RAS Inhibitor Is Not Associated With Cardiovascular Benefits in Patients Undergoing Hemodialysis in Japan

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Abstract: Definitive evidence of whether renin angiotensin system (RAS) inhibition is beneficial on cardiovascular events (CVE) among patients undergoing hemodialysis (HD) is lacking. The objective of this study was to investigate the association of RAS inhibitor usage with CVEs in patients enrolled in the Dialysis Outcomes Practice Pattern Study in Japan (J-DOPPS). Association of RAS inhibitor prescription with outcomes including all-cause death, death caused by CVE, and hospitalization due to cardiac failure was investigated by using a multivariable Cox proportional hazards model. Of the 3848 patients enrolled, 1784 (45%) patients were treated by RAS inhibitors. After adjusting for potential confounders by Cox proportional hazards models, we found a statistically insignificant but positive association of RAS inhibitor usage with death caused by CVE (HR: 1.46, 95%CI: 0.96–2.23, P = 0.08). Similar results were observed in the association of RAS inhibitor with all-cause death, hospitalization due to cardiac failure, and hospitalization due to CV disease (HR for all-cause death: 1.24, 95%CI: 0.84–1.48, P = 0.28, HR for hospitalization due to cardiac failure: 1.24, 95%CI: 0.84–1.81, P = 0.28, and HR for hospitalization due to CV disease: 1.20, 95%CI: 0.95–1.51, P = 0.13). Sensitivity analyses using propensity scores gave similar results. RAS inhibition did not show favorable association with CVEs suggesting that RAS inhibition alone was insufficient to reduce the risk of CV complications in patients undergoing HD. Some strategies in addition to RAS inhibition may be needed to protect against CVEs in this population. Key Words: Cardiovascular disease, Hemodialysis, Renin-angiotensin system inhibitor.

Cardiovascular (CV) disease is the leading cause of death in patients receiving hemodialysis (HD), with mortality rates several fold higher than the general population (1,2). It is present in more than 50% of patients undergoing dialysis (3).

Despite the significant frequency of morbidity and mortality, limited therapeutic options are available to prevent progression of CV disease in this growing patient population. The majority of CV primary and secondary prevention clinical trials have excluded patients undergoing dialysis. Therefore, it remains unknown if the results from clinical trials establishing the efficacy of treatment strategies in the management of CV disease apply to the patients undergoing dialysis.

Renin angiotensin system (RAS) inhibitor such as angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) is one of the therapeutic options, which has been established to prevent fatal and nonfatal CV events (CVEs) in general population (4–7). However, their effects on clinical endpoints in patients receiving HD also remain uncertain. In addition, therapeutic agents such as erythropoiesis-stimulating agents (8,9) or statins (10–12) with proven benefit in the general population failed to display similar efficacy in these patients.

In the present study, we investigated the association of RAS inhibitor usage with CVEs in patients enrolled in the Dialysis Outcomes Practice Pattern Study in Japan (J-DOPPS).
MATERIALS AND METHODS

Study data
We used data from J-DOPPS, a prospective cohort study performed on a nationally representative sample of adult HD patients from more than 60 randomly selected dialysis facilities in Japan. J-DOPPS was part of the Dialysis Outcomes and Practice Patterns Study (DOPPS) aimed at clarifying the association between HD practice and patient outcomes using worldwide samples across countries. Details of the DOPPS sampling and study methods have been described previously (13). All participants provided informed consent, and the study was approved by the institutional review board of Kyoto University Graduate School and Faculty of Medicine, Ethics Committee. The study subjects were selected from J-DOPPS III (2005–2008) and IV (2009–2011) if data on the usage of RAS inhibitor at the start of observation (baseline) were available.

Outcomes and exposure
The outcomes of interest were the incidences of death and hospitalization. We examined four outcomes: (i) deaths caused by cardiovascular disease (CVD) including ischemic heart disease, sudden death, cardiac tamponade, cardiomyopathy, stroke, and pulmonary edema; (ii) all-cause deaths; (iii) hospitalizations due to congestive heart failure (CHF) including fluid overload, pulmonary edema, and cardiac tamponade, and (iv) hospitalizations due to CVD including cardiac revascularization and respiratory failure in addition to the CVDs listed above. The date of incidence of these outcomes was identified for each patient, and the survival time was defined as the period from the start of observation to the occurrence of the first event. A subject was censored after the first event.

The exposure of interest was the use of a RAS inhibitor at the baseline.

Statistical analysis
To describe patient characteristics, continuous variables were shown as means and standard deviations, and categorical variables as percentages. The occurrences of death and hospitalization were described as incidence rates.

In analyses of associations between use of RAS inhibitor and outcomes, non-adjusted and multivariate-adjusted Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs). In the multivariate-adjusted model, the following possible confounders were included: age, gender, years of dialysis, smoking status, body mass index (BMI), end-systolic blood pressure, single-pool Kt/V, fluid removal rate at the start visit of a week, seven comorbid statuses (diabetes, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, pulmonary disease, neurological disease, and malignancy), the presence of residual renal function, the number of drugs prescribed (polypharmacy), serum levels of phosphorus, calcium, intact parathyroid hormone (PTH), albumin, hemoglobin, C-reactive protein (CRP) and potassium, and administration of calcium channel blockers, beta blockers, other antihypertensive drugs, oral and intravenous vitamin D receptor activators, and calcium-containing and non-calcium-containing phosphate binders.

Two sensitivity analyses using propensity scores were carried out to confirm the results from multivariable Cox regression. First, propensity-score matching (PS matching) was used to identify patients with similar baseline characteristics. The propensity score was estimated by using a logistic regression model, with the use of a RAS inhibitor as the dependent variable and all of the covariates mentioned above as the independent variables. A 1:1 matching algorithm was used with a caliper width of 0.01 (available at www2.sas.com/proceedings/sugi26/p214-26.pdf), which identified 936 pairs. Hazard ratios were estimated using a Cox regression. Secondly, weighted Cox regression with the inverse probability of treatment weighting (IPTW) and robust variance was carried out. The IPTW approach compares outcomes in two pseudo-populations with and without the exposure (the use of a RAS inhibitor), which have the similar covariate distributions. Balance and imbalance of covariates between two exposure groups before and after the matching or weighting were assessed using standardized differences. Standardized differences of less than 10% for a given covariate indicate a relatively small imbalance.

Hazard ratios were also obtained in subgroups stratified by the presence of comorbid CVD or presence of comorbid diabetes. Statistical tests for interactions of CVD or diabetes were carried out using regression models with an interaction term and likelihood ratio tests.

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).
RESULTS

Patient characteristics
Among the 4,118 patients included in DOPPS III and IV, data on the baseline use of RAS inhibitor were available for 3,848 (93.4%). The mean age of these subjects was 63.5 years, 37.0% were women, and 46.4% were administered a RAS inhibitor at the baseline. Table 1 shows the patient characteristics of the total population and subgroups divided according to the use of RAS inhibitor. In comparison with non-users, RAS inhibitor users were younger, more likely to be male, more likely to have diabetes, more likely to have higher blood pressure, and more likely to have received antihypertensive medications other than RAS inhibitor.

Incidences of death and hospitalization
Among the 3,848 patients with a mean follow-up period of 2.1 years, there were 127 deaths caused by CVD (incidence rate, 1.6/100 person-years), 368 deaths due to any cause (4.5/100 person-years), 411 hospitalizations due to CVD (5.4/100 person-years), and 154 hospitalizations due to CHF (1.9/100 person-years) (Table 2). These incidence rates stratified by the use of RAS inhibitor at the baseline are also presented in Table 2. A lower incidence rate of all-cause deaths was observed in the RAS inhibitor user group compared with the non-user group, while higher incidence rates of the other three outcomes were noted in the RAS user group.

Association between use of RAS inhibitor and death or hospitalization
Hazard ratios estimated using Cox regression models for the four outcomes are summarized in Table 3. Adjusted HRs for the RAS inhibitor user group versus the non-user group were greater than 1.0 for all four outcomes, indicating higher risks of

| TABLE 1. Baseline characteristics of the study population |
|----------------------------------------------------------|
| Variable                                               | Total population (N = 3848) | No (N = 2064) | Yes (N = 1784) | P-value |
| Age, years                                             | 63.5 (12.3)                 | 64.0 (12.4)   | 62.9 (12.1)    | 0.006   |
| Sex, Female                                            | 37.0%                       | 39.4%         | 34.2%          | 0.001   |
| Duration of dialysis, years                            | 7.4 (7.4)                   | 8.5 (8.1)     | 6.1 (6.2)      | <0.001  |
| Comorbid disease                                       |                             |              |               |         |
| Diabetes                                               | 36.6%                       | 30.0%         | 44.3%          | <0.001  |
| Cardiovascular disease                                 | 50.5%                       | 52.4%         | 48.3%          | 0.013   |
| Cerebral vascular disease*                              | 14.5%                       | 15.0%         | 14.0%          | 0.396   |
| Peripheral vascular disease                            | 2.5%                        | 2.1%          | 2.9%           | 0.120   |
| Pulmonary disease                                       | 3.2%                        | 3.7%          | 2.7%           | 0.082   |
| Neurologic disease                                     | 12.9%                       | 15.3%         | 10.0%          | <0.001  |
| Cancers                                                | 10.7%                       | 11.0%         | 10.4%          | 0.579   |
| BMI, kg/m²                                              | 21.1 (3.3)                  | 21.1 (3.3)    | 21.2 (3.4)     | 0.459   |
| Systolic blood pressure, mmHg                          | 150.7 (22.5)                | 146.4 (23.2)  | 155.6 (20.7)   | <0.001  |
| Fluid removal, %                                       | 4.4 (2.3)                   | 4.3 (2.0)     | 4.4 (2.5)      | 0.160   |
| Kt/V, single pool                                       | 1.3 (0.3)                   | 1.4 (0.3)     | 1.3 (0.3)      | <0.001  |
| Serum phosphorus, mg/dL                                | 5.5 (1.4)                   | 5.4 (1.4)     | 5.6 (1.4)      | 0.008   |
| Serum calcium, mg/dL                                   | 9.0 (0.9)                   | 9.0 (0.9)     | 8.9 (0.8)      | 0.163   |
| Serum iPTH, pg/ml                                       | 185.6 (216.8)               | 182.5 (183.8) | 189.2 (249.4)  | 0.407   |
| Serum albumin, mg/dL                                   | 3.8 (0.4)                   | 3.8 (0.4)     | 3.8 (0.4)      | 0.009   |
| Serum potassium, mEq/L                                 | 5.0 (0.8)                   | 4.9 (0.8)     | 5.0 (0.8)      | <0.001  |
| Hemoglobin, g/dL                                        | 10.4 (1.3)                  | 10.5 (1.3)    | 10.3 (1.2)     | <0.001  |
| C-reactive protein, mg/dL                              | 2.1 (23.1)                  | 2.3 (22.7)    | 1.8 (23.8)     | 0.591   |
| Drug prescription                                       |                             |              |               |         |
| Calcium channel blocker                                 | 23.3%                       | 13.6%         | 34.6%          | <0.001  |
| Beta blocker                                            | 5.6%                        | 4.3%          | 7.2%           | <0.001  |
| Other antihypertensive                                 | 53.3%                       | 31.3%         | 78.9%          | <0.001  |
| Antithrombolytic                                        | 33.4%                       | 33.5%         | 33.4%          | 0.909   |
| Anticoagulants                                          | 19.0%                       | 19.1%         | 19.0%          | 0.945   |
| Vitamin D receptor activator, oral                     | 18.8%                       | 16.8%         | 21.1%          | 0.001   |
| Vitamin D receptor activator, intravenous              | 20.5%                       | 19.9%         | 21.3%          | 0.271   |
| Phosphate binder, calcium containing                    | 61.7%                       | 60.7%         | 62.6%          | 0.240   |
| Phosphate binder, non-calcium containing               | 29.2%                       | 28.9%         | 29.5%          | 0.675   |
| Number of drugs prescribed                             | 7.9 (3.8)                   | 7.0 (3.6)     | 8.9 (3.9)      | <0.001  |

Data are presented as mean (standard deviation) for continuous variables.
*Including coronary artery disease, cardiac arrest, cardiac arrhythmia and congestive cardiac failure.
events in the RAS inhibitor user group although statistically insignificant [adjusted HR of 1.46 (95% CI 0.96 to 2.23) for death caused by CVD; 1.15 (0.89 to 1.48) for all-cause death; 1.24 (0.84 to 1.81) for hospitalization due to CHF; and 1.20 (0.95 to 1.51) for hospitalization due to CVD].

The two sensitivity analyses, using PS matching and IPTW, respectively, gave HRs similar to those obtained using multivariate approach (Suppl. Table 1). The standardized difference indicates balanced covariate distribution after IPTW (Suppl. Fig. 1, 2).

Table 4 shows the adjusted HRs in subgroups stratified by the presence or absence of comorbid CVD. In the absent group, the use of RAS inhibitor was associated with death caused by CVD, but the association did not reach statistical significance (adjusted HR: 2.79, 95% CI: 0.99–7.82, \( P = 0.05 \)). There was no notable heterogeneity of individual causes of CVD (ischemic heart disease, stroke, etc.) between the treatment groups (data not shown). The adjusted HRs were greater than 1.0 for other three outcomes but statistically insignificant [adjusted HR of 1.26 (95% CI 0.73 to 2.18) for all-cause death; 1.77 (0.57 to 5.47) for hospitalization due to CHF; and 1.63 (0.98 to 2.71) for hospitalization due to CVD]. Adjusted HRs for the four outcomes were smaller in the present group than in the absent group, none of the differences were statistically significant.

Table 5 shows the adjusted HRs in subgroups stratified by the presence or absence of comorbid diabetes. In both groups, the adjusted HRs were greater than 1.0 for all of the four outcomes. Although HRs were generally higher in the subgroup with comorbid diabetes than in the group without, none of the differences were statistically significant.

**DISCUSSION**

RAS inhibitor has been shown to have a beneficial role in CVE in general population (4–7). However, most results based on randomized control trials (RCTs) addressing CVEs did not include patients with even early stages of chronic kidney disease. In case of patients undergoing HD, there are only a few studies involving a few participants examining the association of RAS inhibitor with CVEs. Thus, it is uncertain whether RAS inhibitor improves CV outcomes in these populations. This observational study revealed that RAS inhibitor did not have the beneficial association with CV outcomes including cardiovascular death and hospitalization due to CVD in patients enrolled in J-DOPPS.

RAS inhibition is established therapy for prevention of CVEs in patients with ischemic heart disease (14). This recommendation is based on the results of several large clinical studies (5,15–21). On the other hand, some trials have demonstrated that RAS inhibition does not associate with CV mortality,

### Table 2. Incidence rates of death and hospitalization in the study population

| Outcome                                      | Total person-years at risk | Number of events | Rate (/100 person-years) | RAS inhibitor use at baseline |
|----------------------------------------------|----------------------------|------------------|--------------------------|-----------------------------|
| Deaths caused by cardiovascular disease      | 8145                      | 127              | 1.6                      | 8145                        | 4430                         | 3715                        |
| Number of events                            |                            |                  |                          |                             | 56                           | 71                          |
| All-cause deaths                             | 8145                      | 368              | 4.5                      | 7994                        | 4357                         | 3637                        |
| Hospitalizations due to congestive heart failure | 7994                      | 154              | 1.9                      |                              | 76                           | 78                          |
| Hospitalizations due to cardiovascular disease | 7679                      | 411              | 5.4                      |                              | 202                          | 209                         |

Data are presented as the point estimate (95% confidence interval), \( P \)-value.

### Table 3. Associations between the use of RAS inhibitors and death or hospitalization

| Outcome                                      | Crude hazard ratio | Adjusted hazard ratio |
|----------------------------------------------|--------------------|-----------------------|
| Deaths caused by cardiovascular disease      | 1.51 (1.07 to 2.15), \( P = 0.02 \) | 1.46 (0.96 to 2.23), \( P = 0.08 \) |
| All-cause deaths                             | 0.93 (0.76 to 1.14), \( P = 0.48 \) | 1.15 (0.89 to 1.48), \( P = 0.28 \) |
| Hospitalizations due to congestive heart failure | 1.23 (0.89 to 1.68), \( P = 0.21 \) | 1.24 (0.84 to 1.81), \( P = 0.28 \) |
| Hospitalizations due to cardiovascular disease | 1.25 (1.03 to 1.52), \( P = 0.02 \) | 1.20 (0.95 to 1.51), \( P = 0.13 \) |
indicating the complexity of the effect of RAS inhibition on CV health even in non-dialysis patients. The CHARM-Preserved trial (22) compared the effect of addition of ARB to current treatment compared with that of placebo in patients with left ventricle ejection fraction (LVEF) higher than 40%. In the RCT, CV death did not differ between groups. Another RCT, the I-Preserve trial (23) investigated whether ARB improved the CV outcome in patients with LVEF of at least 45%. Similar to the CHARM-Preserved trial, this I-Preserve trial also failed to find the superiority of ARB on any of CV outcomes including death. More noteworthy is the evidence that in patients with cardiac disease (symptomatic HF and systolic dysfunction or with preserved LVEF), RAS inhibition did not reduce CV mortality when compared with a placebo, indicated according to the large, systematic reviews even though patients undergoing HD were not included (24). Accordingly, whether this expertise adapts to a large population of patients undergoing HD at high risk of CVEs is uncertain.

While lowering blood pressure has been shown to be associated with lower risks of CVEs in patients with dialysis (25) as well as in the general population (26,27), the clinical studies investigating the CV benefits specific to RAS inhibition for these populations have reported conflicting results. One RCT comparing the effect of antihypertensive agents with ARB with that without ARB on CVEs has shown that the treatment with ARB signifi cantly reduced the risk of CVEs in patients undergoing HD (28). Another RCT has demonstrated that treatment for lowering blood pressure along with ARB failed to reduce the risk compared with that without ARB (29). Taking these results into consideration, although designs including baseline data and definitions of CVEs differ in the studies, we have not been able to have a clear recognition that RAS inhibition is favorable for the reduction in the risk of CVEs especially in patients undergoing HD.

In the present study, the treatment with RAS inhibitor did not show the beneficial association with CV mortality in patients undergoing HD. The reasons for the lack of benefit with RAS inhibition are uncertain, however, several explanations warrant consideration. One possibility is the characteristic of this cohort. Incidence rates of death due to any of cause (4.5/100 person years) and CV disease (1.6/100 person years) were much lower than that in any other HD cohort (30). Thus, it would be unlikely to find the beneficial association of RAS inhibition with CVEs. The second consideration is the association of duration of HD with blood pressure control by RAS inhibitor. It has been demonstrated that the relationship of blood pressure control with mortality varied in duration of HD. High blood pressure was associated with mortality in patients undergoing HD more than at least 3 years (31,32). Mean duration of HD in this study was 7.4 years and the baseline data of mean systolic blood pressure was 150.7 mm Hg, which was much higher than the recommended targets in clinical practice guidelines (33). Thus, the beneficial association of RAS

### Table 4

| Outcome                                      | Absent                     | Present                     | Test for interaction |
|----------------------------------------------|----------------------------|-----------------------------|----------------------|
| Deaths caused by cardiovascular disease      | 2.79 (0.99 to 7.82), \( P = 0.05 \) | 1.30 (0.80 to 2.11), \( P = 0.29 \) | \( P = 0.38 \)      |
| All-cause deaths                             | 1.26 (0.73 to 2.18), \( P = 0.41 \) | 1.12 (0.84 to 1.49), \( P = 0.45 \) | \( P = 0.55 \)      |
| Hospitalizations due to congestive heart failure | 1.77 (0.57 to 5.47), \( P = 0.32 \) | 1.19 (0.78 to 1.81), \( P = 0.43 \) | \( P = 0.63 \)      |
| Hospitalizations due to cardiovascular disease | 1.63 (0.98 to 2.71), \( P = 0.06 \) | 1.14 (0.88 to 1.49), \( P = 0.32 \) | \( P = 0.31 \)      |

Data are presented as the point estimate (95% confidence interval), \( P \)-value.

### Table 5

| Outcome                                      | Absent                     | Present                     | Test for interaction |
|----------------------------------------------|----------------------------|-----------------------------|----------------------|
| Deaths caused by cardiovascular disease      | 1.41 (0.72 to 2.77), \( P = 0.31 \) | 1.39 (0.77 to 2.49), \( P = 0.27 \) | \( P = 0.52 \)      |
| All-cause deaths                             | 1.02 (0.71 to 1.46), \( P = 0.92 \) | 1.34 (0.92 to 1.93), \( P = 0.13 \) | \( P = 0.38 \)      |
| Hospitalizations due to congestive heart failure | 1.04 (0.58 to 1.84), \( P = 0.90 \) | 1.51 (0.86 to 2.65), \( P = 0.15 \) | \( P = 0.43 \)      |
| Hospitalizations due to cardiovascular disease | 1.05 (0.74 to 1.48), \( P = 0.79 \) | 1.34 (0.97 to 1.85), \( P = 0.07 \) | \( P = 0.41 \)      |

Data are presented as the point estimate (95% confidence interval), \( P \)-value.
inhibitor with CVEs might be offset in this population due to longer HD duration and higher blood pressure, both of which have been shown to be a predictor for mortality (34,35). The third is the variation of antihypertensive prescription. The RAS inhibitor users were given more antihypertensive agents than non-users. Drugs that lower blood pressure increase the risk of intradialytic hypotension, which may contribute to the risk of all-cause mortality (36). Despite adjustment for antihypertensive agents other than RAS inhibitor, RAS inhibitor itself might increase the risk of intradialytic hypotension in RAS inhibitor users. Not only intradialytic, but also interdialytic blood pressure lowering should also be considered. Serum ACE levels, plasma renin activity and plasma aldosterone have been shown to increase after an HD session (37,38). Thus, RAS activation after HD session was truly blocked by RAS inhibitor, which might contribute to symptomatic hypotension leading CV events. The effect of RAS inhibitor on interdialytic blood pressure remains to be elucidated. The forth possibility is the involvement of serum potassium levels since hyperkalemia is recognized as a risk factor of CVEs. Inhibition of RAS with RAS inhibitor can cause hyperkalemia in pre-dialysis CKD patients, presumably by inhibiting renal potassium excretion. However, it has also been shown that RAS inhibitor was associated with the risk of developing hyperkalemia in patients undergoing dialysis, which was likely due to a reduction in the gastrointestinal excretion of potassium or to a defect in the shift into cell of potassium (39–41). Even though serum potassium at baseline was considered as a covariant, it was uncertain whether serum potassium levels were increased in RAS inhibitor users at the time of CVEs. Furthermore, as previously shown, intervention with erythropoiesis-stimulating agents or statins has failed to prove their beneficial effect in patients undergoing dialysis (8–12), and so RAS inhibitor also might have a minor effect on CVEs. The reason for this might be due to the unique and complex characteristics of these patients including the dialysis vintage and prescription, comorbidity, mineral metabolism disturbance, chronic inflammation, or malnutrition.

The beneficial effect of RAS inhibitor on diabetic nephropathy has mainly been demonstrated in the CKD stage but not in the ESRD stage (42). In addition, it has been reported that intradialytic hypotension is partly due to autonomic nervous system dysregulation (43), and that autonomic nervous system disturbance is common in diabetes (44). Taken together, HD patients with diabetes are likely to be at a high risk for hypotension due to autonomic nervous system disturbance in addition to antihypertensive agents. Thus, we suppose that RAS inhibitor is prone to inducing severe hypotension in HD patients with diabetes, which might result in the higher HRs for death and hospitalization in the subgroup. Furthermore, recent studies have suggested that not only intradialytic hypotension, but also visit-to-visit BP viability is associated with cardiovascular mortality (45). RAS inhibitor treatment to HD patients with diabetes who possess autonomic nervous system disturbance might exacerbate BP viability resulting in the unfavorable association of RAS inhibitor with cardiovascular events in this population. Contrary to a previous report showing that spironolactone reduced CV morbidity and mortality in HD patients (46), we could not confirm the beneficial association of RAS inhibition with CVEs. It has been reported that an aldosterone antagonist was superior to an ARB in the cardioprotection in hypertensive animal models (47), indicating that the mechanisms by which each RAS inhibitor blocks local (cardiovascular tissues) RAS activity are not identical. Thus, we suppose that the cardiac effect may be different in each individual RAS inhibitor in HD patients. Further studies are needed to determine the precise action of each RAS inhibitor on cardiovascular tissues in the uremic milieu.

The major strength of this study is the population-based design, the large sample size, the replication cohort, and the use of a standardized data across facilities. This study also has several limitations. First, some demographic variables differed between the RAS inhibitor users and non-users, but our statistical analyses controlled for these by adjusting for important covariates. However, we cannot exclude the effects of other unmeasured confounders on our results. Second, the class (ACEI or ARB) and dose of RAS inhibitor was not considered in the present study. Unmeasured confounders may also have affected our comparison with the groups. Another potential limitation is the study’s observational nature. Although we found the association of RAS inhibitor treatment with CV mortality, the nature does not allow us to determine whether this relationship is causal.

**CONCLUSION**

In conclusion, renin-angiotensin system inhibition did not show association with cardiovascular benefits suggesting that RAS inhibition alone was insufficient to reduce the risk of cardiovascular complications in
patients undergoing hemodialysis. Some strategies in addition to RAS inhibition may be needed to protect against cardiovascular events in this population.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. Associations between the use of RAS inhibitors and death or hospitalization analyzed by using Cox regression with the propensity score matching (PS matching) and with the inverse probability of treatment weighting (IPTW) as a sensitivity analysis.

Figure S1. Absolute standardized differences assessing the imbalance and balance of covariates before and after propensity-score-matching (PS matching). Abbreviations: iv-VDRA, intravenous vitamin D receptor activator; po-VDRA: oral vitamin D receptor activator; c-PB, calcium containing phosphate binder; nc-PB, non-calcium containing phosphate binder.

Figure S2. Absolute standardized differences assessing the imbalance and balance of covariates before and after the inverse probability of treatment weighting (IPTW). Abbreviations: iv-VDRA, intravenous vitamin D receptor activator; po-VDRA: oral vitamin D receptor activator; c-PB, calcium containing phosphate binder; nc-PB, non-calcium containing phosphate binder.