

Lorundrostat Mitigates Cardiorenal Injury Independent of Blood Pressure Reduction in an L-NAME/Angiotensin II Rat Model

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INTRODUCTION

- Inappropriate aldosterone levels and mineralocorticoid receptor (MR) activation have been linked to cardiac and renal damage^{1,2}
- Animals treated with a combination of high-salt diet, the nitric oxide synthase inhibitor, N^ω-nitro-L-arginine (L-NAME), and the potent arteriolar vasoconstrictor and upstream aldosterone inducer, angiotensin II (AngII), are an established model for the consequences of treatment-resistant hypertension, including severely elevated blood pressure, reduced NO-mediated vasodilation, increased vasoconstriction, vascular inflammation, cardiovascular and renal fibrosis, and hypertension-mediated target organ damage^{3,4}
 - This model induces cardiorenal damage after 14 days of treatment and results in severe renal failure and/or stroke if left untreated
 - The model also enables investigators to differentiate between blood pressure-dependent and -independent effects⁵
- Reducing aldosterone levels and signaling in L-NAME/AngII-treated animals by either adrenalectomy or addition of the mineralocorticoid receptor antagonist, eplerenone, to the L-NAME/AngII regimen, has been shown to prevent cardiovascular and renal end-organ damage without affecting the high blood pressure induced by the model⁵
- To date, no studies have assessed whether lowering aldosterone levels with an aldosterone synthase inhibitor (ASI) has beneficial effects on cardiorenal damage
- Lorundrostat, a novel ASI, has been shown to significantly reduce albuminuria (placebo-adjusted p=0.0015) and systolic blood pressure (placebo-adjusted p=0.0024) in individuals with chronic kidney disease and uncontrolled hypertension who were taking ≥2 antihypertensive medications⁶
 - However, the impact of lorundrostat treatment on cardiorenal damage is as yet unknown

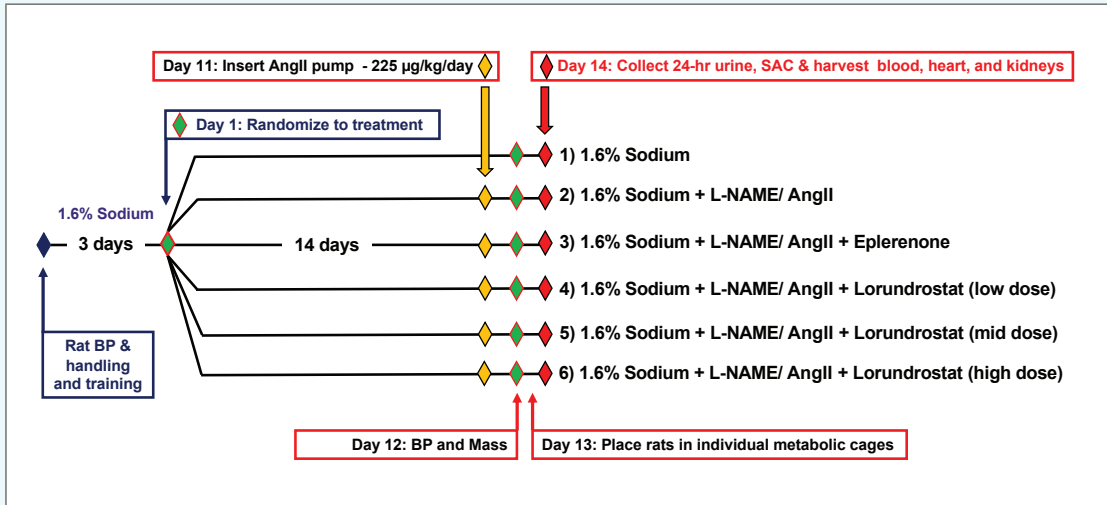
OBJECTIVE

- To evaluate the effects of lorundrostat on target-organ damage in the L-NAME/AngII animal model of resistant hypertension

METHODS

- Male Wistar rats (8-10 weeks old) were maintained on a high-salt diet (HSD) containing 1.6% sodium
- On Day 1, rats were randomized (9-14/group) to receive HSD alone (Controls) or to HSD plus one of six treatments (**Figure 1**)
 - L-NAME (0.2 mg/mL in drinking water) or L-NAME plus one of the following:
 - Oral eplerenone,
 - Oral lorundrostat (low dose),
 - Oral lorundrostat (mid dose), or
 - Oral lorundrostat (high dose)
- Except for the Controls, all other randomized groups received AngII (225 µg/kg/day) administered via subcutaneous minipump infusion from Day 12 to Day 14
- On Day 14, 24-hour urine samples were collected, the animals were sacrificed, and the blood, heart, and kidneys were harvested
- The primary study outcomes included assessments of the effect of lorundrostat on L-NAME/AngII-induced aldosterone secretion, myocardial inflammatory damage, and albuminuria (assessed as 24-hour urinary albumin-to-creatinine ratio [UACR])
 - For the assessment of myocardial damage, cardiac tissue from both ventricles was fixed, paraffin-embedded, and stained with hematoxylin and eosin for light microscopy^{5,7}
 - Sections were evaluated by a pathologist (blinded to treatment) and scored using a 0–3 myocardial injury scale, (0 = no damage; 3 = severe damage)
- Secondary outcomes included assessments of lorundrostat's effect on L-NAME/AngII-induced excretion of kidney injury molecule-1 (KIM-1), a biomarker of acute and chronic kidney injury⁸ assessed as the KIM-1-to-creatinine ratio, and blood pressure (measured on Day 14 prior to sacrifice)
- Treatment differences were assessed using analysis of covariance (ANCOVA)

Figure 1: Study Design



AngII, angiotensin II; BP, blood pressure; SAC, sacrifice.

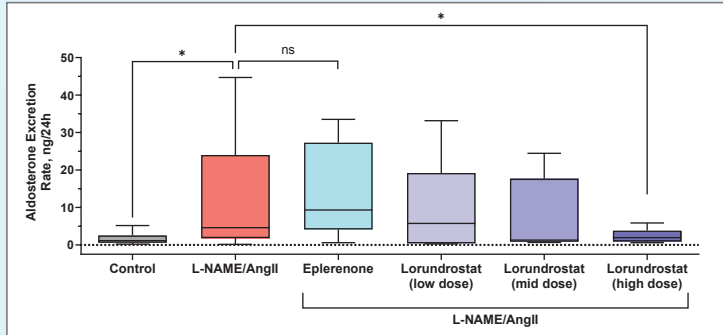
RESULTS

- Rats treated with HSD plus L-NAME/AngII showed significantly greater urinary aldosterone excretion (**Figure 2**), myocardial injury (**Figure 3**), albuminuria (**Figure 4**), KIM-1 excretion (**Figure 5**), and blood pressure (**Figure 6**) than control animals treated with HSD alone (all p<0.05)

Primary Study Endpoints

- Lorundrostat reduced urinary aldosterone secretion induced by L-NAME/AngII in a dose-dependent manner (p<0.05 for high-dose lorundrostat; **Figure 2**)
 - As expected, aldosterone secretion was not affected by treatment with eplerenone
- In addition, rats who received high-dose lorundrostat also had significant reductions in L-NAME/AngII-induced cardiac damage (p<0.01; **Figure 3**) and albuminuria (p<0.01; **Figure 4**)
 - Similarly, rats treated with eplerenone also showed significant reductions in cardiac damage (p<0.01) and 24-hour UACR (p<0.05)

Figure 2. Lorundrostat Reduces Excess Aldosterone Excretion



Control = HSD alone. The bottom and top boundaries of the boxes represent the 25th and 75th percentiles, respectively, the horizontal lines depict the mean values, and the whiskers show the range. *p<0.05. **p<0.01. ***p<0.0001. AngII, angiotensin II; HSD, high-salt diet; L-NAME, N^ω-nitro-L-arginine; ns, not significant; UACR, urinary albumin-to-creatinine ratio.

Figure 3. Lorundrostat Reduces L-NAME/AngII-Induced Myocardial Damage

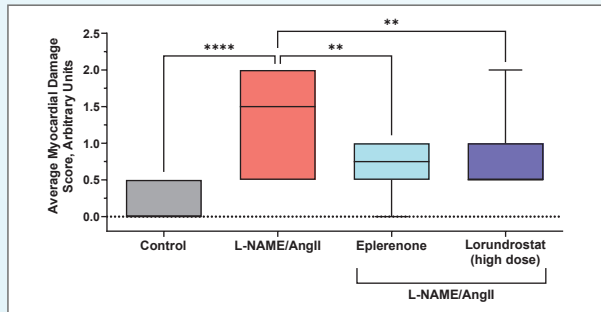
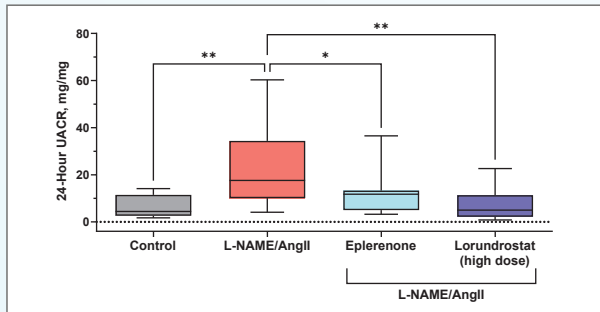


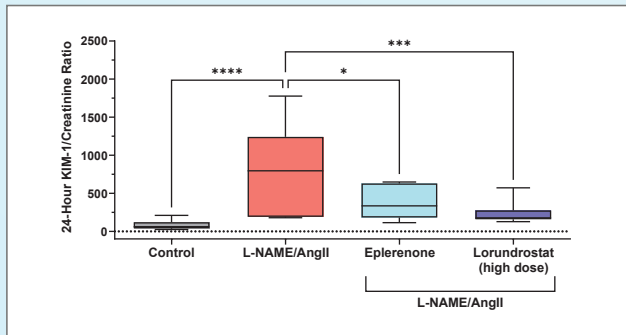
Figure 4. Prevention of Albuminuria by Lorundrostat and Eplerenone



Secondary Study Endpoints

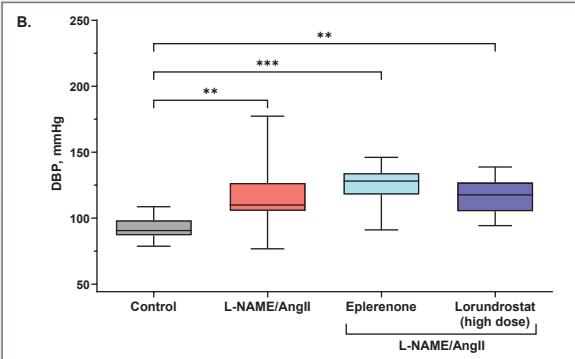
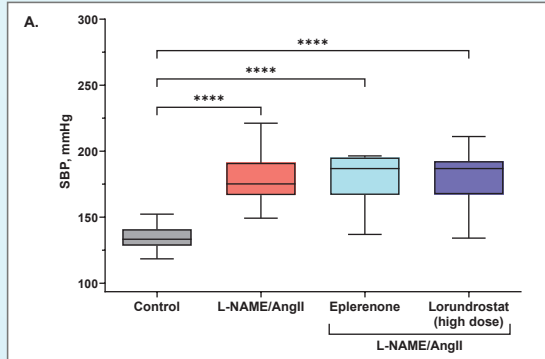
- L-NAME/AngII-induced excretion of the kidney damage biomarker, KIM-1, was significantly reduced by high-dose lorundrostat (p<0.001) and, to a lesser extent, by eplerenone (p<0.05) (**Figure 5**)
- As anticipated, neither eplerenone nor lorundrostat significantly reduced elevated blood pressure in L-NAME/AngII-treated animals (**Figure 6**)

Figure 5. Increased KIM-1 Excretion Induced by L-NAME/AngII Is Reduced by Treatment with Lorundrostat or Eplerenone



Control = HSD alone. The bottom and top boundaries of the boxes represent the 25th and 75th percentiles, respectively, the horizontal lines depict the mean values, and the whiskers show the range. *p<0.05. **p<0.01. ***p<0.001. ****p<0.0001. AngII, angiotensin II; DBP, diastolic blood pressure; HSD, high-salt diet; KIM-1, kidney injury molecule-1; L-NAME, N^ω-nitro-L-arginine; SBP, systolic blood pressure.

Figure 6. No Effect of Lorundrostat or Eplerenone on L-NAME/AngII-Induced Increase in (A) Systolic or (B) Diastolic Blood Pressure



CONCLUSIONS

- In this animal model of hypertension-induced end-organ damage, lorundrostat treatment significantly reduced aldosterone levels and albuminuria induced by L-NAME/AngII
- Lorundrostat also prevented an L-NAME/AngII-induced increase in KIM-1 excretion, a biomarker of acute and chronic renal damage
- Lorundrostat's effects were independent of blood pressure and NO levels, suggesting that targeted aldosterone suppression with an ASI can substantially reduce end-organ damage separately from its effect on blood pressure

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Disclosures

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