The effect of renin-angiotensin system blockades on renal protection in chronic kidney disease patients with hyperkalemia

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The effect of renin-angiotensin system blockades on renal protection in chronic kidney disease patients with hyperkalemia

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I would like to thank my parents and husband. They have always encouraged me with love.

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ABSTRACT

The effect of renin-angiotensin system blockades on renal protection in chronic kidney disease patients with hyperkalemia

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Background:

Renin-angiotensin system (RAS) blockades are widely used in patients with chronic kidney disease (CKD), however, hyperkalemia as an adverse effect remains an obstacle in this population. It is not clear whether maintenance of RAS blockade is beneficial in CKD patients with elevated potassium levels. The aim of this study was to determine the effects of RAS blockade maintenance on renal protection in CKD patients with hyperkalemia occurred during treatment with RAS blockade.

Methods:

CKD III or IV patients, who were prescribed with RAS blockers and accompanied with hyperkalemia, were included. The study population was

divided into two groups based on maintenance or withdrawal of RAS blocker. Renal outcomes (doubling creatinine or progression to ESRD) and incidence of hyperkalemia were compared between the two groups.

Results:

Out of 258 subjects who were developed hyperkalemia during the treatment with RAS blockers, 150 (58.1%) patients continued RAS blockades, while RAS blockades were discontinued for more than 3 months in the remaining 108 patients. Renal event-free survival was significantly higher in the maintenance group compared to the withdrawal group (p=0.04). Cox proportional hazard ratio for renal outcomes was 1.35 (95% CI; 1.08-1.92, p=0.04) in the withdrawal group compared to the maintenance group. In addition, prognostic significance was much greater in subgroup of patients with urine protein to creatinine ratio above 1.0 mg/mg (p=0.02). However, the incidence of hyperkalemia and hyperkalemia-related hospitalization or mortality during the follow up period did not differ between the two groups.

Conclusion:

This study demonstrated that the maintenance of RAS blockade is beneficial for preservation of renal function and relatively tolerable in CKD patients with hyperkalemia occurred during treatment with RAS blockade.

Key words : renin-angiotensin blockade, hyperkalemia, renal outcomes

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I. INTRODUCTION

The renin-angiotensin system (RAS) plays an important role in the pathogenesis and progression of chronic kidney disease (CKD). Numerous studies have reported that activation of the intra-renal RAS contributes to glomerular hypertrophy, mesangial expansion, and glomerulosclerosis in various renal diseases[1]. Previous clinical and experimental studies have demonstrated that inhibition of RAS using angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) results in reduction in proteinuria and retards progression of renal disease in addition to lowering blood pressure. Even in normotensive or well-controlled hypertensive patients with CKD, the use of RAS blockade resulted in reduction in proteinuria and might be beneficial in the preservation of renal function[2-8]. However, RAS

blockade is frequently associated with several adverse events, including angioedema, dry cough, hyperkalemia, and aggravation of the underlying renal insufficiency[9]. In particular, the incidence of hyperkalemia is increased in patients with reduced GFR and limits the use of RAS blockade in patients with advanced CKD[10]. If serum potassium level increases above 5.5 mmol/L during use of the RAS blockade, discontinuation of the RAS blockade should be considered with management of hyperkalemia such as by prescription of low potassium diet, thiazide or loop diuretics, and correction of metabolic acidosis[11,12]. However, there are different approaches to cope with RAS blockers according to physicians' preferences and decisions. A practical strategy for maintaining RAS blockade is needed not only for control of blood pressure, but also to delay the progression of CKD. In order to maintain the blocking effect of RAS, ACEi or ARB were frequently maintained in CKD patients with elevated potassium levels. Still, it is not clear whether or not maintenance of RAS blockade is beneficial in CKD patients with elevated potassium levels.

I examined renal outcomes (doubling creatinine or progression to ESRD) in order to determine the effect of RAS blockade maintenance in patients with CKD stages III and IV who had developed hyperkalemia during use of RAS blockade. In addition, I evaluated the impact of maintenance with RAS blockade on hyperkalemia in this population.

II. MATERIALS AND METHODS

This study was approved by the Institutional Review Board (IRB) of Yonsei University Health System Clinical Trial Center. This study was a retrospective medical record-based study and the IRB waived the requirement for written consent from the patients.

1. Study subjects

Patients with stage III or IV CKD, prescribed ACEi or ARB and accompanied with hyperkalemia during use of RAS blockade, were included in this study. We initially recruited 2124 patients who were followed up for CKD at Yonsei University Health System from July 2008 to December 2011. ACEis or ARBs were prescribed to 1239 patients, and 351 patients developed hyperkalemia during treatment with the RAS blocker. Of these patients, 83 patients were excluded for the following reasons: age younger than 18 years or older than 75 years, terminal malignancy, previous history of kidney transplantation, and follow-up duration of less than 12 months. Patients whose serum creatinine and potassium levels at baseline or during the follow-up period were not available, or who were transiently discontinued RAS blockers less than 3 months were also excluded. Therefore, a total of 258 patients were included for final analysis (Figure 1).

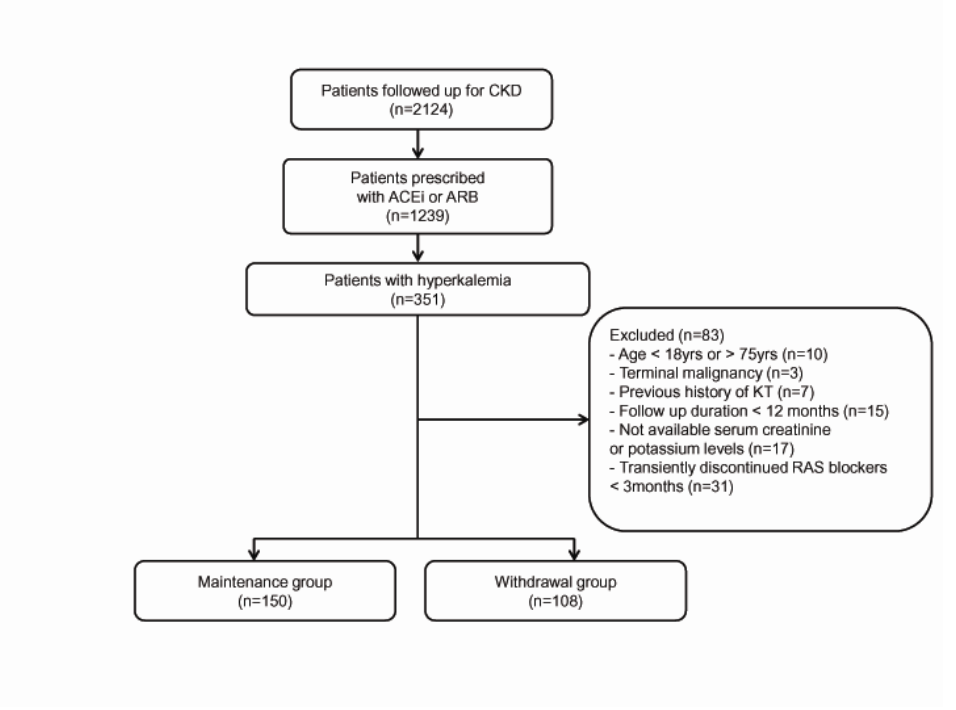


Figure 1. Flow diagram of the study. A total of 351 patients developed hyperkalemia during treatment with RAS blockers. Excluding 83 patients, a total of 258 patients were enrolled for final analysis. CKD, chronic kidney disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; KT, kidney transplantation.

2. Data collection

Using medical records, demographic and clinical data from medical records were reviewed retrospectively for age, sex, medical history, medications, time to doubling of baseline serum creatinine levels and ESRD, and history of admission after study enrollment. Laboratory data included urinary protein-to-creatinine ratio (PCR) and serum creatinine, and potassium levels. The four-variable Modification of Diet in Renal Disease study equation was used for calculation of the estimated glomerular filtration (eGFR).

3. Definitions

CKD was defined as an estimated GFR of less than 60 mL/min/1.73m^2 and hyperkalemia was defined as potassium $\geq$ 5.5 mmol/L in a non-hemolyzed serum sample. Patients with hyperkalemia that occurred after initiation of renal replacement treatment were not included in the study. When hyperkalemia developed during treatment with RAS blockade, three kinds of clinical practice patterns were recognized contingent on the maintenance of RAS blockade, 1) discontinuation of RAS blockade, 2) reduction, or 3) maintenance of doses of RAS blockade with supportive management for potassium reduction. Patients were categorized as the maintenance group if they were maintained on RAS blockade without discontinuation of the drugs, and as withdrawal group if RAS blockade had been discontinued for >3 months after development of hyperkalemia.

4. Outcome endpoints

The main outcomes were a doubling of baseline serum creatinine concentration and ESRD. ESRD was defined as initiation of renal replacement therapy, including permanent hemodialysis, peritoneal dialysis, or renal transplantation. In addition, incidences of hyperkalemia and hyperkalemia-related hospitalization were also evaluated during follow-up period.

5. Statistical analysis

SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis. Continuous variables were expressed as mean ± standard deviation and categorical variables are expressed as percentages. T-test and chi-square test were used for comparison of the two groups. The Kolmogorov-Smirnov test was used for analysis of normality of the distribution of parameters. Cumulative renal survival curves were derived using the Kaplan–Meier method, and differences between survival curves were compared using the log-rank test. Multivariate Cox proportional hazards models were used for determination of the risk factors for renal outcomes. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the estimated regression coefficients and standard errors in the Cox regression analysis. A p-value <0.05 was considered statistically significant.

III. RESULTS

1. Baseline characteristics

The baseline demographic, clinical and biochemical data of study subjects are shown in Table 1. The mean age of patients was 61.8 ± 14.5 years, and 145 (56%) patients were male. The mean eGFR and urinary protein to creatinine ratio (PCR) were 29.0 ± 13.1 mL/min/1.73m^2 and 2.3 ± 3.0 mg/mg, respectively. Based on maintenance of RAS blocker, 150 (58.1%) of 258 patients were maintained RAS blockade, however, 108 patients were discontinued for more than three months. There were no significant differences in underlying renal diseases, serum potassium levels, eGFR, or urine PCR at baseline between the two groups.

Table 1. Baseline demographic, clinical, and biochemical characteristics of the subjects

	Maintenance group (n = 150)	Withdrawal group (n = 108)	p
Age (years)	61.8 ± 14.8	60.3 ± 13.2	0.82
Gender (Male : Female)	82 : 68	63 : 45	0.38
Diabetes mellitus, *n* (%)	72 (48.0%)	49 (45.4%)	0.46
Systolic blood pressure (mmHg)	133.5 ± 21.8	132.9 ± 18.9	0.96
Diastolic blood pressure (mmHg)	74.9 ± 14.2	78.9 ± 8.4	0.16
Total cholesterol (mg/dL)	187.0 ± 44.4	173.9 ± 55.2	0.39
Serum potassium (mmol/L)	5.79 ± 0.38	5.77 ± 0.48	0.44
tCO2 (mmol/L)	20.8 ± 4.7	20.2 ± 5.2	0.15
Albumin (g/dL)	3.8 ± 1.1	3.7 ± 0.7	0.81
BUN (mg/L)	39.6 ± 17.6	34.5 ± 15.7	0.12
Creatinine (mg/dL)	2.4 ± 1.2	2.3 ± 1.2	0.83
eGFR (ml/min/1.73m^2)	28.3 ± 13.2	30.1 ± 12.9	0.23
Urine PCR (mg/mg)	2.5 ± 3.0	2.0 ± 2.4	0.66
Primary renal disease			
Diabetic nephropathy	65 (43.3%)	46 (42.6%)	
Hypertensive nephrosclerosis	24 (16.0%)	18 (13.0%)	0.61
Chronic glomerulonephritis	36 (24.0%)	24 (22.2%)	
Others	25 (16.7%)	20 (18.5%)	

Data are expressed as n (%) or mean ± SD. eGFR, estimated glomerular filtration rate; PCR, protein to creatinine ratio.

2. Renal outcomes

During a mean follow-up period of 45.7 ± 18.3 months, 129 (50%) patients reached to the primary outcome. ESRD or doubling of serum creatinine occurred in 68 (63%) of the patients in the withdrawal group compared to 61 (41%) patients in maintenance group. Renal survival rate was significantly higher in maintenance group compared to withdrawal group ($p=0.04$, hazard ratio in withdrawal group: 1.35, 95% CI; 1.08-1.92). In subgroup analysis based on the levels of baseline proteinuria, prognostic significance between two groups was much greater in subgroup of patients with urine PCR above 1.0 ($p=0.02$, Figure 2).

In multivariate Cox proportional hazard models, use of RAS blockers still remained a significant prognostic factor for renal survival. However, after adjusting for baseline proteinuria (HR; 1.028, $p<0.01$) and baseline GFR (HR; 1.248, $p<0.01$), the significance of the RAS blocker maintenance as a predictor of renal progression disappeared (HR; 1.135, CI; 0.937-1.546, $p=0.17$, Table 2).

Figure 2-(A)

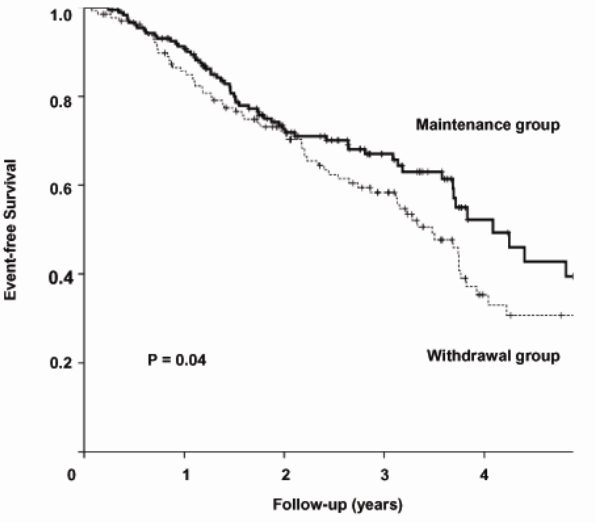
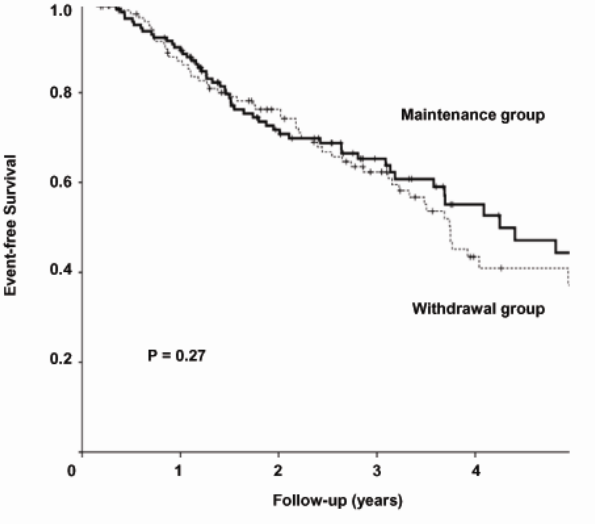


Figure 2-(B)



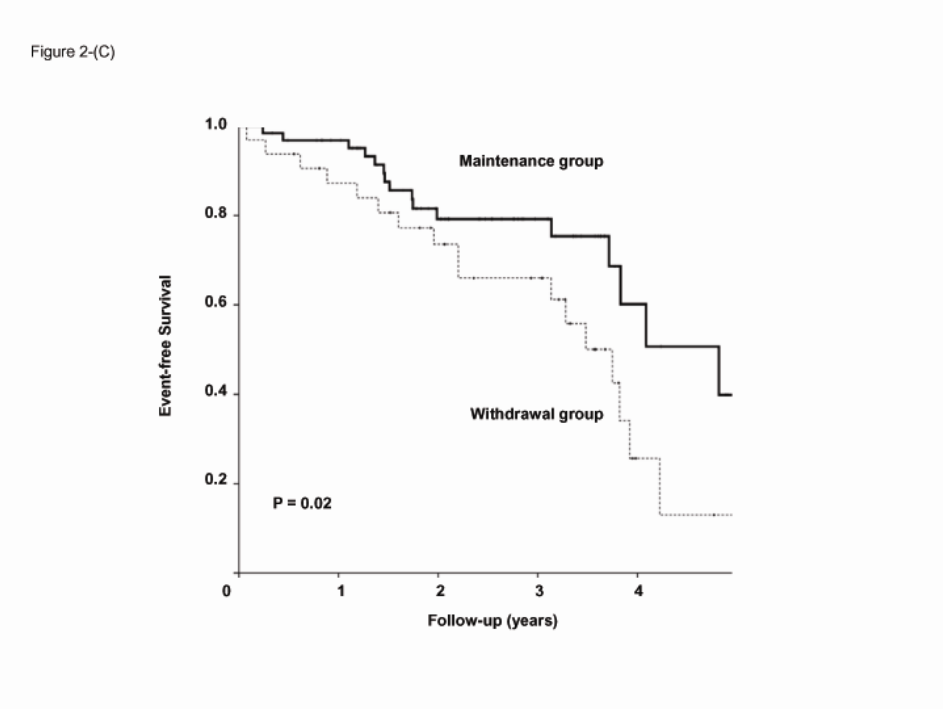


Figure 2. Kaplan-Meier plots for renal event-free survival based on the maintenance of RAS blockers including (A) all study subjects, (B) patients with baseline urine PCR ratio of less than 1, (C) patients with baseline urine PCR ratio of more than 1. The cumulative renal event-free survival was significantly higher in patients maintained with RAS blockers.

Table 2. Hazard ratios and 95% confidence intervals for renal survival based on treatment with RAS blockade (Cox proportional hazards analysis)

	HR (vs. RAS blockade use)	95% CI	p
[1]Model 1	1.35	1.08-1.92	0.04
[2]Model 2	1.48	1.05-2.10	0.03
[3]Model 3	1.135	0.937-1.546	0.17

[1]Model 1: unadjusted relative risk; [2]Model 2: adjusted for age, sex; and original renal disease [3]Model 3: adjusted for Model 2 plus MDRD-GFR and urine protein/creatinine ratio.

3. Incidence of hyperkalemia

Baseline potassium levels were 5.79 ± 0.38 mmol/L vs. 5.77 ± 0.48 mmol/L in maintenance and withdrawal group. During the follow up period, 0.58 episodes per patient year of hyperkalemia occurred in maintenance group, and 0.47 episodes per patient year of hyperkalemia were developed per patient year in withdrawal group (p=0.19). In addition, neither hyperkalemia-related hospitalizations nor mortality differed between the two groups (0.18 episodes per patient-year vs. 0.14 episodes per patient-year, p=0.42).

IV. DISCUSSION

This study demonstrated that maintenance of RAS blockade is beneficial for preservation of renal function, even in hyperkalemic CKD patients treated with RAS blocker. In addition, cautious use of RAS blockade does not lead to a significant increase in episodes of hyperkalemia in CKD patients, who develop hyperkalemia during treatment with ACEi or ARB.

Based on previous reports, long-term blockade of renin angiotensin aldosterone system (RAAS) by ACEis or ARBs resulted in increased levels of plasma renin or angiotensin II[13]. In addition, occurrences of aldosterone breakthrough has been also reported during long-term ARB therapy, mainly by angiotensin-II-dependent mechanisms[14]. Since renin or angiotensin II levels are already elevated in conditions of chronic blocking of RAS, it is possible that renal failure and hypertension might be aggravated due to the abrupt disappearance of RAS blocking effect. Blocking of RAS might be maintained in order to prevent rebound hypertension and progression of renal failure. My data support that maintenance of RAS blockade, rather than withdrawal is beneficial for preservation of renal function in CKD patients accompanied by hyperkalemia during treatment with RAS blockade.

Renoprotective effect of RAS blocker was much more prominent in the subgroup with baseline urinary PCR of more than 1 mg/mg. This finding is consistent with previous studies, indicating an association of higher urinary protein excretion rate with a rapid decline in renal function[8], and ACEi has a

distinguishable renoprotective effect in patients with baseline proteinuria more than 3g/day[3]. Present result suggests that maintenance of RAS blockade should be considered in highly proteinuric CKD patients.

In patients with CKD, development of hyperkalemia frequently occurred due to various causes such as reduced renal excretion of potassium or metabolic acidosis[15-17]. Besides discontinuation of RAS blockade, various approaches should be considered. Potassium imbalance might be treatable by restricting potassium intake and correction of underlying causes, while maintaining treatment with the RAS blockade. A previous study showed that most of patients with hyperkalemia were resolved with either a low-potassium diet alone or with dietary advice and a decrease in the dose of ACEi[18]. Although the incidences of hyperkalemia after treatment with ACEi or ARB in CKD patients were highly variable, clinical trials showed that prolonged use of RAS blockade did not lead to an increase in additional episodes of hyperkalemia in CKD patients. In addition, another study conducted in CKD population reported no significant difference in the overall mortality rate among patients on ACEi/ARB therapy compared to patients on placebo or conventional anti-hypertensive drugs[3,4,7,19]. Present study also demonstrated that the incidence of hyperkalemia as well as hyperkalemia-related hospitalizations in study subjects was similar in both groups whether RAS blockade has been maintained. Therefore, maintenance of RAS blocker with careful monitoring rather than only discontinuing RAS blockade could be applied.

This study has several limitations. Because the study design is retrospective, this study may include sampling errors. However, due to safety and ethical issues, it would be difficult to conduct a prospective study using RAS blockade in CKD patients who have hyperkalemia. Thus, in spite of the retrospective nature of the current study, we think that the study results are still valuable. Second, even though other drugs and conditions may have had an influence on serum potassium levels including dietary potassium intake, were not evaluated. Therefore, further large scaled analysis is needed to confirm the risk and benefit of RAS blockade in this special population.

V. CONCLUSION

In conclusion, the renoprotective effects of RAS blockade in CKD patients with hyperkalemia have disappeared after withdrawing RAS blockade. The results of the current study suggest that maintenance of the RAS blockade retards the progression of renal failure, and those beneficial effects are more prominent in proteinuric CKD patients. In addition, ACEi/ARB is well tolerated in stage III or IV CKD patients with hyperkalemia occurring during treatment with RAS blockade.

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ABSTRACT (IN KOREAN)

레닌-안지오텐신계 차단제 사용 후 고칼륨혈증이 발생한 만성 신질환 환자에서 레닌-안지오텐신계 차단제의 신기능 보존 효과

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배경

레닌-안지오텐신계 차단제는 만성 신질환 환자에서 널리 사용되고 있으나, 레닌-안지오텐신계 차단제 사용 후 발생하는 고칼륨혈증은 레닌-안지오텐신계 차단제 사용에 제한이 되고 있다. 고칼륨혈증이 발생한 만성 신질환 환자에서 레닌-안지오텐신계 차단제를 유지하는 것이 신기능 보존에 미치는 효과에 대해서는 보고된 바가 없다. 본 연구는 레닌-안지오텐신계 차단제 사용 후 고칼륨혈증이 발생한 만성 신질환 환자에서 레닌-안지오텐신계 차단제 사용의 효과를 확인하고자 하였다.

방법

만성 신질환 3기 또는 4기의 환자중에서, 레닌-안지오텐신계 차단제 투약 후 고칼륨혈증이 발생된 환자가 대상군에 포함되었다. 대상환자를 레닌-안지오텐신계 차단제의 유지 여부에 따라 유지한 군과 중단한 군으로 분류하여 비교하였다. 고칼륨혈증이 발생한 시점의 혈중 크레아티닌과 비교하여 혈중 크레아티닌이 두 배 이상 증가하는 시점까지의 기간, 또는 고칼륨혈증이 발생한 시점부터 신 대체 요법을 시작한 시점까지의 기간을 primary end point로 정의하였으며, 각 군에서의 신 생존율을 비교하였다.

결과

레닌-안지오텐신계 차단제 투약 중 고칼륨혈증이 발생한 258명 중, 레닌-안지오텐신계 차단제를 유지한 군은 150 명이었으며, 3개월 이상 중단한 군은 108 명이였다. 신 생존율은 차단제를 유지한 군과 비교하여 중단한 군에서 의미있게 낮았다 (p=0.04). 콕스 비례위험 회귀모형에서 유지한 군에 비하여 중단한 군에서 primary end point에 도달한 위험비는 1.35 였다 (95% 신뢰구간; 1.08-1.92, p=0.04). 연구 시작 당시의 단회뇨 단백/크레아티닌 비가 1.0 mg/mg 이상인 경우, 양 군간에 신 생존율은 뚜렷한 차이를 보였다 (p=0.02).

그러나, 고칼륨혈증에 의한 입원율과 사망률은 양군간에 의미있는 차이가 없었다.

결론

레닌-안지오텐신계 차단제 사용 후 고칼륨혈증이 발생한 만성 신질환 환자에서 레닌-안지오텐신계 차단제를 지속하는 것이 추가적인 고칼륨혈증의 위험도를 증가시키지 않으면서, 신 생존율을 의미있게 향상시켰다.

핵심되는 말: 레닌-안지오텐신계 차단제, 고칼륨혈증, 신 생존율