

Effect of Renin – Angiotensin – Aldosterone System Blockade on Outcomes in Patients With ESRD: A Prospective Cohort Study in Korea



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Introduction: Conflicting results still exist regarding the benefit of renin–angiotensin–aldosterone system (RAAS) blockade on clinical outcomes in dialysis patients. The aim of this study was to evaluate the effects of RAAS blockade on survival in Korean patients with end-stage renal disease (ESRD).

Methods: Our analysis was based on the data of 5223 patients enrolled from the Clinical Research Center for ESRD, a nationwide prospective observational cohort. Multivariate Cox regression was applied for risk factor analysis with the cumulative duration of RAAS blockade use as time-varying covariate. The risks for mortality from all causes and major cardiovascular event–free survival were estimated.

Results: Compared to the control group, patients in the RAAS group were younger but had a higher proportion of diabetes mellitus, had higher systolic blood pressure, required a greater number of prescribed antihypertensive drugs, and had a longer dialysis duration. On multivariate time-varying Cox regression analysis, the RAAS group with cumulative duration of >90 days was significantly associated with a lower risk of mortality from all causes after adjustment for confounding (hazard ratio [HR] = 0.45, 95% confidence interval [CI] = 0.35–0.58, $P < 0.0001$). Major cardiovascular event–free survival was also better for the RAAS group than for the control group on multivariate analysis (HR = 0.27, 95% CI = 0.20–0.37, $P < 0.0001$), considering the cumulative duration of RAAS blockade use.

Conclusion: In Korean patients with ESRD, we reported a specific benefit of RAAS blockade in improving overall survival after adjustment for confounding factors from real-world data.

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KEYWORDS: ACE inhibitor; ARB; dialysis; ESRD; mortality

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Cardiovascular disease is a leading cause of mortality in patients with ESRD, accounting for 30% to 50% of all deaths.^{1,2} Hypertension is a major risk factor for cardiovascular complications, both in the general

population and among patients undergoing chronic hemodialysis therapy, with the prevalence of hypertension increasing dramatically in patients with chronic kidney disease (CKD) as renal function decreases.^{3,4} With hypertension being identified in approximately 70% to 90% of patients at the start of dialysis therapy,⁵ adequate blood pressure (BP) control is crucial in patients with CKD. In fact, in patients undergoing hemodialysis, a J-shaped relationship has been described between BP and prognosis, with the mortality rate being high in this clinical population, in the presence of either hypertension or hypotension.^{6–8}

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Previous studies have reported clinical benefits of treatment of hypertension using RAAS blockade in patients with diabetes mellitus,⁹ early (stages 1–3) chronic kidney disease,¹⁰ and nondialysis CKD, including stages 4 and 5.¹¹ Several studies of patients in chronic heart failure with preserved renal function have reported benefits of RAAS blockade treatment in improving exercise capacity and quality of life,^{12,13} in which improvements in quality of life were largely related to decrease in dyspnea and improvement of the left ventricular (LV) ejection fraction. However, there is conflicting evidence regarding the clinical benefit of using RAAS blockade for the management of hypertension in patients with ESRD on maintenance dialysis.

In patients on chronic hemodialysis, randomized controlled trials evaluating the effects of RAAS blockade on clinical outcomes did not provide conclusive evidence, with only a benefit of RAAS blockade treatment in reducing the mass of the left ventricle being reported, with no clarification of the effect of the treatment on cardiovascular mortality provided.¹⁴ Another meta-analysis revealed that active treatment to lower BP provided a benefit in reducing the risk of overall mortality and of cardiovascular-specific mortality in patients on maintenance dialysis.¹⁵ However, similar to a previous study,¹⁴ subgroup analysis specific to RAAS blockade treatment failed to identify a significant benefit of the treatment in reducing the incidence of cardiovascular events (HR = 0.64; 95% CI = 0.38–1.07).

In this study, we investigated the use of RAAS blockades in dialysis patients in our real-world setting for a large nationwide prospective cohort in Korea. Our final aim was to evaluate the clinical benefits of RAAS blockade used for the treatment of hypertension among patients on maintenance dialysis, as well as cardiovascular-related and overall survival in Korean ESRD patients.

MATERIALS AND METHODS

Data Source and Study Participants

We conducted analyses using the Clinical Research Center for End Stage Renal Disease (CRC for ESRD, NCT00931970) database, which is the only nationwide multicenter prospective cohort of patients with ESRD from 31 tertiary hospitals in Korea. In our study, we included the data from 5223 patients ≥ 18 years of age who were undergoing dialysis between August 2008 and December 2014. Among this cohort, 2320 patients were treated using RAAS blockade (RAAS group), with the other 2903 patients not receiving RAAS blockade comprising the control group. Thirteen subjects whose tracking clinical variables were not accurate were

excluded from the final analysis. Our methods to identify eligible dialysis patients in the CRC for the ESRD cohort and for enrollment in research have been previously published.^{16–18} All of the patients were informed about the study and provided written informed consent. Our study was approved by the institutional review board at each center, and all investigators conducted this study in accordance with the guidelines of the 2008 Declaration of Helsinki.

Clinical Parameters

Our methods for extracting medical history records from the overall CRC for ESRD cohort has previously been described (<http://webdb.crc-esrd.or.kr>).^{16–18} For this study, the following clinical parameters were extracted from the Web-based medical records at the time of enrollment into the study cohort: age, sex, history of diabetes mellitus (DM), cardiovascular disease (CVD), smoking behavior; and dialysis-related information, including primary cause of ESRD, dialysis modality, and dialysis duration. Body mass index was calculated as the body weight divided by the square of the body height (kg/m^2). The Modified Charlson Comorbidity Index (MCCI), which has been validated in patients on dialysis,¹⁹ was determined by reviewing patients' medical history at the time of enrollment. The MCCI was investigated in accordance with International Classification of Diseases, Tenth Revision (ICD-10) code, and its distribution was observed from minimum to maximum as point.

Clinical Outcomes

The primary outcome of our study was the cumulative overall survival rate over the period of observation, with the secondary outcome being the occurrence of a major adverse cardiac event (MACE), defined as all causes of hospitalization due to nonfatal myocardial infarction, hemorrhagic and ischemic stroke, and coronary artery bypass graft surgery or percutaneous coronary intervention. In this study, hospitalization was tracked in the cohort study, and cases of hospitalization with a cardiovascular event were defined as MACE, whereas fatal events were excluded. We also performed a stratified analysis by cardiac parameters based on electrocardiogram (ECG) and echocardiogram findings, as well as cardiac enzymes such as cardiac troponin T and brain natriuretic peptide in incident dialysis patients (patients who started dialysis at the time of study enrollment).

Assessment of Cardiovascular Parameters

Our methods for the evaluation of cardiac parameters have previously been described.²⁰ In our prospective observation protocol, only patients with incident

Table 1. Between-group comparison of baseline characteristics based on RAAS blockade use

Variable ^a	Control group (n = 2903)	RAAS group (n = 2320)	P
Age, yr	57.12 ± 14.05	55.39 ± 12.90	<0.001
Sex, male	1669 (57.5%)	1401 (60.4%)	0.035
Primary renal disease			<0.001
Diabetes	1196 (41.2%)	1069 (46.1%)	
Hypertension	514 (17.7%)	445 (19.2%)	
Glomerulonephritis	396 (13.6%)	329 (14.2%)	
Cystic kidney disease	95 (3.3%)	46 (2.0%)	
Unknown	153 (5.3%)	120 (5.2%)	
Others	549 (19.9%)	311 (13.4%)	
History of CVD	819 (28.2%)	710 (30.6%)	0.059
History of DM	1356 (46.7%)	1174 (50.6%)	0.005
Proportion of prevalent dialysis	1416 (48.8%)	1612 (69.5%)	<0.001
Dialysis modality, hemodialysis, n (%)	2091 (73.0%)	1287 (55.6%)	<0.001
Dialysis duration, mo	53.03 ± 53.58	60.83 ± 50.41	<0.001
Current smoking, n (%)	247 (8.5%)	253 (10.9%)	0.003
Systolic BP, mm Hg	138.3 ± 22.3	141.3 ± 21.8	<0.001
Diastolic BP, mm Hg	77.8 ± 19.0	78.6 ± 13.2	0.092
BMI, kg/m ²	22.8 ± 3.4	22.9 ± 3.3	0.391
MCCI	5.2 ± 2.3	4.9 ± 2.3	0.001
Number of antihypertensive medications	1.3 ± 1.1	2.9 ± 1.0	<0.001
Calcium channel blocker	1326 (45.7)	1588 (68.4)	<0.001
β-Blocker	1062 (36.6)	1402 (60.4)	<0.001
Diuretics	1259 (43.4)	1074 (46.3)	0.035
α-Blocker	259 (8.9)	410 (17.7)	<0.001

BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; ESRD, end-stage renal disease; MCCI, Modified Charlson Comorbidity Index; RAAS, renin–angiotensin–aldosterone system.

^aValues are presented as n (%) for categorical variables and as mean ± SD for continuous variables.

dialysis underwent 2-dimensional (2D) echocardiography, and therefore we present the contents of the cardiologic evaluation of overall incident dialysis patients. In our study cohort, prior to the start of each dialysis session, systolic and diastolic blood pressures were measured using a cuff sphygmomanometer, and the 2D ECG was recorded at rest for 15 minutes. Left ventricular hypertrophy was defined from the ECG using the Cornell voltage criteria,²¹ with the 2D echocardiography procedure consistently performed according to the recommendations by the American Society of Echocardiography.²² Echocardiogram monitoring was discontinued when BP exceeded 250 mm Hg, in the presence of symptoms such as chest pain that did not allow continued examination, or in the event of significant changes on the ECG. The following parameters were measured from the 2D echocardiogram: left atrial dimension (cm), left ventricular end-systolic dimension (cm), left ventricular end-diastolic dimension (cm), left ventricular mass index (g/m²), and left ventricular ejection fraction (%).

Definition of RAAS Blockade Group and RAAS Blockade Use Assessment

Information regarding medication used was determined from medical records at the time of enrollment into the

study, at 3 months after enrollment, and every 12 months thereafter. The following drug prescriptions were recorded at each visit in the CRD for ESRD database: antihypertensive agents, anticoagulants, erythropoiesis-stimulating agents (weekly or monthly dose recorded), vitamin D or calcium supplements, vitamin D receptor activators, and phosphate binders.

First, the RAAS group was formed of patients using an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) at the time of enrollment into the study (0 month) and for the first visit at 3 months for intention-to treat (ITT) analysis (Table 1 and Figure 1). Second, the use of RAAS blockade after the study enrollment was applied as a time-dependent variable in the models. RAAS group was presented for time-varying Cox regression analysis as follows (Tables 2 and 3): RAAS current use (vs. nonuse), cumulative duration of use (>90 days, ≤90 days vs. no use). As mentioned above, this study investigated drug information at 0, 3, and 12 months. At the start point (0 months, the time of enrollment), the person with RAAS use history was defined as taking ~30 days from the index date. Initially, RAAS use history was defined as use 60 days from 30 days after the index date if the patient did not take the RAAS agent at the start time or did not know whether to take it and thus took it at the third month, and the duration of use was defined as 90 days from the index date if it was taken at 0 months and 3 months. If the RAAS agent was taken at 12 months and not taken at 0 or 3 months, the cumulative duration was defined as 275 days after the 90th day; if taken at 0, 3, and 12 months, it was defined as being taken for 365 days. Finally, the RAAS blockade current-use group in this cohort refers to patients in whom use of the drug was confirmed at any point in time and at any dose. The results of multivariate time-varying Cox regression analysis are shown in Tables 2 and 3.

Statistical Analysis

Continuous and categorical variables were compared between the RAAS and control groups using the Student *t* test and χ^2 test, respectively. The figure of the cumulative incidence function for MACE and death, by RAAS group definition for ITT, was adjusted for competing risk.²³ A formal test for differences in survival between the RAAS and non-RAAS group was performed using the modified χ^2 statistic outlined in Gray's previous study.^{23,24}

Multivariate time-varying Cox regression analysis was used to estimate HRs with 95% CIs for risk factor analysis of events, and clinically relevant attributes that were statistically significant on univariate analysis were considered candidate covariates on the multivariate Cox

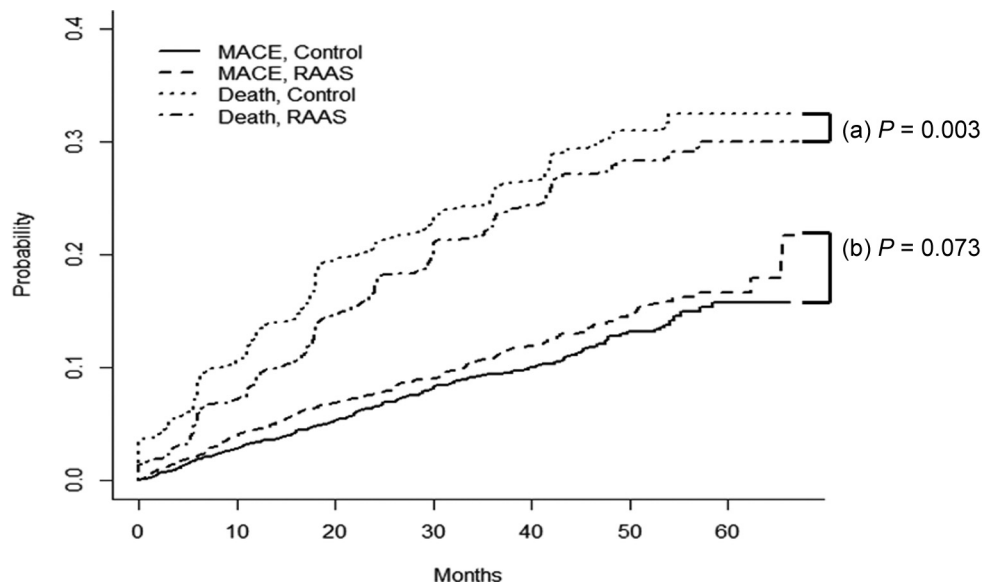


Figure 1. Comparison of the cumulative incidence function between the renin–angiotensin–aldosterone system (RAAS) treatment group and control group for (a) overall survival and (b) major adverse cardiac event (MACE)–free survival in overall study participants. The comparison of MACE probability curves for the study participants between the RAAS group and control group was applied considering the competing risk of death event. The RAAS group was defined as patients who took RAAS for the first 3 months for the intention-to-treat analysis (at the time of enrollment into the study and those who took RAAS for 3 months).

regression. We chose to use a multivariate time-varying Cox regression model to minimize the possibility of bias, as mentioned in previous studies.^{25–27} In this study, we included all possible variables that were clinically relevant from the CRC for ESRD cohort set in the final model. For risk factor analysis, we adjusted for covariates including sex, age, history of DM and CVD, dialysis type, MCCI, smoking history, primary disease of ESRD, prevalent dialysis (vs. incident dialysis), number of antihypertensive medications, and dialysis vintage. Because of the small number of cases in the morbidity categories, we decided to use our model, which had fewer variables but still had the adjusted effects of other comorbidities. Thus, we used the MCCI variable instead of including all of the comorbidities in the time-varying Cox analysis.

All statistical analyses were conducted using the SPSS version 20.0 and R version 2.14 for Windows (<http://cran.r-project.org/>). SAS version 9.3 (SAS Institute, Inc., Cary, NC) was also used for the time-varying Cox regression analysis.

RESULTS

Between-Group Differences in Baseline Characteristics

Patients' baseline characteristics were compared between the RAAS group and the control group (Table 1). Between-group differences in age, sex, primary renal diseases, and comorbidities were identified and are summarized as follows. Patients in the RAAS group were younger than in the control group (55.4 years vs. 57.1 years, respectively; $P < 0.001$) and had a lower likelihood of hemodialysis (55% vs. 73%, respectively;

$P < 0.001$). However, the RAAS group had a significantly higher proportion of patients with DM, CVD, and current smoking as well as a higher prevalence of patients on dialysis and for a longer duration than patients in the control group. Moreover, patients in the RAAS group used a greater number of different types of antihypertensive drugs, and had higher systolic BP (141 mm Hg vs. 138 mm Hg, respectively; $P < 0.001$).

Cumulative Incidence of MACE, With All-Cause Mortality as a Competing Risk

Over the follow-up period, the crude mortality rate from all causes was 19.9% in the RAAS group (462 of 2320 patients) and 19.6% in the control group (570 of 2903 patients), with the RAAS group having a significantly better overall cumulative incidence of death in study participants overall ($P = 0.003$) (Figure 1). The crude rate of MACE was higher among patients in the RAAS group at 13.9% (323 patients) compared to 11.0% in the control group (319 patients) over the follow-up period. Cumulative incidence of competing risk analysis showed that the MACE-free survival did not reach statistical significance between groups ($P = 0.073$) (Figure 1) in study participants overall.

Between-Group Comparison of Risk Factors for Considering the Cumulative Duration of RAAS Blockade Use by Time-Varying Cox Regression Analysis

The risk factors for all-cause mortality and MACE in the RAAS group, as identified using time-varying Cox regression analysis, are summarized in Table 2 and 3.

Table 2. Multivariate time-varying Cox regression analysis for overall mortality considering the duration of RAAS blockade use

Analysis of maximum likelihood estimates ^a			
Parameter	P	Hazard ratio	95% Confidence interval limits
RAAS on cumulative duration >90 days (vs. nonuse)	<.0001	0.45	0.35 0.58
RAAS on cumulative duration ≤90 days (vs. nonuse)	<.0001	0.47	0.38 0.59
RAAS current use (vs. nonuse) ^b	<.0001	5.84	5.05 6.75
Age (per yr)	<.0001	1.03	1.03 1.04
MCCI (per point)	<.0001	1.17	1.14 1.20
Number of antihypertension medications	<.0001	0.89	0.86 0.92
Male sex (vs. female)	0.010	1.12	1.02 1.22
Prevalent dialysis (vs. incident dialysis)	<.0001	2.45	2.19 2.73
Dialysis vintage (<12 mo)	Reference		
Dialysis vintage (12–36 mo)	<.0001	0.35	0.30 0.39
Dialysis vintage (> 36 mo)	<.0001	0.15	0.13 0.17
Current smoker (vs. nonsmoker)	0.254	1.08	0.94 1.25
Primary renal disease			
DM	Reference		
Hypertension	0.008	0.80	0.67 0.94
Glomerulonephritis	<.0001	0.64	0.52 0.79
Cystic kidney disease	0.016	0.65	0.46 0.92
Unknown	0.293	0.88	0.71 1.10
Others	0.001	0.74	0.62 0.88
Peritoneal dialysis (vs. hemodialysis)	<.0001	1.53	1.39 1.67
History of DM	0.134	0.88	0.76 1.03
History of CVD	<.0001	1.29	1.18 1.40

DM, diabetes mellitus; CVD, cardiovascular disease; MCCI, Modified Charlson Comorbidity Index; RAAS, renin–angiotensin–aldosterone system.

^aTime-varying multivariate analysis adjusted for sex, age, diabetes mellitus, cardiovascular disease, dialysis type, Modified Charlson Comorbidity Index, smoking history, primary disease of end-stage renal disease, prevalent dialysis, dialysis vintage, and the number of antihypertension medications.

^bRAAS current-use group: the use of the RAAS blockade in this cohort refers to a case in which the use of the drug is confirmed at any point in time and at any dose.

On multivariate analysis, the RAAS group on a cumulative duration >90 days was associated with a lower risk of mortality from all causes compared to non-RAAS group (HR = 0.45; 95% CI = 0.35–0.58; $P < 0.0001$) and the RAAS group by ≤90 days (HR = 0.47, 95% CI = 0.38–0.59, $P < 0.001$), after adjustment for sex, age, diabetes, CVD, dialysis type, MCCI, smoking, primary disease of ESRD, prevalent dialysis, the number of antihypertensive medications, and dialysis vintage. On the contrary, the RAAS current-use group did not show protective effect in multivariate time-varying Cox regression analysis (HR = 6.04, 95% CI = 5.02–7.26, $P < 0.001$) (Table 2).

The MACE-free survival was also better for the RAAS group than for the control group, after adjustment for covariates on multivariate time-varying Cox analysis. The RAAS group also showed significant benefit in regard to the RAAS group by >90 days compared to the nonuse group (HR = 0.27, 95% CI = 0.20–0.37, $P < 0.001$) and the RAAS group by ≤90 days (HR = 0.28, 95% CI = 0.22–0.35, $P < 0.001$) but not the RAAS current-use group (HR = 6.04, 95%

Table 3. Multivariate time-varying Cox regression analysis for MACE considering the duration of RAAS blockade use

Analysis of maximum likelihood estimates ^a			
Parameter	P	Hazard ratio	95% Confidence interval limits
RAAS on cumulative duration >90 days (vs. nonuse)	<.0001	0.27	0.20 0.37
RAAS on cumulative duration ≤90 days (vs. nonuse)	<.0001	0.28	0.22 0.35
RAAS current use (vs. nonuse) ^b	<.0001	6.04	5.02 7.26
Age (per yr)	<.0001	1.01	1.01 1.02
MCCI (per point)	0.486	1.01	0.97 1.05
Number of antihypertension medications	<.0001	0.90	0.86 0.94
Male sex (vs. female)	0.062	1.10	0.99 1.23
Prevalent dialysis (vs. incident dialysis)	0.125	0.90	0.79 1.02
Dialysis vintage (<12 mo)	Reference		
Dialysis vintage (12–36 mo)	0.013	1.38	1.06 1.78
Dialysis vintage (>36 mo)	<.0001	1.82	1.40 2.37
Current smoker (vs. nonsmoker)	0.008	0.76	0.63 0.93
Primary renal disease			
DM	Reference		
Hypertension	0.380	1.10	0.88 1.36
Glomerulonephritis	0.603	0.93	0.73 1.19
Cystic kidney disease	0.282	0.79	0.52 1.20
Unknown	0.562	0.91	0.67 1.23
Peritoneal dialysis (vs. hemodialysis)	0.073	0.81	0.64 1.02
History of DM	0.003	0.84	0.75 0.94
History of CVD	0.012	1.30	1.05 1.59
History of CVD	<.0001	1.93	1.73 2.16

CVD, cardiovascular disease; DM, diabetes mellitus; MACE, major adverse cardiac event; MCCI, Modified Charlson Comorbidity Index; RAAS, renin–angiotensin–aldosterone system.

^aTime-varying multivariate analysis adjusted for sex, age, diabetes mellitus, cardiovascular disease, dialysis type, Modified Charlson Comorbidity Index, smoking history, primary disease of end-stage renal disease, prevalent dialysis, dialysis vintage, and number of antihypertension medications.

^bRAAS current use group: the use of the RAAS blockade in this cohort refers to a case in which the use of the drug is confirmed at any point in time and at any dose.

CI = 5.02–7.26, $P < 0.001$) on multivariate analysis. As expected, history of CVD was the factor with the highest prognostic value for MACE-free survival (HR = 1.93; 95% CI = 1.73–2.16; $P < 0.0001$) (Table 3).

Between-Group Comparison Based on Cardiac Parameters in Incident Dialysis Patients Including 2D Echocardiography

In this study, RAAS blockade was used for hypertension, but there was no defined treatment indication. According to the prospective observation protocol, only patients with incident dialysis underwent 2D echocardiography, and we added the content of the cardiologic evaluation of overall incident dialysis patients.

Among patients with newly stated dialysis, 690 patients were classified in the RAAS group and 1372 patients in the control group (Table 4). Compared to the RAAS group, a higher proportion of patients in the control group used calcium channel blockers (70.5%) and β blockers (57.1%). There was a significant between-group difference in left atrial dimension

Table 4. Echocardiographic evaluation between RAAS treatment and control groups in overall participants with newly started dialysis therapy

Variables	Control group (n = 1372)	RAAS group (n = 690)	P
Systolic BP (mm Hg)	141 ± 23	143 ± 23	0.092
Diastolic BP (mm Hg)	78 ± 14	78 ± 14	0.263
Proportion of DM	756 (50.8)	427 (60.3)	<0.001
Proportion of CVD	392 (26.4)	185 (26.1)	0.908
Antihypertensive medications (%)			
Calcium channel blockers	883 (59.4)	499 (70.5)	<0.001
β-Blockers	685 (46.1)	404 (57.1)	<0.001
Diuretics	766 (51.5)	395 (55.8)	0.061
α-Blockers	160 (10.8)	83 (3.8)	0.501
Cardiologic evaluation			
LVH on ECG	320 (21.5)	156 (22.0)	0.890
cTnT	0.11 ± 0.27	0.12 ± 0.44	0.569
BNP	15,279 ± 27,325	15,588 ± 23,291	0.858
Echocardiographic parameters			
LAD (cm)	4.12 ± 0.75	4.22 ± 0.69	0.031
LVESD (cm)	3.46 ± 0.82	3.53 ± 0.73	0.173
LVEDD (cm)	5.05 ± 0.79	5.16 ± 0.68	0.013
LVMI (g/m ²)	403.6 ± 198.1	357.9 ± 124.1	0.658
LVEF (%)	58.2 ± 11.7	57.9 ± 10.9	0.669

BNP, brain natriuretic peptide; BP, blood pressure; cTnT, cardiac troponin T; CVD, cardiovascular disease; DM, diabetes mellitus; LVH, left ventricular hypertrophy; ECG, electrocardiogram; LAD, left atrial dimension; LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; RAAS, renin–angiotensin–aldosterone system.

(4.22 ± 0.69 in the RAAS vs. 4.12 ± 0.75 in the control group, respectively; $P = 0.031$), and left ventricular end-diastolic dimension (5.16 ± 0.68 in the RAAS vs. 5.05 ± 0.79 in the control group, respectively; $P = 0.013$), with all other cardiac parameters being comparable between the RAAS and control groups.

DISCUSSION

In this study, we used multivariate time-varying Cox analysis, controlling for confounding, to evaluate the clinical effects of RAAS blockade treatment among patients with ESRD. Overall, patients receiving RAAS blockade treatment tended to be younger than patients in the control group, as well as being more likely to have started dialysis due to diabetes, to be undergoing peritoneal dialysis, and to be using other antihypertensive drugs (Table 1). After correction for covariate, a clinical advantage of RAAS blockade treatment >90 days on overall mortality existed (HR = 0.45; 95% CI = 0.35–0.58; $P < 0.0001$), and similar tendency was shown in MACE-free survival (HR = 0.27; 95% CI = 0.20–0.37; $P < 0.0001$) (Tables 2 and 3). Based on previously published reports of a clinical benefit of RAAS blockade treatment in improving left ventricular hypertrophy in patients with advanced kidney disease,¹⁴ we evaluated the clinical indication for RAAS blockade treatment specifically in patients newly diagnosed with ESRD, taking into account cardiac

parameters such as echocardiography, left ventricular hypertrophy on ECG, and levels of selected cardiac enzymes. There was no significant difference in the other variables. The difference between the 2 groups was that left ventricular mass index was larger in the control group, but this was not statistically significant. Left atrial dimension and left ventricular end-diastolic dimension were significantly larger in the RAAS group, and in this study we could infer that RAAS is indicated mainly in diabetic patients and patients with heart failure and in incident dialysis patients with large left ventricular size (Table 4).

According to the first definition of the RAAS group (the RAAS group was formed of patients using an ACEi or ARB at the time of enrollment in the study and for the first visit at 3 months), this group showed a significantly better overall survival rate for mortality ($P = 0.003$), and the MACE-free survival did not achieve statistical significance between the groups in the competing risk analysis ($P = 0.073$) (Figure 1). In addition, we performed a time-varying Cox regression analysis according to cumulative duration of RAAS blockade use, taking into account the point that actual treatment duration of RAAS blockade could be crucial.²⁵ There are conceptual and analytical challenges in modeling the effects of complex time-varying exposures. Exposure to RAAS blockade after the study enrollment was applied as a time-dependent variable to minimize the immortal time biases. In this study, to avoid length biases due to modeling cumulative exposure duration as a time-fixed covariate, we also used cumulative exposure duration as time-varying covariate.²⁸

The results were quite different for the RAAS current-use group and the group that knew the cumulative duration to specify the duration of RAAS. The RAAS current-use group was defined with the use of the RAAS blockade in this cohort referring to cases in which where the use of the drug was confirmed at any point in time and at any dose. Patients with poor general condition (especially in those with hyperkalemia or intradialytic hypotension) and unable to continue to use of RAAS blockade may be included in this RAAS current-use group. The observational nature of this study means that it is difficult to prove the correct causality by distinguishing the sicker patients, and those with more complicated disease are more likely to include the treatment that was presented in the RAAS current-use group. We have acknowledged that this cohort is a well-recognized cohort with a large number of studies,^{16,17,29,30} including close to 10% of dialysis patients in Korea.³¹ In this regard, we suggest that this tendency reflects the actual real-world data in Korea. Although there may be unresolved bias, at least

in large cohorts of Korea, it is meaningful to have the previously discussed results, and a further study on a well-designed randomized controlled trial with a controlled treatment pattern is needed.

Our results regarding a specific clinical benefit of RAAS treatment among patients with ESRD is not consistent with previously reported data from 2 meta-analyses,^{14,15} from randomized controlled trials,^{32–34} and from a *post hoc* analysis of the outcomes of the HEMO Study.³⁵ One possible explanation is that a difference in the use of ACEi and ARB among patients in the RAAS group may have influenced clinical outcomes. In this study, the RAAS group was defined as RAAS treatment group using only 1 of ACEi and ARB. In some cases (<5%), dual RAAS blockade was prescribed, and this part was also included in the RAAS group. The proportion of ACEi versus ARB users in the RAAS group was somewhat different between the incident dialysis patient group and the maintenance dialysis patient group. In the newly started dialysis patient group, 7.7% received ACEi and 50.2% received ARB. In the maintenance dialysis group, 9.1% received ACEi and 48.1% received ARB. The use of ARB was more frequent than ACEi, reflecting the real-world characteristics of hypertension treatment in Korean ESRD patients. A previous meta-analysis reported clinical benefit of ACEi, but not ARB, on MACE and all-cause mortality among a diabetic population with preserved renal function.⁹ However, other trials evaluating the long-term benefit of ACEi in patients with ESRD on maintain dialysis reported mostly negative results.^{32,35} In the case of ARB, the conflicting results were that positive results were reported regarding the benefit of ARB on cardiovascular outcomes,^{33,36} with negative randomized controlled trial results on cardiovascular and all-cause mortality among patients with chronic hemodialysis.³⁴ In their observational study of >6 years' follow-up of 28,628 patients on hemodialysis in the United States, Chan *et al.* reported a 4-fold increase of ACEi over ARB using a propensity-matched analysis of patients taking ACEi + other drugs and those taking ARB + other drugs.³⁶ Similarly, in our study, we identified about a 5-fold increase in the use of ARB over ACEi, with a rate of MACE-specific mortality of 25% among patients using ARB compared to 28% among patients using ACEi, as in the study by Chan *et al.*, who reported a benefit of ARB + other drugs on cardiovascular survival.

The clinical outcomes of patients on dialysis with RAAS blockade who have an underlying heart condition have previously been evaluated. Using clinical data of patients with ESRD from the US Renal Data System database, Berger *et al.* reported a 43% reduction in the risk of mortality from all causes 30 days

after an acute myocardial infarction among patients treated with ACEi compared to patients not receiving treatment.³⁷ In their evaluation of the effects of different hypertensive drugs in 902 hemodialysis patients with congestive heart failure after a myocardial infarction, the risk of mortality was significantly lower in patients treated with ACEis or ARBs, compared to patients treated with other classes of hypertensive drugs.³⁸ Despite these reported benefits of ACEis and ARBs in patients with previous CVD history, we could not identify specific effects on left ventricular function in study participants overall. In our prospective observation protocol, only patients with incident dialysis underwent 2D echocardiography, so that additional analysis could identify cardiovascular risk factors in the RAAS group in incident dialysis patients (Table 4). As expected, incident dialysis patients with diabetes were significantly more likely to use RAAS treatment, but there was no difference in previous cardiovascular history. Both the left atrial dimension and left ventricular end-diastolic dimension were significantly larger in the RAAS group, and in this study we could infer that RAAS is indicated mainly in diabetic patients and patients with heart failure with large left ventricular size among incident dialysis patients. Moreover, the residual renal function has a great influence on the results of the association between RAAS blockade use and dialysis patients' outcomes.

The limitations of our study need to be acknowledged. Several limitations such as use of prevalent patients (patients who already started dialysis before study enrollment), no adjustment for heart failure in the main study participants, no definite indications for RAAS treatment, residual confounding due to the observational study nature, and low power for some of the outcomes remain. The definition of the RAAS treatment group in this prospective study cohort is also a limitation of this study. This study is a real-world observational cohort study that examined patients from 31 university hospitals and their physicians' decisions on which BP medications were used and which cases of hypertension received treatment. Due to the nature of the research design, it is impossible to control for treatment indications in all patients. Therefore, we designed the additional time-varying analysis to reflect the actual RAAS blockade duration to the nearest actual treatment.

In conclusion, we have reported a specific benefit in the RAAS blockade group with cumulative duration in improving overall survival and MACE-free survival after adjusting for confounding factors in real-world data from Korea. Further research, evaluating the clinical importance of RAAS blockade in Korean ESRD patients with specific subpopulations, is warranted.

DISCLOSURE

All the authors declared no competing interests.

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