DOCTORAL THESIS

Role of renin-angiotensin system inhibitors in retardation of progression of end-stage renal failure: a retrospective study

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ORIGINAL ARTICLE

Role of renin–angiotensin system inhibitors in retardation of progression of end-stage renal failure: a retrospective study

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Abstract
Background Few studies have examined how renin–angiotensin system inhibitors (RASI) delay dialysis initiation in patients with advanced chronic kidney disease (CKD). We conducted a retrospective survey to examine this subject.
Methods We reviewed the records of patients with advanced CKD for the 60-month period before dialysis initiation between 1990 and 2015. Patients were classified based on the decade of dialysis initiation into the 1990s, 2000s, and 2010s groups. The rates of antihypertensive medications administered were assessed. The rate of decline of renal function was evaluated by the slope of reciprocal serum creatinine (SRSC). Multiple regression analyses were conducted to evaluate factors contributing to renoprotection.
Results The duration of RASI administration was longer in the 2010s than in 2000s and 1990s. Both diabetic and non-diabetic patients had lower SRSC in the 2010s compared to the 2000s. In the 2010s, the rate of RASI administration during the 60-month pre-dialysis period showed an initial rise followed by a downward trend, although the rates of administration of the other classes of antihypertensives increased continuously. Multivariate regression analyses identified age, blood pressure, diuretics, α-blockers, α-methyldopa and RASI as independent predictors of SRSC in the 2010s. The rate of RASI administration correlated with serum potassium concentration.
Conclusion Our findings suggest that in the 2010s, RASI with other antihypertensive agents contributed to renoprotection in advanced CKD patients, but they were underused because of the concern over hyperkalemia. In real-world clinical practice, physicians may feel great hesitation in using RASI in patients with advanced CKD.

Keywords Renin–angiotensin system inhibitors · End-stage renal failure

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Introduction

Renin–angiotensin system (RAS) inhibitors (RASI) comprising angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) have been available for more than 30 years, and both show potent antihypertensive effects. In 1985, Taguma et al. [1] reported that ACEI decreased urinary protein excretion even in patients with impaired renal function. Since then, a large number of studies [2–4] demonstrated that RASI not only have renoprotective effects including decreasing urinary protein excretion, but also other organ protection effects such as inhibiting myocardiac hypertrophy and remodeling in hypertensive patients with advanced chronic kidney disease (CKD). However, physicians (at least in Japan) had been reluctant to use these medications in hypertensive patients with advanced CKD, because of the pharmacologic effects of RASI to increase serum potassium levels and decrease renal blood flow if patients have

advanced renal insufficiency [5] or bilateral renal artery stenosis [6]. This trend has changed since around the 2000s with the availability of several new ARBs that show favorable effects on renoprotection. Consequently, major guidelines for hypertension management [7, 8] have recommended prioritized use of RASI in those patients.

More than one decade has passed since a flurry of RASI was released for hypertensive patients with CKD, but few studies have reviewed to what extent the RASI contribute to renoprotection in patients with advanced CKD and delay long-term dialysis therapy. Therefore, studies are crucial to verify whether the renoprotective effects of RASI really lead to better preservation of kidney function. We performed a retrospective study by reviewing the medical records prior to dialysis initiation of patients with advanced CKD during the last 26 years. We examined first, how often RASI were used in those patients before they eventually received dialysis therapy; second, whether there are differences in retardation of renal failure among the decades; and third, which factors play more important roles in renoprotection.

Materials and methods

Patient selection

In the present retrospective cohort study, we reviewed patients with end-stage renal failure who had accurate medical records for at least 24 months and up to 60 months prior to the initiation of hemodialysis therapy between January 1990 and March 2015. To unmask referral bias, patients in four hospitals were enrolled in the study. Patients were categorized as diabetic or non-diabetic based on whether they had a documented diagnosis of diabetes at baseline. The clinical definition of diabetes included fasting serum glucose concentration $\geq$126 mg/dL, hemoglobin A1c $\geq$6.5 %, and use of oral hypoglycemic medication or insulin. Patients who did not fulfill any of the diabetes criteria were classified as non-diabetic. Non-diabetic CKDs included nephrosclerosis, glomerulonephritis, and autosomal dominant polycystic kidney disease. Nephrosclerosis was diagnosed if a patient had a history of hypertension or receiving antihypertensive medicines but was not diagnosed with diabetes. Chronic glomerulonephritis was diagnosed by biopsy-based pathologic findings. Autosomal dominant polycystic kidney disease was diagnosed based on the family history and presence of polycystic kidneys. Patients with malignant diseases and acute renal failure were excluded. The mean values obtained 24 months prior to dialysis initiation were used as baseline data.

All patients were classified based on the time of dialysis initiation into three groups: 1990s (from 1990 to 1999), 2000s (from 2000 to 2009), and 2010s (from 2010 to 2015). The study protocol was approved by the ethical committees of each participating institution.

Evaluation of the rate of progression to end stage renal failure

The rate of progression to end-stage renal failure was expressed by the slope of reciprocal serum creatinine levels, as an accurate measure of the rate of decline of renal function. The slope was calculated by linear regression analysis of 1/serum creatinine versus time in each patient, and the data were compared among three decades.

Treatment pattern of antihypertensive medications

Treatment patterns were assessed by the rates of administration of antihypertensive medications every 6 months between 60 and 12 months, and every 3 months between 12 and 0 month before dialysis initiation. Patients who took ACEIs or ARBs or both were defined as the RASI group. If patients received antihypertensive medications, the exact duration of each medication was reviewed. Patients who received an antihypertensive medication for more than one-half of each period of study were classified as user of that medication.

Multiple regression analyses

Multiple regression analyses were conducted to evaluate which clinical factors contributed to renoprotection. The multivariate model consisted of the slope of reciprocal serum creatinine as the dependent variable and other potential confounding predictors as independent variables, including age, gender, diabetes, hemoglobin, serum potassium, serum calcium, serum phosphate, systolic and diastolic blood pressure, and durations of antihypertensive medication including diuretics, calcium channel blockers (CCB), α-blockers, β-blockers, α-methyldopa, and RASI.

Comparison between RASI administration and serum potassium concentrations

The correlation between RASI administration and serum potassium concentration during 60 months before the initiation of dialysis therapy was analyzed.

Statistics

Data are expressed as mean ± SD. Clinical and laboratory data were compared between two groups by independent *t* test. Clinical and laboratory data were compared among the three decades by ANOVA followed by Tukey's post

hoc test. Categorical data were compared between two groups by χ^2 test for paired samples. The correlation between two parameters was calculated based on Pearson's correlation analysis. Multivariate regression analyses were used to determine the contribution of the variables to the slope of reciprocal serum creatinine levels. A p value less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 23 (SPSS, Chicago, IL, USA).

Results

Demographic and baseline characteristics in all patients enrolled and comparison of parameters among three decades

We screened 601 Asian patients in four hospitals, who initiated dialysis therapy between January 1990 and March 2015. Among those screened, 301 patients aged from 18 to 91 years with medical records for periods of longer than 24 months before dialysis initiation were enrolled in this study cohort. The demographics and baseline clinical characteristics for the patients are summarized in Table 1. Patient age at initiation of dialysis therapy and the rate of diabetes were the highest in the 2010s. There were no differences in hemoglobin and serum creatinine, potassium, calcium and phosphate concentrations in the three groups. The slope of reciprocal serum creatinine was the lowest in the 2010s (Table 1; Fig. 1). Systolic and diastolic blood pressure were lower in the 2000s and 2010s than in the 1990s. The durations of diuretic, CCB and RASI administration increased in chronological order. The duration of α-blocker administration was longer in the 2000s than that in the 1990s. The use of β-blockers increased after 2000, but there were no differences in duration of α-methyldopa administration among the three decades.

Comparison of the slope of reciprocal serum creatinine levels in diabetic and non-diabetic patients

In diabetic patients, the mean slope of reciprocal serum creatinine during the predialysis period of 60 months in the

Table 1 Demographic and clinical baseline characteristics of the study population and comparison of groups classified into decades according to the time of dialysis initiation

	All patients	Grouping by decade			P
		1990s	2000s	2010s	
Number	301	96	126	79	
Age (years) at dialysis initiation	68.0 ± 13.7 (18–91)	64.9 ± 15.0	66.9 ± 13.2	73.3 ± 11.5[ab]	<0.01
Gender (male/female)	188/113	64/32	72/54	52/27	0.27
Number of diabetic patients (%)	125 (41.5 %)	28 (29.2 %)	58 (46.0 %)	39 (49.4 %)	0.01[c]
Hemoglobin (g/dL)	10.7 ± 1.9	11.1 ± 2.3	10.4 ± 1.9	10.8 ± 1.5	0.1
Serum creatinine concentrations (mg/dL)	3.1 ± 1.2	3.3 ± 1.4	3.0 ± 1.2	3.2 ± 1.0	
Serum potassium concentrations (mEq/L)	4.7 ± 0.7	4.8 ± 0.7	4.6 ± 0.7	4.7 ± 0.6	
Serum calcium concentrations (mg/dL)	8.8 ± 0.6	8.7 ± 0.9	8.8 ± 0.5	8.8 ± 0.6	0.41
Serum phosphate concentrations (mg/dL)	3.9 ± 0.7	4.0 ± 1.0	3.9 ± 0.7	3.8 ± 0.5	0.45
Slope of 1/creatinine/month (dL/mg/month)	0.0098 ± 0.0087	0.0099 ± 0.0033	0.0115 ± 0.0050	0.0068 ± 0.0033[ab]	<0.01
Systolic blood pressure (mm Hg)	145 ± 20	153 ± 23	140 ± 17[a]	143 ± 16[a]	<0.01
Diastolic blood pressure (mm Hg)	79 ± 12	85 ± 12	76 ± 10[a]	75 ± 11[a]	<0.01
Duration of antihypertensive administration during 60 months before dialysis initiation (months)					
Diuretics	19.7 ± 20.0	14.3 ± 18.2	19.3 ± 20.7	20.3 ± 21.1[a]	0.03
Calcium channel blockers	29.0 ± 22.3	16.3 ± 17.0	29.0 ± 24.1[a]	37.5 ± 22.0[ab]	<0.01
α-Blockers	8.3 ± 15.0	4.9 ± 10.4	10.6 ± 18.3[a]	7.5 ± 15.0	<0.01
β-Blockers	9.1 ± 17.6	2.5 ± 7.3	11.8 ± 19.8[a]	11.0 ± 19.8[a]	<0.01
α-Methyldopa	2.2 ± 8.1	1.8 ± 7.0	1.2 ± 5.2	2.3 ± 8.8	0.41
RASIs	21.3 ± 23.3	4.5 ± 10.7	26.2 ± 26.2[a]	40.8 ± 28.5[ab]	<0.01

Baseline data are mean values obtained 24 months prior to dialysis initiation, unless specified otherwise

RASI renin angiotensin system inhibitor

[a] Significant difference vs. the 1990s using Tukey's test

[b] Significant difference vs. the 2000s using Tukey's test

[c] χ^2 test

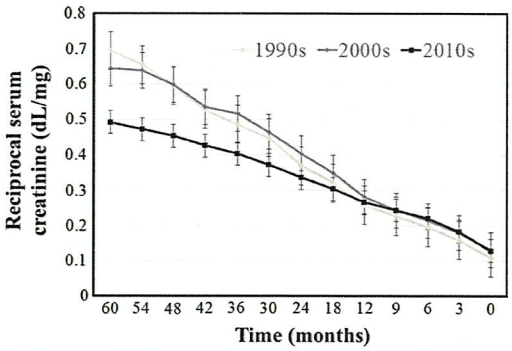

Fig. 1 The slope of reciprocal serum creatinine concentrations during 60 months prior to initiation of dialysis therapy in patients classified into three decades

2010s was 0.0078 ± 0.0038 dL/mg/month, which was lower ($P < 0.01$) than 0.0151 ± 0.0144 dL/mg/month in the 2000s and 0.0162 ± 0.0149 dL/mg/month in the 1990s (Fig. 2a). In non-diabetic patients, the slope of reciprocal serum creatinine in the 2010s was 0.0058 ± 0.0023 dL/mg/month, which was lower ($P = 0.02$) than 0.0086 ± 0.0068 dL/mg/month in the 2000s but not significantly ($P = 0.17$) different from 0.0077 ± 0.0046 dL/mg/month in the 1990s (Fig. 2b).

The administration rates of various antihypertensive drugs

Six different classes of antihypertensive medications comprising RASI, CCB, diuretics, α-blockers, β-blockers and centrally acting drugs (α-methyldopa) were used. The proportions of patients administered antihypertensive drugs during 60 months before dialysis initiation are shown in Figs. 3, 4 and 5. In the 1990s (Fig. 3), diuretics and CCB were predominantly used throughout 60 months before dialysis. These two classes of antihypertensive were used in almost 75 % of the patients at around 6 months before dialysis. The remaining antihypertensive drugs increased in use by some 10 % at around 24 months and were maintained at steady levels until 3 months prior to dialysis initiation. Uses of all six classes of drugs decreased at the time of dialysis initiation.

In the 2000s (Fig. 4), RASI and CCB were the most common antihypertensive drugs used during the earlier stage of renal disease. However, the rate of RASI administration declined gradually, whereas the rate of CCB prescription maintained a high level. Diuretics use increased progressively in line with progression of renal failure.

In the 2010s (Fig. 5), RASI were the most commonly administered medication at 60 months before initiation of dialysis. Although the proportions for most antihypertensive drugs increased steadily or at least maintained at similar levels with progression of CKD, only RASI showed an initial rise with an early peak at 36 months followed by a decline thereafter.

Multivariate regression analyses of clinical parameters and drugs associated with the slope of reciprocal serum creatinine

Multivariate regression analyses were conducted to identify predictors of the slope of reciprocal serum creatinine for each of the three decades (Table 2). The analyses identified serum calcium and phosphate as the only independent predictors in the 1990s. The independent predictors found in the 2000s were age, diabetes, serum

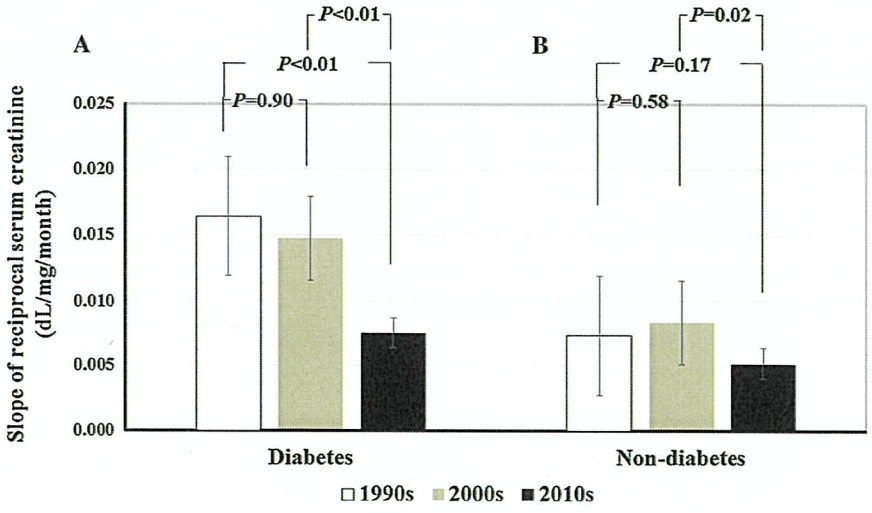

Fig. 2 Comparison of the slope of reciprocal serum creatinine concentration for three decades in diabetic patients (**a**) and non-diabetic patients (**b**). *White column* 1990s, *gray column* 2000s, *black column* 2010s

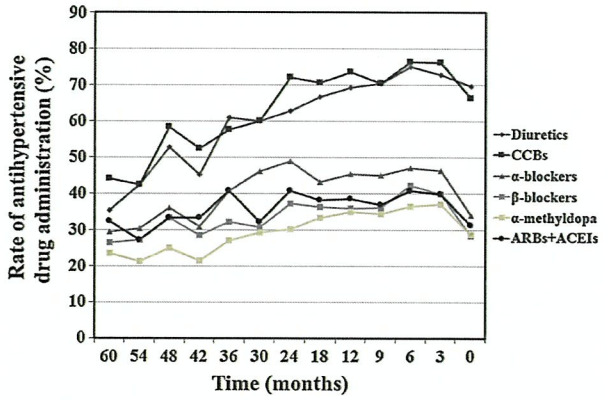

Fig. 3 The proportions of patients with advanced CKD administered various antihypertensive agents during 60 months before the initiation of dialysis treatment during the 1990s. *CCB* calcium channel blocker, *ARB* angiotensin II receptor blocker, *ACEI* angiotensin converting enzyme inhibitor

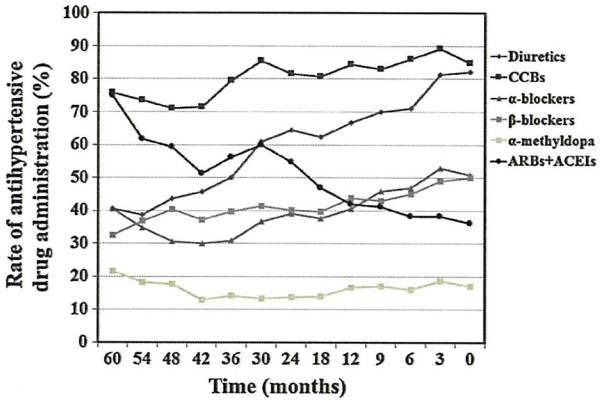

Fig. 4 The proportions of patients with advanced CKD administered various antihypertensive agents during 60 months before the initiation of dialysis treatment during the 2000s. *CCB* calcium channel blocker, *ARB* angiotensin II receptor blocker, *ACEI* angiotensin converting enzyme inhibitor

potassium and CCB. In the 2010s, the independent predictors identified were age, systolic and diastolic blood pressure, diuretics, α-blockers, α-methyldopa, and RASI.

Comparison between RASI administration rate and mean serum potassium concentration

The time course of serum potassium concentrations during the predialysis period of 60 months in all participants was parallel to that of the rate of RASI administration (Fig. 6), showing an initial increase until around 30 months prior to the start of dialysis followed by a decline thereafter. The rate of RASI administration correlated with mean serum potassium concentration ($P = 0.049$, $r = 0.55$).

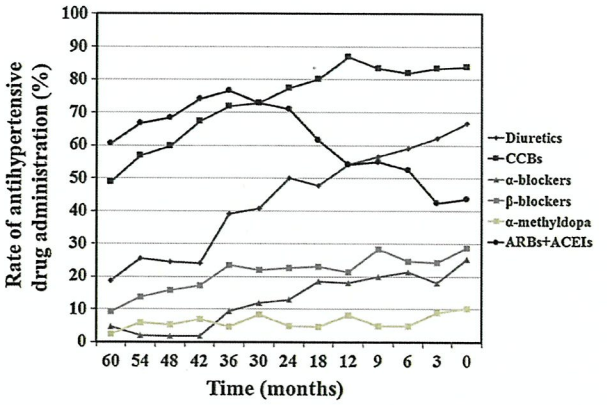

Fig. 5 The proportions of patients with advanced CKD administered various antihypertensive agents during 60 months before the initiation of dialysis treatment during the 2010s. *CCB* calcium channel blocker, *ARB* angiotensin II receptor blocker, *ACEI* angiotensin converting enzyme inhibitor

Discussion

In the present study of patients initiated on dialysis in four hospitals spanning three decades, we demonstrated that the duration of RASI treatment increased significantly over the decades. The slope of reciprocal serum creatinine levels, an index of renal impairment rate, was lower in the 2010s group than that in the 1990s and 2000s groups, showing the greatest retardation of renal function deterioration in the most recent decade. Accompanying this change, blood pressure was lowered over the decades, but serum potassium levels were not different among three decades. These findings suggest that in the 2010s, patients were initiated on dialysis at an older age, after a longer period of treatment for CKD and blood pressure control with RASI. This finding is consistent with a recent study reported by Hsu et al. [9].

Our chronological findings also demonstrated an increasing number of diabetic patients receiving dialysis therapy. Diabetic patients with advanced CKD often have cardiovascular complications and show rapid decline of renal function, requiring earlier dialysis therapy compared to non-diabetic patients [10]. This implies a possibility that the status of diabetes may have major impact on the progression of renal dysfunction. We therefore conducted further analyses by classifying patients into diabetic and non-diabetic for each decade. In patients with diabetes, the slope of reciprocal serum creatinine was significantly improved in the 2010s compared with the 1990s and 2000s. Even in patients without diabetes, the slope of reciprocal serum creatinine declined significantly in the 2010s compared with the 2000s. These results indicate that the significant improvement in the slope of reciprocal serum

Table 2 Multivariate regression analyses of clinical parameters and medications associated with the slope of reciprocal serum creatinine concentrations

Variables	Grouping by decade					
	1990s		2000s		2010s	
	Standardized β coefficient	*P*	Standardized β coefficient	*P*	Standardized β coefficient	*P*
Age	−0.038	0.75	0.301	<0.01	0.365	<0.01
Gender	−0.066	0.58	−0.161	0.10	−0.019	0.83
Rate of diabetes	−0.191	0.09	−0.318	<0.01	−0.108	0.26
Hemoglobin	−0.654	0.44	−0.433	0.41	−0.105	0.79
Serum potassium concentration	0.109	0.32	0.208	0.02	−0.036	0.67
Serum calcium concentration	−1.463	<0.01	0.599	0.06	0.268	0.39
Serum phosphate concentration	−2.119	<0.01	1.100	0.12	0.251	0.71
Systolic blood pressure	0.072	0.52	3.750	0.27	−0.374	<0.01
Diastolic blood pressure	0.038	0.79	5.366	0.25	0.309	0.01
Duration of drug administration						
Diuretics	0.109	0.39	0.146	0.18	0.218	0.03
Calcium channel blockers	0.160	0.23	0.224	0.03	0.171	0.09
α-Blockers	0.070	0.59	0.123	0.32	0.207	0.04
β-Blockers	−0.035	0.75	0.035	0.76	−0.046	0.62
α-Methyldopa	0.012	0.91	0.051	0.63	0.215	0.02
RASIs	−0.174	0.11	0.005	0.96	0.254	0.01

RASI renin–angiotensin system inhibitor

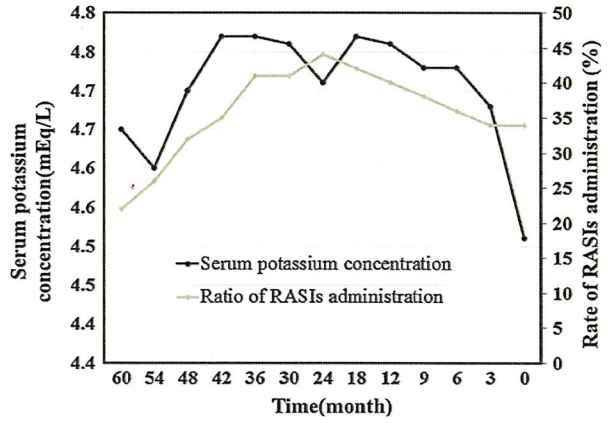

Fig. 6 Changes in the rate of RASI administration and serum potassium concentration during 60 months before the initiation of dialysis therapy. *RASI* renin angiotensin system inhibitor

creatinine observed in the most recent decade may be related to the longer duration of treatment with RASI, regardless of whether or not patients had diabetes.

As aforementioned, there was no difference in serum potassium level among the three decades, despite the increase in duration of RASI administration. Measures to control serum potassium level such as using potassium-binding resins and strict dietary support may have contributed to prevent hyperkalemia. However, we have no data in our survey on how many patients received resins. Therefore, this speculation remains to be proven.

Our chronological survey suggests that by increasing RASI use in patients with end-stage CKD, RASI could postpone the initiation of long-term hemodialysis treatment. However, these findings need to be considered with caution because of the diversity of patient background in different periods. Thus, we separated the whole data into three groups according to decade and analyzed all the clinical parameters by multiple regression. The results obtained in the three decades differed. In the earliest decade, serum calcium and phosphate were identified as the only independent predictors that correlated with reciprocal serum creatinine. Hyperphosphatemia is associated with accelerated vascular calcification and the development of arteriosclerosis [11]. This condition causes renal artery calcification and may result in decline of kidney function. In this decade, antihypertensive agents were not identified as independent predictor. Suboptimal use of antihypertensive agents resulting in inadequate control of blood pressure and lack of renoprotection may partially explain why antihypertensive agents were not predictors of renal function outcome. The role of antihypertensive agent as an independent predictor was demonstrated in the 2000s for CCB only. During this decade, the duration of administration of CCB was the longest among all antihypertensives, corresponding to a significant decrease in blood

pressure compared with the former decade. In the 2010s, the analyses identified not only age, systolic and diastolic blood pressure, but also antihypertensive agents including diuretics, α-blockers, α-methyldopa and RASI as independent predictors. There were no differences in blood pressure between the 2000s and 2010s, but the rate of renal function deterioration was improved in the 2010s compared to the 2000s. Among the antihypertensives identified as independent predictors, only RASI showed increased use in the 2010s. This infers that the pleiotropic effects of RASI other than blood pressure lowering may contribute to the decrease in renal impairment rate.

Our study showed that in the last two decades, RASI, CCB and diuretics have been the most preferentially used antihypertensive agents throughout the predialysis periods. However, the rate of RASI administration showed a different pattern from other agents. In the 1990s RASI administration rates were as high as those of α- and β-blockers as well as α-methyldopa, but lower than those of diuretics and CCB, suggesting that RASI were prescribed in moderation. In the 2000s, RASI were the most frequently used agent in the earlier stage of CKD, but their use declined in parallel with the deterioration of renal function. Then in the 2010s, the use of RASI increased initially with a peak at 36 months before dialysis initiation, followed by a downward trend. We demonstrated a parallel pattern between the rate of RASI administration and serum potassium concentration. These findings suggest that RASI might have been discontinued or administered at relatively low doses than the recommended dosages, which is followed by a decline in serum potassium level. Due to the concern over hyperkalemia, physicians possibly abstained from aggressive treatment with RASI [9, 12]. Consequently maximal renoprotective effect of RASI was not achieved.

On the other hand, there were no limitations in dosage for antihypertensive agents except RASI. The use of maximum dosages may contribute to better blood pressure control and renoprotective effects. The renal protective effects of antihypertensive agents other than RASI are obtained when the systemic blood pressure is substantially controlled [13, 14]. Consequently these classes of medications may have favorable effects on renal function. These factors may partially explain the association of the slope of reciprocal serum creatinine with RASI and other agents in the 2010s. Thus, strict blood pressure regulation by careful co-administration of RASI at a relatively low dose with other multiple antihypertensive drugs for a longer duration probably contributes to the retardation of renal dysfunction progression.

Our retrospective observational study has limitations compared with prospective trials. Since the assessment of antihypertensive medication data was based on physicians' records, compliance could not be determined. Besides, our study did not examine the dosages of individual agents in each class of antihypertensive. To minimize these biases, prospective randomized studies in patients with advanced CKD are essential to compare the findings with versus without RASI and other specified antihypertensive agents. However, such comparison would have ethical issues because of the risk of adverse effects including life-threatening hyperkalemia.

In conclusion, the present study revealed that although RASI use played an influential role in retarding the progression of renal failure, the rate of RASI administration declined when patients progressed toward advanced CKD. It is difficult to continue using RASI long-term for renoprotection in end-stage kidney disease because of the risk of hyperkalemia. In real-world clinical practice, physicians may feel great hesitation in using RASI in patients with advanced CKD.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest exists.

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論文目録

Ⅰ　主論文

Role of renin-angiotensin system inhibitors in retardation of progression of end-stage renal failure: a retrospective study

Tomoyuki Murakami, Tamio Iwamoto, Gen Yasuda, Michiko Taniguchi, Akira Fujiwara, Nobuhito Hirawa, and Satoshi Umemura: Clinical Experimental Nephrology Vol. 20, Page 603-610, 2016