Effect of renin-angiotensin system inhibitor on the renal prognosis of patients with advanced chronic kidney disease related to diabetic nephropathy

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Introduction

Large-scale clinical studies have demonstrated the renoprotective effect of renin-angiotensin system (RAS) inhibitors on diabetic nephropathy [1),2]. However, most studies involved patients with relatively mild kidney dysfunction, and the effects of RAS inhibitors on diabetic nephropathy in patients with advanced CKD remain to be clarified.

Objectives

The purpose of this study was to examine the effects of RAS inhibitors on the renal prognosis and rate of renal function decline in patients with GFR category G4-5 diabetic nephropathy by conducting multidisciplinary treatment.

Methods

- **Design:** a single-center retrospective cohort study
- **Patients:** 244 patients with GFR category G4-5 diabetic nephropathy among 1062 patients who admitted to our hospital for the purpose of CKD education between March 2004 and June 2016.
- **Exposure**: Use of RAS inhibitors
- **Outcome:**
  1.**I**nitiation of renal replacement therapy (RRT)
  2. Rate of renal function decline

-Statistics:

Kaplan-Meire method and log-rank test was used for analysis of renal prognosis. Hazard ratios of renal prognosis were analyzed using Cox's hazard proportional model after ajusting with other clinical data related to renal prognosis. Propensity score-matched analysis was also performed to compare the effect of RAS inhibitors. P<0.05 was considered as significant.

-Contents of CKD educational admission

Drug adjustment involving blood pressure, glucose, hemoglobin by nephrologist , life style guidance by nurse and dietary guidance involving salt/protein/ potassium restriction by dietitian.

Results

Table 1. Patient's characteristics

	Total	RAS(+)	RAS(-)	p value
n	244	150	94	
gender (%male)	74.6	72.0	78.7	0.24
age (yrs)	67.5±11.6	66.7±11.9	68.8±11.0	0.20
BMI	24.7±4.2	24.8±3.8	24.7±4.8	0.42
History of CVD	28.2	28.7	28.3	0.86
smoke (%)	36.9	38.0	35.1	0.65
eGFR (ml/min/1.73m^2)	14.9±6.1	16.0±6.4	13.0±5.3	0.0003
Urinary protein excretion (g/d)	3.4±2.8	3.3±2.7	3.4±2.8	0.90
Hematuira score	0.3±0.7	0.3±0.7	0.4±0.8	0.15
HbA1c (%)	6.8±1.2	6.9±1.2	6.8±1.3	0.62
Hemoglobin (g/dL)	10.1±1.7	10.2±1.6	10.0±1.8	0.38
Total cholesterol (mg/dL)	197.4±57.3	198.3±53.7	195.9±63.1	0.56
Triglycerid (mg/dL)	159.4±102.5	168.2±113.7	144.7±78.6	0.04
HDL cholesterol (mg/dL)	52.1±20.0	50.5±17.4	54.5±23.5	0.44
non HDL (mg/dL)	144.8±55.9	146.7±53.9	141.7±59.4	0.28
Uric acid (mg/dL)	7.8±5.0	7.2±1.5	8.7±7.8	0.0003
Follow-up SBP (mmHg)	139.2±12.4	139.3±10.8	139.1±14.8	0.61
Follow-up DBP (mmHg)	71.8±8.5	72.0±7.9	71.3±9.4	0.63
Use of statin (%)	38.5	35.3	38.5	0.20
Use of anti-UA agents (%)	28.3	30.7	24.5	0.29

*Hematuria score: U-RBC/HPF <5/HPF=0, 5-9/HPF=1, 10-29/HPF=2, 30-49/HPF=3, >50/HPF=4, macrohematuria=5,

Table 2. HRs for initiation of renal replacement therapy

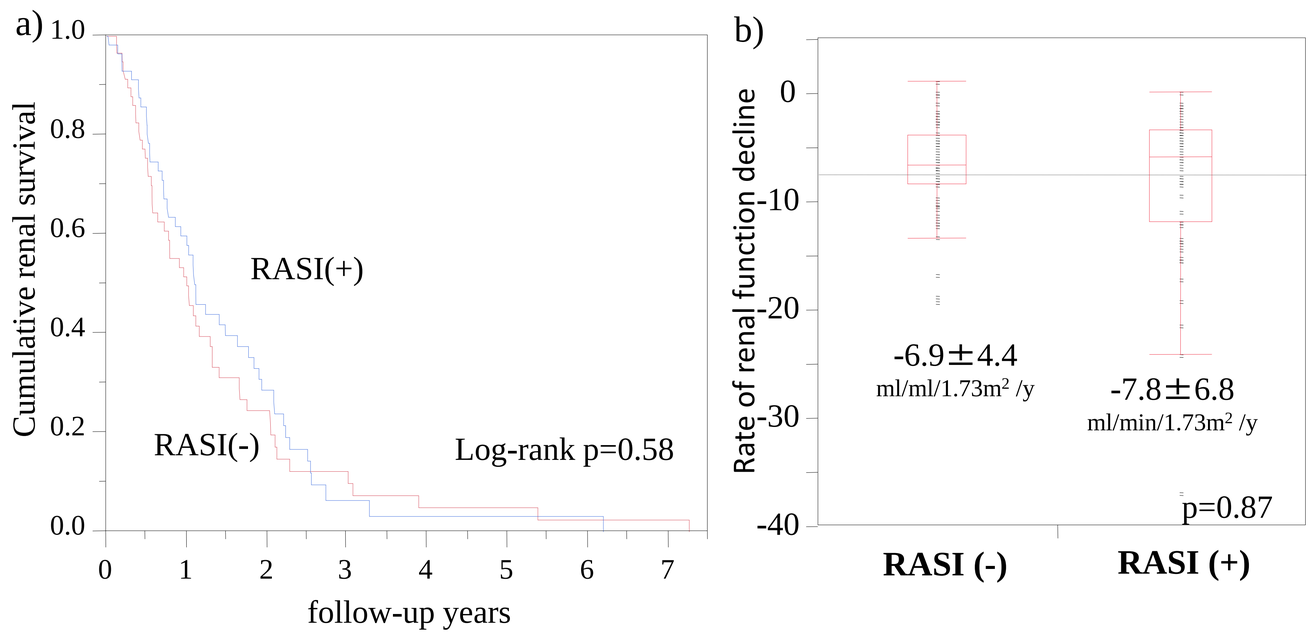
	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Gender (male vs female)	1.05	0.75-1.49	0.79	1.51	0.96-2.42	0.07
Age	0.99	0.97-0.99	0.004	1.01	0.99-1.03	0.31
BMI	1.02	0.98-1.06	0.38	0.97	0.92-1.01	0.14
Smoke (yes vs no)	1.07	0.79-1.44	0.65	1.21	0.84-1.74	0.30
History of CVD (yes vs no)	0.90	0.64-1.25	0.54	0.93	0.63-1.37	0.73
eGFR (ml/min/1.73m^2)	0.85	0.82-0.88	<0.0001	0.86	0.82-0.89	<.0001
Urinary protein excretion (g/d)	1.17	1.10-1.23	<0.0001	1.14	1.06-1.23	0.0008
Hematuria score (<3 as refernce)	0.69	0.25-1.52	0.39	0.74	0.23-1.91	0.55
HbA1c	0.87	0.75-0.98	0.003	0.93	0.81-1.06	0.30
Hemoglobin	0.81	0.74-0.89	<0.0001	0.87	0.78-0.98	0.02
Total cholesterol	1.00	0.99-1.00	0.98			
Triglycerid	1.00	0.99-1.00	0.11			
HDL-cholesterol	1.00	0.99-1.00	0.99			
non HDL cholesterol	1.00	0.99-1.00	0.66	1.00	0.99-1.00	0.59
Uric acid	1.06	1.03-1.09	0.003	1.06	1.02-1.09	0.01
Follow-up data						
Systoric BP	1.03	1.02-1.04	<0.0001	1.03	1.01-1.04	0.002
Diastoric BP	1.04	1.02-1.06	<0.0001	1.03	1.01-1.06	0.01
Medication						
RASI (yes vs no)	0.60	0.45-0.81	0.001	0.97	0.68-1.40	0.89
Statin (yes vs no)	0.92	0.68-1.24	0.59	1.01	0.71-1.44	0.95
anti-UA agents (yes vs no)	0.90	0.64-1.24	0.52	0.84	0.56-1.24	0.40

Table 3. Propensity score- matched cohort

	RAS(+)	RAS(-)	p value
n	59	59	
Gender (%male)	72.9	78.0	0.52
Age (yrs)	66.2±10.1	68.5±10.7	0.74
BMI	25.0±4.4	24.5±4.6	0.76
History of CVD (%)	28.7	28.3	0.86
Smoke (%)	27.1	22.0	0.52
eGFR (ml/min/1.73m^2)	13.1±4.8	13.2±5.2	0.97
Urinary protein excretion (g/d)	3.3±3.0	3.5±2.8	0.57
Hematuira score	0.2±0.6	0.4±0.8	0.07
HbA1c (%)	6.7±0.9	6.8±1.2	0.83
Hemoglobin (g/dL)	10.1±1.9	10.1±1.8	0.8
Total cholesterol (mg/dL)	197.1±49.9	194.2±56.1	0.83
Triglycerid (mg/dL)	157.3±90.4	158.0±84.2	0.53
HDL cholesterol (mg/dL)	53.7±20.3	52.7±25.0	0.41
Non HDL (mg/dL)	143.7±51.7	141.5±54.1	0.64
Uric acid (mg/dL)	7.2±1.5	7.7±1.4	0.73
Follow-up SBP (mmHg)	140.8±10.7	140.1±15.2	0.50
Follow-up DBP (mmHg)	71.9±7.1	70.9±8.5	0.57
Use of statin (%)	62.7	56.7	0.57
Use of anti-UA agents (%)	23.7	27.1	0.12

Ajusted with gender, age, BMI, History of CVD, smoke, eGFR, Urinary protein excretion, HbA1c, Hemoglobin, Total cholesterol, Triglycerid, HDL cholesterol, Uric acid, follow-up SBP, follow-up DBP, use of statin and use of anti-UA agents.

Figure 1. renal outcome among RASI(+) and RASI(-) group



Summary

● Of 244 patients with CKD G4-5 diabetic nephropathy who admitted to our hospital for CKD education, 180 patients reached renal outcome.

●Univariate analysis showed that the hazard ratio of RRT initiation related to the administration of RAS inhibitors was 0.60 (95%CI: 0.45-0.81).

● However, multivariate analysis involving adjustment with clinical relevant factors showed that the hazard ratio of RRT initiation was 0.96 (95%CI 0.68-1.36): there was no efficacy of RAS inhibitors. On the other hand, follow-up systolic and diastolic BP and baseline urinary protein level and eGFR were shown to be significant factors.

●Furthermore, regarding renal survival, in propensity score-matched cohorts, non significant difference was observed between the RAS inhibitor-treated and non RAS inhibitor-treated patients. In addition, the rate of renal function decline was similar among two group (RASI+ and RASI-).

Discussion

● Most of clinical practice guideline recommend the use of RAS inhibitors in patients with diabetic nephropathy, because of their renoprotective effect, such as reducing intraglomerular pressure and proteinuria.

● Actually, RENAAL study showed that losartan, angiotensin II receptor antagonist , reduced the level of proteinuria and the renal outcome, doubling of serum creatinine by 25% and ESKD by 28%, in diabetic nephropathy [1)].

● However, in patients with advanced stage of CKD, the adverse effect, such as deterioration of renal function or hyperpotassemia due to the lowering intraglomerular pressure was sometimes observed. Therefore, RAS inhibitors should be carefully administrated in patients with advanced stage of CKD.

● Present study using a multivariate analysis or propensity score-matched cohort demonstrated that no efficacy of RAS inhibitors on diabetic nephropathy with advanced CKD. However, our study design is retrospective observational study, so that, we can not preciously refer to the efficacy of RAS inhibitors on advanced diabetic nephropathy.

Conclusion

In this study, analysis after multidisciplinary treatment for CKD indicated that the renal prognosis of diabetic nephropathy patients with advanced CKD was associated with the mean systolic blood pressure during the course, baseline urinary protein level, and eGFR; the efficacy of RAS inhibitors was not demonstrated.

References

(1) Brenner BM et al,Effects of losartan on renal and cardiovascular outcomes on patients with type 2 diabetes and nephropathy. NEJM 345: 861-9, 2001.
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