

## Azilsartan is More Effective as Compared to Olmesartan in Hemodialysis Patients with Uncontrolled Hypertension

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### Abstract

**Background:** Azilsartan is a new angiotensin receptor blocker with more continuous antihypertensive effects. The objective of this study was to demonstrate the efficacy and safety of azilsartan in hemodialysis patients with uncontrolled hypertension.

**Methods:** Twenty-two hemodialysis patients treated with multiple antihypertensive drugs including olmesartan (20-40 mg/day) were enrolled in this retrospective observational study. Blood pressure was measured in the morning and evening for a week at baseline and after switching from olmesartan to azilsartan. The patients' mean blood pressure at baseline was 171/71 mmHg. Olmesartan (20-40 mg/day) was switched to azilsartan with the same dose. An electrocardiogram, an echocardiogram, and measurement of the ankle-brachial index were performed in all patients, and the echocardiogram showed left ventricular hypertrophy in all patients. Home-measured blood pressure, heart rate, and serum potassium were followed for 9 months after switching.

**Results:** Systolic blood pressure was significantly decreased at 1, 3, 6, and 9 months after switching. Diastolic blood pressure was significantly decreased at 3 and 6 months after switching. Switching did not alter the serum potassium level.

**Conclusions:** Switching from olmesartan to azilsartan significantly and safely decreased home-measured blood pressure in hemodialysis patients.

**Keywords:** Hemodialysis; Uncontrolled hypertension; Olmesartan; Azilsartan

### Introduction

Hypertension is a major risk factor for cardiovascular events in the general population. Hypertension is also very common in hemodialysis patients and is a risk factor for the development and progression of left ventricular hypertrophy, cardiovascular disease, and total mortality [1-3]. Using various definitions of hypertension, 60-90% of hemodialysis patients are estimated to have hypertension [4,5]. The majority of hemodialysis patients are given antihypertensive drugs, although not all patients achieve the target blood pressure (BP) [6-8]. We control the BPs of about 400 hemodialysis patients in three outpatient hemodialysis units of Sanko Hospital Group in Osaka, Japan, usually using multiple antihypertensive drugs in the majority of patients in the units, but BP is poorly controlled in about 10% of patients with multiple antihypertensive drugs.

On the other hand, home BP measurement is recommended by guidelines for hypertension management [9-11]. BP varies greatly during the interdialysis period, and BP is frequently overestimated in outpatient hemodialysis units. It has been reported that home BP measurement may be useful for adjusting blood pressure control among hemodialysis patients [12].

Azilsartan is a new angiotensin receptor blocker (ARB) that selectively inhibits the binding of angiotensin II (AII) to AII type 1 receptors [13,14]. It has been reported that azilsartan provides greater BP reduction than candesartan over the entire 24-h monitoring period, as well as during the specific daytime, night-time, and early morning periods, by analysis of ambulatory blood pressure monitoring records [15,16]. The objective of this study was to demonstrate the efficacy and safety of switching from olmesartan to azilsartan in hemodialysis patients with uncontrolled hypertension.

### Materials and Methods

This study was a retrospective observational study. Hemodialysis patients with uncontrolled hypertension who had been treated with multiple antihypertensive drugs including olmesartan (20-40 mg/day) for more than 3 months were enrolled. BP was measured twice a day, in the morning and evening, at home for a week by the patients, so BP was measured 14 times a week. Recordings were carried out in a sitting position using an automatic device that was based on the cuff-oscillometric method after taking a least a 5-min rest. The patients were asked to record the BP measured at home with their own machine. The average home-measured blood pressures for a week before and after switching were then evaluated. Patients whose average systolic BP was >160 mmHg, or temporary systolic BP was >180 mmHg were enrolled. An electrocardiogram (ECG), ankle-brachial index (ABI), and echocardiogram were recorded at baseline and at the 6 month follow-up. Home-measured blood pressure, heart rate, serum sodium, and serum potassium levels were followed for 9 months. The protocol was approved by the independent ethics committee of Sanko Hospital Group. Patients were given a detailed explanation of the study protocol and aims before being enrolled, and their written, informed consent was obtained.

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BP, serum sodium, and serum potassium levels are expressed as means ± standard error. A mixed model pairwise comparisons test with the Bonferroni correction compared to before switching was performed. A P value < 0.05 was considered significant. Age, duration of hemodialysis therapy, and echocardiogram data are expressed as means ± standard deviation. All statistical analyses were performed using IBM SPSS Statistics 21.0 (Armonk, New York, USA).

## Results

The baseline characteristics of the 22 patients are shown in Table 1. The average age was 67.0 ± 10.0 years, and the mean duration of hemodialysis therapy was 59.5 ± 31.6 months. The etiology of end-stage renal disease was: 10 (45%) diabetes mellitus, 7 (32%) glomerulonephritis, 4 (18%) renal sclerosis, and 1 (5%) polycystic kidney. Patients with atrial fibrillation were excluded. Echocardiography showed left ventricular hypertrophy in all patients, but ECG findings showed left ventricular hypertrophy in 7 (32%) patients. The ABI was abnormal in 4 (18%) patients. All patients received a combination of antihypertensive drugs including olmesartan (30.7 ± 5.4 mg); 3 patients received 6 antihypertensive drugs, 5 received 5 antihypertensive drugs, 9 received 4 antihypertensive drugs, 4 received 3 antihypertensive drugs, and 1 received 2 antihypertensive drugs. Twenty patients were treated with calcium channel blockers. Calcium channel blockers were contraindicated in 2 patients because of side effects.

The mean systolic blood pressure before switching was 170.7 ± 12.5 mmHg. The mean diastolic blood pressure before switching was 71.5 ± 7.5 mmHg. Systolic blood pressure was significantly decreased at 1 month (160.0 ± 14.2 mmHg; p<0.001), 3 months (158.2 ± 14.0 mmHg; p<0.001), 6 months (157.4 ± 14.8 mmHg; p<0.001), and 9 months (153.0 ± 17.3 mmHg; p<0.001) after switching. Diastolic blood pressure was significantly decreased at 3 months (69.2 ± 7.3 mmHg; p<0.05) and 6 months (67.7 ± 7.4 mmHg; p<0.01) after switching. Diastolic blood pressure was 69.2 ± 7.3 mmHg (not significant) at 1 month and 67.3 ± 6.7 mmHg at 9 months (not significant) after switching. Switching from olmesartan to azilsartan did not alter serum sodium or serum potassium levels. These data are shown in Figure 1. ECG, ABI, and echocardiography 6 months after switching showed no significant differences compared to baseline (data not shown). We changed dry weight in only one patient during the study. We did not change any other conditions of hemodialysis during the study. There were no cardiovascular events during 9-month follow-up.

## Discussion

Many trials have shown the cardiovascular benefits of lowering blood pressure in the general population. Ciccone et al. reported that age and sex could influence the noninvasive parameters to assess the cardiovascular risk profile [17]. It has been reported that the mortality rate for hemodialysis patients is 20% during the first year and 70% after 5 years of treatment [1-5]. Cardiovascular disease is common and the leading cause of morbidity and mortality in hemodialysis patients, since hemodialysis patients have multiple risk factors [7]. Patients with atrial fibrillation were excluded in the study, because atrial fibrillation is clinically significant arrhythmia and the relationship between atrial fibrillation and physical activity was reported [18]. It has been reported that treatment with antihypertensive drugs should be considered for hemodialysis patients to reduce the very high cardiovascular morbidity and mortality rate in this population [6,7,19]. BP measurement is particularly important in hemodialysis patients, because disparate outcomes are obtained depending on the timing, location, frequency, and technique of BP measurement [8,9]. Difficulties in making an

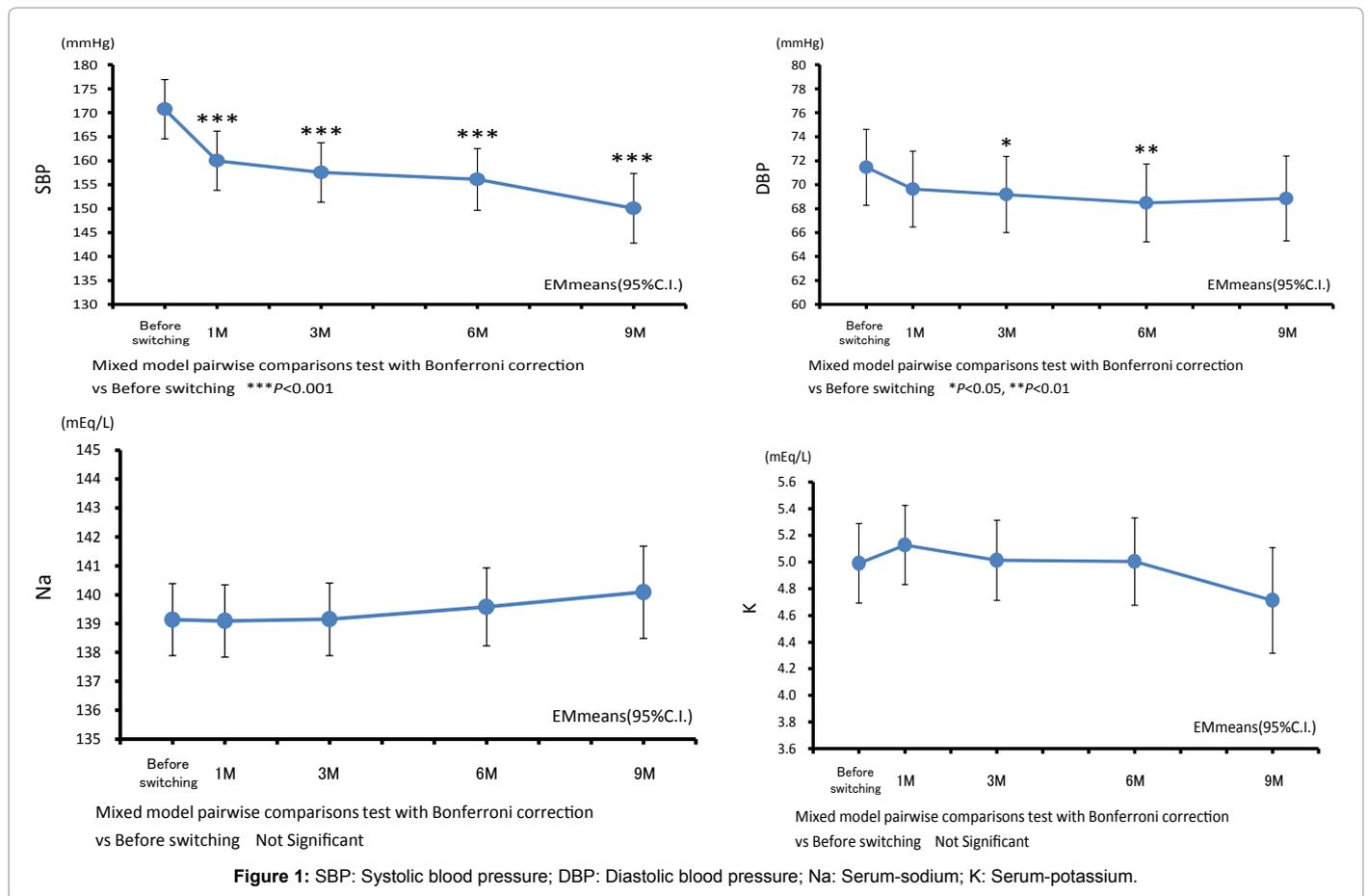
accurate diagnosis of hypertension in hemodialysis patients arise in part due to large swings in BP with the hemodialysis procedure [20]. High pre-hemodialysis systolic BP is also a risk factor for death, but the target levels are not known [21,22].

Ambulatory blood pressure monitoring provides not only static and but also dynamic information about BP that should be considered to ensure effective management of hypertension and cardiovascular diseases, but ambulatory blood pressure monitoring is uncommon [15,23]. Moriya et al. reported that one-point measurement of BP is insufficient to evaluate hypertension and the prognosis of hemodialysis patients, and weekly averaged blood pressure is a useful marker because it averages fluctuations of BP over one week [24]. It has also been reported that weekly averaged BP could be a good prognostic marker of the incidence of both cardiovascular events and all-cause mortality in hemodialysis patients [25]. It has been reported that home-measured BP, especially systolic BP in the morning on hemodialysis days, can provide pivotal information for the management of hemodialysis patients [26,27]. Thus, home-measured BP was evaluated for a week before and after switching.

In hemodialysis patients, non-volume mechanisms, such as activation of the renin angiotensin system, are important for sustaining

Baseline Characteristics of 22 patients	
Age(years)	67.0 ± 10.0
Gender(Male/Female)	59%(13/9)
History of hemo-dialysis(months)	59.5 ± 31.6
Etiology of end-stage renal disease	
Diabetes Mellitus	10(45%)
Glomerulonephritis	7(32%)
Renal Sclerosis	4(18%)
Polycystic Kidney	1(5%)
ECG Findngs	
LVH	7(32%)
CRBBB	2(22%)
WNL	13(59%)
Echocardiogram Findings	
IVS	13.5 ± 1.3 mm
PW	12.8 ± 1.3 mm
EF	68.8 ± 6.2%
ABI Findings	
Abnormal(ABI<0.9)	4(18%)
Normal	19(86.4%)
Antihyperensive Drugs(number of patients)	
6 drugs	3(14%)
5 drugs	5(23%)
4 drugs	9(41%)
3 drugs	5(23%)
2 drugs	1(5%)
Mean dose of olmesaltan	30.7 ± 5.4 mg
Calcium channel bolers(number of patients)	
Beta bloklers	17(77%)
Alpha bloklers	13(59%)
Methyldopa	8(36%)
Clonidine	4(18%)
Others	6(27%)

**Table 1:** ECG: electrocardiogram; ABI: ankle-brachial index; LVH: left ventricular hypertrophy; CRBBB: complete right bundle branch block; WNL: within normal limits; IVS: thickness of the intraventricular wall; PW: thickness of the posterior wall; EF: ejection fraction.



hypertension [7,8]. Yang reported that ARBs reduce left ventricular hypertrophy in hemodialysis patients [28]. Takahashi reported that candesartan significantly reduced cardiovascular events in hemodialysis patients [29]. Suzuki reported that the use of ARBs may be effective in reducing non-fatal cardiovascular events in hemodialysis patients [30]. Tai reported a meta-analysis that showed that ARBs are associated with a greater reduction in left ventricular hypertrophy in hemodialysis patients [31]. However, Iseki reported that treatment with olmesartan did not significantly reduce the risks of major cardiovascular events or death among hypertension patients on chronic hemodialysis [32]. On the other hand, the combination of angiotensin receptor blockers and angiotensin converting enzyme inhibitors did not show additional benefits for left ventricular hypertrophy and the prognosis of hemodialysis patients [33]. Thus, intensive further research should not only address appropriate medications, but also the optimal BP in hemodialysis patients.

Azilsartan is a new ARB, and ARBs may reduce cardiac mortality rates in hemodialysis patients [13,14,34]. In an *in vitro* study, azilsartan was shown to have higher affinity for and slower dissociation from AT 1 receptors than other ARBs, including olmesartan, telmisartan, valsartan, and irbesartan [13,14]. It has been reported that once-daily administration of azilsartan produced a more potent 24-h sustained antihypertensive effect than candesartan in Japanese patients with grade I-II essential hypertension, and it had an equivalent level of safety in a randomized, double-blind, comparative study [15]. It has also been reported that azilsartan provides greater BP reduction than candesartan over the entire 24-h monitoring period, as well as during

the specific daytime, night-time, and early morning periods, by analysis of ambulatory blood pressure monitoring records [34]. Rothwell reported that increased residual variability in systolic BP in patients with treated hypertension is associated with a high risk of vascular events [35]. Nocturnal BP variation is important for preventing cardiovascular events, because non-dipping patterns are associated with sympathetic nervous activity. It has also been reported that in the non-dipping group, a greater reduction from baseline in nighttime than daytime BP was produced by treatment with azilsartan.

Switching from olmesartan to azilsartan significantly decreased home-measured blood pressure in hemodialysis patients with left ventricular hypertrophy in the previous study. Switching did not alter serum potassium levels. Lin also reported that renin angiotensin blockade is not associated with hyperkalemia in chronic hemodialysis patients [36]. Azilsartan seemed to be useful for controlling the BP of hemodialysis patients in whom calcium channel blockers are contraindicated because of their strong effects. Thus, the switch to azilsartan might improve the prognosis of hemodialysis patients. We suggest that the strong antihypertensive effect of azilsartan originates from a combination of its primary ARB class-effect and stronger suppression of the sympathetic nervous system.

There are some limitations to the present study. This was a retrospective study, ambulatory blood pressures were not measured, the number of patients was small. All patients do not use the same type of machine in measurement of BP, and the long-term outcomes of patients were not analyzed.

## Conclusion

In conclusion, switching from olmesartan to azilsartan significantly and safely decreased home-measured blood pressure in hemodialysis patients.

## Conflicts of Interest

The authors have no conflicts of interest to declare in relation to this article.

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