Effect of lisinopril on glomerular and tubular injury in a surgical rat model of progressive chronic kidney disease and kidney failure

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Background & Aim

Development of renal fibrosis is a hallmark of chronic kidney disease (CKD), underlying the progressive loss of kidney function and progression to end-stage kidney disease. The 5/6 nephrectomy (Nx) rat model of CKD displays progressive albuminuria, glomerulosclerosis, tubulointerstitial fibrosis, and loss of kidney function. Here, we characterised the effect of lisinopril, a standard ACE inhibitor, on kidney histopathology, renal biochemical markers, and kidney function in 5/6 Nx rats.

Methods

Male Wistar rats (9 weeks old) underwent either sham operation or 2/3 nephrectomy of the right kidney at week -4 and nephrectomy of left kidney at week -2. Rats were randomised into study groups at week -1 based on plasma urea, creatinine, and body weight. 5/6 Nx rats received either vehicle or Lisinopril (20 mg/kg, PO, QD), for a total of 8 weeks, starting on day 1. The albumin-to-creatinine ratio (ACR) was measured at week 7 and the glomerular filtration rate (GFR) at week 8. Terminal plasma was sampled for analysis of urea and creatinine. The remaining right kidney was harvested for quantitative histological assessment of glomerulosclerosis (PAS staining), macrophage infiltration (CD68), tubular injury (KIM-1), and fibrosis (Col1a1).

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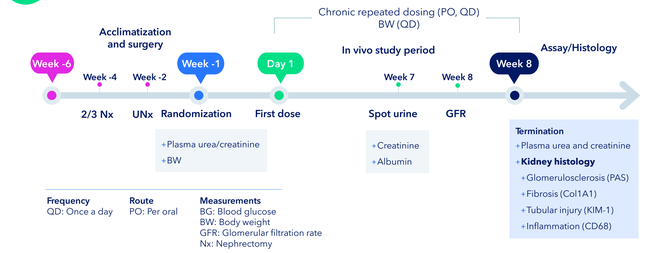
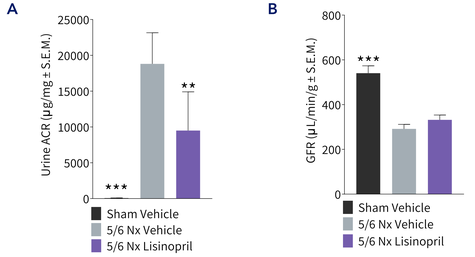
1 Study outline



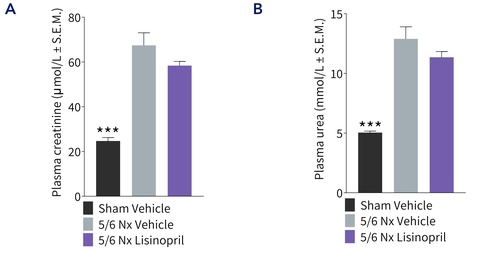
Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing volume	Dosing concentration
1	Sham	Male	12	-	-	-	-	-
2	5/6 Nx Vehicle	Male	17	**Vehicle**	PO	QD	5 ml/kg	-
3	5/6 Nx Lisinopril	Male	17	**Lisinopril**	PO	QD	5 ml/kg	**20 mg/kg**

2 Albuminuria and GFR



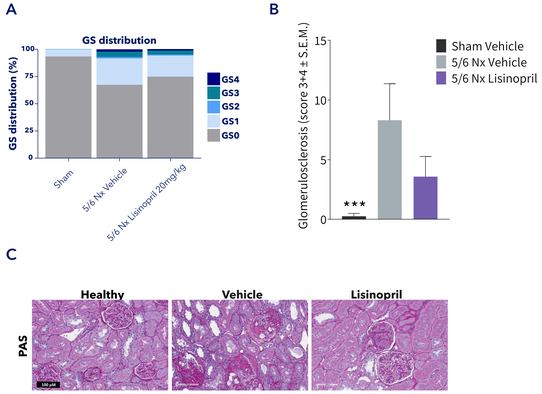
Albuminuria and GFR. (A) Urine ACR at week 7. **(B)** GFR at week 8. **p<0.01, ***p<0.001 compared to 5/6 Nx Vehicle rats (Dunnett's test one-factor linear model).

3 Plasma creatinine and urea



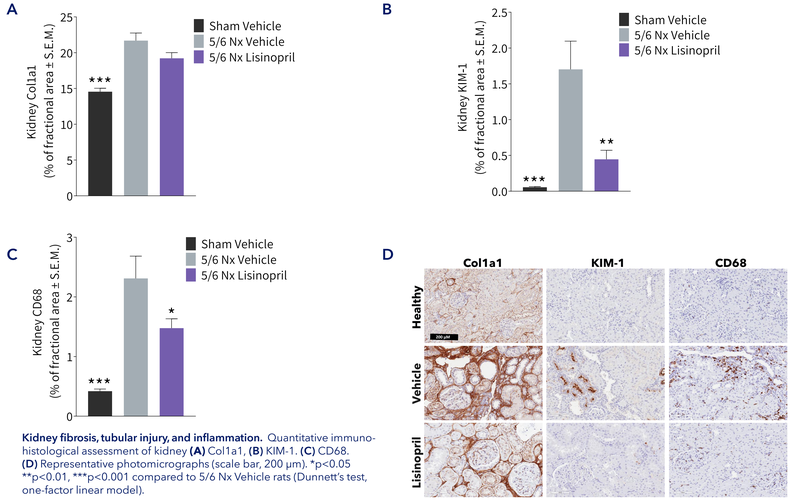
Plasma creatinine and urea. (A) Plasma creatinine at week 8. **(B)** Plasma urea at week 8. ***p<0.001 compared to 5/6 Nx Vehicle rats (Dunnett's test one-factor linear model).

4 Glomerulosclerosis



Glomerulosclerosis. The percentage of animals with score 0 (normal), score 1 (up to 25% involvement), score 2 (up to 50% involvement), score 3 (up to 75% involvement), and score 4 (global, more than 75% involvement). **(A)** Distribution of all scores. **(B)** Glomerulosclerosis score 3 and 4 (mean ±S.E.M.)
(C) Representative photomicrographs (scale bar, 100 µm). ***p<0.001 compared to 5/6 Nx Vehicle rats (Dunnett's test one-factor linear model).

5 Histological markers of kidney injury



Kidney fibrosis, tubular injury, and inflammation. Quantitative immunohistological assessment of kidney **(A)** Col1a1, **(B)** KIM-1. **(C)** CD68.
(D) Representative photomicrographs (scale bar, 200 µm). *p<0.05 **p<0.01, ***p<0.001 compared to 5/6 Nx Vehicle rats (Dunnett's test, one-factor linear model).

Conclusion

The present study in 5/6 Nx rats establishes that lisinopril

+ Improves albuminuria
+ Reduces tubular injury
+ Reduces renal inflammation

These findings support nephroprotective effects of lisinopril in CKD and highlights the applicability of the 5/6 Nx rat model in preclinical drug development.

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