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Inhibition of the Renin-Angiotensin System and Cardiovascular Mortality in Chronic Hemodialysis Patients

——RAS Inhibition and Mortality in Hemodialysis

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ABSTRACT

Introduction*:** *Since the outcomes associated with the use of renin-angiotensin-system inhibitors* (*RASi*) *by hemodialysis* (*HD*) *patients are not fully known*, *we investigated their effect on the cardiovascular mortality of chronic HD patients.* ***Methods*:** *Data from* 388 *HD patients* (237 *men and* 151 *women*) *who were routinely treated for at least 6 months were analyzed*. *Treatment with a RASi was the major predictor variable*. *The main outcome measure was cardiovascular mortality*. *Cox regression analysis was used to assess for the use of RASi and risk of death*. ***Results*:** *Hypertension was diagnosed in* 320 *patients* (82.5%), *and* 197 (50.8%) *of them were treated with a RASi* (*treated group*) *and* 191 (49.2%) *were not* (*untreated group*). *The treated group had a higher prevalence of hypertension*, *history of congestive heart failure*, *and presence of ST-T changes*. *Kaplan-Meier analysis revealed a reduction in risk of cardiovascular death in the treated group during the follow-up period* (Figure* 2**; *log-rank*: $p = 0.0379$). *The multivariate analysis showed that treatment with a RASi was also independently associated with reduced cardiovascular mortality* (*hazard ratio* = 0.184; $p = 0.0161$). ***Conclusions*:** *The results of this study suggest a possible association between the treatment with RASi and reduced risk of cardiovascular mortality*, *independent of their effect of lowering blood pressure.*

Keywords: *Renin-Angiotensin-System Inhibitors*, *Cardiovascular Outcomes*, *Hypertension*, *Hemodialysis*

1. Introduction

The high mortality rate of dialysis patients has been well documented by previous studies [1-2]. Cardiovascular diseases are responsible for about half of the deaths of patients with end-stage renal disease (ESRD) and are a major cause of mortality [3]. Hypertension may be the underlying cause of cardiovascular morbidity in hemodialysis (HD) patients [4]. Epidemiological studies in HD patients have suggested that low blood pressure (BP), not high is associated with all-cause mortality of dialysis patients [5-8]. Based on this paradoxical epidemiological finding, some have cautioned against lowering the BP of hypertensive patients on long-term HD therapy [9].

Several randomized trials have investigated whether antihypertensive therapy, including with angiotensin-converting enzyme (ACE) inhibitors [10], angiotensin receptor blockers (ARBs) [11-12], and β-blockers [13], as well as calcium channel blockers (CCBs) [14] can prevent cardiovascular events in dialysis patients. However, there is evidence that a large proportion of dialysis patients with cardiac disease do not receive appropriate treatment with antihypertensive agents, including with renin-angiotensin system inhibitors (RASi), at least in part because of nephrologist's concerns regarding the possibility of adverse reactions [15-16].

This study was designed to investigate the effects of RASi, such as ACE inhibitors and ARBs, on all-cause and cardiovascular mortality in patients who are undergoing long-term HD therapy.

2. Methods

Patients were recruited from among those who had been routinely treated for at least 6 months in the dialysis unit of the Yoshikawa Hospital and Saiseikai-Kurihashi Hos-

pital in March 2006. The criteria for inclusion in the cohort were absence of congestive heart failure, diagnosed based on the presence of dyspnea in addition to two of the following conditions: raised jugular pressure, bibasilar crackles, pulmonary venous hypertension, and interstitial edema on a chest X-ray that required hospitalization or extra ultrafiltration [17]. The original cohort consisted of 457 patients, but 69 patients were excluded because of inappropriate prescriptions, transfer to another dialysis facility, or death in a traffic accident, and the remaining 388 patients (237 men and 151 women) who agreed to enroll this study were included in the final cohort.

Every HD patients underwent a monthly standard 12-lead ECG., and ST-T changes were evaluated by two investigators based on the Minesota code (MC) for ST-T segment depression (MC 4-1 to 4-4) or for a negative or flat T wave (MC 5-1 to 5-3) [18]. Exclusion criteria were: malignancy, active infection, pericardial effusion, and evidence of major valvular heart disease. The Institutional Research Ethics Committee of both hospitals approved the study protocol, and all patients gave written informed consent.

HD was performed three times weekly (4 hrs/day) with a standard technique. The potassium concentration of the dialysate was 2.0 mEq/L, and the calcium concentration was 3.0 mEq/L. Dry-weight estimates are performed routinely in our institution based on clinical signs of hydration, BP behaviors during the HD session. BP was recorded three times with a brachial sphygmomanometer after the subject had rested in the supine position for at least 10 min, and the average value of the three measurements was recorded. Hypertension was defined as systolic blood pressure (SBP) was ≥140 mmHg and/or diastolic blood pressure (DBP) was ≥90 mmHg, or the use of antihypertensive agents. Diabetes mellitus (DM) was defined o the basis of the World Health Organization (WHO) criteria [19]. Medical records were carefully checked for prescriptions of antihypertensive agents, including ACE inhibitors, ARBs, CCBs, and alpha- or beta-blockers (α/β-Bs). Parameters measured at the time of baseline examination included SBP, DBP, heart rate, and intradialysis weight gain (△BW). This study was conducted in compliance with the Declaration of Helsinki.

In order to measure routine laboratory markers, including the hematocrit and serum levels of urea nitrogen, uric acid, albumin, potassium (K), calcium (Ca), phosphorus (P), and total cholesterol, blood sampling was performed every month during the follow-up period. The mean values of each parameter during the follow-up period were used for statistical analyses.

Continuous variables are presented as means ± standard deviation. Categorical variables are reported as numbers and percentages. Differences between mean values were tested for significance by the paired t test (continuous variables) or chi-square test (categorical variables), as appropriate. The main outcome measures were all-cause and cardiovascular mortality. Their association between treatment with RASi and mortality was analyzed. A survival curve was estimated by the Kaplan-Meier product limit method, and a log-rank test was used to examine the difference in survival curves between the treated group and untreated group for significance. A multivariate analysis was performed using a Cox regression model. Adjusted hazard ratios (HRs) and their 95% confidence intervals are reported. A p value less than 0.05 was considered significant. The statistical analyses were performed with SPSS 9.0 software program (SPSS Inc., Chicago, IL, USA).

3. Results

Table 1 shows the subjects' clinical and demographic characteristics and whether they were treated or untreated with a RASi. A total of 388 HD patients (237 men and 151 women) met all of the eligibility criteria and consented to participate. Their mean age was 65.5 ± 6.5 years, and their mean duration of HD therapy (dialysis vintage) at the time of enrollment was 5.9 ± 3.2 years. There were 127 patients (53.6%) with diabetes and 102 (26.3%) with ST-T changes. Hypertension was diagnosed in 320 patients (82.5%), and 197 patients (50.8%) were treated with a RASi (treated group) and 191 patients (49.2%) were not (untreated group). The treated group had a higher prevalence of hypertension, history of congestive heart failure, and presence of ST-T changes. The serum levels of albumin, K, and P were higher in the treated group than in the untreated group. A higher proportion of the patients in the treated group also received CCBs and beta-blockers than in the untreated group. There were no statistically significant differences in age, gender, DM, presence of atrial fibrillation, hematocrit, or serum levels of urea nitrogen, uric acid, or total cholesterol between the treated group and the untreated group.

During the mean follow-up period of 2.74 ± 0.49 years, 62 patients (16.0%) died, and 40 of the deaths were due to cardiovascular disease (**Table 2**). The all-cause mortality rate was lower in the treated group (p = 0.0088). The time course of the relationship between RASi prescription and survival is shown by Kaplan-Meier survival curves (**Figure 1** and **Figure 2**). The survival rate was higher in the treated group, and treatment with a RASi did significantly affect all-cause mortality risk (**Figure 1**; log-rank: p = 0.0009). A reduction in risk of cardiovascular death in the treated group was also observed during the follow-up period (**Figure 2**; log-rank: p = 0.0379).

Table 1. Baseline demographic characteristics of eligible patients.

	All (*n* = 388)	RASi (*n* = 197)	RASi (–) (*n* = 191)	*p* value
Age (years)	**65.5 ± 6.5**	**64.9 ± 6.6**	**66.0 ± 6.4**	**n.s.**
Gender (men: women)	**237 : 151**	**119 : 78**	**118 : 73**	**n.s.**
Diabetes (n)	**127**	**73**	**54**	**n.s.**
Hypertension (n)	**320**	**194**	**126**	**<0.0001**
Congestive heart failure (n)	**53**	**34**	**19**	**0.0355**
Hematocrit (%)	**31.8 ± 1.1**	**31.9 ± 0.9**	**31.7 ± 1.3**	**n.s.**
Serum urea nitrogen (mg/dl)	**63.9 ± 5.7**	**64.8 ± 5.6**	**63.0 ± 5.9**	**n.s.**
Albumin (g/dl)	**3.68 ± 0.19**	**3.74 ± 0.16**	**3.62 ± 0.23**	**0.003**
Uric acid (mg/dl)	**7.34 ± 0.62**	**7.31 ± 0.52**	**7.37 ± 0.71**	**n.s.**
Potassium (mEq/l)	**4.98 ± 0.30**	**5.10 ± 0.28**	**4.86 ± 0.31**	**<0.0001**
Calcium (mg/dl)	**8.84 ± 0.35**	**8.77 ± 0.33**	**8.91 ± 0.36**	**0.0434**
Phosphorus (mg/dl)	**5.29 ± 0.49**	**5.44 ± 0.42**	**5.15 ± 0.56**	**0.0039**
Total cholesterol (mg/dl)	**152.3 ± 17.0**	**152.5 ± 16.4**	**152.1 ± 17.8**	**n.s.**
Chronic atrial fibrillation (n)	**27**	**15**	**12**	**n.s.**
ST-T changes in resting ECG (n)	**102**	**72**	**30**	**<0.0001**

Table 2. Cause of death.

	All	RASi (+)	RASi (–)	*p* value
Cardiovascular death				
Congestive heart failure	6	1	5	0.0793
Cardiac sudden death	9	5	4	0.7713
Cerebral infarction	7	2	5	0.2288
Cerebral hemorrhage	5	3	2	0.6767
Aortic or Peripheral artery disease	10	4	6	0.4888
Other cardiac death	3	1	2	0.5407
Death of other cause				
Infection	6	2	4	0.3851
Hepatic failure	5	0	5	0.0075
Cancer	4	1	3	0.2898
Respiratory failure	3	2	1	0.5765
Others	4	1	3	0.2898
All-cause death	62	22	40	0.0088

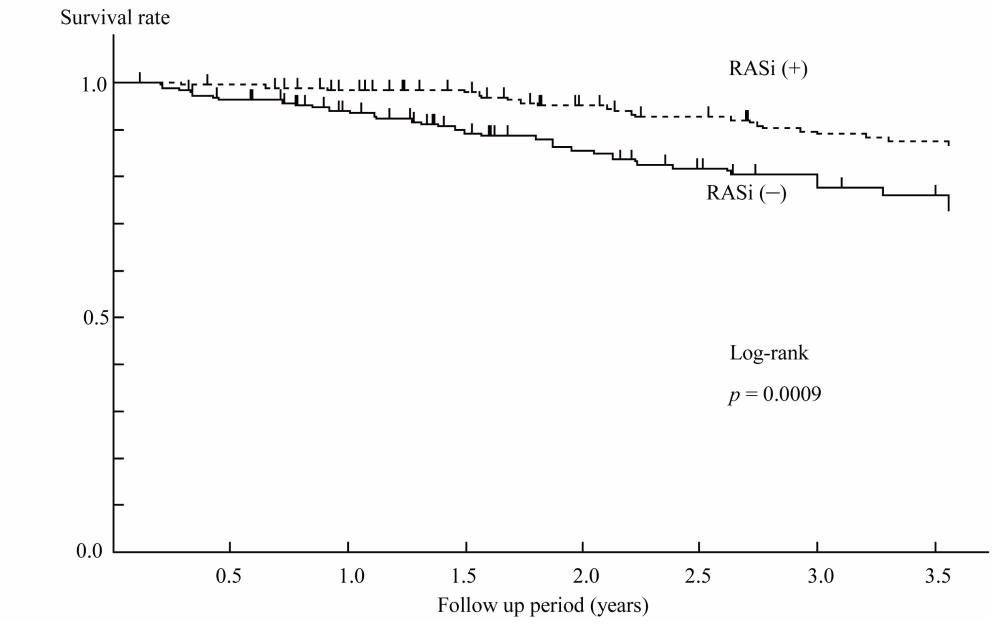

Figure 1. Kaplan-Meier curve showing the relationship between the all-cause mortality of chronic hemodialysis patients and treatment with renin-angiotensin system inhibitors (RASi).

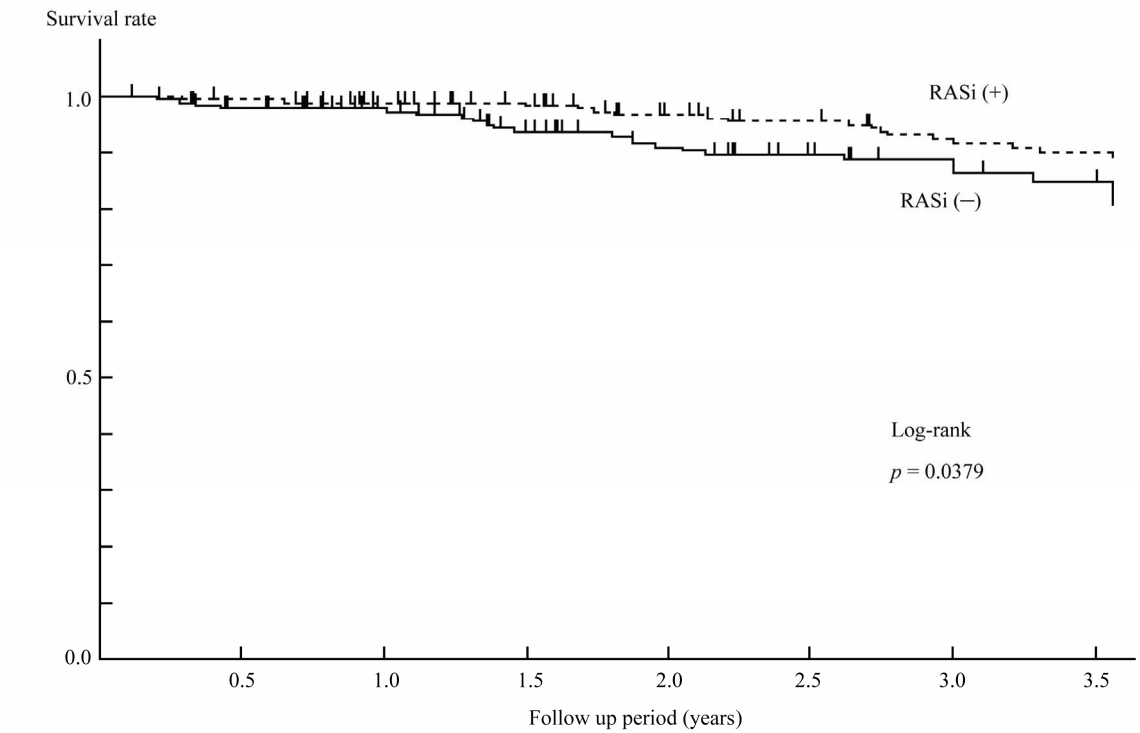

Figure 2. Kaplan-Meier survival analysis of cardiovascular mortality among chronic HD patients according to whether they were treated with a renin-angiotensin system inhibitor (RASi).

The multivariate analysis showed that treatment with a RASi was independently associated with lower all-cause mortality (HR = 0.204; p = 0.0051) based on the Cox proportional hazards regression model (**Table 3**). Age, comorbidity of DM, serum levels of albumin and K were also prognostic factors for all-cause mortality. Treatment with a RASi was also independently associated with lower cardiovascular mortality (HR = 0.184; p = 0.0161) based on the Cox proportional hazards regression model (**Table 4**). Age, serum levels of albumin and K and prescription of a CCB were also extracted as prognostic factors for cardiovascular mortality.

Table 2 shows the causes of death of the 62 patients. Cardiovascular disease accounted for 40 of the deaths (64.5%), and the causes of the other 22 deaths (35.5%) included infection, hepatic failure, cancer, and respiratory failure. The proportion of cause of cardiovascular death in the treated group and untreated group did not reach statistical significance.

4. Discussion

The results of this prospective observational study showed a significant association between treatment with a RASi and reduced the risk of all-cause or cardiovascular mortality of HD patients. The association remained statistically significant after adjusting for several risk factors for death, including age, gender, dialysis vintage,

Table 3. Prognostic factors for all-cause mortality.

	Hazard Ratio	95% CI	*p* value
Age (years)	1.063	1.012 - 1.117	0.0151
Diabetes	4.737	1.752 - 12.81	0.0022
Albumin (g/dl)	0.174	0.050 - 0.601	0.0057
Potassium (mEq/l)	0.181	0.064 - 0.509	0.0012
RASi	0.204	0.067 - 0.620	0.0051
Calcium channel blockers	0.441	0.172 - 1.134	0.0892

RASi, renin-angiotensin-system inhibitors; 95% CI, 95% Confidential interval.

Table 4. Prognostic factors for cardiovascular mortality.

	Hazard Ratio	95% CI	*p* value
Age (years)	1.066	1.006 - 1.130	0.0294
Diabetes	3.276	0.979 - 10.96	0.0542
Albumin (g/dl)	0.208	0.048 - 0.905	0.0363
Potassium (mEq/l)	0.159	0.046 - 0.553	0.0038
RASi	0.184	0.047 - 0.731	0.0161
Calcium channel blockers	0.301	0.103 - 0.879	0.0280

RASi, renin-angiotensin-system inhibitors; 95% CI, 95% Confidential interval.

presence of ST-T changes, hematocrit, treatment with other antihypertensive agents, and serum levels of urea nitrogen, albumin, uric acid, total cholesterol. It is noteworthy that the patients treated with a RASi had other known risk factors associated with higher mortality, such as hypertension, history of congestive heart failure, and ST-T changes. It is likely that treatment with a RASi is strongly associated with survival, and is protective of HD patients despite their higher prevalence of the risk factors.

Hypertension is one of the most important risk factors for cardiovascular complications in HD patients [20]. Controlling hypertension in patients with ESRD is a well-recognized problem and often requires treatment with more than one drug. Antihypertensive agents of different classes are available for BP control, but there is a lack of evidence of their efficacy and of BP targets for HD patients. Two recent systematic reviews and meta-analyses collected evidence from randomized trials and concluded that hypertension in HD patients should be treated, but that antihypertensive drugs were demonstrated to be superior [21-22].

The cause of hypertension in HD patients is multifactorial, but the major cause is volume retention [23]. Interdialysis weight gain is a reflection of salt-water intake and is related to excess volume. The salt intake on the basis of the ultrafiltration rate was approximately 9 g/day, of patients registered with the Japanese Society of Dialysis Therapy (JSDT), and lower than the national Japanese average [24]. However, it was still higher than the recommended salt intake for essential hypertension [25]. It should be noted that the effects of weight reduction or correction of volume excess on BP emerge slowly because of a lag phenomenon [26].

Activation of the RAS is also recognized as essential to the development of hypertension and the increased risk of cardiovascular events in HD patients. It has been shown that the RAS of such patients is often chronically over-reactive and that they have increased plasma renin activity (PRA) [27]. These factors together with expansion of the extracellular volume and interdialysis weight gain create a vicious circle in which the management of hypertension in HD patients remains difficult. However, there is enough evidence to state that HD patients, especially those with increased PRA, would benefit from adding drugs that inhibit the RAS to their antihypertensive regimen. A number of studies have shown significantly reduced mortality risk for ESRD patients with cardiovascular disease who were treated with an ACE inhibitors [28-29]. Two studies showed a survival benefit for HD patients treated with ACE inhibitors [30-31]. However, ACE inhibitors have been shown to be prescribed for only 30% to 50% patients on dialysis [32-33].

Based on the JSDT registry, Iseki *et al*. recently showed a better survival rate among 163,668 HD patients for whom antihypertensive drugs had been prescribed, particularly a RASi, than among those for whom not been prescribed antihypertensive drugs [34]. They observed the relationship between higher serum albumin levels and a greater prevalence of hypertension in Japanese HD patients. The HD patients with high serum albumin might eat well and have a high intake of salt and water. The survival rate in our study was also closely related to the serum albumin levels, suggesting that patients with a high serum albumin level might have better survival when the patients even though they were hypertensive if the patients treated with RASi.

There were several limitations in our study. First, the study was observational, and the study population was relatively small. Any negative findings may have been attributable to its low statistical power. Second, despite using multiple methods to address potential bias, we cannot rule out the possibility of residual confounding factors having contributed to the better outcomes of the patients treated with a RASi than the patients who were not. However, there was a trend toward higher risk of death, e.g., due to hypertension and congestive heart failure in the group treated with a RASi. Third, we could not address the effects of the classes, dosage, or duration of treatment with a RASi, all of which may be associated with the effect of RASi on survival, or whether any of the medications had previously been used and later discontinued.

In conclusion, the results of this study suggest a possible association between the use of RASi and reduced risk of all-cause or cardiovascular mortality in chronic HD patients, independent of their effect of lowering BP. These observations need to be confirmed in further randomized controlled trials before prescribing RASi to prevent cardiovascular death in chronic HD patients.

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