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ORIGINAL ARTICLE

Effects of Aliskiren on blood pressure and the predictive biomarkers for cardiovascular disease in hemodialysis-dependent chronic kidney disease patients with hypertension

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The renin–angiotensin–aldosterone system (RAAS) has pivotal roles in the pathogenesis of hypertension in hemodialysis-dependent chronic kidney disease (HDD-CKD) patients. Activated RAAS also increases inflammatory mediators by directly increasing proinflammatory gene expression and by putting oxidative stress on the vascular endothelium. Both hypertension and inflammation are major risk factors for cardiovascular disease (CVD) in HDD-CKD patients. In this study, we assessed the efficacy of a direct renin inhibitor, aliskiren, on blood pressure (BP) and CVD predictive biomarkers, such as brain natriuretic peptide (BNP), high-sensitivity C-reactive protein (hs-CRP) and diacron-reactive oxygen metabolite (d-ROM). A total of 30 hypertensive HDD-CKD patients were assigned to receive aliskiren (150 mg) orally once daily with their existing antihypertensives. After 8 weeks, aliskiren treatments reduced systolic blood pressure (SBP) from 169.0 ± 20.1 to 153.7 ± 19.6 mm Hg ($P<0.001$) and diastolic blood pressure (DBP) from 78.1 ± 12.0 to 73.0 ± 13.6 mm Hg ($P=0.048$). RAAS was suppressed by aliskiren treatment as follows: PRA (from 3.6 ± 4.0 to 1.0 ± 1.5 ng ml^{-1} h^{-1} ($P=0.004$)), angiotensin I (from 1704.0 ± 2580.9 to 233.7 ± 181.0 pg ml^{-1} ($P=0.009$)), angiotensin II (from 70.2 ± 121.5 to 12.4 ± 11.5 pg ml^{-1} ($P=0.022$)) and aldosterone (from 107.9 ± 148.0 to 73.1 ± 34.6 pg ml^{-1} (NS)). The biomarkers for CVD were inhibited by aliskiren: BNP (from 362.5 ± 262.1 to 300.0 ± 232.0 pg ml^{-1} ($P=0.043$)), hS-CRP (from 6.2 ± 8.1 to 3.5 ± 3.7 mg l^{-1} ($P=0.022$)) and d-ROM (from 367.0 ± 89.8 to 328.3 ± 70.9 U.CARR ($P=0.022$)). The inhibition levels of biomarkers for CVD by aliskiren did not correlate with the decreased levels of SBP and DBP. These results suggested that aliskiren was effective for BP control and may have cardiovascular protective effects in hypertensive HDD-CKD patients.
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Keywords: aliskiren; blood pressure; biomarkers for cardiovascular disease; hemodialysis-dependent chronic kidney disease patients

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in hemodialysis-dependent chronic kidney disease (HDD-CKD) patients. Hypertension is a major risk factor for CVD. The renin–angiotensin–aldosterone system (RAAS) has pivotal roles in the pathogenesis of hypertension in HDD-CKD patients, although volume overload is considered the most critical factor.[1] The renin levels of hypertensive HDD-CKD patients were found to be approximately twice as high as those of normal subjects.[2] Parenchymal renal injury and renovascular disease may cause increased renin secretion in end-stage renal failure.[1,2] The role of RAAS in hypertensive HDD-CKD patients was confirmed by the normalization of blood pressure (BP) by administration of an angiotensin antagonist, saralasin.[3]

Persistent inflammation in uremic conditions has been shown to be an independent predictor of CVD in HDD-CKD patients.[4,5] Activated RAAS also increased inflammatory mediators by directly increasing proinflammatory gene expression and by putting oxidative stress on vascular endothelium.[6] Therefore, the blockade of RAAS is important to control BP and suppress inflammation leading to CVD in HDD-CKD patients. Although the blockade of RAAS by angiotensin I converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) has been reported to show effects on BP control and to suppress inflammation,[7,8] it does not completely suppress RAAS, leading to a reactive rise in plasma renin activity (PRA).

Aliskiren, an oral direct renin inhibitor, is effective against essential hypertension by reducing PRA, resulting in more complete suppression of RAAS;[9] however, little is known about the effects of aliskiren on hypertensive HDD-CKD patients. In this study, we assessed the efficacy of aliskiren on BP and the biomarkers for CVD, such as brain natriuretic peptide (BNP), high-sensitivity C-reactive protein (hs-CRP) and diacron-reactive oxygen metabolite (d-ROM), in hypertensive HDD-CKD patients.

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METHODS

This study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Jichi Medical University. Written informed consent was obtained from all patients.

Patients

HDD-CKD patients with hypertension were enrolled in the study. All patients had oliguria or anuria. Patients were classified as hypertensive when clinic BP was $\geqslant$140 mm Hg for systolic BP (SBP) and $\geqslant$90 mm Hg for diastolic BP (DBP) before an hemodialysis (HD) session on the last HD day of the week. Exclusion criteria were as follows: age $<$20 years or $>$80 years, type I diabetes mellitus or type II diabetes mellitus with poor glucose control (glycosylated hemoglobin (HbA_{1c}) $>$9% at the start of the observation period), hyperpotassemia (5.5 mEq ml^{-1}) before the HD session, history of stroke, coronary heart disease, severe arrhythmia or any medical or surgical condition that may have affected the pharmacokinetics of the study drug and pregnant women.

Study protocol

The study was a 12-week multicenter study consisting of a 4-week observation period to fix dry weight and any drugs, including existing antihypertensives, and an 8-week treatment period with aliskiren. After the 4-week observation period, all eligible patients entered the 8-week treatment period during which they received aliskiren at 150 mg orally in the morning once daily. BP was measured three times before all HD sessions. The reported BP was the average of all three measurements. Blood samples were obtained from arteriovenous shunt before HD sessions. PRA, angiotensin I (AT I), angiotensin II (AT II), aldosterone, BNP and hs-CRP were measured at baseline (week 0), and weeks 4 and 8 in the treatment period. d-ROM was measured at baseline and at week 8 in the treatment period. The standard laboratory tests were performed in the observation period and at baseline, and weeks 4 and 8 in the treatment period. In addition, serum electrolytes (sodium, potassium, chloride) were measured at week 2.

Laboratory methods

PRA and aldosterone levels were determined by the radioimmunoassay method. AT I and AT II levels were measured by double antibody radioimmunoassay method; the details of these methods have been described elsewhere.[10,11] The plasma level of BNP was measured by radioimmunoassay method. The plasma level of hs-CRP was measured by latex agglutination immunoassay methods. PRA, AT I, AT II, BNP, hs-CRP and other blood chemistry levels were determined by a clinical chemistry laboratory (Sanritsu, Chiba, Japan). d-ROM values were measured using the Free carpe diem (Wismerll, Tokyo, Japan) the details of this method have been described elsewhere.[12,13]

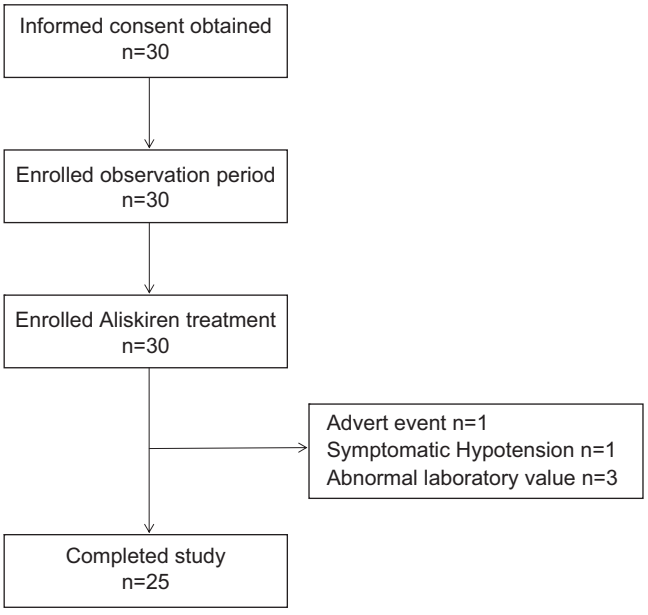

Figure 1 Patient flowchart.

Statistical analysis

All data are expressed as the mean ± s.d. The paired Student's *t*-test or repeated measures analysis of variance was used to compare continuous data. Relationships between continuous variables were analyzed by Pearson's correlation tests. Differences with a *P*-value of $<$0.05 were considered significant.

RESULTS

A total of 30 patients entered the treatment period after the observation period (Figure 1). Of these 30 patients, 25 completed the study.

Table 1 Patient baseline characteristics (*n*=25)

Parameter	*Statistics*	*Standard value*
Age (years)	68.0 ± 8.6	
Gender		
Male	16	
Female	9	
BMI (kg m^{-2})	24.7 ± 4.2	
Time on dialysis (week)	2.9 ± 0.3	
Duration of hemodialysis (years)	6.8 ± 7.5	
Initial nephropathy		
Chronic glomerulonephritis	4	
Diabetic nephropathy	14	
ANCA-associated glomerulonephritis	1	
Drug nephropathy	1	
Malignant hypertension	1	
Unknown	4	
SBP (mm Hg)	169.0 ± 20.1	
DBP (mm Hg)	78.1 ± 12.0	
HR (beats per min)	83.2 ± 11.2	
PRA (ng ml^{-1} h^{-1})		
All (*n*=25)	3.6 ± 4.0	(0.2–2.7)
ACEIs/ARBs (−) (*n*=6)	4.1 ± 4.5	
(+) (*n*=19)	2.5 ± 2.2	
AT 1 (pg ml^{-1})		
All	1704.0 ± 2580.9	($\leqslant$500)
ACEIs/ARBs (−)	1257.1 ± 1626.8	
(+)	2653.7 ± 3907.9	
AT 2 (pg ml^{-1})		
All	70.2 ± 121.5	($\leqslant$22)
ACEIs/ARBs (−)	38.2 ± 41.6	
(+)	138.0 ± 197.2	
Ald (pg ml^{-1})		
All	107.9 ± 148.0	(3–15)
ACEIs/ARBs (−)	85.4 ± 56.7	
(+)	155.8 ± 252.9	
BNP (pg ml^{-1})	362.5 ± 262.1	($\leqslant$18.4)
hs-CRP (mg l^{-1})	6.2 ± 8.1	($\leqslant$0.6)
d-ROM (U.CARR)	367.0 ± 89.8	(250–300)

Abbreviations: ACEI, angiotensin I converting enzyme inhibitor; Ald, aldosterone; ANCA, antineutrophil cytoplasmic antibody; ARB, angiotensin receptor blocker; AT 1, angiotensin I; AT 2, angiotensin II; BMI, body mass index; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; d-ROM, diacron-reactive oxygen metabolite; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; PRA, plasma renin activity; SBP, systolic blood pressure.

Two discontinued treatment owing to an adverse event and symptomatic hypotension by aliskiren. The adverse event was eyebrow alopecia (1 patient). A possible connection to aliskiren treatment could not be excluded for the eyebrow alopecia. The symptomatic hypotension recovered to the basal level after aliskiren withdrawal. Increased serum potassium was not observed in any patients. Three patients were excluded from analysis because of abnormal laboratory values due to severe infectious diseases during the treatment period. Table 1 shows the characteristics of the study patients. Of the 25 patients, 23 had been taking antihypertensive drugs before the treatment period, including calcium antagonists (16 patients), ACEIs (6 patients), ARBs (18 patients), β-blockers (4 patients), α-blockers (7 patients), αβ-blockers (4 patients) and α-methyldopa (5 patients).

Effect of aliskiren on BP

Figure 2a shows that SBP (±s.d) decreased from 169.0 ± 20.1 mm Hg at baseline to 162.9 ± 21.2 mm Hg at week 4, followed by a further decrease to 153.7 ± 19.6 mm Hg at week 8 ($P<0.001$). DBP (±s.d) also decreased from 78.1 ± 12.0 mm Hg at baseline to 75.6 ± 13.2 mm Hg at week 4, followed by a further decrease to 73.0 ± 13.6 mm Hg at week 8 ($P=0.048$). Figure 2b shows the BP change by aliskiren treatment in the group that received aliskiren combined with existing ACEIs and/or ARBs ($n=19$) and the group for which the treatment was not combined with ACEI and/or ARBs ($n=6$). The antihypertensive effect of aliskiren was comparable in the two groups.

Blockade of RAAS by aliskiren

Each factor of RAAS at week 0 in HDD-CKD patients was increased compared with the standard values (Table 1). PRA in the group that received ACEIs and/or ARBs was not higher than that in those not receiving these drugs. AT I, AT II and aldosterone in the group that received ACEIs and/or ARBs were higher than in those not receiving these drugs. The blockade effect of RAAS by aliskiren in all patients ($n=25$) is shown in Figure 3a. PRA (±s.d) decreased from 3.6 ± 4.0 ng ml^{-1} h^{-1} at baseline to 1.2 ± 1.7 ng ml^{-1} h^{-1} at week 4, followed by a further decrease to 1.0 ± 1.5 ng ml^{-1} h^{-1} at week 8 ($P=0.004$). AT I decreased from 1704.0 ± 2580.9 pg ml^{-1} at baseline to 180.4 ± 159.5 pg ml^{-1} at week 4, followed by 233.7 ± 181.0 pg ml^{-1} at week 8 ($P=0.009$). AT II decreased from 70.2 ± 121.5 pg ml^{-1} at baseline to 13.0 ± 10.2 pg ml^{-1} at week 4 to 12.4 ± 11.5 pg ml^{-1} at week 8 ($P=0.022$). Aldosterone decreased from 107.9 ± 148.0 pg ml^{-1} at baseline to 67.4 ± 39.0 pg ml^{-1} at week 4 to 73.1 ± 34.6 pg ml^{-1} at week 8 (NS). Figure 3b shows blockade effects of RAAS by aliskiren in the group receiving aliskiren combined with existing ACEIs and/or ARBs ($n=19$), and the group for which the treatment was not combined with ACEI and/or ARBs ($n=6$). Aliskiren inhibited RAAS in HDD-CKD patients regardless of the combination with ACEIs and/or ARBs.

Inhibition of BNP, HS-CRP and d-ROM by aliskiren

BNP (±s.d.) did not decrease (362.5 ± 262.1 pg ml^{-1} at baseline to 362.6 ± 278.2 pg ml^{-1} (NS)) at week 4; however, it significantly decreased to 300.0 ± 232.0 pg ml^{-1} at week 8 ($P=0.043$; Figure 4). hs-CRP decreased from 6.2 ± 8.1 mg l^{-1} at baseline to 4.9 ± 8.4 mg l^{-1} at week 4, followed by a further decrease to 3.5 ± 3.7 mg l^{-1} at week 8 ($P=0.022$) (Figure 4). d-ROM significantly decreased from 367.0 ± 89.8 U.CARR at baseline to 328.3 ± 70.9 U.CARR at week 8 ($P=0.022$; Figure 4). The extent of the decreases of BNP, hS-CRP and d-ROM did not correlate with reduced levels of SBP and DBP (Figure 5).

DISCUSSION

The results of this study show that aliskiren significantly decreased SBP and DBP in HDD-CKD patients. There are few studies that have evaluated the efficacy of a direct renin inhibitor (aliskiren) in

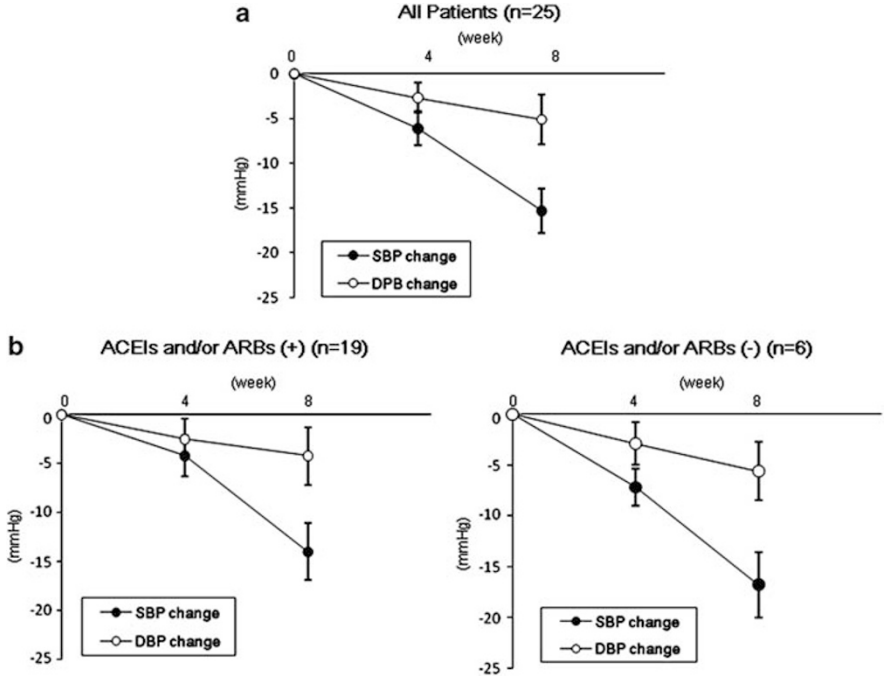

Figure 2 (**a**) Change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline (week 0) to week 8. (**b**) The change in SBP and DBP from baseline to week 8 in the group in which aliskiren treatment was combined with angiotensin I converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), and the group in which it was not combined with ACEIs and ARBs.

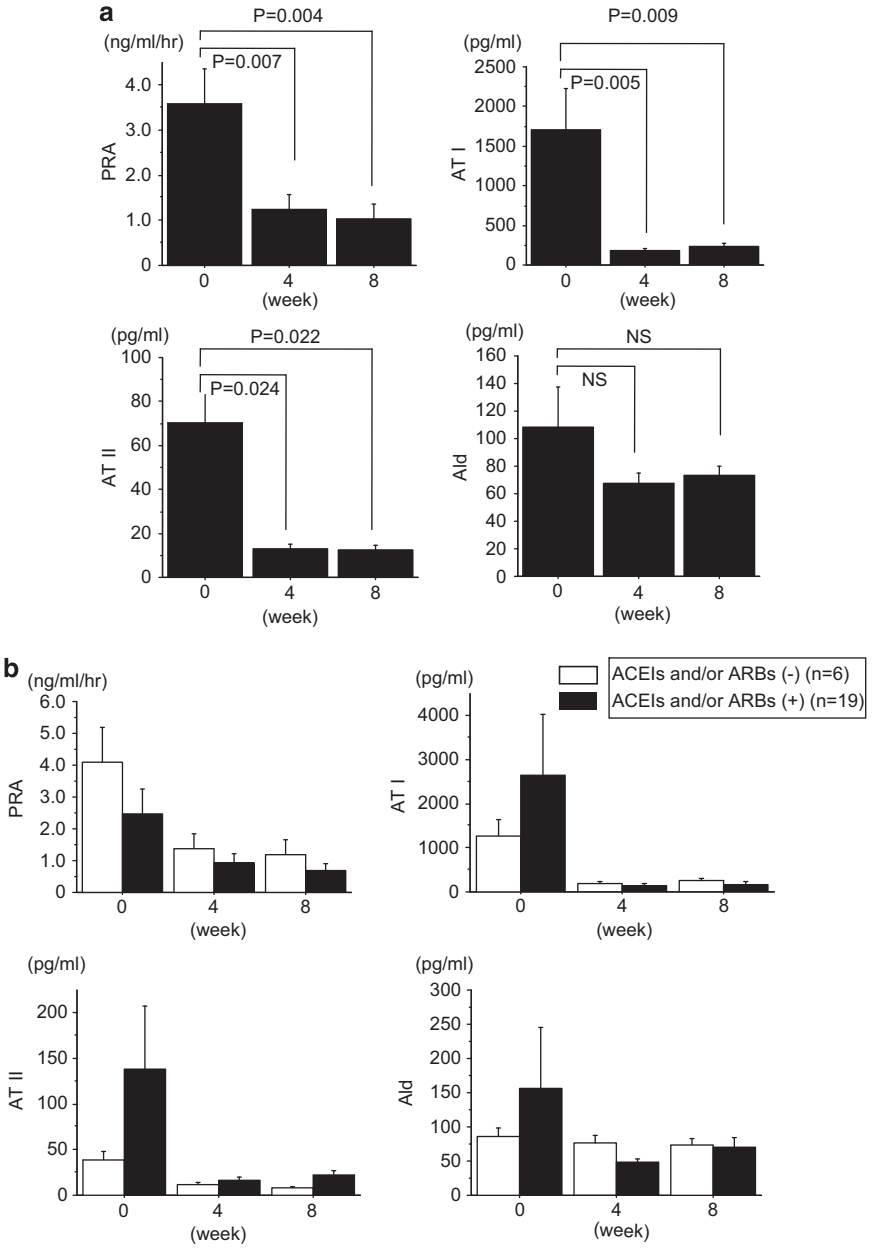

Figure 3 (**a**) Change in plasma renin activity (PRA), angiotensin I (AT I), angiotensin II (AT II) and aldosterone (Ald) by aliskiren treatment. (**b**) Change in PRA, AT I, AT II and Ald by aliskiren treatment in the group in which aliskiren treatment was combined with angiotensin I converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), and the group in which it was not combined with ACEIs and ARBs.

HDD-CKD patients with hypertension.[14] This antihypertensive effect was comparable between the group that received ACEIs and/or ARBs and the group that did not receive ACEIs and/or ARBs. This result could be because of the fact that the dose of ACEIs and/or ARBs for HDD-CKD patients in this study was insufficient to block RAAS leading to BP control and cardiovascular protection because their hypertension was not controlled well and biomarkers for CVD did not decrease regardless of ACEI and/or ARB treatment. Although the sample number was small, the fact that ACEIs and/or ARBs did not lead to a reactive rise in PRA in the group that received ACEIs and/or ARBs also supports this possibility.

Activated RAAS has pivotal roles in developing CVD in HDD-CKD patients.[15] Accumulated evidence has demonstrated that blockade of RAAS not only prevents the progression, but also the regression of cardiovascular remodeling in HDD-CKD patients.[8,16,17] In the present study, we evaluated BNP as a marker of heart function, predictably leading to CVD under aliskiren treatment because BNP reduction has consistently been associated with an improved outcome in heart failure.[18–20] For instance, an increment of 10 pg ml^{-1} in BNP was associated with a 1.2% increased risk of death.[18] Activated RAAS increased the inflammatory mediator that is an independent risk factor for CVD.[4–6] Activated RAAS directly increases proinflammatory gene expression and activates oxidative stress, leading to progressive inflammation of the vascular endothelium.[6] The elevated hs-CRP caused by persistent inflammation in uremic conditions has been shown to be an independent predictor of cardiovascular death in

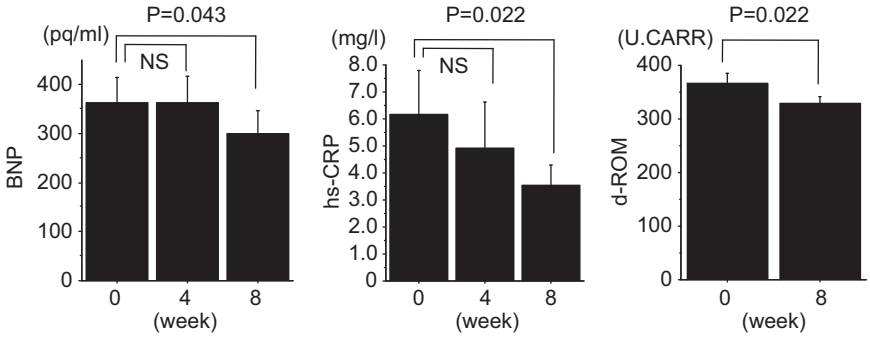

Figure 4 Change in brain natriuretic peptide (BNP), highly sensitive C-reactive protein (hs-CRP) and diacron-reactive oxygen metabolite (d-ROM) by aliskiren treatment.

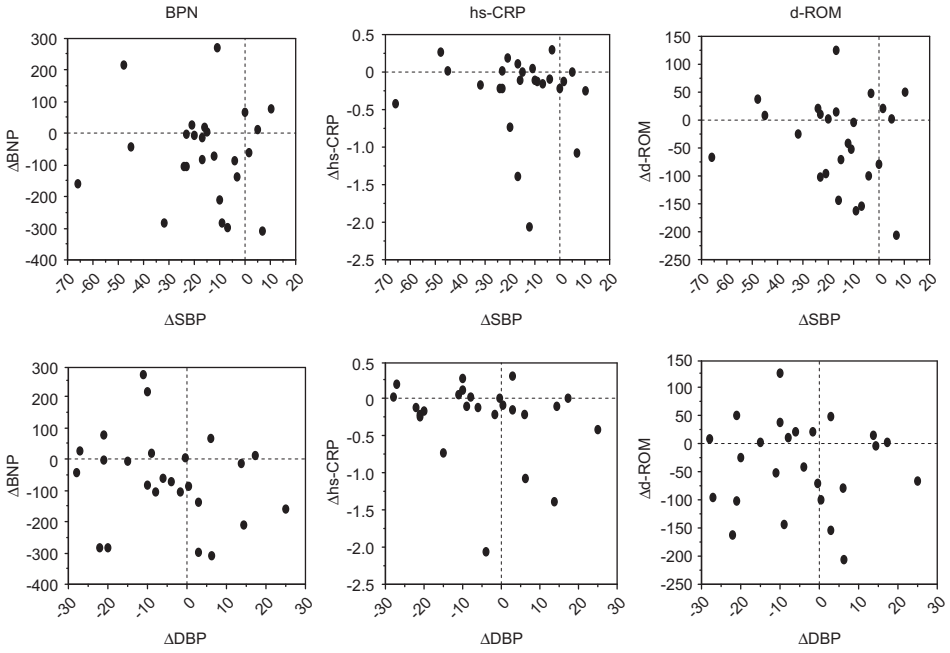

Figure 5 Correlation of the change in brain natriuretic peptide (BNP), highly sensitive C-reactive protein (hs-CRP) and diacron-reactive oxygen metabolite (d-ROM), and the change in SBP (ΔSBP) and DBP (ΔDBP) by aliskiren treatment.

HDD-CKD patients.[4,5] The d-ROM level represents the total level of peroxidized metabolites. d-ROM has been used to evaluate the oxidative status, and its significance as a clinical marker has been reported in various fields, including HDD-CKD patients.[12,13] Therefore, we evaluated the change of hs-CRP as an inflammation marker and d-ROM as an oxidative stress marker by aliskiren treatment. In the present study, BNP, hs-CRP and d-ROM were significantly decreased by aliskiren treatment. These results suggest that aliskiren could decrease cardiovascular events in HDD-CKD patients. Previous studies reported that aliskiren has a cardiovascular protective effect. Left Ventricular Assessment of Hypertrophy (ALLAY) study demonstrated that aliskiren reduced left ventricular hypertrophy in hypertensive patients.[21] Moreover, several studies demonstrated that the cardiovascular protective effect of aliskiren was independent of BP-lowering effect. The Aliskiren Observation of Heart Failure Treatment (ALOFT) study demonstrated that aliskiren decreased BNP in heart failure patients not by a BP-lowering effect but possibly by increased natriuresis.[22] Westermann *et al.*[23] reported that aliskiren improved cardiac function and remodeling after myocardial infarction by normalization of intracellular signaling stimulated by AT II without altering BP in an animal model. Imanishi *et al.*[24] reported that aliskiren improved vascular endothelial function and protected against atherosclerosis by impaired nitric oxide bioavailability and decreased inflammatory mediators without altering BP in an animal model. In this study, the decreased levels of BNP, hs-CRP and d-ROM by aliskiren treatment did not correlate with the decreased levels of SBP and DBP. These results suggested that aliskiren may have cardiovascular protective effects not only by an antihypertensive effect but also by a non-antihypertensive effect in HDD-CKD patients with hypertension. In this study, aliskiren may have decreased biomarkers for CVD by improving intracellular signaling and vascular endothelial function by decreasing inflammatory mediators but not by increasing natriuresis in addition to a BP-lowering effect because all enrolled patients had oliguria or anuria. Further studies will need to investigate the mechanism of cardiovascular protective effects by aliskiren in HDD-CKD patients with hypertension

Several studies reported that mean trough plasma aliskiren concentrations increased by renal impairment;[25,26] however, an increase in exposure does not correlate with the severity of renal impairment.[25] Moreover, renal clearance of aliskiren represents only a small fraction (0.1–1.0%).[9] These data suggest that adjustment of the aliskiren dose is unlikely to be required in HD patients. Further studies will be required to investigate the pharmacokinetics of aliskiren in HD patients.

In conclusion, aliskiren was effective for BP control and has cardiovascular protective effects in hypertensive HDD-CKD patients.

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