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Impact of serum potassium on therapeutic prognosis of maintenance hemodialysis patients on angiotensin receptor antagonists

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Abstract

Background: In chronic kidney disease patients, angiotensin receptor blockers (ARBs) have been known to increase serum potassium (K) levels. On the other hand, it has been reported that in patients on maintenance dialysis, both hyperkalemia and hypokalemia were related to poor prognosis. In this study, the prognosis with ARB treatment was investigated using a prospective cohort of dialysis patients that were divided into two groups according to pre-dialysis serum K levels: these were the low serum K group (below 4.6 mEq/L) and the high serum K group (4.6 mEq/L and higher).

Methods: A total of 260 patients in our dialysis database were classified into four groups according to their serum K level and ARB use. The survival curves of these groups were estimated by Kaplan–Meier method and compared using a log-rank test. Using Cox regression model, prognostic factors for all-cause mortality were extracted from background factors, including the three classifications; high serum K and ARB group that served as the control.

Results: In terms of all-cause mortality rates, the low serum K and ARB group had the highest, whereas the high serum K and ARB group had the lowest. In the Cox regression model, all three classifications, except the control group, were factors for poor prognosis.

Conclusions: In this study, pre-dialysis serum K level and ARB use affected all-cause mortality of dialysis patients. Multi-center prospective randomized study will be needed in the future to validate our findings.

Keywords: Angiotensin receptor blocker, Serum potassium, All-cause mortality, Hemodialysis patients

Background

In recent years, angiotensin receptor blockers (ARBs) have been widely used in Japan as first-line drugs for the treatment of hypertensive patients on maintenance dialysis. However, renin–angiotensin system (RAS) inhibitors, including ARBs, have been reported to induce critical hyperkalemia in normokalemic patients with chronic kidney disease or heart failure [1, 2]. In dialysis patients, excessive hyperkalemia has been known as one of the causes of sudden death [3] and hypokalemia lower than 4.0 mEq/L has been reported to be associated with poor prognosis [4]. Therefore, the appropriate control of pre-dialysis serum potassium (K) at a level of 4.6–5.5 mEq/L is important for good prognosis in dialysis patients [5].

At present, it is not clear whether the use of ARB is one of the risk factors for fatal hyperkalemia, which may affect the prognosis of dialysis patients. Furthermore, it is also unclear whether the efficacy and safety of ARB treatment are consistent, regardless of serum K levels, in hypokalemic and hyperkalemic patients before dialysis. In this study, we performed multivariate analysis on our prospective cohort of dialysis patients to examine the association between ARB treatment and prognosis in both hypokalemic (serum K below 4.6 mEq/L) and normo- to hyperkalemic (serum K 4.6 mEq/L or more) groups.

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Methods

This was a prospective cohort study that enrolled 309 out-patients on dialysis at Yoshikawa Clinic between April 2006 and October 2010. Written informed consent was obtained from the patients who were registered on a dialysis database. The original cohort consisted of 309 patients; of these, 49 were excluded because of inappropriate prescriptions and transfer to another dialysis facility within less than 1 month from registration. The remaining 260 patients (149 men and 111 women) were included in the final cohort.

Hemodialysis (HD) was performed thrice weekly with a standard technique. The dialysate contained 2.0 mEq/L of K and 3.0 mEq/L of calcium. Dry weight estimates were routinely measured in our institution based on clinical signs of hydration, blood pressure pattern during dialysis sessions, and cardiothoracic ratio on chest radiograph. The protocol of this study was approved by the ethics committee of our hospital. This investigation conformed to the principles outlined in the Declaration of Helsinki.

Investigation of therapeutic prognosis with ARB treatment

Eligible patients were followed up until October 2010 from the time of registration in our database. The survival curves of the ARB and non-ARB groups were estimated by Kaplan–Meier method and compared. The main outcome measured was all-cause mortality, the prognostic factors of which were extracted by Cox regression model using descriptive variables, such as age, gender, co-morbidities, vintage of dialysis, presence of atrial fibrillation (AF) or ST–T segment changes on electrocardiogram (ECG), medication at the time of registration, pre-dialysis average systolic blood pressure (SBP) and diastolic blood pressure (DBP) within 1 month after registration, average dialysis efficiency (Kt/V), and average values of laboratory blood tests during the entire observational period.

Comorbidities included were diabetes mellitus, heart failure, ischemic heart disease, and stroke. Having diabetes mellitus, as a comorbidity, was defined as following one or more of the following criteria of the Japan Diabetes Society: the primary cause of end-stage renal disease was diabetic nephropathy; random blood sugar level over 200 mg/dL; or HbA1c over 6.5 % in more than one occasion. Congestive heart failure (CHF) was defined by a history of decompensated heart failure or left ventricular ejection fraction of less than 40 % on echocardiography. Coronary artery disease (CAD) was defined by a history of myocardial infarction or coronary stenosis confirmed by coronary angiography or another imaging techniques. Stroke was defined as the presence of definitive findings of cerebral infarction or hemorrhage on computed tomography or magnetic resonance imaging. Standard 12-lead ECG was recorded every 3 months at our hospital; the nearest tracing to the time of registration was used. Changes in ST–T segment on resting ECG were evaluated by two investigators based on the Minnesota code of 4–1 to 4–4 for ST depression and 5–1 to 5–3 for negative or flat T wave [6]. Medications used were ARBs, angiotensin-converting enzyme inhibitors (ACEi), calcium (Ca) channel blockers (CCBs), beta-blockers (Beta-B), and vitamin D3 (VD). SBP and DBP were recorded by a brachial sphygmomanometer in the supine position every 30 min during dialysis sessions, and from the time of registration, the monthly average values of SBP and DBP at the beginning of every dialysis session were used.

Laboratory blood tests that were measured included blood urea nitrogen (BUN), albumin (Alb), hemoglobin (Hb), C-reactive protein (CRP), serum K, Ca, phosphorus (P), total cholesterol (TC), blood sugar (BS), and hepatitis C virus (HCV) antibody. Of these variables, serum K was regarded as categorical data and was classified as 0 (serum K below 4.6 mEq/L) or 1 (serum K equal to or more than 4.6 mEq/L). Measurements of Kt/V and laboratory markers were performed twice a month; the average values for each were calculated during the entire observational period.

Investigation of the relationship between pre-dialysis serum K level and prognosis with ARB therapy

Eligible patients were classified into the following four groups according to serum K levels and the use or non-use of ARB: (1) ARB non-use and serum K below 4.6 mEq/L (group 1); (2) ARB use and serum K below 4.6 mEq/L (group 2); (3) ARB non-use and serum K equal to or more than 4.6 mEq/L (group 3); and (4) ARB use and serum K equal to or more than 4.6 mEq/L (group 4). Survival curves of these four groups were estimated by the Kaplan–Meier method and were compared. Using the four groups as descriptive variables, multivariate analysis using Cox regression model was performed to determine the prognostic factors for all-cause mortality, cardiovascular mortality and non-cardiovascular mortality. Groups 1 to 3 were included in the analysis as binary variables, with group 4 serving as the control.

Statistical analysis

Continuous variables were presented as mean ± standard deviation. Categorical variables were reported as numbers and percentages. Continuous variables were compared by paired Student's t test; categorical variables were compared by the chi-square test, as appropriate. The differences among survival curves were tested for significance by the log-rank test. Extraction of prognostic factors was performed using Cox regression model, according to the variable decrease likelihood ratio method. Adjusted hazard ratios (HR) and their 95 % confidence intervals (CI) were reported. A p value of less

than 0.05 was considered statistically significant. The statistical analyses were performed by the Dr SPSS II software program (v11.0.1J; SPSS Inc., 1991–2000).

Results

Therapeutic prognosis with ARB in all subjects

Table 1 shows the clinical and demographic characteristics of the study population according to ARB use. A total of 260 HD patients, comprising 149 men and 111 women with a mean age of 68.8 ± 6.33 years, participated in this study. The mean duration of HD therapy at the time of enrollment was 5.61 ± 3.25 years. There were 89 patients with diabetes and 101 patients with ST–T segment changes. Hypertension was diagnosed in 214 patients; 167 patients were in the ARB group and 93 patients were in the non-ARB group. At the beginning of the dialysis, mean blood pressure was 148.5 ± 9.40 mmHg for SBP and 74.5 ± 5.44 mmHg for DBP. Compared with the non-ARB group, the ARB group showed significantly higher mean SBP and DBP values and significantly higher proportion of patients who also received CCBs, beta-Bs, and VD. There were no statistically significant differences between the ARB group and non-ARB group in terms of age, gender, vintage of dialysis, comorbidities, laboratory data, ECG changes, and frequency of ACEi prescription.

During a mean follow-up period of 3.28 ± 0.74 years, 69 patients died; 43 of these deaths were due to cardiovascular disease (Tables 1 and 2). All-cause mortality rate was the same for ARB group (25.1 %) and non-ARB groups (29.0 %). The time course of the relationship

Table 1 Patient profile

			ARB		
		Total	(+)	(–)	*p* value
Age	(Years old)	68.8 ± 6.33	68.1 ± 6.10	70.1 ± 6.71	0.234
Gender (M to F ratio)		149:111	95:72	54:39	0.855
Vintage of dialysis	(Years)	5.61 ± 3.25	5.63 ± 3.30	5.56 ± 3.18	0.939
Diabetes		89	63	26	0.112
CAD		50	37	13	0.109
CHF		30	18	12	0.609
Stroke		21	13	8	0.817
SBP at the beginning of session	(mmHg)	148.5 ± 9.40	153.2 ± 7.99	140.1 ± 10.3	<0.001
DBP at the beginning of session	(mmHg)	74.5 ± 5.44	75.6 ± 5.16	72.4 ± 5.81	0.024
BUN	(mg/dL)	63.0 ± 5.25	63.4 ± 5.16	62.5 ± 5.42	0.503
Kt/V		0.96 ± 0.12	0.96 ± 0.11	0.96 ± 0.11	0.997
Alb	(g/dL)	3.63 ± 0.19	3.65 ± 0.17	3.60 ± 0.21	0.354
Hb	(g/dL)	10.0 ± 0.33	10.0 ± 0.32	10.1 ± 0.35	0.570
CRP	(mg/dL)	1.00 ± 0.99	0.97 ± 1.10	1.07 ± 0.77	0.701
K	(mEq/L)	5.0 ± 0.3	5.0 ± 0.3	4.9 ± 0.3	0.053
Ca	(mg/dL)	8.6 ± 0.3	8.6 ± 0.3	8.5 ± 0.3	0.096
P	(mg/dL)	5.3 ± 0.4	5.3 ± 0.4	5.3 ± 0.5	0.928
TC	(mg/dL)	155.4 ± 18.4	154.8 ± 18.0	156.3 ± 19.1	0.769
Blood glucose	(mg/dL)	123.4 ± 19.9	122.4 ± 19.5	125.3 ± 20.9	0.576
AF		21	10	11	0.098
Changes of ST–T segment in ECG		101	71	30	0.105
HCV infection		18	10	8	0.428
ACEI		20	12	8	0.683
ARB		167	167	0	–
CCB		186	139	47	<0.001
beta-B		88	66	22	0.009
VD		157	111	46	0.007
Weekly dose of Erythropoietin/DW	(U/w/kg)	119.7 ± 44.4	121.5 ± 44.5	116.6 ± 44.6	0.354

CAD coronary artery disease, *CHF* congestive heart failure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BUN* blood urea nitrogen, *Alb* albumin, *Hb* hemoglobin, *CRP* C-reactive protein, *K* serum potassium, *Ca* calcium, *P* phosphorus, *TC* total cholesterol, *AF* atrial fibrillation, *HCV* hepatitis C virus, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *CCB* calcium channel blocker, *beta-B* beta receptor blocker, *VD* vitamin D3, *DW* dry weight

Table 2 Causes of death

	Total	ARB (+)	ARB (–)
Cardiovascular death	43	27	16
CHF	9	6	3
Acute coronary syndrome	2	1	1
Cardiac sudden death	14	7	7
Cerebral infarction	8	5	3
Cerebral hemorrhage	4	2	2
Aortic or peripheral artery disease	6	6	0
Death of other cause	26	15	11
Infection	13	7	6
Hepatic failure	2	1	1
Malignancy	3	3	0
Others	8	4	4
Total	69	42	27

CHF congestive heart failure

between ARB intake and survival was similar for the two groups ($p = 0.420$) (Fig. 1).

Multivariate analysis (Table 3) showed that treatment with ARB was not an independent prognostic factor for all-cause mortality. Age, gender, SBP at the beginning of dialysis, serum levels of albumin, CRP, and BS, serum K below 4.6 mEq/L, presence of AF on ECG, and intake of VD were extracted as significant prognostic factors for all-cause mortality.

Comparison of therapeutic prognosis with ARB according to pre-dialysis serum K levels

Groups 1, 2, 3, and 4 comprised 27, 36, 66, and 131 patients, respectively (Table 4). Vintage of dialysis, SBP, DBP, BUN, Kt/V, Alb, Hb, CRP, Ca, P, BS, and frequency of prescriptions of CCB, Beta-B, and VD were significantly different among these four groups. Group 4, as the control for multivariate analysis, included patients who have been on HD for a relatively longer time and showed good nutritional status, low CRP levels, and high frequency of CCB, Beta-B, and VD prescriptions. In terms of all-cause mortality, patients in group 2 had the highest rate, whereas those in group 4 had the lowest ($p < 0.001$) (Fig. 2). Multivariate analysis showed that groups 1–3 had high all-cause mortality rates (Table 5). Age, SBP, Kt/V, Alb, CRP, BS, and presence of AF were also determined as prognostic factors for all-cause mortality. In terms of cardiovascular mortality, groups 1 and 2 had high cardiovascular mortality rates and hazard ratio was 3.469 (1.180–10.19, $p = 0.024$) in group 1 and 4.980 (2.117–11.71, $p < 0.001$) in group 2.

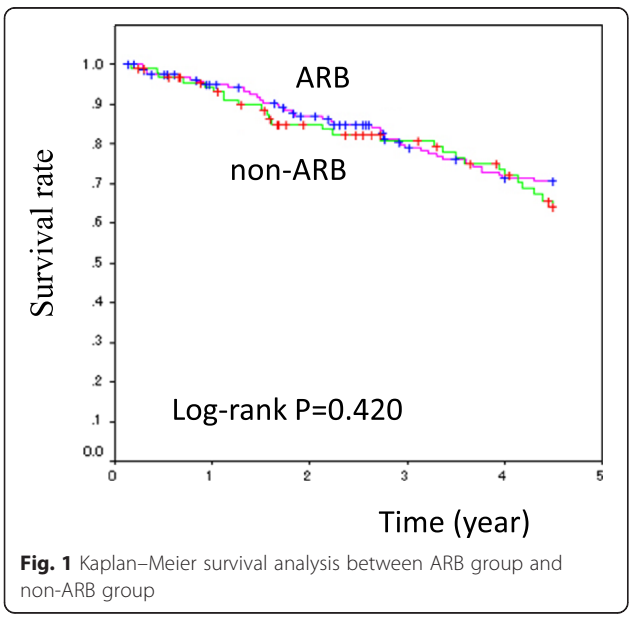

Fig. 1 Kaplan–Meier survival analysis between ARB group and non-ARB group

Table 3 Prognostic factors in the eligible patients for all-cause mortality

	Exp(B)	95 % CI	*p* value
Age (per +1 year old)	1.047	1.020–1.075	0.001
Gender (male)	2.114	1.172–3.813	0.013
SBP at the beginning of session (per +1 mmHg)	1.018	1.004–1.032	0.012
Albumin (per +1 g/dL)	0.151	0.071–0.321	<0.001
CRP (per +1 mg/dL)	1.147	1.038–1.268	0.007
SK < 4.6 mEq/L	2.453	1.469–4.095	0.001
Blood glucose (per +1 mg/dL)	1.009	1.002–1.016	0.008
AF	2.586	1.221–5.474	0.013
VD	0.580	0.350–0.962	0.035

SBP systolic blood pressure, *CRP* C-reactive protein, *SK* serum potassium, *AF* atrial fibrillation, *VD* vitamin D3

Discussion

Pre-dialysis serum K level is one of the prognostic factors in patients on dialysis. Hypokalemia has been reported to be associated with poor prognosis in terms of all-cause mortality; similarly, remarkable hyperkalemia has also been reported to evoke lethal arrhythmia [4, 5]. Specifically, among patients on ARB use, those with normokalemia or hyperkalemia before dialysis had the lowest all-cause mortality rate, whereas those with hypokalemia before dialysis showed the poorest prognosis. On the other hand, for dialysis patients who were not on ARB treatment, hyperkalemia before dialysis was associated with better prognosis than for those with hypokalemia before dialysis. In addition, the characteristics of groups 1–3 were independent risk factors that increased all-cause mortality.

Several studies have indicated that RAS inhibitors, including ACEi and ARBs, decreased cardiovascular events, ameliorated renal function decline, and decreased mortality

Table 4 Patient profile grouping by predialysis potassium and ARB treatment

		Predialysis potassium				
		<4.6 mEq/L		≥4.6 mEq/L		
		ARB(−)	ARB(+)	ARB(−)	ARB(+)	
		Group 1	Group 2	Group 3	Group 4	*p* value
		(*n* = 27)	(*n* = 36)	(*n* = 66)	(*n* = 131)	
Age	(Years old)	70.2 ± 7.19	72.7 ± 6.54	70.0 ± 6.56	66.8 ± 5.85	0.060
Gender (M to F ratio)		17:10	27:9	37:29	68:63	0.087
Vintage of dialysis	(Years)	2.18 ± 2.07	3.67 ± 2.32	6.95 ± 3.31	6.17 ± 3.48	0.002
Diabetes		8	18	18	45	0.131
CAD		5	5	8	32	0.166
CHF		3	3	5	7	0.710
Stroke		4	5	4	8	0.230
SBP at the beginning of session	(mmHg)	132.9 ± 11.6	153.7 ± 9.62	143.0 ± 9.43	153.0 ± 7.52	<0.001
DBP at the beginning of session	(mmHg)	69.6 ± 5.03	73.3 ± 6.00	73.6 ± 6.04	75.3 ± 4.87	0.019
BUN	(mg/dL)	59.4 ± 5.15	55.4 ± 5.23	63.7 ± 5.44	65.6 ± 4.58	<0.001
Kt/V		0.87 ± 0.09	0.83 ± 0.12	0.99 ± 0.11	0.99 ± 0.09	<0.001
Alb	(g/dL)	3.55 ± 0.22	3.40 ± 0.23	3.62 ± 0.20	3.71 ± 0.14	<0.001
Hb	(g/dL)	10.22 ± 0.39	9.75 ± 0.46	10.02 ± 0.34	10.11 ± 0.26	0.016
CRP	(mg/dL)	1.45 ± 1.03	1.96 ± 2.09	0.91 ± 0.63	0.69 ± 0.54	0.004
K	(mEq/L)	4.2 ± 0.2	4.2 ± 0.2	5.2 ± 0.2	5.2 ± 0.2	–
Ca	(mg/dL)	8.3 ± 0.3	8.5 ± 0.2	8.6 ± 0.3	8.7 ± 0.3	0.027
P	(mg/dL)	5.1 ± 0.6	4.6 ± 0.4	5.4 ± 0.4	5.5 ± 0.4	<0.001
TC	(mg/dL)	164.5 ± 21.9	142.3 ± 15.6	152.8 ± 17.7	157.9 ± 18.3	0.083
Blood glucose	(mg/dL)	131.3 ± 21.8	139.6 ± 25.3	122.9 ± 20.7	118.3 ± 17.3	0.040
AF		4	2	7	8	0.363
Changes of ST–T segment in ECG		6	16	24	55	0.230
HCV infection		2	4	6	6	0.464
ACEI		1	1	7	11	0.442
ARB		0	36	0	131	–
CCB		14	30	33	109	<0.001
beta-B		4	8	18	58	0.002
VD		12	19	34	92	0.010
Weekly dose of erythropoietin/DW	(U/w/kg)	111.5 ± 41.9	146.4 ± 41.4	118.6 ± 45.9	114.6 ± 44.8	0.272
Observational period		2.66 ± 0.81	2.19 ± 0.74	3.40 ± 0.71	3.65 ± 0.66	<0.001
All-cause death		8	24	19	18	<0.001
Cardiovascular death		5	14	11	13	<0.001

CAD coronary artery disease, *CHF* congestive heart failure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BUN* blood urea nitrogen, *Alb* albumin, *Hb* hemoglobin, *CRP* C-reactive protein, *K* serum potassium, *Ca* calcium, *P* phosphorus, *TC* total cholesterol, *AF* atrial fibrillation, *HCV* hepatitis C virus, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *CCB* calcium channel blocker, *beta-B* beta receptor blocker, *VD* vitamin D3, *DW* dry weight

rates of hypertensive or diabetic patients [7–9]. In dialysis patients, several reports have shown the suppressive effects of RAS inhibitors on left ventricular hypertrophy; however, whether or not antihypertensive therapy with RAS inhibitors can ameliorate all-cause or cardiovascular mortality remains to be determined [10]. A randomized trial on fosinopril in 397 dialysis patients failed to show improved cardiovascular prognosis [11]. In a meta-analysis of randomized controlled trials of peritoneal dialysis patients, antihypertensive therapy with ACEi or ARB did not reduce mortality rates and cardiovascular events [12]. A retrospective investigation on the efficacy ACEi or ARB for good cardiovascular prognosis in 1950 dialysis patients did not show an association between the use of these RAS inhibitors and reduction of cardiovascular events [13]. On the other hand, a retrospective study based on the DOPPS

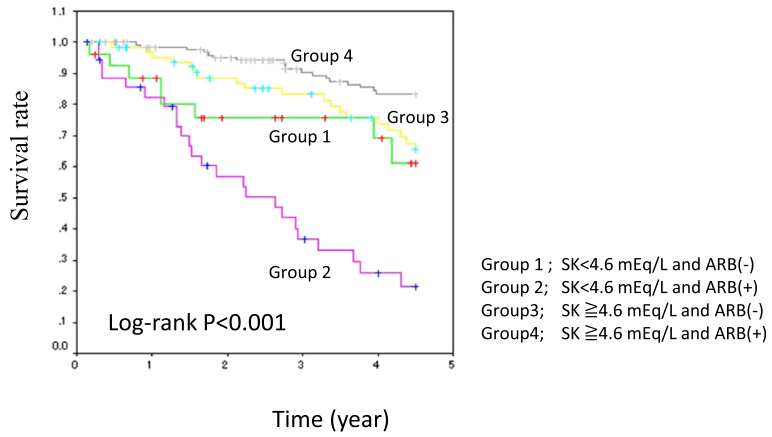

Fig. 2 Impact of serum potassium level above median on the relationship between ARB treatment and all-cause mortality

I and II registries by Lopes et al. [14] and an observational study on 28,628 dialysis patients by Chan et al. [15] similarly showed that the use of ARB was associated with reduction of mortality rates.

In this study, all patients had the same all-cause mortality regardless of ARB; however, those who were on ARB and had pre-dialysis normokalemia or hyperkalemia showed lower mortality than the others. From these results, antihypertensive therapy with ARB would seem to improve prognosis only in patients with pre-dialysis serum K level of 4.6 mEq/L or more. Because low pre-dialysis serum K (below 4.6 mEq/L) was a risk factor for all-cause mortality in this study, it is necessary to determine whether the demonstrated efficacy of ARB in group 4 was secondary to an increased serum K level or was due to the suppression of the RAS.

Although there was no significant difference in pre-dialysis serum K levels between the ARB and non-ARB groups, normokalemic or hyperkalemic patients on ARBs had lower mortality rates than did those who were not on ARBs. Furthermore, our results on multivariate analysis suggest that ARB treatment improved prognosis regardless of serum K levels. However, the influence of ARBs on serum K levels was not accounted for and may have confounded the outcomes of our study population.

In pre-dialysis patients with renal failure, it is generally accepted that the frequency of hyperkalemia due to ARB use may increase along with deterioration of renal function [1]. In contrast, it has not been clarified whether antihypertensive therapy with RAS inhibitors is a risk factor for lethal hyperkalemia in dialysis patients. Knoll et al. reported that the risk for hyperkalemia in dialysis patients increased 2.1–2.3 times due to the use of RAS inhibitors [16]. In other literature, the relationship between the use of ARB and changes in serum K was not shown in dialysis patients [17, 18]. This present study was observational and based on our dialysis database; in addition, patients who were on ARB at the time of registration to the database were assigned to the ARB group. Therefore, changes in serum K that may be secondary to ARB administration have not been recorded. In all patients, univariate

Table 5 Prognostic factors of eligible patients including three groups as explanatory factors

	Exp(B)	95 % CI	*p* value
Age (per +1 year old)	1.048	1.019–1.078	0.001
SBP at the beginning of session (per +1 mmHg)	1.024	1.008–1.040	0.003
Kt/V (per +1.0)	0.228	0.067–0.776	0.018
Albumin (per +1 g/dL)	0.200	0.094–0.427	<0.001
CRP (per +1 mg/dL)	1.163	1.055–1.281	0.002
Blood glucose (per +1 mg/dL)	1.007	1.000–1.013	0.043
AF	3.244	1.549–6.795	0.002
Group 1 (SK < 4.6 mEq/L, ARB(−))	3.957	1.599–9.794	0.003
Group 2 (SK < 4.6 mEq/L, ARB(+))	3.707	1.889–7.277	<0.001
Group 3 (SK ≥ 4.6 mEq/L, ARB(−))	2.445	1.211–4.934	0.013

SBP systolic blood pressure, *CRP* C-reactive protein, *AF* atrial fibrillation, *SK* serum potassium

regression analysis showed a positive correlation between ARB use and pre-dialysis serum K ($p = 0.016$); conversely, multivariate linear regression analysis using stepwise backward elimination did not demonstrate a significant relationship between ARB use and serum K (Table 6). Factors, such as age, vintage of dialysis, SBP, BUN, Kt/V, Alb, P, and Beta-B use, were positively correlated with serum K. Among these related factors, SBP, BUN, Kt/V, Alb, and P were indicators of nutritional status, suggesting that serum K may also be associated with nutritional status, regardless of ARB use. This association between pre-dialysis serum K and nutritional status was similarly suggested by Kovesdy et al. [7]. Furthermore, in a post hoc analysis of 4D, hypokalemia was evaluated as one of the indicators of malnutrition [19]. Consequently, RAS suppression by ARB use, rather than serum K changes, has been suggested to contribute to the favorable prognosis of group 4 patients in this study.

In this study, the difference in prognosis between hypokalemic and normokalemic or hyperkalemic patients on ARB may be explained by some humoral factors that could have influenced the effect of serum K on therapeutic prognosis of ARB. Based on previous literature, changes in plasma aldosterone concentration (PAC) positively correlated with serum K level in anuric dialysis patients [20]. In this present study, measurement of PAC was incidentally performed in nine patients during the observation period; Fig. 3 shows a positive correlation of PAC/plasma renin-activity ratio with serum K level in these patients. Similarly, dependency of aldosterone secretion on serum K level in dialysis patients was suggested in this study. High levels of aldosterone induce vascular and organ damage, such as atherosclerosis, renal fibrosis, myocardial hypertrophy, and fibrosis [21]. In vascular smooth muscle cells, the link between aldosterone and angiotensin II receptor was also reported [21]. The randomized aldactone evaluation study (RALES) revealed that spironolactone reduced all-cause mortality in patients with severe heart

Table 6 Correlation with serum potassium in the eligible patients

	Standardized B	*p* value
Age	0.126	0.019
Vintage of dialysis	0.165	0.002
SBP at the beginning of session	0.161	<0.001
BUN	0.327	<0.001
Kt/V	0.221	<0.001
Albumin	0.164	0.003
Phosphorus	0.229	<0.001
Use of beta-B	0.129	0.008

SBP systolic blood pressure, *BUN* blood urea nitrogen, *beta-B* beta receptor blocker

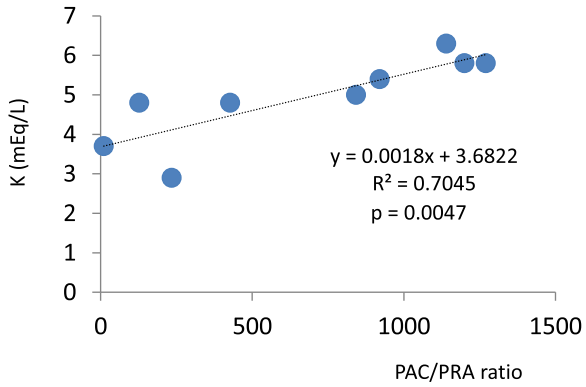

Fig. 3 Correlation between serum potassium (K) level and plasma aldosterone level/plasma renin-activity (PAC/PRA) ratio

failure [22]. In a recent randomized study on dialysis patients, spironolactone reduced cardiovascular events and deaths [23]. Consequently, excess secretion of aldosterone due to hyperkalemia in groups 3 and 4 was inferred in this study. It is possible that antihypertensive therapy with ARB in group 4 suppressed aldosterone secretion or the cross-talk with aldosterone receptor to reduce all-cause mortality.

In contrast, low aldosterone secretion due to hypokalemia in groups 1 and 2 was inferred based on the finding that ARB use with serum K below 4.6 mEq/L had increased all-cause mortality. Low aldosterone level as a risk factor for all-cause mortality was reported in dialysis patients by Kohagura et al. [24]. However, the therapeutic prognosis of ARB in dialysis patients with hypokalemia or low aldosterone levels has not been clarified at the moment. In hypokalemic dialysis patients, antihypertensive therapy with ARB may further reduce aldosterone secretion and increase all-cause mortality. Accordingly, based on aldosterone levels, it is necessary to confirm the therapeutic prognosis and appropriate use of ARB in dialysis patients.

Regarding ACEI treatment, there was no significant difference in the mortality risk among the four groups according to serum K levels (4.6 mEq/L) and the use or non-use of ACEI monotherapy and combination therapy with ARB. Multiple analyses showed that groups 1–3 did not have high all-cause mortality rates. However, the number of patients with ACEI treatment was so small, especially two patients in group 2. It will be necessary to confirm the safety of ACEI treatment in patients with serum K levels below 4.6 mEq/L.

Limitations: This was a single-center observational study on a relatively small study population. Despite using multiple methods to address potential bias, we cannot rule out the possibility of residual confounding factors that may have affected the outcomes of patients on ARB use. In addition, the effects of dosage or

duration of antihypertensive therapy with ARB were not addressed.

Conclusions

In conclusion, pre-dialysis serum K may influence the efficacy of ARB on all-cause mortality. Hyperkalemic dialysis patients were suggested as the best candidates for antihypertensive therapy with ARB. In contrast, dialysis patients with serum K below 4.6 mEq/L may need to reconsider intake of antihypertensive agents other than ARBs. The relationship between therapeutic prognosis with ARB and serum K or aldosterone level must be confirmed by prospective randomized studies in the future.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KO and TO participated in the design of the study, performed the statistical analysis and drafted the manuscript. MY, HS and KN participated in its design and coordination. All authors read and approved the final manuscript.

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