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Original Paper

Combination Therapy with Renin-Angiotensin System Blockers and Vitamin D Receptor Activators for Predialysis Patients Is Associated with the Incidence of Cardiovascular Events after Dialysis Initiation: A Multicenter Nonrandomized Prospective Cohort Study

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Keywords
Chronic kidney disease · Vitamin D · Renin-angiotensin system blocker · Cardiovascular events · Dialysis · Vitamin D receptor activator

Abstract
Background: Several human studies reported that the combined use of renin-angiotensin system blockers (RASBs) and vitamin D receptor activators (VDRAs) resulted in decreased urinary protein excretion. However, it is unknown whether this combination therapy influences the incidence of cardiovascular (CV) events in dialysis patients. ***Methods:*** The study was a multicenter nonrandomized prospective cohort analysis including 1,518 patients. Patients were classified into 4 groups based on medications prescribed before dialysis initiation: those who did not receive RASBs or oral VDRAs (N group), those receiving only RASBs, those receiving only VDRAs, and those receiving a combination of RASBs and VDRAs (RD group). CV events after dialysis initiation were compared using the log-rank test. Factors contributing to the incidence of CV events were examined using multivariate Cox proportional hazard regression analysis. ***Results:*** Significant differences were observed in the incidence of CV events and

D.I., E.I., and S.K. are members of the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP) Group.

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all-cause mortality between the 4 groups (p = 0.021 and p = 0.001, respectively). Cox proportional hazard analysis revealed that the incidence of CV events was significantly lower in the RD group than in the N group (hazard ratio [HR] = 0.65, 95% confidence interval [CI]: 0.50–0.86, p = 0.002). Multivariate analysis revealed that the incidence of CV events was significantly lower in the RD group than in the N group (HR = 0.66, 95% CI: 0.47–0.93, p = 0.016). ***Conclusion:*** Combination therapy with RASBs and VDRAs in patients before dialysis initiation was associated with a reduction in CV events during maintenance dialysis.

Introduction

Chronic kidney disease (CKD) eventually progresses to end-stage renal disease and is also associated with cardiovascular (CV) mortality. Antihypertensive drugs, particularly renin-angiotensin system blockers (RASBs), such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ARBs), are often administered to CKD patients. The Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends the use of RASBs for patients with predialysis CKD because RASBs slow the decline of the glomerular filtration rate (GFR) [1, 2]. RASBs prevent the progression of cardiac remodeling, an important pathological mechanism for chronic heart failure. In addition, the anti-inflammatory effect of RASBs leads to a decrease in the incidence of CV events [3–5].

CKD-mineral and bone disease (CKD-MBD) is an important complication in CKD patients. Progression of vascular calcification accompanied by CKD-MBD is associated with increased mortality. Vitamin D receptor activators (VDRAs) play an important role in decreasing serum parathyroid hormone (PTH) level. The KDIGO guideline recommends the use of VDRAs when the serum PTH level progressively increases over the upper limit of normal, even if serum mineral levels, such as adjusted calcium and phosphorus, can be normalized [6]. However, there is insufficient evidence concerning the management of CKD-MBD using VDRAs in patients with predialysis CKD. Recently, it was noted that vitamin D status is associated with CV events due to the pleiotropic effects of activated vitamin D [7–9]. Several reports showed that administration of VDRAs or native vitamin D supplementation decreased the incidence of CV events [10–14].

Both RASBs and VDRAs probably prevent the onset of CV events. Some studies indicated that a combination therapy using both drugs resulted in reduced proteinuria [15, 16]. Nonetheless, there are no studies regarding the association between this combination therapy and the onset of CV events. Hence, we examined the relationship between this combination therapy administered from predialysis to the dialysis initiation period and the occurrence of CV events during maintenance dialysis. We believe that this is the first study to evaluate this association.

Materials and Methods

Subjects

The study subjects were patients in whom dialysis had recently been initiated at the 17 centers that participated in the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP) Group centers between October 2011 and September 2013 [17]. Patients who were withdrawn from dialysis or did not agree to be registered were excluded. The study was a multicenter nonrandomized prospective cohort analysis and enrolled 1,520 patients who were at least 20 years old, had CKD, and provided written informed consent. We excluded 2 patients whose RASB and VDRA administration at dialysis initiation was unknown. Thus, we included 1,518 patients in the final analysis.

Patient Characteristics and Data at the Time of Dialysis Initiation (Baseline)

Baseline was defined as the time at which dialysis was initiated. Body mass index (BMI) was measured at the first dialysis session. CV history was determined from medical records and defined as coronary artery disease, heart valve disease, congestive heart failure requiring hospitalization, cerebral infarction, cerebral hemorrhage, or aortic disease. Information about drug usage was obtained from the medical records. Medication use refers to the drugs taken at the time of dialysis initiation. Laboratory tests were performed using blood samples taken before the first dialysis session. Blood pressure was also measured before the first dialysis session.

Classification according to Usage of RASBs and VDRAs

Patients were classified into 4 groups: those who did not receive RASBs (angiotensin-converting enzyme inhibitors or/and ARBs) or oral VDRAs (alfacalcidol or calcitriol, 0.25–0.5 μg/day) (N group, n = 459), those treated with RASBs only (R group, n = 648), those treated with VDRAs only (D group, n = 142), and those treated with a combination of RASBs and VDRAs (RD group, n = 269).

Outcome

Study outcomes included the incidence of CV events and mortality in the 4 groups. The incidence of CV events between the start of dialysis and the end of September 2016 was compared. CV events were defined as heart failure requiring hospitalization, acute coronary syndrome, stroke, or peripheral artery disease requiring hospitalization. Heart failure was defined as hypoxemia and pulmonary congestion, pulmonary edema, or pleural effusion on chest radiograph. Acute coronary syndrome was defined as stenosis or occlusion on coronary angiography or by percutaneous coronary intervention, coronary artery bypass surgery, or electrocardiogram findings consistent with acute coronary syndrome. Stroke was defined as the presence of neurological symptoms plus brain computed tomography or magnetic resonance imaging findings indicative of hemorrhage or infarction. We defined the day of dialysis initiation as the start of the follow-up period and used "first onset of CV events," "lost to follow-up," or "no events during the follow-up period" as assessment points for CV events.

Survey of CV Events and Mortality

Answers to the prognostic survey were obtained from medical records of the AICOPP Group institutions or by sending letters to facilities where patients had been transferred for maintenance dialysis. These letters included a questionnaire regarding the category of CV events (e.g., acute coronary syndrome or ischemic stroke), date of onset, and clinical outcome.

Statistical Processing

SPSS statistics version 24 and the Easy R program were used for statistical processing [18]. Patient characteristics and baseline data were compared between the 4 groups using analysis of variance for continuous variables and the Fisher exact test for nominal variables. Incidence of CV events and mortality in the 4 groups were compared using the log-rank test for the Kaplan-Meier curves. The factors that contributed to the incidence of CV disease events were examined using univariate regression analysis. Factors that were significant in the univariate analysis (i.e., age, gender, diabetes mellitus, history of CV disease, BMI, systolic blood pressure, diastolic blood pressure, cardiothoracic ratio on chest X-ray, estimated GFR, serum creatinine, serum albumin, serum phosphorus, serum high-density lipoprotein cholesterol, serum PTH, use of calcium channel blockers, use of β-blockers, use of statins, and use of temporary catheter for vascular access) served as explanatory variables for the multivariate Cox proportional hazards analysis. The propensity score, which we calculated using logistic regression models, represented the probability that a patient would be assigned to the R group or the RD group. Using a propensity score matching procedure, the 2 groups were similarly distributed, indicating that the differences in covariates between groups were minimized. Continuous variables are expressed as means and standard deviations or medians and interquartile ranges, and categorical variables are presented as percentages. p values less than 5% were considered statistically significant.

Table 1. Comparison of baseline characteristics and laboratory data

Variables	All (n = 1,518)	N group (n = 459)	R group (n = 648)	D group (n = 142)	RD group (n = 269)	p value
Age, years	67.5 (13.1)	68.8 (13.6)	67.8 (12.6)	67.3 (13.1)	64.7 (12.8)	0.001
Female, %	32.4	34.9	29.5	36.7	33.1	0.171
Diabetes mellitus, %	51.1	47.1	55.4	40.8	53.2	0.003
History of CVD, %	45.1	45.1	46.5	44.4	42.4	0.726
BMI	23.5 (4.4)	23.0 (4.8)	23.8 (4.1)	22.2 (4.3)	24.2 (4.3)	<0.001
SBP, mm Hg	151 (26)	150 (27)	151 (26)	151 (25)	153 (24)	0.341
DBP, mm Hg	77 (15)	77 (17)	76 (15)	80 (14)	78 (14)	0.015
CTR, %	55.2 (7.2)	56.1 (7.3)	55.2 (6.8)	54.9 (8.0)	53.6 (7.0)	<0.001
Hemoglobin, g/dL	9.4 (1.5)	9.1 (1.7)	9.3 (1.5)	9.7 (1.5)	9.7 (1.4)	<0.001
eGFR, ml/min/1.73 m^2	5.4 (2.2)	5.6 (2.4)	5.4 (2.2)	5.4 (1.9)	5.3 (2.2)	0.380
Serum creatinine, mg/dL	8.97 (3.21)	8.95 (3.78)	8.95 (2.96)	8.69 (2.56)	9.18 (3.04)	0.519
BUN, mg/dL	91.8 (30.5)	95.8 (35.8)	91.5 (28.3)	87.3 (28.7)	88.0 (25.4)	0.002
Serum albumin, g/dL	3.20 (0.60)	3.10 (0.60)	3.18 (0.58)	3.28 (0.59)	3.37 (0.60)	<0.001
Serum uric acid, mg/dL	8.8 (2.4)	9.2 (2.9)	8.7 (2.3)	8.5 (1.9)	8.4 (2.0)	<0.001
Serum potassium, mEq/L	4.6 (0.8)	4.5 (0.9)	4.6 (0.8)	4.4 (0.7)	4.6 (0.8)	0.019
Serum adjusted calcium, mg/dL	8.6 (1.1)	8.6 (1.1)	8.6 (1.0)	8.6 (1.0)	8.7 (1.1)	0.255
Serum phosphorus, mg/dL	6.4 (1.9)	6.6 (2.2)	6.3 (1.7)	6.2 (1.8)	6.2 (1.7)	0.016
Bicarbonate, mmol/L	19.6 (4.9)	19.3 (5.4)	19.5 (4.9)	19.5 (4.7)	20.3 (4.1)	0.078
Serum LDL cholesterol, mg/dL	90 (34)	94 (36)	88 (34)	91 (39)	85 (29)	0.011
Serum HDL cholesterol, mg/dL	45 (17)	47 (18)	43 (16)	47 (17)	43 (16)	0.003
Serum triglyceride, mg/dL	125 (71)	128 (69)	121 (61)	124 (66)	130 (92)	0.351
CRP, mg/dL	1.8 (4.2)	2.3 (4.4)	1.6 (3.7)	2.4 (6.2)	1.3 (3.1)	0.002
Serum intact PTH, pg/mL	354 (293)	362 (325)	369 (276)	340 (339)	316 (244)	0.097
Serum 1,25-dihydroxyvitamin D, pg/mL	13.7 (7.7)	12.1 (6.6)	11.5 (6.8)	17.3 (7.3)	18.3 (8.0)	<0.001
Use of calcium channel blockers, %	78.9	67.3	84.4	71.8	88.5	<0.001
Use of β-blockers, %	34.8	30.3	38.3	31.7	35.7	0.041
Use of statins, %	40.0	33.6	44.3	35.9	42.8	0.002
Use of ESAs, %	85.9	78.6	87.8	92.3	90.7	<0.001
Use of temporary VA, %	20.8	33.6	18.7	16.7	6.7	<0.001

Values are expressed as means (standard deviations) unless otherwise indicated. CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CTR, cardiothoracic rate; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; PTH, parathyroid hormone; ESA, erythropoiesis-stimulating agents; VA, vascular access.

Results

Comparison of Patient Characteristics and Baseline Data

Table 1 shows patients' characteristics and baseline data in the 4 groups. Significant differences between the 4 groups were observed in age, prevalence of diabetes mellitus, BMI, diastolic blood pressure, cardiothoracic rate, hemoglobin level, blood urea nitrogen level, serum albumin level, serum uric acid level, serum potassium level, serum phosphorus level, serum cholesterol level, serum C-reactive protein level, serum 1,25-dihydroxyvitamin D level, calcium channel blocker use, β-blocker use, statin use, erythropoiesis-stimulating agent use, and use of temporary catheter for vascular access. We confirmed the duration of treatment before dialysis initiation in 359 cases for VDRAs and 710 cases for RASBs. The median (interquartile range) usage periods were 182 (55–462) and 886 (277–1,794) days, respectively.

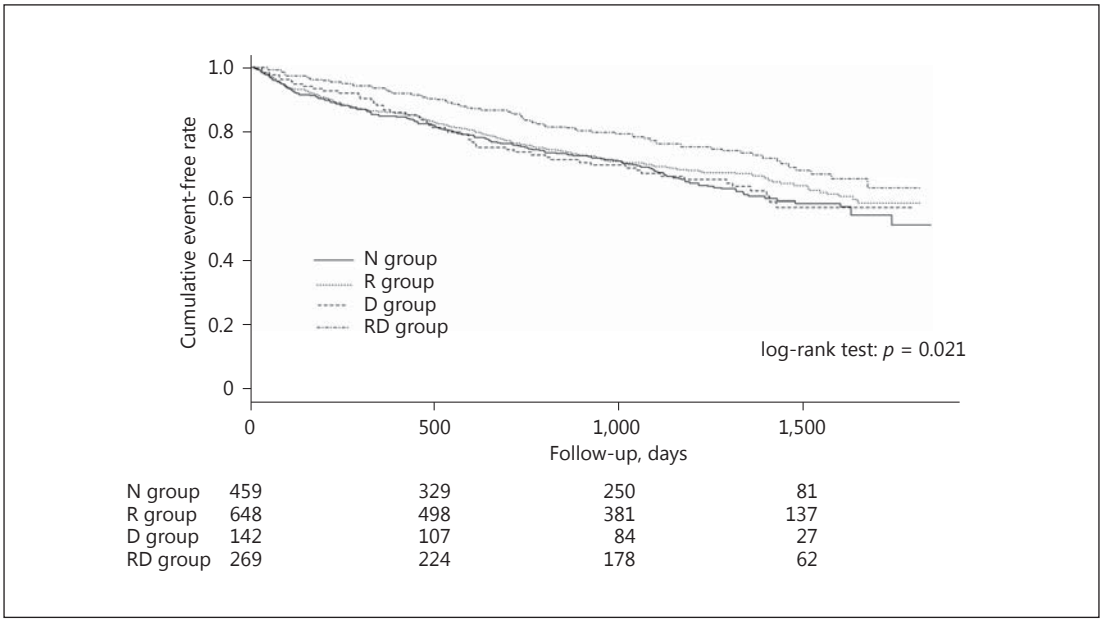

Fig. 1. Comparison of cardiovascular events between the 4 groups. Significant differences were observed between the 4 groups' cumulative event-free rates ($p = 0.021$). N group, no use of RASBs (ACEIs or ARBs) or VDRAs; R group, use of RASBs only; D group, use of VDRAs; RD group, use of both RASBs and VDRAs; RASB, renin-angiotensin system blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; VDRA, vitamin D receptor activator.

Comparison of Incidence of CV Events between the 4 Groups

Figure 1 shows the comparison of the incidence of CV disease events in the 4 groups. The median (interquartile range) of the follow-up period was 1,165 (535–1,418) days. There were 503 CV events during the follow-up period (N group, 164 events [35.7%]; R group, 214 events [33.0%]; D group, 52 events [36.6%]; RD group, 73 events [27.1%]). Significant differences were observed between the 4 groups' cumulative CV event-free rates ($p = 0.021$).

Factors Affecting the Incidence of CV Events

Table 2 shows the results of univariate analysis with the incidence of CV events as a response variable. The incidence of CV events was significantly lower in the RD group than in the N group (hazard ratio = 0.65, 95% confidence interval: 0.50–0.86, $p = 0.002$). In addition, the incidence of CV events was found to be associated with some factors, including age, sex, diabetes mellitus, and history of CV events. Table 3 shows the results of multivariate analyses. The incidence of CV events was significantly lower in the RD group than in the N group (hazard ratio = 0.66, 95% confidence interval: 0.47–0.93, $p = 0.016$). In addition, age, sex, diabetes mellitus, history of CV events, cardiothoracic rate, serum high-density lipoprotein cholesterol level, and use of calcium channel blockers were identified as independent factors affecting the incidence of CV events.

Propensity Score-Matched Cohort

We performed logistic regression analysis using age and sex to obtain the propensity score for patients to be in the R group or the RD group. We conducted propensity score matching between the 2 groups due to the following reasons. First, we examined whether additional administration of VDRA in addition to RASB was effective. Second, it was difficult

Table 2. Univariate regression analysis for the incidence of CV events

Variables	HR	95% CI	*p* value
R group (vs. N group)	0.96	0.70–1.31	0.801
D group (vs. N group)	0.87	0.71–1.06	0.167
RD group (vs. N group)	0.65	0.50–0.86	0.002
Age (10 years)	1.30	1.20–1.40	<0.001
Female gender	0.71	0.58–0.86	<0.001
Diabetes mellitus	1.63	1.36–1.95	<0.001
History of CVD	2.54	2.12–3.04	<0.001
BMI (kg/m^2)	0.97	0.95–0.99	0.005
SBP (10 mm Hg)	0.96	0.94–0.99	0.005
DBP (10 mm Hg)	0.90	0.86–0.94	<0.001
CTR (%)	1.03	1.02–1.05	<0.001
Hemoglobin (g/dL)	1.02	0.97–1.08	0.470
eGFR (ml/min/1.73 m^2)	1.09	1.06–1.13	<0.001
Serum creatinine (mg/dL)	0.91	0.88–0.94	<0.001
BUN (10 mg/dL)	0.99	0.96–1.02	0.507
Serum albumin (g/dL)	0.84	0.73–0.97	0.019
Serum uric acid (mg/dL)	1.02	0.98–1.06	0.285
Serum potassium (mEq/L)	0.97	0.87–1.08	0.551
Serum adjusted calcium (mg/dL)	1.09	1.00–1.18	0.057
Serum phosphorus (mg/dL)	0.91	0.87–0.96	<0.001
Bicarbonate (mmol/L)	1.01	0.99–1.03	0.190
Serum LDL cholesterol (10 mg/dL)	0.98	0.95–1.01	0.185
Serum HDL cholesterol (10 mg/dL)	0.87	0.82–0.93	<0.001
Serum triglyceride (10 mg/dL)	1.01	1.00–1.02	0.261
CRP (mg/dL)	1.01	0.99–1.03	0.215
Serum intact PTH (10 pg/mL)	0.99	0.99–1.00	0.001
Serum 1,25-dihydroxyvitamin D (pg/mL)	0.99	0.98–1.01	0.463
Use of calcium channel blockers	0.73	0.60–0.90	0.003
Use of β-blockers	1.55	1.30–1.85	<0.001
Use of statins	1.38	1.16–1.65	<0.001
Use of ESAs	0.89	0.69–1.15	0.371
Use of temporary VA	1.27	1.03–1.56	0.027

CV, cardiovascular; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CTR, cardiothoracic rate; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; PTH, parathyroid hormone; ESA, erythropoiesis-stimulating agents; VA, vascular access.

to adjust the patient profiles and baseline data among the 4 groups by logistic regression analysis. There were 247 patients in each group. Table 4 shows patient characteristics and baseline data in the 2 groups after propensity score matching. There were no significant differences in variables except for cardiothoracic rate, estimated GFR, serum uric acid, C-reactive protein, serum intact PTH, serum 1,25-dihydroxyvitamin D, use of erythropoiesis-stimulating agents, and use of temporary vascular access at dialysis initiation.

Comparison of CV Events in the 2 Groups after Propensity Score Matching

There were 157 CV events during the follow-up period (R group, 88 events; RD group, 69 events). Figure 2 displays the Kaplan-Meier curves for the 2 groups after propensity score matching in terms of CV events. The incidence of CV events was significantly higher in the R

Table 3. Multivariate regression analysis for the incidence of CV events

Variables	HR	95% CI	*p* value
R group (vs. N group)	0.96	0.66–1.39	0.823
D group (vs. N group)	0.83	0.64–1.08	0.164
RD group (vs. N group)	0.66	0.47–0.93	0.016
Age (10 years)	1.17	1.03–1.31	0.012
Female gender	0.66	0.50–0.88	0.005
Diabetes mellitus	1.57	1.24–1.98	<0.001
History of CVD	1.78	1.41–2.24	<0.001
BMI (kg/m^2)	0.97	0.94–1.00	0.075
SBP (10 mm Hg)	0.99	0.93–1.05	0.796
DBP (10 mm Hg)	1.02	0.90–1.14	0.794
CTR (%)	1.03	1.01–1.04	0.001
eGFR (ml/min/1.73 m^2)	0.98	0.91–1.06	0.566
Serum creatinine (mg/dL)	0.93	0.86–1.00	0.060
Serum albumin (g/dL)	1.06	0.87–1.28	0.573
Serum phosphorus (mg/dL)	1.02	0.95–1.10	0.592
Serum HDL cholesterol (10 mg/dL)	0.89	0.83–0.97	0.005
Serum intact PTH (10 pg/mL)	1.00	0.99–1.00	0.150
Use of calcium channel blockers	0.70	0.53–0.93	0.013
Use of β-blockers	1.24	0.99–1.55	0.059
Use of statins	1.24	1.00–1.55	0.054
Use of temporary VA	1.16	0.85–1.57	0.362

CV, cardiovascular; HR, hazard ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CTR, cardiothoracic rate; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; PTH, parathyroid hormone; VA, vascular access.

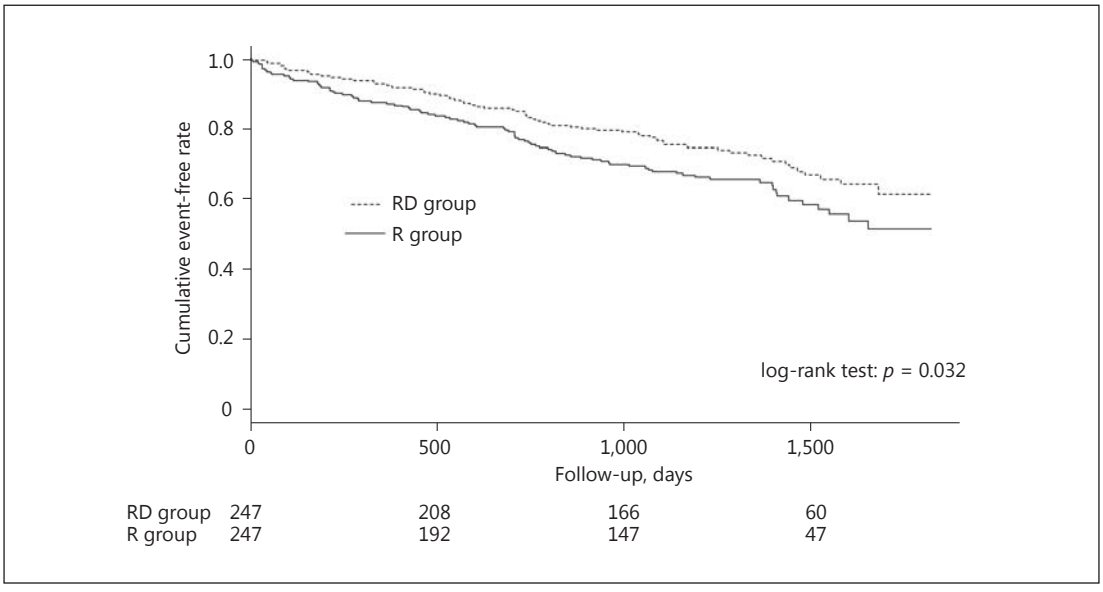

Fig. 2. Comparison of cardiovascular events between the R and RD groups after propensity score matching. Significant differences were observed between the 2 groups' cumulative event-free rates ($p = 0.032$). R group, use of RASBs only; RD group, use of both RASBs and VDRAs; RASB, renin-angiotensin system blocker; VDRA, vitamin D receptor activator.

Table 4. Baseline characteristics of the R and RD groups after propensity score matching

Variables	R group (n = 247)	RD group (n = 247)	p value
Age, years	66.0 (11.4)	66.0 (11.4)	1.000
Female, %	31.6	31.6	1.000
Diabetes mellitus, %	62.3	55.1	0.120
History of CVD, %	49.0	43.7	0.279
BMI	23.8 (3.9)	24.1 (4.2)	0.465
SBP, mm Hg	151 (26)	153 (24)	0.282
DBP, mm Hg	76 (14)	78 (13)	0.124
CTR, %	55.1 (6.5)	53.7 (7.0)	0.018
Hemoglobin, g/dL	9.4 (1.5)	9.5 (1.4)	0.089
eGFR, ml/min/1.73 m^2	5.8 (2.7)	5.3 (2.2)	0.016
Serum creatinine, mg/dL	8.63 (3.34)	9.11 (2.99)	0.091
BUN, mg/dL	89.4 (28.3)	88.5 (25.5)	0.698
Serum albumin, g/dL	3.21 (0.62)	3.33 (0.60)	0.092
Serum uric acid, mg/dL	8.9 (2.3)	8.3 (1.9)	0.004
Serum potassium, mEq/L	4.6 (0.9)	4.6 (0.8)	0.795
Serum adjusted calcium, mg/dL	8.9 (1.0)	8.7 (1.1)	0.211
Serum phosphorus, mg/dL	6.2 (1.6)	6.2 (1.7)	0.963
Bicarbonate, mmol/L	19.6 (4.6)	20.3 (4.2)	0.106
Serum LDL cholesterol, mg/dL	91 (35)	85 (29)	0.069
Serum HDL cholesterol, mg/dL	44 (16)	44 (16)	0.957
Serum triglyceride, mg/dL	125 (66)	128 (93)	0.721
CRP, mg/dL	2.1 (5.1)	1.3 (3.2)	0.045
Serum intact PTH, pg/mL	232 (149)	308 (242)	<0.001
Serum 1,25-dihydroxyvitamin D, pg/mL	10.5 (5.7)	18.5 (8.1)	<0.001
Use of calcium channel blockers, %	84.2	88.7	0.189
Use of β-blockers, %	41.3	36.4	0.310
Use of statins, %	43.7	42.5	0.856
Use of ESAs, %	83.4	91.1	0.015
Use of temporary VA, %	22.7	6.1	<0.001

Values are expressed as means (standard deviations) unless otherwise indicated. CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CTR, cardiothoracic rate; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; PTH, parathyroid hormone; ESA, erythropoiesis-stimulating agents; VA, vascular access.

group (p = 0.032). There were 43 CV-related deaths during the follow-up period (R group, 23 patients; RD group, 20 patients). No significant difference was observed in the 2 groups' cumulative CV-related mortality (p = 0.570).

Discussion

The results of this study revealed an association between combination therapy with RASBs and VDRAs at the predialysis stage and a reduced incidence of CV events after dialysis was initiated. Moreover, we used propensity score matching to adjust for variables between the R and RD groups. We confirmed that there was a correlation between combination therapy and incidence of CV events after propensity score matching.

We would like to highlight 2 features of this study as follows: (1) to our knowledge, this study is the first to examine the relationship between this combination therapy and the incidence of CV events among dialysis patients; (2) we set the baseline period as dialysis initiation, in contrast to many previous studies that have examined patients during predialysis or maintenance dialysis separately. The use of combination therapy before dialysis initiation might be effective in reducing the incidence of CV events in patients on dialysis by acting on the myocardium and suppressing the inflammatory cascade.

As for combination therapy with RASBs and VDRAs, there are a few basic or clinical studies that have been reported [19, 20]. Ali et al. [20] reported that the combination of angiotensin-converting enzyme inhibitors and VDRAs had a superior effect to monotherapy on reducing cardiac oxidative stress by raising antioxidant activity in diabetic rats. Concerning clinical studies, Tiryaki et al. [15] indicated that administration of VDRAs in combination with RASBs had the additional benefit of lowering albuminuria in patients with diabetic nephropathy. De Zeeuw et al. [16] conducted a multinational, placebo-controlled, double-blind trial; this study demonstrated that the addition of 2 μg/day paricalcitol to RAS inhibition safely lowered residual albuminuria in patients with diabetic nephropathy and could be a novel approach to reducing residual renal risk in patients with diabetes. As described above, previous studies showed that RASB/VDRA combination therapy reduced urinary protein excretion; these studies did not evaluate the incidence of CV events as an outcome measure. This is the first report demonstrating the association between combination therapy with RASBs and VDRAs and the incidence of CV events. There are several possible explanations for our results: (1) VDRAs inhibit renin activity, which RASBs might increase; (2) the combination of these 2 drugs may have an additive effect on systemic inflammation; (3) combination therapy could have additive effects on the suppression of left ventricular hypertrophy via direct action on the myocardium.

The present study has the following limitations. First, this was an observational analysis, and there were some differences in the baseline characteristics and laboratory data between the 4 groups. We considered the possibility of residual confounding, although we also used the propensity score-matched cohort of the R and RD groups. Second, the duration of combination therapy before dialysis initiation was unclear. Therefore, we analyzed the duration in some patients. We considered that the patients in the R and RD groups would have received medication since the early stage of CKD because the guidelines for predialysis CKD recommend the use of RASBs. However, the appropriate timing for starting VDRAs is unclear. Hence, VDRA administration was commenced at a later stage of CKD. Third, the study did not reflect the effects of treatment after the start of dialysis. Starting dialysis would likely affect the outcomes in many ways, including blood pressure management, anemia, electrolyte balance, ultrafiltration rate, Kt/V, and hemodialysis time/session. However, we could not collect the appropriate data.

Conclusion

Combination therapy with RASBs and VDRAs in patients with CKD before dialysis initiation is associated with a reduced incidence of CV events. To the best of our knowledge, this is the first study to analyze the relationship between this treatment combination and CV outcomes. Further work is required to define this effect based on controlled studies.

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Statement of Ethics

This study was conducted by following the *Ethical Guidelines for Clinical Research* by the Japanese Ministry of Health, Labor, and Welfare (created July 30, 2003; full revision December 28, 2004; full revision July 31, 2008) and the Helsinki Declaration (revised 2013) and was approved by the clinical research ethics committees at each AICOPP Group facility (approval No. 20110823-3). The subjects received oral and written explanations of the purpose of the study and provided their consent in writing. The trial registration No. is UMIN 7096 (registered January 18, 2012).

Disclosure Statement

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