Angiotensin II Infusion in Invasively Ventilated COVID-19 Patients

APPENDIX

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DEFINITION OF OUTCOMES

Bacterial pneumonia

The CDC defines pneumonia as follows:

- Two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease):
    - new or progressive and persistent infiltrates; or
    - consolidation; or
    - cavitation.
- At least one of the following clinical signs:
    - fever (> 38.8°C) with no other recognized cause; or
    - leukopenia (white cell count < $4x10^{9}1^{-1}$) or leukocytosis (white cell count >$12x10^{9}1^{-1}$); or
    - for adults >70 years old, altered mental status with no other recognized cause.
- At least one of the following clinical signs:
    - new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements;
    - new onset or worsening cough, or dyspnea, or tachypnoea;
    - rales or bronchial breath sounds;
    - worsening gas exchange (hypoxemia, increased oxygen requirement, increased ventilator demand).

Acute Respiratory Distress Syndrome

The Berlin definition of Acute Respiratory Distress Syndrome.

- Timing. Within one week of a known clinical insult or new or worsening respiratory symptoms; and
- Chest imaging (Chest radiograph or computed tomography scan). Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules; and
- Origin of edema. Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present; and
- Oxygenation
    - Mild. PaO2:FIO2 between 26.7 and 40.0 kPa (200–300 mmHg) with PEEP or CPAP ≥ 5 cmH2O. This may be delivered non-invasively in the mild acute respiratory distress syndrome group.
    - Moderate. PaO2:FIO2 between 13.3 and 26.6 kPa (100–200 mmHg) with PEEP ≥ 5 cmH2O
    - Severe. PaO2:FIO2 13.3 kPa (100 mmHg) with PEEP ≥ 5 cmH2O
    - If altitude is higher than 1000 m, a correction factor should be calculated (PaO2:FiO2 x [barometric pressure/101 kPa]).

Pneumothorax

Air in the pleural space with no vascular bed surrounding the visceral pleura

Stroke / Cerebrovascular accident

The ACS-NSQIP defines stroke as an embolic, thrombotic or hemorrhagic cerebral event with persistent residual motor, sensory or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory).

Acute congestive heart failure

New in-hospital signs or symptoms of dyspnea or fatigue, orthopnea, paroxysmal nocturnal dyspnea, increased jugular venous pressure, pulmonary rales on physical examination, cardiomegaly or pulmonary vascular engorgement.

Myocarditis / pericarditis

Myocarditis should be suspected when otherwise healthy patients with no cardiac risk factors present with symptoms of heart failure or arrhythmias. ECG, cardiac enzymes, and cardiac imaging are not specific for myocarditis but can be diagnostic in the appropriate clinical setting.

ECG can be normal or abnormal in patients with myocarditis. ST segment abnormalities are common and can mimic myocardial ischemia. ST segment elevation is sometimes seen but more common findings include nonspecific ST-T wave changes. Patients may experience conduction delays and atrial or ventricular arrhythmias, including sinus tachycardia, ventricular tachycardia, and ventricular fibrillation. Cardiac enzymes can be abnormal in patients with acute myocarditis. Cardiac troponin and CK-MB (creatine kinase muscle band isoenzyme) can both be elevated due to necrosis of cardiac myocytes.

Cardiac imaging can be abnormal in patients with myocarditis. Echocardiogram can be normal in early or mild myocarditis. Segmental wall motion abnormalities (mimicking myocardial ischemia) can be seen. Left ventricular dilation and systolic dysfunction can also be seen as in dilated cardiomyopathy. Diastolic relaxation parameters are often abnormal on echocardiography. Cardiac MRI is becoming increasingly important in the diagnosis of myocarditis. Cardiac MRI of patients with myocarditis may show a characteristic pattern of late gadolinium enhancement in the subepicardial and mid-myocardial walls (in contrast to ischemia where late gadolinium enhancement is usually subendocardial with extension to mid-myocardial and epicardial walls). Other diagnostic features of myocarditis on cardiac MRI are the presence of myocardial edema and myocardial hyperemia relative to skeletal muscle.

Cardiac arrhythmia

Arrhythmia is defined as electrocardiograph (ECG) evidence of cardiac rhythm disturbance.

Cardiac ischemia / infarction

Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria: symptoms of ischemia; new or presumed new significant ST segment or T wave ECG changes or new left bundle branch block; development of pathological Q waves on ECG; radiological or echocardiographic evidence of new loss of viable myocardium or new regional

wall motion abnormality; identification of an intracoronary thrombus at angiography or autopsy.

Cardiac arrest

Cardiac arrest is the sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation. If corrective measures are not taken rapidly, this condition progresses to sudden death. Cardiac arrest should be used to signify an event as described above, that is reversed, usually by CPR and/or defibrillation or cardioversion, or cardiac pacing. Sudden cardiac death should not be used to describe events that are not fatal.

Bacteremia

The CDC defines laboratory confirmed bloodstream infection as one which meets at least one of the following criteria which should not be related to infection at another site:

- Patient has a recognized pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site; or
- Patient has at least one of the following signs or symptoms: fever >38.8°C, chills or hypotension, and at least one of the following:
    - common skin contaminant cultured from two or more blood cultures drawn on separate occasions; or

- common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy; or
- positive blood antigen test.

Other infections

We included under this definition all secondary infection not mentioned above.

We also included infection of unknown source, defined below:

The CDC defines infection, source uncertain as one where there is strong clinical suspicion of infection but the source has not been confirmed because clinical information suggests more than one possible site, meeting two or more of the following criteria:

- Core temperature < 36.8°C or > 38.8°C; and/or
- White cell count > $12x10^{9}l^{-1}$ or < $4x10^{9}l^{-1}$; and/or
- Respiratory rate > 20 breaths per minute or $PaCO_2$ < 4.7 kPa (35 mmHg); and/or
- Heart rate > 90 beats per minute.

Fungal infection

Same as for all other infections, but with fungal isolation instead of bacterial isolation.

Coagulation disorder / Disseminated Intravascular Coagulation

Disseminated intravascular coagulation is suspected in patients with unexplained bleeding or venous thromboembolism, especially if a predisposing

condition exists. If DIC is suspected, platelet count, PT, PTT, plasma fibrinogen level, and plasma D-dimer levels (an indication of in vivo fibrin polymer generation and degradation) are obtained.

Rhabdomyolysis / Myositis

Rhabdomyolysis is suspected based on history, clinical signs, and symptoms. Confirmation is by laboratory testing of elevated CK. Although a cut-off threshold has not been established, a CK level of > 5 times the upper limit of normal is typically required for diagnosis. Other corroborating laboratory testing includes the presence of myoglobin in urine. Myoglobinuria is detected when urinary myoglobin exceeds 250 mcg/mL. Other laboratory features include rapidly rising serum creatinine, hyperkalemia, hyperuricemia, hypocalcemia, or hypercalcemia, hyperphosphatemia, lactic acidosis, and thrombocytopenia.

Acute kidney injury

Classified and staged using KDIGO criteria or the need for renal-replacement therapy.

2.1.1: AKI is defined as any of the following (*Not Graded*):

- **Increase in SCr by ⩾0.3 mg/dl (⩾26.5 µmol/l) within 48 hours; or**
- **Increase in SCr to ⩾1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or**
- **Urine volume <0.5 ml/kg/h for 6 hours.**

2.1.2: AKI is staged for severity according to the following criteria (Table 2). (*Not Graded*)

Table 2 | Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 µmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

Gastrointestinal hemorrhage

Gastrointestinal bleed is defined as unambiguous clinical or endoscopic evidence of blood in the gastrointestinal tract. Upper gastrointestinal bleeding (or hemorrhage) is that originating proximal to the ligament of Treitz, in practice from the esophagus, stomach and duodenum. Lower gastrointestinal bleeding is that originating from the small bowel or colon.

Gastrointestinal perforation

We defined gastrointestinal perforation as intraoperative evidence of perforation or clinical signs and symptoms suggestive of GI perforation together with radiographic evidence of free air in the abdomen.

Liver dysfunction

Acute liver dysfunction was defined as elevated liver function test, possibly associated with coagulopathy and hepatic encephalopathy without underlying chronic liver disease, which was relevant enough to be reported in the medical chart.

Hyperglycemia

Blood sugar level persistently > 180 mg/dL despite insulin therapy

Acute limb ischemia

Acute onset (<2 weeks) of signs/symptoms of ischemia (limb pain, pallor, paresthesia, poikilothermia, pulselessness, paralysis) together with echography or angiographic evidence of acute vascular occlusion.

Pulmonary embolism

Evidence of thrombi in the arterial pulmonary vascular bed documented by contrast computed tomography of the chest or by echocardiography.

We also included sudden respiratory and/or hemodynamic compromise with evidence of acute right ventricular dilation and dysfunction in patients with compatible history (e.g. clinical deterioration following patient's movement) and no other causes.

Life-threatening bleeding

Life-threatening bleeding was defined as in the Perioperative Ischemic Evaluation (POISE) 2 trial: a life-threatening bleed was defined as a bleeding event that was fatal or led to: significant hypotension that required inotrope or vasopressor therapy, emergent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.

Major bleeding

Major bleeding was defined as in the Perioperative Ischemic Evaluation (POISE) 2 trial: a major bleed was defined as a bleeding event that was not specified under life- threatening bleeding and resulted in any one of the following:

1. Hemoglobin ≤70 g/L and the patient received a transfusion of ≥2 units of red blood cells;
2. Hemoglobin drop of ≥50 g/L and the patient received a transfusion of ≥2 units of red blood cells;
3. Patient received a transfusion of ≥4 units of red blood cells within a 24 hour period;
4. Any one of the following interventions (i.e., embolization, superficial vascular repair, nasal packing); o
5. Retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging) bleeding.

Minor bleeding

All bleeding episodes not fulfilling definition of life-threatening or major bleeding.

Table S1 - Clinical Characteristics at Hospital Admission According to the Use of Angiotensin II

	Angiotensin II (*n* = 46)	No Angiotensin II (*n* = 53)	*p* value
Duration from symptoms, days			
To hospital admission	7.0 (4.0 – 10.0)	7.0 (4.0 – 10.0)	0.872
To intensive care unit admission	10.0 (7.0 – 14.0)	10.0 (7.0 – 13.0)	0.748
Vital signs			
Temperature, ºC	38.0 (37.5 – 38.7)	38.0 (37.0 – 38.6)	0.484
Fever (temperature > 37.8 ºC)	23 / 39 (59.0)	21 / 39 (53.8)	0.820
SpO_2, %	90.0 (83.2 – 95.0)	94.5 (84.8 – 97.0)	0.087
At room air	90.5 (80.8 – 96.0)	92.0 (80.0 – 96.0)	0.694
No. (%)	28 (60.9)	24 / 48 (50.0)	0.308
With oxygen supplementation	89.0 (85.2 – 94.0)	95.0 (87.5 – 97.0)	0.072
No. (%)	18 (39.1)	23 / 48 (47.9)	0.413
Systolic blood pressure, mmHg	125 (120 – 140)	127 (111 – 141)	0.997
Diastolic blood pressure, mmHg	75 (68 – 80)	70 (60 – 80)	0.113
Heart rate, beats per minute	100 (86 – 110)	99 (86 – 108)	0.713
Respiratory rate, breaths per minute	30 (27 – 37)	29 (25.0 – 35.0)	0.999
History of symptoms – no. (%)			
Fever in the previous 14 days	42 / 45 (93.3)	49 / 49 (100.0)	0.106
Cough	27 / 35 (77.1)	32 / 45 (71.1)	0.614
Sore throat	2 / 27 (7.4)	5 / 35 (14.3)	0.455
Arthralgia	0 / 28 (0.0)	1 / 33 (3.0)	0.999
Fatigue	7 / 29 (24.1)	7 / 35 (20.0)	0.766
Shortness of breath	28 / 39 (71.8)	32 / 43 (74.4)	0.808
Altered level of consciousness	0 / 27 (0.0)	1 / 35 (2.9)	0.999
Laboratory tests			
Hemoglobin, g/dL	13.4 (12.5 – 15.1)	13.5 (11.6 – 14.6)	0.225
White blood cell count, $x10^3$ per mm^3	8.50 (5.60 – 12.00)	9.50 (5.73 – 12.73)	0.495
Lymphocyte count, $x10^3$ per mm^3	0.77 (0.58 – 0.98)	0.79 (0.62 – 1.02)	0.623
Lymphocytopenia	30 (75.0)	30 (71.4)	0.908
Total bilirubin, mg/dL	0.6 (0.5 – 1.0)	0.5 (0.4 – 0.7)	0.272
Urea, mg/dL	57.0 (37.2 – 88.2)	43.0 (29.0 – 77.5)	0.426
Creatinine, mg/dL	1.14 (0.89 – 1.33)	1.02 (0.85 – 1.28)	0.404
Lactate, mmol/L	1.64 (1.25 – 2.27)	1.59 (1.04 – 2.29)	0.412
C-reactive protein, mg/dL	218.8 (107.2 – 278.2)	178.6 (103.6 – 244.1)	0.354

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. To convert the values for creatinine to µmol per liter, multiply by 88.4

Table S2 - Daily Characteristics of the Patients According to the Use of Angiotensin II

	Day 01			Day 02			Day 03		
	Angiotensin II (*n* = 46)	**No Angiotensin II (*n* = 53)**	***p* value**	**Angiotensin II (*n* = 46)**	**No Angiotensin II (*n* = 53)**	***p* value**	**Angiotensin II (*n* = 46)**	**No Angiotensin II (*n* = 53)**	***p* value**
Laboratory tests									
PaO_2 / FiO_2	108.5 (79.0 – 154.0)	107.1 (75.8 – 140.4)	0.681	155.8 (110.8 – 182.0)	109.3 (92.1 – 142.8)	0.006	156.6 (116.7 – 197.4)	116.6 (90.2 – 164.6)	0.021
PaO_2	78.8 (66.1 – 90.5)	71.0 (58.5 – 87.2)	0.111	76.7 (67.3 – 89.0)	69.8 (59.3 – 85.7)	0.176	75.0 (65.0 – 82.9)	69.8 (61.1 – 78.1)	0.063
$PaCO_2$	48.3 (39.5 – 53.6)	46.0 (41.2 – 54.2)	0.836	47.8 (43.3 – 53.3)	49.3 (43.2 – 53.2)	0.958	50.0 (44.5 – 52.6)	47.8 (43.3 – 54.1)	0.557
Arterial pH	7.38 (7.31 – 7.46)	7.38 (7.30 – 7.42)	0.405	7.41 (7.34 – 7.46)	7.42 (7.36 – 7.47)	0.458	7.42 (7.38 – 7.48)	7.44 (7.37 – 7.49)	0.987
Vital signs									
Mean arterial pressure	84.5 (72.0 – 99.0)	77.0 (63.0 – 89.0)	0.070	89.0 (78.0 – 107.2)	78.0 (67.0 – 91.0)	0.003	96.0 (85.8 – 110.2)	79.0 (68.0 – 91.0)	< 0.001
Urine output (24 hours)	2437 (1287 – 4025)	2190 (1662 – 2667)	0.452	3280 (2290 – 4800)	3535 (2632 – 4087)	0.744	3550 (2690 – 4455)	3215 (2390 – 4285)	0.179
Ventilatory support									
Previous use of NIV – no. (%)	14 (31.1)	12 (26.1)	0.647	---	---	---	---	---	---
Mode of ventilation – no. (%)									
Controlled	43 (95.6)	40 (90.9)	0.434	39 (86.7)	33 (71.7)	0.152	36 (81.8)	30 (69.8)	0.218
Assisted	2 (4.4)	4 (9.1)		6 (13.3)	12 (26.1)		8 (18.2)	13 (30.2)	
Tidal volume, mL/kg predicted body weight	7.0 (6.1 – 7.6)	6.4 (6.0 – 7.0)	0.134	6.9 (6.1 – 7.5)	6.3 (6.0 – 7.5)	0.470	6.8 (6.2 – 7.5)	6.5 (6.1 – 7.0)	0.300
Positive-end expiratory pressure, cmH_2O	12 (10 – 15)	12 (10 – 14)	0.789	13 (11 – 15)	12 (10 – 13)	0.027	12 (10 – 15)	11 (10 – 13)	0.014
Inspired fraction of oxygen	0.80 (0.64 – 0.90)	0.70 (0.60 – 0.95)	0.766	0.50 (0.40 – 0.65)	0.65 (0.52 – 0.80)	0.004	0.50 (0.40 – 0.56)	0.60 (0.46 – 0.70)	0.017
Peak airway pressure, cmH_2O	29.0 (25.0 – 30.0)	28.0 (25.8 – 30.5)	0.876	27.0 (22.8 – 28.2)	27.0 (23.0 – 32.0)	0.507	26.0 (24.0 – 29.2)	28.0 (23.0 – 30.0)	0.681
Driving pressure, cmH_2O*	18.5 (15.8 – 22.5)	8.0 (6.0 – 9.0)	0.027	11.0 (9.0 – 16.0)	7.5 (5.2 – 9.8)	0.110	11.0 (9.5 – 11.0)	10.5 (7.5 – 14.2)	0.919
Dynamic compliance, mL/cmH_2O**	25.0 (23.5 – 33.3)	30.0 (23.8 – 34.6)	0.522	30.0 (25.0 – 34.3)	33.3 (25.2 – 40.5)	0.587	31.2 (25.7 – 35.0)	27.8 (22.5 – 35.8)	0.669
Clinical support									

Table S2 - Daily Characteristics of the Patients According to the Use of Angiotensin II

	Day 01			Day 02			Day 03		
	Angiotensin II (*n* = 46)	**No Angiotensin II (*n* = 53)**	***p* value**	**Angiotensin II (*n* = 46)**	**No Angiotensin II (*n* = 53)**	***p* value**	**Angiotensin II (*n* = 46)**	**No Angiotensin II (*n* = 53)**	***p* value**
ECMO – no. (%)***	1 (2.2)	3 (6.4)	0.617	1 (2.2)	3 (6.7)	0.616	1 (2.3)	3 (6.5)	0.617
Tracheostomy – no. (%)	0 (0.0)	0 (0.0)	---	0 (0.0)	1 (2.2)	0.999	1 (2.2)	0 (0.0)	0.495
Renal replacement therapy – no. (%)	0 (0.0)	0 (0.0)	---	0 (0.0)	3 (6.7)	0.242	1 (2.3)	3 (6.5)	0.617
Norepinephrine	25 (54.3)	32 (68.1)	0.205	27 (60.0)	36 (78.3)	0.072	24 (53.3)	28 (60.9)	0.528
Maximum dose, µg/kg/min	0.20 (0.09 – 0.35)	0.15 (0.10 – 0.20)	0.176	0.20 (0.09 – 0.25)	0.10 (0.05 – 0.20)	0.092	0.10 (0.08 – 0.21)	0.10 (0.10 – 0.20)	0.766
Angiotensin II maximum dose, ng/kg/min	5.0 (5.0 – 20.0)	---	---	7.0 (5.0 – 20.0)	---	---	5.0 (5.0 – 20.0)	---	---
Neuromuscular blocking agents – no. (%)	35 (77.8)	35 (76.1)	0.999	27 (62.8)	29 (63.0)	0.999	25 (55.6)	26 (56.5)	0.999
Prone positioning – no. (%)	21 (47.7)	16 (34.0)	0.206	32 (71.1)	17 (37.0)	0.002	21 (46.7)	19 (42.2)	0.832
Duration, hours	12 (10 – 19)	13 (11 – 18)	0.902	14 (8 – 17)	17 (14 – 20)	0.105	12 (9 – 16)	16 (11 – 17)	0.276

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding.
ECMO: extracorporeal membrane oxygenation; NIV: non-invasive ventilation
* calculated as plateau pressure - positive end expiratory pressure and available only in 9 patients (9.1%) in day 1, 15 patients (15.1%) in day 2 and 17 patients (17.2%) in day 3
** calculate as tidal volume / peak pressure - positive end expiratory pressure and available only in 28 patients (28.3%), 34 patients (34.3%) in day 2 and 42 patients (42.4%) in day 3

Table S3 - Daily Laboratory Tests of the Patients According to the Use of Angiotensin II

	Day 01			Day 02			Day 03		
	Angiotensin II (*n* = 46)	**No Angiotensin II (*n* = 53)**	***p* value**	**Angiotensin II (*n* = 46)**	**No Angiotensin II (*n* = 53)**	***p* value**	**Angiotensin II (*n* = 46)**	**No Angiotensin II (*n* = 53)**	***p* value**
Hemoglobin, g/dL	12.8 (11.7 – 14.1)	12.6 (11.4 – 13.6)	0.223	12.8 (11.3 – 14.1)	11.9 (10.8 – 13.6)	0.155	12.4 (11.5 – 13.8)	11.7 (11.0 – 13.7)	0.223
White blood cell count, $x10^3$ per mm^3	9.60 (7.20 – 13.00)	10.80 (7.30 – 16.20)	0.484	9.90 (6.50 – 12.30)	10.70 (7.30 – 15.70)	0.222	9.80 (7.57 – 13.05)	12.10 (7.80 – 17.30)	0.236
Lymphocyte count, $x10^3$ per mm^3	0.69 (0.47 – 0.99)	0.75 (0.60 – 0.92)	0.637	0.69 (0.52 – 0.84)	0.60 (0.33 – 0.82)	0.196	0.71 (0.48 – 1.11)	0.83 (0.54 – 1.08)	0.910
Platelets, $x10^3$ per mm^3	234.0 (190.0 – 340.0)	271.0 (190.0 – 332.0)	0.711	259.0 (173.0 – 359.0)	252.0 (188.0 – 385.0)	0.940	249.0 (181.0 – 348.0)	261.0 (173.0 – 381.0)	0.877
N-terminal pro b-type Natriuretic Peptide, pg/mL	535.0 (155.0 – 1015.0)	413.0 (100.2 – 951.5)	0.560	408.0 (193.0 – 837.8)	261.5 (113.5 – 780.0)	0.337	326.0 (127.0 – 610.0)	377.0 (143.0 – 828.0)	0.722
Aspartate aminotransferase, U/L	60.5 (50.5 – 98.0)	52.0 (38.0 – 75.0)	0.044	63.5 (42.0 – 79.5)	49.0 (33.8 – 62.8)	0.043	50.5 (42.0 – 85.0)	49.0 (36.5 – 80.5)	0.397
Alanine aminotransferase, U/L	50.0 (36.5 – 67.5)	38.0 (29.0 – 61.0)	0.118	37.0 (27.5 – 65.8)	40.0 (29.0 – 51.8)	0.477	45.5 (31.0 – 73.2)	37.5 (30.2 – 48.0)	0.340
Total bilirubin, mg/dL	0.9 (0.6 – 1.3)	1.0 (0.6 – 1.6)	0.455	0.9 (0.6 – 1.8)	1.1 (0.7 – 2.3)	0.194	0.9 (0.6 – 1.5)	1.4 (0.8 – 2.3)	0.063
Urea, mg/dL	64.0 (39.8 – 86.0)	55.0 (43.0 – 80.0)	0.667	67.0 (51.0 – 96.0)	61.5 (41.5 – 89.5)	0.297	76.0 (54.5 – 118.5)	66.0 (54.0 – 95.0)	0.326
Lactate, mmol/L	1.9 (1.5 – 2.3)	1.9 (1.3 – 2.5)	0.624	2.0 (1.6 – 2.8)	2.0 (1.5 – 2.5)	0.683	2.2 (1.5 – 2.4)	2.0 (1.7 – 2.5)	0.600
Creatinine, mg/dL	1.15 (1.01 – 1.49)	1.02 (0.78 – 1.51)	0.144	1.35 (1.04 – 1.97)	1.15 (0.93 – 1.55)	0.096	1.43 (1.01 – 1.94)	1.33 (0.90 – 1.82)	0.270
Pro-calcitonin, mg/L*	1.1 (0.6 – 2.1)	2.2 (1.0 – 4.2)	0.064	0.8 (0.6 – 1.8)	2.1 (0.8 – 3.8)	0.054	0.7 (0.4 – 2.0)	2.2 (1.1 – 7.2)	0.010
C-reactive protein, g/dL	195.8 (158.6 – 262.9)	231.4 (129.0 – 309.9)	0.549	182.6 (118.1 – 262.0)	229.5 (120.8 – 321.2)	0.385	148.0 (74.7 – 240.8)	170.0 (98.7 – 295.0)	0.371

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding.
* available in 41 patients (41.4%) in day 1, 64 patients (64.6%) in day 2 and 64 patients (64.6%) in day 3

Table S4 - Complications at the Latest Follow-up According to Angiotensin II Use

	Angiotensin II (*n* = 46)	No Angiotensin II (*n* = 53)	Odds Ratio (95% confidence interval)	*p* value
Bacterial pneumonia	5 (10.9)	4 (8.3)	1.34 (0.33 to 5.75)	0.677
Pneumothorax	4 (9.1)	7 (14.9)	0.57 (0.14 to 2.04)	0.400
Stroke	1 (2.2)	1 (2.2)	---	---
Heart failure	3 (6.7)	5 (10.9)	0.59 (0.11 to 2.54)	0.483
Cardiac arrhythmia	8 (17.4)	9 (19.6)	0.87 (0.30 to 2.50)	0.788
Acute myocardial infarction	0 (0.0)	1 (2.2)	---	---
Myocarditis/pericarditis	0 (0.0)	0 (0.0)	---	---
Cardiac arrest	3 (6.5)	3 (6.5)	1.00 (0.18 to 5.67)	1.000
Bacteremia	19 (42.2)	12 (25.5)	2.13 (0.89 to 5.26)	0.093
Other secondary infection	1 (2.2)	2 (4.3)	0.50 (0.02 to 5.40)	0.577
Disseminated intravascular coagulation	3 (6.7)	2 (4.3)	1.57 (0.25 to 12.38)	0.630
Transfusion of > 2 units of red blood cells	14 (31.1)	11 (23.9)	1.44 (0.57 to 3.69)	0.443
Rhabdomyolysis	0 (0.0)	2 (4.3)	---	---
Acute kidney injury	36 (78.3)	36 (72.0)	1.40 (0.55 to 3.64)	0.480
Stage 1	16 (44.4)	17 (47.2)		
Stage 2	8 (22.2)	7 (19.4)	---	0.953
Stage 3	12 (33.3)	12 (33.3)		
Minor gastrointestinal hemorrhage	0 (0.0)	1 (2.1)	---	---
Gastrointestinal perforation	0 (0.0)	1 (2.2)	---	---
Liver dysfunction	5 (11.1)	13 (28.3)	0.32 (0.09 to 0.94)	0.046
Hyperglycemia	6 (13.3)	8 (17.4)	0.73 (0.22 to 2.30)	0.593
Clinically relevant limb ischemia	1 (2.2)	3 (5.7)	0.37 (0.02 to 3.01)	0.397
Clinically relevant pulmonary embolism	2 (4.3)	4 (7.5)	0.56 (0.07 to 3.00)	0.511
Minor (non-life threatening) bleeding	4 (9.1)	5 (10.4)	0.86 (0.20 to 3.47)	0.831
Fungal infection	6 (13.6)	8 (16.7)	0.79 (0.24 to 2.48)	0.686

Data are No (%). Percentages may not total 100 because of rounding

PE: pulmonary embolism

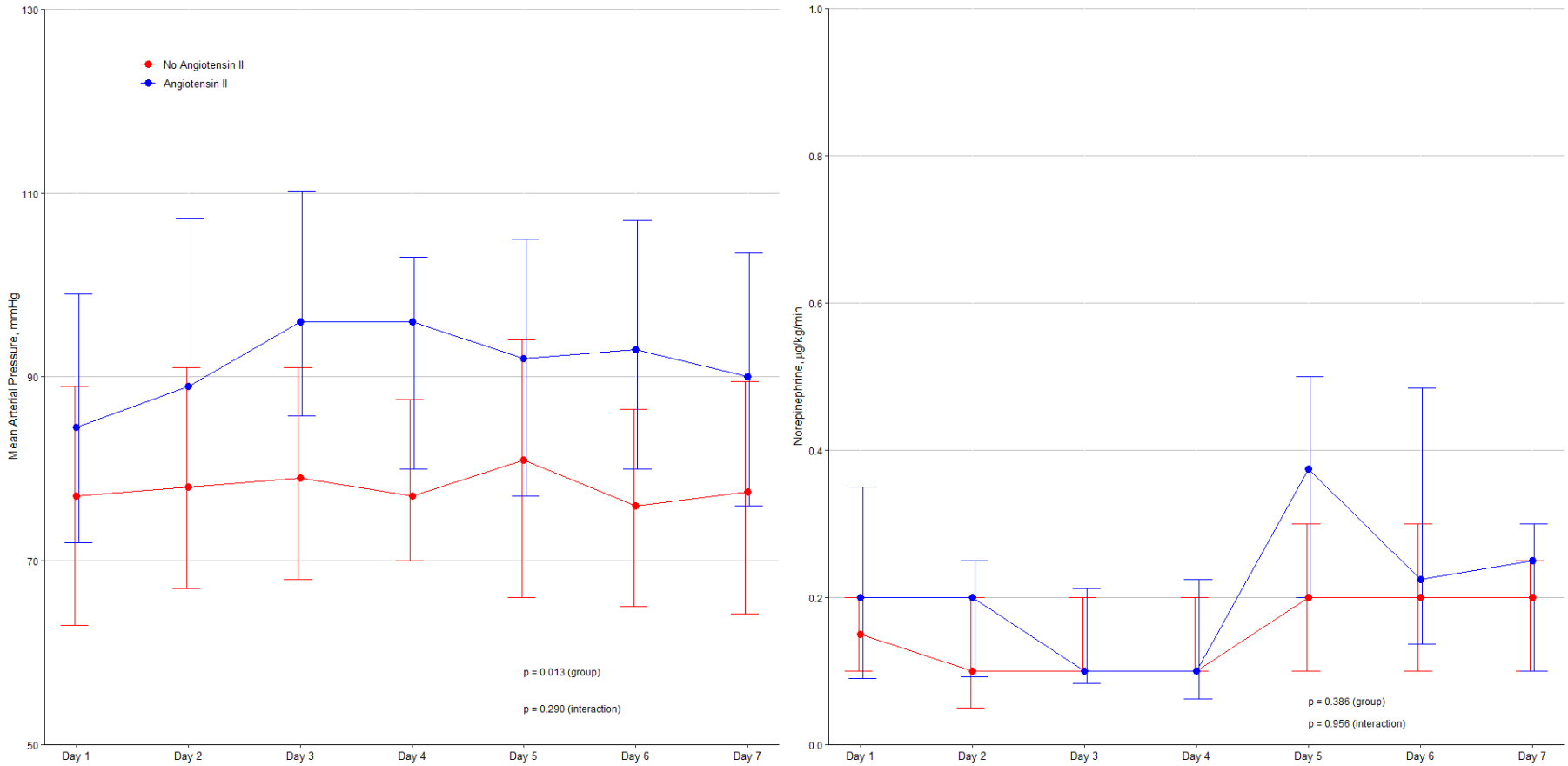
Table S5 - Characteristics of Patients Who Were or Not Discharged Alive at Day 28

	Not Discharged or Death (*n* = 59)	Discharged Alive (*n* = 40)	*p* value
Age, years	65.0 (56.5 – 70.0)	58.5 (52.5 – 64.2)	0.009
Male gender – no. (%)	48 (81.4)	35 (87.5)	0.579
Body mass index, kg/m^{2}[,a]	28.6 (26.0 – 31.6)	26.8 (24.5 – 30.2)	0.310
Normal – no. (%)	6 (15.0)	5 (22.7)	
Overweight – no. (%)	18 (45.0)	11 (50.0)	
Obesity class 1 – no. (%)	12 (30.0)	2 (9.1)	0.234
Obesity class 2 – no. (%)	4 (10.0)	3 (13.6)	
Obesity class 3 – no. (%)	0 (0.0)	1 (4.5)	
Coexisting disorder – no. (%)			
Hypertension	27 (49.1)	15 (38.5)	0.400
Diabetes	12 (21.8)	4 (10.5)	0.176
Coronary artery disease	5 (9.8)	1 (2.9)	0.394
Cardiac arrhythmias	6 (11.8)	1 (2.9)	0.233
Cerebrovascular disease	1 (2.0)	1 (2.9)	0.999
Chronic respiratory disease*	0 (0.0)	1 (2.9)	0.412
Asthma	3 (6.0)	1 (2.9)	0.640
Chronic obstructive pulmonary disease	2 (4.0)	0 (0.0)	0.510
Chronic neurological disease**	1 (2.0)	1 (2.9)	0.999
Moderate/severe chronic kidney disease[b]	4 (8.2)	2 (5.9)	0.999
Solid tumor	3 (6.1)	0 (0.0)	0.274
Tobacco smoker			0.999
Current	1 (2.6)	1 (3.7)	
Former	2 (5.1)	1 (3.7)	
Medications on chronic use – no. (%)			
Angiotensin converting enzyme inhibitors	10 (20.0)	2 (5.7)	0.111
Angiotensin 2 receptor blockers	6 (12.0)	6 (17.1)	0.540
Calcium channel blockers	5 (10.0)	3 (8.6)	0.999
Beta-blockers	8 (16.0)	6 (17.1)	0.999
Vitamin-K antagonists	1 (2.0)	0 (0.0)	0.999
Novel oral anticoagulants	1 (2.0)	0 (0.0)	0.999
Anti-arrhythmic	4 (7.8)	1 (2.9)	0.644
Aspirin	12 (23.1)	3 (8.3)	0.088
Other antiaggregant	2 (3.9)	1 (2.9)	0.999
Statins	6 (11.8)	4 (11.1)	0.999
Corticosteroids	2 (3.9)	1 (2.8)	0.999

Table S5 - Characteristics of Patients Who Were or Not Discharged Alive at Day 28

	Not Discharged or Death (*n* = 59)	Discharged Alive (*n* = 40)	*p* value
Use of angiotensin II			0.999
Vasopressor	16 (57.1)	10 (55.6)	
Low dose	12 (42.9)	8 (44.4)	
Duration from symptoms, days			
To hospital admission	6.0 (4.0 – 9.2)	7.0 (4.0 – 12.0)	0.203
To intensive care unit admission	10.0 (7.0 – 14.0)	10.0 (7.0 – 14.0)	0.835
Vital signs			
Temperature, ºC	38.0 (37.4 – 38.8)	38.0 (36.8 – 38.6)	0.683
Fever (temperature > 37.8 ºC)	24 (54.5)	20 (58.8)	0.819
SpO_2, %	90 (80 – 95)	95 (86 – 97)	0.015
At room air	90 (79 – 95)	94 (85 – 97)	0.115
With oxygen supplementation	90 (84 – 95)	95 (90 – 97)	0.071
Systolic blood pressure, mmHg	130 (115 – 140)	125 (119 – 135)	0.663
Diastolic blood pressure, mmHg	75 (66 – 80)	70 (61 – 80)	0.285
Heart rate, beats per minute	99 (85 – 109)	100 (86 – 115)	0.430
Respiratory rate, breaths per minute	30 (27 – 36)	31 (25 – 39)	0.888
History of symptoms – no. (%)			
Fever in the previous 14 days	54 (98.2)	37 (94.9)	0.568
Cough	34 (73.9)	25 (73.5)	0.999
Sore throat	4 (11.1)	3 (11.5)	0.999
Shortness of breath	38 (79.2)	22 (64.7)	0.206
Laboratory tests			
Hemoglobin, g/dL	13.5 (12.5 – 14.9)	13.4 (11.9 – 14.9)	0.693
White blood cell count, $x10^3$ per mm^3	7.85 (5.68 – 11.75)	10.70 (5.65 – 12.65)	0.412
Lymphocyte count, $x10^3$ per mm^3	0.78 (0.58 – 0.98)	0.79 (0.60 – 1.02)	0.756
Lymphocytopenia	36 (75.0)	24 (70.6)	0.848
Total bilirubin, mg/dL	0.5 (0.4 – 0.8)	0.6 (0.4 – 1.0)	0.280
Urea, mg/dL	50.0 (32.0 – 93.5)	52.5 (28.0 – 73.2)	0.491
Creatinine, mg/dL	1.06 (0.89 – 1.42)	1.09 (0.79 – 1.25)	0.202
Lactate, mmol/L	1.62 (1.28 – 2.48)	1.45 (0.98 – 2.02)	0.112
C-reactive protein, mg/dL	178.7 (95.8 – 264.5)	211.8 (117.4 – 266.7)	0.636

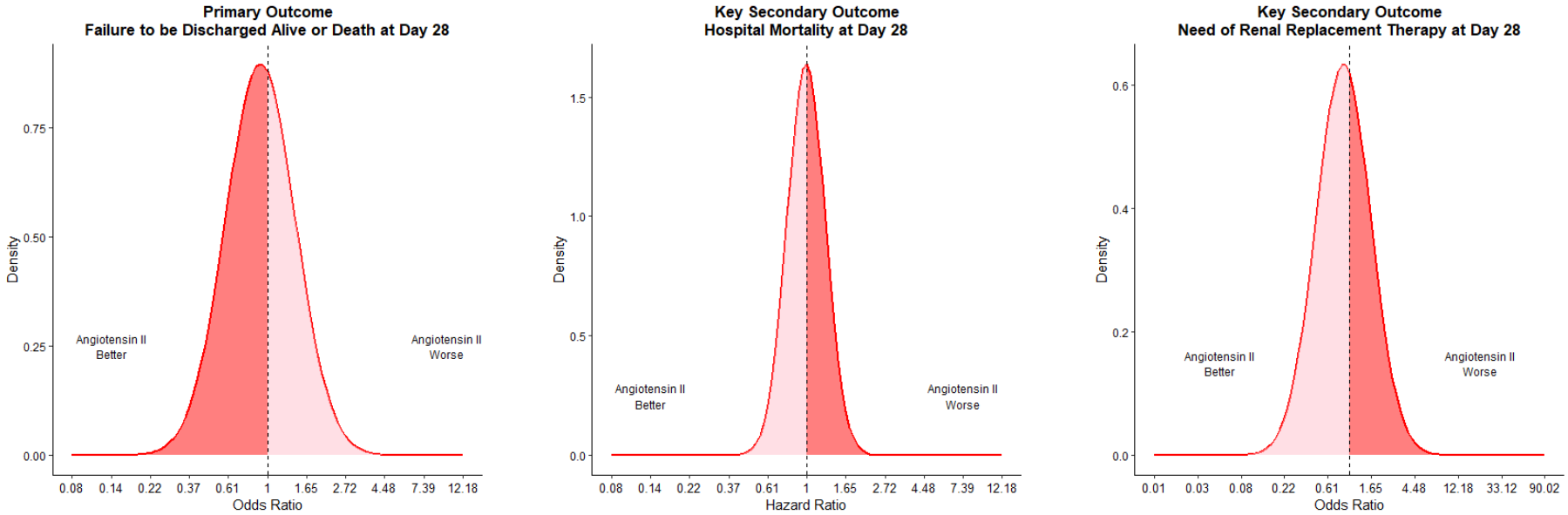
Figure S1 - Daily Mean Arterial Pressure and Norepinephrine Requirements According to Use of Angiotensin II



Data are median and quartile 25% - quartile 75%

p values calculated from a mixed-effect quantile model considering a τ = 0.50, an asymmetric Laplace distribution and *p* values were extracted after 1,000 bootstrapping samplings. Overall *p* values from this analysis represent the overall difference among groups over time and *p* values from interaction represent if the trend over time differs among the groups.

Figure S2 - Posterior Density of Odds or Hazard Ratio for Primary Outcome, Key Secondary Outcomes and ICU Mortality According to the Data



Light red area represents where angiotensin II is beneficial while dark red area represents where angiotensin II is harmful. Data are present in Table 2