ORIGINAL ARTICLE

Mineralocorticoid Receptor Antagonist Use and Hard Renal Outcomes in Real-World Patients With Chronic Kidney Disease

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BACKGROUND: Real-world evidence about mineralocorticoid receptor antagonist (MRA) use has been limited in chronic kidney disease, particularly regarding its association with hard renal outcomes.

METHODS: In this retrospective cohort study, adult chronic kidney disease outpatients referred to the department of nephrology at an academic hospital between January 2005 and December 2018 were analyzed. The main inclusion criteria were estimated glomerular filtration rate ≥10 and <60 mL/min per 1.73 m^2 and follow-up ≥90 days. The exposure of interest was MRA use, defined as the administration of spironolactone, eplerenone, or potassium canrenoate. The primary outcome was renal replacement therapy initiation, defined as the initiation of chronic hemodialysis, peritoneal dialysis, or kidney transplantation. A marginal structural model using inverse probability of weighting was applied to account for potential time-varying confounders.

RESULTS: Among a total of 3195 patients, the median age and estimated glomerular filtration rate at baseline were 66 years and 38.4 mL/min per 1.73 m^2, respectively. During follow-up (median, 5.9 years), 770 patients received MRAs, 211 died, and 478 started renal replacement therapy. In an inverse probability of weighting-weighted pooled logistic regression model, MRA use was significantly associated with a 28%-lower rate of renal replacement therapy initiation (hazard ratio, 0.72 [95% CI, 0.53–0.98]). The association between MRA use and renal replacement therapy initiation was dose-dependent (*P* for trend <0.01) and consistent across patient subgroups. The incidence of hyperkalemia (>5.5 mEq/L) was somewhat higher in MRA users but not significant (hazard ratio, 1.14 [95% CI, 0.88–1.48]).

CONCLUSIONS: MRA users showed a better renal prognosis across various chronic kidney disease subgroups in a real-world chronic kidney disease population. (*Hypertension.* 2022;79:679–689. DOI: 10.1161/HYPERTENSIONAHA.121.18360.) ●
Supplemental Material

Key Words: glomerular filtration rate ■ kidney diseases ■ mineralocorticoid receptor antagonists ■ nephrology ■ renal replacement therapy

Preventing kidney failure with replacement therapy (KFRT) is an ultimate treatment goal for patients with chronic kidney disease (CKD).[1,2] Unfortunately, the global number of patients receiving renal replacement therapy (RRT) has been increasing,[3] despite guideline-recommended therapies for CKD, including the use of ACE (angiotensin-converting enzyme) inhibitors and ARB (angiotensin II receptor blockers). This may be partly because of the phenomenon of aldosterone breakthrough. In patients on long-term ACE inhibitor and ARB therapy, plasma aldosterone levels can increase, which attenuates the renoprotective effects of ACE inhibitors and ARBs.[4–6] Thus, reinforcing the conventional treatment strategy for patients with CKD remains a major clinical issue.

NOVELTY AND RELEVANCE

What Is New?

Even after adjustment for time-varying confounding, mineralocorticoid receptor antagonist (MRA) use was associated with a lower risk of renal replacement therapy initiation in a dose-dependent manner in a real-world chronic kidney disease (CKD) population.

A better renal prognosis in MRA users was consistently observed in patients without diabetes and those with an advanced stage of CKD, who were not included in the FIDELIO-DKD trial.

What Is Relevant?

The clinical benefit of MRA use may extend to MRA subtypes other than finerenone.

MRAs could be renoprotective across various CKD subgroups.

The present study spotlights MRA use, which can reinforce conventional treatment plans for various CKD patients not on dialysis.

Clinical/Pathophysiological Implications?

The present findings suggest the effectiveness of MRA use for preventing kidney failure with replacement therapy across various CKD subgroups in real world. Our observed association of MRA use with better renal prognosis in patients without diabetes and those with severe renal dysfunction can be a valuable complement to the findings from FIDELIO-DKD, which showed the renoprotection by finerenone in those with type 2 diabetes and mild-to-moderate renal dysfunction. Future well-powered randomized controlled trials could be performed to determine whether MRA use decreases the risk of kidney failure with replacement therapy in various CKD subgroups, including patients without diabetes and those with severe renal dysfunction.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ARBs	angiotensin II receptor blockers
CKD	chronic kidney disease
CRP	C-reactive protein
eGFR	estimated glomerular filtration rate
HR	hazard ratio
IPCW	inverse probability of censoring weight
IPW	inverse probability weight
KFRT	kidney failure with replacement therapy
MRA	mineralocorticoid receptor antagonist
MSM	marginal structural model
RCT	randomized controlled trial
RRT	renal replacement therapy
SGLT2	sodium-glucose cotransporter 2

It has been suggested that mineralocorticoid receptor antagonists (MRAs) exert renoprotective effects.[7,8] Inhibition of mineralocorticoid receptor (MR) signaling attenuates glomerulosclerosis, interstitial fibrosis, and podocyte injuries by suppressing inflammation and oxidative stress in CKD model animals.[9] Randomized controlled trials (RCTs) have shown an antiproteinuric effect of MRAs in CKD patients treated with ACE inhibitors or ARBs.[7,8] Furthermore, in a recent RCT of patients with type 2 diabetes, a nonsteroidal selective MRA, finerenone, reduced the risk of hard renal outcomes.[10] However, this finding was limited to albuminuric patients with type 2 diabetes and mild-to-moderate renal dysfunction because of the trial population. Notably, there has been a lack of real-world evidence examining the association between MRA use and hard renal outcomes, including KFRT.

In analyzing the association between MRA use and renal outcomes in an observational study, time-varying confounding should be considered. This is because estimated glomerular filtration rate (eGFR), a potent time-varying confounder, could change after initiation of MRAs, and this change in eGFR may, in turn, affect future MRA use (Figure 1). In the presence of such a bidirectional relationship between the time-varying exposure and confounder, Cox proportional hazards models provide biased estimates.[11,12] Here, we used a marginal structural model (MSM) to examine the effect of MRA use on the risk of progression to KFRT in a real-world CKD population.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

This retrospective, cohort study analyzed consecutive patients with CKD referred to the outpatient department of nephrology at Osaka University Hospital between January 2005 and December 2018. Patients who met all of the following criteria were included: (1) age ≥20 years; (2) eGFR at baseline ≥10 and <60 mL/min per 1.73 m²; (3) followed-up for >90 days; and (4) no prior history of undergoing RRT. The follow-up period was from the first visit date to the date of death, RRT initiation, loss to follow-up, or the end of the study period (May 31, 2019), whichever came first.

The present study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of Osaka
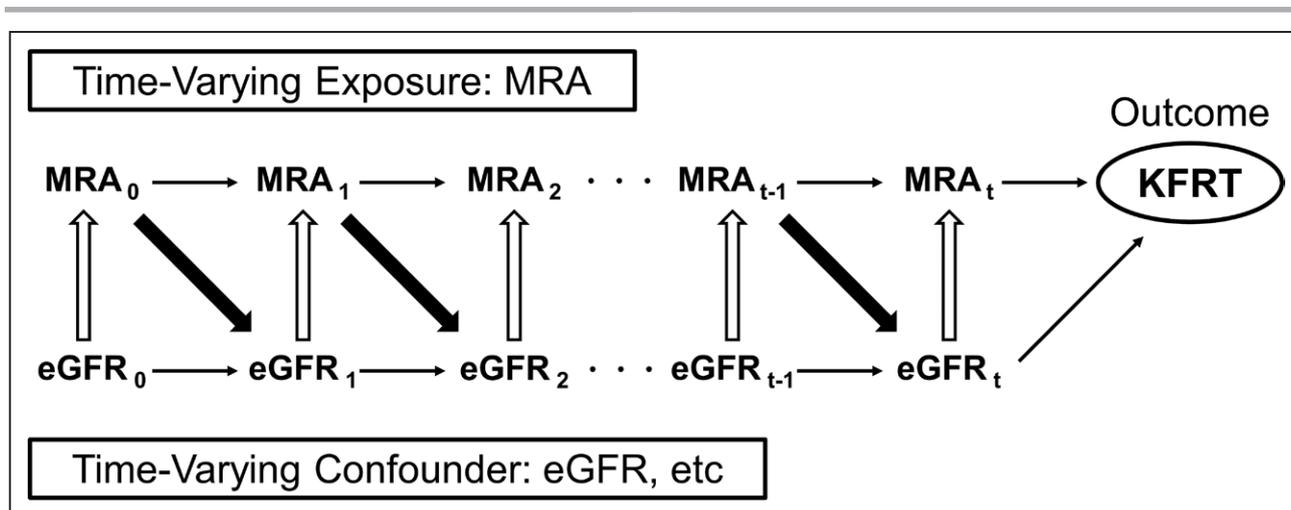
Figure 1. Bidirectional relationship between the time-varying exposure and confounders.
A potential time-varying confounder (eg, estimated glomerular filtration rate [eGFR]) could change after previous treatment (mineralocorticoid receptor antagonists [MRAs]), while this change may, in turn, affect the subsequent treatment (MRAs). Other potential time-varying confounders include urinary protein, angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), and loop and thiazide diuretics in this situation. KFRT indicates kidney failure with replacement therapy.

University Hospital approved the study protocol, waiving the need for informed consent given its retrospective nature (approval number: 20352).

Exposure of Interest and Study Outcomes

The exposure of interest was MRA use, which was treated as a binary time-dependent variable. In Japan, spironolactone, eplerenone, and potassium canrenoate were clinically available. As a sensitivity analysis, the dose of MRAs was also examined as described below.

The primary outcome was RRT initiation, defined as the initiation of chronic hemodialysis, peritoneal dialysis, or kidney transplantation. The secondary outcomes were the composite of death from any cause and RRT initiation, and the composite of eGFR <15 mL/min per 1.73 m^2 and RRT initiation. The events of RRT initiation and death were ascertained based on electronic medical records.

Patients' Characteristics and Laboratory Measurements

Patients' demographics and comorbidities were extracted from electronic medical records. These included age, sex, body mass index, blood pressure, and comorbidities (diabetes, congestive heart failure, coronary heart disease, valvular heart disease, peripheral artery disease, cerebral infarction, intracranial hemorrhage, and liver cirrhosis).

Laboratory and prescription data were collected using an automated data extraction system. Laboratory data included serum albumin, creatinine, sodium, potassium, chloride, CRP (C-reactive protein), hemoglobin, and urinary protein. Urinary protein was measured both semiquantitatively with a dipstick test and quantitatively using the urine protein to creatinine ratio (g/gCre). The eGFRs were calculated using the following Japanese standard formula: $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287}$ (if female, $\times$ 0.739).[13] All data measured throughout the study period were used as time-dependent variables.

Prescription data included loop and thiazide diuretics, ACE inhibitors, ARBs, potassium-lowering agents, SGLT2 (sodium-glucose cotransporter 2) inhibitors, and MRAs. These data were also treated as time-dependent variables.

Statistical Analyses

Data are presented as medians and interquartile range for continuous variables and as numbers and percentages for categorical variables.

Missing values at baseline were imputed by multiple imputation by chained equations.[14] Since covariates with missing values (body mass index, systolic blood pressure, urine protein to creatinine ratio, eGFR, hemoglobin, sodium, potassium, chloride, albumin, and CRP) were continuous variables, we performed linear regression imputation and yielded 5 imputed data sets. These data sets were analyzed separately and combined using Rubin's rules.

Statistical tests were 2-tailed with $P<0.05$ considered significant. All statistical analyses were performed using Stata/IC 14.0 software (Stata Corp, College Station, TX).

Marginal Structural Model

For the main analyses, the MSM was used to validly determine the associations between MRA use and study outcomes. The MSM creates at each time point a pseudo-population in which no time-varying confounding exists (Figure 1) and compares subjects' hazards of outcome events as if they had continuously received the therapy, with those as if they had never received it.[15–17] In the present MSM, the inverse probability weight (IPW), which is the product of the stabilized inverse probability of treatment weight and the stabilized inverse probability of censoring weight (IPCW), was estimated at each patient visit. The inverse probability of treatment weight (or IPCW) was the reciprocal of the probability of receiving MRAs (or being uncensored) predicted by a logistic regression model with baseline and time-varying covariates. The inverse probability of treatment weight (or IPCW) was then stabilized by multiplying them by the probability of receiving MRAs (or being uncensored)

predicted by another logistic regression model with baseline covariates only. The IPWs were truncated at the first and 99th percentiles. Through this MSM approach, it was assumed that MRAs were provided to patients based on their clinical conditions at the current, most recent, and baseline visits. Hazard ratios (HRs) were estimated based on IPW-weighted pooled logistic regression models, which produce estimates equivalent to those of Cox regression models. To minimize potential residual confounding from the variables already included in the IPWs, IPW-weighted models were further adjusted for baseline covariates, which were used to estimate IPWs.[16] In these analyses, an intention-to-treat-like approach[18] was used. This indicates that, once a patient started taking an MRA, they were assumed to remain on it until the end of the follow-up. In the secondary analysis for the composite of eGFR <15 mL/min per 1.73 m² and RRT initiation, patients with eGFR <15 mL/min per 1.73 m² at baseline were excluded.

Baseline covariates included age, sex, body mass index, systolic blood pressure, diabetes, congestive heart failure, coronary heart disease, valvular heart disease, peripheral artery disease, cerebral infarction, intracranial hemorrhage, urinary protein, hemoglobin, eGFR, sodium, potassium, chloride, albumin, CRP, MRAs (for IPCWs only), ACE inhibitors/ARBs, loop diuretics, thiazide diuretics, potassium-lowering agents, SGLT2 inhibitors, and calendar date at baseline.

Time-varying covariates included age, urinary protein, hemoglobin, eGFR, sodium, potassium, chloride, albumin, CRP, MRAs (for IPCWs only), ACE inhibitors/ARBs, loop diuretics, thiazide diuretics, potassium-lowering agents, SGLT2 inhibitors, in- or out-of-hospital setting, and lagged variables of these laboratory data, medications, and hospital setting.

Subgroup analyses were performed to evaluate the interactions between MRA use and prespecified baseline covariates: age, sex, body mass index, systolic blood pressure, diabetes, hemoglobin, sodium, potassium, albumin, CKD stage, urine protein, and ACE inhibitors/ARBs. As recommended in the previous literature,[19,20] P values for interaction were computed by adding each interaction to the IPW-weighted pooled logistic regression model used in the main analysis. The IPWs were then refitted in each subgroup to estimate the HR.

Sensitivity Analyses

Some sensitivity analyses were performed using the MSM approach. First, the association between MRA use and RRT initiation was reassessed by reclassifying patients receiving MRAs for <1 year as MRA nonusers. Second, the association was also reassessed by restricting the analysis to patients without liver cirrhosis. Third, the association between the MRA dose and RRT initiation was analyzed. Multinomial logistic regression models were used to create the stabilized inverse probability of treatment weights for 3 categories of MRA doses (high dose [intravenous injection of potassium canrenoate or ≥50 mg/d of spironolactone/eplerenone] versus low dose [<50 mg/d of spironolactone/eplerenone] versus MRA nonuse). Finally, changes in eGFR over time were compared between those with and without MRAs, using an IPW-weighted mixed-effects model. Interaction terms between MRAs and time (up to a cubic term of time) were incorporated into the model.

Additional Analyses

Progression of proteinuria, defined as worsening category of semi-quantitative urinary protein, was compared between those with and without MRAs, using the MSM approach. The incidence of hyperkalemia, defined as serum potassium levels >5.5 mEq/L, was also compared. In this safety analysis, patients receiving an MRA were additionally censored at the time of its discontinuation. In addition, to assess the potential indication bias that drugs for heart failure, such as MRAs, statins, nitrates, and anticoagulants, might have been prescribed to CKD patients expected to have a favorable renal outcome, further MSM analyses were performed. The associations between the use of these drugs and RRT initiation were examined.

RESULTS

Study Population and Patients' Characteristics

A total of 3195 outpatients with CKD were included in the analyses (Figure 2). The median baseline eGFR was 38.4 mL/min per 1.73 m² (Table S1); the prevalence of patients with eGFR of 30 to 59 (stage 3), 15 to 29 (stage 4), and 10 to 14 mL/min per 1.73 m² (stage 5) was 67%, 25%, and 8%, respectively. Forty-one percent of patients had diabetes, and 6% had heart failure. Of the 104 MRA users at baseline, 91 received spironolactone, and 13 received eplerenone. In total, 770 patients received at least one dose of MRAs during follow-up. Patients' characteristics at MRA initiation in MRA users versus those at baseline in nonusers are shown in the Table. MRA users were older and more likely to have diabetes. MRA users had lower levels of hemoglobin, albumin, and eGFR, and a higher CRP level than nonusers. The percentage of patients receiving ACE inhibitors/ARBs or diuretic agents was higher in MRA users. For some variables, baseline data were missing in some patients, but the frequency was low (at most, 8.6% of the total patients).

Follow-Up and Study Outcomes

During a median (interquartile range) follow-up period of 5.9 (2.9–9.9) years, 1900 patients received ACE inhibitors/ARBs, 211 died (1.00 per 100 person-years), and 478 started RRT (2.26 per 100 person-years). Of 2936 patients with eGFR ≥15 mL/min per 1.73 m² at baseline, 917 reached eGFR <15 mL/min per 1.73 m². In the MSM, MRA use was significantly associated with a 28%-lower rate of RRT initiation (HR, 0.72 [95% CI, 0.53–0.98]; Figure 3, Figure S1), and a 24%-lower rate of the composite of RRT initiation and death (HR, 0.76 [95% CI, 0.59–0.99]; Figure 3). A similar association was observed when the outcome was the composite of eGFR <15 mL/min per 1.73 m² and RRT initiation (HR, 0.75 [95% CI, 0.57–0.99]).

In additional analyses, MRA use was significantly associated with a lower risk of progression of proteinuria (HR, 0.75 [95% CI, 0.59–0.95]). The incidence of hyperkalemia was somewhat higher in MRA users, but not statistically significant (HR, 1.14 [95% CI, 0.88–1.48]). When restricting the analysis to those receiving ACE inhibitors or ARBs at baseline, this association was strengthened but still not
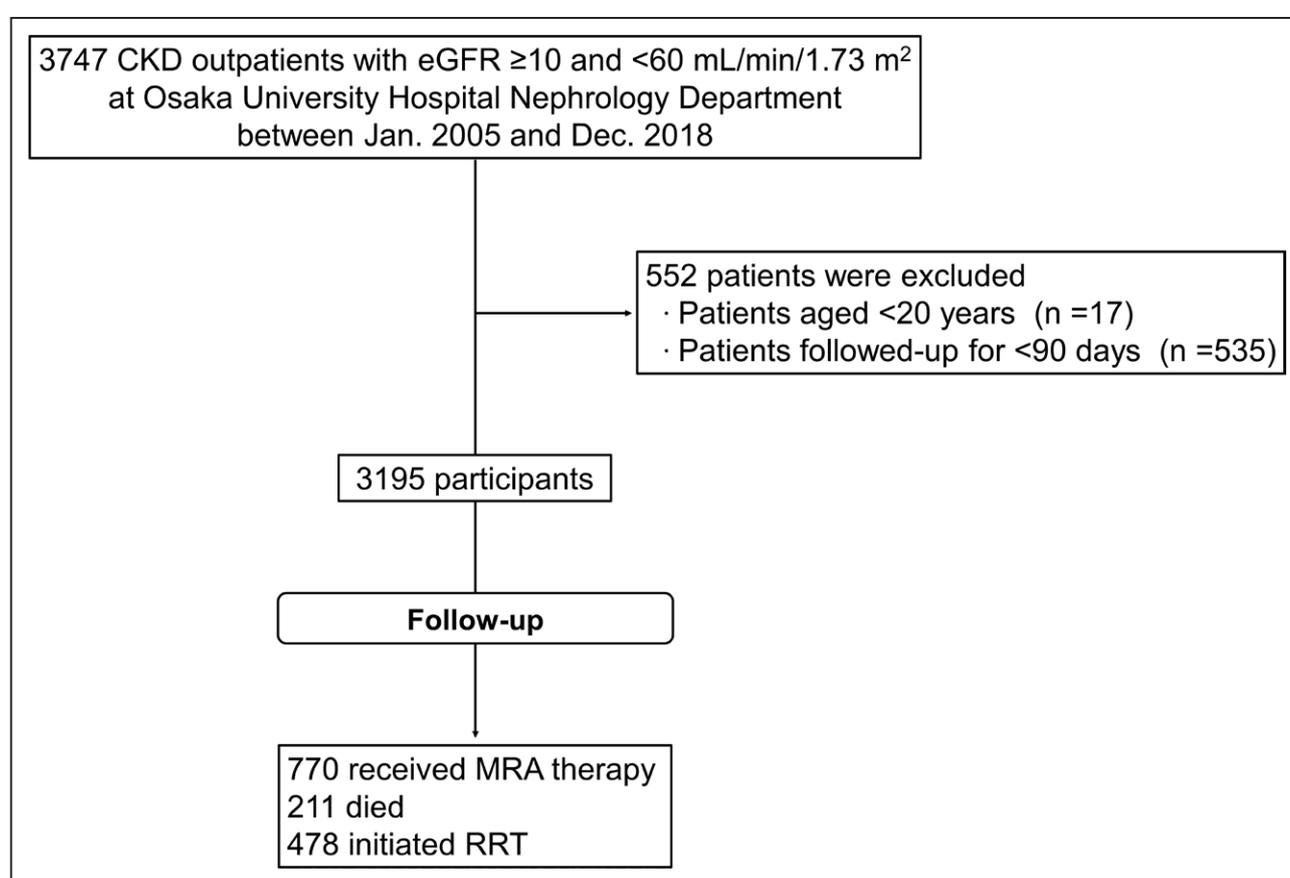
Figure 2. Flow diagram of the study.
CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonists; and RRT, renal replacement therapy.

significant (HR, 1.45 [95% CI, 0.93–2.24]). No significant associations were observed between the use of heart failure drugs, such as statins, warfarin, direct oral anticoagulants, and nitrates, and RRT initiation.

Sensitivity Analyses

Reclassifying patients receiving MRAs for <1 year as MRA nonusers yielded a somewhat stronger association between MRA use and RRT initiation (HR, 0.58 [95% CI, 0.40–0.85]). Restricting the analysis to patients without liver cirrhosis did not change the results substantially (Table S2). Higher MRA doses were associated with more pronounced risk reductions in terms of RRT initiation (P for trend <0.01; Figure S1). A similar association was observed when MRA use was redefined as the use of spironolactone only (Figure S2). In the IPW-weighted mixed-effects model, MRA use was associated with higher eGFRs over time than no MRA use (P<0.01; Figure 4).

Exploratory Subgroup Analyses

The associations between MRA use and the risk of RRT initiation were consistent across all the prespecified

subgroups (Figure 5). Significantly lower risks were observed in patients with and without diabetes, those with CKD stage 4–5, and those with overt proteinuria. Although not statistically significant (P for interaction =0.10), ACE inhibitor/ARB users showed a relatively lower risk of RRT initiation when using MRAs than ACE inhibitor/ARB nonusers.

DISCUSSION

In the present study, MRA use was associated with a lower risk of RRT initiation in a dose-dependent manner in patients with CKD. MRA use was also associated with lower risks of the composite event (RRT initiation and all-cause death) and the progression of proteinuria, than its nonuse. The effect of MRA use on the risk of RRT initiation was consistent across patient subgroups.

Whereas strong survival benefits of spironolactone were shown in hemodialysis patients in previous RCTs,[21,22] the clinical evidence for the renoprotective effects of MRAs has been limited in CKD. Most previous observational studies, RCTs, and meta-analyses focused not on hard renal end points but on surrogate end points, including short-term changes in proteinuria levels and eGFRs.[9,23,24] A recent meta-analysis addressed hard

Table. **Patient's Characteristics at MRA Initiation in MRA Users Versus Those at Baseline in Nonusers**

Characteristics	MRA users (n=770)	Nonusers (n=2425)	*P* value
Demographic characteristics			
Age, y	68 (56–76)	66 (55–74)	<0.001
Sex (male)	502 (65.2%)	1578 (65.1%)	0.950
Body mass index, kg/m²	22.4 (20.2–25.2)	22.7 (20.4–25.0)	0.921
Office systolic BP, mm Hg	126 (110–140)	132 (119–145)	<0.001
Office diastolic BP, mm Hg	71 (61–80)	76 (66–85)	<0.001
Comorbidities			
Diabetes	450 (58.4%)	868 (35.8%)	<0.001
Heart failure	148 (19.2%)	49 (2.0%)	<0.001
Coronary heart disease	123 (16.0%)	177 (7.3%)	<0.001
Valvular heart disease	96 (12.5%)	48 (2.0%)	<0.001
Peripheral artery disease	6 (0.8%)	13 (0.5%)	0.445
Cerebral infarction	24 (3.1%)	52 (2.1%)	0.123
Intracranial hemorrhage	14 (1.8%)	23 (1.0%)	0.049
Liver cirrhosis	42 (5.5%)	33 (1.4%)	<0.001
Medications			
ACE inhibitors/ARBs	411 (53.4%)	216 (8.9%)	<0.001
Loop diuretics	532 (69.1%)	58 (2.4%)	<0.001
Thiazide diuretics	128 (16.6%)	28 (1.2%)	<0.001
SGLT2 inhibitors	4 (0.5%)	0 (0.0%)	0.003
Potassium-lowering agents	61 (7.9%)	89 (3.7%)	<0.001
Laboratory data			
Hemoglobin, g/dL	11.4 (10.0–12.9)	12.3 (10.9–13.8)	<0.001
Albumin, g/dL	3.5 (2.9–3.9)	3.9 (3.6–4.2)	<0.001
Sodium, mEq/L	139 (136–141)	140 (138–141)	<0.001
Potassium, mEq/L	4.3 (3.9–4.6)	4.4 (4.1–4.8)	<0.001
Chloride, mEq/L	105 (102–107)	106 (104–108)	<0.001
Total cholesterol, mg/dL	178 (147–209)	194 (167–222)	<0.001
Blood urea nitrogen, mg/dL	27 (21–40)	24 (18–33)	<0.001
Creatinine, mg/dL	1.5 (1.2–2.0)	1.4 (1.1–2.1)	0.099
eGFR, mL/min per 1.73 m²	34.8 (24.7–45.9)	37.4 (24.1–49.8)	0.013
High-sensitivity CRP, g/dL	1.9 (0.4–17.3)	0.6 (0.2–3.0)	<0.001
uPCR, g/gCre	0.58 (0.13–1.93)	0.52 (0.12–1.80)	0.208

ACE inhibitor indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium-glucose cotransporter 2; and uPCR, urine protein to creatinine ratio.

renal end points but concluded that the effect of MRAs on hard end points was uncertain.[25] The FIDELIO-DKD (The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) trial recently demonstrated that finerenone reduced the risk of hard renal outcomes.[10] However, this trial did not include patients without diabetes, those with advanced CKD (eGFR <25 mL/min per 1.73 m²), or those not receiving ACE inhibitors or ARBs. Therefore, the finding cannot be extrapolated to these patients. While including a more comprehensive patient population, previous observational studies did not consider time-varying confounding between MRA use and renal outcomes.[26,27] Addressing these issues, we showed significant associations of MRAs with hard renal outcomes in a large, real-world CKD population. Importantly, the present data suggest the clinical benefit of MRA use across various CKD subgroups, including patients receiving MRA subtypes other than finerenone, those without diabetes, and those with severely impaired renal function, who were not included in FIDELIO-DKD.

Some underlying mechanisms are proposed for the renoprotective effect of MRAs. First, MRAs could decrease intraglomerular pressure, preventing podocyte injury, progression of albuminuria, and subsequent albuminuria-induced tubular injury.[28–30] Indeed, a
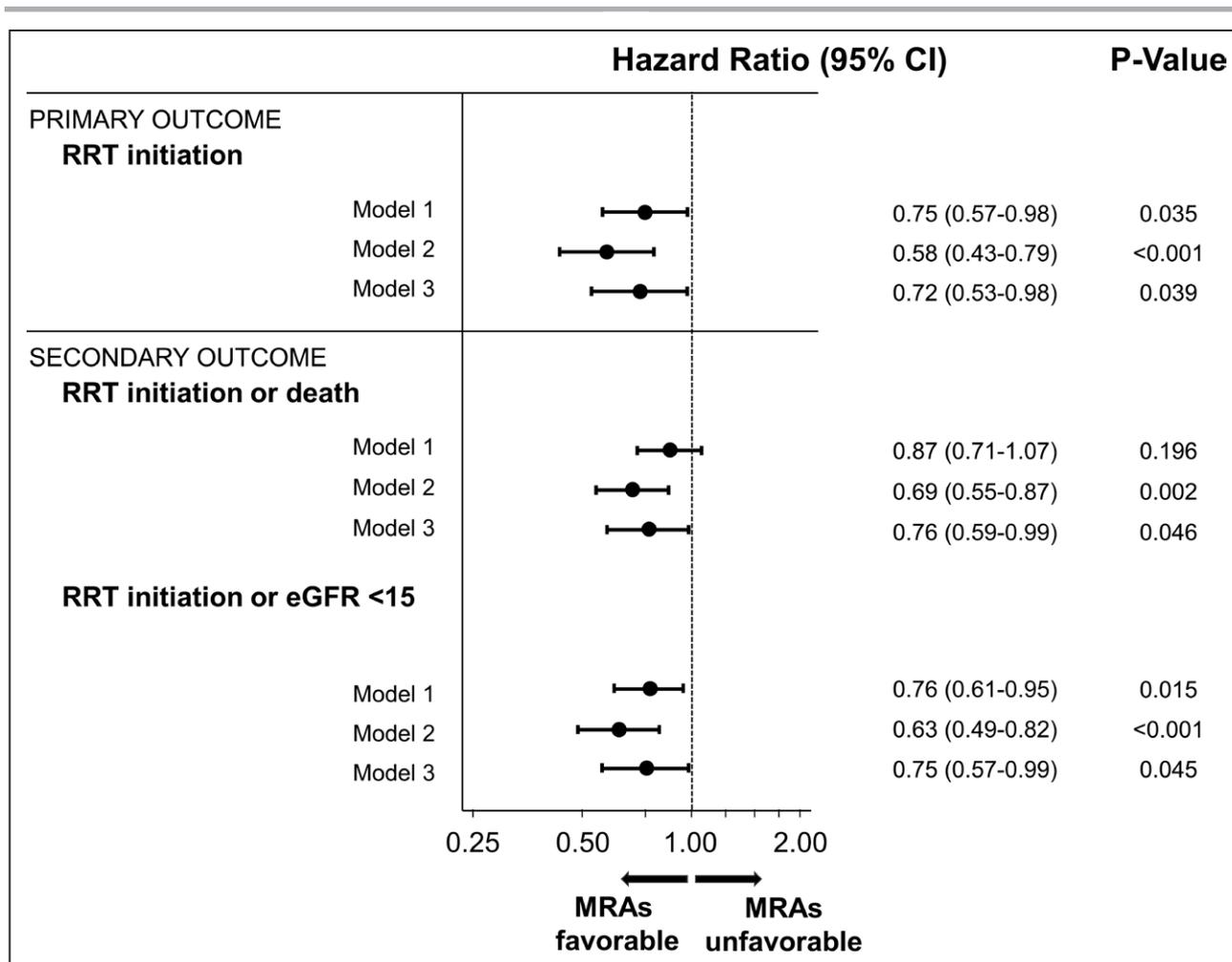
Figure 3. Associations between mineralocorticoid receptor antagonist (MRA) use and study outcomes.
Hazard ratios (HRs) were estimated using pooled logistic regression models, which produce estimates equivalent to those of Cox regression models. The exposure, MRA use, was entered as a time-dependent variable into the model. Model 1: Adjusted for baseline covariates (age, sex, body mass index [BMI], systolic blood pressure [BP], diabetes, congestive heart failure, coronary heart disease, valvular heart disease, peripheral artery disease, cerebral infarction, intracranial hemorrhage, urinary protein, hemoglobin, estimated glomerular filtration rate (eGFR), sodium, potassium, chloride, albumin, C-reactive protein (CRP), ACE (angiotensin-converting enzyme) inhibitors/ARBs (angiotensin II receptor blockers), loop diuretics, thiazide diuretics, potassium-lowering agents, SGLT2 (sodium-glucose cotransporter 2) inhibitors, and calendar date). Model 2: Inverse probability weights (IPW)-weighted model. Model 3: IPW-weighted model with further regression adjustment for baseline covariates (age, sex, BMI, systolic BP, diabetes, congestive heart failure, coronary heart disease, valvular heart disease, peripheral artery disease, cerebral infarction, intracranial hemorrhage, urinary protein, hemoglobin, eGFR, sodium, potassium, chloride, albumin, CRP, ACE inhibitors/ARBs, loop diuretics, thiazide diuretics, potassium-lowering agents, SGLT2 inhibitors, and calendar date), which were already included in the IPW. RRT indicates renal replacement therapy.

meta-analysis reported that drug-induced reduction in proteinuria predicts subsequent renoprotection.[31] This mechanism can reasonably be assumed in the present study because our additional analysis confirmed the lower risk of the progression of proteinuria in MRA users. Second, direct MR blockade could attenuate the deleterious effect of aldosterone breakthrough on renal function.[4–6] In the present subgroup analysis, the association between MRA use and the lower incidence of KFRT was stronger in ACE inhibitor/ARB users than in nonusers, although the P value for interaction was not significant. Third, cardioprotective effects of MR blockade[10,32–34] could prevent long-term worsening renal function, the so-called cardio-renal syndrome type 2.[35] Fourth, effective decongestion

by adding MRAs could provide long-term renoprotection because overhydration was associated with CKD progression.[36,37] Finally, MR blockade could directly reduce oxidative stress and inflammation in the kidney, leading to the prevention of glomerulosclerosis, tubular injury, and fibrosis.[9,38–40] Although the present study did not focus on nonsteroidal MRAs, increasing evidence suggests that some of these renoprotective and cardioprotective effects might be enhanced by finerenone. Compared with steroidal MRAs such as spironolactone, eplerenone, and canrenoate, finerenone works as a bulkier and more passive MR antagonist, reducing the recruitment of inflammatory- and fibrosis-inducing cofactors to the MR, and it has a more balanced kidney-heart distribution.[41]
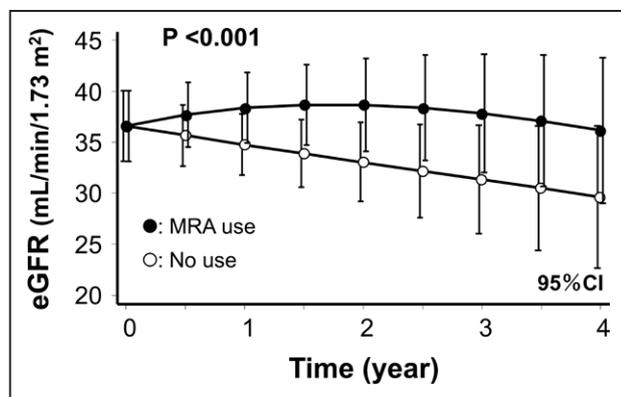
Figure 4. Comparison of changes in estimated glomerular filtration rate (eGFR) over time between patients with and without mineralocorticoid receptor antagonists (MRAs). An inverse probability weight (IPW)-weighted mixed-effects model with time-varying eGFR as a dependent variable was used. Interaction terms between MRAs and time (up to a cubic term of time) were incorporated into the model.

Although recent clinical interest in diabetic kidney disease is shifting toward nonsteroidal MRAs, including finerenone, the present results could rekindle interest in the effectiveness of the use of steroidal MRAs for preventing KFRT. In the present study, steroidal MRA use appeared to be renoprotective, consistent with FIDELIO-DKD[10] and FIGARO-DKD (the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease),[42] the latter of which analyzed patients with earlier stages of CKD than FIDELIO-DKD and showed similar but statistically insignificant renoprotection by finerenone. Admittedly, the present results should be interpreted carefully due to the observational nature of the study. However, it is unlikely that a selection bias due to physicians' preference for MRA use exaggerated the present associations between MRA use and better renal outcomes. This is because this bias, if any, would have affected these associations toward the null, given the relatively poor physical status, including lower eGFR, of MRA users (Table). In addition, reclassifying short-term MRA users as nonusers yielded the somewhat stronger association between MRA use and RRT initiation than that in the primary analysis. This indicates that short-term MRA use did not enhance the observed association, and the present intention-to-treat-like analyses should have been conservative.

To the best of our knowledge, the present study is the first to show the association of MRAs with the risk of hard renal outcomes in a real-world CKD population, addressing time-varying confounding. Extensive adjustment for various potential time-varying confounders was performed using MSM. The study had a large sample size (n=3195) and a long follow-up period (median, 5.9 years). We confirmed the robustness of this association, by showing the dose-dependency of MRAs and comparing eGFRs over time between MRA users and nonusers. The present findings are clinically relevant because

the observed renal benefit of MRA use was confirmed in various CKD subgroups, including patients with and without diabetes, those with advanced CKD stages, and those with overt proteinuria.

This study has some limitations. First, given the nature of the retrospective observational study, a causal relationship between MRAs and hard renal outcomes cannot be proven. Although extensive adjustment for numerous covariates was performed, subgroup analyses were included, and the dose-response relationship between MRA use and RRT initiation was shown, the possibility of residual confounding by unmeasured variables cannot be excluded. Indeed, the retrospective design led to some missing values at baseline in some patients, though not frequently, which was addressed using multiple imputation by chained equations. In addition, physicians' preference for MRA use could have led to a selection bias in the analyses. However, this would have biased the main results toward the null. Second, the prescription data did not show whether patients actually filled their prescriptions. Third, the drug effects were not compared among MRA subtypes because of the limited number of patients receiving eplerenone or potassium canrenoate. Fourth, given that the sample sizes were small in specific subgroups, the insignificant associations between MRA use and KFRT in some subgroups could merely be due to low statistical power. Fifth, our patients were carefully followed-up by nephrologists primarily based on the recommendations made by the Japanese CKD guidelines. Therefore, the present findings cannot necessarily be extrapolated to different clinical settings. Finally, the generalizability of the present results to non-Asian CKD populations is uncertain.

In summary, we examined the association between MRA use and hard renal outcomes in a large, real-world CKD population. Even after adjustment for time-varying confounding, MRA use was found to be associated with lower risks of KFRT and the composite of death and KFRT. This association was consistently observed in patients without diabetes and those with advanced CKD, who were not included in FIDELIO-DKD. The present results suggest that the clinical benefit of MRA use may extend to MRA subtypes other than finerenone. The present study spotlights MRA use by nephrologists, which can reinforce conventional treatment plans in patients with CKD not on dialysis. Well-powered RCTs could be performed in the future to determine whether MRA use decreases the risk of KFRT in various CKD subgroups, such as patients without diabetes and those with severe renal dysfunction.

PERSPECTIVES

Real-world evidence about MRA use has been limited in CKD, particularly with regard to its association
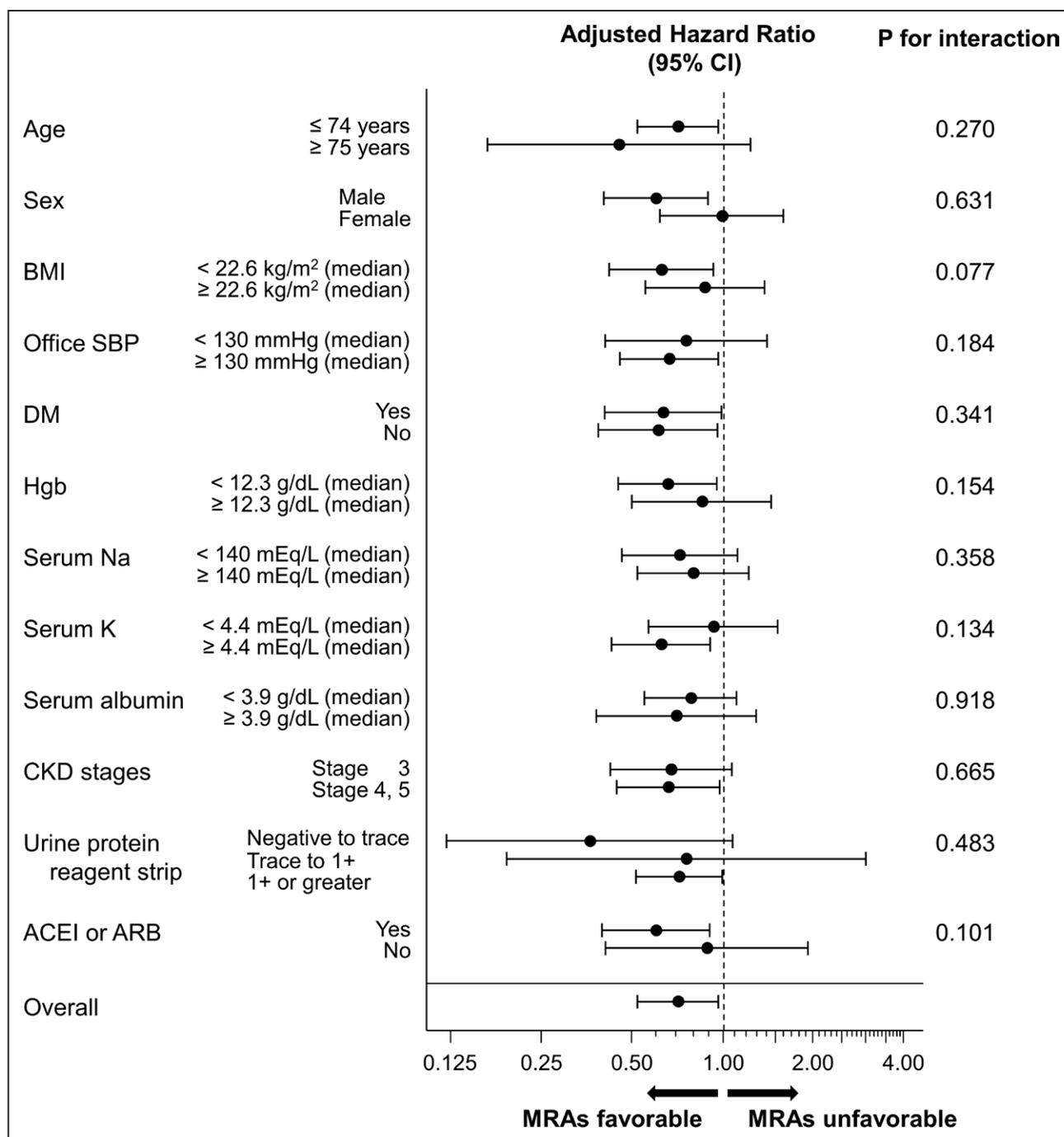
Figure 5. Associations between mineralocorticoid receptor antagonist (MRA) use and renal replacement therapy (RRT) initiation in different subgroups of patients.
ACE inhibitor indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes; and SBP, systolic blood pressure.

with hard renal outcomes. Importantly, time-varying confounding should be considered to validly assess this association. Addressing this issue, the present study first showed that MRA use was significantly associated with a lower risk of RRT initiation in a real-world CKD population. This association was consistently observed in patients with and without diabetes, those with advanced CKD, and those with overt proteinuria, some of whom were not included

in the recent FIDELIO-DKD trial which elucidated the renoprotective effect of finerenone. The present study spotlights MRA use, which can reinforce conventional treatment plans for various CKD patients not on dialysis.

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