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# Effects of Azilsartan Compared to Other Angiotensin Receptor Blockers on Left Ventricular Hypertrophy and the Sympathetic Nervous System in Hemodialysis Patients

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**Abstract:** Hypertension is a major risk factor for cardiovascular and cerebrovascular events, and most patients with hypertension are administered antihypertensive drugs. However, not all patients achieve normal blood pressure levels. The new angiotensin receptor blocker azilsartan (Takeda Pharmaceutical Company Limited, Osaka, Japan) has been reported to have a strong hypotensive effect. Our study investigated the efficacy of azilsartan compared with other angiotensin receptor blockers. This study included 17 hypertensive patients on HD, who had been administered angiotensin receptor blockers, except for azilsartan, for more than 6 months before enrolling, and after enrollment, they were switched to azilsartan. Blood tests, Holter electrocardiogram, ambulatory blood pressure monitoring, and echocardiography were performed at baseline and at the 6-month follow-up. The blood pressure from baseline to 6 months had significantly decreased (24-h systolic blood pressure from 150.9 ± 16.2 mm Hg to 131.3 ± 21.7 mm Hg, $P = 0.008$), awakening time systolic blood pressure from 152.1 ± 16.9 mm Hg to 131.7 ± 23.2 mm Hg, $P = 0.01$, sleep-time systolic blood pressure from 148.1 ± 19.7 mm Hg to 130.0 ± 20.1 mm Hg, $P = 0.005$). There was a significant reduction in serum noradrenaline levels as well as left ventricular mass index after switching to azilsartan (from 550.1 ± 282.9 pg/mL, to 351.7 ± 152.3 pg/mL, $P = 0.002$; from 117.0 ± 26.4 g/m$^2$ to 111.3 ± 23.9 g/m$^2$, $P = 0.01$, respectively). Azilsartan had a significantly stronger hypotensive effect than other angiotensin receptor blockers. Thus, the switch to azilsartan might improve prognosis of hemodialysis patients. We suggest that the strong anti-hypertensive effect of azilsartan originated from a combination of primary angiotensin receptor blocker class-effect and a stronger suppression of sympathetic nervous system.
**Key Words:** Ambulatory blood pressure monitoring, Azilsartan, Left ventricular mass index, Noradrenaline, Sympathetic nervous system.

Hypertension is a major risk factor for cardiovascular disease, and various antihypertensive drugs, in particular, angiotensin receptor blockers (ARBs), are used worldwide (1). ARBs are used because the renin-angiotensin-aldosterone system (RAAS) is involved in not only hypertension but also congestive heart failure (CHF) and left ventricular remodeling after myocardial infarction (2–6). Several studies demonstrated that azilsartan (Takeda Pharmaceutical Company, Osaka, Japan) has a stronger hypotensive effect than other ARBs (7). However, the mechanism behind this effect remains unclear. Animal studies have demonstrated that azilsartan induces improvement in the insulin-sensitizing effect and urine norepinephrine secretion, suggesting that a strong hypotensive effect of azilsartan may be due to its effect on the sympathetic nervous system (8,9). This result is consistent with those of other reports in which the relationship between RAAS and the sympathetic nervous system has been studied (10,11).

Antihypertensive drugs are required for a strong hypotensive effect for inducing a systemic antiatherogenic action. In patients with renal dysfunction and hypertension, achieving optimal blood pressure control is difficult (12). In particular, HD patients are known to be at an extremely high-risk for cerebrocardiovascular diseases. These patients need an intensive antihypertensive therapy for improving

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their prognosis. Currently, no studies have compared the hypotensive effects of azilsartan and other ARBs and their effects on the sympathetic nervous system and cardiac function. The purpose of this study was to compare the effects of azilsartan and other ARBs on blood pressure as well as on cardiac function and to determine its effect on the sympathetic nervous system in HD patients.

## PATIENTS AND METHODS

### Study population

This study included 17 hypertensive patients on HD who had visited the Tsukazaki Hospital after excluding those with atrial fibrillation (Af), poor adherence to medication, poor fluid restriction, and hospitalization upon enrolling in this study. Although all of the 17 patients had been receiving ARBs such as losartan, valsartan, telmisartan, or olmesartan for more than 6 months before enrollment in this study, they could not achieve ideal blood pressure control. After enrollment, these patients were switched to azilsartan. Patients who had previously received 40 mg telmisartan, 50 mg losartan, or 20 mg olmesartan were switched to 20 mg azilsartan. Patients who had received higher doses were switched to 40 mg azilsartan per day. During the study period, patients' records of major adverse cardiovascular and cerebrovascular adverse events were obtained (all-cause death, myocardial infarction, coronary revascularization, or cerebrovascular disease). This study was approved by the local ethics committee, and written informed consent was obtained from all patients before enrollment.

### Laboratory data collection and evaluation of fluid restriction

Blood tests were performed at baseline and at the 6-month follow-up to check for: liver enzymes and levels of electrolytes, human atrial natriuretic peptide (hANP), brain natriuretic peptide (BNP), dopamine, noradrenaline, adrenaline, and C-reactive protein (CRP). All the blood tests were performed at the start of HD in the supine position to eliminate the possibility of the changes in catecholamine concentrations caused by postural changes. Dry weight and cardiothoracic ratio (CTR) in chest X-rays were compared before and after the study period.

### Echocardiography

Echocardiography was performed at baseline and at the 6-month follow up (Vivid7, GE Healthcare, Milwaukee, WI, USA). The analysis of echocardiogram was performed independent of clinical conditions by one sonographer following: left ventricular internal dimension in systole and diastole, interventricular septal thickness, posterior thickness (parasternal long-axis view), ejection fraction (EF), left ventricular (LV) mass, LV mass index, left atrial (LA) volume, mitral valve inflow pattern, and the ratio of early peak mitral flow velocity to early mitral annulus velocity (E/e′). Because one patient was diagnosed with atrial fibrillation by electrocardiogram at 3 months, the patient was excluded from the echocardiography analysis.

### Holter electrocardiogram (ECG) and ambulatory blood pressure monitoring (ABPM) data collection

HolterRecorder (ABPM) RAC-3502 monitor (Nihon Kohden, Tokyo, Japan) was used for ABPM, to measure the average heart rate (HR) and HR variability (RR50), standard deviation of the RR interval (SDRR), and the coefficient of variation of RR intervals (CVRR). Information about the time the patients woke up and slept was obtained from the patients. ABPM was performed post-dialysis. We measured the average of 24-h, awakening, and sleep-time blood pressures. The quality control criteria were as follows: if more than two consecutive measurements were failed from the patient, the patient's ABPM data was excluded from the analysis, a minimum of 80% of the blood pressure measurements was considered successful, and the record of awakening and sleeping times was reliable. The patients were included in the analysis if the Holter ECG and ABPM data both at baseline and at the follow-up were acceptable. One patient who was detected to have Af at 3 months was excluded from the ABPM analysis.

### Statistical analyses

All analyses were performed using IBM SPSS Statistics 21.0 (International Business Machines Corp, Armonk, NY, USA). Values were expressed as mean ± SD and tested by two-tailed paired *t*-tests or Wilcoxon signed-rank test. A $P$-value $<0.05$ was considered statistically significant.

## RESULTS

### Patient enrollment and baseline characteristics

Seventeen patients were enrolled in this study. One patient was excluded because he withdrew consent. Patients' characteristics are shown in Table 1. During the study period, no major cardiovascular or cerebrovascular events were observed. No patients discontinued azilsartan use.

**TABLE 1.** *Patients' characteristics* (N = *16)*

| | *N* = 16 |
|---|---|
| Age | 66.8 ± 11.6 |
| Sex (male) | 11/16 (68.8%) |
| Complications | |
| Hypertension | 16/16 (100%) |
| Hyperlipidemia | 1/16 (6.3%) |
| Diabetes mellitus | 7/16 (43.8%) |
| Hemodialysis period (months) | 77.4 ± 43.8 |
| Antihypertensive drugs (baseline) | |
| Calcium channel antagonist | 13/16 (81.3%) |
| β blocker | 2/16 (12.5%) |
| α blocker | 4/16 (25.0%) |
| ACE inhibitor | 0/16 (0.0%) |
| Diuretics | 5/16 (31.3%) |
| ARB alone | 1/16 (6.3%) |

ACE inhibitor, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker.

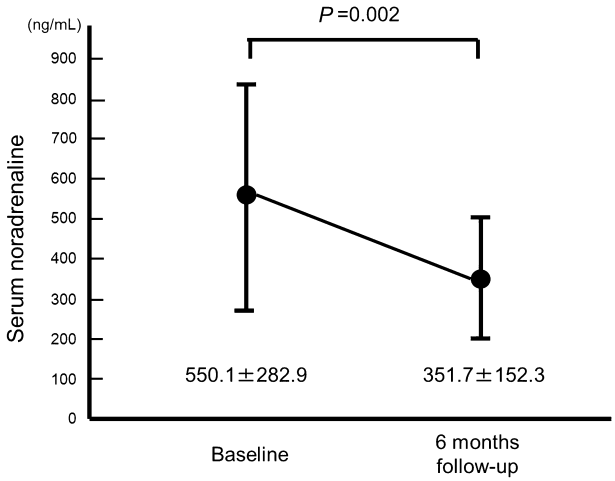


**FIG. 1.** Serum concentration of noradrenaline before and after switching to azirsartan.

### Comparison of laboratory data and fluid restriction before and after switching to azilsartan

Table 2 shows that noradrenaline levels significantly decreased after the switch to azilsartan (from 550.1 ± 282.9 pg/mL to 351.7 ± 152.3 pg/mL, $P = 0.002$) (Fig. 1). There was tendency to reduce dopamine from 36.1 ± 18.6 pg/mL to 27.8 ± 13.8 pg/mL ($P = 0.059$). No significant differences in levels of serum potassium, hANP, BNP, adrenaline, and CRP were observed before or after switching to azilsartan. No liver dysfunction was observed after switching to azilsartan. There were no significant differences in dry weight or CTR in chest X-rays (Table 2).

### Echocardiography

The switch to azilsartan significantly decreased LV mass from 173.9 ± 38.7 g to 165.5 ± 34.9 g ($P = 0.01$), and LV mass index from 117.1 ± 26.4 g/m$^2$ to 111.3 ± 23.9 g/m$^2$ ($P = 0.01$) (Fig. 2). On the other hand, there was no significant difference in LV dimension, systolic and diastolic function, or LA volume (Table 3).

### ABPM and Holter ECG after switching to azilsartan

The average systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) were calculated from ABPM data obtained from 24-h, awakening time, and sleep-time blood pressures (Table 4). The ABPM data showed that azilsartan significantly reduced 24-h SBP (from 150.9 ± 16.2 mm Hg to 131.3 ± 21.7 mm Hg, $P = 0.008$), awakening time SBP (from 152.1 ± 16.9 mm Hg to 131.7 ± 23.2 mm Hg, $P = 0.01$), and sleep-time SBP (from 148.1 ± 19.7 mm Hg to 130.0 ± 20.1 mm Hg, $P = 0.005$). Except for the sleep-time DBP ($P = 0.051$), DBP and MBP significantly reduced before and after the study period. These results demonstrated that switching to azilsartan significantly decreased blood pressure throughout the day.

**TABLE 2.** *Laboratory data and fluid restriction* (N = *16)*

| | Before | After | *P*-value |
|---|---|---|---|
| **Laboratory data** | | | |
| Serum potassium (mEq/L) | 4.62 ± 0.67 | 4.73 ± 0.82 | 0.51 |
| Brain natriuretic peptide (pg/mL) | 339.9 ± 230.1 | 399.5 ± 362.4 | 0.33 |
| Atrial natriuretic peptide (pg/mL) | 177.6 ± 105.2 | 193.6 ± 171.4 | 0.56 |
| Adrenaline (ng/mL) | 48.9 ± 36.8 | 35.8 ± 31.1 | 0.12 |
| Noradrenaline (ng/mL) | 550.1 ± 282.9 | 351.7 ± 152.3 | 0.002 |
| Dopamine (ng/mL) | 36.1 ± 18.6 | 27.8 ± 13.8 | 0.059 |
| C-reactive protein (mg/dL) | 0.45 ± 1.1 | 0.29 ± 0.71 | 0.24 |
| **Fluid restriction** | | | |
| Dry weight (kg) | 49.5 ± 13.0 | 52.4 ± 5.7 | 0.31 |
| CTR (%) | 50.6 ± 5.4 | 49.6 ± 6.5 | 0.24 |

CTR, cardiothoracic ratio.

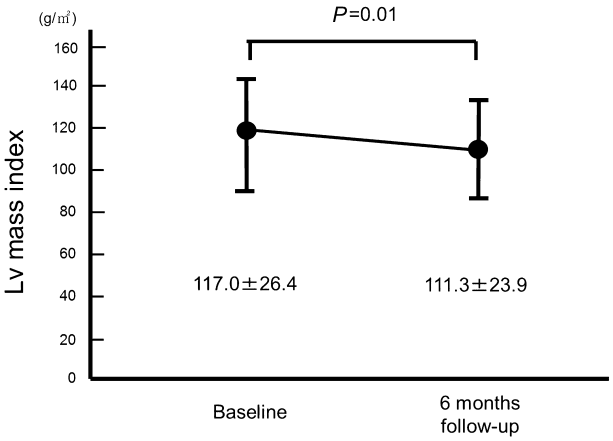


**FIG. 2.** Left ventricular mass index before and after switching to azilsartan

Holter ECG indicated that the mean heart rate did not significantly decrease (from 72.5 ± 7.1 beats/min to 70.1 ± 8.6 beats/min, $P = 0.07$). Also, for HR variability, azilsartan did not exert any significant improvement (Table 4).

## DISCUSSION

This study demonstrated that azilsartan had a stronger hypotensive effect than other ARBs. The lowering of blood pressure is essential for preventing cardiovascular events, and this reduction leads to the regression of left ventricular hypertrophy (13–15). Studies have reported that a reduction in LV mass during treatment is a favorable prognostic marker predicting less risk for cardiovascular events and all-cause and cardiac mortality (16,17). In the present study, ABPM showed that switching to azilsartan from other ARBs significantly reduced blood pressure throughout the day. Not all hypertensive patients achieve adequate reduction of blood pressure. Especially in hypertensive patients with renal dysfunction, the control of blood pressure is more difficult (12). Although the population in this study was on HD, switching to azilsartan from the other ARBs lowered blood pressure levels. Moreover, LV mass and LV mass index was significantly reduced after switching to azilsartan. Therefore, azilsartan can improve the prognosis of hypertensive patients.

On the other hand, many studies have shown that ARBs exert a protective effect on adverse cardiovascular events and CHFs via their pleiotropic effect other than hypotensive effects. Pleiotropic effects are characteristic of the ARB family. Van Zwieten et al. reviewed the interaction between the sympathetic nervous system and the RAAS (10). A review by Nap et al. indicated that sympatho-inhibition is a class effect of AT1-receptor antagonists (12). Several reports demonstrated that plasma noradrenaline level is a sensitive index of the activity of the sympathetic nervous system (18–20). The concentration of noradrenaline was found to be an indicator of prognosis in patients with CHF and was found to be a predictor of survival and cardiovascular events in dialysis patients (21,22). The activation of the sympathetic nervous system stimulates RAAS by release of renin from juxtaglomerular cells. The stimulation of RAAS causes the elevation of total peripheral resistance (afterload) and retention of salt and water (preload) (10). Especially, elevation of total

**TABLE 3.** *Echocardiography* (N = *15)*

| | Before | After | *P*-value |
|---|---|---|---|
| LVDd (mm) | 45.0 ± 3.5 | 45.4 ± 3.4 | 0.55 |
| LVDs (mm) | 28.9 ± 3.8 | 29.5 ± 3.2 | 0.48 |
| IVST (mm) | 12.0 ± 1.5 | 11.9 ± 1.6 | 0.85 |
| PWT (mm) | 11.9 ± 1.2 | 11.8 ± 1.5 | 0.55 |
| EF (%) | 61.5 ± 3.4 | 61.3 ± 5.0 | 0.89 |
| LV mass (g) | 173.9 ± 38.7 | 165.5 ± 34.9 | 0.01 |
| LV mass index (g/m$^2$) | 117.0 ± 26.4 | 111.3 ± 23.9 | 0.01 |
| LA volume (mL) | 28.1 ± 7.3 | 28.4 ± 9.1 | 0.74 |
| MV inflow | | | |
| E wave (cm/s) | 64.3 ± 13.7 | 65.5 ± 14.9 | 0.71 |
| A wave (cm/s) | 88.1 ± 22.3 | 87.5 ± 30.5 | 0.88 |
| E/A | 0.77 ± 0.17 | 0.79 ± 0.16 | 0.51 |
| Deceleration time (ms) | 245.1 ± 53.1 | 244.2 ± 43.2 | 0.94 |
| Tissue Doppler | | | |
| E/e′ | 11.5 ± 3.8 | 13.2 ± 5.7 | 0.08 |

EF, ejection fraction; IVST, interventricular septum thickness; LA, left atrium; LV, left ventricular; LVDd, left ventricular dimension in diastole; LVDs, left ventricular dimension in systole; PWT, posterior wall thickness.

**TABLE 4.** *Ambulatory blood pressure monitoring (*N = *9) and Holter ECG (*N = *15)*

| Ambulatory blood pressure monitoring (mm Hg) | | | |
|---|---|---|---|
| | Before | After | *P*-value |
| 24-h SBP | 150.9 ± 16.2 | 131.3 ± 21.7 | 0.008 |
| 24-h DBP | 84.1 ± 6.3 | 74.9 ± 8.3 | 0.004 |
| 24-h MBP | 109.4 ± 11.9 | 93.6 ± 12.2 | 0.01 |
| Awakening time SBP | 152.1 ± 16.9 | 131.7 ± 23.2 | 0.01 |
| Awakening time DBP | 84.9 ± 5.8 | 75.2 ± 8.3 | 0.006 |
| Awakening time MBP | 111.0 ± 14.9 | 94.1 ± 12.9 | 0.02 |
| Sleep-time SBP | 148.1 ± 19.7 | 130.0 ± 20.1 | 0.005 |
| Sleep-time DBP | 81.5 ± 12.2 | 73.2 ± 10.1 | 0.051 |
| Sleep-time MBP | 103.7 ± 13.9 | 91.8 ± 12.0 | 0.009 |
| Holter ECG | | | |
| | Before | After | *P*-value |
| Mean heart rate (beat/min) | 72.5 ± 7.1 | 70.1 ± 8.6 | 0.07 |
| RR50 (beat/day) | 5986 ± 10712 | 3903 ± 5709 | 0.27 |
| SDRR (ms) | 98.4 ± 42.7 | 102.0 ± 30.8 | 0.74 |
| CVRR (%) | 20.4 ± 21.5 | 12.3 ± 3.2 | 0.25 |

CVRR, coefficient of variation of RR intervals; DBP, diastolic blood pressure; ECG, electrocardiogram, MBP, mean blood pressure; SBP, systolic blood pressure; SDRR, standard deviation of the RR.

peripheral resistance induces left ventricular hypertrophy. As a result, the activation of the sympathetic nervous system makes achievement of ideal blood pressure control difficult. This study showed that the switch to azilsartan significantly decreased the concentration of serum noradrenaline. This result further suggested that azilsartan exerted a significantly stronger effect on the sympathetic activity as compared with other ARBs. The stronger hypotensive effect of azilsartan results from both the primary effect of the antihypertensive drug and the suppression of sympathetic nervous system.

Left ventricular hypertrophy results from hypertension. Verdecchia et al. reported the degree of 24-h blood pressure control over time was important to the degree of left ventricular hypertrophy regression (16). Therefore, in this study, the regression of left ventricular hypertrophy was mainly attributed to 24-h stronger hypotensive effect of azilsartan.

Muller et al. demonstrated that circadian variation of blood pressure, serum adrenaline concentration, and the onset of cardiocerebrovascular events are correlated (23). Azilsartan has the potential to inhibit cardiovascular and cerebrovascular events by suppressing the sympathetic nervous system.

Recently, two randomized double-blind trials compared the hypotensive effect of azilsartan with that of valsartan or candesartan (24,25). However, no study reported on the switch from other ARBs to azilsartan. To the best of our knowledge, this is the first study that compared azilsartan and other ARBs based on the effect on the sympathetic nervous system and the echocardiography results.

This current study found that azilsartan has a higher potential to suppress sympathetic nervous system compared to other ARBs (as indicated by reduction in noradrenalin levels) that importantly contributes to the strong pressure-lowering effects of azilsartan. The strong hypotensive effect of azilsartan is thought to result from polyphenic causes. Our results revealed a part of the polyphenic causes.

Many studies have proved the strong pressure-lowering effect of azilsartan. This is the first study to demonstrate that azilsartan significantly reduces LV mass, LV mass index, and serum noradrenaline levels.

Our study has a few limitations. First, since the RAAS is a very complex system, the present study may have only partially elucidated the mechanism of the hypotensive effects of azilsartan. Second, our study population was small.

## CONCLUSIONS

Our results suggest that the new angiotensin receptor blocker, azilsartan, may improve the prognosis of hemodialysis patients not only by exerting its strong hypotensive effect but also by strongly suppressing the sympathetic nervous system compared with other angiotensin receptor blockers. These results suggested that the switch to azilsartan from other angiotensin receptor blockers might improve the prognosis of hemodialysis patients with hypertension. However,

further large-scale studies with all types of hypertensive patients will be required to reveal the entire antihypertensive mechanism of azilsartan.

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**Conflict of interest:** The authors have no conflicts of interest to report.

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