

Age-Related Difference in the Sleep Pressure-Lowering Effect Between an Angiotensin II Receptor Blocker and a Calcium Channel Blocker in Asian Hypertensives

The ACS1 Study

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Abstract—Sleep blood pressure (BP), which is partly determined by salt sensitivity and intake, is an important cardiovascular risk in hypertensives. However, there have been no studies on age-related differences in the sleep BP-lowering effect between angiotensin II receptor blockers and calcium channel blockers in Asians. Azilsartan Circadian and Sleep Pressure—the 1st Study was a multicenter, randomized, open-label, 2-parallel-group study conducted to compare the efficacy of 8-week oral treatment with an angiotensin II receptor blocker (azilsartan 20 mg) or a calcium channel blocker (amlodipine 5 mg) on sleep BP as evaluated by ambulatory BP monitoring. Among the overall population, amlodipine treatment achieved significantly greater reduction in sleep BP, awake BP, and 24-hour BP than azilsartan treatment. BP reduction by amlodipine was particularly pronounced in elderly hypertensive patients aged ≥ 60 years old. Among patients ≥ 60 years old, the amlodipine group had numerically, but not significantly, higher control rate of sleep BP compared with the azilsartan group. Similar results were found for awake BP and 24-hour BP. These results suggest a greater BP reduction/control by amlodipine compared with azilsartan and that reduction/control of BP by amlodipine was also more effective in the elderly population. As recommended in the American Society of Hypertension/The international Society of Hypertension and the National Institute for Health and Clinical Excellence guidelines for differentiating treatment according to age, amlodipine should be one of the options for starting treatment in the elderly population.

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• **Online Data Supplement**

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High sleep blood pressure (BP) like high awake BP is associated with an increased risk of cardiovascular events.¹ In addition, a disrupted circadian BP rhythm may have harmful effects on the brain, heart, kidneys, and other organs²⁻⁴ and is closely associated with the occurrence of cardiovascular events. Ambulatory BP monitoring (ABPM) assists in determining the time-course profile of 24-hour BP. Ideal 24-hour BP control by appropriate treatment would lower the sleep BP and restore the normal circadian BP pattern and could thus reduce the incidence of cardiovascular events.

Angiotensin II receptor blockers (ARBs) and calcium channel blockers (CCBs) have potent and stable antihypertensive effects on hypertension. It has been reported that

azilsartan, a novel ARB, is more effective to lower the BP than other ARBs and to have a potent antihypertensive effect over 24 hours.⁵⁻⁷ Amlodipine, on the other hand, is deemed to have the most potent and sustained antihypertensive effect among the existing CCBs.⁸⁻¹¹ Our previous studies showed that amlodipine lowered sleep and awake BP comparably in patients with a nondipper-type (reduced dipping of sleep BP) circadian BP rhythm,⁸ whereas azilsartan lowered sleep BP more extensively than awake BP in patients with a nondipper-type rhythm.⁷ These results indicate that the effects of these 2 drugs on the sleep BP and on sleep BP reduction may be different, which could open a path to hypertension management through the analysis of sleep BP patterns. To the best of our knowledge, however, there have been no direct

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comparison studies of differences between these 2 classes of drugs on sleep BP reduction and accompanying improvement of sleep BP patterns. Thus, we designed an investigator-initiated multicenter, randomized (dynamic allocation), open-label, 2-parallel-group study, Azilsartan Circadian and Sleep Pressure—the 1st Study (ACS1) to investigate the efficacy of azilsartan on sleep BP and the circadian BP rhythm in comparison with amlodipine, as evaluated by ABPM in hypertensive patients.

In this study, we also performed an additional exploratory analysis to identify the age-dependent drug effects. As for evaluation of the antihypertensive effects, we not only analyzed BP reduction, but also control rate (the percentage of patients who achieved BP goals [sleep BP: systolic blood pressure (SBP) <120 mmHg and diastolic blood pressure (DBP) <70 mmHg; awake BP: SBP<135 mmHg and DBP<85 mmHg; 24-hour BP: SBP<130 mmHg and DBP<80 mmHg; clinic BP: SBP<140 mmHg and DBP<90 mmHg]).

Methods

Study Protocol

A total of 99 sites participated in the study. The study procedures, patient inclusion/exclusion criteria, dosage regimens, primary and secondary end points, statistical analyses, and ethical provisions have been described in the previous ACS1 protocol paper,¹² and thus will be described only briefly in this exploratory analysis report. This study was approved by an institutional review committee, and the subjects gave informed consent. This study conformed to the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects. The primary objective of the study was to evaluate the efficacy of an 8-week oral treatment with azilsartan 20 mg to lower sleep SBP in comparison with amlodipine 5 mg in patients with stage I or II primary hypertension. The rationale for comparing azilsartan 20 mg, a normal dose, with amlodipine 5 mg was as follows: (1) amlodipine 5 mg is reported to be effective in reducing sleep SBP; (2) the study was designed to compare the 2 drugs administered at their normal daily doses; and (3) the decrease in sleep BP with azilsartan 20 mg was estimated to be equivalent to that with azilsartan 40 mg.¹²

Subjects started treatment with oral azilsartan (Takeda Pharmaceutical Company, Ltd. Osaka, Japan) 20 mg or amlodipine (Pfizer Japan Inc., Tokyo, Japan) 5 mg once daily before or after breakfast in the morning at Week 0 and visited the study site every 2 weeks until the end of the treatment (Week 8).

Ambulatory Blood Pressure Monitoring

As recommended by the European Society of Hypertension position paper on ambulatory BP monitoring,¹³ noninvasive ABPM was performed at the start of the run-in period and the end of treatment with an automatic device (TM-2431; A & D Inc., Saitama, Japan) that recorded BP every 30 minutes for ≥ 26 hours. The accuracy of these devices was validated previously. The ambulatory BP data used in the present study were those obtained by the oscillometric method. Sleep BP was defined as the average of BPs from the time when the patient went to bed until the time he or she got up, and awake BP was defined as the average of BPs recorded during the rest of the day. We subclassified the patients according to the type of awake-sleep BP variation determined based on the data from ABPM at the start of the run-in period as follows: patients were considered risers if the decrease in sleep SBP was <0%; nondippers if the decrease in sleep SBP was $\geq 0\%$ and <10%; dippers if the decrease in sleep SBP was $\geq 10\%$ and <20%; and extreme-dippers if the decrease in sleep SBP was $\geq 20\%$.

Statistical Analysis

For the primary and secondary end points, the differences between the azilsartan group and the amlodipine group in the mean change of several BPs (sleep, awake, 24-hour, and clinic BP) with a 2-sided 95% confidence interval were determined using the Full Analysis Set (the primary end point was a change in the mean sleep SBP). In this study, subgroup analyses, for example, the comparison of BPs between younger (<60 years) and older (≥ 60 years) patients were also performed as several post hoc analyses not specified in the predefined statistical analysis plan. The differences in the changes of the measured values from Week 8 between the drugs were evaluated with 2-sample *t*-tests.

The post hoc analyses in this study included the following statistical tests: a chi-squared test of comparison and difference between the percentages of patients who achieved BP goals; a regression analysis of baseline BP and changes in BP, which involved calculating the Pearson product-moment correlation coefficient and performing a Z-test of the equivalence of correlation coefficients between the 2 groups; and a 2-way analysis of covariance of baseline BP used as a covariate and changes in BP, together with a logistic regression analysis of the percentages of patients who achieved BP goals, to analyze the interaction between the drugs and age. The tests were performed with a 2-sided significance level of 5%. The analyses were performed with SAS software version 9.3 (SAS Institute, Cary, NC).

Results

Of the 957 patients enrolled in this study, 718 were randomized and 239 were withdrawn during the run-in period (Figure 1). The reasons for the withdrawal were as follows:

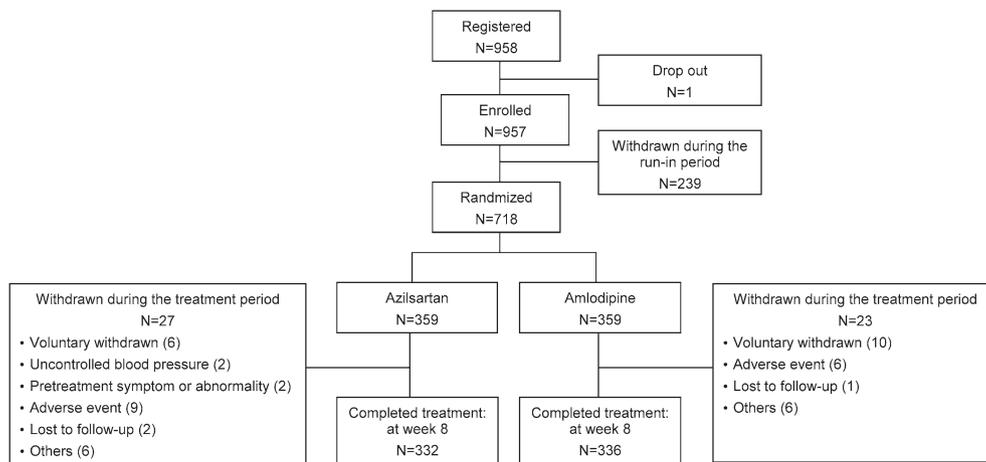


Figure 1. Patient disposition.

did not meet the inclusion criteria or met the exclusion criteria ($n=157$); spontaneous discontinuation by the patients ($n=45$); poor BP control ($n=16$); others ($n=21$). An equal number of patients ($n=359$ each) were assigned to take azilsartan and amlodipine, respectively. The numbers (27 versus 23 patients, respectively) and the reasons for withdrawal were similar between the 2 groups.

Patients' Baseline Characteristics

Of the 359 patients in each treatment group, 152 patients (42.3%) in the azilsartan group and 148 patients (41.2%) in the amlodipine group were <60 years old. The baseline characteristics in the group of <60 years old, the group of ≥ 60 years old, and the overall group, respectively, were similar for the 2 drugs (Table 1).

BP Reduction

In the overall groups, azilsartan did not reduce sleep BP more than amlodipine (primary end point; Table 2). Amlodipine demonstrated significantly greater reduction in sleep SBP than azilsartan (azilsartan versus Amlodipine) (-12.6 mmHg versus -17.5 mmHg; $P<0.001$)/DBP (-7.1 mmHg versus -8.9 mmHg, $P=0.006$), awake SBP (-14.9 mmHg versus -17.6 mmHg; $P=0.011$), 24-hour SBP (-14.0 mmHg versus -17.5 mmHg; $P<0.001$), and clinic SBP (-17.0 mmHg versus -19.6 mmHg; $P=0.016$) at Week 8.

Baseline BP and BP Response

In regression analysis, both drugs showed a statistically significant correlation between baseline sleep SBP and the change in sleep SBP at Week 8: azilsartan, $r=-0.317$, $P<0.001$; amlodipine, $r=-0.608$, $P<0.001$ (Figure 2). The linear relationship observed in sleep BP (Figure 2) was essentially similar to that observed at other times (clinic SBP: azilsartan, $r=-0.174$, $P=0.001$; amlodipine, $r=-0.398$, $P<0.001$; 24-hour SBP: azilsartan, $r=-0.211$, $P<0.001$; amlodipine, $r=-0.483$, $P<0.001$; awake SBP: azilsartan, $r=-0.235$, $P<0.001$; amlodipine, $r=-0.448$, $P<0.001$; Figures S2–S4 in the online-only Data Supplement). Patients with a higher baseline sleep SBP achieved a greater reduction in sleep SBP. The distribution variance was smaller in the amlodipine group than in the azilsartan group ($P<0.001$), suggesting that amlodipine provided smaller individual differences in the sleep SBP reduction levels among different patients compared with azilsartan. The slope of the regression line was significantly steeper in the amlodipine group than in the azilsartan group ($P=0.001$) (azilsartan, -0.298 ; amlodipine, -0.500), indicating that amlodipine reduced the sleep SBP to a greater extent than azilsartan in patients with a higher baseline sleep SBP.

Age-Related Subanalysis

To explore age-related differences in the drug effects, post hoc subgroup analysis was performed, stratified by age as <60 or ≥ 60 years old, which were the age categories used in 2 of the latest overseas guidelines.^{14,15} In the analysis, amlodipine showed a significantly greater reduction in sleep SBP than azilsartan in patients of ≥ 60 years old ($P<0.001$): sleep SBP (azilsartan versus amlodipine), -12.0 mmHg

Table 1. Baseline Characteristics of the Patients

Variable	<60 y old		≥ 60 y old	
	Azilsartan (N=152)	Amlodipine (N=148)	Azilsartan (N=207)	Amlodipine (N=211)
Age, y, mean (SD)	50 (7)	49 (7)	69 (7)	69 (7)
Sex, n (%)				
Male	94 (61.8)	86 (58.1)	108 (52.2)	116 (55.0)
Female	58 (38.2)	62 (41.9)	99 (47.8)	95 (45.0)
Height, cm, Mean (SD)	165 (9)	166 (9)	158 (9)	159 (9)
Body mass index, kg/m ² , Mean (SD)	26 (4)	26 (4)	24 (3)	24 (3)
Smoking, n (%)				
Never	69 (45.4)	69 (46.6)	100 (48.3)	101 (47.9)
Current	34 (22.4)	38 (25.7)	39 (18.8)	25 (11.8)
Once	49 (32.2)	41 (27.7)	68 (32.9)	85 (40.3)
Sleeping hours, Mean (SD)	6 (1)	6 (1)	7 (1)	7 (1)
Duration of hypertension, days, Mean (SD)	1438 (2513)	1099 (1513)	2114 (2844)	2116 (2716)
Sleep blood pressure pattern, n (%)				
Riser	11 (7.2)	11 (7.4)	20 (9.7)	16 (7.6)
Non-dipper	45 (29.6)	47 (31.8)	78 (37.7)	75 (35.5)
Dipper	70 (46.1)	73 (49.3)	88 (42.5)	88 (41.7)
Extreme-dipper	26 (17.1)	17 (11.5)	21 (10.1)	32 (15.2)
Complication of CKD, n (%)				
Yes	3 (2.0)	7 (4.7)	9 (4.3)	4 (1.9)
No	149 (98.0)	141 (95.3)	198 (95.7)	207 (98.1)
Complication of type II diabetes mellitus, n (%)				
Yes	28 (18.4)	25 (16.9)	43 (20.8)	46 (21.8)
No	124 (81.6)	123 (83.1)	164 (79.2)	165 (78.2)
Previous hypertension drugs, n (%)				
ARB	29 (19.1)	18 (12.2)	56 (27.1)	59 (28.0)
CCB	15 (9.9)	14 (9.5)	51 (24.6)	54 (25.6)
Diuretics	1 (0.7)	0 (0.0)	2 (1.0)	2 (0.9)
β -blockers	2 (1.3)	0 (0.0)	1 (0.5)	2 (0.9)
Others	0 (0.0)	0 (0.0)	2 (1.0)	3 (1.4)
None	108 (71.1)	117 (79.1)	97 (46.9)	95 (45.0)
Baseline BP, mmHg, Mean (SD)				
Sleep SBP	137.3 (16.5)	140.1 (17.1)	139.8 (16.3)	140.1 (17.1)
Sleep DBP	84.0 (10.1)	86.3 (10.0)	80.2 (9.1)	80.5 (10.0)
Awake SBP	156.6 (14.1)	158.4 (14.6)	156.0 (12.8)	157.8 (13.5)
Awake DBP	96.4 (8.5)	98.4 (8.7)	90.3 (8.5)	90.7 (9.2)
24-hour SBP	150.6 (13.8)	152.8 (14.3)	150.7 (12.4)	152.1 (13.3)
24-hour DBP	92.5 (8.3)	94.7 (8.3)	86.9 (8.0)	87.4 (8.7)
Clinic SBP	148.6 (10.4)	147.9 (10.0)	150.4 (10.0)	152.3 (9.9)
Clinic DBP	94.5 (8.5)	93.8 (8.4)	87.3 (8.8)	87.1 (9.4)

ARB indicates angiotensin II receptor blocker; BP, blood pressure; CCB, calcium-channel blocker; CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; and SD, standard deviation.

Table 2. Changes in the Blood Pressure and Control Rates at Week 8

BP Type	Change in the BP, mm Hg*			P value†
	Azilsartan (N=359)	Amlodipine (N=359)	Azilsartan–Amlodipine (95% CI)	
Sleep SBP‡	–12.6	–17.5	4.8 (2.6, 7.1)	<0.001
Sleep DBP	–7.1	–8.9	1.8 (0.5, 3.0)	0.006
Awake SBP	–14.9	–17.6	2.7 (0.6, 4.8)	0.011
Awake DBP	–8.6	–8.9	0.4 (–0.8, 1.6)	0.529
24-hour SBP	–14.0	–17.5	3.5 (1.6, 5.4)	<0.001
24-hour DBP	–7.9	–8.9	0.9 (–0.1, 2.0)	0.082
Clinic SBP	–17.0	–19.6	2.6 (0.5, 4.7)	0.016
Clinic DBP	–10.6	–10.0	–0.7 (–2.0, 0.7)	0.327

BP indicates blood pressure; CI, confidence interval; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*Data are shown as the change in the mean (95% CI).

†P value for (azilsartan–amlodipine).

‡Primary end point.

versus –18.3 mm Hg ($P<0.001$ for group difference); awake SBP, –14.1 mm Hg versus –18.7 mm Hg ($P=0.002$); 24-hour SBP, –13.2 mm Hg versus –18.6 mm Hg ($P<0.001$); clinic SBP, –16.4 mm Hg versus –21.5 mm Hg ($P<0.001$; Table 3). On the other hand, BP reduction by amlodipine showed a numerically, but not significantly, greater change in patients of <60 years old (Table 4). Analysis of covariance indicated that there was a significant interaction between age and treatment for sleep SBP ($P=0.024$), suggesting that the BP-lowering effects of amlodipine and azilsartan differed between patients of ≥ 60 and those of <60 years old. Most of the other BPs were similar between the 2 drug treatments (data not shown).

The control rates in patients of <60 years old in the azilsartan group were statistically higher than those in the amlodipine group, except for the clinic BP: sleep

Table 3. Changes in the Blood Pressure and Control Rates, Stratified by Age ≥ 60 Years Old

BP Type	Azilsartan (n=207)	Amlodipine (n=211)	Azilsartan–Amlodipine	P Value*
Change in the BP, mm Hg†				
Sleep SBP‡	–12.0	–18.3	6.3 (3.3, 9.3)	<0.001
Sleep DBP	–6.2	–8.4	2.2 (0.7, 3.8)	0.005
Awake SBP	–14.1	–18.7	4.6 (1.8, 7.5)	0.002
Awake DBP	–7.0	–8.6	1.6 (0.0, 3.2)	0.049
24-hour SBP	–13.2	–18.6	5.4 (2.8, 8.0)	<0.001
24-hour DBP	–6.6	–8.5	1.9 (0.6, 3.3)	0.006
Clinic SBP	–16.4	–21.5	5.2 (2.5, 7.9)	<0.001
Clinic DBP	–9.8	–10.5	0.7 (–1.0, 2.3)	0.416
Control rate, %†				
Sleep BP§	30.0	34.7	–4.8 (–14.2, 4.6)	0.317
Awake BP	35.9	37.8	–1.9 (–11.6, 7.8)	0.703
24-hour BP¶	33.2	37.2	–4.1 (–13.7, 5.5)	0.404
Clinic BP#	61.4	75.1	–13.7 (–22.7, –4.7)	0.003

BP indicates blood pressure; CI, confidence interval; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*P Value for (azilsartan–amlodipine).

†Data are shown as change in the mean (95% CI) or control rate (95% CI).

‡Primary end point.

§SBP<120 mm Hg and DBP<70 mm Hg.

||SBP<135 mm Hg and DBP<85 mm Hg.

¶SBP<130 mm Hg and DBP<80 mm Hg.

#SBP<140 mm Hg and DBP<90 mm Hg.

BP (azilsartan versus amlodipine), 33.3% versus 20.3% ($P=0.014$ for group difference); awake BP, 34.8% versus 21.0% ($P=0.011$); 24-hour BP, 30.5% versus 17.4% ($P=0.010$; Table 4). For patients of ≥ 60 years old, there were no significant differences in the control rates between azilsartan and amlodipine, except in clinic BP (61.4% versus 75.1% [$P=0.003$]; Table 3).

In patients of ≥ 60 years old, the slope of the regression line was also significantly steeper in the amlodipine group than in the azilsartan group ($P=0.01$), but there were no differences between the 2 groups for patients of <60 years old (data not shown).

Control Rates in Patients Well-Controlled for Clinic BP

In this study, the control rates for each BP were also calculated by targeting patients who achieved clinic BP goals (ie, well-controlled patients defined as clinic SBP <140 mm Hg and DBP <90 mm Hg in each treatment group; Table S1) at Week 8. The patients in the azilsartan group showed significantly higher control rates in awake BP (azilsartan versus amlodipine: 50.0% versus 37.6% [$P=0.009$ for the group difference]) and 24-hour BP (45.6% versus 35.0% [$P=0.024$]). The subgroup analysis by age showed that in patients of <60 years old, the azilsartan group had significantly higher control rates compared with the amlodipine group for sleep BP (44.1% versus 23.3% [$P=0.003$]), awake BP (45.2% versus 29.1% [$P=0.026$]), and 24-hour BP (40.9% versus 23.3% [$P=0.012$]; Table S2); however, no significant differences were found in

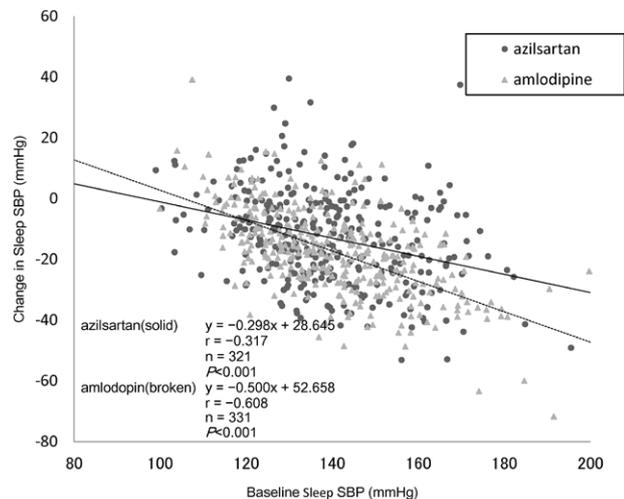


Figure 2. Scatter plot of the linear relationship between the baseline sleep systolic blood pressure (SBP) level and the change in sleep SBP.

Table 4. Changes in the Blood Pressure and Control rates, Stratified by Age <60 Years Old

BP Type	Azilsartan (n=152)	Amlodipine (n=148)	Azilsartan– Amlodipine	P Value*
Change in the BP, mmHg†				
Sleep SBP‡	–13.5	–16.4	2.8 (–0.6, 6.3)	0.104
Sleep DBP	–8.3	–9.5	1.2 (–0.9, 3.3)	0.274
Awake SBP	–15.9	–15.9	0.0 (–3.0, 3.0)	0.990
Awake DBP	–10.7	–9.5	–1.2 (–3.0, 0.6)	0.179
24-hour SBP	–15.0	–15.9	0.9 (–1.9, 3.6)	0.532
24-hour DBP	–9.8	–9.4	–0.4 (–2.0, 1.3)	0.661
Clinic SBP	–18.0	–16.9	–1.1 (–4.3, 2.2)	0.514
Clinic DBP	–11.7	–9.2	–2.5 (–4.7, –0.3)	0.024
Control rate, %†				
Sleep BP§	33.3	20.3	13.0 (2.8, 23.3)	0.014
Awake BP	34.8	21.0	13.7 (3.4, 24.1)	0.011
24-hour BP¶	30.5	17.4	13.1 (3.2, 23.0)	0.010
Clinic BP#	66.0	62.2	3.76 (–7.2, 14.7)	0.502

BP indicates blood pressure; CI, confidence interval; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*P Value for (azilsartan–amlodipine).

†Data are shown as change in the mean (95% CI) or control rate (95% CI).

‡Primary end point.

§SBP<120 mm Hg and DBP<70 mm Hg.

||SBP<135 mm Hg and DBP<85 mm Hg.

¶SBP<130 mm Hg and DBP<80 mm Hg.

#SBP<140 mm Hg and DBP<90 mm Hg.

the control rates between the 2 groups for any BPs in patients of ≥ 60 years old (Table S3).

Relation to Nocturnal Dipping Status

The 24-hour SBP profiles at baseline (before administration) and at Week 8 (end of the treatment period) in both treatment groups according to dipping status are shown in Figure S1. As shown by the profiles, both azilsartan and amlodipine reduced the night-time SBP from baseline at Week 8 in riser, nondipper, dipper, and extreme dipper patients. Similar profiles were shown in patients stratified by <60 or ≥ 60 years of age (data not shown). The mean change in the absolute difference (%) from the target decrease (15%) in sleep BP in the azilsartan and amlodipine groups was –7.3% versus –10.1% ($P=0.195$ for group difference) in riser patients; –0.7% versus –2.1% ($P=0.078$) in nondipper patients; 4.5% versus 3.1% ($P=0.011$) in dipper patients; and –1.9% versus –3.1% ($P=0.400$) in nondipper patients, respectively (Table S4).

Safety

The incidence of drug-related adverse events (azilsartan versus amlodipine) was 6.1% versus 1.7%; all events except 1 were mild (Table S5).

Discussion

In this study, azilsartan did not meet the primary efficacy end point of superiority to amlodipine in reducing sleep SBP. In the age-related subanalyses, amlodipine was significantly

superior to azilsartan in elderly patients of ≥ 60 years old in all BP subgroups except clinic DBP.

Blood Pressure Reduction

Amlodipine decreased the sleep SBP/DBP, awake SBP, 24-hour SBP, and clinic SBP more than azilsartan at Week 8 (Table 2).

CCBs are particularly effective against large vessel stiffness, one of the common causes of elevated SBP in elderly patients.¹⁶ In this study, as shown in a previous small scale study,¹¹ CCBs had a consistent BP-lowering effect depending on the patients' pretreatment BP levels. Compared with other ARBs, azilsartan has a more potent antihypertensive effect because of its (1) higher affinity for and slower dissociation from angiotensin II type 1 receptors,⁵ (2) more sustainable effect over 24 hours with a longer half-life of around 13 hours, and (3) increased lipophilicity.¹⁷ Indeed, azilsartan showed a statistically significant correlation between baseline sleep SBP and the change in sleep SBP at Week 8 ($P<0.001$); however, based on the steeper slope of the regression line in the amlodipine group compared with the azilsartan group ($P=0.001$), amlodipine reduced the sleep SBP to a greater extent in patients with a higher baseline sleep SBP.

With respect to the effects of CCBs in the Asian population, a meta-analysis of various randomized controlled trials conducted in Eastern Asian countries¹⁸ showed that the 24-hour BP reduction with CCBs was greater than with antihypertensive drugs from other classes and also revealed a baseline BP-dependent reduction.^{18,19} The findings of the present study were generally consistent with those obtained from the previous meta-analysis.¹⁸

Control Rate

The Japanese Society of Hypertension 2014 guidelines have proposed different criteria for hypertension according to the BP under consideration: $\geq 120/70$ mmHg for sleep BP, $\geq 135/85$ mmHg for awake BP, $\geq 130/80$ mmHg for 24-hour BP, and $\geq 140/90$ mmHg for clinic BP.²⁰

In our study, only $\approx 30\%$ of patients with high BP were well-controlled, except for patients with high clinic BP, suggesting that neither amlodipine nor azilsartan monotherapy provided sufficient control of sleep, awake, and 24-hour BP. To achieve BP control for the reduction of cardiovascular events, combination therapy is necessary.²¹

At week 8, the rate of masked hypertension in the azilsartan group was significantly lower than in the amlodipine group (44% versus 55%, $P=0.01$). This difference in the rate of masked hypertension between the 2 groups might have contributed to the control rate results.

Age-Related Analysis

The American Society of Hypertension/The international Society of Hypertension guidelines¹⁴ recommend that an angiotensin converting enzyme inhibitor or ARB should be used for nonblack patients of <60 years old and a CCB or thiazide for nonblack patients of ≥ 60 years old. This concept of age-related differentiation in treatment is also found in the National Institute for Health and Clinical Excellence

guidelines (an angiotensin converting enzyme inhibitor or ARB for patients of <55 years old and a CCB for patients of ≥55 years old).²² As people age, the blood vessels become stiffer and the function of the renin-angiotensin system becomes weaker,²⁰ which could lead to higher effectiveness of CCBs relative to ARBs. On the other hand, a prospective meta-analysis comparing the benefits of different antihypertensive regimens in patients <65 years or >65 years showed that there is no evidence that different classes have different efficacy in younger versus older patients.²³ As shown in Table 3, amlodipine achieved a significantly greater reduction in sleep SBP than azilsartan in patients of ≥60 years old ($P<0.001$). In patients of <60 years old, amlodipine obtained numerically greater, but not significantly greater reduction in sleep SBP (Table 4).

Study Limitations

There are 2 limitations in this study. First, the statistical power was low in the age-related subanalysis. Second, the limited reproducibility of each single ABPM before and after treatment has to be considered.

In conclusion, the present results suggest a greater BP reduction in amlodipine compared with azilsartan. In addition, reducing/controlling BP with amlodipine was more effective in the elderly population than the younger population, supporting the recommendations of the American Society of Hypertension/The international Society of Hypertension and National Institute for Health and Clinical Excellence guidelines to differentiate treatment according to age.

Perspectives

Considering the age-related BP-lowering effects of azilsartan and amlodipine, treatment with CCBs is more appropriate in an elderly population, especially if these populations are Asian. The treatment methods are consistent with those recommended in the overseas guidelines. In future studies, subjects' characteristics like ethnic background should be included as one of the factors in analyses.

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Disclosures

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Novelty and Significance

What Is New?

- Age-related differences in sleep blood pressure-lowering effects were found between angiotensin II receptor blockers and calcium channel blockers in Asians: it was suggested that calcium channel blockers are more effective than angiotensin II receptor blockers to reduce and control blood pressure in elderly hypertensives.

What Is Relevant?

- The present results suggest that guidelines, such as the American Society of Hypertension/The international Society of Hypertension 2013 and the National Institute for Health and Clinical Excellence 2011, recommending age-related options of antihypertensives are preferable to those without any such recommendations.

Summary

Azilsartan (angiotensin II receptor blocker) and amlodipine (calcium channel blocker) were directly compared in a randomized controlled trial. Amlodipine demonstrated significantly greater reductions in blood pressure than azilsartan in the overall group of subjects. In addition, the subgroup analyses suggested that amlodipine is more effective in reducing/controlling blood pressure in the elderly population, supporting the recommendations of the American Society of Hypertension/The international Society of Hypertension and National Institute for Health and Clinical Excellence guidelines for differentiating treatment according to age. As suggested in this study, age-related options of antihypertensives may also be effective in the Asian population.