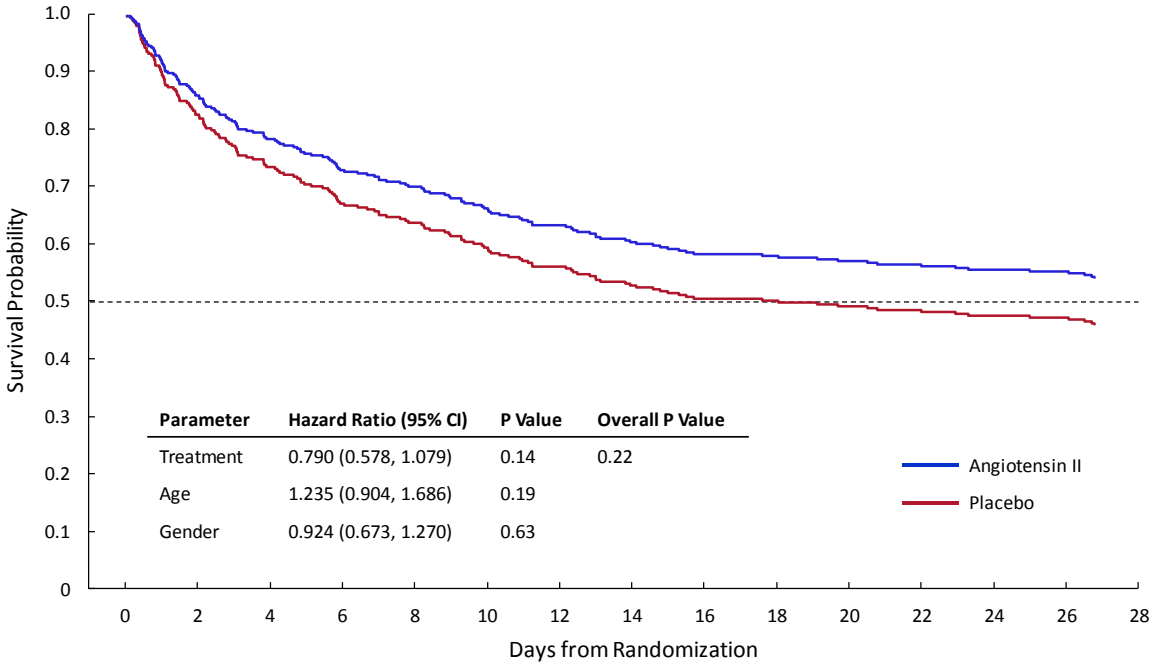

Table S1. Conversion to Norepinephrine Equivalent

Drug	Dose	Norepinephrine equivalent
Epinephrine[a]	0.1 μg/kg/min	0.1 μg/kg/min
Norepinephrine[a]	0.1 μg/kg/min	0.1 μg/kg/min
Dopamine[a]	15 μg/kg/min	0.1 μg/kg/min
Phenylephrine[b]	1.0 μg/kg/min	0.1 μg/kg/min
Vasopressin	0.04 U/min	0.1 μg/kg/min

The conversion scale was developed based on the cardiovascular Sequential Organ Failure Assessment score[a] and the medical literature[b].[5,6] Vasopressin equivalence to norepinephrine was developed with the use of the Vasopressin and Septic Shock Trial data set (by JAR).[7]

Table S2. Titration Schema: Hour 0 Through Hour 3 (binding)

Current MAP	Initial Study Drug Dose	Study Drug Titration Interval	Study Drug Dose Titration	Study Drug Maximal Dose	Study Drug Minimal Dose
mm Hg	ng/kg/min	min	ng/kg/min	ng/kg/min	ng/kg/min
≤ 59	20	5	Increase to 80[a] then by increments of 20	200	2.5
60-74	20	15	Increase by 10	200	2.5
75-84	N/A	15	Maintain dose	200	2.5
≥ 85	N/A	5	Decrease by 10[b]	200	2.5[c]

[a] Dosing may be modified by consensus opinion of the data safety monitoring board to as low as 60 ng/kg/min and as high as 120 ng/kg/min if deemed necessary for safety purposes.

[b] Once a dose of 10 ng/kg/min has been reached, study drug may be further reduced by halving each titration until the minimum dose is achieved.

[C] Dosing may be modified to as low as 1.25 ng/kg/min for those patients considered "hyper-responders", i.e., MAP remains ≥85 mmHg despite discontinuation of vasopressin and all catecholamines.

N/A, not applicable (such patients are not eligible for study participation); MAP, mean arterial pressure.

Table S3. Titration Schema: Hour 3 Through Hour 48 (non-binding)

Current MAP	Study Drug Titration Interval	Study Drug Dose Titration	Study Drug Maximal Dose	Study Drug Minimal Dose
mm Hg	min	ng/kg/min	ng/kg/min	ng/kg/min
≤ 59	5	Increase to 40	40	2.5
60-64	15	Increase by 10	40	2.5
65-70	15	Maintain dose[a]	40	2.5
≥ 70	15	Decrease by 10[b]	40	2.5[c]

[a] If the sum of the norepinephrine + epinephrine dose is ≥0.03 but <0.1 μg/kg/min, study drug dose should be maintained.

[b] If vasopressin is being used, vasopressin should be weaned off first. Then, titrate standard-of-care vasopressors until the sum of the norepinephrine + epinephrine dose is as low as 0.03 μg/kg/min.

[c] Dosing may be modified to as low as 1.25 ng/kg/min for those patients considered "hyper-responders", i.e., MAP remains ≥ 70 mmHg despite discontinuation of vasopressin and reduction of sum norepinephrine + epinephrine dose to as low as 0.03 μg/kg/min.

MAP, mean arterial pressure.

Table S4. The Sequential Organ Failure Assessment (SOFA) Score [5]

	SOFA Score				
	0	**1**	**2**	**3**	**4**
Respiration					
PaO_2 / FiO_2 (mm Hg)	>400	≤400	≤400	≤200 [a]	≤100 [a]
Coagulation					
Platelets × 10^3/μL	>150	≤150	≤100	≤50	≤20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (<20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12 (>204)
Cardiovascular [b]					
Hypotension	No hypotension	MAP <70 mm Hg	dop ≤5 or dob (any dose) [c]	dop >5, epi ≤0.1, or norepi ≤0.1 [c]	dop >15, epi >0.1, or norepi >0.1 [c]
Central nervous system					
Glasgow Coma Scale	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg/dL (μmol/L) or urine output, mL/d	<1.2 (<110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) or <500 mL/d	>5 (>440) or <200 mL/d

Dob, dobutamine; dop, dopamine; epi, epinephrine; MAP, mean arterial pressure; norepi, norepinephrine.

[a] Values are with respiratory support.

[b] Adrenergic agents administered for ≥1 hr.

[c] Dosages are in μg/kg/min. For CV SOFA score of 3 and 4, norepinephrine equivalent doses were utilized for determining scoring.

Table S5. Multivariate Analysis of Obtaining Target Mean Arterial Pressure at Hour 3 (mITT)

Parameter	Odds Ratio (95% CI)	P value
Treatment with angiotensin II vs placebo	12.4 (6.72-22.8)	< 0.001
Age ≥ 65 vs < 65 years	0.99 (0.56-1.74)	0.98
Male vs female	1.32 (0.74-2.34)	0.34
MAP at baseline < 65 vs ≥ 65 mm Hg	0.67 (0.36-1.23)	0.20
APACHE II score at baseline > 30 vs ≤ 30	1.04 (0.58-1.85)	0.90
Albumin at baseline < 2.5 vs ≥ 2.5 g/dL	0.40 (0.22-0.72)	0.002
Prior exposure to ARBs vs no exposure	0.24 (0.07-0.79)	0.02
Chest x-ray finding of ARDS vs no finding	2.03 (1.07-3.86)	0.03
Baseline NE equivalent dose ≥ 0.5 vs < 0.5 µg/kg/min	0.40 (0.21-0.77)	0.006

Parameters in red were statistically significant (P <0.05).

ACE, angiotensin converting enzyme; APACHE, Acute Physiology and Chronic Health Evaluation; ARB, angiotensin receptor blocker; ARDS, acute respiratory disease syndrome; MAP, mean arterial pressure; NE, norepinephrine.

Table S6: Site Enrollment by Country (mITT Population)

Country	Patients Enrolled	Region
USA	200 (62.3)	North America
Australia	43 (13.4)	Australasia
Canada	36 (11.2)	North America
United Kingdom	18 (5.6)	Western Europe
New Zealand	9 (2.8)	Australasia
Finland	7 (2.2)	Western Europe
France	6 (1.9)	Western Europe
Belgium	1 (0.3)	Western Europe
Germany	1 (0.3)	Western Europe
Total	**321**	

Table S7. Baseline Laboratory Parameters

Parameter	Angiotensin II N=163	Placebo N=158	All Patients N=321
White blood cells			
Median (range) 10^9/L	16.5 (1.7 – 117.1)	17.4 (0.6 – 256.9)	17.2 (0.6 – 256.9)
Missing data, n	1	0	1
Hemoglobin [a]			
Median (range) g/dL	10.1 (6.5 – 17.1)	9.2 (5.1 – 15.5)	9.8 (5.1 – 17.1)
Missing data, n	1	0	1
Hematocrit [b]			
Median (range) percent	30.5 (20.2 – 54.3)	28.2 (15.7 – 47.0)	29.9 (15.7 – 54.3)
Missing data, n	1	0	1
Platelets			
Median (range) 10^9/L	145.0 (19 – 503)	150.5 (11 – 541)	147.0 (11 – 541)
Missing data, n	1	0	1
Sodium			
Median (range) mEq/L	138.0 (121 – 153)	139.0 (128 – 156)	138.0 (121 – 156)
Missing data, n	1	0	1
Potassium			
Median (range) mEq/L	4.2 (2.7 – 6.7)	4.3 (3.1 – 6.9)	4.2 (2.7 – 6.9)
Missing data, n	1	0	1
Chloride			
Median (range) mEq/L	104 (85 – 126)	104 (86 – 121)	104 (85 – 126)
Missing data, n	2	2	4
Bicarbonate			
Median (range) mEq/L	19 (6 – 37)	19 (8 – 36)	19 (6 – 37)
Missing data, n	7	7	14
Blood urea nitrogen			
Median (range) mg/dL	24.0 (1.3 – 170)	26.8 (4.1 – 115)	24.6 (1.3 – 170)
Missing data, n	2	0	2
Creatinine			
Median (range) mg/dL	2.0 (0.4 – 11.9)	2.2 (0.4 – 8.8)	2.1 (0.4 – 11.9)
Missing data, n	1	0	1
Glucose			
Median (range) mg/dL	129.7 (21 – 568)	140.6 (42 – 371)	138.8 (21 – 568)
Missing data, n	7	6	13
pH			
Median (Q1 – Q3)	7.31 (7.25 – 7.37)	7.32 (7.25 – 7.40)	7.32 (7.25 – 7.38)
PCO2			
Median (Q1 – Q3) mmHg	38 (31 – 45)	37 (32 – 43)	37 (32 – 44)
PO2			
Median (Q1 – Q3) mmHg	89 (76 – 112)	86 (76 – 109)	88 (76 – 111)

Parameter	Angiotensin II N=163	Placebo N=158	All Patients N=321
FiO2			
Median (Q1 – Q3) %	45 (35 – 60)	44.5 (35 – 60)	45 (35 – 60)
Angiotensin I			
Median (range) pg/mL	260 (10.5 – 9180)	230 (10.5 – 4500)	246 (10.5 – 9180)
Missing data, n	12	14	26
Angiotensin II			
Median (range) pg/mL	105 (10.5 – 3340)	68 (10.5 – 2740)	81 (10.5 – 3340)
Missing data, n	12	15	27
Urine output			
Median (range) mL/hr	23.0 (0.0 – 339)	19.2 (0.0 – 1750)	20.0 (0.0 – 1750)
Missing data, n	1	1	2

For parameters reporting missing data, summary data are based on the adjusted N.

All differences between treatment groups in patients with events were not significant except: [a]P=0.003, and [b]P=0.003.

Table S8. Reasons for Nonresponse: Primary Efficacy Endpoint (mITT Population)

Category	Angiotensin II N=163 n (%)	Placebo N=158 n (%)	Total N=321 n (%)
Responder	114 (69.9)	37 (23.4)	151 (47.0)
Non-responder	49 (30.1)	121 (76.6)	170 (53.0)
Reason for nonresponse			
NE-equivalent (NED) dose increase	7 (4.3)	12 (7.6)	19 (5.9)
MAP <75 mmHg or change <10 mmHg	34 (20.9)	74 (46.8)	108 (33.6)
NED increase **and** MAP <75/change <10	8 (4.9)	35 (22.2)	43 (13.4)

Table S9. Vasopressor Use at Baseline, Hour 3, Hour 6, and Every 6 Hours to Hour 48

Vasopressor	Angiotensin II N=163			Placebo N=158		
Time Point	n (%)	Mean (SD)	Median (Range)	n (%)	Mean (SD)	Median (Range)
Norepinephrine, µg/kg/min						
Baseline	160 (98.2)	0.35 (0.345)	0.25 (0.02 - 2.58)	151 (95.6)	0.36 (0.352)	0.25 (0.03 - 2.68)
Hour 3	155 (95.1)	0.34 (0.366)	0.20 (0.02 - 2.58)	151 (95.6)	0.38 (0.410)	0.26 (0.03 - 3.00)
Hour 6	147 (90.2)	0.32 (0.416)	0.20 (0.01 - 3.00)	146 (92.4)	0.35 (0.385)	0.25 (0.01 - 3.00)
Hour 12	134 (82.2)	0.27 (0.349)	0.15 (0.01 – 2.62)	137 (86.7)	0.30 (0.296)	0.22 (0.01 - 2.04)
Hour 18	117 (71.8)	0.27 (0.401)	0.13 (0.01 – 2.67)	126 (79.7)	0.30 (0.399)	0.19 (0.00 - 3.00)
Hour 24	103 (63.2)	0.25 (0.558)	0.12 (0.01 – 4.83)	117 (74.1)	0.23 (0.277)	0.15 (0.01 - 1.80)
Hour 30	91 (55.8)	0.19 (0.255)	0.10 (0.02 – 1.78)	111 (70.3)	0.23 (0.339)	0.14 (0.00 - 3.00)
Hour 36	84 (51.5)	0.16 (0.223)	0.09 (0.01 – 1.13)	98 (62.0)	0.20 (0.220)	0.12 (0.00 - 1.22)
Hour 42	76 (46.6)	0.19 (0.280)	0.07 (0.01 – 1.50)	84 (53.2)	0.22 (0.256)	0.12 (0.01 - 1.50)
Hour 48	67 (41.1)	0.19 (0.206)	0.10 (0.01 - 0.94)	71 (44.9)	0.21 (0.300)	0.11 (0.01 - 2.13)
Vasopressin, U/min						
Baseline	110 (67.5)	0.04 (0.011)	0.04 (<0.005 - 0.08)	105 (66.5)	0.04 (0.014)	0.04 (< 0.005 - 0.10)
Hour 3	94 (57.7)	0.04 (0.010)	0.04 (0.02 - 0.08)	101 (63.9)	0.04 (0.015)	0.04 (0.01 - 0.10)
Hour 6	71 (43.6)	0.04 (0.012)	0.04 (0.01 - 0.08)	95 (60.1)	0.04 (0.016)	0.04 (0.01 - 0.12)
Hour 12	59 (36.2)	0.04 (0.011)	0.04 (0.01 - 0.08)	83 (52.5)	0.04 (0.018)	0.04 (0.01 - 0.12)
Hour 18	50 (30.7)	0.04 (0.013)	0.04 (0.01 - 0.08)	65 (41.1)	0.04 (0.015)	0.04 (0.01 - 0.10)
Hour 24	37 (22.7)	0.04 (0.010)	0.04 (0.01 - 0.07)	50 (31.6)	0.04 (0.012)	0.04 (0.02 - 0.10)
Hour 30	31 (19.0)	0.03 (0.014)	0.04 (0.01 - 0.07)	47 (29.7)	0.04 (0.011)	0.04 (0.02 - 0.10)
Hour 36	27 (16.6)	0.04 (0.010)	0.04 (0.02 - 0.07)	40 (25.3)	0.04 (0.012)	0.04 (0.02 - 0.10)

Vasopressor	Angiotensin II N=163			Placebo N=158		
Time Point	n (%)	Mean (SD)	Median (Range)	n (%)	Mean (SD)	Median (Range)
Hour 42	21 (12.9)	0.04 (0.011)	0.04 (0.02 - 0.07)	39 (24.7)	0.04 (0.012)	0.04 (0.02 - 0.10)
Hour 48	15 (9.2)	0.04 (0.012)	0.04 (0.01 - 0.07)	32 (20.3)	0.04 (0.013)	0.04 (0.02 - 0.10)
Epinephrine, µg/kg/min						
Baseline	21 (12.9)	0.10 (0.120)	0.06 (0.01 - 0.50)	21 (13.3)	0.24 (0.363)	0.15 (< 0.005 - 1.50)
Hour 3	20 (12.3)	0.12 (0.154)	0.06 (0.01 - 0.67)	22 (13.9)	0.26 (0.448)	0.10 (< 0.005 - 2.00)
Hour 6	16 (9.8)	0.12 (0.116)	0.08 (0.02 - 0.40)	20 (12.7)	0.16 (0.226)	0.08 (0.00 - 1.00)
Hour 12	19 (11.7)	0.11 (0.113)	0.07 (0.01 - 0.40)	20 (12.7)	0.12 (0.129)	0.07 (0.00 - 0.50)
Hour 18	17 (10.4)	0.06 (0.038)	0.04 (0.02 - 0.18)	14 (8.9)	0.08 (0.049)	0.07 (0.03 - 0.19)
Hour 24	17 (10.4)	0.26 (0.659)	0.06 (0.01 - 2.78)	11 (7.0)	0.08 (0.062)	0.04 (0.03 - 0.22)
Hour 30	13 (8.0)	0.08 (0.088)	0.04 (0.01 - 0.31)	12 (7.6)	0.05 (0.040)	0.04 (0.02 - 0.16)
Hour 36	11 (6.7)	0.11 (0.149)	0.04 (0.01 - 0.50)	8 (5.1)	0.04 (0.024)	0.04 (0.01 - 0.09)
Hour 42	9 (5.5)	0.14 (0.174)	0.04 (0.01 - 0.50)	9 (5.7)	0.06 (0.042)	0.04 (0.02 - 0.16)
Hour 48	8 (4.9)	0.12 (0.181)	0.04 (0.01 - 0.50)	6 (3.8)	0.07 (0.049)	0.05 (0.03 - 0.16)
Dopamine, µg/kg/min						
Baseline	2 (1.2)	5.25 (3.889)	5.25 (2.50 - 8.00)	4 (2.5)	9.50 (7.594)	7.50 (3.00 - 20.00)
Hour 3	2 (1.2)	5.25 (3.889)	5.25 (2.50 - 8.00)	4 (2.5)	10.00 (7.071)	7.50 (5.00 - 20.00)
Hour 6	2 (1.2)	4.25 (2.475)	4.25 (2.50 - 6.00)	4 (2.5)	12.50 (8.660)	10.00 (5.00 - 25.00)
Hour 12	1 (0.6)	2.50 (NA)	2.50 (2.50 - 2.50)	2 (1.3)	10.00 (0.000)	10.00 (10.00 - 10.00)
Hour 18	1 (0.6)	2.50 (NA)	2.50 (2.50 - 2.50)	2 (1.3)	10.00 (0.000)	10.00 (10.00 - 10.00)
Hour 24	1 (0.6)	2.50 (NA)	2.50 (2.50 - 2.50)	2 (1.3)	10.00 (0.000)	10.00 (10.00 - 10.00)
Hour 30	1 (0.6)	2.49 (NA)	2.49 (2.49 - 2.49)	2 (1.3)	10.00 (0.000)	10.00 (10.00 - 10.00)

Vasopressor	Angiotensin II N=163			Placebo N=158		
Time Point	n (%)	Mean (SD)	Median (Range)	n (%)	Mean (SD)	Median (Range)
Hour 36	1 (0.6)	2.49 (NA)	2.49 (2.49 - 2.49)	1 (0.6)	10.00 (NA)	10.00 (10.00 - 10.00)
Hour 42	3 (1.8)	2.83 (0.294)	3.00 (2.49 - 3.00)	1 (0.6)	10.00 (NA)	10.00 (10.00 - 10.00)
Hour 48	2 (1.2)	2.75 (0.360)	2.75 (2.49 - 3.00)	1 (0.6)	10.00 (NA)	10.00 (10.00 - 10.00)

Table S10. Numbers of Vasopressors Used by Hour

Study Hour	Angiotensin II Number of Vasopressors, n (%)					Placebo Number of Vasopressors, n (%)				
	N	1	2	3	4	N	1	2	3	4
Baseline	163	49 (30.1)	81 (49.7)	26 (16.0)	7 (4.3)	158	43 (27.2)	83 (52.5)	28 (17.7)	4 (2.5)
3	160	60 (37.5)	72 (45.0)	22 (13.8)	6 (3.8)	157	45 (28.7)	78 (49.7)	30 (19.1)	4 (2.5)
6	154	76 (49.4)	57 (37.0)	17 (11.0)	4 (2.6)	154	51 (33.1)	71 (46.1)	29 (18.8)	3 (1.9)
12	142	76 (53.5)	49 (34.5)	12 (8.5)	5 (3.5)	146	53 (36.3)	64 (43.8)	25 (17.1)	4 (2.7)
18	127	73 (57.5)	39 (30.7)	13 (10.2)	2 (1.6)	135	61 (45.2)	52 (38.5)	20 (14.8)	2 (1.5)
24	113	71 (62.8)	29 (25.7)	11 (9.7)	2 (1.8)	128	73 (57.0)	39 (30.5)	14 (10.9)	2 (1.6)
30	100	62 (62.0)	28 (28.0)	10 (10.0)	0	122	70 (57.4)	37 (30.3)	12 (9.8)	3 (2.5)
36	94	64 (68.1)	21 (22.3)	9 (9.6)	0	112	70 (62.5)	33 (29.5)	7 (6.3)	2 (1.8)
42	86	59 (68.6)	22 (25.6)	3 (3.5)	2 (2.3)	100	62 (62.0)	29 (29.0)	8 (8.0)	1 (1.0)
48	75	53 (70.7)	17 (22.7)	5 (6.7)	0	81	49 (60.5)	26 (32.1)	6 (7.4)	0

Data indicate the numbers (percent) of patients at each time point using the number of vasopressors in the column heading.

Table S11. Cardiovascular and Total SOFA Scores (mITT)

Parameter	Time Point Statistic	Angiotensin II N=163	Placebo N=158	Total N=321
Cardio-vascular SOFA score	**Screening**			
	Mean (SD)	4.00 (0.00)	4.00 (0.00)	4.00 (0.00)
	Median (range)	4 (4 - 4)	4 (4 - 4)	4 (4 - 4)
	Hour 3			
	Mean (SD)	3.87 (0.550)	3.99 (0.112)	3.93 (0.404)
	Median (range)	4 (0 - 4)	4 (3 - 4)	4 (0 - 4)
	Change, screening to hour 3			
	Mean (SD)	-0.13 (0.550)	-0.01 (0.112)	-0.07 (0.404)
	Median (range)	0 (−4 – 0)	0 (-1 – 0)	0 (−4 – 0)
	van Elteren Wilcoxon rank	0.0019		
	Hour 48			
	Mean (SD)	2.25 (1.771)	2.72 (1.654)	2.48 (1.729)
	Median (range)	3 (0 – 4)	4 (0 – 4)	3 (0 – 4)
	Score distribution, n (%)			
	0	54 (33.1)	36 (22.8)	90 (28.0)
	1	12 (7.4)	9 (5.7)	21 (6.5)
	2	2 (1.2)	0	2 (0.6)
	3	30 (18.4)	31 (19.6)	61 (19.0)
	4	44 (27.0)	51 (32.3)	95 (29.6)
	4 (LOCF)	0	2 (1.3)	2 (0.6)
	4 (worst case, death)	21 (12.9)	29 (18.4)	50 (15.6)
	Change, screening to hour 48			
	Mean (SD)	-1.75 (1.771)	-1.28 (1.654)	-1.52 (1.729)
	Median (range)	-1 (-4 – 0)	0 (-4 – 0)	-1 (-4 – 0)
	van Elteren Wilcoxon rank	0.0129		
Total SOFA score	**Screening**	N=158	N=158	N=316
	Mean (SD)	11.77 (2.839)	12.72 (3.310)	12.24 (3.115)
	Median (range)	12 (5 – 18)	13 (5 – 21)	12 (5 – 21)
	Hour 3	N=163	N=158	N=321
	Mean (SD)	12.53 (3.007)	13.18 (3.308)	12.85 (3.170)
	Median (range)	13.00 (4 – 20)	13.00 (5 – 21)	13.00 (4 – 21)
	Change, screening to hour 3	N=158	N=158	N=316
	Mean (SD)	0.81 (1.932)	0.47 (1.819)	0.64 (1.881)
	Median (range)	1.00 (−6 – 7)	0.00 (−3 – 7)	0.00 (−6 – 7)
	van Elteren Wilcoxon rank	0.1362		
	Hour 48			
	Mean (SD)	12.69 (6.033)	13.76 (6.700)	13.22 (6.382)
	Median (range)	11.00 (2 - 24)	13.50 (1 - 24)	12.00 (1 - 24)

Parameter	Time Point Statistic	Angiotensin II N=163	Placebo N=158	Total N=321
	Score Calculation			
	No imputation	122 (74.8)	109 (69.0)	231 (72.0)
	LOCF	20 (12.3)	20 (12.7)	40 (12.5)
	Worst case assignment	21 (12.9)	29 (18.4)	50 (15.6)
	Change, screening to hour 48	N=158	N=158	N=316
	Mean (SD)	1.05 (5.500)	1.04 (5.336)	1.05 (5.410)
	Median (range)	0.00 (-10 – 15)	0.00 (-9 – 16)	0.00 (-10 – 16)
	van Elteren Wilcoxon rank	0.9755		

For missing scores, last observation was carried forward; for deaths, worst case (4) was used.
LOCF, last observation carried forward; mITT, modified intent to treat; SOFA, sequential organ failure assessment.

Table S12. Mean Arterial Pressure at Hour 3. Primary Efficacy Analysis (Logistic Regression). ITT Population.

Analysis	Angiotensin II N=172	Placebo N=172	Total N=344
Number responding	116	41	157
Percent responding	67.4%	23.8%	45.6%
95% confidence interval	59.9% - 74.4%	17.7% - 30.9%	40.3% - 51.1%
Primary analysis			
Independent variable:	**Odds Ratio (95% CI)**		**P value**
Treatment, angiotensin II	6.96 (4.27 - 11.3)		< 0.001
Baseline MAP, <65 mmHg	0.50 (0.30 - 0.86)		0.011
Baseline APACHE II score	0.99 (0.96 - 1.02)		0.66
Vasopressin during 6 h prior to randomization	1.06 (0.63 - 1.80)		0.82
Average NED in 6 h prior to randomization	0.60 (0.30 - 1.22)		0.16

MAP data were available and utilized to determine the Hour 3 MAP outcome for 15 of 23 patients who were randomized but discontinued prior to initiating study drug. The other 8 patients were classified as not achieving the Hour 3 MAP response.

Table S13. Adverse Events Occurring After Initiation of Study Drug With Frequency ≥5% in Either Treatment Arm

	Angiotensin II N=163		Placebo N=158		Total N=321	
Adverse Event	**Events, n**	**Patients, n (%)**	**Events, n**	**Patients, n (%)**	**Events, n**	**Patients, n (%)**
Any adverse event	669	142 (87.1)	562	145 (91.8)	1231	287 (89.4)
Cardiac disorders	91	57 (35.0)	98	66 (41.8)	189	123 (38.3)
Atrial fibrillation	23	22 (13.5)	23	21 (13.3)	46	43 (13.4)
Bradycardia	7	7 (4.3)	11	11 (7.0)	18	18 (5.6)
Cardiac arrest	10	7 (4.3)	10	9 (5.7)	20	16 (5.0)
Ventricular tachycardia	6	5 (3.1)	11	8 (5.1)	17	13 (4.0)
Metabolism and nutrition disorders	72	53 (32.5)	60	43 (27.2)	132	96 (29.9)
Hypokalemia	14	13 (8.0)	10	10 (6.3)	24	23 (7.2)
Hypophosphatemia	6	6 (3.7)	11	11 (7.0)	17	17 (5.3)
Infections and infestations [a]	60	49 (30.1)	35	30 (19.0)	95	79 (24.6)
Septic shock	18	18 (11.0)	10	10 (6.3)	28	28 (8.7)
Vascular disorders	68	43 (26.4)	34	31 (19.6)	102	74 (23.1)
Hypotension	21	17 (10.4)	10	10 (6.3)	31	27 (8.4)
Hypertension	11	9 (5.5)	9	9 (5.7)	20	18 (5.6)
Respiratory, thoracic, and mediastinal disorders	60	39 (23.9)	54	41 (25.9)	114	80 (24.9)
Pleural effusion	9	9 (5.5)	9	9 (5.7)	18	18 (5.6)
Respiratory failure	9	9 (5.5)	12	12 (7.6)	21	21 (6.5)
Gastrointestinal disorders	49	38 (23.3)	44	32 (20.3)	93	70 (21.8)
Blood and lymphatic system disorders	39	28 (17.2)	30	25 (15.8)	69	53 (16.5)
Anemia	12	12 (7.4)	10	10 (6.3)	22	22 (6.9)
Thrombocytopenia	16	16 (9.8)	11	11 (7.0)	27	27 (8.4)
Psychiatric disorders	23	21 (12.9)	15	11 (7.0)	38	32 (10.0)

	Angiotensin II N=163		Placebo N=158		Total N=321	
Adverse Event	**Events, n**	**Patients, n (%)**	**Events, n**	**Patients, n (%)**	**Events, n**	**Patients, n (%)**
Agitation	6	6 (3.7)	8	8 (5.1)	14	14 (4.4)
Delirium [b]	9	9 (5.5)	1	1 (0.6)	10	10 (3.1)
Nervous system disorders	22	14 (8.6)	23	19 (12.0)	45	33 (10.3)
Hepatobiliary disorders	10	8 (4.9)	10	10 (6.3)	20	18 (5.6)
Skin and subcutaneous tissue disorders	28	22 (13.5)	15	11 (7.0)	43	33 (10.3)
Renal and urinary disorders	17	16 (9.8)	21	18 (11.4)	38	34 (10.6)
Acute kidney injury	8	8 (4.9)	11	10 (6.3)	19	18 (5.6)
General disorders & administration site conditions	55	45 (27.6)	57	39 (24.7)	112	84 (26.2)
Multi-organ failure	25	25 (15.3)	24	24 (15.2)	49	49 (15.3)
Investigations	44	30 (18.4)	38	30 (19.0)	82	60 (18.7)
Injury, poisoning, and procedural complications	14	11 (6.7)	11	9 (5.7)	25	20 (6.2)

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). http://www.meddra.org.

All differences between treatment groups in patients with events were not significant except: [a] P = 0.029, and [b] P = 0.036.

Table S14. Adverse Events Leading to Discontinuation of Study Drug

Patients With Event, n (%)	Angiotensin II[a] N=163	Placebo N=158	Total N=321
All events	23 (14.1)	34 (21.5)	57 (17.8)
Septic shock	8 (4.9)	4 (2.5)	12 (3.7)
Multi-organ failure	6 (3.7)	6 (3.8)	12 (3.7)
Cardiogenic shock	2 (1.2)	4 (2.5)	6 (1.9)
Peripheral ischemia	1 (0.6)	1 (0.6)	2 (0.6)
Cardiopulmonary failure	1 (0.6)	0 (0.0)	1 (0.3)
Distributive shock	1 (0.6)	0	1 (0.3)
Hepatic cancer	1 (0.6)	0	1 (0.3)
Sepsis	1 (0.6)	0	1 (0.3)
Stevens-Johnson syndrome	1 (0.6)	0	1 (0.3)
Necrotizing fasciitis	1 (0.6)	0	1 (0.3)
Pneumonia	1 (0.6)	0	1 (0.3)
Cardiac arrest	0	5 (3.2)	5 (1.6)
Acute hepatic failure	0	1 (0.6)	1 (0.3)
Bradycardia	0	1 (0.6)	1 (0.3)
Brain edema	0	1 (0.6)	1 (0.3)
Cardiorespiratory arrest	0	1 (0.6)	1 (0.3)
Circulatory collapse	0	1 (0.6)	1 (0.3)
Hepatic failure	0	1 (0.6)	1 (0.3)
Hyperkalemia	0	1 (0.6)	1 (0.3)
Hypotension	0	1 (0.6)	1 (0.3)
Intestinal ischemia	0	1 (0.6)	1 (0.3)
Myocardial infarction	0	1 (0.6)	1 (0.3)
Pancreatitis	0	1 (0.6)	1 (0.3)
Peritonitis	0	1 (0.6)	1 (0.3)
Respiratory failure	0	1 (0.6)	1 (0.3)
Supraventricular tachycardia	0	1 (0.6)	1 (0.3)

[a]Some patients experienced >1 event.

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). http://www.meddra.org.

No differences between treatment groups were statistically significant.

Table S15. Adverse Events (Any Grade) of Special Interest

Event, n (%)	Angiotensin II N=163	Placebo N=158	Total N=321
Overall	51 (31.3)	55 (34.8)	106 (33.0)
Nervous system disorders	4 (2.5)	1 (0.6)	5 (1.6)
Brain hypoxia	1 (0.6)	0	1 (0.3)
Cerebral infarction	1 (0.6)	0	1 (0.3)
Cerebral ischemia	0	1 (0.6)	1 (0.3)
Hypoxic-ischemic encephalopathy	1 (0.6)	0	1 (0.3)
Ischemic stroke	1 (0.6)	0	1 (0.3)
Cardiac disorders	42 (25.8)	42 (26.6)	84 (26.2)
Acute myocardial infarction	2 (1.2)	3 (1.9)	5 (1.6)
Arrhythmia	3 (1.8)	0	3 (0.9)
Atrial fibrillation	22 (13.5)	21 (13.3)	43 (13.4)
Atrial flutter	2 (1.2)	5 (3.2)	7 (2.2)
Atrial tachycardia	0	1 (0.6)	1 (0.3)
Atrioventricular block	1 (0.6)	0	1 (0.3)
Bundle branch block right	2 (1.2)	0	2 (0.6)
Myocardial infarction	0	1 (0.6)	1 (0.3)
Nodal arrhythmia	0	1 (0.6)	1 (0.3)
Pulseless electrical activity	1 (0.6)	1 (0.6)	2 (0.6)
Sinus arrest	1 (0.6)	0	1 (0.3)
Sinus tachycardia	3 (1.8)	1 (0.6)	4 (1.2)
Supraventricular extrasystole	0	1 (0.6)	1 (0.3)
Supraventricular tachycardia	3 (1.8)	4 (2.5)	7 (2.2)
Tachycardia	8 (4.9)	4 (2.5)	12 (3.7)
Ventricular extrasystoles	1 (0.6)	3 (1.9)	4 (1.2)
Ventricular fibrillation	2 (1.2)	0	2 (0.6)
Ventricular tachycardia	5 (3.1)	8 (5.1)	13 (4.0)
Vascular disorders	9 (5.5)	5 (3.2)	14 (4.4)
Peripheral coldness	0	1 (0.6)	1 (0.3)
Peripheral ischemia	7 (4.3)	4 (2.5)	11 (3.4)
Poor peripheral circulation	2 (1.2)	0	2 (0.6)
Vasospasm	1 (0.6)	0	1 (0.3)
Gastrointestinal disorders	1 (0.6)	3 (1.9)	4 (1.2)
Intestinal ischemia	1 (0.6)	3 (1.9)	4 (1.2)
Hepatobiliary disorders	2 (1.2)	4 (2.5)	6 (1.9)
Ischemic hepatitis	2 (1.2)	4 (2.5)	6 (1.9)
Skin & subcutaneous tissue disorders	1 (0.6)	1 (0.6)	2 (0.6)
Skin necrosis	1 (0.6)	1 (0.6)	2 (0.6)
Investigations	1 (0.6)	4 (2.5)	5 (1.6)
Electrocardiogram QT prolonged	1 (0.6)	4 (2.5)	5 (1.6)

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). http://www.meddra.org.

No differences between treatment groups were statistically significant.

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