Effect of azilsartan versus candesartan on morning blood pressure surges in Japanese patients with essential hypertension

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Morning blood pressure (BP) surge is reported as a risk factor for cardiovascular events and end-organ damage independent of the 24-h BP level. Controlling morning BP surge is therefore important to help prevent onset of cardiovascular disease. We compared the efficacy of azilsartan and candesartan in controlling morning systolic BP (SBP) surges by analyzing relevant ambulatory BP monitoring data in patients with/without baseline BP surges. As part of a 16-week randomized, double-blind study of azilsartan (20–40 mg once daily) and candesartan (8–12 mg once daily) in Japanese patients with essential hypertension, an exploratory analysis was carried out using ambulatory BP monitoring at baseline and week 14. The effects of study drugs on morning BP surges, including sleep trough surge (early morning SBP minus the lowest night-time SBP) and prewaking surge (early morning SBP minus SBP before awakening), were evaluated. Patients with sleep trough surge of at least 35 mmHg were defined by the presence of a morning BP surge (the 'surge group'). Sleep trough surge and prewaking surge data were available at both baseline and week 14 in 548 patients, 147 of whom (azilsartan 76; candesartan 71) had a baseline morning BP surge. In surge group patients, azilsartan significantly reduced both the sleep trough surge and the prewaking surge at week 14 compared with candesartan (least squares means of the between-group differences − 5.8 mmHg, P=0.0395; and − 5.7 mmHg, P=0.0228, respectively). Once-daily azilsartan improved sleep trough surge and prewaking surge to a greater extent than candesartan in Japanese patients with grade I–II essential hypertension. *Blood Press Monit* 19:164–169 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Introduction

Cardiovascular events such as acute myocardial infarction and stroke occur frequently in the period from early morning to noon [1–6]. Early morning blood pressure (BP) elevation/hypertension is significantly related to an increased risk to organs such as the brain, heart, and kidney [7,8], and it is therefore very important to manage early morning hypertension to help prevent the onset of cardiovascular events.

Two types of early morning hypertension have been reported: one that transitions from night-time hypertension (nondipper) and the other where BP increases markedly in the early morning (surge). Both types are reported to be risks for cardiovascular disease [9]. Although a moderate morning surge in BP is a normal physiological phenomenon, a marked BP surge is a risk factor for cardiovascular events and end-organ damage independent of the 24-h BP level [10–19]. For example, in the recent IDACO (International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes) study, a meta-analysis of cohort studies using ambulatory blood pressure monitoring (ABPM), it was found that morning BP surge was a risk factor for cardiovascular events independent of both the 24-h BP level and the fall of BP during the night (night-time BP/daytime BP) [20]. Similarly, the JMS-ABPM study (Wave 1) reported that morning BP surge is a risk factor for strokes independent of the 24-h BP level and that a morning systolic BP (SBP) surge of 10 mmHg increases the risk of stroke by 22% [10,21]. Therefore, controlling morning BP surge is important to prevent the onset of cardiovascular disease. However, few antihypertensive agents administered once daily are capable of maintaining a BP-lowering effect over a full 24-h period. Thus, the following morning, when the antihypertensive effects begin to wear off, BP variations from the previous night may not be corrected; thus, early morning BP surges and hypertension may occur.

Azilsartan is a new angiotensin II receptor blocker (ARB) that is expected to exert a more potent and sustained BP-lowering effect compared with existing ARBs because of its receptor binding properties. In-vitro studies have shown that azilsartan exerts a more potent inhibitory effect on angiotensin II type 1 (AT_1) receptors and dissociates more slowly from the receptor than other currently marketed ARBs, including olmesartan, telmisartan, valsartan, and irbesartan [22]. In a recent randomized, double-blind, comparative study in Japanese patients with stage I–II essential hypertension, azilsartan was found to have safety and tolerability similar to that of candesartan, but it showed superior antihypertensive efficacy. In addition, ABPM data indicated that azilsartan had a more sustained BP-lowering effect than candesartan, and was effective for a full 24-h period [23]. Moreover, a follow-up analysis from the randomized, double-blind, comparative study showed the efficacy of azilsartan against changes in night-time BP [24].

In this exploratory analysis, we evaluated the efficacy of azilsartan relative to that of candesartan in controlling morning SBP surges by analyzing relevant ABPM data in patients with and without baseline BP surges.

Methods
In the previous study, azilsartan was compared with candesartan in Japanese patients over a period of 16 weeks at 33 centers in Japan between May 2009 and June 2010 (clinical trial identifier: JapicCTI-090762) [23]. The study procedures, patient inclusion/exclusion criteria, dosage regimens, efficacy and safety endpoints, statistical analyses, and ethical provisions have been reported in detail previously [23], and will be described only briefly here. Patients received either azilsartan 20 mg daily for the first 8 weeks, followed by 40 mg daily for the second 8 weeks, or candesartan cilexetil (candesartan) 8 mg daily for the first 8 weeks, followed by 12 mg daily for the second 8 weeks. At baseline (week 0) and subsequently at week 14, ABPM was performed over a period of 26 h or higher, during which time BP was measured at 30-min intervals starting at 10:00 h (± 1 h); full details of the ABPM method have been described in the previous report [23].

Analysis of morning BP surge by ABPM
Patients who underwent ABPM at baseline were classified as having a sleep trough surge (defined using criteria similar to those of the IDACO study [20]) or no sleep trough surge. The following definitions were applied: early morning SBP was defined as the mean SBP measured during the 2-h period after awakening. SBP before awakening was defined as the mean SBP measured during the 2-h period before awakening. Lowest night-time SBP was defined as the mean SBP measured during the period 35 min before and after measurement of the lowest sleep SBP. Sleep trough surge was defined as an increase in SBP from the lowest night-time SBP to the early morning SBP, whereas prewaking surge was defined as the early morning SBP minus the SBP before awakening. The presence of a morning BP surge was defined as a sleep trough surge of at least 35 mmHg.

Statistical analysis
Differences between azilsartan and candesartan in controlling morning BP surges were analyzed by comparing the mean ($\pm$SD) decreases from baseline in sleep trough surge and prewaking surge recorded in the two treatment groups. Least squares means and two-sided 95% confidence intervals (CIs) for the differences between the two groups (azilsartan minus candesartan) were calculated using an analysis of covariance model with a two-sided significance level of 5%, with the plasma renin activity (< 0.5 or ≥ 0.5 ng/ml/h) at week 2 and treatment group as independent variables, and baseline values as a covariate. Differences with P value less than 0.05 were considered to be significant.

Results
Patient characteristics
Overall, 636 patients were randomized to treatment and both baseline and week 14 ABPM data were available for 548 patients; 273 received azilsartan and 275 received candesartan. A morning BP surge was experienced by 147 patients (azilsartan 76; candesartan 71) at baseline (the 'surge group'), whereas 401 patients did not experience a morning BP surge (azilsartan 197; candesartan 204) at baseline (the 'nonsurge group'). The proportions of patients classified as surge/nonsurge were similar in the two treatment groups. The demographic and clinical characteristics of the two treatment groups according to surge status are shown in Table 1. In the azilsartan group, more women than men had a sleep trough surge (55.3 vs. 44.7%), whereas the converse was true in the candesartan group (45.1 vs. 54.9%). In all other respects, there were no remarkable differences in the characteristics of patients with and without surges.

Changes in ABPM parameters in patients with a morning BP surge
The mean ($\pm$SD) changes in SBP from baseline to week 14 in the 24-h mean, daytime, night-time, lowest night-time, early morning, and BP before awakening for patients with a morning BP surge at baseline are shown in Table 2. These ABPM parameters were significantly reduced at week 14 from baseline in patients treated with both azilsartan ($P < 0.0001$) and candesartan ($P < 0.001$) in the surge group. Furthermore, the reductions were significantly greater with azilsartan than with candesartan for each ABPM parameter (Table 2). Notable differences between azilsartan and candesartan in the surge group were observed in the 24-h mean SBP, mean daytime SBP, lowest night-time SBP, and early morning SBP. Changes in these parameters in the two groups were as follows: -15.1 versus -10.0 mmHg ($P = 0.0103$), -16.1 versus -9.9 mmHg

Table 1　Baseline (week 0) demographic and clinical characteristics in patients in whom the morning BP surge status could be determined by ABPM

Characteristics	Azilsartan		Candesartan	
	Surge ($n=76$)	Nonsurge ($n=197$)	Surge ($n=71$)	Nonsurge ($n=204$)
Age	57.4±9.57	56.7±9.50	58.5±9.96	56.4±9.95
Sex				
Male	34 (44.7)	126 (64.0)	39 (54.9)	131 (64.2)
Female	42 (55.3)	71 (36.0)	32 (45.1)	73 (35.8)
BMI (kg/m^2)	25.28±4.14	25.69±4.22	25.45±3.91	25.30±3.76
Duration of hypertension (years)	9.06±8.06	8.38±7.97	7.56±6.98	7.78±7.22
Sitting BP (mmHg)				
SBP	159.7±7.64	159.9±7.86	158.9±6.80	159.5±7.07
DBP	99.7±3.81	100.5±4.38	99.8±3.85	100.5±4.19
Pulse (bpm)	69.9±8.96	70.9±9.02	69.5±8.32	68.7±8.34
ABPM (mmHg)				
(a) SBP				
24-h mean BP	153.8±12.30	154.7±14.05	153.8±11.74	154.7±14.16
Daytime mean BP (waking state)	162.5±13.64	159.0±13.67	161.8±12.27	158.8±14.29
Night-time mean BP (sleeping state)	135.7±13.26	145.6±17.46	136.7±15.53	145.9±16.70
Lowest night-time BP	122.6±14.53	137.9±17.34	122.4±14.26	137.7±16.47
Early morning mean BP	167.3±14.19	157.3±16.03	166.8±13.48	156.3±14.95
BP before awakening	140.5±15.48	146.6±18.87	140.9±14.76	147.1±16.78
Sleep trough surge (early morning BP – lowest night-time BP)	44.7±9.92	19.5±10.19	44.4±9.17	18.6±10.56
Prewaking surge (early morning BP – BP before awakening)	26.8±13.13	10.7±12.08	26.0±11.74	9.2±11.45
Nocturnal SBP fall (%)	16.3±6.47	8.4±7.61	15.4±6.65	8.1±7.60
(b) DBP				
24-h mean BP	93.8±8.67	94.5±10.02	92.9±8.55	94.9±9.81
Daytime mean BP (in waking state)	99.4±9.99	97.7±10.31	97.8±8.75	97.9±10.13
Night-time mean BP (sleeping state)	82.5±8.59	87.5±11.14	82.1±9.48	88.6±10.47
BP before awakening	86.0±9.82	88.9±12.01	86.1±11.70	90.2±11.58
Prewaking surge (early morning BP – BP before awakening)	16.3±9.40	8.9±9.77	15.9±10.17	8.1±9.56
Plasma renin activity (ng/ml/h)	0.63±0.67	0.63±0.50	0.72±0.91	0.58±0.47
eGFR (ml/min/1.73 m^2)	80.01±13.82	75.76±13.96	77.10±16.82	76.45±13.94
Pretreatment antihypertensives				
Yes	60 (78.9)	149 (75.6)	53 (74.6)	150 (73.5)
No	16 (21.1)	48 (24.4)	18 (25.4)	54 (26.5)
Concurrent disease (diabetes)				
Yes	17 (22.4)	36 (18.3)	13 (18.3)	49 (24.0)
No	59 (77.6)	161 (81.7)	58 (81.7)	155 (76.0)
Concurrent disease (hyperlipidemia)				
Yes	45 (59.2)	118 (59.9)	39 (54.9)	111 (54.4)
No	31 (40.8)	79 (40.1)	32 (45.1)	93 (45.6)

Values are means±SD or numbers of patients (%) (sex, pretreatment antihypertensives, and concurrent disease).
ABPM, ambulatory BP monitoring; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

($P=0.0071$), −11.9 versus −6.7 mmHg ($P=0.0236$), and −21.3 versus −11.1 mmHg ($P=0.0002$), respectively.

Changes in sleep trough surge and prewaking surge in patients with a morning BP surge

In patients with a morning BP surge at baseline, the mean (±SD) changes in the sleep trough surge (i.e. early morning SBP minus lowest night-time SBP) and prewaking surge (i.e. early morning SBP minus SBP before awakening) from baseline to week 14 in the two treatment groups are shown in Table 2. For both surge types, the mean changes at week 14 with azilsartan were significantly greater than those with candesartan (sleep trough surge: −9.3 vs. −4.4 mmHg, respectively; $P=0.0395$; prewaking surge: −5.7 vs. +0.1 mmHg, respectively; $P=0.0228$) (Fig. 1).

Changes in ABPM parameters and BP surges in patients without a morning BP surge

In patients without a morning BP surge at baseline, the mean SBP changes for 24-h mean, daytime, night-time, lowest night-time, and early morning and BP before awakening were

significantly reduced at week 14 from baseline in patients treated with either azilsartan or candesartan ($P<0.0001$, respectively). The reductions were also significantly greater with azilsartan than with candesartan for the 24-h mean SBP (−12.2 vs. −9.1 mmHg; $P=0.0114$) and the mean daytime SBP (−10.6 vs. −6.8 mmHg; $P=0.0038$). Although the mean changes in SBP in night-time, lowest night-time, and early morning and BP before awakening were slightly greater with azilsartan than with candesartan, the differences between the two treatment groups were not statistically significant (Table 2).

The sleep trough surges and prewaking surges were increased in both treatment groups (8.3 and 4.9 mmHg with azilsartan, 9.1 and 6.7 mmHg with candesartan). The results for azilsartan and candesartan with respect to surges in nonsurge patients showed similar trends.

Discussion

The efficacy of antihypertensive therapy in suppressing morning BP surges has been reported for some drugs,

Table 2 Magnitude of changes in SBP from baseline to week 14 in patients receiving azilsartan and candesartan according to their baseline morning BP surge status

|	Azilsartan		Candesartan			
Variables	Number of patients	Magnitude of change	Number of patients	Magnitude of change	LS mean (95% CI)[a] (Azil − Cand)	P value (Azil vs. Cand)
24-h mean BP (mmHg)						
Surge	76	− 15.1±18.00	71	− 10.0±12.59	− 6.3 (− 11.16, − 1.52)	0.0103
Nonsurge	197	− 12.2±12.54	204	− 9.1±11.07	− 2.8 (− 4.99, − 0.64)	0.0114
Daytime mean BP (mmHg)						
Surge	76	− 16.1±20.02	71	− 9.9±13.79	− 7.3 (− 12.66, − 2.03)	0.0071
Nonsurge	197	− 10.6±13.14	204	− 6.8±12.20	− 3.5 (− 5.79, − 1.12)	0.0038
Night-time mean BP (mmHg)						
Surge	76	− 14.0±17.05	71	− 10.3±13.91	− 5.0 (− 9.81, − 0.21)	0.0407
Nonsurge	197	− 15.8±15.95	204	− 13.3±13.33	− 2.3 (− 4.91, 0.39)	0.0951
Lowest night-time BP (mmHg)						
Surge	76	− 11.9±18.33	71	− 6.7±14.45	− 5.9 (− 10.96, − 0.80)	0.0236
Nonsurge	197	− 17.0±18.47	204	− 15.2±16.00	− 1.4 (− 4.54, 1.66)	0.3618
Early morning mean BP (mmHg)						
Surge	76	− 21.3±23.67	71	− 11.1±16.35	− 11.7 (− 17.90, − 5.56)	0.0002
Nonsurge	197	− 8.7±18.71	204	− 6.1±15.50	− 2.0 (− 5.26, 1.16)	0.2106
BP before awakening (mmHg)						
Surge	76	− 15.6±21.31	71	− 11.2±16.99	− 5.7 (− 11.20, − 0.13)	0.0451
Nonsurge	197	− 13.6±17.71	204	− 12.8±14.92	− 0.7 (− 3.71, 2.23)	0.6248
Sleep trough surge (mmHg)[b]						
Surge	76	− 9.3±19.64	71	− 4.4±15.18	− 5.8 (− 11.34, − 0.28)	0.0395
Nonsurge	197	8.3±17.96	204	9.1±16.15	− 0.3 (− 3.41, 2.74)	0.8303
Prewaking surge (mmHg)[c]						
Surge	76	− 5.7±18.78	71	0.1±15.98	− 5.7 (− 10.68, − 0.81)	0.0228
Nonsurge	197	4.9±17.37	204	6.7±15.36	− 0.7 (− 3.35, 1.99)	0.6148

Values are means±SD.
ANCOVA, analysis of covariance; Azil, azilsartan; BP, blood pressure; Cand, candesartan; CI, confidence interval; LS, least squares; SBP, systolic blood pressure.
[a]Determined by an ANCOVA model, with the plasma renin activity (<0.5 or ≥ 0.5 ng/ml/h) and treatment group at week 2 as independent variables and baseline values as a covariate.
[b]Sleep trough surge=mean early morning BP minus lowest night-time BP.
[c]Prewaking surge=mean early morning BP minus BP before awakening.

Fig. 1
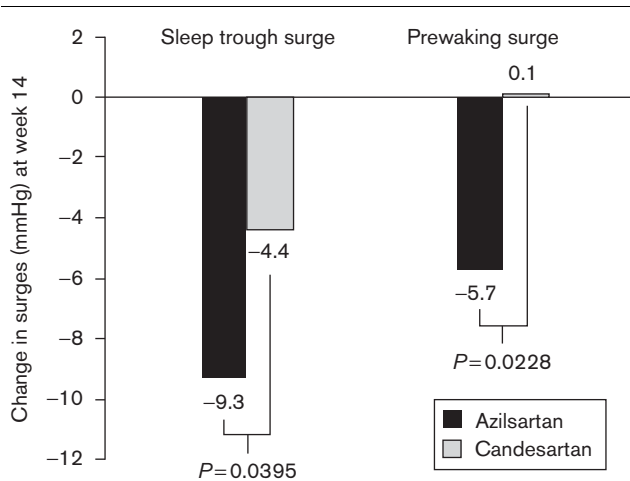
Changes in sleep trough surge (mean early morning BP minus lowest night-time BP) and the prewaking surge (mean early morning BP minus BP before awakening) from baseline (week 0) to week 14 in patients receiving treatment with azilsartan (*n*=76) and candesartan (*n*=71) in the surge group. BP, blood pressure.

daily administration of candesartan has been reported to regulate sleep trough surges more potently than the ACE inhibitor lisinopril [26]. In the present analysis, we compared the efficacy of azilsartan on morning BP surges with that of candesartan by analyzing ABPM data according to the presence or absence of sleep trough surge in a previously reported randomized, double-blind study of the two ARBs in Japanese patients with stage I–II essential hypertension [23]. The key findings of the study were that in patients with sleep trough surge at baseline, administration of azilsartan decreased the lowest night-time SBP, the early morning SBP, and the SBP before awakening to a significantly greater extent than candesartan. As a result of the marked reduction in early morning SBP, both the sleep trough surge and the prewaking surge in these patients were significantly reduced by azilsartan in comparison with candesartan (least square means of the between-treatment differences − 5.8, 95% CI − 11.34, − 0.28 mmHg, *P* = 0.0395; and − 5.7, 95% CI − 10.68, − 0.81 mmHg, *P* = 0.0228, respectively).

In patients without a sleep trough surge at baseline (nonsurge group), the magnitude of changes in sleep trough surges and prewaking surges was mildly increased in both treatment groups (Table 2). Azilsartan and candesartan considerably reduced night-time mean SBP and lowest night-time SBP from baseline; therefore, both drugs increased the absolute values of surges. However, in the nonsurge group, both drugs also reduced early

including the long-acting calcium channel blocker amlodipine, which has been shown to reduce early morning BP in comparison with night-time BP and to control sleep trough surges by exerting an antihypertensive effect that corresponds to the BP level [25]. Among the ARBs, once-

morning SBP at week 14 from baseline (– 8.7 mmHg), which was relatively lower at baseline. In other words, in the nonsurge group, both drugs increased the absolute values of surges, but with the positive potential that enables them to control and maintain SBPs lower from night-time to early morning. Thereby, these mild increased surges in the nonsurge group were not considered to be clinically meaningful.

The effects of antihypertensive agents on morning BP surges vary according to their mechanisms of action and the duration of their effects [27]. Early-morning enhancement of the renin–angiotensin system (RAS), endothelial functional disorder, and progression of vascular remodeling are considered to be involved in the enhancement of morning BP surges [28]. As RAS inhibitors are expected to have a morning BP surge-regulating action, by controlling the early morning enhancement of RAS, they may also improve small vessel remodeling, thereby stabilizing early morning BP in the long term [29].

Several clinical studies have shown that the effects of RAS inhibitors on morning BP surges vary from one drug to another. Whereas once-daily administration of candesartan has been shown to have a potent effect in regulating sleep trough BP surges [26], valsartan had no effect in regulating sleep trough surges [25]. This difference is believed to be related to the duration of the antihypertensive effect of these ARBs.

In an earlier in-vitro study, azilsartan was shown to have a more potent inhibitory effect on AT_1 receptors and to dissociate more slowly from the receptor than other ARBs [22]. In the randomized, double-blind comparative study in Japanese patients with stage I–II essential hypertension from which ABPM data for the present study were derived, once-daily administration of azilsartan exerted a more potent and sustained 24-h BP-lowering effect than candesartan [23]. Therefore, the effect of azilsartan on morning BP surges may be related to its sustained action on the AT_1 receptor.

Limitations of this study include the fact that several different definitions have been applied in studies of morning BP surges carried out to date. Although there is consensus that morning BP surges are associated with cardiovascular events, no consensus on their precise definition has been reached as yet [30]. In this analysis, the lowest night-time SBP, the early morning SBP, the SBP before awakening, the sleep trough surge, and the prewaking surge were defined as mentioned above (see the Methods section) using the study of Kario et al. [10] as a reference. In addition, the occurrence of a sleep trough BP surge was defined as an increase of SBP from the lowest night-time SBP to the mean early morning SBP of at least 35 mmHg by reference to the definition in the IDACO study, which is the largest study of the correlation between morning BP surges and cardiovascular events published to date (IDACO used the definition of at least 37 mmHg) [20]. However, in the study of Kario and colleagues, an increase in SBP of at least 55 mmHg from the lowest sleep level to the early morning level was applied to examine the prognostic implications of morning BP surges for silent and clinical cerebrovascular disease in elderly hypertensive patients; this higher morning BP surge was associated with a higher risk of stroke than lower morning SBP surges (less than 55 mmHg) [10]. A further limitation of the present study relates to the reproducibility of morning BP surges measured by conventional ABPM. This is because the time at which surges arise cannot be determined accurately and the extent of the surge is influenced by day-to-day variability of physical activity [30]. Because arising and ambulating from supine sleep is the major determinant of morning BP surges, BP may show little change if the patient remains supine after awakening [30]. Also, this study was a short-term evaluation, and did not evaluate the efficacy of the study medication in reducing cardiovascular events. The dosage selection of candesartan in this study should also be considered as another limitation. The rationale for increasing candesartan up to 12 mg daily is that, in Japan, the approved maximum daily dosage of candesartan is 12 mg. The antihypertensive efficacy of candesartan 12 mg, telmisartan 80 mg, valsartan 160 mg, and olmesartan 40 mg has been shown to be equivalent to that of enalapril 20 mg in Japanese patients with hypertension [31–34]. Therefore, further evaluations using large-scale databases are needed to determine the threshold morning BP surge level associated with an increased cardiovascular risk.

Although no study has scientifically shown that selective regulation of morning BP surges will limit the onset of cardiovascular events and target organ damage, it is clear that a sustained morning BP surge is a risk factor for cardiovascular events and organ damage independent of the 24-h BP level [10–19]. The current study has shown that azilsartan exerts a more pronounced effect in suppressing morning BP surges than candesartan. Thus, in addition to its potent and sustained antihypertensive effect, azilsartan may be expected to control morning BP surges and thereby help prevent the onset of cardiovascular events.

Conflicts of interest
H.R. and K.K. served as medical experts for this study. H.R. received honoraria from Takeda Pharmaceutical Company for lectures he gave during the study period.

K.E., K.S., and Y.I. are all employees of Takeda Pharmaceutical Company.

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