Interactive Effectiveness of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers or Their Combination on Survival of Hemodialysis Patients

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Abstract
Background: Does the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers individually or as a combination confer a survival benefit in hemodialysis patients? The answer to this question is yet unclear. ***Methods:*** We performed a case-cohort study using data from the Mineral and Bone Disorder Outcomes Study for Japanese CKD stage 5D patients (MBD-5D), a 3-year multicenter prospective case-cohort study, including 8,229 hemodialysis patients registered from 86 facilities in Japan. All patients had secondary hyperparathyroidism, a condition defined as a parathyroid hormone level ≥180 pg/mL and/or receiving vitamin D receptor activators. We compared all-cause mortality rates between those receiving ACEI, ARB, and their combination and non-users with interaction testing. We used marginal structural Poisson regression (causal model) to estimate the causal effect and interaction adjusted for possible time-dependent confounding. Cardiovascular mortality was also evaluated. ***Results:*** Among 3,762 randomly sampled subcohort patients, those taking ACEI, ARB, and their combination at baseline accounted for 4.0, 31.6, and 3.8%, respectively. Over 3 years, 1,226 all-cause and 462 cardiovascular deaths occurred. Compared to non-users, ARB-alone users had a lower all-cause mortality rate (adjusted incident rate ratio [aIRR] 0.62, 95% CI 0.50–0.76), whereas ACEI-alone users showed a statistically similar rate (aIRR 1.01, 95% CI 0.57–1.77). On the contrary, combination users had a greater mortality rate (aIRR 2.56, 95% CI 1.22–5.37), showing significant interaction (*p* = 0.03). Analysis for cardiovascular mortality showed similar results. ***Conclusion:*** Among hemodialysis patients with secondary hyperparathyroidism, unlike ACEI use, ARB use was associated with greater survival than non-use. Conversely, combination use was associated with greater mortality. Controlled trials are warranted to verify the causality factors of these associations.

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Introduction

Hemodialysis patients experience a higher mortality rate than the general population [1]. The leading cause of this mortality is cardiovascular disease (CVD) [2]. Despite the importance of identifying modifiable patient or dialysis factors or interventions that improve prognosis in these patients, interventions for handling traditional cardiovascular risk factors that reduce mortality in the general population, as well as hemoglobin normalization, modification of dialysis prescription, and mineral metabolism have failed to decrease all-cause or cardiovascular death in these patients [3–7].

Renin-angiotensin system inhibitors (RASIs), angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers are widely used in hemodialysis patients [8]. Despite this, few studies have evaluated the impact of RASIs on the mortality of these patients. Although several randomized control trials (RCTs) showed that RASI reduced the incidence of deaths, patient numbers were small and the studies used an open-label design [9–12]. Similar results were obtained from observational studies, but these did not estimate the effect of ACEI and ARB separately [13–15] and did not consider the possibility of time-dependent confounding: blood pressure (BP) levels probably associated with mortality [16] are both affected by previous RASI use and influence the future prescription of RASI. This time-dependent confounding cannot be adjusted appropriately and produces bias if conventional analysis such as time-dependent Cox regression is used [17, 18]. Thus, it remains unclear whether ACEI or ARB independently confers a survival benefit on hemodialysis patients. In particular, the effect of their combined therapy probably used for better control of BP and further cardiovascular protection on mortality versus no treatment or their interaction has not been investigated.

Here, we explored the association of ACEI, ARB, and their combination with mortality in hemodialysis patients, with interaction testing. We used marginal structural models (MSMs) that allow the estimation of causal effects and interactions adjusted for baseline and time-dependent variables, with consideration to possible time-dependent confounding [18, 19].

Materials and Methods

Data Source and Study Design
The study was conducted under a case-cohort design using data from the Mineral and Bone Disorder Outcomes Study for Japanese CKD stage 5D patients (MBD-5D), a 3-year prospective multi-center case-cohort study [20]. MBD-5D recorded clinical outcomes, including all-cause and cardiovascular mortality, from December 2007 to January 2011 in 8,229 maintenance hemodialysis patients with secondary hyperparathyroidism (SHPT) registered at 86 facilities in Japan. Participants were followed every 3 months (from visit 0 at registration to visit 12). Clinical data were prospectively updated every 6 months as time-dependent variables, excluding serum albumin, MBD-related serum markers (calcium, phosphorus, intact parathyroid hormone [iPTH]) and prescriptions (vitamin D receptor activators, phosphate binder, and calcimimetics), which were updated every 3 months. A total of 3,276 patients were randomly selected from the whole cohort at a sampling rate of 40% (Fig. 1). Subcohort participant data were collected prospectively, while data for those outside the subcohort were collected retrospectively only when they died. Age, gender, and iPTH were collected in all 8,229 participants to clarify eligibility.

Study Population
The study population consisted of hemodialysis patients who participated in the MBD-5D. Candidates were all patients in the participating facilities who had received hemodialysis for more than 3 months as of January, 2008. Of these, patients with an iPTH level more than 180 pg/dL, the definition of SHPT in Japan according to the 2008 guideline [21], or receiving an intravenous or oral vitamin D receptor activator for SHPT treatment, were enrolled into the whole cohort.

Outcomes, Exposures, and Covariates
Primary outcome was all-cause mortality. Cardiovascular mortality was also evaluated, defined as death due to heart failure, myocardial infarction, cerebrovascular disease, sudden death, arrhythmia, aortic disease, or other CVD.

Exposure of interest was RASI use. The data were categorized into 4 classes: ACEI, ARB, combination, and none. They were handled as time-dependent variables updated every 6 months.

Covariates were collected as baseline-fixed variables (age, gender, cause of end-stage kidney disease, vintage of dialysis, smoking, and comorbid conditions; online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000482013), and time-dependent variables (body mass index, and data at the section of dialysis, laboratory data, and prescription of drugs; online suppl. Table 1). In Japan, calcimimetics became available in January, 2008. For missing covariates, we conducted multiple imputations with IVE ware [22]. Each of the 5 imputed data sets was constructed by repeating 10 iterations of sequential imputation for missing data based on a regression model according to the type of variable missing [23], and used to compute the final estimates.

Statistical Analysis
The primary analysis estimated the adjusted incidence mortality rate ratio (aIRR) using MSMs (online suppl. method). These allow the results for exposure effects obtained in nonrandomized studies to be interpreted as an estimation of the average causal effect of exposure after pseudo-randomization of patients to different use of RASI while balancing the distribution of potential time-dependent confounders [18, 19] called causal models. A marginal structural Poisson regression model with robust variance was used to compare the outcomes (visit t) for ACEI,

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Fig. 1. Design of this case-cohort study and number of deaths. Of the total of 8,229 participants as the whole cohort, 40% were randomly sampled as a subcohort. Over 3 years, clinical data of patients included in the colored area were actually collected prospectively in subcohort patients and retrospectively in cases outside the subcohort when they died.
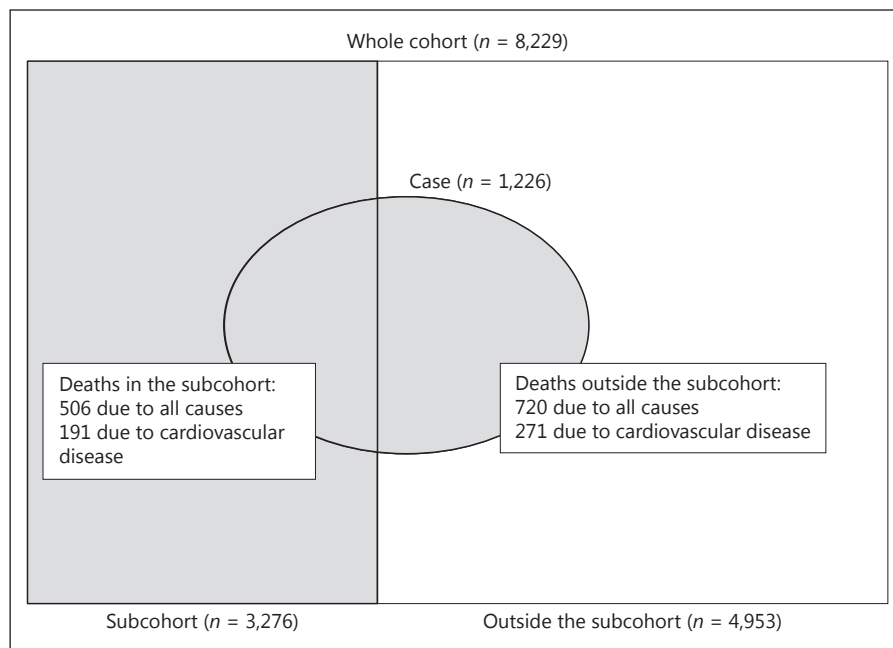
ARB, or their combination use, versus no treatment (visit t-1), with an interaction test between ACEI and ARB for mortality [24], while controlling for possible time-dependent confounding by covariates (visit t-2) such as time-dependent systolic or diastolic BP; these were modeled as sixth-degree polynomials that influence both future RASI use and mortality, and might also act as intermediates between past RASI use and mortality.

The models for aIRR estimation included the main effect of RASI use and the baseline-fixed variables mentioned above with weighting by the stabilized inverse probability of RASI treatment weight (SW). The final estimated weights for aIRR estimation also took account of censoring weights from the inverse probability of loss to follow-up and sampling fraction of the random subcohort for SWs [25, 26]. Primary analysis was conducted with standard MSMs (i.e., untruncated) to avoid exacerbating the inaccuracy of estimations by truncation [27].

Sensitivity Analysis

We checked that the distribution of SWs was the mean of the one that was required for the correct model specification to conduct appropriate weighting, as well as the distribution of the finally estimated weights to confirm the presence of extremely large weights [27, 28]. We also examined the truncation of SWs at 100, 50, and 10 to assess the influence of large weights on our results [29]. Then, to explore the model specification for estimating inverse probability weights [27], we first examined the influence of a change in the number of pre-dialysis BP categories on the effect estimate of exposure. Second, we assessed the influence of the step-by-step addition of potential confounders to the models in calculating weights on the effect estimate.

Secondary Analysis

We compared the mortality of ACEI or ARB users to that of combination users, or each other, using the same models as in the primary analysis by changing the reference category of RASI. We then evaluated the consistency of the association between RASI and mortality in the models with longer time-lags among outcomes (visit t), RASI use (visit t-2), and time-dependent confounders (visit t-3). Further, we calculated aIRR with conventional analysis of baseline-fixed or time-dependent Poisson regression models in this population. The same covariates as in the primary analysis were used for the models, while the time-dependent variables were fixed at baseline for the baseline-fixed model.

A 2-sided *p* < 0.05 indicated statistical significance. Data were analyzed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics

The 3,276 patients in the random subcohort had a median hemodialysis duration of 8.3 years and diabetes mellitus rate of 31.6% (Table 1). Baseline age, gender, and iPTH levels were similar to those of other participants (online suppl. Table 2). Baseline RASI use was 31.6% for ARB, 4.0% for ACEI, and 3.8% for combination. Over 3 years, these remained similar at every visit, whereas the cumulative proportion of patients who changed RASI class once or more increased to 41.2% during follow-up (online suppl. Fig. 1). Median pre-dialysis systolic and diastolic BP fluctuated between 140 and 150 or 70 and 80 mm Hg respectively. Compared to other RASI users, combination users had higher BP and proportion of using antihypertensive drugs and diabetes, while they had similar or fewer proportion of other car-

Table 1. Baseline characteristics related to blood pressure and antihypertensive treatment in participants enrolled in the subcohort (n = 3,276), and their stratification by 4 classes of RAS inhibitor use

Variable	Total value	Total n	None (n = 1,985)	ACEI (n = 131)	ARB (n = 1,034)	ACEI and ARB (n = 126)	p value
Age, years	63 (54–71)	3,276	63 (55–71)	62 (54–68)	62 (54–71)	62 (53–69)	0.09
Gender, female, %	38.5	3,276	41.4	31.3	35.8	22.2	<0.001
Duration of dialysis, years	8.3 (3.7–14.3)	3,273	8.9 (4.1–15.9)	9.6 (4.3–15.5)	6.8 (3.0–11.9)	6.7 (2.9–11.4)	<0.001
Diabetes mellitus, %	31.6	3,250	27.3	38.5	37.3	45.2	<0.001
Coronary artery disease, %	27.7	3,238	28.3	33.9	25.5	30.2	0.13
Cerebrovascular disease, %	16.3	3,239	15.6	16.3	18.1	12.7	0.22
Pre-dialysis blood pressure, mm Hg							
Systolic	151 (136–166)	3,262	148 (131–164)	155 (140–170)	155 (141–170)	160 (147–176)	<0.001
Diastolic	80 (70–88)	3,201	79 (70–87)	80 (72–90)	80 (71–90)	80 (72–90)	<0.001
Post-dialysis blood pressure, mm Hg							
Systolic	137 (120–153)	3,110	132 (116–148)	136 (124–150)	145 (129–160)	148 (132–164)	<0.001
Diastolic	74 (65–82)	3,030	72 (63–80)	76 (70–84)	77 (70–85)	75 (68–85)	<0.001
Ultrafiltration rate, L/h	0.65 (0.48–0.8)	3,272	0.63 (0.48–0.78)	0.69 (0.53–0.85)	0.65 (0.5–0.8)	0.73 (0.53–0.88)	<0.001
Calcium channel blocker, %	43.7	3,276	27.8	67.9	66.1	85.7	<0.001
Beta blocker, %	7.1	3,276	4.8	13.7	9.4	18.3	<0.001
Diuretic, %	13.0	3,276	10.9	14.5	15.7	22.2	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RAS, renin-angiotensin system. For continuous variables, median and interquartile range (IQR) are shown. Differences were evaluated by the Kruskal-Wallis test for continuous variables, and by the χ^2 test for categorical variables.

All baseline characteristics used for statistical analysis as covariates were described in online supplemental Table 1.

diovascular risk factors such as past history of CVD (online suppl. Table 1).

Compared to controls, cases were older and had a higher proportion of comorbidity with diabetes, CVD, and antiplatelet and anticoagulant drug users (online suppl. Table 3). They also had lower pre- and post-dialytic BP and baseline proportion using antihypertensive drugs such as calcium channel blockers and RASI.

Crude Incidence Rate and Rate Ratio of Deaths

Crude incidence curves over 3 years and rate ratio of deaths are shown in online supplemental Figure 2. In all, 1,226 patients experienced all-cause death, 506 in the subcohort and 720 outside it (Fig. 1). The incidence rate of all-cause death was 5.5 events/100 person-years. Of these 1,226 deaths, 462 were due to CVD (incidence rate, 2.1 events/100 person-years). Compared to non-users, any of ACEI, ARB, and combination use had a lower crude all-cause mortality rate. The

results for cardiovascular mortality were similar, except for no significant difference for ACEI and combination users.

Association of ACEI, ARB, or Their Combination with Mortality

Figure 2 shows the association of RASI use with mortality, adjusted for time-dependent confounding with MSMs. Compared to non-users, ARB users had a lower all-cause mortality rate (adjusted incidence rate ratio [aIRR] 0.62, 95% CI 0.50–0.76), whereas ACEI users had a statistically similar rate (aIRR 1.01, 95% CI 0.57–1.77). Conversely, combination users had a greater mortality rate (aIRR 2.56, 95% CI 1.22–5.37), showing significant interaction (p = 0.03). The results for cardiovascular mortality were similar. ARB users had a lower mortality rate (aIRR 0.61, 95% CI 0.44–0.84), whereas ACEI users did not (aIRR 0.81, 95% CI 0.37–1.75). Combination users had a greater mortality rate (aIRR 2.84, 95% CI 1.62–2.98) with significant interaction (p = 0.02).
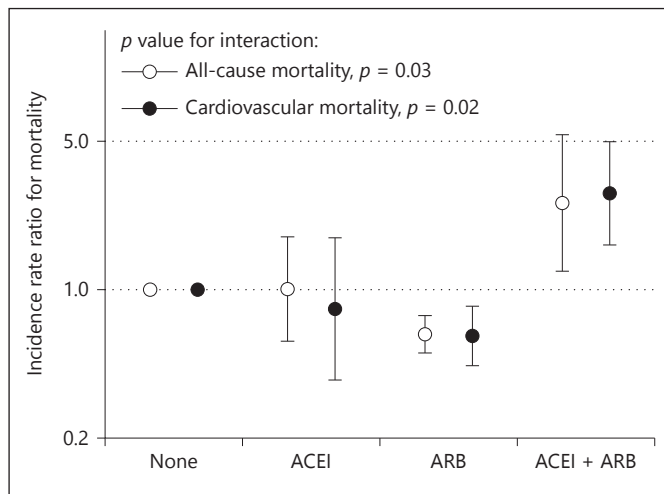
Fig. 2. Association of ACEI, ARB, and their combination use with all-cause and cardiovascular mortality rate. Incidence rate ratios and results of interaction tests have been adjusted for possible time-dependent confounding using marginal structural Poisson regression models. The none category is provided as a reference for comparison. Bars denote 95% CIs. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Sensitivity Analysis

Distribution of the estimated stabilized inverse probability of RAS inhibitor treatment weight (SW) showed a mean of near-one in all 5 datasets for multiple imputation (online suppl. Table 4). Few patients had an extremely large weight, even after considering both censoring weights and random sampling fraction. Truncation of SWs at 100, 50, and 10 did not change the results, except that the significant association between combination and mortality was lost with truncation at 10 (online suppl. Table 5).

When an increasing number of BP categories and the method of step-by-step addition of covariates were introduced to explore model construction for estimating SWs (online suppl. Table 6, 7), the effect estimate increased to maximum in the model that fully included the covariates with 6 BP categories, which we therefore adopted. Variance similarly increased but changed toward the null with this adopted model. With 7 BP categories, the effects could not be computed. Elimination of variables with many missing values at baseline before imputation did not change the results.

Secondary Analysis

Compared with either ACEI or ARB users, combination users had greater all-cause and cardiovascular mortality rates (Table 2). ACEI users had a statistically similar

but greater mortality rate than ARB users. The longer time-lag association of RASI with mortality showed similar results to those of the primary analysis, while the association of ARB with cardiovascular mortality was not statistically significant (online suppl. Table 8). Conventional analysis and analyses with MSMs differed in this study population (online suppl. Table 9). Compared to non-users, any class of RASI user trended toward lower all-cause and cardiovascular mortality. Of these, ARB users in all analyses and ACEI or combination users in the baseline-fixed analysis for all-cause mortality reached statistical significance.

Discussion

We found that ARB use in maintenance hemodialysis patients with SHPT was associated with lower all-cause mortality, whereas ACEI use was not. Moreover, combination use was conversely associated with greater mortality, with significant interaction between ACEI and ARB use. Analysis for cardiovascular mortality showed similar results. To our knowledge, this is the first study to address the effect of combined ACEI and ARB versus no treatment on mortality in a hemodialysis setting, with concurrent evaluation of the individual effects of ACEI and ARB and their interaction. Thus, our results from MSMs estimating the average causal effect of exposure suggest that ARB use may help decrease mortality in hemodialysis patients with SHPT over ACEI therapy, and that their combination may be conversely detrimental.

Our results are consistent with most previous reports in hemodialysis patients. Several RCTs evaluated composite cardiovascular events, including all-cause or cardiovascular death, and demonstrated that ARB reduced these events, whereas ACEI did not [9–11]. Although one RCT failed to show a survival benefit of ARB, adherence to ARB use was only 51%, possibly causing misclassification that attenuated the effect of ARB [12]. Observational studies indicated a significant association of RASI treated as a binomial variable with all-cause mortality [13–15]. Only one study assessed the associations of ARB and ACEI separately in subgroup analysis, and the results again suggested that ARB was beneficial, whereas ACEI was not [14]. For combination use, a comparative effectiveness study showed an association with increased risk of cardiovascular death compared to ARB alone, as was showed in this study [30]. In non-dialysis patients with vascular disease or high-risk diabetes, combination use was also associated with more ad-

Table 2. Comparative effectiveness among ACEI, ARB, and their combination on all-cause and cardiovascular mortality

	RAS inhibitor use		
	ACEI vs. ARB	ACEI + ARB vs. ARB	ACEI + ARB vs. ACEI
All-cause mortality			
Crude incidence rate ratio	1.15 (0.78–1.69)	1.12 (0.74–1.68)	0.98 (0.57–1.68)
Adjusted incidence rate ratio	1.63 (0.92–2.91)	4.15 (2.02–8.52)	2.56 (1.04–6.32)
Cardiovascular mortality			
Crude incidence rate ratio	1.35 (0.77–2.39)	1.42 (0.81–2.51)	1.05 (0.49–2.24)
Adjusted incidence rate ratio	1.34 (0.60–2.98)	4.70 (2.67–8.25)	3.50 (1.49–8.26)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RAS, renin-angiotensin system.
Values and 95% CIs calculated using marginal structural Poisson regression models were shown.

verse events without an increase in benefit compared to ACEI alone [31].

Meanwhile, inconsistent with our results, a recent RCT limited to hemodialysis patients with CHF reported that combination use had a lower all-cause mortality rate than the use of ACEI alone [32]. No other investigation of RASI focused on CHF patients in hemodialysis settings has appeared. In non-dialysis patients, however, one RCT, which similarly enrolled CHF patients only, showed a survival benefit for combination use beyond that of ACEI-alone use [33]. Also, ACEI has been shown to reduce mortality or composite cardiovascular events not only in CHF patients [34] but also in non-CHF patients with high vascular risk [35]. These findings suggest that ACEI or combination use might benefit CHF patients, including dialysis patients. Until our present results can be conclusively confirmed, it may be preferable that ACEI be precautionarily withheld, and used only in combination for CHF patients.

Mechanisms of the differential effects of RASI on mortality have not been determined. A recent study in hemodialysis patients demonstrated that molecular regulation of the RAS system was highly distorted by ACEI and ARB, both alone and in combination [36]. ARB increased angiotensin II (Ang2) and suppressed Ang1–7 to a minimum, whereas ACEI and combination showed similar regulation, increasing Ang1–7 and suppressing the others (excluding increased Ang1–10 with ACEI). Ang1–7 activates G protein-coupled MAS receptor as an alternative RAS pathway, which might have both beneficial and detrimental clinical effects [37, 38]. ACEI also blocks Ang2 type1 receptor incompletely, because Ang2 is generated through an ACE-independent pathway, and is strongly removed by dialysis, whereas ARB is not affected. Further, ACEI activates the kallikrein-kinin system, which is

further activated by contact of blood with the dialyzer and dialysate [39]; and also promotes the generation of bradykinin, which also has both beneficial and detrimental effects [40, 41]. Concerning the detrimental effect of combination use, a recent explanation plausibly suggested that this resulted from the activation of a pathway induced by renin and prorenin under dual suppression of RAS, through highly efficient generation and activity of Ang2, and activation of the intracellular signal transduction pathway directly involved in tissue damage [42]. Thus, these complex interplays between beneficial and detrimental effects, when further affected by the unique characteristics of hemodialysis, may yield the differential effects of RASI in hemodialysis patients, particularly regarding the attenuation of the beneficial effects of both ACEI alone and in combination with ARB.

One of the strengths of our study is the use of MSMs. No previous study was considered for possible time-dependent confounding; therefore, our results are more likely to be true than such previous nonrandomized studies. Crude and conventional analyses in this study population were inconsistent with those from MSMs, indicating that considerable time-dependent confounding is in fact present. Exploring the construction of the model as sensitivity analysis confirmed that our effect estimate in MSMs had high precision and better control of confounding. Truncation of SW did not influence our results, while statistical significance in the association of combination with mortality disappeared only with truncation at 10. This might have been due to insufficient adjustment for confounding, because approaching truncation toward 1 means approaching the state of adjustment for baseline variables only [27]. The longer time-lag analyses as secondary analysis were also consistent with our results. Although the association between ARB and mortality did

not reach significance, misclassification of RASI use during long time-lags may attenuate the association. In fact, 41.2% of the random subcohort experienced one or more changes in RASI class during the study.

This study population was limited to hemodialysis patients with SHPT. They are likely to have higher cardiovascular and mortality risk by exposure to abnormal mineral and bone metabolism represented by high iPTH levels or their treatments, partially through vascular calcification or fraction [43]. This might increase power to estimate the effect of RASI use for mortality in a precise manner. Also, Japanese physicians had made efforts to control iPTH levels within the target level of 60–180 pg/mL until recently according to the 2008 guideline [21]. Although prevalence in Japan is not known, a nationwide annual survey in 2009 reported that those with an iPTH level over 180 pg/mL accounted for 32.9%, while oral or intravenous vitamin D receptor activator users accounted for 38.3 and 26.5% respectively [44]. Hemodialysis patients with both iPTH levels below 180 pg/mL and no vitamin D receptor activator use may show different results from our study. However, this limitation applies to many previous studies conducted in hemodialysis patients with only hypertension, CHF, or left ventricular hypertrophy [9–12, 14]. Our consistency with these published studies may support the generalizability of our results. Second, the small number of ACEI and combination user might reduce power to estimate their effect precisely. If a larger number of patients taking ACEI, especially those with CHF, were randomly selected to study population as representative for target population, ACEI use might show significant association with reduction of mortality. Nonetheless, we believe that our finding of statistical significant difference from such study population suggests the association of RASI use with mortality and their interaction is robust. Why few participants were taking ACEI or combination is unclear. Japanese physicians might be affected by hard-to-use characteristics of ACEI such as activation of generating bradykinin by contacting dialyzer, a side effect of cough, or removal by dialysis, and possibly by excessive pharmaceutical promotion for beneficial effect of ARB, reported by some since-retracted papers. Third, our study design might have included residual confounding. Even MSMs cannot adjust for unmeasured confounders, such as indications for RASI use, similar to other propensity score techniques including the matching. We also had no information on drug dose. An insufficient dose of ACEI may prevent the detection of an association with mortality. Further, we did not collect data on side effects of

RASI such as serum potassium levels to be detected for their abnormal elevation and intradialytic hypotension; because these affect future use of RASI, they might be important time-dependent confounders. Finally, subgroup analysis was not achieved because marginal structural analysis did not converge, likely due to the small number of patients following stratification.

In conclusion, among hemodialysis patients with SHPT, ARB use was associated with greater survival than non-use, whereas ACEI use was not. Combination use was conversely associated with greater mortality, showing significant interaction. These inconsistent effects of RASI reinforce the importance of clearly differentiated use of ACEI, ARB, and their combination in clinical practice, despite their categorization as RASIs. Controlled trials are warranted to verify the causality of these associations.

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