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The Renin-Angiotensin-Aldosterone System in Dialysis Patients

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1. Introduction

Hypertension (HT) and cardiovascular disease (CVD) are common in dialysis-dependent chronic kidney disease (DD-CKD) patients. The renin-angiotensin-aldosterone system (RAAS) plays pivotal roles in the pathogenesis of HT in DD-CKD patients. Activated RAAS also increases inflammatory mediators, which was shown to be an independent predictor of CVD in DD-CKD patients. Recent meta-analyses suggested that antihypertensive pharmacotherapy may reduce CVD in DD-CKD patients. This review focuses on the physiological roles and blockade effects of RAAS for HT and CVD in DD-CKD patients.

2. The physiological roles of RAAS in DD-CKD patients

The role of RAAS in hypertensive DD-CKD patients was confirmed by the normalization of blood pressure (BP) upon administration of an angiotensin antagonist, saralasin. Normally, volume overload and elevation of BP result in suppression of RAAS production. Since this feedback is often incomplete in CKD patients, CKD patients often show HT and high or normal RAAS. Weidmann et al. reported that the renin levels of hypertensive hemodialysis-dependent CKD (HDD-CKD) patients were approximately twice as high as those of normal subjects. Parenchymal renal injury and renovascular disease may cause increased renin secretion in end-stage CKD. The prevalence of renal artery stenosis may be as high as 40% in patients starting HD, although the diagnosis was determined in only one-quarter of such a group before entering a dialysis program. Kimura et al. reported that plasma rennin activity (PRA) increased from 2.3±0.5 ng/ml/hr at just before initiation of HD to 6.5±1.3 ng/ml/hr over an 8- to 10-year period in HDD-CKD patients. These data suggested that renin secretion continued even after disuse atrophy of kidney with almost complete deterioration of its excretory function.

Activated RAAS increased inflammatory mediators, which is an independent risk factor for CVD. The mechanism is thought to be as follows. Activated RAAS directly increases pro-

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inflammatory gene expression and activates oxidative stress, leading to progressive inflammation of the vascular endothelium. In addition, among RAAS, mainly angiotensin II (AT II) stimulates vascular reactive oxygen species (ROS) production from sources such as NADPH oxidase and uncoupled endothelial nitric oxide (NO) synthesis. Increased ROS down-regulates NO activity that leads to endothelial dysfunction. AT II also directly increases pro-inflammatory gene expressions, such as VCAM-1 and MCP-1. Both processes lead to further recruitment of inflammatory cells and accelerate the vascular inflammatory response. On the other hand, the prognostic value of a high plasma aldosterone concentration (PAC) in HDD-CKD patients is unknown, where PAC is known to be associated with poor outcome in patients with cardiac disease. Kohagura et al. reported that lower PAC was independently predictive of death in hypertensive DD-CKD patients. The adjusted hazard ratio (95% confidence interval) of the lower PAC group was 2.905 (1.187–7.112, p=0.020). The significance of PAC became marginal when normalized with albumin or potassium. These results suggested that higher PAC was not associated with an increase in total and cardiovascular deaths among hypertensive HDD-CKD patients. The association between lower PAC and poor survival may be driven by volume retention and/or lower potassium level. Diskin et al. also reported that HDD-CKD patients with higher aldosterone levels tended to have longer survival.

Recently, it was found that RAAS components are expressed in many tissues, such as the heart, kidney, placenta, testis, eye, and lymphocytes. These local tissue RAAS components are suggested to contribute to tissue damage. Prorenin, which is a biosynthetic precursor of renin, is secreted not only by the kidney but also by many other tissues, whereas circulating renin is derived exclusively from juxta-glomerular cells of the kidney. Prorenin does not have enzymatic activity itself; however, several studies have reported that circulating prorenin could be taken up by tissues and contribute to activating local RAAS by binding (pro)renin receptor [(P)RR] and then that inactive prorenin is converted to the active form, which obtains enzymatic activity by conformational change. Recent studies have demonstrated that prorenin-(P)RR interaction activated tissue RAAS and contributed to the pathogenesis of organ damage in several diseases, such as HT and diabetes end organ damage; however, few studies have reported the role of tissue RAAS and prorenin in DD-CKD patients. Takemitsu et al. reported that arterial (P)RR may contribute to activate arterial tissue RAAS in HDD-CKD patients since arterial (P)RR mRNA expression was correlated with arterial angiotensin-converting enzyme (ACE) mRNA expression. Takemitsu et al. also reported that plasma prorenin concentration was correlated with PRA, plasma AT I level, plasma AT II level, and PAC level in HDD-CKD patients. Recently, we reported that the plasma prorenin level increased in HDD-CKD patients [147.1 +/- 118.9 pg/ml (standard value <100 pg/ml)]. The (P)RR mRNA expression level in peripheral mononuclear cells (PBMCs) also increased 1.41 +/- 0.39-fold in HDD-CKD patients compared with that in healthy control subjects ($p < 0.001$) (Figure 1). Plasma prorenin significantly correlated with plasma 8-hydroxydeoxyguanosine (8-OHdG) level ($r = 0.535$, $p < 0.001$), which is a useful marker for assessment of oxidative DNA damage in reactive oxygen species (ROS) including in HDD-CKD patients (Figure 2). These results suggested that tissue RAAS activated by circulating prorenin contributes to the regulation of plasma 8-OHdG level in HDD-CKD patients.

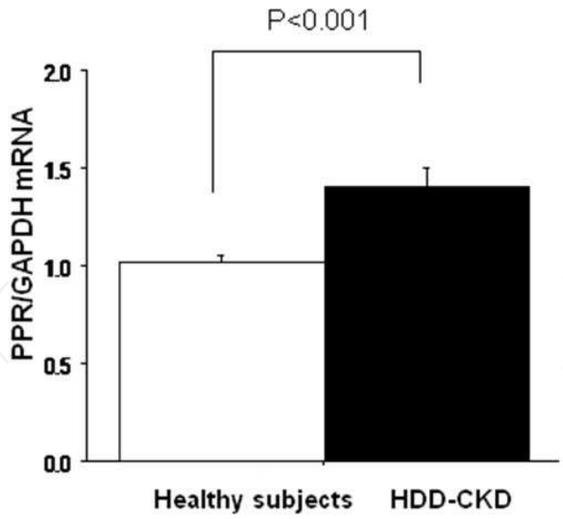

Fig. 1. (P)RR expression in peripheral blood mononuclear cells in healthy subjects (n=10) and HDD-CKD patients (n=49). Columns represent the mean ± s.e. (P)RR, prorenin receptor; HDD-CKD, hemodialysis-dependent chronic kidney disease (Morishita *et al.*, 2011).

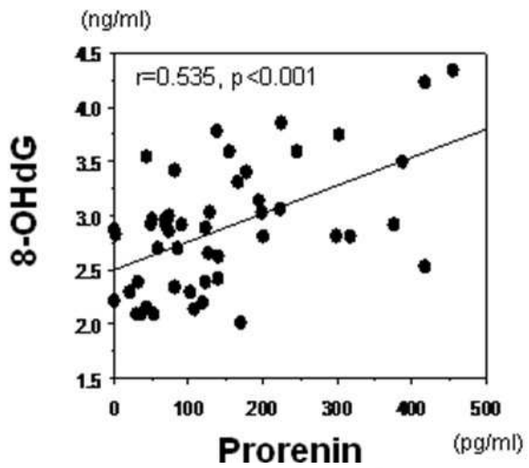

Fig. 2. Correlations of plasma prorenin level and 8-OHdG in hemodialysis-dependent chronic kidney disease patients. 8-OHdG, 8-hydroxydeoxyguanosine (Morishita *et al.*, 2011).

3. The blocked effect of RAAS in DD-CKD patients

3.1 HDD-CKD patients

Angiotensin-converting enzyme inhibitors in HDD-CKD patients

Tradolapril and captopril have been reported to be effective for HT in HDD-CKD patients. Zheng et al. reported that systolic BP (SBP) was decreased from 122.2±7.1 to 116.4±11.6 mmHg and diastolic BP (DBP) was decreased from 75.3±10.4 to 70.4±11.4 mmHg after 2-10 weeks by the administration of tradopril (2-8 mg/thrice a week (TIW)) after each HD session in 10 HDD-CKD patients. In that study, atenolol (25-50 mg/TIW) and/or amlodipine (10 mg/TIW) were also given if the patients had any member of these classes of drugs as part of their daily regimen. Wauterd et al. reported that captopril was administered

orally in 2 daily doses of 25 to 200 mg in 8 HDD-CKD patients. These patients showed HT despite intensive ultrafiltration and conventional antihypertensive therapy. For 4 patients with the highest PRA, their BP was normalized by captopril alone. For the 4 remaining patients, captopril therapy was complemented by salt subtraction, which consisted of replacement of 1-2 liters of ultrafiltrate by an equal volume of 5% dextrose until BP was controlled. After an average treatment period of 5 months, BP of all 8 patients was reduced from 179/105 ± 6/3 (mean ±SEM) to 134/76 ± 7/5 mmHg ($p < 0.001$) without a significant change in body weight. These clinical studies demonstrated that ACE inhibitor has beneficial effects to control BP in HDD-CKD patients. In addition, some studies reported that ACE inhibitors showed cardiovascular protective effects in HDD-CKD patients as follows. London et al. reported that perindopril (2-4 mg after each HD session) significantly reduced left ventricular mass (317±18 to 247±21 g, $p=0.036$) after 12 months in 14 HDD-CKD patients whereas a calcium channel antagonist, nitredipine (20-40 mg/day), did not when perindopril and nitredipine showed similar reductions of BP. Matsumoto et al. reported that imidapril (2.5 mg/day) significantly reduced left ventricular mass index (132±10 to 109±6 g/m², $p<0.05$) after 6 months; however, placebo did not produce a change in HDD-CKD patients. SBP and DBP were not significantly changed in either imidapril or placebo group. In that study, ACE was reduced (12±1 to 5±2 U/I, $p<0.01$) and PRA was increased (3.3±0.8 to 8.1±3.2 ng/ml/h, $p<0.01$) but plasma AT II and aldosterone (Ald) were not significantly changed (13±3 to 17±3 pg/ml and 365±125 to 312±132 pg/ml, respectively). These results suggested that the beneficial effect of imidapril against left ventricular mass was independent of BP lowering effect. Zannad et al. reported that no significant benefit was found with fosinopril (5-20 mg/day) for the prevention of cardiovascular events such as cardiovascular death, resuscitated death, nonfatal stroke, heart failure, myocardial infarction, or revascularization in HDD-CKD patients; however, there was a trend that fosinopril treatment may be associated with a lower risk of cardiovascular events after adjustment for risk factors. These lines of evidence suggested that ACE inhibitors are effective in controlling BP and preventing CVD in HDD-CKD patients. It is highly likely that the cardioprotective effects of ACE inhibitors are independent of their BP lowering effect in HDD-CKD patients.

Angiotensin receptor blockers in HDD-CKD patients

Saracho et al. reported on a multicenter, open 6 month study designed to test the tolerability and efficacy of losartan as an antihypertensive in 406 hypertensive HDD-CKD patients who were previously untreated, treated but uncontrolled, or treated with poor tolerability. There were significant reductions in pre- and postdialysis SBP and DBP at 3 months (pre SBP/DBP: 155 ± 15/84± 9 mmHg, post SBP/DBP: 140 ± 19/78± 10 mmHg) and 6 months (pre SBP/DBP: 152 ± 16/83± 9 mmHg, post SBP/DBP: 139± 18/77± 9 mm Hg) compared with those at baseline (pre SBP/DBP: 163 ± 16/88± 10 mmHg, post SBP/DBP: 148± 18/82± 9 mmHg). Shibasaki et al. reported that losartan (50 mg/day) reduced left ventricular mass index (-24.7±3.2%) after 6 months more than a calcium channel antagonist, amlodipine (5 mg/day: -10.5±5.2%), or an ACE inhibitor, enalapril (5 mg/day: -11.2±4.1%), although all three groups had similar decreases in mean BP. Kanno et al. reported that losartan (100 mg/TIW) reduced left ventricular hypertrophy (145±5 to 122±3 g/m², $p<0.001$) after 12 months in 24 diabetic patients on HD therapy whereas a placebo group showed no change. In this study, SBP and DBP were controlled below 140/90 mmHg with a calcium antagonist,

benidipine (4-12 mg/day), and an α-blocker, doxazosin (2-4 mg/day). SPB was significantly decreased in both placebo and losartan groups after 12 months.These results suggested that this beneficial effect of losartan for left ventricular hypertrophy was independent of a BP lowering effect. Takahashi et al. stated that candesartan (4-8 mg/day) reduced cardiovascular events and mortality compared with placebo (16.3% vs. 45.9 and 0.0 vs. 18.9%, respectively) after 19.4±1.2 months in HDD-CKD patients in a stable condition and with no clinical evidence of cardiac disorder. In this study, the brain natriuretic peptide (BNP) level did not differ between the two groups at enrolment, whereas in patients who had not experienced a cardiovascular event at 12 months, the BNP levels were significantly increased in the control group but not in the candesartan group. Suzuki et al. reported that angiotensin receptor blockers (ARBs) (valsartan: 160 mg/day, candesartan: 12 mg/day, or losartan: 100 mg/day) treatment was independently associated with reduced cardiovascular events (hazard ratio, 0.51; 95% confidence interval, 0.33 to 0.79; p=0.002) compared with no ARB treatment group for 180 HDD-CKD patients in each group during a 3 year observation period. There were 34 (19%) fatal or nonfatal CVD events in the ARBs group and 59 (33%) in the no ARB group. BP did not differ between the ARBs group and the no ARB group during the observation period. After adjustment for age, sex, diabetes, and SBP, treatment with an ARB was independently associated with reduced fatal and nonfatal CVD events (hazard ratio, 0.51; 95% confidence interval, 0.33 to 0.79; p=0.002). These results demonstrated that ARBs are effective in controlling BP and preventing CVD in HDD-CKD patients. We predict that the cardioprotective effects of ARBs may be independent of their BP lowering effect in HDD-CKD patients.

Direct renin inhibitor

An oral direct renin inhibitor, aliskiren, is effective against essential HT by reducing PRA, resulting in suppression of RAAS; however, little was known about the effects of aliskiren in HDD-CKD patients. Recently, we reported on antihypertensive and potential cardiovascular protective effects of aliskiren, in hypertensive HDD-CKD patients. Aliskiren (150 mg/day) significantly reduced SBP and DBP after 2 month in hypertensive HDD-CKD patients (Figure 3). RAAS was suppressed by aliskiren treatment (PRA: 3.6±4.0 to 1.0 ±1.5 ng/ml/hr, p=0.004; AT I: 1704.0±2580.9 to 233. 7±181.0 pg/ml, p=0.009; AT II: 70.2±121.5 to 12.4±11.5 pg/ml, p=0.022) (Figure 4). Surrogate markers for cardiovascular disease such as BNP, high-sensitivity CRP (hs-CRP), and an oxidative stress marker, diacron-reactive oxygen metabolite (d-ROM), were inhibited by aliskiren (BNP: 362.5±262.1 to 300.0±232.0 pg/ml, p=0.043; hs-CRP: 6.2±8.1 to 3.5±3.7 mg/l, p=0.022; d-ROM: 367.0±89.8 to 328.3±70.9 U.CARR, p=0.022) (Figure 5). The levels of inhibition of these surrogate markers for CVD by aliskiren did not correlate with the decreased levels of BP. Two treatments were discontinued owing to an adverse event and symptomatic hypotension by aliskiren. The adverse event was eyebrow alopecia (1 patient). A possible connection of this event to aliskiren treatment could not be excluded. The symptomatic hypotension recovered to the basal level after aliskiren withdrawal. Increased serum potassium was not observed in any patients. Several studies reported that mean trough plasma aliskiren concentrations were increased by renal impairment; however, an increase in exposure did not correlate with the severity of renal impairment. Moreover, renal clearance of aliskiren was found to occur for only a small fraction (0.1-1.0%). These data suggest that adjustment of the aliskiren dose is

unlikely to be required in HDD-CKD patients. Further studies will be required to investigate the pharmacokinetics of aliskiren in HDD-CKD patients. In summary, these results suggest that aliskiren is effective in BP control and extend the possibility that aliskiren may have cardiovascular protective effects in hypertensive HDD-CKD patients.

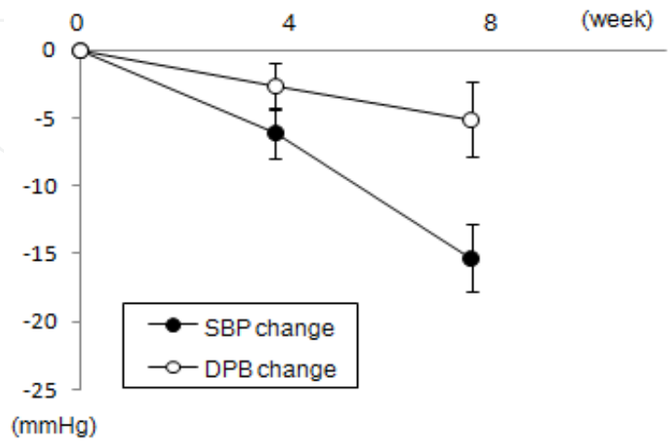

Fig. 3. Change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline (Week 0) to Week 8 with aliskiren (150 mg/day) treatment in hemodialysis-dependent chronic kidney disease patients (Morishita *et al.*, 2011a).

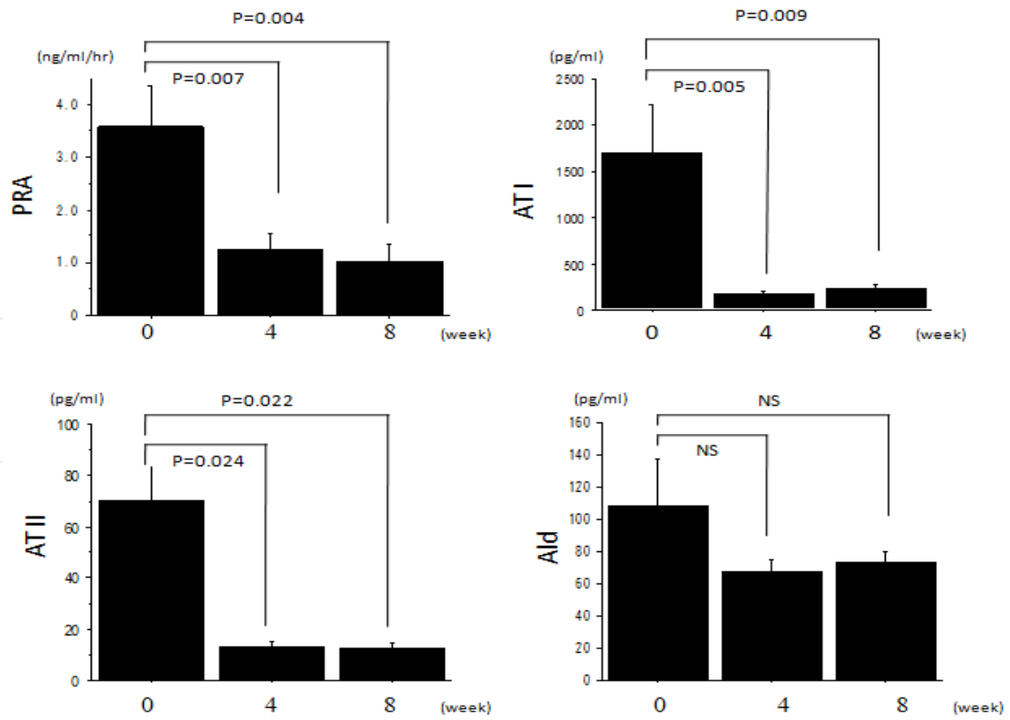

Fig. 4. Change in plasma renin activity (PRA), angiotensin I (ATI), angiotensin II (ATII), and aldosterone (Ald) by aliskiren treatment in hemodialysis-dependent chronic kidney disease patients (Morishita *et al.*, 2011a).

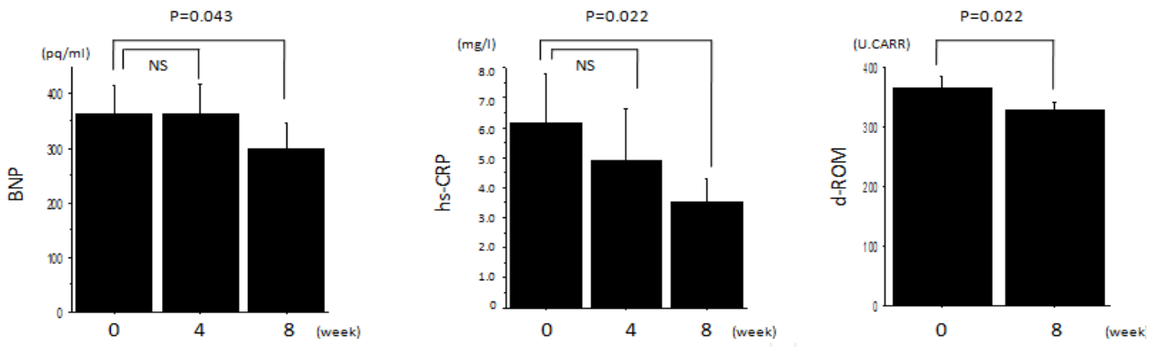

Fig. 5. Change in brain natriuretic peptide (BNP), highly sensitive C-reactive protein (hs-CRP), and diacron-reactive oxygen metabolite (d-ROM) by aliskiren treatment in hemodialysis-dependent chronic kidney disease patients (Morishita *et al.*, 2011a).

3.2 PDD-CKD patients

A few studies reported on a RAAS blockade effect in peritoneal dialysis-dependent CKD (PDD-CKD) patients. Fang et al. reported that a group (n=165) treated with ACE inhibitors/ARBs had a significantly longer survival than an untreated group (n= 141) (log rank 19.191, $P < 0.001$) in PDD-CKD patients. After adjusting for age, BP, and other demographic and clinical parameters, multivariable Cox proportional hazards modeling showed that the use of ACE inhibitors/ARBs was associated with 62% reduced risk of death (HR 0.382, 95% CI 0.232-0.631, $P < 0.001$) in PDD-CKD patients. Jing et al. reported that ultrafiltration of a group treated with ACE inhibitors/ARBs group (n=38) had not changed after 12 months whereas that of an untreated group (n=28) had decreased ($P < 0.05$). The expressions of fibronectin, Transforming growth factor-β1 (TGF-β1) and vascular endothelial growth factor (VEGF) in dialysate effluent were significantly increased in the untreated group, but not in the group treated with ACE inhibitors/ARBs. These results suggested that RAAS blockade has beneficial effects for mortality and peritoneal function in PDD-CKD patients. Suzuki et al. reported that ARB (valsartan) slowed the decline in residual renal function independent of BP lowering effect in PDD-CKD patinets.

3.3 Caridioprotective effects of RAAS blockers independent of their BP lowering effect in DD-CKD patients

Increasing evidence suggested that elevation of RAAS contributes directly to cardiac hypertrophy via its growth factor properties on smooth muscle cells and cardiac myocytes among DD-CKD patients, independent of BP effects. RAAS also plays a role in cardiac fibrosis by stimulating TGF-β1 gene expression and induction of fibroblast proliferation and collagen deposition. RAAS blockers may directly effects for cardiac hypertrophy and fibrosis via these pathways independent of their BP lowering effects in DD-CKD patients. In addition, several studies reported that RAAS blockers showed beneficial effects for pulse wave velocity which is recognized as a potent predictor of mortality in DD-CKD patients, independent of their BP lowering effects. Further studies will be needed to investigate the mechanism of cardioprotective effects of RAAS blockade on DD-CKD patients.

3.4 Adverse effects of RAAS blockers in DD-CKD patients

ACE inhibitors showed several adverse effects in HDD-CKD patients. High-dose ACE inhibitors suppressed erythropoiesis and induced resistance to erythropoietin therapy in HDD-CKD patients. Occasionally, ACE inhibitors may cause anaphylactoid reactions with AN69 dialysis membrane in HDD-CKD patients by elevation of bradykinin level (Kammerl *et al.*, 2000). Hyperkalemia, which is a frequent concern in HDD-CKD patients independently of medication use, is the primary danger from RAAS blocking medications. Several clinical trials of ACE inhibitors, ARBs, and renin inhibitor in HDD-CKD patients tracked potassium levels. Increased hyperkalemia by these RAAS blockers in HDD-CKD patients was not observed in these trials. These results suggested that the risk of hyperkalemia by RAAS blocking is small.

4. Conclusion

From previous studies, it is suggested that RAAS blockade has a beneficial effect in controlling BP and preventing CVD in DD-CKD patients. However, the choice of the RAAS inhibitor as well as its use in the treatment of DD-CKD patients have to be carefully determined considering the possible adverse effects and potential interactions with other drugs being used in the treatment of DD-CKD patients. Further studies with an adequate sample size and a thorough design are still needed to determine the effect of RAAS blockade on DD-CKD patients.

5. Conflict of interest statement

None declared

Some parts of this manuscript were reported in Cardiovascular & Hematological Agents in Medical Chemistry (submitted), Hypertension Research (2011), 34, 308-313 and Clinical Experimental Nephrology(2011), 15, 398-404.

6. References

Agarwal, R., Nissenson, A.R., Batlle, D., Coyne, D.W., Trout, J.R., Warnock, D.G., 2003. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. Am J Med 115, 291-297.

Agarwal, R., Sinha, A.D., 2009. Cardiovascular protection with antihypertensive drugs in dialysis patients: systematic review and meta-analysis. Hypertension 53, 860-866.

Austin, E.W., Parrish, J.M., Kinder, D.H., Bull, R.J., 1996. Lipid peroxidation and formation of 8-hydroxydeoxyguanosine from acute doses of halogenated acetic acids. Fundam Appl Toxicol 31, 77-82.

Blankestijn, P.J., Ligtenberg, G., 2004. Volume-independent mechanisms of hypertension in hemodialysis patients: clinical implications. Semin Dial 17, 265-269.

Collins, A.J., Roberts, T.L., St Peter, W.L., Chen, S.C., Ebben, J., Constantini, E., 2002. United States Renal Data System assessment of the impact of the National Kidney Foundation-Dialysis Outcomes Quality Initiative guidelines. Am J Kidney Dis 39, 784-795.

Cooper, A.C., Robinson, G., Vinson, G.P., Cheung, W.T., Broughton Pipkin, F., 1999. The localization and expression of the renin-angiotensin system in the human placenta throughout pregnancy. Placenta 20, 467-474.

Crawford, D.C., Chobanian, A.V., Brecher, P., 1994. Angiotensin II induces fibronectin expression associated with cardiac fibrosis in the rat. Circ Res 74, 727-739.

Diskin, C.J., Stokes, T.J., Dansby, L.M., Carter, T.B., Radcliff, L., 2004. The clinical significance of aldosterone in ESRD: Part II. Nephrol Dial Transplant 19, 1331-1332; author reply 1332.

Dostal, D.E., Baker, K.M., 1999. The cardiac renin-angiotensin system: conceptual, or a regulator of cardiac function? Circ Res 85, 643-650.

Fang, W., Oreopoulos, D.G., Bargman, J.M., 2008. Use of ACE inhibitors or angiotensin receptor blockers and survival in patients on peritoneal dialysis. Nephrol Dial Transplant 23, 3704-3710.

Heerspink, H.J., Ninomiya, T., Zoungas, S., de Zeeuw, D., Grobbee, D.E., Jardine, M.J., Gallagher, M., Roberts, M.A., Cass, A., Neal, B., Perkovic, V., 2009. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. Lancet 373, 1009-1015.

Herzog, C.A., Ma, J.Z., Collins, A.J., 2002. Long-term survival of dialysis patients in the United States with prosthetic heart valves: should ACC/AHA practice guidelines on valve selection be modified? Circulation 105, 1336-1341.

Hsueh, W.A., Baxter, J.D., 1991. Human prorenin. Hypertension 17, 469-477.

Huang, W.H., Hsu, C.W., Chen, Y.C., Hung, C.C., Huang, J.Y., Lin, J.L., Yang, C.W., 2007. Angiotensin II receptor antagonists supplementation is associated with arterial stiffness: insight from a retrospective study in 116 peritoneal dialysis patients. Ren Fail 29, 843-848.

Ichihara, A., Hayashi, M., Kaneshiro, Y., Suzuki, F., Nakagawa, T., Tada, Y., Koura, Y., Nishiyama, A., Okada, H., Uddin, M.N., Nabi, A.H., Ishida, Y., Inagami, T., Saruta, T., 2004. Inhibition of diabetic nephropathy by a decoy peptide corresponding to the "handle" region for nonproteolytic activation of prorenin. J Clin Invest 114, 1128-1135.

Ichihara, A., Hayashi, M., Kaneshiro, Y., Takemitsu, T., Homma, K., Kanno, Y., Yoshizawa, M., Furukawa, T., Takenaka, T., Saruta, T., 2005. Low doses of losartan and trandolapril improve arterial stiffness in hemodialysis patients. Am J Kidney Dis 45, 866-874.

Ichihara, A., Kaneshiro, Y., Takemitsu, T., Sakoda, M., Suzuki, F., Nakagawa, T., Nishiyama, A., Inagami, T., Hayashi, M., 2006. Nonproteolytic activation of prorenin contributes to development of cardiac fibrosis in genetic hypertension. Hypertension 47, 894-900.

Ito, S., Nakura, N., Le Breton, S., Keefe, D., 2010. Efficacy and safety of aliskiren in Japanese hypertensive patients with renal dysfunction. Hypertens Res 33, 62-66.

Jing, S., Kezhou, Y., Hong, Z., Qun, W., Rong, W., 2010. Effect of renin-angiotensin system inhibitors on prevention of peritoneal fibrosis in peritoneal dialysis patients. Nephrology (Carlton) 15, 27-32.

Jurewicz, M., McDermott, D.H., Sechler, J.M., Tinckam, K., Takakura, A., Carpenter, C.B., Milford, E., Abdi, R., 2007. Human T and natural killer cells possess a functional

renin-angiotensin system: further mechanisms of angiotensin II-induced inflammation. J Am Soc Nephrol 18, 1093-1102.

Kammerl, M.C., Schaefer, R.M., Schweda, F., Schreiber, M., Riegger, G.A., Kramer, B.K., 2000. Extracorporal therapy with AN69 membranes in combination with ACE inhibition causing severe anaphylactoid reactions: still a current problem? Clin Nephrol 53, 486-488.

Kanno, Y., Kaneko, K., Kaneko, M., Kotaki, S., Mimura, T., Takane, H., Suzuki, H., 2004. Angiotensin receptor antagonist regresses left ventricular hypertrophy associated with diabetic nephropathy in dialysis patients. J Cardiovasc Pharmacol 43, 380-386.

Kimura, G., Takahashi, N., Kawano, Y., Inenaga, T., Inoue, T., Nakamura, S., Matsuoka, H., Omae, T., 1995. Plasma renin activity in hemodialyzed patients during long-term follow-up. Am J Kidney Dis 25, 589-592.

Kohagura, K., Higashiuesato, Y., Ishiki, T., Yoshi, S., Ohya, Y., Iseki, K., Takishita, S., 2006. Plasma aldosterone in hypertensive patients on chronic hemodialysis: distribution, determinants and impact on survival. Hypertens Res 29, 597-604.

Krop, M., Danser, A.H., 2008. Circulating versus tissue renin-angiotensin system: on the origin of (pro)renin. Curr Hypertens Rep 10, 112-118.

Kupfahl, C., Pink, D., Friedrich, K., Zurbrugg, H.R., Neuss, M., Warnecke, C., Fielitz, J., Graf, K., Fleck, E., Regitz-Zagrosek, V., 2000. Angiotensin II directly increases transforming growth factor beta1 and osteopontin and indirectly affects collagen mRNA expression in the human heart. Cardiovasc Res 46, 463-475.

Landomesser, U., Drexler, H., 2003. oxidative stress, the renin-angiotensin system, and atherosclerosis. european heart journal 5, A3-A7.

Lenz, T., Sealey, J.E., Maack, T., James, G.D., Heinrikson, R.L., Marion, D., Laragh, J.H., 1991. Half-life, hemodynamic, renal, and hormonal effects of prorenin in cynomolgus monkeys. Am J Physiol 260, R804-810.

Leung, P.S., Wong, T.P., Lam, S.Y., Chan, H.C., Wong, P.Y., 2000. Testicular hormonal regulation of the renin-angiotensin system in the rat epididymis. Life Sci 66, 1317-1324.

London, G.M., Pannier, B., Guerin, A.P., Marchais, S.J., Safar, M.E., Cuche, J.L., 1994. Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease. Comparative effects of ACE inhibition and calcium channel blockade. Circulation 90, 2786-2796.

Macdougall, I.C., 1999. The role of ACE inhibitors and angiotensin II receptor blockers in the response to epoetin. Nephrol Dial Transplant 14, 1836-1841.

Matsumoto, N., Ishimitsu, T., Okamura, A., Seta, H., Takahashi, M., Matsuoka, H., 2006. Effects of imidapril on left ventricular mass in chronic hemodialysis patients. Hypertens Res 29, 253-260.

Methot, D., Silversides, D.W., Reudelhuber, T.L., 1999. In vivo enzymatic assay reveals catalytic activity of the human renin precursor in tissues. Circ Res 84, 1067-1072.

Mimran, A., Shaldon, S., Barjon, P., Mion, C., 1978. The effect of an angiotensin antagonist (saralasin) on arterial pressure and plasma aldosterone in hemodialysis-resistant hypertensive patients. Clin Nephrol 9, 63-67.

Morishita, Y., Hanawa, S., Chinda, J., Iimura, O., Tsunematsu, S., Kusano, E., 2011a. Effects of aliskiren on blood pressure and the predictive biomarkers for cardiovascular

disease in hemodialysis-dependent chronic kidney disease patients with hypertension. Hypertens Res 34, 308-313.

Morishita, Y., Hanawa, S., Miki, T., Sugase, T., Sugaya, Y., Chinda, J., Iimura, O., Tsunematsu, S., Ishibashi, K., Kusano, E., 2011b. The association of plasma prorenin level with an oxidative stress marker, 8-OHdG, in nondiabetic hemodialysis patients. Clin Exp Nephrol 15, 398-404.

Nussberger, J., Wuerzner, G., Jensen, C., Brunner, H.R., 2002. Angiotensin II suppression in humans by the orally active renin inhibitor Aliskiren (SPP100): comparison with enalapril. Hypertension 39, E1-8.

Prescott, G., Silversides, D.W., Reudelhuber, T.L., 2002. Tissue activity of circulating prorenin. Am J Hypertens 15, 280-285.

Racki, S., Zaputovic, L., Mavric, Z., Vujicic, B., Dvornik, S., 2006. C-reactive protein is a strong predictor of mortality in hemodialysis patients. Ren Fail 28, 427-433.

Sadoshima, J., Izumo, S., 1993. Molecular characterization of angiotensin II--induced hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblasts. Critical role of the AT1 receptor subtype. Circ Res 73, 413-423.

Saracho, R., Martin-Malo, A., Martinez, I., Aljama, P., Montenegro, J., 1998. Evaluation of the Losartan in Hemodialysis (ELHE) Study. Kidney Int Suppl 68, S125-129.

Schaefer, R.M., Schaefer, L., Horl, W.H., 1994. Anaphylactoid reactions during hemodialysis. Clin Nephrol 42 Suppl 1, S44-47.

Shibasaki, Y., Masaki, H., Nishiue, T., Nishikawa, M., Matsubara, H., Iwasaka, T., 2002. Angiotensin II type 1 receptor antagonist, losartan, causes regression of left ventricular hypertrophy in end-stage renal disease. Nephron 90, 256-261.

Siragy, H.M., 2000. AT(1) and AT(2) receptors in the kidney: role in disease and treatment. Am J Kidney Dis 36, S4-9.

Suzuki, H., Kanno, Y., Sugahara, S., Ikeda, N., Shoda, J., Takenaka, T., Inoue, T., Araki, R., 2008. Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: an open-label randomized controlled trial. Am J Kidney Dis 52, 501-506.

Suzuki, H., Kanno, Y., Sugahara, S., Okada, H., Nakamoto, H., 2004. Effects of an angiotensin II receptor blocker, valsartan, on residual renal function in patients on CAPD. Am J Kidney Dis 43, 1056-1064.

Takahashi, A., Takase, H., Toriyama, T., Sugiura, T., Kurita, Y., Ueda, R., Dohi, Y., 2006. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis--a randomized study. Nephrol Dial Transplant 21, 2507-2512.

Takemitsu, T., Ichihara, A., Kaneshiro, Y., Sakoda, M., Kurauchi-Mito, A., Narita, T., Kinouchi, K., Yamashita, N., Itoh, H., 2009. Association of (pro)renin receptor mRNA expression with angiotensin-converting enzyme mRNA expression in human artery. Am J Nephrol 30, 361-370.

Tarng, D.C., Huang, T.P., Wei, Y.H., Liu, T.Y., Chen, H.W., Wen Chen, T., Yang, W.C., 2000. 8-hydroxy-2'-deoxyguanosine of leukocyte DNA as a marker of oxidative stress in chronic hemodialysis patients. Am J Kidney Dis 36, 934-944.

Vaidyanathan, S., Bigler, H., Yeh, C., Bizot, M.N., Dieterich, H.A., Howard, D., Dole, W.P., 2007. Pharmacokinetics of the oral direct renin inhibitor aliskiren alone and in combination with irbesartan in renal impairment. Clin Pharmacokinet 46, 661-675.

van Ampting, J.M., Penne, E.L., Beek, F.J., Koomans, H.A., Boer, W.H., Beutler, J.J., 2003. Prevalence of atherosclerotic renal artery stenosis in patients starting dialysis. Nephrol Dial Transplant 18, 1147-1151.

Vlahakos, D.V., Hahalis, G., Vassilakos, P., Marathias, K.P., Geroulanos, S., 1997. Relationship between left ventricular hypertrophy and plasma renin activity in chronic hemodialysis patients. J Am Soc Nephrol 8, 1764-1770.

Wagner, J., Jan Danser, A.H., Derkx, F.H., de Jong, T.V., Paul, M., Mullins, J.J., Schalekamp, M.A., Ganten, D., 1996. Demonstration of renin mRNA, angiotensinogen mRNA, and angiotensin converting enzyme mRNA expression in the human eye: evidence for an intraocular renin-angiotensin system. Br J Ophthalmol 80, 159-163.

Wang, A.Y., Li, P.K., Lui, S.F., Sanderson, J.E., 2004. Angiotensin converting enzyme inhibition for cardiac hypertrophy in patients with end-stage renal disease: what is the evidence? Nephrology (Carlton) 9, 190-197.

Wauters, J.P., Waeber, B., Brunner, H.R., Guignard, J.P., Turini, G.A., Gavras, H., 1981. Uncontrollable hypertension in patients on hemodialysis: long-term treatment with captopril and salt subtraction. Clin Nephrol 16, 86-92.

Weidmann, P., Maxwell, M.H., Lupu, A.N., Lewin, A.J., Massry, S.G., 1971. Plasma renin activity and blood pressure in terminal renal failure. N Engl J Med 285, 757-762.

Zannad, F., Kessler, M., Lehert, P., Grunfeld, J.P., Thuilliez, C., Leizorovicz, A., Lechat, P., 2006. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. Kidney Int 70, 1318-1324.

Zheng, S., Nath, V., Coyne, D.W., 2007. ACE inhibitor-based, directly observed therapy for hypertension in hemodialysis patients. Am J Nephrol 27, 522-529.

Zoccali, C., Benedetto, F.A., Mallamaci, F., Tripepi, G., Fermo, I., Foca, A., Paroni, R., Malatino, L.S., 2000. Inflammation is associated with carotid atherosclerosis in dialysis patients. Creed Investigators. Cardiovascular Risk Extended Evaluation in Dialysis Patients. J Hypertens 18, 1207-1213.

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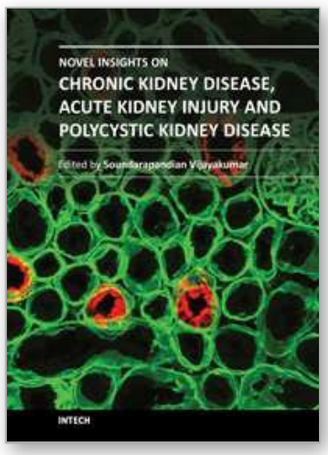

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