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Clinical Implication of the Renin-angiotensin-aldosterone Blockers in Chronic Kidney Disease Undergoing Hemodialysis

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Abstract: The renin-angiotensin-aldosterone system (RAAS) blockers have been widely used in chronic kidney disease patients undergoing hemodialysis; however, whether RAAS blockers have beneficial effects for cardiovascular disease in those patients has not been fully defined. This review focuses on the effects of RAAS blockers in chronic kidney disease undergoing hemodialysis for cardiovascular disease.

Keywords: Hemodialysis, clinical study, renin, angiotensin I, angiotensin II, aldosterone, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, direct renin inhibitor, cardiovascular disease.

INTRODUCTION

The cardiovascular diseases (CVD) are often complicated in chronic kidney disease undergoing hemodialysis (HD). CVD are main factor which affects the prognosis of HD patients [1-3]. Accumulated evidence suggested that antihypertensive therapy may have beneficial effects for the development of CVD in HD patients [4, 5]. The renin-angiotensin-aldosterone system (RAAS) has been reported to contribute to the hypertension, and to increase chronic inflammation and oxidative stress on vascular endothelium that may result in CVD in HD patients [6-8]. These lines of evidence suggest that RAAS blockers may have beneficial effects to prevent CVD and improve prognosis in HD patients; however, their effects have not been fully defined. This review focuses on the clinical studies of RAAS blockers in HD patients in terms of CVD.

Clinical Studies of RAAS Blockers in HD Patients

The clinical studies that investigated the effects of RAAS blockers for the CVD in HD patients are summarized in Table **1**.

Angiotensin-converting Enzyme Inhibitors (ACEIs)

Angiotensin-converting enzyme inhibitors (ACEIs) block the conversion of angiotensisn I (Ang I) to angiotensisn II (Ang II) which leads the constriction of blood vessels, and increase blood pressure. Tradolapril and captopril have been reported to be effective for control hypertension in HD patients [9, 10]. Zheng *et al*. reported tradopril (2-8 mg/thrice a week) after HD session with atenolol and/or amlodipine (they were given if the patients had any member of these classes drugs as their daily regimen) significantly decrease blood pressure (from 122.2±7.1 / 75.3±10.4 mmHg to 116.4±11.6 / 70.4±11.4 mmHg) in ten HD patients [9]. Wauterd *et al*. reported that the effect of captopril (25 to 200 mg) for hypertension in eight HD patients that showed resistant hypertension for ultrafiltration and conventional antihypertensive therapy [10]. They reported that four HD patients decreased blood pressure at normal level with captopril alone and the four remaining patients also showed significant blood pressure reduction by the combination of captopril and salt removal by replacement of 1-2 liters of ultrafiltrate by an equal volume of 5% dextrose without a significant change in body weight [10]. These studies showed that ACEIs has beneficial effects for hypertension in HD patients. In addition, several studies reported that ACEIs showed cardio protective effects in HD patients as follows. The perindopril (2-4 mg after each HD session) and imidapril (2.5 mg/day) have been reported to significantly reduce left ventricular mass in HD patients compared with control group that were treated with a calcium channel antagonist or placebo respectively [11, 12]. In addition to that, this cardio protect effect by these ACEIs was suggested to be independent of blood pressure lowering effect because there was no difference in terms of the change of blood pressure between ACEIs treatment groups and control groups [11, 12].

On the other hands, there are several reports that ACEIs have no beneficial effect for CVD in HD patients. Zannad *et al*. reported that no significant benefit was found in fosinopril (5-20 mg/day) for the prevention of CVD (cardiovascular death, resuscitated death, nonfatal stroke, heart failure, myocardial infarction or revascularization) in HD patients [13]. Chang *et al*. reported that there were no significant associations among ACEIs use and total mortality and hospitalization due to CVD in HD patients [14]. Furthermore, ACEIs use was associated with a higher risk of hospitalization due to heart failure [14]. These contradict results required further large scale clinical trials to investigate the effects of ACEIs for CVD and in HD patients.

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Table1. Clinical studies of RAAS blockers in HD patients.

RAAS Blockers	References	Number	Duration (month)	Intervention		Results			
				Treatment	Control	Treatment ⊿SBP/DBP (mmHg)	Control ⊿SBP/DBP (mmHg)	Treatment CVD	Control CVD
ACEIs	Zheng *et al*. (9)	10	0.5-2	tradopril (2-8mg/ TIW)		-5.8 / -4.9			
	Wauterd *et al*. (10)	8	5	captopril (25-200mg/ 2 day)		-45 / -29			
	London *et al*. (11)	24	12	perindopril (2-4mg/ after each HD)	nitrendipine (20-40mg/ after each HD) placebo	-27 / -15	-20 / -10	-70 g (LVM)	NS
	Matsumoto *et al*. (12) 30		6	imidapril (2.5mg / day)		NS	NS	-36 g (LVM)	NS
	Zannad *et al*. (13)		397	24	Fosinopril (5-20mg / day)		placebo + convention-al therapy	No significant benefit for fosinopril	
	Chang *et al*. (14)		1846	16-52	ACE inhibitor +CCB, β-blocker	CCB, β-blocker		ACE inhibitor: Hazard ratio 1.41	
ARBs	Saracho *et al*. (15)	406	6	losartan		-11 / -5			
	Shibasaki *et al*. (16)	24	30	losartan (50mg / day)	amlodipine (5mg/day), enalapril (5mg/day)	-11 (MBP) amlodipine:-11(MBP) enalapril: -11 (MBP)		-24.7% (LVMI)	amlodi-pine: -10.5% (LVMI) enalapril: -11.2% (LVMI)
	Kannno *et al*. (17)	12	24	losartan (100mg / TIW) + exist-ing CCB, α-blocker or centrally acting agents	Placebo+ exist-ing CCB, α-blocker or centrally acting agents			-23 g/m2 (LVMI)	NS
	Takahashi *et al*. (18)	19	80	candesartan (4-8mg / day)+ ACE in-hibitor + CCB, α-blocker or centrally acting agents	placebo+ACE inhibitor+CCB, α-blocker or centrally acting agents	NS	NS	Treatment group 16.3 % vs. control group 45.9 %	
	Onishi *et al*.(19)	17	3	Irbesartan (50-100 mg)		-15.5/-6.7			

Table 1. Contd…..

RAAS Blockers	References	Number	Duration (month)	Intervention		Results			
				Treatment	Control	Treatment ⊿SBP/DBP	Control ⊿SBP/DBP	Treatment CVD	Control CVD
	Suzuki *et al*. (20)	366	36	valsartan(160 mg / day), candesartan(12 mg / day) or losartan (100 mg / day) + CCB, α-blocker or centrally acting agents	CCB, α-blocker or centrally acting agents	-14 / -1	-16 / -4	Treatment group 19 % vs. control group 33 %	
ACEIs/ARBs	Bajaj *et al*. (21)	1950	30	ACEIs or ARBs	CCB or statins	Primary outcome (mortality and cardiovascular events) was no significant difference among ACEIs/ARBs group (HR 0.95) and statin group (HR 1.08) compared with CCB group			
	Iseki *et al*. (22)	469	42	Olmesartan (10-40 mg)	no ACEIs and ARBs	Primary outcome (mortality and cardiovascular events) was no significant difference between			
						olmesartan group (HR 1.00) compared with no ACEI/ARB group			
Direct renin inhibitor	Morishita *et al*. (24)	30	2	Aliskiren (150 mg / day) + existing ACE inhibitor, ARB, CCB, α-blocker or centrally acting agents		-15 / -5			
	Ishimitsu *et al*.(25)	23	6	Aliskiren (150mg)		-8 (SBP)			
	Takenaka *et al*.(26)	30	6	Alsikiren (150-300 mg)		-5 (SBP)			
Aldosteron-receptor blocker	Gross *et al*. (31)	8	0.5	spironolactone (50 mg / twice daily)		-11 (SBP)			
	Shavit et.al. (32)	8		eplerenone (25mg / twice daily)		-13 (SBP)			

SBP: systolic blood pressure, DBP: diastolic blood pressure, CVD: cardio vascular disease, LVM: left ventricular mass, LVMI: left ventricular mass index, NS, no siginicant, CCB calcium channnel blocker, MBP mean blood pressure

Angiotensin Receptor Blockers (ARBs) in HD Patients

Angiotensin receptor blockers (ARBs) works to block the activation of Ang II by competitive antagonism of angiotensin II receptor type1 (AT1 receptor). Losartan has been reported to reduce blood pressure at before and after HD in hypertensive HD patients in large size clinical study [15]. Losartan reported to reduce left ventricular mass index after compared with amlodipine (calcium channel antagonist) or an enalapril (ACEI), although similar blood pressure lowering were detected in all three groups [16]. Another studies also reported that losartan (100 mg/thrice a week) reduced left ventricular hypertrophy in 24 HD patients whereas a placebo group showed no change [17]. These results suggested that this beneficial effect of losartan for cardio protection was independent of a blood pressure lowering effect. The effects of another ARBs for CVD also have been reported. Candesartan (4-8 mg/day) reduced cardiovascular events and mortality compared with placebo after in HD patients [18]. In this study, the brain natriuretic peptide (BNP) levels were significantly increased in the control group but not in

the candesartan group [18]. Irbesartan (50-100mg/day) significantly reduced blood pressure in stable maintaining HD patients [19]. Suzuki *et al*. reported that several ARBs (valsartan, candesartan or losartan) treatment was reduced CVD compared with no ARB treatment group for HD patients in each group during a three-year observation period [20]. There were 19% fatal or nonfatal CVD events in the ARBs group and 33% in the no ARB group [20]. Blood pressure did not differ between the ARBs group and the no ARB group. After adjustment for age, sex, diabetes, and systolic blood pressure, treatment with an ARBs was independently associated with reduced fatal and nonfatal CVD events [20]. These lines of evidence demonstrated that ARBs are effective to control blood pressure and prevent CVD in HD patients. A certain level of cardio protective effects of ARBs may be independent from a blood pressure lowering effect in HD patients.

On the other hands, recently several clinical studies have been reported that ARBs have no beneficial effect for CVD and mortality in HD patients. Bajaj *et al*. reported that ARBs or ACEIs treatment was not associated with an overall reduction in CVD events compared with calcium channel blockers or statins treatment groups in elderly HD patients during the 2.4 years observation period [21]. Iseki *et al*. also reported that olmesartan treatment did not alter mortality and CVD events compared with non ACEIs and ARBs group in hypertensive HD patients during 3.5 years follow-up period [22]. These contradict results required a large size and long term clinical studies to investigate the effects of ARBs in terms of the prevention of CVD events in HD patients.

Direct Renin Inhibitor in HD Patinets

An oral direct renin inhibitor; aliskiren inhibits renin activity [23]. Although renin level will increase due to negative feedback of aliskiren, Ang I, Ang II level and PRA will decrease. Little was known the effects of aliskiren in HD patients. Previously, we reported on an blood pressure lowering effect and potential CVD protective effect of aliskiren in hypertensive HD patients [24]. In that study, aliskiren significantly reduced blood pressure in HD patients [24]. In addition to that, aliskiren reduced the surrogate markers for CVD such as BNP, high-sensitivity CRP (hs-CRP), and an oxidative stress marker [24]. Isimitsu *et al*. also reported that alsikiren (150mg/day) significantly reduced blood pressure in maintaining HD patients [25]. Takenaka *et al*. reported that the alsikiren reduced morning blood pressure measured at home in HD patients with diabetic nephropathy [26]. These lines of evidence suggested that alsikiren has beneficial effects for blood pressure control in HD patients.

It should be noted that the combination of aliskiren and other class RAAS blockers should be careful because of the severe advert effects. ALTITUDE study to investigate the effects of aliskiren added to ACEIs or ARBs in patients at high risk for CVD and with diabetes and renal impairment was suspended because more adverse effects such as stroke, renal impairment, hyperkalemia and hypotension were observed in patients who received aliskiren than in patients who received a placebo [27-29]. We also reported that when we followed up the HD patients who had been received aliskiren treatment in the previous study for 20 months, high rate (44%) of discontinuation of aliskiren owing to symptomatic hypotension was observed [30]. In that study, most patients had been received alsikiren added on their existing antihypertensives including AECIs and ARBs [30]. Taken together, the careful observation for blood pressure change is required for aliskiren treatment in hypertensive HD patients especially the combination with the other class of RAAS blockers such as ACEIs or ARBs, and further studies will be required to establish the effects of aliskiren in HD patients.

Aldosterone-receptor Blockers in HD Patients

Aldosterone-receptor blockers are receptor antagonists at the mineralocorticoid receptor. Antagonism of these receptors inhibits sodium resorption in the collecting duct of the kidney. There are a few studies to investigate the efficacy of aldosterone-receptor blocker in HD patients. Gross *et al*. reported spironolactone (50 mg/ twice daily) significantly reduced pre-dialysis systolic blood pressure after 2 weeks in 8 oligo-anuric HD patients [31]. Shavit et la. reported that eplerenone (20 mg/ twice daily) significantly reduced systolic blood pressure after 4 weeks by in oligo-anuric HD patients [32]. These lines of evidence suggested that beneficial effect of aldosterone-receptor blockers as antihypertensive drugs in HD patients; however, the additional large size and long term studies will be required to confirm the efficacy of aldosterone-receptor blockers in HD patients.

The Combination Therapy of RAAS Blockades in HD Patients

There are a few clinical studies to investigate the combination therapy of RAAS blockers in HD patients. Chan *et al*. reported that initiated on combined ACE and ARB therapy were at increased risk of CVD compared with initiated on an ARB and non-ACEI after adjustment for risk factors in large size clinical study [33]. These results suggested that combination of ARB and ACEI may not have a beneficial effect on CVD in HD patients.

Adverse Effects of RAAS Blockers

ACEIs showed several adverse effects in HD patients. ACEIs may suppress erythropoiesis and induce resistance to erythropoietin [34]. Several possible mechanisms have been described: Ang II can stimulate erythroid progenitor cell growth and that ACEIs can inhibit this [35], ACEIs increase plasma levels of a natural stem cell regulator which inhibits the recruitment of pluripotent haemopoietic stem cells, hence inhibit erythroid growth [36], ACEIs have been shown to reduce production of interleukin-12 which can stimulate erythropoiesis [37]. Occasionally, ACEIs may cause anaphylactoid reactions with AN69 dialysis membrane by increase serum bradykinin level [38-40]. Therefore it is better to avoid the combination of AN69 membranes with ACEIs in HD patients. Hyperkalemia, which is a frequent concern in HD patients, is the primary danger from RAAS blocking medications. The blockade RAAS leads to a decrease in aldosterone levels. Since aldosterone has a central role for the excretion of potassium, the RAAS blocker can cause retention of potassium. Several clinical trials of ACEIs, ARBs, a renin inhibitor and an aldosterone receptor-blocker in HD patients tracked potassium levels [13, 18, 20,

24, 31]. Significant trend for increased hyperkalemia by these RAAS blockers in HD patients was not observed in these trials. Although careful and periodical monitoring of plasma potassium level is required, these results suggested that the risk of hyperkalemia by RAAS blocking in HD patients is small.

SUMMARY

RAAS blockers have been reported to have beneficial effects for blood pressure control and CVD to some extent in HD patients. However, the effects of those have not been fully established. Hence, the choice of the RAAS inhibitors in the treatment of HD patients should be carefully determined with close monitoring blood pressure. Further high-quality studies are still required to confirm the effects of RAAS blockade on CVD in HD patients.

CONFLICT OF INTEREST

None declared

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None declared

ABBREVIATION

ACEIs = Angiotensin-converting enzyme inhibitors

ARBs = Angiotensin receptor blockers

AngI = angiotensin I

Ang II = angiotensin II

BNP = brain natriuretic peptide

CVD = cardiovascular disease

HD = hemodialysis

hs-CRP = high-sensitivity CRP

PRA = plasam renin activity

RAAS = renin-angiotensin-aldosterone system

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