ORIGINAL ARTICLE

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Impaired aldosterone response to potassium and hyperkalemia in patients receiving a renin-angiotensin-aldosterone system inhibitor

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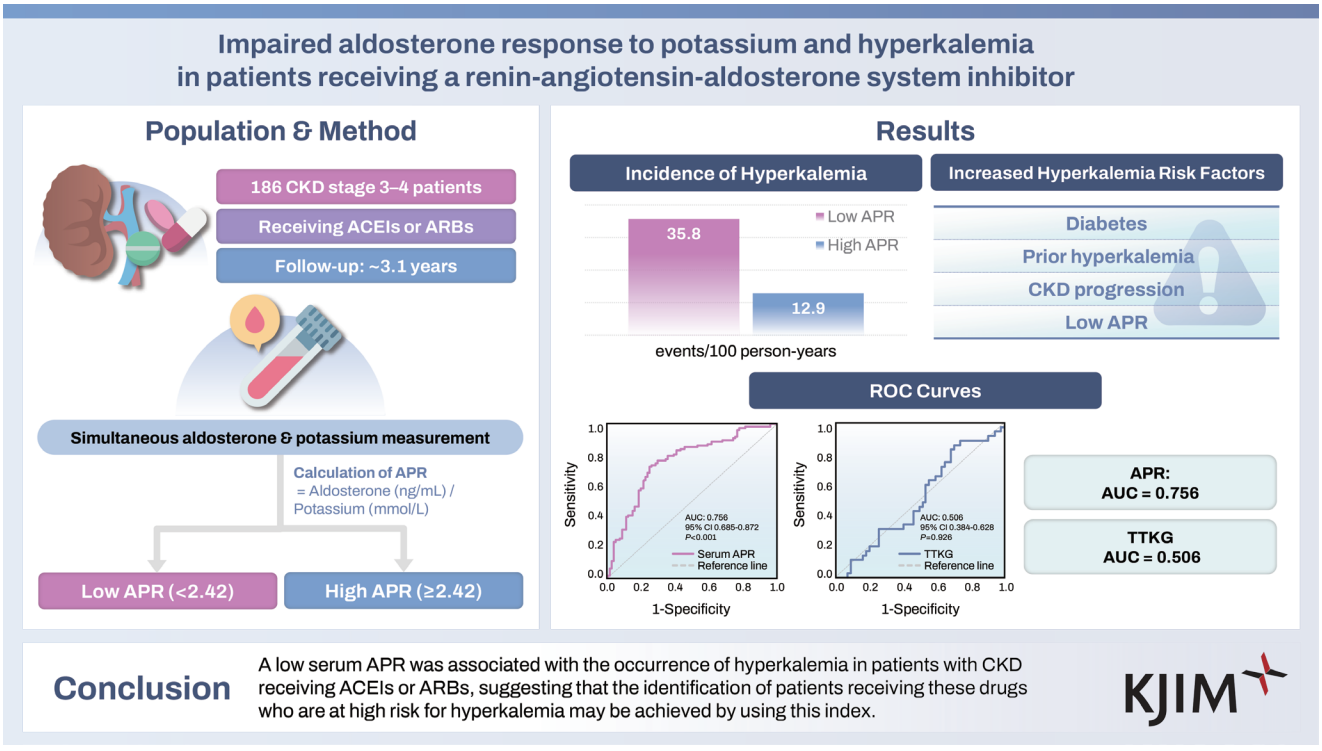

Background/Aims: Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are associated with the development of hyperkalemia. We evaluated the relationship between the serum aldosterone-to-potassium ratio (APR) and the risk of developing hyperkalemia in patients with chronic kidney disease (CKD) receiving ACEIs or ARBs.

Methods: One hundred eighty-six patients with stage 3–4 CKD receiving an ACEI or ARB for at least 3 months were evaluated. Serum aldosterone and potassium concentrations were measured simultaneously, and serum APR was calculated (ng/mL per mmol/L). Patients were divided into two groups for comparison according to the median value above or below 2.42. The primary outcome was the difference between the two groups in the development of hyperkalemia (defined as a serum potassium level > 5.5 mmol/L). Incidence rates and risk factors of hyperkalemia were assessed.

Results: During the follow-up period, 144 hyperkalemic events in 81 patients (43.5%) were identified, yielding an incidence rate of 24.6 events/100 person-years. The incidence rate was significantly higher in patients with a low serum APR than in

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patients with a high APR (35.8 events/100 patient-years vs. 12.9 events/100 patient-years, $p < 0.001$). In addition, diabetes mellitus, history of hyperkalemia, CKD progression during the follow-up period, and low serum APR were predictors of the development of hyperkalemia.

Conclusions: Low serum APR was associated with the occurrence of hyperkalemia in patients with CKD receiving ACEIs or ARBs, suggesting that the identification of patients administered these drugs who are at high risk for hyperkalemia may be achieved using this index.

Keywords: Aldosterone; Angiotensin-converting enzyme inhibitors; Angiotensin receptor antagonists; Chronic kidney disease; Hyperkalemia

INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are effective at slowing the progression of kidney disease and improving outcomes in patients with chronic kidney disease (CKD) [1]. However, these medications have been associated with adverse events, including hyperkalemia [2-6], by interfering with angiotensin II-mediated stimulation of aldosterone production in the adrenal gland [2]. This process may lead to underutilization, suboptimal dosing, or discontinuation of these medications, resulting in subsequent adverse clinical outcomes, including death [7-9]. Therefore, several studies have evaluated the frequency of hyperkalemia in patients with CKD receiving ACEIs or ARBs [10-12] and its impact on clinical outcomes [8,13]. However, data on the identification of patients at high risk of developing hyperkalemia among patients with CKD receiving ACEIs or ARBs are limited.

When kidney function is normal, circulating aldosterone levels and renal tubule flow rates to the distal nephrons are the major factors that maintain potassium homeostasis by regulating the fractional excretion of potassium [14]. However, in patients with CKD, the flow rate in the remaining functional renal tubules is elevated. Thus, aldosterone plays a major role in regulating renal potassium excretion [15]. Although a variety of factors can modify aldosterone production, the two primary regulators of chronic aldosterone secretion are the concentrations of extracellular potassium and circulating angiotensin II [16,17]. When intravascular volume is reduced, angiotensin II appears to be the most important stimulator of aldosterone production [18]. However, in the absence of an intact renin-angiotensin system, potassium ions may play a predominant role in aldosterone synthesis and release [19,20], suggesting that the serum potassium level is the most powerful regulator of long-term aldosterone production in patients receiving ACEIs or ARBs.

Low serum aldosterone levels in patients with CKD may be associated with the development of hyperkalemia [2,19]. However, serum aldosterone concentrations are widely distributed in patients with CKD; one of the multiple compensatory mechanisms upregulated in CKD to maintain potassium homeostasis is increased aldosterone production [21-23]. Thus, the level of serum aldosterone alone may not be useful in identifying patients at high risk of developing hyperkalemia, and assessment of the physiologic appropriateness of aldosterone production requires consideration of influencing factors such as angiotensin II and serum potassium concentrations.

Plasma aldosterone values corrected for plasma potassium levels have been used to differentiate hyperkalemia due to aldosterone deficiency from renal tubular aldosterone resistance [19,24-26]. However, whether this measure is useful to evaluate the risk of developing hyperkalemia in patients with CKD who are taking ACEIs or ARBs remains unknown. We hypothesized that patients who are unable to increase aldosterone production in response to changes in serum potassium concentrations may develop hyperkalemia upon renin-angiotensin-aldosterone system (RAAS) inhibition. In this study, we evaluated the relationship between the serum aldosterone-to-potassium ratio (APR) and the risk of developing hyperkalemia in patients with CKD receiving ACEIs or ARBs.

METHODS

Participants

Patients with stage 3–4 CKD (estimated glomerular filtration

rate [eGFR], 15–59 mL/min/1.73 m^2) who were managed at the Nephrology Clinic of Jeju National University Hospital in South Korea were evaluated in this study. Eligible participants were required to be 18 years of age or older, had their serum aldosterone levels measured between January 2017 and December 2021, and had been administered an ACEI or ARB for at least 3 months before the time of serum aldosterone measurement. Participants were excluded if they had volume overload indicated by peripheral pitting edema, pleural effusion or ascites, dehydration, hypokalemia (defined as a serum potassium level < 3.5 mmol/L), acute kidney injury (AKI, defined as an increase in serum creatinine ≥ 0.3 mg/dL within 48 hours, or increase in serum creatinine to ≥ 1.5 times baseline within the prior 7 days) [27], or advanced CKD (defined as an eGFR < 15 mL/min/1.73 m^2) at the time of serum aldosterone measurement. Those who were receiving medications known to affect serum potassium levels, such as potassium-sparing diuretics (spironolactone and amiloride), nonsteroidal anti-inflammatory drugs, and potassium exchange resins (calcium polystyrene sulfonate), and those who had inadequate follow-up data on serum potassium (< 1 year) were also excluded. Moreover, patients with serum aldosterone concentrations ≥ 70 ng/dL were excluded because they already had renal aldosterone resistance [26]. Patient compliance was assessed through personal interviews and calculation of the number of prescribed and remaining drugs. A pill count percentage of 80–100% was considered compliant [28]. This retrospective, single-center, observational study was approved with a waiver of patient consent by the Institutional Review Board of Jeju National University Hospital, South Korea (approval number: 2024-01-022) and conducted in accordance with the Declaration of Helsinki.

Measurements

Demographic data, including age; sex; cause of CKD; medication history; and presence of diabetes mellitus (DM), hypertension, and cardiovascular diseases (CVDs), including coronary artery disease, cerebrovascular disease, peripheral vascular disease, and heart failure, were obtained from our hospital database. Baseline serum aldosterone and potassium concentrations and plasma renin activity were simultaneously measured with patients in the sitting position after 5 minutes of rest. Based on these results, the serum APR was calculated (ng/mL per mmol/L), and patients were divided into two groups for comparison according to whether the median value was above or below 2.42. Follow-up serum potassium concentrations were measured every 2–3 months according to the degree of renal dysfunction, or on demand. Serum aldosterone concentration and plasma renin activity were measured using radioimmunoassay. The spot urinary sodium and potassium concentrations were measured using an automated ion electrode method, and the urinary creatinine level was determined using the modified Jaffe method. The ratios of urinary sodium to creatinine and potassium to creatinine were expressed as millimoles of sodium and potassium per gram of urinary creatinine and were used as proxies for dietary sodium and potassium intake [29]. The transtubular potassium gradient (TTKG) was calculated using the following formula [30]: TTKG = $[K^+]$ urine / (urine/serum) osmolality / $[K^+]$ serum.

We estimated the baseline eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation [31] and defined CKD as an eGFR < 60 mL/min/1.73 m^2. In addition, CKD progression was defined as a composite of a ≥ 50% decline in eGFR from the baseline value or onset of end-stage renal disease (ESRD), which was defined as an eGFR < 15 mL/min/1.73 m^2. Patients who were administered ≥ 50% and < 50% of the European Society of Cardiology guideline-recommended target dose of ACEIs or ARBs (Table 1) were categorized into high and low dose groups, respectively [32].

Table 1. Recommended doses of ACEIs or ARBs in patients with heart failure with reduced ejection fraction

	Starting dose	Target dose
ACEIs		
Captopril	6.25 mg t.i.d.	50 mg t.i.d.
Enalapril	2.5 mg b.i.d.	10–20 mg b.i.d.
Lisinopril	2.5–5.0 mg o.d.	20–35 mg o.d.
Ramipril	2.5 mg o.d.	10 mg o.d.
Trandolapril	0.5 mg o.d.	4.0 mg o.d.
ARBs		
Candesartan	4 mg o.d.	32 mg o.d.
Losartan	50 mg o.d.	150 mg o.d.
Valsartan	40 mg b.i.d.	160 mg b.i.d.

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; b.i.d., twice a day; o.d., once daily; t.i.d., three times a day.
Adapted from McDonagh et al. Eur Heart J 2021;42:3599-3726 [32].

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Table 2. Baseline characteristics of patients according to serum aldosterone-to-potassium ratio

Characteristic	Overall (n = 186)	Aldosterone/K ratio < 2.42 (n = 93)	Aldosterone/K ratio ≥ 2.42 (n = 93)	*p* value
Age (yr)	68.4 ± 12.9	70.1 ± 12.4	66.7 ± 13.3	0.074
Sex, male	148 (79.6)	77 (82.8)	71 (76.3)	0.275
Body mass index (kg/m^2)	25.2 ± 4.0	24.7 ± 3.9	25.7 ± 4.0	0.127
Cause of CKD				0.465
Diabetes mellitus	99 (53.2)	54 (58.1)	45 (48.4)	
Hypertension	66 (35.5)	28 (30.1)	38 (40.9)	
CGN	16 (8.6)	9 (9.7)	7 (7.5)	
ADPKD	4 (2.2)	2 (2.2)	2 (2.2)	
Unknown	1 (0.5)	0 (0.0)	1 (1.0)	
Comorbidities				
Diabetes mellitus	111 (59.7)	58 (62.4)	53 (57.0)	0.455
Hypertension	181 (97.3)	90 (96.8)	91 (97.8)	0.650
CVDs	93 (50.0)	52 (55.9)	41 (44.1)	0.107
Heart failure	21 (11.3)	10 (10.8)	11 (11.8)	0.817
Medications at baseline				
ACEIs	16 (8.6)	10 (10.8)	6 (6.5)	0.434
ARBs	170 (91.4)	83 (89.2)	87 (93.5)	0.296
Beta-blockers	77 (41.4)	39 (41.9)	38 (40.9)	0.882
CCBs	112 (60.2)	53 (57.5)	59 (63.4)	0.369
Loop diuretics	41 (22.0)	22 (23.7)	19 (20.4)	0.596
Thiazide diuretics	35 (18.8)	18 (19.4)	17 (18.3)	0.851
Sodium bicarbonate	13 (7.0)	7 (7.5)	6 (6.5)	0.774
Compliant patient	146 (78.5)	74 (79.6)	72 (77.4)	0.721
High dose ACEI or ARB	120 (64.5)	63 (67.7)	57 (61.3)	0.358
Potassium binders	55 (29.6)	33 (35.5)	22 (23.7)	0.077
History of hyperkalemia	68 (36.6)	44 (47.3)	24 (25.8)	0.002
CKD stages				0.052
III	136 (73.1)	75 (80.6)	61 (65.6)	
IV	50 (26.9)	18 (19.4)	32 (34.4)	
Serum Cr (mg/dL)	1.97 ± 0.64	1.87 ± 0.52	2.07 ± 0.72	0.034
eGFR (mL/min/1.73 m^2)	37.8 ± 11.1	39.1 ± 9.8	36.4 ± 12.2	0.103
Serum Na^+ (mmol/L)	140.1 ± 2.7	139.9 ± 2.8	139.8 ± 3.0	0.820
Serum K^+ (mmol/L)	4.8 ± 0.5	4.8 ± 0.5	4.7 ± 0.5	0.745
Serum HCO_3^- (mmol/L)	23.7 ± 3.1	23.8 ± 3.3	23.6 ± 3.0	0.580
Serum aldosterone (ng/dL)	11.0 (7.1–16.3)	7.0 (5.2–9.2)	16.1 (13.3–23.5)	< 0.001
Plasma renin activity (ng/mL/h)	1.12 (0.45–3.30)	1.05 (0.48–2.28)	1.05 (0.41–2.57)	0.793
Urine protein/Cr ratio (g/g)	0.76 (0.16–2.34)	0.98 (0.15–2.53)	0.71 (0.16–1.73)	0.140
No. of K measurement	13.5 ± 6.6	13.7 ± 6.7	13.3 ± 6.5	0.697
TTKG	5.2 ± 2.5	5.4 ± 2.7	5.0 ± 2.1	0.476
Duration of follow-up (yr)	3.1 ± 1.2	3.2 ± 1.2	3.1 ± 1.3	0.468

Table 2. Continued

Characteristic	Overall (n = 186)	Aldosterone/K ratio < 2.42 (n = 93)	Aldosterone/K ratio ≥ 2.42 (n = 93)	*p* value
AKI during follow-up	35 (18.8)	18 (19.4)	17 (18.3)	0.851
CKD progression	50 (26.9)	24 (25.8)	26 (28.0)	0.741
Urine K/Cr ratio during follow-up (mmol/g)	49.4 ± 16.9	47.4 ± 15.9	52.0 ± 16.9	0.074
Urine Na/Cr ratio during follow-up (mmol/g)	111.0 ± 56.6	111.2 ± 55.2	111.0 ± 58.2	0.960

Values are presented as mean±standard deviation, number (%), or median (interquartile range) unless otherwise indicated.
CKD, chronic kidney disease; CGN, chronic glomerulonephritis; ADPKD, autosomal dominant polycystic kidney disease; CVDs, cardiovascular diseases; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; Cr, creatinine; eGFR, estimated glomerular filtration rate; K, potassium; TTKG, transtubular potassium gradient; AKI, acute kidney injury; Na, sodium.

Outcomes

The date of the simultaneous measurement of serum aldosterone and potassium concentrations was considered the index date. Patients were censored at the time of the final serum potassium measurement prior to April 30, 2023, loss to follow-up, death, or the occurrence of ESRD, whichever occurred first. The primary endpoint of this study was the difference in the development of hyperkalemia, defined as a serum potassium level > 5.5 mmol/L between the low (< 2.42) and high (≥ 2.42) serum APR groups. The incidence of hyperkalemic events was computed as the ratio of the total number of hyperkalemic events to the total patient time at risk. Owing to the potential causal association between hyperkalemia and AKI, hyperkalemic events after AKI were excluded from the analysis of the incidence rate.

Statistical analysis

Characteristics at the time of enrollment are presented as mean ± standard deviation (SD) or median (interquartile range, IQR), depending on the data distribution (continuous variables) or frequencies and percentages (categorical variables), as appropriate. The two groups were divided on the basis of a median serum APR of more or less than 2.42 and compared using the Student's t-test or Mann–Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables. The incidence rates of hyperkalemic events and their 95% confidence intervals (CIs) based on Poisson regression models were calculated for each group and expressed per 100 person-years. In addition, the time from the index date to the first occurrence of hyperkalemia in each group was computed and compared using the Kaplan–Meier method and the log-rank test, respectively. A Cox proportional hazards model was used to identify patients at high risk of hyperkalemia. The significant risk factors reported in the univariate analysis, including age, history of DM and hyperkalemia, serum bicarbonate concentrations, CKD progression, as well as high serum APR, and possible risk factors for hyperkalemia, such as sex, dose of ACEIs or ARBs, use of loop or thiazide diuretics, baseline eGFR, urinary sodium-to-creatinine and potassium-to-creatinine ratios, and AKI occurrence during the follow-up period, were analyzed using multivariate regression analysis. Moreover, receiver operating characteristic (ROC) curve analysis was used to assess the predictive power of serum APR and TTKG levels for subsequent occurrence of hyperkalemia. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS Statistics software (version 18.0; IBM Corp., Armonk, NY, USA).

RESULTS

Baseline patient characteristics

A total of 271 patients with stage 3 or 4 CKD were evaluated for eligibility, of whom 85 were excluded from the present investigation for the following reasons: hypokalemia (n = 5), AKI (n = 14), prescription of potassium-sparing diuretics (n = 23) or nonsteroidal anti-inflammatory drugs (n = 12) at the time of enrollment, and inadequate follow-up data on serum potassium levels (n = 31). Finally, a total of 186 patients were enrolled in this study. The baseline characteristics of the study population are shown in Table 2. There were 148 male (79.6%) and 38 female (20.4%) with a mean ± SD age of 68.4 ± 12.9 years. The causes of CKD were DM (n = 99, 53.2%), hypertension (n = 66, 35.5%), chronic glomerulonephritis (n = 16, 8.6%), autosomal dom-

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inant polycystic kidney disease (n = 4, 2.2%), and unknown etiology (n = 1, 0.5%). A total of 111 patients (59.7%) had DM. CVDs were present in 93 patients (50.0%), and 21 (11.3%) had heart failure. Most patients (n = 181, 97.3%) received antihypertensive medications, including ACEIs (n = 16, 8.6%), ARBs (n = 170, 91.4%), beta-blockers (n = 77, 41.4%), calcium channel blockers (n = 112, 60.2%), and loop (furosemide or torsemide; n = 41, 22.0%), or thiazide (hydroxychlorthiazide or chlorthalidone; n = 35, 18.8%) diuretics. Thirteen (7.0%) and 5 patients (2.7%) were taking sodium bicarbonate and sodium-glucose co-transporter 2 inhibitors, respectively. Approximately two-thirds of the patients (n = 120, 64.5%) received high-dose ACEIs or ABRs. None of the patients were administered ACEIs or ARBs simultaneously or immunosuppressive agents such as cyclosporine and tacrolimus, which may alter the potassium balance.

The mean baseline eGFR was 37.8 ± 11.1 mL/min/1.73 m^2. One hundred thirty-six (73.1%) and 50 patients (26.9%) were categorized as CKD stages 3 and 4, respectively. The mean serum potassium concentration at baseline was 4.8 ± 0.5 mmol/L and more than one-third (n = 68, 36.6%) of the patients had a history of hyperkalemia before enrollment. The median baseline serum aldosterone concentration and mean TTKG value were 11.0 ng/dL (IQR, 7.1–16.3 ng/dL) and 5.2 ± 2.5, respectively. While more than four-fifths (n = 156, 83.9%) of the patients had serum aldosterone concentrations within the normal range of 5.0–30.0 ng/dL, only 22 (11.8%) and 8 patients (4.3%) had serum aldosterone concentrations higher and lower than normal values, respectively. The median value for baseline serum APR was 2.42 ng/dL per mmol/L (IQR, 1.54–3.43 ng/dL per mmol/L). The serum APR distribution was not symmetrical; therefore, we divided the study participants into two groups, a low serum APR (< 2.42 ng/dL per mmol/L) and a high serum APR (≥ 2.42 ng/dL per mmol/L) group, according to the median value.

Comparisons between the two serum APR groups of patients

The characteristics of the patients whose serum APR was less (group 1) or more than 2.42 (group 2) are listed in Table 2. There were no significant differences in age, sex, body mass index, prevalence of comorbid DM, hypertension, history of CVDs, heart failure, or CKD etiology or stage. Both groups had similar frequencies of antihypertensive drug use such as ACEIs, ARBs, beta-blockers, calcium channel blockers, and loops or thiazide diuretics. Moreover, the baseline serum sodium, potassium, and bicarbonate levels and TTKG and eGFR values were similar between the two groups. The urinary sodium-to-creatine (111.2 ± 55.2 mmol/g vs. 111.0 ± 58.2 mmol/g, $p = 0.960$) and potassium-to-creatinine ratios (47.4 ± 15.9 mmol/g vs. 52.0 ± 16.9 mmol/g, $p = 0.074$) during the follow-up period were also comparable between the low and high serum APR groups. However, baseline serum creatinine (1.87 ± 0.52 mg/dL vs. 2.07 ± 0.72 mg/dL; $p = 0.034$) and aldosterone concentrations (median, 7.0 ng/dL; IQR, 5.2–9.2 ng/dL vs. median, 16.1 ng/dL; IQR, 13.3–23.5 ng/dL; $p < 0.001$) were lower in group 1 than in group 2. Furthermore, the history of hyperkalemic events was higher in group 1 than in group 2 (47.3% vs. 25.8%, $p = 0.002$).

Outcomes

The patients were followed up for a mean ± SD of 3.1 ± 1.2 years, during which 2,505 measurements of serum potassium levels were obtained (mean ± SD number of potassium measurements per patient, 13.5 ± 6.6, 4.5 ± 1.7 measurements/year per patient). Approximately 7% of the patients (n = 12, 6.5%) had 1–2 serum potassium tests per year, 33.3% (n = 62) had 3–4 tests per year, and 60.2%

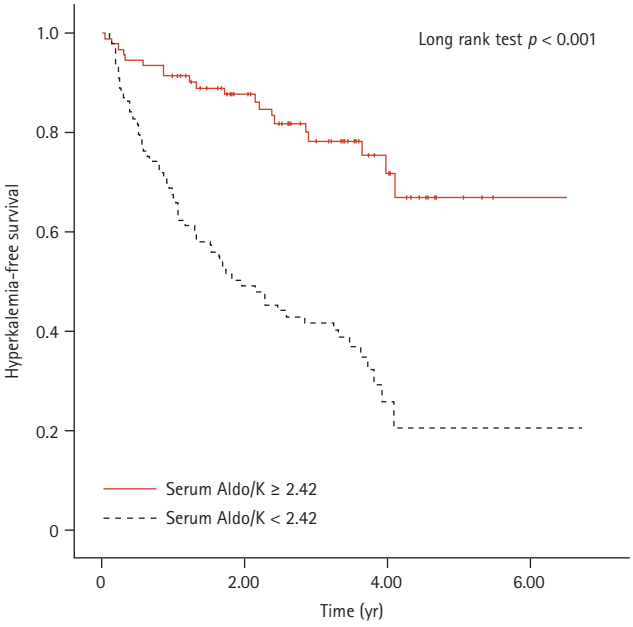

Figure 1. Hyperkalemia-free survival in the low (< 2.42, dotted line) and high (≥ 2.42, solid line) serum aldosterone-to-potassium ratio groups during the follow-up period. Aldo, aldosterone; K, potassium.

(n = 112) had more than 4 tests per year. During the follow-up period, 50 patients (26.9%) had CKD progression; 4 (2.2%) experienced a ≥ 50% eGFR decline and 46 (24.7%) progressed to ESRD. Thirty-five (18.8%), 24 (12.9%), and 8 patients (4.3%) experienced AKI, were lost to follow-up, and died, respectively. The proportion of compliant patients was 78.6%. A total of 144 hyperkalemic events (5.7% of total laboratory tests) in 81 patients (43.5%) were identified over the mean follow-up period of 3.1 years, yielding an incidence rate of 24.6 events (95% CI, 20.4–28.8) per 100 person-years. Of the patients who experienced hyperkalemia, 48 (59.3%) experienced only one event, and the remaining 33 patients (40.7%) experienced recurrent hyperkalemia. Ten patients (12.3%) experienced more than four hyperkalemic events. Of the 81 patients who experienced hyperkalemia, 55 (67.9%) were treated with calcium polystyrene sulfonate to lower their serum potassium levels, and 71 (87.7%) continued ACEIs or ARBs without changing the treatment regimens. In contrast, 10 patients (12.3%) had changes in their prescriptions of ACEIs or ARBs; 8 patients

Table 3. Univariate predictors for the occurrence of hyperkalemia during the follow-up

Risk factor	Hyperkalemia	
	Hazard ratio (95% CI)	*p* value
Age, per year	1.020 (1.001–1.039)	0.035
Sex, male vs. female	1.257 (0.726–2.176)	0.415
Body mass index, per kg/m^2	0.957 (0.902–1.015)	0.145
Diabetes mellitus	2.168 (1.328–3.540)	0.002
Hypertension	2.203 (0.306–15.857)	0.433
Cardiovascular diseases	1.432 (0.923–2.221)	0.109
Heart failure	1.060 (0.530–2.120)	0.869
History of hyperkalemia	3.289 (2.110–5.127)	< 0.001
ACEI vs. ARB	1.431 (0.738–2.776)	0.288
Dose of ACEI or ARB, high vs. low dose	1.603 (0.988–2.601)	0.056
Beta-blockers	0.826 (0.526–1.297)	0.407
Calcium channel blockers	1.250 (0.793–1.969)	0.336
Loop diuretics	0.747 (0.446–1.250)	0.267
Thiazide diuretics	0.687 (0.372–1.269)	0.231
Patient compliance, compliant vs. non-compliant	0.754 (0.458–1.240)	0.265
Baseline serum Cr, per mg/dL	1.371 (0.972–1.934)	0.072
Serum HCO_3^-, per mmol/L	0.881 (0.818–0.948)	0.001
Baseline eGFR, per mL/min/1.73 m^2	0.984 (0.965–1.005)	0.127
eGFR at the time of hyperkalemia, per mL/min/1.73 m^2	0.988 (0.973–1.003)	0.116
CKD, IV vs. III	1.572 (0.970–2.547)	0.066
Urine Na/Cr ratio during follow-up, per mmol/g	1.002 (0.998–1.006)	0.349
Urine K/Cr ratio during follow-up, per mmol/g	0.992 (0.977–1.007)	0.303
TTKG	1.022 (0.917–1.139)	0.697
AKI occurrence during follow-up	1.398 (0.739–2.645)	0.304
CKD progression	1.824 (1.135–2.931)	0.013
Log-serum aldosterone/K ratio	0.490 (0.382–0.630)	< 0.001
Serum aldosterone/K ratio (< 2.42 vs. ≥ 2.42)	4.166 (2.505–6.927)	< 0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Cr, creatinine; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; Na, sodium; K, potassium; TTKG, transtubular potassium gradient; AKI, acute kidney injury; CI, confidence interval.

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(9.9%) discontinued ACEIs or ARBs and 2 (2.5%) were prescribed a reduced dose of these agents.

Hyperkalemia rates were similar in male (27.0 events [95% CI, 24.6–29.4] per 100 person-years) and female (16.2 events [95% CI, 12.7–19.7] per 100 person-years; $p = 0.206$). However, the rates were substantially higher in patients with stage 4 CKD (40.5 events [95% CI, 34.8–46.2] per 100 person-years) than the rates in those with stage 3 CKD (20.4 events [95% CI, 18.3–22.5] per 100 person-years; $p < 0.001$). When the patients were divided according to a median serum APR of 2.42, hyperkalemia occurred more frequently in patients with a low serum APR (65.6%) than in those with a high APR (21.5%; $p < 0.001$). The incidence of hyperkalemic events was also significantly higher in patients with a low serum APR (35.8 events [95% CI, 28.9–42.7] per 100 patient-years) than that in those with a high serum APR (12.9 events [95% CI, 8.8–17.0] per 100 patient-years; $p < 0.001$). In addition, hyperkalemia-free survival was compared between the low- and high-APR groups and was lower in the patients with low serum APR than those with high serum APR ($p < 0.001$, Fig. 1).

Risk factors for hyperkalemia in patients receiving ACEIs or ARBs

To evaluate the clinical predictors of hyperkalemia, we first performed a univariate Cox proportional hazards analysis (Table 3). Older age (hazard ratio [HR], 1.020; 95% CI, 1.001–1.039; $p = 0.035$), DM (HR, 2.168; 95% CI, 1.328–3.540; $p = 0.002$), history of hyperkalemia (HR, 3.289; 95% CI, 2.110–5.127; $p < 0.001$), lower serum bicarbonate concentrations (HR, 0.881; 95% CI, 0.818–0.948; $p = 0.001$), CKD progression (HR, 1.824; 95% CI, 1.135–2.931; $p = 0.013$) during the follow-up period, and a low serum APR (HR, 4.166; 95% CI, 2.505–6.927; $p < 0.001$) were significantly associated with an increased occurrence of hyperkalemia. In contrast, the presence of heart failure (HR, 1.060; 95% CI, 0.530–2.120; $p = 0.869$), the use of beta-blockers (HR, 0.826; 95% CI, 0.526–1.297; $p = 0.407$) and loop (HR, 0.747; 95% CI, 0.446–1.250; $p = 0.267$) or thiazide (HR, 0.687; 95% CI, 0.372–1.269; $p = 0.231$) diuretics, patient compliance (HR, 0.754; 95% CI, 0.458–1.240; $p = 0.265$), and urinary sodium-to-creatinine (HR, 1.002; 95% CI, 0.998–1.006; $p = 0.349$) and urinary potassium-to-creatinine ratios (HR, 0.992; 95% CI, 0.977–1.007; $p = 0.303$) during the follow-up period were not associated with the occurrence of hyperkalemia. The independent risk factors for the primary outcome were assessed using multivariate Cox proportional hazards analysis (Table 4). Older age (HR, 1.000; 95% CI, 0.976–1.025; $p = 0.975$), lower serum bicarbonate concentration (HR, 0.928; 95% CI, 0.846–1.019; $p = 0.116$), and the development of AKI (HR, 1.333; 95% CI, 0.648–2.739; $p = 0.435$) during the fol-

Table 4. Multivariate predictors for the occurrence of hyperkalemia during the follow-up

Risk factor	Hyperkalemia	
	Hazard ratio (95% CI)	*p* value
Age, per year	1.000 (0.976–1.025)	0.975
Sex, male vs. female	1.457 (0.678–3.128)	0.335
Diabetes mellitus	1.967 (1.100–3.516)	0.022
History of hyperkalemia	2.344 (1.372–4.006)	0.002
Dose of ACEI or ARB, high vs. low dose	1.094 (0.593–2.019)	0.774
Loop and/or thiazide diuretics	0.587 (0.332–1.040)	0.068
Baseline eGFR, per ml/min/1.73 m^2	0.990 (0.962–1.018)	0.477
Serum HCO_3^-, per mmol/L	0.928 (0.846–1.019)	0.116
Urine Na/Cr ratio during follow-up, per mmol/g	1.006 (0.999–1.012)	0.086
Urine K/Cr ratio during follow-up, per mmol/g	1.000 (0.978–1.024)	0.977
AKI occurrence during follow-up	1.333 (0.648–2.739)	0.435
CKD progression	2.263 (1.196–4.280)	0.012
Serum aldosterone/K ratio (< 2.42 vs. ≥ 2.42)	3.060 (1.636–5.726)	< 0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; Na, sodium; Cr, creatinine; K, potassium; AKI, acute kidney injury; CKD, chronic kidney disease; CI, confidence interval.

low-up period were not associated with the development of hyperkalemia. Only DM (HR, 1.967; 95% CI, 1.100–3.516; p = 0.022), history of hyperkalemia (HR, 2.344; 95% CI, 1.372–4.006; p = 0.002), CKD progression (HR, 2.263; 95% CI, 1.196–4.280; p = 0.012) during the follow-up period, and a low serum APR (HR, 3.060; 95% CI, 1.636–5.726; p < 0.001) were predictors of the subsequent development of hyperkalemia. When the risk of hyperkalemia was separately analyzed by dividing the patients into stage 3 and 4 CKD groups, a low serum APR was associated with the development of hyperkalemia in both patients with stage 3 (HR, 5.789; 95% CI, 2.325–14.415; p < 0.001) and those with stage 4 CKD (HR, 3.148; 95% CI, 1.204–8.230; p = 0.019). However, the association between baseline eGFR and the development of hyperkalemia remained significant in patients with stage 4 CKD (HR, 0.896; 95% CI, 0.804–0.998; p = 0.045) but not in those with stage 3 CKD (HR, 1.006; 95% CI, 0.959–1.058; p = 0.829) after adjusting for other variables, including a low serum APR.

Predictive performance of the serum APR and TTKG

The ROC curve analysis revealed that the serum APR (area under the ROC curve [AUC], 0.756; 95% CI, 0.685–0.872; p < 0.001), but not the TTKG (AUC, 0.506; 95% CI, 0.384–0.628; p = 0.926), had predictive power for the subsequent occurrence of hyperkalemia (Fig. 2).

DISCUSSION

Hyperkalemia is one of the most common reasons for suboptimal dosing or discontinuation of ACEIs or ARBs in patients with indications for these drugs, such as those with CKD [11,12], and may result in adverse clinical outcomes [7]. Therefore, identifying patients with CKD who are at high risk of developing hyperkalemia is important, particularly those receiving ACEIs or ARBs. In this study, we evaluated whether serum APR can be used for hyperkalemia risk prediction among patients with CKD receiving ACEIs or ARBs, and showed that a high serum APR is associated with the occurrence of hyperkalemia in these patients.

Although aldosterone is the main regulator of potassium balance, evaluating the risk of hyperkalemia based on its serum concentration alone is difficult because aldosterone production may increase, and its serum concentrations are widely distributed in patients with CKD [21-23]. Thus, circulating aldosterone levels that are within the normal range

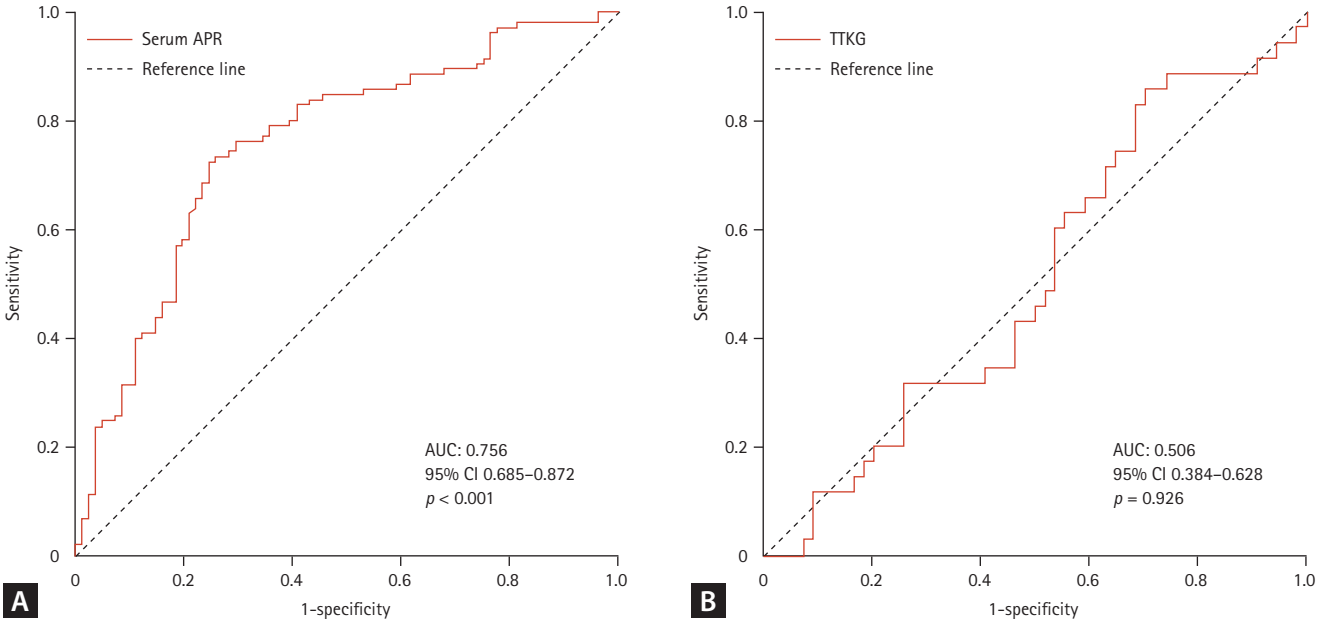

Figure 2. ROC curves for serum APR (A) and TTKG (B) for detecting patients with chronic kidney disease receiving ACEIs or ARBs at risk of hyperkalemia. APR, aldosterone to potassium ratio; ROC, receiver-operating characteristics; AUC, area under the ROC curve; CI, confidence interval; TTKG, transtubular potassium gradient; CKD, chronic kidney disease; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

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may be abnormally low in some patients with CKD. In the present study, more than four-fifths of the patients had serum aldosterone levels within the normal range, indicating that serum aldosterone levels alone may not be useful in determining the risk of hyperkalemia among patients with CKD receiving ACEIs or ARBs.

The plasma APR has been used to differentiate the cause of hyperkalemia between aldosterone deficiency and renal tubular aldosterone resistance [24-26] in patients with CKD. Arruda et al. [24] reported that none of the patients with selective hypoaldosteronism had a volume contraction-stimulated plasma APR above 2 ng/dL per mmol/L, suggesting that this ratio can be used to identify isolated hypoaldosteronism in CKD patients with hyperkalemia (> 5.0 mmol/L). However, their study was limited in that they included only a small number of patients (n = 25) with hyperkalemia, and the GFR variability in the patients was relatively broad, ranging from 10 to 105 mL/min. Adam [26] showed that the calculated factored aldosterone (defined as plasma aldosterone/[plasma potassium - 4.2]) may help distinguish hypoaldosteronism from renal aldosterone resistance in patients with hyperkalemia, suggesting that a value below 10 ng/dL per mmol/L indicates hypoaldosteronism and above this value indicates renal aldosterone resistance. In their study, the cutoff value of the plasma APR between hypoaldosteronism and renal aldosterone resistance was approximately 2 ng/dL per mmol/L. However, the researchers assessed factored aldosterone only in patients with plasma potassium levels > 5.3 mmol/L. In addition, these two studies did not report whether the patients were taking RAAS inhibitors. Moreover, a small prospective study (n = 33) revealed that all of the patients with hypoaldosteronism (n = 16) and pseudohypoaldosteronism (n = 6) had a furosemide- or postural change-stimulated plasma APR below 3 and above 8, respectively, and the mean supine and stimulated plasma APRs were 3.15 ± 0.18 and 5.40 ± 0.43 in the controls (n = 11), respectively, suggesting that the ratio may be a simple and reliable method to evaluate the potassium-aldosterone axis and is a good index to diagnose hypoaldosteronism irrespective of age and renal function [25]. However, in that study, ACEIs were discontinued at least 1 week before commencement of the study. To our knowledge, no clinical study has examined whether plasma APR is useful for evaluating the risk of developing hyperkalemia among CKD patients taking ACEIs or ARBs. In the present study, serum aldosterone concentration was expressed as a function of serum potassium level because serum potassium is the most powerful stimulator of aldosterone production among patients who take RAAS inhibitors [17], and a low serum APR (< 2.42) was associated with the occurrence of hyperkalemia in these patients during the follow-up period. TTKG is considered a more practical index of the activity of the renal potassium secretory process than plasma aldosterone concentration, which is not readily available [33]. In general, a TTKG value of < 6 in patients with hyperkalemia indicates impaired renal potassium excretion [34]. However, the usefulness of TTKG for predicting hyperkalemia in patients with CKD is unknown. One small study reported that TTKG values were lower in CKD patients with drug-induced hyperkalemia than in those without these conditions [35]. However, that study enrolled only a small number of patients (n = 10), and there was a slight overlap in the TTKG values between the patients with and without hyperkalemia, suggesting that a low TTKG does not completely discriminate between CKD patients with and without drug-induced hyperkalemia. In our study, TTKG values were not associated with the occurrence of hyperkalemia and had no predictive power for the subsequent occurrence of hyperkalemia, suggesting that TTKG is not an accurate indicator for estimating hyperkalemia risk in patients with CKD taking ACEIs or ARBs, in contrast to serum APR. Although the reasons that TTKG was not a significant predictor of hyperkalemia in our study are unclear, we can hypothesize that TTKG may be altered in patients with CKD [36,37] and in those who are taking medications that interfere with tubular function, such as ACEIs or ARBs [35].

Patients with mild to moderate CKD can maintain potassium balance via an adaptive increase in renal potassium secretion mediated by elevated plasma potassium and aldosterone concentrations and an increased urinary flow rate [38]. These adaptive changes disappear in patients with advanced stages of CKD. However, the apparent GFR threshold at which these measures become ineffective is not clear, ranging from 10 to 20 mL/min, and the threshold may differ among individuals [39,40]. In the present study, the significant relationship between low serum APR and hyperkalemia was more pronounced, and baseline eGFR was not associated with the development of hyperkalemia in patients with stage 3 CKD. These results suggest that impaired aldosterone response to potassium is a major risk factor for hyperkalemia in patients with stage 3 CKD. In contrast, the combined effects of severely decreased kidney function and low serum APR are responsible for the development of hy-

perkalemia in patients with stage 4 CKD, as indicated by the fact that both baseline eGFR and low serum APR were associated with the development of hyperkalemia in these patients.

The estimated incidence of hyperkalemia (defined as a serum potassium value > 5.5 mmol/L) secondary to ACEIs or ARBs therapy is less than 2% in the general population without risk factors such as CKD [4,10] and has been reported to progressively increase as kidney function worsens [11,12]. However, the exact incidence of hyperkalemia with the intake of a single RAAS inhibitor in patients with CKD is not well known. The definitions of hyperkalemia vary in previous studies and the enrolled patients have different baseline characteristics. An analysis of the United States Veterans Health Administration data reported a hyperkalemia (serum potassium > 5.5 mmol/L) incidence of 92.0 events per 100 person-years in a subgroup of RAAS inhibitors users with CKD (defined by an eGFR < 60 mL/min/1.73 m^2) [3]. However, some patients in the aforementioned study were taking both ACEIs and ARBs, which may result in a relatively increased hyperkalemia rate compared with that of other studies, including ours. A retrospective cohort study conducted in Sweden showed that the incidence of hyperkalemia (serum potassium > 5.5 mmol/L) within the first year of ACEI or ARB therapy initiation was 3.8% among patients with CKD (defined as an eGFR < 60 mL/min per 1.73 m^2) [10]. However, that study reported a hyperkalemic incidence just 1 year after the initiation of ACEI or ARB therapy. Two recent CKD population-based retrospective cohort studies conducted in Australia and Italy reported an overall hyperkalemia incidence in adult patients with CKD treated with RAAS inhibitors of 3.1 events per 100 person-years and 9.2%, respectively [11,12]. However, the definitions of hyperkalemia differed between the two studies (defined as serum potassium > 6.0 mmol/L and > 5.0 mmol/L, respectively), making it difficult to compare the exact incidence of hyperkalemia in these patients. In the present study, we defined hyperkalemia as a serum potassium level > 5.5 mmol/L according to the European Resuscitation Council Guidelines for Resuscitation [41]. This value has been most widely used in previous studies [3,4,13,42]. Our results showed that the overall incidence of hyperkalemia was more than two-fifths (43.5%) during the mean follow-up period of 3.1 ± 1.2 years (an incidence rate of 24.6 events per 100 person-years), indicating that hyperkalemia is frequently observed in CKD patients taking RAAS inhibitors. Therefore, clinicians must monitor these patients closely.

Prior studies have assessed the risk factors for ACEI- or ARB-related hyperkalemia in patients with CKD and revealed that several risk factors such as age [42], male sex [12], reduced baseline GFR [4,11,12,43], baseline serum potassium level [43], urinary potassium level [43], the presence of DM [11,12] or heart failure [4,11], a history of hyperkalemia [13], the use of loop or thiazide diuretics [42], and the dosage of ACEIs or ARBs administered [44] are associated with the development of hyperkalemia. In the present study, heart failure, loop or thiazide diuretic use, and urinary sodium-to-creatinine and potassium-to-creatinine ratios during the follow-up period were not associated with the occurrence of hyperkalemia. DM, history of hyperkalemia, CKD progression during the follow-up period, and low serum APR were predictors of hyperkalemia, indicating that patients with these risk factors should be surveyed more carefully to detect hyperkalemia. Similarly, patients with CKD for whom treatment with ACEIs or ABRs is indicated should be checked for serum potassium levels within 2–4 weeks after initiating or increasing the dose of an ACEI or ARB [45]. However, the frequency of monitoring in real-world clinical practice is not well defined. In our study, we measured serum potassium level every 2 to 3 months (mean annual number of potassium measurements per patient, 4.5 ± 1.7 measurements per year) and observed an incidence rate of 24.6 events (95% CI, 20.4–28.8) per 100 person-years. However, this may not reflect the actual incidence because hyperkalemia can only be detected at visits with serum potassium measurements. Therefore, our data may have underestimated the real-world incidence of hyperkalemia. For example, several population-based cohort studies have reported that the incidence of hyperkalemia was higher among patients in whom serum potassium levels were measured more frequently [10,11].

The most recent Kidney Disease: Improving Global Outcomes guidelines for the management of blood pressure in CKD recommend that patients with CKD and hyperkalemia who are taking RAAS inhibitors should be managed by potassium-lowering strategies including dietary potassium restriction, discontinuation of potassium supplements, certain salt substitutes and hyperkalemic drugs, and adding potassium-wasting diuretics or oral potassium binders rather than decreasing the dose of or stopping RAAS inhibitors. Hyperkalemia is a manageable adverse effect of RAAS inhibitor-containing treatment regimens, and the dose of RAAS

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inhibitors should only be reduced or discontinued in patients whose serum potassium levels failed to normalize despite medical treatment [45]. In the present study, of the 81 patients who experienced hyperkalemia, only 2 (2.5%) and 8 patients (9.9%) had ACEIs or ARBs reduced and discontinued, respectively. Seventy-one patients (87.7%) continued ACEIs or ARBs without changing the treatment regimens after using oral potassium binders and receiving dietary advice on potassium restriction, indicating that measures for hyperkalemia management can allow for the continued use of ACEIs or ARBs in most patients even after the development of hyperkalemia.

Our study had several limitations. First, the study was a small, retrospective, single-center, observational study, and patients with severe renal diseases, such as ESRD, were excluded. Therefore, the results may not apply to patients with general CKD, including those with ESRD. Second, dietary sodium and potassium intakes, which are known to influence serum potassium concentrations, were not measured using the 24 hours urinary sodium and potassium excretion. However, we calculated the spot urinary sodium-to-creatinine and potassium-to-creatinine ratios during the follow-up period and used them as proxies for dietary sodium and potassium intakes. These results did not differ between the low- and high-serum APR groups, indicating that dietary sodium and potassium intakes were comparable between the two groups. Third, we selected patients who were followed up for more than 1 year after the measurement of serum aldosterone concentrations, which may have slightly underestimated the rates of hyperkalemia. Fourth, serum aldosterone levels may be affected by sampling time and position [46]. In the present study, the time of blood sampling for serum aldosterone was not standardized, and the levels were single measurements obtained at varying times. Thus, we could not evaluate the association between changes in serum APR during the follow-up period and the risk of hyperkalemia. In addition, we measured serum aldosterone concentrations in the sitting position but not in the supine or upright positions, making it difficult to compare the serum APR between our results and those reported in previous studies.

Our study revealed that low serum APR was strongly associated with the occurrence of hyperkalemia in patients with CKD receiving ACEIs or ARBs. Our findings suggest that the identification of patients receiving these drugs who are at high risk for subsequent hyperkalemia may be achieved by measuring serum aldosterone and potassium levels simultaneously. We conclude that patients with a higher risk profile for hyperkalemia, such as those with DM, a history of hyperkalemia, CKD progression during the follow-up period, and a low serum APR, require a more thorough evaluation of the serum potassium concentration. However, as stated in the limitations, the sample size in our study (n = 186) was relatively small. Therefore, larger studies are needed to provide more robust conclusions.

KEY MESSAGE

1. In Korean patients with stage 3–4 CKD receiving ACEIs or ARBs, more than two-fifths experienced at least one episode of hyperkalemia over a mean follow-up period of 3.1 years.
2. A low serum APR was strongly associated with the occurrence of hyperkalemia in patients with CKD receiving ACEIs or ARBs.
3. Patients receiving ACEIs or ARBs who are at high risk for subsequent hyperkalemia may be identified by measuring serum aldosterone and potassium levels simultaneously.

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