Renin and Survival in Patients Given Angiotensin II for Catecholamine-Resistant Vasodilatory Shock

Running title: Renin and Survival in Vasodilatory Shock

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Impact of Research

Angiotensin II therapy increases mean arterial pressure in patients with catecholamine-resistant vasodilatory shock. This secondary analysis of the ATHOS-3 dataset demonstrates that serum renin concentration is markedly elevated in some patients with catecholamine-resistant vasodilatory shock. It also demonstrates that elevated serum renin may identify a subset of patients who gain a survival advantage when treated with angiotensin II. These findings support the need for further research into this novel approach to the treatment of catecholamine-resistant vasodilatory shock.

Author Contributions

Acquisition of data: RB, LSC, MO, LWB, MTM, KRH, DWB, JH, AKK, TEA, JT, KS

Conception and design: LSC, RB

Analysis and interpretation: RB, LGF, MO, LWB, MTM, TEA, JT, DH, GFT, and LSC

Wrote the manuscript: RB, LGF, MO, and LSC

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All authors approved the final manuscript

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Abstract

Rationale: Exogenous angiotensin II increases mean arterial pressure in patients with catecholamine-resistant vasodilatory shock (CRVS). We hypothesized that renin levels may identify patients most likely to benefit from such therapy.

Objectives: To test the kinetic changes in renin levels and their prognostic value in CRVS patients.

Methods: We analyzed serum samples from patients enrolled in the Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) trial for renin, angiotensin I, and angiotensin II levels prior to the start of administration of angiotensin II or placebo and after 3 hours.

Measurements and Main Results: Baseline serum renin concentration (normal range: 2.13–58.78 pg/ml) was above the upper limits of normal (ULN) in 194/255 (76%) study patients with a median renin concentration of 172.7 pg/mL (interquartile range [IQR]: 60.7–440.6 pg/mL), approximately three-fold higher than ULN. Renin levels correlated positively with angiotensin I/angiotensin II ratios (r =.39; $P<0.001$). At 3 hours after initiation of angiotensin II therapy, there was a 54.3% reduction (IQR: 37.9%–66.5% reduction) in renin concentration compared with a 14.1% reduction (IQR: 37.6% reduction to 5.1% increase) with placebo ($P<0.0001$). In patients with renin concentrations above the study population median, angiotensin II significantly reduced 28-day mortality to 28/55 (50.9%) patients compared with 51/73 patients (69.9%) treated with placebo (unstratified hazard ratio: 0.56; 95% confidence interval: 0.35–0.88; $P=0.012$) (p = 0.048 for the interaction).

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Conclusions: Serum renin concentration is markedly elevated in CRVS and may identify patients for whom treatment with angiotensin II has a beneficial effect on clinical outcomes.

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Introduction

Vasodilatory shock requiring vasopressor therapy is associated with poor outcomes (1, 2). In particular, catecholamine-resistant vasodilatory shock (CRVS), in which hypotension persists despite the use of high-dose vasopressors, carries a 50% to 80% mortality (3). In these patients, first-line vasopressor therapy, which includes norepinephrine followed by epinephrine or vasopressin, may be inadequate to achieve target mean arterial pressure (MAP) (4). Accordingly, and recently, synthetic human angiotensin II has been approved for the treatment of CRVS in the United States and Europe (5, 6).

Angiotensin II is an integral part of the renin-angiotensin-aldosterone system (RAAS) (7, 8) (Figure 1). Angiotensin I, the precursor of angiotensin II, is cleaved from angiotensinogen by renin, a proteolytic enzyme released by juxtaglomerular cells in response to sympathetic nerve activation, hypotension, or decreased sodium delivery to the distal tubule. Renin release is inhibited by high angiotensin II generation and promoted by low angiotensin II generation via a biofeedback loop involving the angiotensin type 1 receptor (9, 10). As such, renin levels are increased when there is insufficient activation of the angiotensin II type 1 receptor. This can be caused by decreased angiotensin II generation or angiotensin II receptor blockade.(11, 12) In this regard, the primary pathway for angiotensin II generation is via angiotensin-converting enzyme (ACE), an endothelial membrane–bound enzyme that cleaves angiotensin I to angiotensin II. Thus, it is logical to suppose that the endothelial injury accompanying CRVS should decrease ACE function, increase angiotensin I to angiotensin II ratios, and promote renin release. If this were true, high renin levels would potentially identify patients most likely to benefit from angiotensin II therapy (13-15). In support of this theory, high ratios of angiotensin I to angiotensin II correlate with negative outcomes in such patients.(16) Moreover, in a study of

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patients with sepsis, reduced angiotensin II and ACE levels outperformed established illness-severity scores in predicting outcomes (17).

Unfortunately, assessing ACE activity is not amenable to simple plasma measurement and measurement of the angiotensin I to angiotensin II ratio is difficult and not available in a timely manner. Renin levels on the other hand, which are expected to increase in CRVS patients with ACE dysfunction and high angiotensin I to angiotensin II levels, could potentially be used to identify such high-risk patients. Laboratory assays that measure renin levels are inexpensive, FDA and EMA approved, have demonstrated established performance, and can be easily set up by most laboratories; importantly, measurement of renin levels outperforms that of maximum serum lactate levels as a predictor of mortality in the intensive care unit (ICU) (18, 19). Accordingly, we hypothesized that plasma renin levels would be high in patients with CRVS, would correlate with angiotensin I to angiotensin II ratios, and when elevated would help to identify those patients most likely to benefit from intravenous angiotensin II therapy.

Methods

Study Design and Patients

The Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3) study has been previously described - NCT02338843 (5, 20). In brief, adults with vasodilatory shock despite volume resuscitation with ≥25 mL/kg and high-dose vasopressors (defined as a norepinephrine equivalent [NED] of greater than 0.2 mcg/kg/min) were randomly assigned 1:1 to receive synthetic human angiotensin II (La Jolla Pharmaceutical Company, San Diego, CA) or saline placebo plus standard vasopressors. Randomization was stratified according to MAP at screening and Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

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Study drug infusion started at 20 ng/kg/min and was adjusted during the first 3 hours to increase the MAP to ≥75 mm Hg while keeping other vasopressors constant. Thereafter, the study drug and other vasopressors were adjusted at the discretion of the treating ICU team to maintain a MAP between 65 and 75 mm Hg. At 48 hours, the infusion was discontinued according to a protocol-specified tapering process. However, continuation was allowed for up to 7 days at the discretion of the ICU team.

Ethics Approval and Consent to Participate

The study, inclusive of the sample collection, was conducted in accordance with Good Clinical Practice guidelines, applicable local regulations, and the ethical principles described in the Declaration of Helsinki. The protocol, informed consent form, and all other documents were reviewed and approved by the respective independent institutional review boards before study initiation. The current analysis was conducted on the deidentified dataset from ATHOS-3.

Serum Renin, Angiotensin I, and Angiotensin II Measurement

Serum concentrations of renin, angiotensin I, and angiotensin II were measured after randomization but prior to administration of the study drug and at 3 hours after initiation of study drug (see the Online Data Supplement).

Statistical Analysis

We used descriptive statistics with 95% confidence intervals (CIs) 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 summarized time-to-event data, including survival, using

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Kaplan–Meier estimates and compared them by log-rank test. We estimated hazard ratios (HRs) from a proportional hazards model. A two-sided alpha level of 0.05 was used to test for differences in treatment outcomes without adjustments for multiplicity. Correlation coefficients were calculated for renin versus angiotensin I and the angiotensin I/II ratio. Correlation coefficients were also calculated for renin versus angiotensin I for hour 0 (baseline) and hour 3.

For multivariate analyses, covariates that were utilized for study stratification (Model A), covariates that were different between groups defined by $P < 0.10$ (Model B), and statistically significant covariates from Models A and B were included in a multivariate logistic regression (Model C). The dichotomized baseline covariates that were utilized for study stratification were MAP <65 mm Hg and APACHE II score >30 (20).

Safety was evaluated by assessment of treatment-emergent adverse events, serious adverse events, and adverse event–related drug discontinuations. Data were analyzed with the use of SAS software, version 9.4 (SAS Institute, Cary, NC) and R version 3.5.3. (R Foundation).

Results

Of the 321 patients with CRVS studied in ATHOS-3, 255 (79.4%) had suitable serum samples available for analysis of renin concentrations at baseline (hour 0) (Supplemental Tables 8-10). In these patients, baseline serum renin concentrations were comparable between the angiotensin II and placebo arms and were elevated to levels above the upper limit of normal in 194 (76%) patients. The median serum renin concentration of the entire population was 172.7 pg/mL (interquartile range [IQR]: 60.7–440.6 pg/mL); this was approximately 3 times the upper limit of normal (ULN; 58.78 pg/ml). Supplemental Table 4 and Figure 7 further show baseline renin levels in patient subsets. As expected, baseline serum renin levels were positively correlated with

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the baseline angiotensin I/angiotensin II ratio ($P < 0.001$) and with angiotensin I ($P < 0.001$) (Supplemental Figures 3, 4). In addition, renin and angiotensin I were also positively correlated at 3 hours of treatment ($P < 0.001$) (Supplemental Figure 4).

Supplemental Table 1 shows patient demographic and clinical data dichotomized by median serum renin levels, and Table 1 shows these data further dichotomized by treatment group within each renin-level stratum. At baseline, patients with serum renin levels above the study population median were similar to those with levels below the study population median, except for baseline levels of angiotensin I, angiotensin II, angiotensin I/II ratio, and norepinephrine-equivalent dose, all of which were significantly higher in the former group.

Figure 2 shows serum levels of angiotensin I and renin in patients who had samples available at baseline and at 3 hours. Median baseline renin levels were similar among patients in the placebo group (193.7 [58.1-489.8] pg/ml) and patients in the angiotensin II group (146.1 [62.4-412.2] pg/ml) (P=0.4277). Patients treated with synthetic angiotensin II experienced a median reduction of 54.3% (IQR: 37.9%–66.5% reduction) in renin concentration compared with a median reduction of 14.1% (IQR: 37.6% reduction to 5.1% increase) in patients treated with placebo ($P < 0.0001$) at hour 3. Median baseline levels of angiotensin I were also similar between treatment groups, and as was seen with serum renin levels, treatment with synthetic angiotensin II led to a significantly greater reduction in angiotensin I levels at hour 3 (40.8% median reduction [IQR: 13.4%-65.1% reduction]) compared to treatment with placebo (8.1% reduction [IQR: 29.9% reduction to 15.2% increase]) ($P < 0.0001$).

The MAP response at 3 hours was not affected by baseline renin levels. MAP response in patients with renin levels below the population median treated with placebo was 30.2%

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compared to 78.1% in patients treated with angiotensin II, whereas in patients with renin levels above the population median, MAP response in patients treated with placebo was 20.5% compared to 61.8% in patients treated with angiotensin II (data not shown). Thus, renin was not identified as significantly modifying the effect of study group assignment (treatment arm by renin interaction OR [95% CI]: 0.76 [0.25 - 2.32]; $P = 0.6266$).

Survival by Baseline Serum Renin Levels

For patients with renin levels above the study population median, baseline characteristics were well balanced between the placebo and angiotensin II treatment arms. (Table 1). In spite of this balance, patients treated with placebo had a 28-day mortality rate of 69.9% compared with 50.9% in patients treated with angiotensin II (unstratified HR, 0.556; 95% CI, 0.35–0.88; $P = 0.0115$) (Table 2 and Figure 3; see also Supplemental Figures 1, 2, and 5). In contrast, there was no statistically significant difference in 28-day mortality for those with serum renin levels below the study population median (Table 2 and Figure 3).

Multivariate logistic regression within the placebo treated arm alone showed that, after adjusting for age, sex, APACHE II score, MAP, and norepinephrine-equivalent dose, elevated serum renin levels were independently associated with an increased risk of death (HR, 2.15; 95% CI, 1.35–3.42; $P = 0.0013$ (Supplemental Table 5). Moreover, in patients with a renin level above the study population median, multivariable analysis identified treatment with angiotensin II as associated with decreased risk of mortality (HR, 0.62; 95% CI, 0.39–0.98; $P = 0.0423$) (Table 3). See also Supplemental Tables 11 and 12 for sensitivity analyses of these multivariable analyses. Figure 4 displays survival by serum renin level as a continuous variable. While the p-value for the interaction term including the dichotomized renin was 0.048 (HR = 0.50 (95% CI: 0.25 –

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0.99), the p-value for the interaction term including continuous renin (log2) was 0.28 (95% CI: 0.78 – 1.08). The difference reflects the apparent non-linear hazard ratio provided in Figure 4.

Other Outcomes of Interest

Table 2 shows rates of ventilator and RRT liberation, as well as ICU discharge according to treatment group in patients dichotomized by serum renin levels. Whereas there were no differences in these outcomes between treatment groups in patients with renin levels below the study population median, in patients with renin levels above the study population median, RRT liberation by day 7 was significantly greater in patients treated with angiotensin II (43%) compared to those treated with placebo (12%; $P = 0.01$) (Table 2; Supplemental Table 3 and Figure 6), as was ICU discharge by day 28 (angiotensin II: 44%; placebo: 22%; $P = 0.02$). The rate of ventilator liberation by day 7, however, did not differ significantly between treatment groups (angiotensin II: 28%; placebo: 14%; P=0.07).

Supplemental Table 7 shows the changes in cardiovascular (CV) and total SOFA scores between baseline and hour 48 according to renin status and treatment group. In the total ATHOS-3 population, the change in CV score was significantly greater in the angiotensin II compared to the placebo group, whereas the change in total SOFA score was not (5). As shown in Supplemental Table 7, neither the change in CV SOFA nor the total SOFA score differed significantly between treatment groups in patients with serum renin levels below the study population median. In patients with serum renin levels above the study population median, the mean (± SD) change in CV SOFA score at 48 hours was significantly greater in the angiotensin II group (-1.56 ± 1.793) compared to the placebo group (-0.78 ± 1.387), whereas the change in total SOFA score was not (angiotensin II: 1.35 ± 6.032; placebo: 2.86 ± 5.611; $P = 0.07$).

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Adverse Events

In patients with elevated renin concentrations at baseline, there was no significant difference in adverse events or serious adverse events between the angiotensin II and placebo groups (Table 4;).

Discussion

In this post hoc analysis of patients enrolled in the ATHOS-3 study, we tested the hypotheses that there is a disturbance in the RAAS likely resulting from insufficient ACE activity in CRVS. We reasoned that such ACE insufficiency could be identified through the analysis of serum renin levels, and that increased serum renin levels would predict worse outcome. We found that serum renin levels were significantly elevated in most patients with CRVS and that they were positively and significantly associated with angiotensin I levels and angiotensin I/II ratios. This ratio, a surrogate for ACE activity, has previously been reported to be associated with increased mortality risk in CRVS (16). As with those patients having elevated angiotensin I/II ratios, patients with serum renin levels above the study population median had a significantly increased risk of mortality. However, treatment with synthetic angiotensin II was associated with a significant reduction in this risk. These data suggest that renin has the potential to be used to identify CRVS patients at high risk for poor outcome and who may benefit from treatment with synthetic angiotensin II.

Our observations are consistent with previous studies demonstrating that patients with septic shock can develop decreased ACE levels, which can lead to impaired ability to convert angiotensin I to angiotensin II (7, 17). This may reflect endothelial injury or ACE gene single nucleotide polymorphisms, both of which are factors that correlate with increased 28-day

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mortality (21, 22). Our findings also confirm previous reports that elevated renin is associated with worse outcomes in patients with septic shock and other critical illness (23-25). Specifically, previous reports in this disease population show that plasma renin activity is elevated while aldosterone levels are inappropriately low, suggesting a defect in the RAAS pathway (Figure 1) (23, 24). Finally, our findings in the CRVS population are consistent with observations in patients treated with ACE inhibitors. Specifically, patients receiving ACE inhibitors have substantial increases in both serum angiotensin I and renin levels, both of which were effectively suppressed following the administration of exogenous angiotensin II (11, 26, 27).

The mechanistic implications of ACE dysfunction for patients with CRVS are potentially important. ACE inhibition induced by drugs (e.g. captopril, enalapril) increases the levels of not only angiotensin I but of vasodilatory angiotensin I metabolites, such as angiotensin 1-7 (27). As the absolute levels of angiotensin II do not decrease significantly during ACE inhibitor therapy, and may actually increase, the hypotensive effects of ACE inhibitors may occur as a consequence of the activity of these vasodilatory angiotensin metabolites.(27) The similar impact of shock on angiotensin I and II levels in the present analysis suggests that ACE dysfunction resulting from endothelial damage may be a significant contributor to the pathophysiology in some patients with CRVS.

We believe that renin levels may modify the effect of treatment group on outcomes independent of blood pressure because renin has other important clinical effects related to its neurohormonal activity. Renin binds the (pro)renin receptor, which has been described on many cell and tissue types, including leukocytes. One study showed that incubation of leukocytes with renin activated the (pro)renin receptor and elicited the production of proinflammatory cytokines independent of downstream angiotensin II effects.(28) Pre-clinical studies of sepsis demonstrate that (pro)renin

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receptor blockade improves survival and is associated with lower levels of pro-inflammatory cytokines.(29) Thus, our finding that synthetic angiotensin II rapidly reduces renin levels compared to patients treated with standard of care vasopressors suggests that synthetic angiotensin II potentially modulates the inflammatory response caused by excess renin and that this mechanism may explain our findings of enhanced survival. In addition, normalization of serum renin levels with angiotensin II may also indicate adequate angiotensin II type 1 receptor activation in end organs such as the kidney. Activation of this receptor by synthetic angiotensin II can increase GFR and urine output in sepsis.(30) This notion is supported by previous findings that patients with severe AKI and shock treated with synthetic angiotensin II experienced enhanced renal recovery and improved survival.(31)

Prospective validation of these data is warranted and if confirmed, these findings may influence patient care since renin assays are widely available and inexpensive. Thus, utilization of this biomarker for vasopressor-targeted therapy is logistically feasible. In this regard, our findings imply that utilizing angiotensin II as a vasopressor, which also lowers renin levels may offer a combined biological and clinical target during angiotensin II administration. Finally, the findings that both renin and angiotensin I are suppressible by exogenous angiotensin II suggests that patients with elevated renin may have insufficient activation of their angiotensin type I receptor.

This study has several strengths. First, the theory that decreased ACE activity may be a key mechanism in CRVS that is sensitive to angiotensin II was proposed prior to the start of the ATHOS-3 trial, and this analysis is mechanistically linked to such a RAAS-disturbance hypothesis (Figure 1) (20). Second, our findings are consistent with the well-described physiology of the RAAS and the effects of ACE inhibition (26, 27). The clear reduction in both renin and angiotensin I with exogenous angiotensin II administration compared with minimal

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changes in the placebo arm gives credence to the concept of decreased activity of the RAAS pathway and relative preservation of a biofeedback response in CRVS. Third, ATHOS-3 was an international, prospective, randomized, placebo-controlled trial in which adequate resuscitation per international consensus guidelines was a prerequisite for trial entry, thus increasing the generalizability to our findings.

We acknowledge several limitations. The current analysis is post hoc, and we did not have enough remaining samples to measure concurrent angiotensin 1-7, bradykinin, or aldosterone levels, which might have provided more indirect information on ACE activity and on the activity of nonclassical angiotensin I and II metabolism by ACE2. We also did not have renin samples for all patients in the cohort; however, the patient characteristics of the patients with missing samples were not different from those with samples available. In addition, we were not able to rigorously assess for the presence or severity of preexisting hypertension, renovascular disease, or chronic kidney disease, all of which can affect background renin levels. Finally, we conducted many sensitivity analyses and the treatment effect of angiotensin II in the high-renin arm did not achieve statistical significance in all assessments. Further, the effect modification of renin on treatment group, present when treating renin as a dichotomous variable, was not evident when treating it as a continuous variable and adjusting for baseline covariates. Therefore, the observed findings may represent chance imbalances between groups in baseline severity of illness.

Conclusions

We show that in most people with CRVS, there is significant disturbance in the RAAS likely resulting from impairment of ACE function. RAAS disturbance may play a significant role in the pathophysiology of vasodilatory shock in a subset of patients, suggesting that such patients may

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benefit from alternative management approaches and specifically from intervention targeting the RAAS. Importantly, we show that patients with RAAS disturbance can be readily identified through simple laboratory assessment of serum renin levels and that their outcomes may be improved when receiving synthetic angiotensin II. Our data further suggest that renin assessment could be used to identify patients without RAAS disturbance, in whom treatment with angiotensin II would likely be futile. While additional data are needed to confirm our findings, this study suggests that a personalized approach to the management of vasodilatory shock may soon be feasible and could potentially improve outcomes in vasodilatory shock. In a setting where mortality rates can reach or even exceed 50%, such an approach is urgently needed. Prospective confirmation of these findings is warranted.

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Table 1. Demographics and Clinical Characteristics of Study Patients

	Study Population Below the Median Renin				Study Population Above the Median Renin		
	Treatment with Placebo *N* = 63	Treatment with Angiotensin II *N* = 64	*P*		Treatment with Placebo *N* = 73	Treatment with Angiotensin II *N* = 55	*P*
Age, years, median (IQR)	66 (53 – 75)	61.5 (51 – 74)	0.51		63 (51–75)	62 (50–72)	0.66*
Gender Female Male	 20 (31.7%) 43 (68.3%)	 28 (43.8%) 36 (56.3%)	 0.20		 26 (35.6%) 47 (64.4%)	 26 (47.3%) 29 (52.7%)	 0.21†
Race White Nonwhite	 52 (82.5%) 11 (17.5%)	 53 (82.8%) 11 (17.2%)	 1.00		 54 (74.0%) 19 (26.0%)	 46 (83.6%) 9 (16.4%)	 0.20†
Baseline albumin (g/dL) Median (IQR)	2.3 (1.8 - 2.8)	2.2 (1.6 - 2.6)	0.21		2.3 (1.9–2.7)	2.3 (1.9–2.7)	0.75*
Baseline MELD Median (IQR)	22 (15 – 25)	20 (14 – 25)	0.26		23 (20–28)	22 (18–26)	0.09*
Baseline MAP (mm Hg) Median (IQR)	66.7 (64.0 - 68.7)	66.0 (63.7 - 67.9)	0.40		66.3 (62.3–68.0)	66.7 (63.3–69.7)	0.28*
Baseline APACHE II score Median (IQR)	29 (20 – 34)	27 (22 – 33)	0.70		31 (25–36)	28 (22–34)	0.14*
ARDS#	17 (27.0%)	17 (27.0%)	1.00		28 (38.4%)	13 (23.6%)	0.088
Medical history, sepsis	56 (88.9%)	50 (78.1%)	0.15		57 (78.1%)	42 (76.4%)	0.83†
Recent ARB Exposure	2 (3.2%)	4 (6.3%)	0.68		7 (9.6%)	3 (5.5%)	0.51
Recent ACEi Exposure	5 (7.9%)	2 (3.1%)	0.27		8 (11.0%)	10 (18.2%)	0.31
Severe AKI	14 (22.2%)	18 (28.1%)	0.54		41 (56.2%)	21 (38.2%)	0.05
ESRD	2 (3.2%)	4 (6.3%)	0.68		1 (1.4%)	2 (3.6%)	0.58
Baseline NED (ug/kg/min)	0.29 (0.22 - 0.49)	0.32 (0.22 - 0.54)	0.40		0.40 (0.29–0.69)	0.36 (0.23–0.50)	0.06*

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	Study Population Below the Median Renin				Study Population Above the Median Renin		
	Treatment with Placebo *N* = 63	Treatment with Angiotensin II *N* = 64	*P*		Treatment with Placebo *N* = 73	Treatment with Angiotensin II *N* = 55	*P*
Median (IQR)							
Angiotensin I (pg/ml)	85.6 (36.70 - 173.00)	133.0 (44.10 - 356.00)	0.15		602 (238–1110)	655 (304.5–1375)	0.45*
Angiotensin II (pg/ml)	52.4 (24.60 - 137.00)	98.2 (24.50 - 168.00)	0.35		108 (16.7–523)	151 (41.4–439)	0.46*
Baseline angiotensin I/II ratio Median (IQR)	1.25 (0.79 - 2.39)	1.34 (0.91 - 2.59)	0.70		3.41 (1.17–10.39)	3.01 (1.17–12.43)	0.96*

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; ESRD = end-stage renal disease; IQR, interquartile range; MAP = mean arterial pressure; MELD = Model for End-stage Liver Disease; NED = norepinephrine equivalent dose. ACE inhibitor exposure was determined by the presence of an ACE inhibitor in the medical chart within 7 days prior to study enrollment. [#]ARDS was determined by chest x-ray reading. Patients with ARDS noted on their chest x-ray during screening were denoted as having ARDS.

*Wilcoxon rank-sum test.

[†]Fisher's exact test.

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Table 2. Outcomes and Renin Level

	Patients Below the Study Population Median Renin				Patients Above the Study Population Median Renin		
	Treatment with Placebo *N* = 63	Treatment with Angiotensin II *N* = 64	*P*		Treatment with Placebo *N* = 73	Treatment with Angiotensin II *N* = 55	*P*
28-day mortality	44% (33%-58%)	45% (34%-58%)	0.70		70% (59%-80%)	51% (39%-65%)	0.01
Ventilator Liberation by Day 7 (alive and vent free)	38% (27%-52%)	27% (18%-40%)	0.20		14% (8%-25%)	28% (18%-43%)	0.07
RRT Liberation by Day 7 (alive and RRT free)	14% (4%-46%)	28% (13%-54%)	0.33		12% (5%-27%)	43% (25%-66%)	0.01
ICU Discharge by Day 28	52% (41%-65%)	39% (28%-52%)	0.13		22% (14%-33%)	44% (32%-58%)	0.02

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Table 3. Multivariable Analysis for the Prediction of Mortality: Patients With Elevated Baseline Renin Concentrations Only

	Hazard Ratio (95% CI)	*P* Value
Model A		
Treatment arm, angiotensin II	0.58 (0.36–0.93)	0.02
Baseline APACHE II score >30	2.02 (1.29–3.18)	0.002*
Baseline MAP <65 mm Hg	1.76 (1.12–2.77)	0.01
Model B		
Treatment arm, angiotensin II	0.62 (0.38–0.99)	0.04
Baseline NED ≥0.5 ug/kg/min	1.88 (1.19–2.98)	0.007
Baseline MELD ≥30	1.43 (0.81–2.50)	0.21
Model C		
Treatment arm, angiotensin II	0.62 (0.39–0.98)	0.04
Baseline APACHE II score >30	2.03 (1.29–3.19)	0.002*
Baseline MAP <65 mm Hg	1.66 (1.06–2.62)	0.03
Baseline NED ≥0.5 ug/kg/min	1.78 (1.13–2.83)	0.01

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; MAP = mean arterial pressure; MELD = Model for End-Stage Liver Disease; NED = norepinephrine equivalent dose. * $p < 0.01$

Model A includes treatment assignment and stratification variables. Model B includes covariates that were imbalanced by $P < 0.10$ in the population clinical characteristics. Model C includes the statistically significant variables from Model A and Model B.

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Table 4. Summary of Adverse Events

Patients with Shock and Renin above the Median			
	Placebo	**Angiotensin II**	**Total**
Patients, n	73	55	128
TEAE	69 (94.5%)	47 (85.5%)	116 (90.6%)
Grade 3/4 TEAE	61 (83.6%)	39 (70.9%)	100 (78.1%)
Serious TEAE	61 (83.6%)	39 (70.9%)	100 (78.1%)
Serious related TEAE	5 (6.8%)	4 (7.3%)	9 (7.0%)
Patients with Shock and Renin below the Median			
	Placebo	**Angiotensin II**	**Total**
Patients, n	63	64	127
TEAE	56 (88.9%)	58 (90.6%)	114 (89.8%)
Grade 3/4 TEAE	40 (63.5%)	40 (62.5%)	80 (63.0%)
Serious TEAE	36 (57.1%)	38 (59.4%)	74 (58.3%)
Serious related TEAE	1 (1.6%)	2 (3.1%)	3 (2.4%)

Legend: TEAE: Treatment emergent adverse event

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Figure 1. Renin-angiotensin-aldosterone system disturbance hypothesis. ACE, angiotensin-converting enzyme.

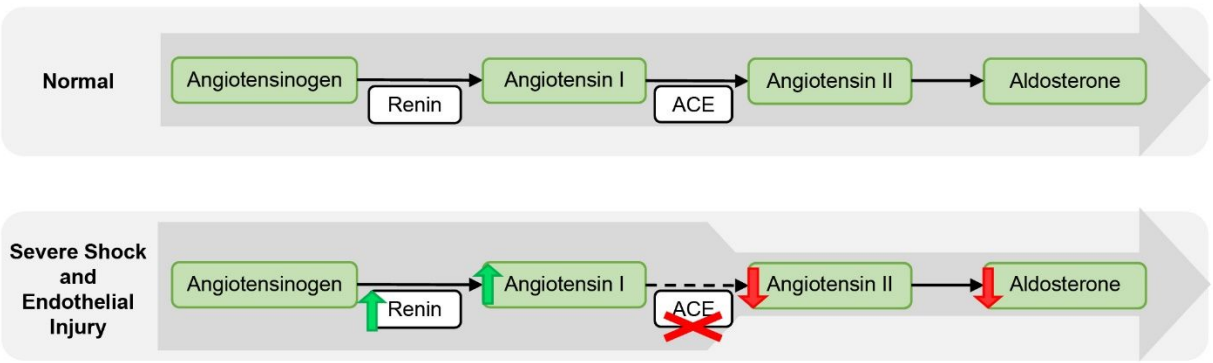

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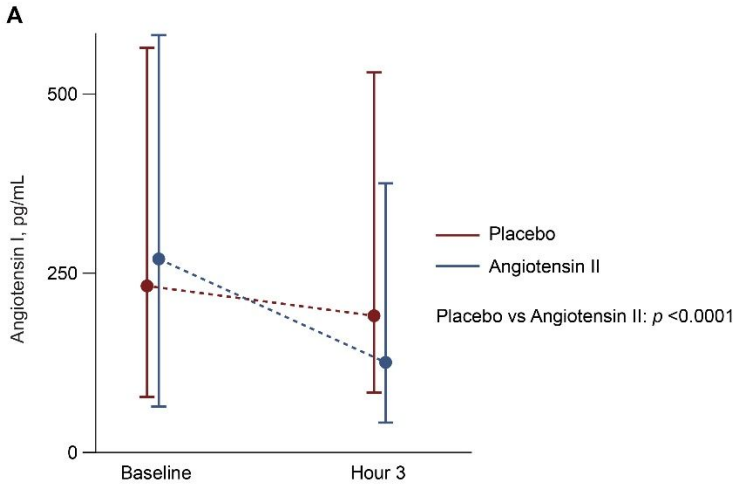
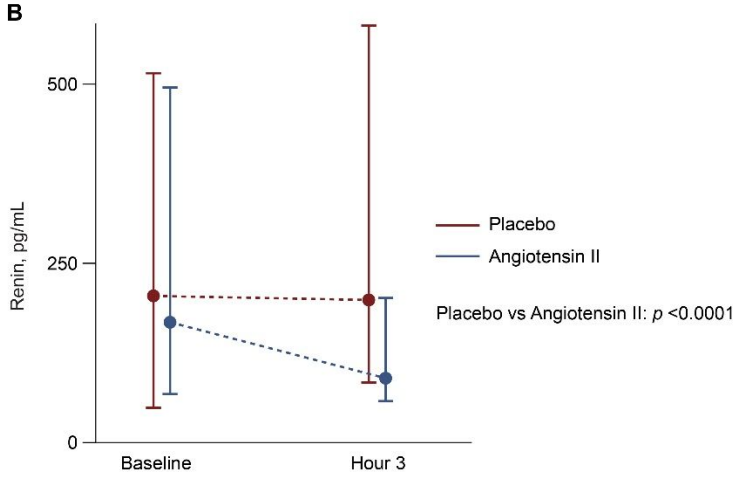
Figure 2. Serum angiotensin I and renin levels. (A) Serum angiotensin I levels. (B) Serum renin levels. All values are median (interquartile range).



Angiotensin I, pg/mL	Placebo	Angiotensin II	*P* Value
Hour 0	238 (75-653)	260 (72-679)	0.66
Hour 3	218 (76-553)	166 (47-383)	0.04
Difference	–10.0 (–78.5 to 42.1)	–76.7 (–264.5 to –12.6)	<0.0001
Difference %	–7.0 (–26.7 to 20.0)	–39.7 (–56.9 to –11.8)	<0.0001



Renin, pg/mL	Placebo	Angiotensin II	*P* Value
Hour 0	193.7 (58.1-489.8)	146.1 (62.4-412.2)	0.43
Hour 3	187.9 (62.3-562.2)	85.0 (52.3-189.1)	0.002
Difference	–15.9 (–72 to 13.7)	–98.9 (–278.9 to –27.4)	<0.0001
Difference %	–14.1 (–37.6 to 5.1)	–54.3 (–66.5 to –37.9)	<0.0001

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Figure 3. Kaplan-Meier survival plot according to renin levels and treatment with angiotensin II or placebo. (A) Day 28 survival: renin level below population median. (B) Day 28 survival: renin level above population median.

Figure 3A

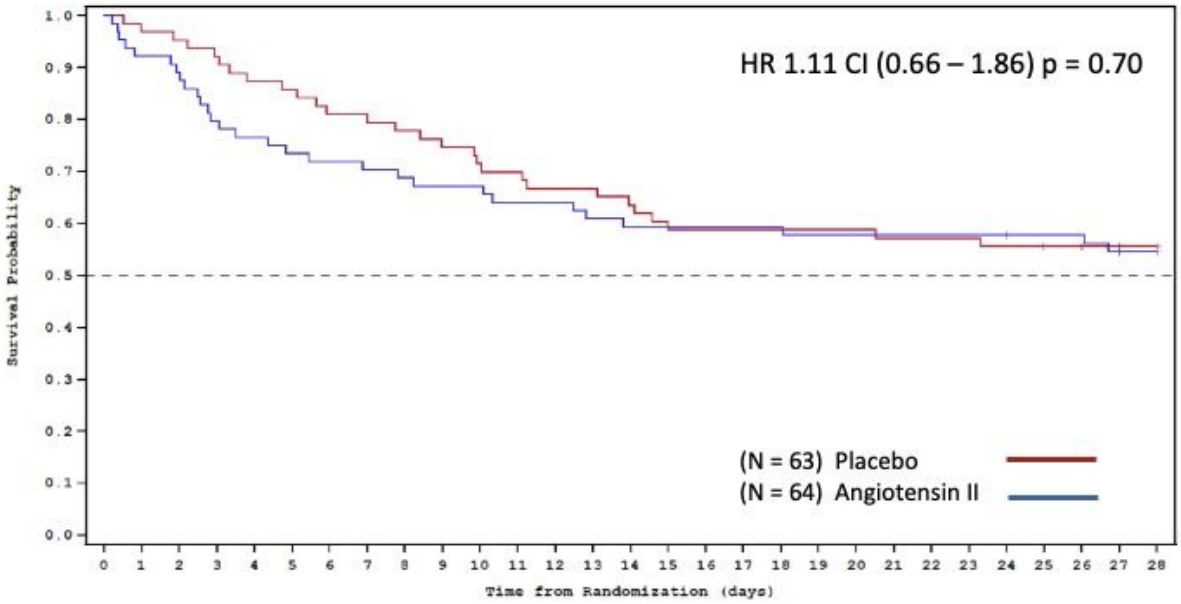

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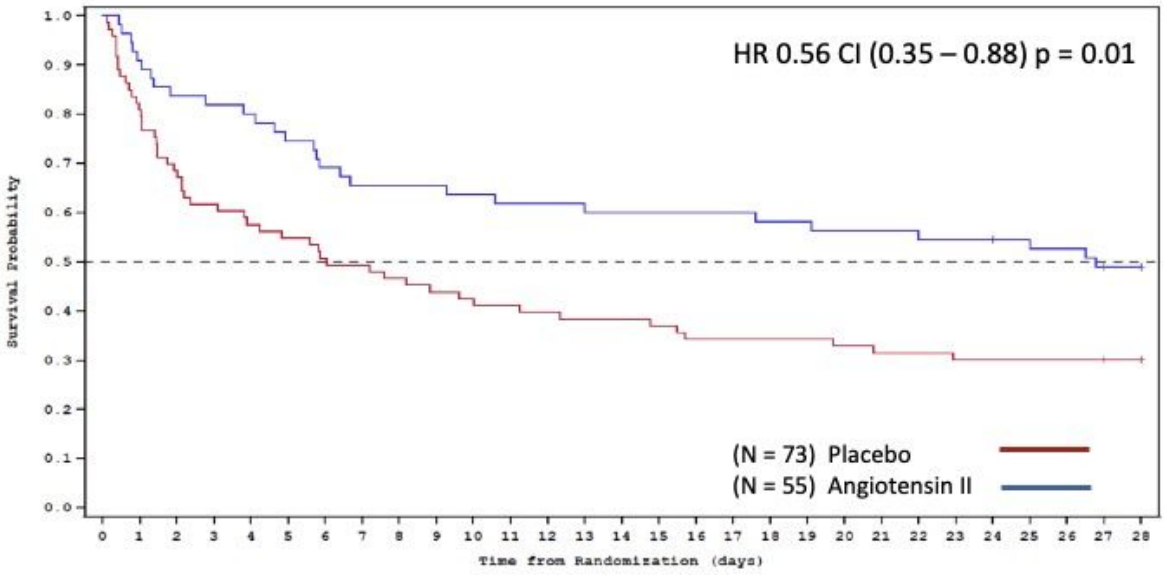
Figure 3B



Definition of abbreviations: CI, confidence interval; HR, hazard ratio. CI = confidence interval; HR = hazard ratio; RR = relative risk.

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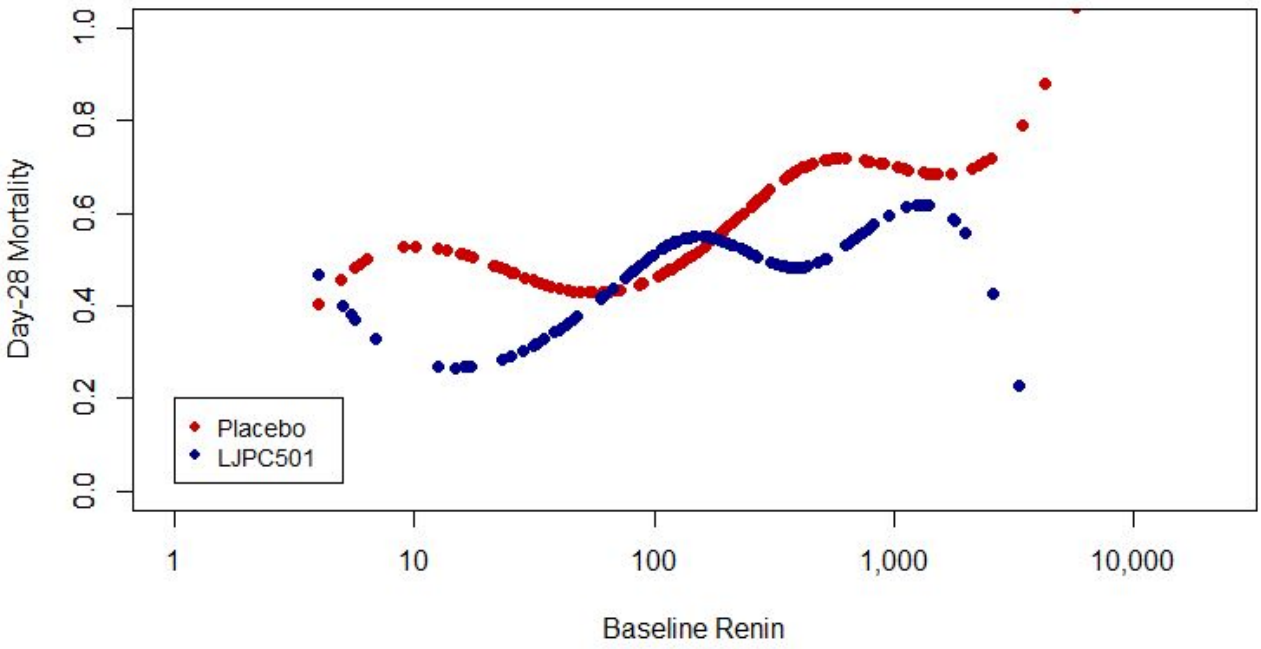
Figure 4. Cubic Splines of Mortality and Baseline Serum Renin



Legend: Baseline renin is shown with log scale.

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Online Data Supplement

Renin and Survival in Patients Given Angiotensin II for Catecholamine-Resistant Vasodilatory Shock

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Methods (Supplementary)

Serum renin was measured with the DRG Renin ELISA Kit (DRG Instruments GmbH, Marburg, Germany). The DRG ELISA Kit is a solid-phase enzyme-linked immunosorbent assay based on the sandwich principle. The microtiter wells are coated with a monoclonal (mouse) antibody directed toward a unique antigenic site of the human active renin molecule. An aliquot of patient sample containing endogenous renin is rapidly thawed in a water bath and incubated in the coated well together with assay buffer. After incubation, unbound components are washed off. Finally, enzyme conjugate, a monoclonal anti-renin antibody conjugated with horseradish peroxidase, is added. After incubation, unbound enzyme conjugate is washed off.

The amount of bound peroxidase is proportional to the concentration of renin in the sample. Having added the substrate solution, the intensity of color developed is proportional to the concentration of active renin in the patient sample. Personnel who conducted the assays were blinded to the study database and treatment allocation.

Angiotensin I and angiotensin II were measured by ultra-performance liquid chromatography with tandem mass spectrometry detection. The ultra-performance liquid chromatographic method (Inventiv, Quebec City, Canada) measured angiotensin peptide levels as low as 10 pg/mL. Blood was collected, centrifuged (2000 g, 10 min), and stored at –80°C until shipped for analysis. Following rapid thawing of the serum, samples were stabilized with a combination of aliskiren, pepstatin A, and o-phenanthroline in acidified dimethyl sulfoxide combined with a mixture of ethylenediaminetetraacetate and 4-(hydroxymercury) benzoic acid in phosphate buffered saline. All samples were spiked with stable-isotope-labeled internal standards for angiotensin I and angiotensin II at a concentration of 50 pg/mL. Following protein precipitation

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using acetonitrile with 1% formic acid and solid-phase extraction (Oasis MCX; Waters Corporation, Milford, MA) of the supernatant, samples underwent liquid chromatography-tandem mass spectrometry analysis using a reverse-phase analytical column (Acquity CSH C18; Waters Corporation) operating in line with a XEVO TQ-S triple quadrupole mass spectrometer (Waters Corporation) in multiple reaction monitoring. The sum of the signal from three different mass transitions per peptide were measured, and angiotensin concentrations were calculated by relating the ratio of peptide signal to internal standard signal.

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Table S1. Overall Study Cohort Demographics and Clinical Characteristics by Study Population Renin Levels

	Overall Study Cohort by Study Population Median		
	Renin Below Median *N* = 127	Renin Above Median *N* = 128	*P*
Age, years, median (IQR)	63 (51-74)	62 (51–74)	0.52*
Gender			
Female	48 (37.8%)	52 (40.6%)	
Male	79 (62.2%)	76 (59.4%)	0.7008†
Race			
White	105 (82.7%)	100 (78.1%)	
Nonwhite	22 (17.3%)	28 (21.9%)	0.4308†
Baseline albumin (g/dL)			
Median (IQR)	2.2 (1.8–2.8)	2.3 (1.9–2.7)	0.6115*
Baseline MELD			
Median (IQR)	21 (14–25)	23 (18–27)	0.0681*
Baseline MAP (mm Hg)			
Median (IQR)	66.3 (63.7–68.3)	66.3 (62.9–68.7)	0.6779*
Baseline APACHE II score Median (IQR)	27 (21–33)	29 (24–35)	0.0691*
Medical history, ARDS			
No	107 (84.3%)	101 (78.9%)	
Yes	20 (15.7%)	27 (21.1%)	0.3328†
Chest X-ray, ARDS			
No	92 (73.0%)	87 (68.0%)	
Yes	34 (27.0%)	41 (32.0%)	0.4108†
Medical history, sepsis			
No	21 (16.5%)	29 (22.7%)	
Yes	106 (83.5%)	99 (77.3%)	0.2697†
Severe AKI			
No	95 (74.8%)	66 (51.6%)	
Yes	32 (25.2%)	62 (48.4%)	0.0002
ESRD			
No	121 (95.3%)	125 (97.7%)	
Yes	6 (4.7%)	3 (2.3%)	0.3339
Baseline NED (ug/kg/min)			
Median (IQR)	0.30 (0.22–0.50)	0.38 (0.25–0.60)	0.0132*
Angiotensin I (pg/ml)	95.5 (39.2–275)	631 (267–1310)	<0.0001*
Angiotensin II (pg/ml)	64.6 (24.5–160)	139.5 (28.2–513.5)	0.0008
Baseline angiotensin I/II ratio			
Median (IQR)	1.29 (0.83–2.59)	3.10 (1.17–11.90)	<0.0001*

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Table S2. Survival in Acute Kidney Injury and ARDS Patient Subsets in High/Low Renin Groups

Population (n)	High-Renin N, HR (95% CI), p value	Low renin N, HR (95% CI), p value
LJPC 501 v. Placebo (All)	N=128, 0.56 (0.35- 0.88), 0.0115	N=127, 1.11 (0.66- 1.86), 0.7002
LJPC 501 v. Placebo (AKI)	N=62, 0.51 (0.26- 0.99), 0.0411	N=32, 0.55 (0.19- 1.58), 0.2574
LJPC 501 v. Placebo (ARDS)	N=41, 0.49 (0.21- 1.16), 0.0964	N=34, 1.38 (0.59- 3.26), 0.4583

Table S3. Likelihood of Renal Recovery in Patients with Severe AKI by Serum Renin Levels

	LJPC 501 v. Placebo N, RR (95% CI), p value
All patients (severe AKI)	N=105*, 2.902 (1.293 - 6.515), 0.0068
Renin above study median	N=62, 4.112 (1.376 - 12.29), 0.0061
Renin below study median	N=32, 2.215 (0.429 - 11.42), 0.3295

Severe AKI = Patients with AKI requiring RRT at the time of study enrollment. Renal recovery was assessed over the first 7 days. *All patients including those without renin level available.

Table S4. Serum Renin Levels in Various Study Sub-populations

	Baseline Serum Renin median (IQR)
All Patients	172.7 (60.7 - 440.6)
AKI Population[1.] (n=94)	352.5 (115.9 - 785.4)
Medical History of ESRD (n=9)	138.3 (96.4 - 193.3)
Non AKI, non ESRD (n=152)	121.6 (40.6 - 343.6)
ARDS by Chest X-ray (n=75)	210.5 (107.8 - 563.2)
Non-ARDS by Chest X-ray (n=179)	148.6 (45.9 - 427.5)
Exposure to ACE Inhibitor (n=25)	346.9 (144.5 - 784.4)
No Exposure to ACE Inhibitor (n=230)	150.2 (55.4 - 427.5)
Exposure to ARB (n=16)	223.4 (121.8 - 382.0)
No Exposure to ARB (n=239)	162.2 (59.6 - 440.6)

[1]**No medical history of end-stage renal disease with dialysis at baseline**

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Table S5. Multivariate Analysis for the Prediction of Mortality: Placebo Arm Only

	Hazard Ratio (95% CI)	*P* Value
Model A		
Renin above population median	2.15 (1.35–3.42)	0.0013
Baseline APACHE II score >30	1.87 (1.19–2.93)	0.0062
Baseline MAP <65 mm Hg	1.86 (1.18–2.93)	0.0076
Model B		
Renin above the population median	2.50 (1.33–4.67)	0.0042
Baseline MELD ≥30	1.61 (0.90–2.86)	0.1081
Baseline APACHE II score >30	1.91 (1.19–3.07)	0.0076
Baseline Angiotensin I <253 pg/mL	1.74 (0.90–3.36)	0.0980
Baseline Angiotensin II <83.75 pg/mL	0.84 (0.45–1.55)	0.5680
Baseline Angiotensin I/II ratio <1.63	0.81 (0.46–1.44)	0.4803
Baseline NED ≥0.5 ug/kg/min	1.98 (1.20–3.27)	0.0071
Model C		
Renin above population median	2.11 (1.33–3.36)	0.0016
Baseline APACHE II score >30	1.88 (1.20–2.95)	0.0056
Baseline MAP <65 mm Hg	1.66 (1.04–2.66)	0.0340
Baseline NED ≥0.5 ug/kg/min	1.60 (1.00–2.57)	0.0518

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; MAP = mean arterial pressure; MELD = Model for End-Stage Liver Disease; NED = norepinephrine equivalent dose.

Model A includes treatment assignment and stratification variables. Model B includes covariates that were imbalanced by $P < 0.10$ in the population clinical characteristics. Model C includes the statistically significant variables from Model A and Model B.

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Table S6. Mortality Sensitivity Analysis: High-renin and Low- Renin demarcated by Multiple of the Upper Limit of Normal of the Renin Assay

Cut-Off	HR	CI	P value
ULN	0.76	0.519 - 1.111	0.1550
2x ULN	0.69	0.456 - 1.045	0.0778
3x ULN	0.57	0.360 - 0.909	0.0167
4x ULN	0.63	0.382 - 1.048	0.0729

Legend: ULN = upper limit of normal

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Table S7. Change in CV and Total SOFA by Renin Status and Treatment Assignment

Table S7A. Hour 48 Change from Baseline in CV SOFA and Total SOFA for Elevated Renin Population

	Placebo	LJPC-501
CV SOFA: N, Mean (SD) Wilcoxon rank test p=0.01	N=73, -0.78 (1.387)	N=55, -1.56 (1.793)
Total SOFA: N, Mean (SD) Wilcoxon rank test p = 0.07	N=73, 2.86 (5.611)	N=54, 1.35 (6.032)

Table S7B. Hour 48 Change from Baseline in CV SOFA and Total SOFA for Low Renin Population

	Placebo	LJPC-501
CV SOFA: N, Mean (SD) Wilcoxon rank test p= 0.77	N=63, -1.81 (1.749)	N=64, -1.77 (1.716)
Total SOFA: N, Mean (SD) Wilcoxon rank test p = 0.12	N=63, -0.84 (4.274)	N=62, 0.85 (5.524)

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Table S8. Summary of Renin Samples Available at Baseline and Hour 3

	Placebo	Angiotensin II	Total
Total Population	158	163	321
Baseline Sample Analyzable	136	119	255
	18 samples unavailable 1 samples QNS	37 samples unavailable 3 samples QNS	55 samples unavailable 4 samples QNS
Hour 3 Sample Analyzable	109	91	200
	40 samples unavailable 9 samples QNS	67 samples unavailable 5 samples QNS	107 samples unavailable 14 samples QNS
Both Baseline and Hour 3 Samples Available	108	90	198

QNS = quantity not sufficient

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Table S9. Population Characteristics Based on Renin Sample Availability

Parameter	Missing at Baseline N=89	Available at Baseline N=255	Overall N=344
Age, years	64(56-75)	63(51-74)	63(52-74)
Gender (female,%)	41.6%	39.2%	39.8%
Race (%)			
White	77.5%	80.4%	79.7%
Black	10.1%	10.6%	10.5%
Asian	5.6%	3.9%	4.4%
Native Hawaiian or Pacific Islander	0.0%	0.4%	0.3%
American Indian or Alaska Native	0.0%	0.4%	0.3%
Other	6.7%	4.3%	4.9%
Albumin g/dL	2.3(1.8-2.7)	2.3(1.9-2.7)	2.3(1.8-2.7)
Baseline $ScvO_2$, %	75.9(73-82)	77.3(73-83)	77(73-83)
CVP mm Hg	12(10-15)	13(10-16)	12(10-16)
Cardiac Index ($L/min/m^2$)	3.2(2.3-5.4)	3.1(2.1-6.6)	3.1(2.1-6.6)
MELD	21(15-26)	22(16-26)	22(16-26)
Baseline MAP, mm Hg	66.7 (64-69)	66.3(63-68)	66.3(64-69)
APACHE II Score	26 (22-32)	28(23-34)	27.5(22-33)
Baseline NED, mcg/kg/min	0.33(0.23-0.56)	0.34(0.23-0.57)	0.34(0.23-0.56)

Legend: All data is presented as either percent or median (IQR) as appropriate

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Table S10. Missing Serum Renin Imputation Results

Available Data

Parameter	Estimate	S.E.
Treatment with Angiotensin II	-0.298	0.17
Renin Level	0.0004	0.0001

With Imputation*

Parameter	Estimate	S.E.
Treatment with Angiotensin II	-0.229	0.16
Renin Level	0.0004	0.0001

*A multiple imputation model was utilized to investigate the sensitivity of missing data on the renin association with Day 28 survival. The imputation model included baseline MAP, APACHII score, NED and Angiotensin I. The renin results were robust and do not suggest an impact from missing data.

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Table S11. Sensitivity Analyses: Multivariate Analyses

Table S11A. Whole cohort: Renin Level, Treatment Assignment, APACHE, NED, and MAP

Characteristic	HR (95% CI), p-value	
Full model		
Treatment Arm - LJPC-501	0.77 (0.54 - 1.08)	0.1275
Baseline MAP - <65 mmHg	1.54 (1.08 - 2.19)	0.0160
Baseline APACHE II Score - >30	1.67 (1.19 - 2.35)	0.0030
Baseline NE Equivalent Dose - >=0.5 ug/kg/min	1.72 (1.20 - 2.46)	0.0030
Renin >= Population Median	1.63 (1.16 - 2.30)	0.0049
Step-wise model		
Treatment Arm - LJPC-501	0.77 (0.54 - 1.08)	0.1275
Baseline MAP - <65 mmHg	1.54 (1.08 - 2.19)	0.0160
Baseline APACHE II Score - >30	1.67 (1.19 - 2.35)	0.0030
Baseline NE Equivalent Dose - >=0.5 ug/kg/min	1.72 (1.20 - 2.46)	0.0030
Renin >= Population Median	1.63 (1.16 - 2.30)	0.0049

Table S11B. Study Population below Median Renin with Treatment Assignment, APACHE, NED, and MAP

Characteristic	HR (95% CI), p-value	
Full model		
Treatment Arm - LJPC-501	1.08 (0.64 - 1.82)	0.7602
Baseline MAP - <65 mmHg	1.32 (0.76 - 2.32)	0.3254
Baseline APACHE II Score - >30	1.19 (0.69 - 2.04)	0.5266
Baseline NE Equivalent Dose - >=0.5 ug/kg/min	1.61 (0.91 - 2.86)	0.1047
Step-wise model		
Treatment Arm - LJPC-501	1.11 (0.66 - 1.86)	0.7001

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Table S11C. Study Population above Median Renin with Treatment Assignment, APACHE, NED, and MAP

Characteristic	HR (95% CI), p-value
Full model	
Treatment Arm - LJPC-501	0.62 (0.39 - 0.98) 0.0423
Baseline MAP - <65 mmHg	1.66 (1.06 - 2.62) 0.0279
Baseline APACHE II Score - >30	2.03 (1.29 - 3.19) 0.0023
Baseline NE Equivalent Dose - >=0.5 ug/kg/min	1.78 (1.13 - 2.83) 0.0137
Step-wise model	
Treatment Arm - LJPC-501	0.62 (0.39 - 0.98) 0.0423
Baseline MAP - <65 mmHg	1.66 (1.06 - 2.62) 0.0279
Baseline APACHE II Score - >30	2.03 (1.29 - 3.19) 0.0023
Baseline NE Equivalent Dose - >=0.5 ug/kg/min	1.78 (1.13 - 2.83) 0.0137

Table S11D. Whole cohort by Renin Level, Treatment Assignment, APACHE, NED, and MAP stratified by Treatment Assignment

Characteristic	HR (95% CI), p-value
Full model	
Treatment Arm - LJPC-501	1.08 (0.64 - 1.81) 0.7734
Baseline MAP - <65 mmHg	1.54 (1.09 - 2.19) 0.0156
Baseline APACHE II Score - >30	1.66 (1.18 - 2.33) 0.0037
Baseline NE Equivalent Dose - >=0.5 ug/kg/min	1.69 (1.18 - 2.42) 0.0039
Renin >= Population Median	2.12 (1.34 - 3.38) 0.0014
Treatment * Renin >= Population Median	0.54 (0.27 - 1.09) 0.0875
Step-wise model	
Treatment Arm - LJPC-501	0.77 (0.54 - 1.08) 0.1275
Baseline MAP - <65 mmHg	1.54 (1.08 - 2.19) 0.0160
Baseline APACHE II Score - >30	1.67 (1.19 - 2.35) 0.0030
Baseline NE Equivalent Dose - >=0.5 ug/kg/min	1.72 (1.20 - 2.46) 0.0030
Renin >= Population Median	1.63 (1.16 - 2.30) 0.0049

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Table S12. Multivariate analysis of mortality with renin as a continuous variable.

Covariate	HR (95% CI), p-value
Total observations: N = 255	
<u>Dependent measure: Day 28 mortality (full model)</u>	
Treatment arm – LJPC-501	1.44 (0.40 – 5.22) 0.5770
Baseline LOG2 (Renin)	1.15 (1.03 – 1.28) 0.0107
Treatment * LOG2 (Renin)	0.93 (0.79 – 1.09) 0.3752
Baseline MAP	0.95 (0.92 – 0.98) 0.0016
Baseline APACHE II	1.04 (1.02 – 1.06) 0.0001
Baseline LOG2 (NED)	1.37 (1.11 – 1.68) 0.0027

Legend: Logistic regression analyses were performed for binary outcome measures (eg, MAP response at Hour 3) and Cox model regression analyses were performed for time to event analyses (eg, Day 28 survival). As renin and NED are more closely lognormally distributed, the log transformation of renin was used in modelling mortality.

Table S13, Adjusted Multivariate Model for MAP Response and Elevated Renin*Treatment

Covariate	OR (95% CI), p-value
Total observations: N = 255	
<u>Dependent measure: MAP Response (full model)</u>	
Treatment arm – LJPC-501	8.27 (3.71 – 18.4) <0.0001
Baseline Renin ≥ Population Median	0.60 (0.27 – 1.31) 0.1990
Treatment * Baseline Renin ≥ Population Median	0.76 (0.25 – 2.32) 0.6266

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Figure S1A. Day-28 Survival by Treatment Arm: Renin >ULN

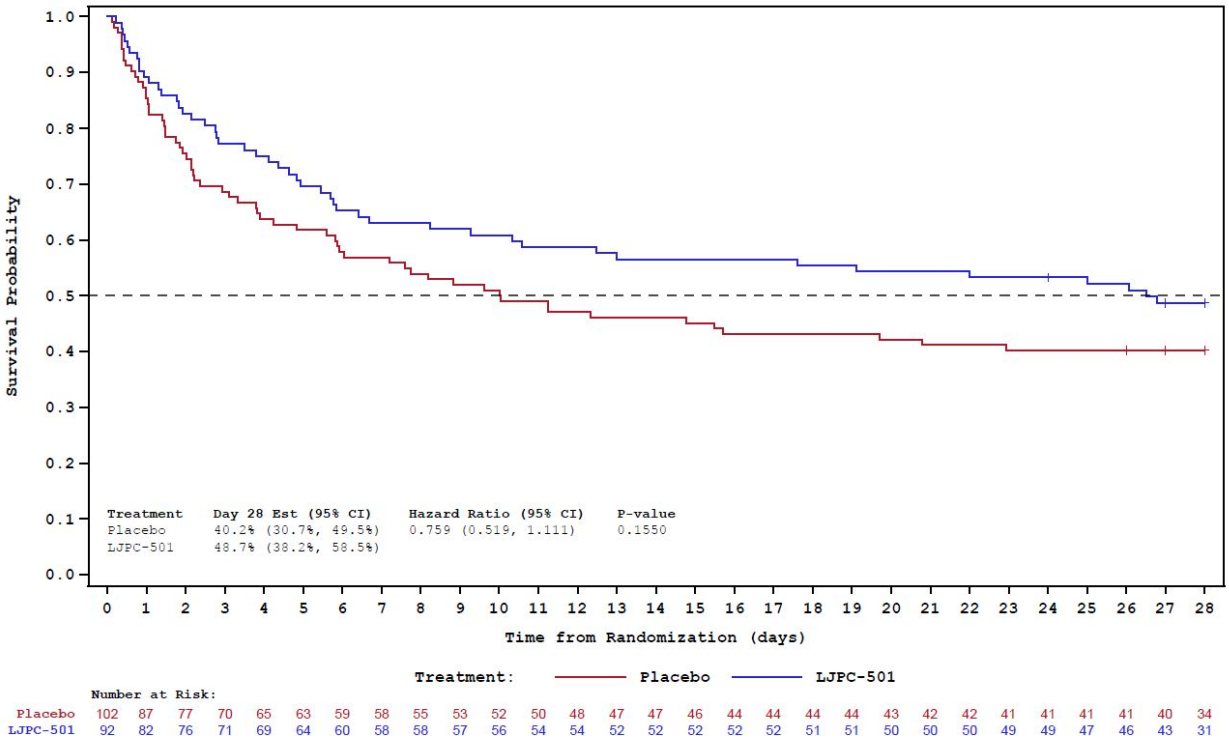

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Figure S1B. Day-28 Survival by Treatment Arm: Renin >2xULN

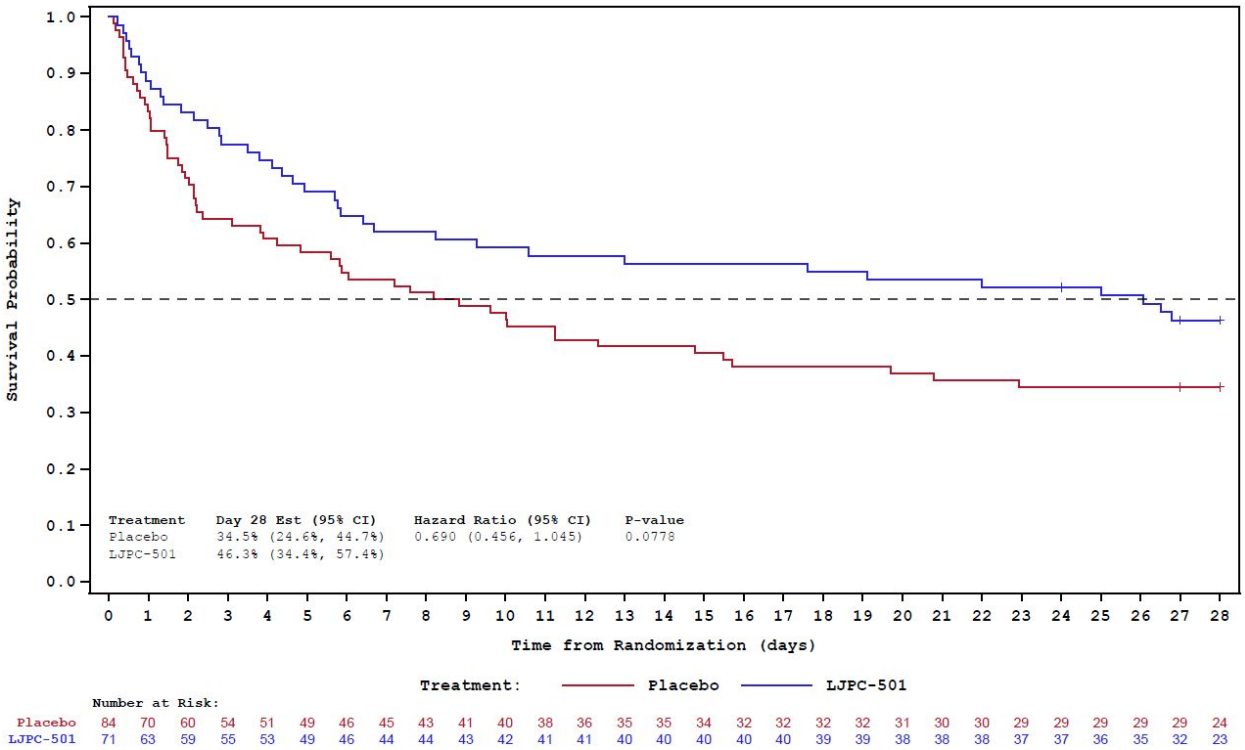

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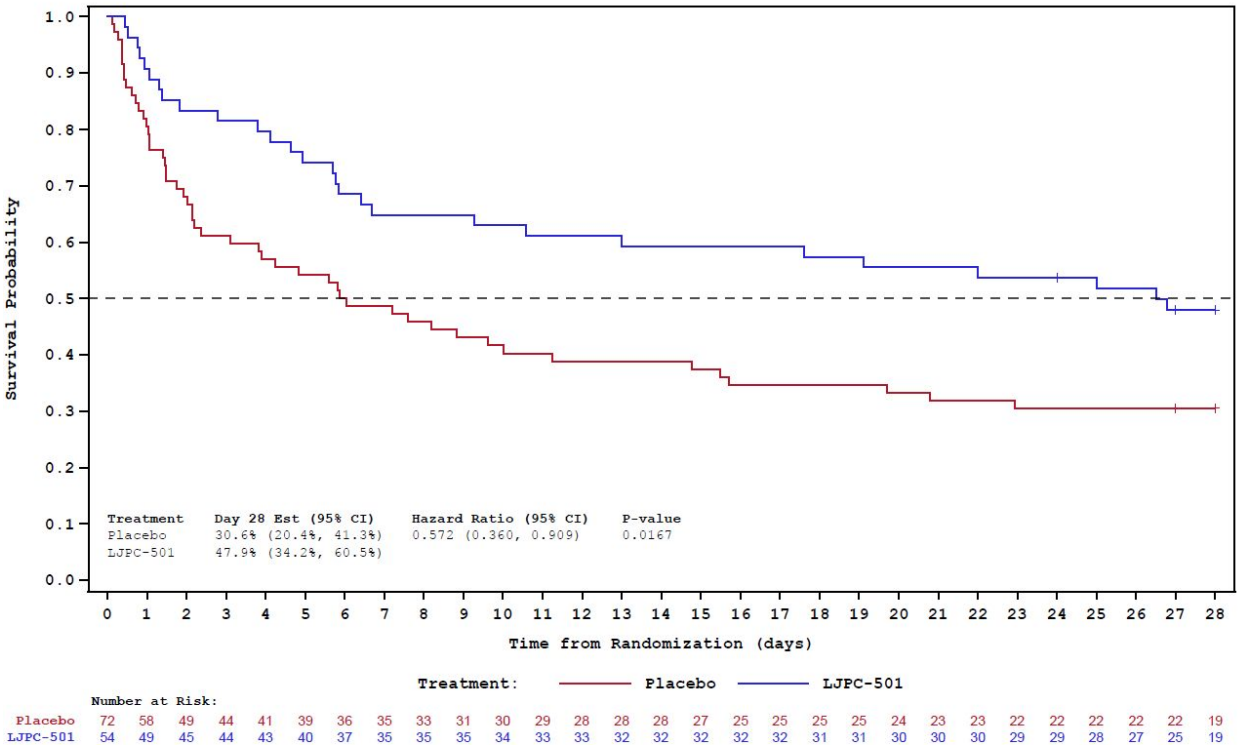
Figure S1C. Day-28 Survival by Treatment Arm: Renin >3xULN



Number at Risk:

Placebo	72	58	49	44	41	39	36	35	33	31	30	29	28	28	28	27	25	25	25	25	24	23	23	22	22	22	22	22	19
LJPC-501	54	49	45	44	43	40	37	35	35	35	34	33	33	32	32	32	32	32	31	31	30	30	30	29	29	28	27	25	19

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Figure S1D. Day-28 Survival by Treatment Arm: Renin >4xULN

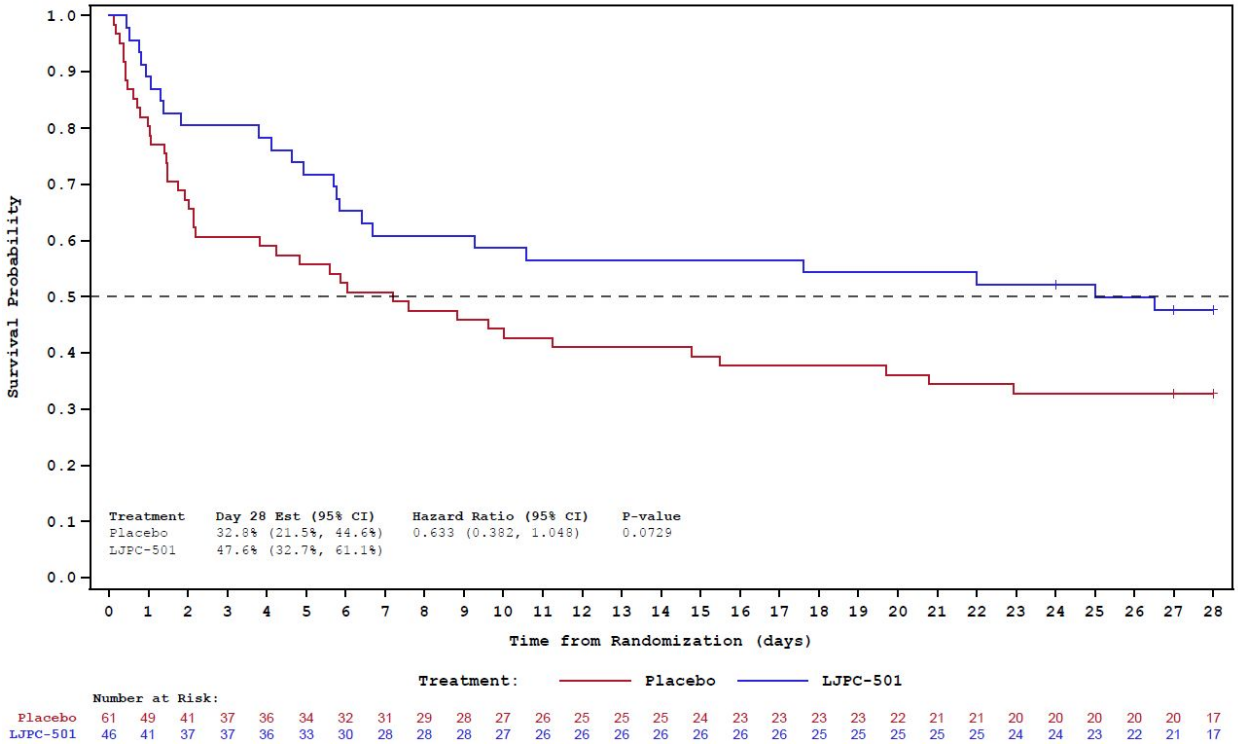

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Figure S2A, Day-28 Survival by Treatment Arm: Renin 1st Quartile

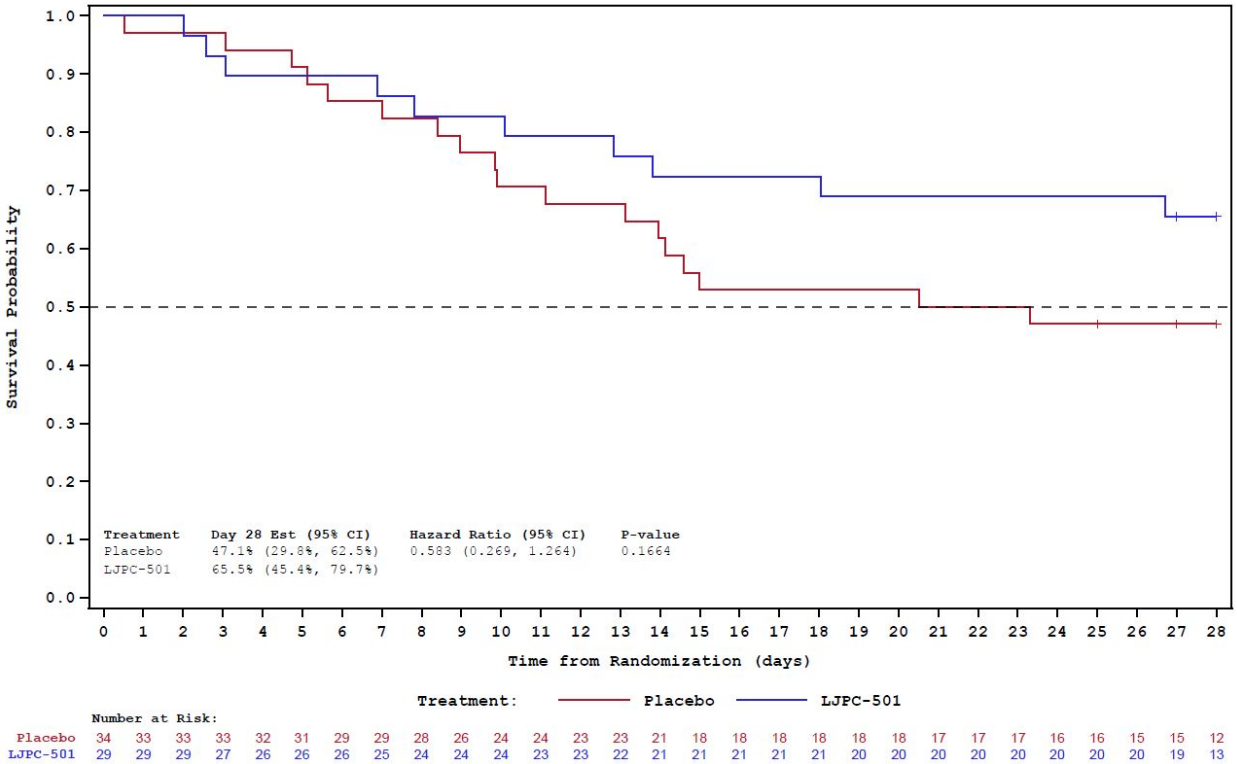

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Figure S2B, Day-28 Survival by Treatment Arm: Renin 2nd Quartile

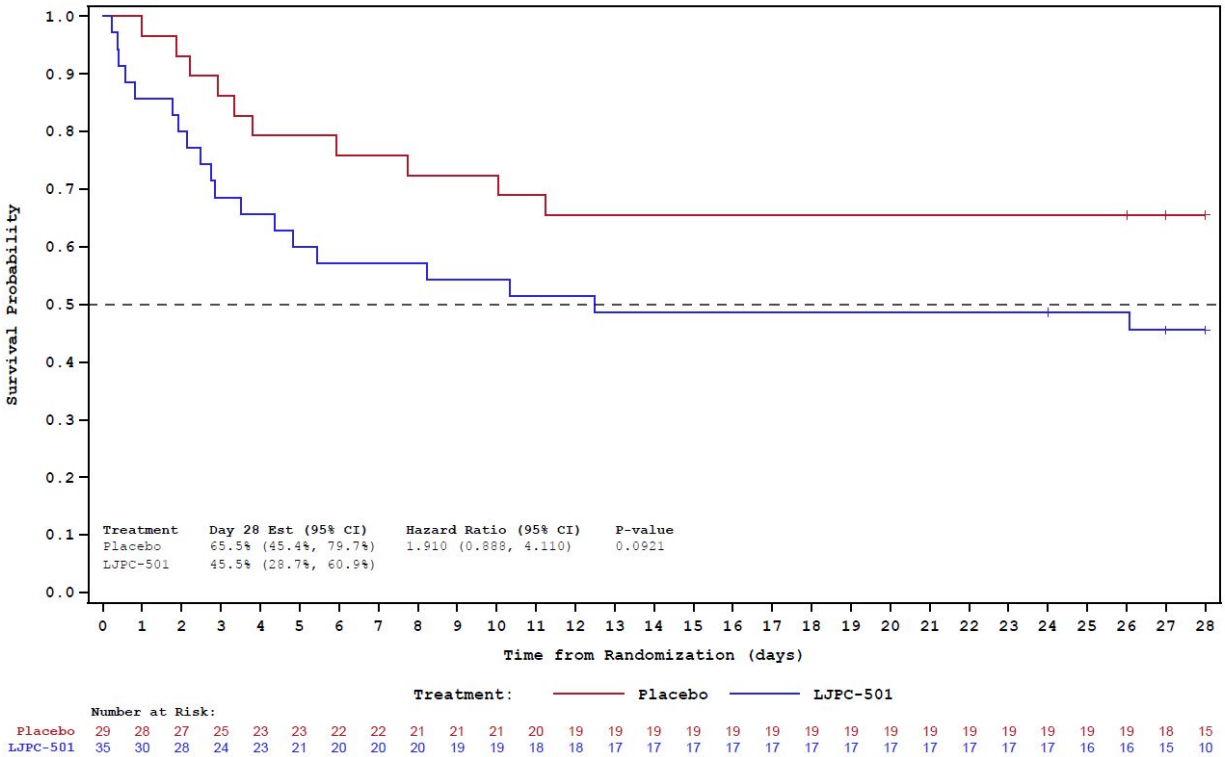

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Figure S2C. Day-28 Survival by Treatment Arm: Renin 3rd Quartile

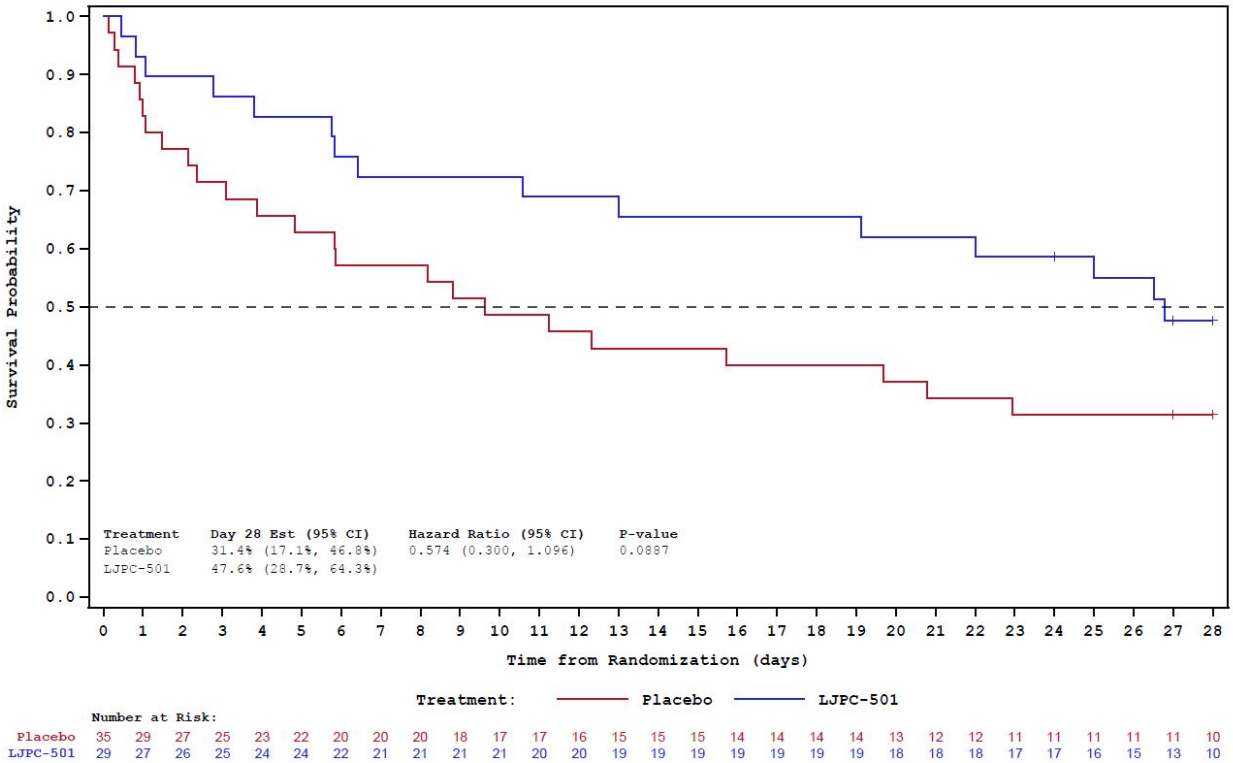

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Figure S2D, Day-28 Survival by Treatment Arm: Renin 4th Quartile

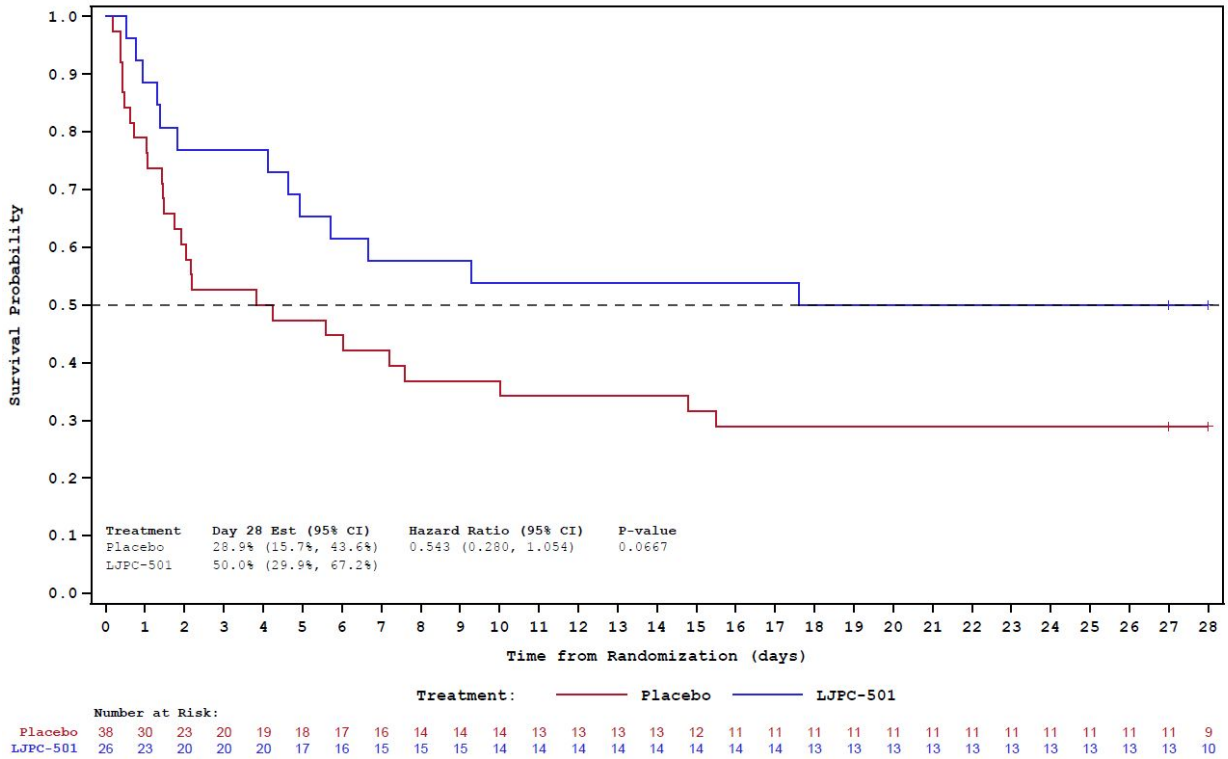

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Figure S3. Correlation of Baseline Serum Renin with Baseline Angiotensin I, II, and Angiotensin I/II ratio

Figure S3 A,B, and C. Renin, angiotensin I, and angiotensin II correlations. (A) Relationship between baseline serum renin and angiotensin I/II ratio. (B) Relationship between baseline serum renin and angiotensin I. (C) Relationship between serum renin and angiotensin I at hour 3

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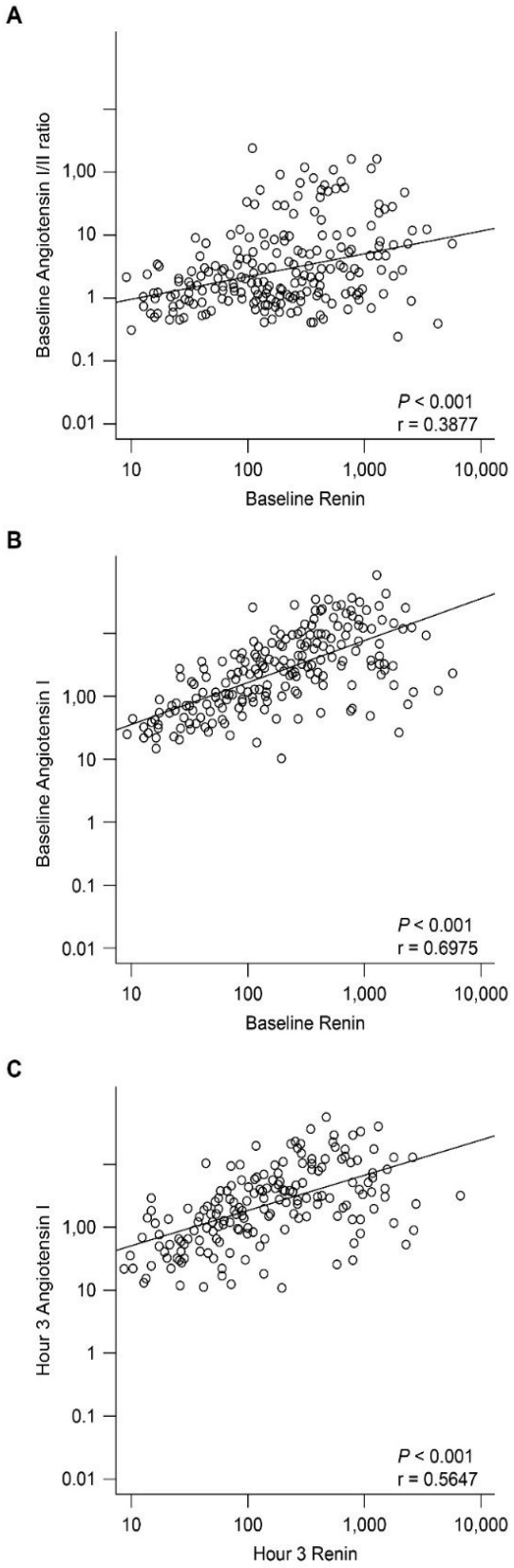

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Figure S4. Correlation of Baseline Serum Renin with Baseline Angiotensin I, II, and Angiotensin I/II ratio by Treatment Assignment

Figure S4A. Baseline Renin and Baseline Angiotensin I

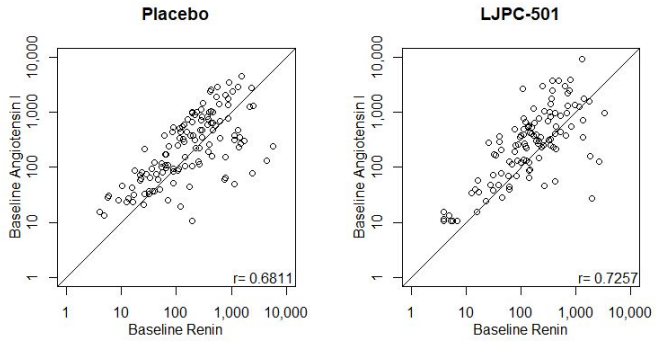

Figure S4B. Baseline Renin and Baseline Angiotensin II

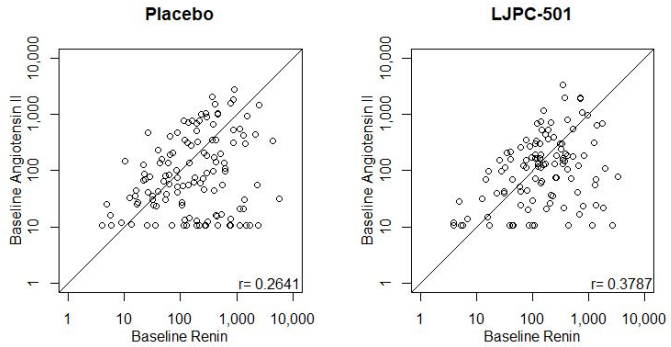

Figure S4C. Baseline Renin and Baseline Angiotensin I/II Ratio

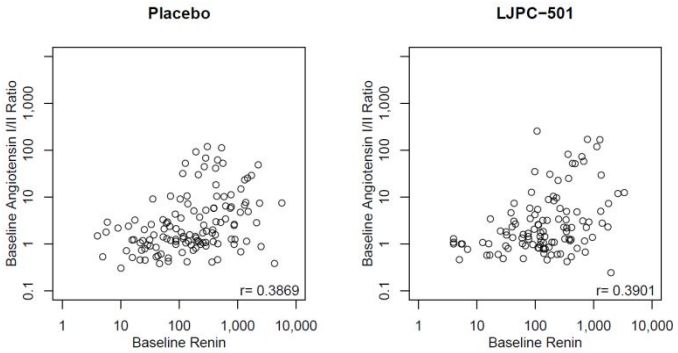

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Figure S4, Correlation of Hour 3 Serum Renin with Hour 3 Angiotensin I, II, and Angiotensin I/II ratio

Figure S4D. Hour 3 Renin and Hour 3 Angiotensin I

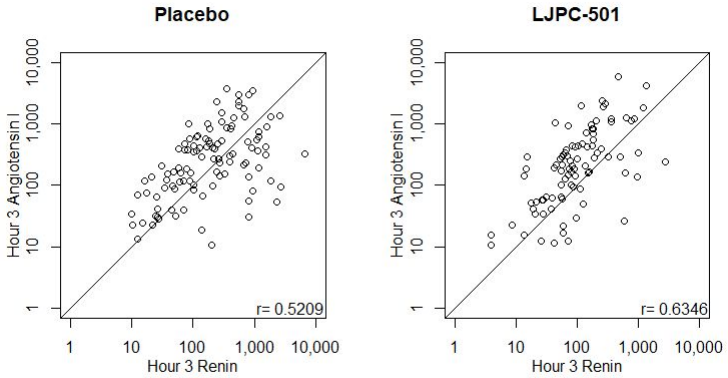

Figure S4E. Hour 3 Renin and Hour 3 Angiotensin II

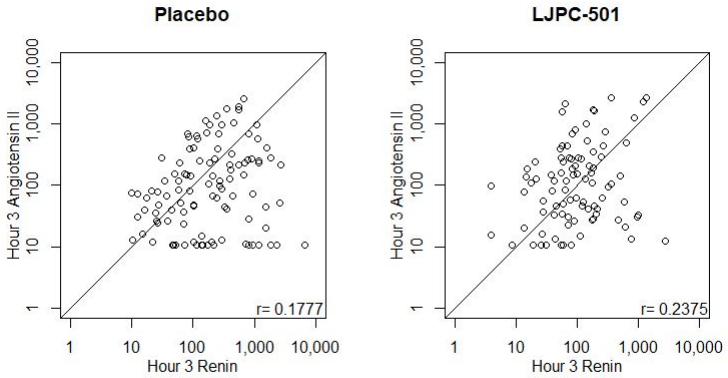

Figure S4F. Hour 3 Renin and Hour 3 Angiotensin I/II Ratio

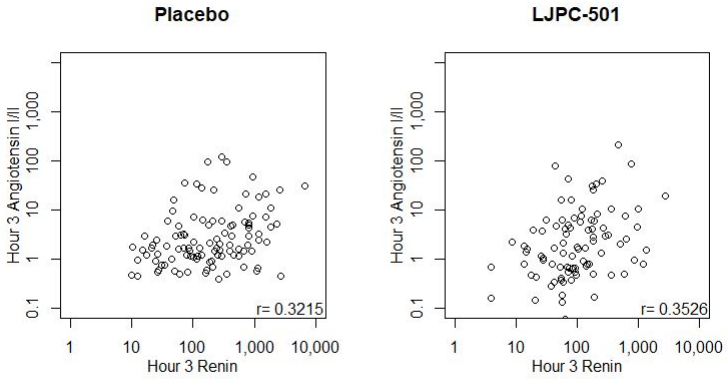

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Figure S5. Survival by Treatment Arm and Renin Level

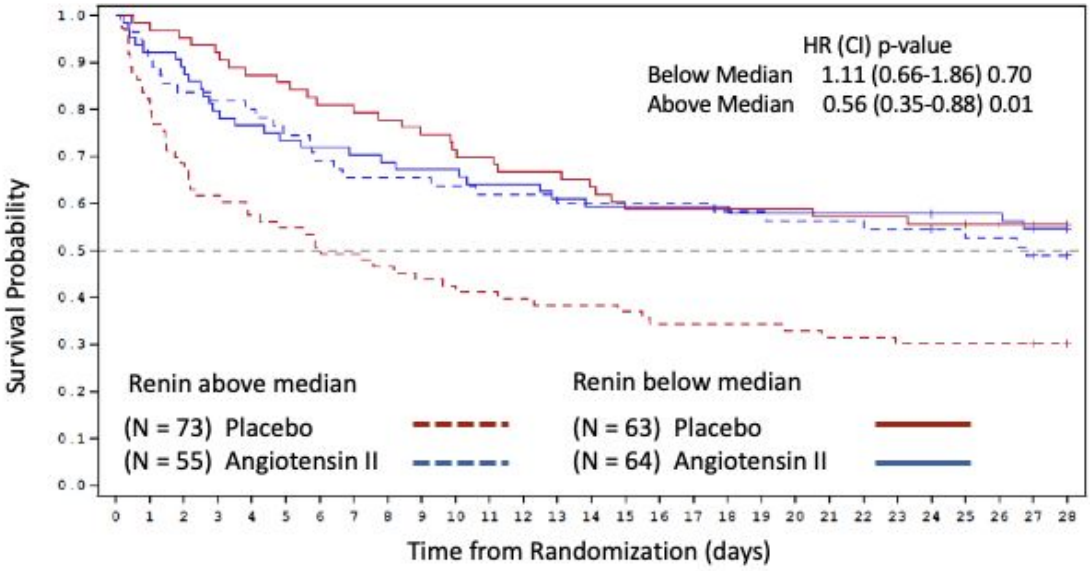

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Figure S6. Renal Recovery in Patients with Severe AKI Treatment by Assignment and Renin Status

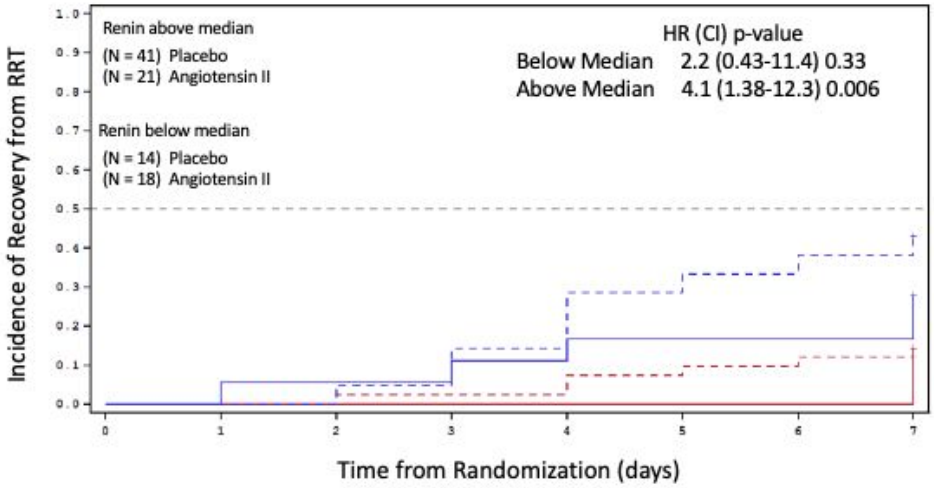

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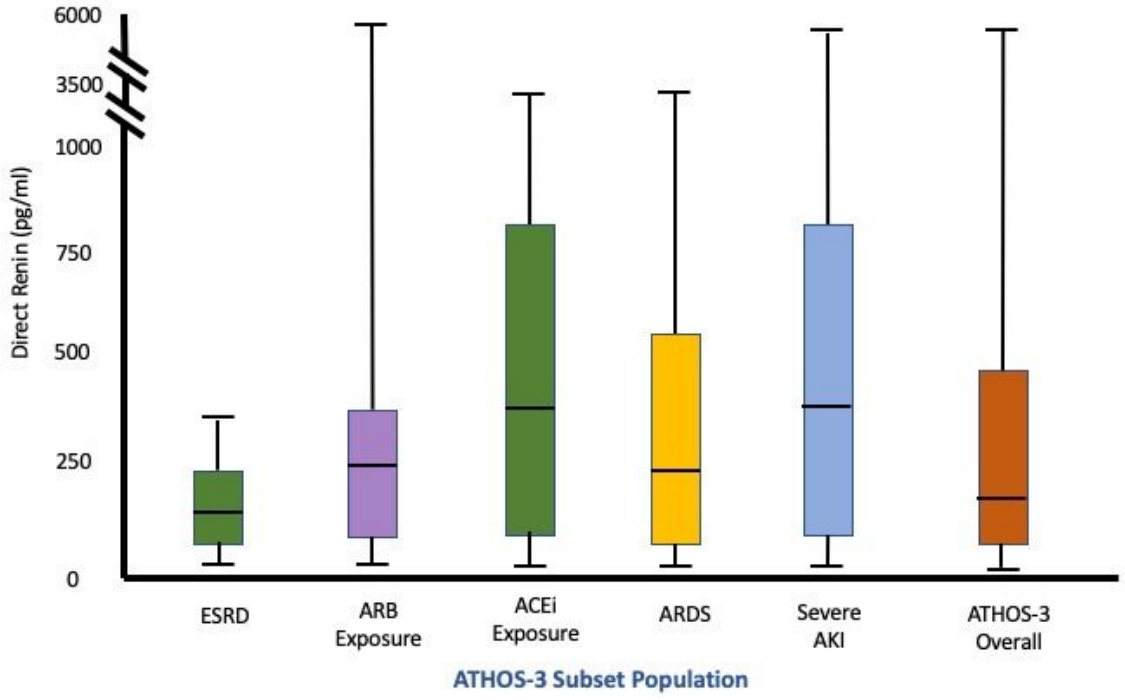
Figure S7. Renin levels in the Subset Populations of ATHOS-3



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