

## Effects of Azilsartan in Ambulatory Patients on Maintenance Hemodialysis: Monitoring at Night and at Home

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### Abstract

**Background:** Recently, a newly developed Angiotensin Receptor Blocker (ARB), azilsartan, has been shown to have a persistent depressor action throughout the day in hypertensive patients. However, there have been few reports discussing the efficacy of azilsartan in patients on Hemodialysis (HD).

**Methods:** Blood Pressure (BP) measurements in the HD center, and at home and ambulatory monitoring during the night were carried out before and after the change from other ARBs to azilsartan. All patients who were persistently hypertensive despite the treatment with antihypertensive drugs including ARB were considered as candidates. All patients were on antihypertensive treatment (12 on calcium channel blockers (CCBs), 6 on alpha blockers, and 2 on beta blockers and 4 on centrally acting antihypertensive drugs). Initially, azilsartan was started at 20 mg once daily in the evening, and increased up to 40 mg once daily in the evening.

**Results:** Pre-dialytic systolic BP (SBP), SBP in the morning at home and during night were all significantly reduced by 3 months' administration of azilsartan: (167.3 ± 10.3 to 145.3 ± 9.6 (pre-dialytic); 167.1 ± 11.0 to 151.8 ± 10.4 (at home); 150.5 ± 13.1 to 134.0 ± 10.3 (during night); mmHg).

**Conclusion:** The present study demonstrated that azilsartan reduced SBP of pre- and post HD session measured at a dialysis center, on the morning of HD days and at the night time after HD. In addition to reduction of SBPs, azilsartan stabilized BP during the night. Furthermore, azilsartan significantly attenuated reduction of SBP from the start to the end of HD session.

**Keywords:** Angiotensin receptor blocker; Blood pressure; Hemodialysis

### Introduction

Hypertension is prevalent and closely associated with cardiovascular disease (CVD) in patients receiving hemodialysis (HD) therapy [1].

A recent meta-analysis and two observational studies including the Japanese Renal Data Registry [2] and US renal Data System [3] have demonstrated better outcomes in patients treated with antihypertensive agents than those without antihypertensive agents in HD patients [4].

Among the antihypertensive agents, the inhibitory role of the renin-angiotensin system (RAS) remains questionable [5-7]. Recently, an in vitro study has shown that azilsartan, a newly developed angiotensin receptor antagonist (ARB), has a higher affinity for and a slower dissociation from the angiotensin type 1 receptor than other ARBs [8]. Furthermore, recent clinical studies [9,10] have clearly demonstrated that once-daily azilsartan administration persistently lowers 24-hour blood pressures (BPs) and improves nocturnal hypertension more effectively than other ARBs.

To examine the effects of azilsartan on BP in HD patients, BP of HD patients was measured by taking interdialytic ambulatory BP measurements during the night and self-measurements of BP at home in addition to regular BP measurements in the HD center.

### Subjects and Methods

#### Subjects

All patients were on antihypertensive treatment (12 on calcium channel blockers (CCBs), 6 on alpha blockers, and 2 on beta blockers and 4 on centrally acting antihypertensive drugs). The protocol conformed with the clinical guidelines of the institutions, and written informed consent was obtained from each patient. No patient had experienced previous CVD. Twelve patients underwent standard

3-times-a-week bicarbonate dialysis. Patients were selected from the electrical chart in the HD center where 126 patients received HD therapy. All patients were persistently hypertensive (more than 140 mm Hg systolic BP or 90 mm Hg diastolic BP) despite treatment with antihypertensive drugs including ARB (8 patients on olmesartan and 4 patients on candesartan), and were considered as candidates for the change from other ARBs to azilsartan.

#### Drug administration

The initial dose of azilsartan was 20 mg once daily in the evening, and increased up to 40 mg once daily in the evening. BP measurements were performed by the staff of the dialysis before and after the HD session. The average value in a one week period was calculated from 3 of these measurements.

#### Home blood pressure measurements

After patients were taught how to measure their own BP, they were instructed to record their BPs at least twice a week at home in the sitting position - once in the morning before breakfast within 30 min of awakening, and again in the evening just before dinner. Home BP measurements were made using the HEM 401C (Omron Life Science

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Co. Ltd, Tokyo, Japan), a semi-automatic device that operates on the cuff-oscillometric principle and generates a digital display of systolic and diastolic BPs and pulse rate. The accuracy of these self-measured BPMs was checked by nurses. A standard arm cuff was used to obtain the clinic and home BPMs because the circumference of patients' arms was less than 14 cm. These BP values were used as a reference for increasing the dose of azilsartan.

### Blood pressure monitoring with BPro

BP monitoring during the night was performed using a radial pulse wave acquisition device (BPro; HealthSTATS, Singapore). Embedded within a wrist strap, the BPro device uses a tonometer which is calibrated to oscillometric brachial BP [11]. When used for ambulatory blood pressure monitoring (ABPM), the BPro device (which is calibrated once at the beginning) captures BP waveforms every 25 minutes (8-10 seconds are needed for each measurement) over 24 hours, allowing for peripheral BP monitoring. The study participants were instructed to hold the hand at heart level during the measurements. Central BP was assessed by applying the n-point moving average method, a mathematical low pass filter, to the radial pulse waves [12]. This method was validated against invasive measurements as well as against validated noninvasive methods for taking central pressure measurements [12]. Night time was defined as from 9:00 PM to 6:00 AM.

### Statistics

Data are expressed as mean ± SD. Statistical comparisons to test differences between two independent groups were by Student's *t*-test or Mann-Whitney's *U*-test, as appropriate.

### Results

The characteristics of the patients are presented in Table 1. In Table 2, the effect of azilsartan is shown in significantly reducing SBPs in the morning of both HD and non-HD sessions ( $p < 0.01$ ). Moreover, SBP before but not after HD session was significantly reduced. However, DBP was not reduced at any of these points where SBP was measured. During the night after HD session, both SBP and DBP showed significant reductions due to azilsartan. Central systolic pressure was significantly lower than peripheral SBP during the night after HD measured by BPro. This pressure was significantly reduced after azilsartan administration. The mean increase of nocturnal SBP was  $9.25 \pm 4.6$  mm Hg and differed significantly after azilsartan administration (Figure 1). The typical nocturnal BP profile including central systolic pressure is shown in Figure 2.

### Discussion

The present study demonstrated that azilsartan reduced SBP of pre- and post HD patients measured at our dialysis center, on the morning of HD days, and after HD days and at night after HD.

In addition to reduction of SBPs, azilsartan stabilized BP during the night. Furthermore, azilsartan significantly attenuated reduction of SBP from the start to the end of HD session. These findings are essentially consistent with previous demonstrations in which azilsartan persistently lowered 24-hour BP and improved nocturnal hypertension in hypertensive patients [9,10,13,14].

Theoretically, volume load might be a major factor, but arterial stiffness produced by volume load and vasoactive substances in combination also contributes to elevation of blood pressure. In addition, it has not been established whether or not RAS inhibitions are effective for reduction of BP in HD patients. In the present study, the

change from ARBs to azilsartan reduced BP in HD patients throughout HD and non-HD days.

Recently, Sueta et al. [15] reported that azilsartan attenuated impairment of autonomic function and reduced aldosterone levels, reduced activity of the Sympathetic Nervous System (SNS) in experiments using no dipper type of hypertensive rats. If this is true in humans as well as in rats, it is possible that azilsartan can block a potential role of vasoactive substances and reduce BP. Moreover,

	Number of Patients (12)
Age (years)	64.1 ± 5.1
Duration (years)	4.2 ± 3.2
DM (%)	20/30 (66)
CRTNN (mg/dl)	10.4 ± 1.7
BUN (mg/dl)	89.7 ± 13
UA (mg/dl)	4.1 ± 1.1
Ca (mg/dl)	9.3 ± 0.6
IP (mg/dl)	6.3 ± 0.9
Hb (g/dl)	10.1 ± 0.6

Table 1: Characteristics of Patients.

		Before (mmHg)	After (mmHg)
In the morning on HD	SBP	167.1 ± 11.0	151.8 ± 10.4**
	DBP	82.8 ± 13.7	77.0 ± 10.0
In the morning on non-HD	SBP	167.3 ± 10.3	145.3 ± 9.6**
	DBP	80.9 ± 10.0	74.0 ± 9.2
Before HD session	SBP	163.1 ± 7.0	151.6 ± 10.4**
	DBP	80.2 ± 11.0	77.0 ± 10.0
After HD Session	SBP	149.8 ± 11.2	143.7 ± 11.0
	DBP	77.0 ± 10.0	70.3 ± 9.3
During night after HD session	SBP	150.5 ± 13.1	134.0 ± 10.3**
	DBP	82.0 ± 2.4	72.0 ± 9.8*
During night after HD session	CSP	141.2 ± 12.1	129.6 ± 10.0**

HD: hemodialysis  
SBP: systolic blood pressure;  
DBP: diastolic blood pressure.  
CSP: central systolic pressure, \* $P < 0.05$  and \*\* $P < 0.01$

Table 2: Values of blood pressures before and after azilsartan administration.

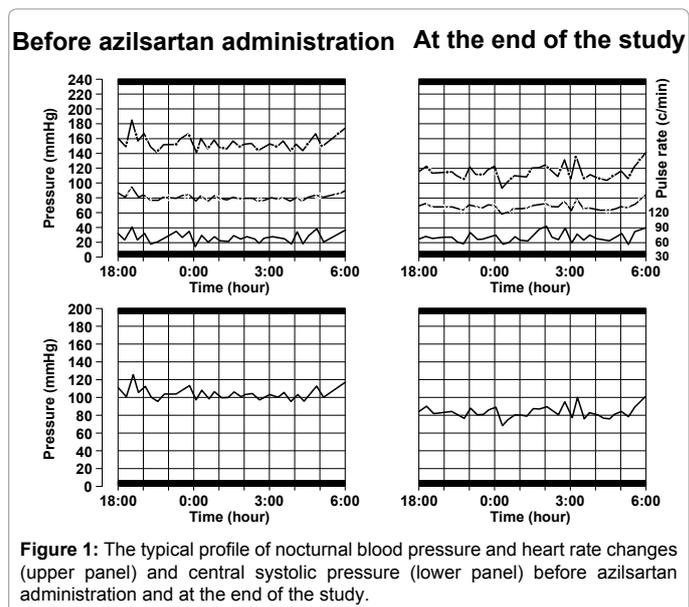
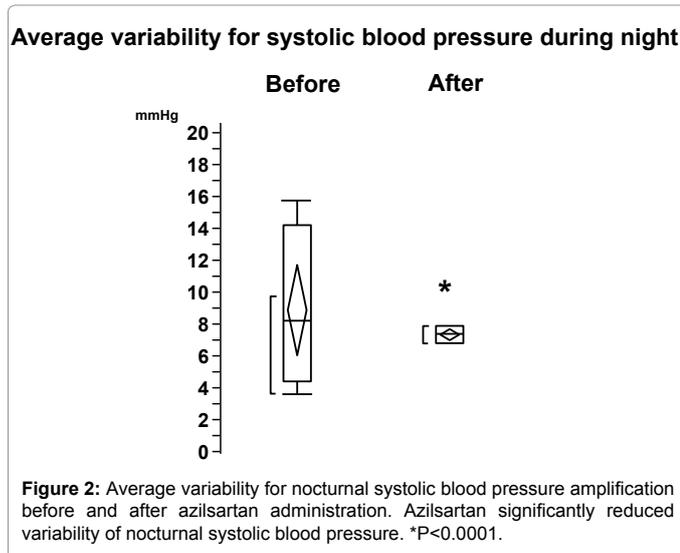


Figure 1: The typical profile of nocturnal blood pressure and heart rate changes (upper panel) and central systolic pressure (lower panel) before azilsartan administration and at the end of the study.



the stabilization of BP during the night, which was evaluated by the SDs of all BP measurements during a nighttime period in individual participants were used to derive the coefficient of variation (within-subject SD divided by BP level), was found in patients on HD similarly as reported in patients with essential hypertension. In the present study, these might also be related to the normalization of both RAS and SNS.

The nighttime average systolic BP values were independently associated with the extent of several markers of cardiovascular remodeling, such as cardiac hypertrophy and pulse wave velocity. People in whom SBP fails to decrease by > 10% during sleep are arbitrarily classified as “non dippers” [16] and these individuals could be at higher risk because nocturnal BP may be a stronger predictor of outcome than daytime SBP [17]. In patients undergoing HD, this nocturnal dip in SBP is attenuated and nocturnal BPs are substantially higher than in people with similar BP who do not have kidney disease. Three months’ administration of azilsartan reduced and normalized BP during the night, indicating that azilsartan might be a powerful antihypertensive drug for protection of CVD in HD patients.

There is increasing evidence that central systolic pressure may be a better predictor than peripheral BP for risk of CVD [18,19]. However, there have been very few reports discussing central systolic pressure in HD patients. Also, we found a mild but significant correlation between systolic blood pressure and central systolic pressure during the nighttime. Although administration of azilsartan for 3 months significantly reduced central systolic pressure as well as SBP, it is unclear whether or not this action is superior to other ARBs. Miyashita et al. [20] reported in a cross-sectional study that combinations of two vasodilators such as the renin-angiotensin system inhibitors and calcium channel blockers lowered central systolic pressure independently of peripheral BP levels. In the present study, for all patients treated with calcium channel blockers and azilsartan in combination a similar reduction of central systolic pressure could have resulted.

This small study has a number of limitations.

First, a very low number of patients were studied. It is clear that the current findings need to be confirmed by studies of larger numbers of patients. Second, no surrogate markers produced by hypertension such as left ventricular hypertrophy were evaluated. It is not known what levels of BP are optimal, and what constitutes the gold standard

for measurements of BP in patients receiving HD remains to be determined. In this study, the target levels of BP were calculated as averages of pre- and post-dialytic BPs. Agarwal et al. [21] criticized BPs obtained before and after dialysis, because there were poor correlations between interdialytic ambulatory BP and the averages of pre- and post-dialytic BPs. Nevertheless, in the present study there were no large differences in SBP among BP values obtained from in at the HD center, at home and with BPro during the night. Third, this study was carried out in a very short duration. It is obvious that a longer duration for evaluation of antihypertensive drugs is needed. Fourth, subjects of this study were patients on HD, and it is not appropriate to include a discussion of patients with essential hypertension. Recently Ogura et al. reported that SBPs in the morning of HD days were significant predictors of CV events for patients on HD. Fifth, since this study was carried out without a control drug, the effect of azilsartan on BP cannot be compared with other ARBs. However, the effects of other ARBs on BP would be similar with the levels of BP before the start of azilsartan, as shown in not having reductions of BP less than 140/90 mm Hg.

## Conclusion

This small study examined the effect of azilsartan, a newly developed ARB, on BP in patients receiving HD. The change from other ARBs to azilsartan reduced SBP throughout 24 hours, before and after HD session, at home BP, and at night BP during sleep.

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